Optical Resolution of *erythro*-2-Amino-1,2-diphenylethanol by Reciprocal Crystallization of the Diastereomeric Salts with (−)-Mandelic Acid on Alternate Seeding

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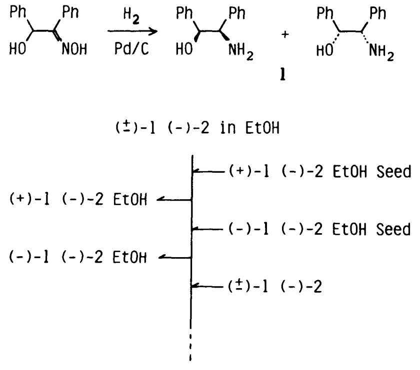
Synopsis. *erythro*-2-Amino-1,2-diphenylethanol was efficiently resolved into a pair of enantiomers by reciprocal crystallization of the diastereomeric salts with (−)-mandelic acid on alternate seeding.

Racemic *erythro*-2-amino-1,2-diphenylethanol (**1**), which can be easily prepared from commercially available benzoin oxime, has a similar fundamental structure to ephedrine. Therefore, optically active **1** is considered to be useful as an artificial chiral source. From this viewpoint optically active **1** has been applied in our laboratory as a chiral auxiliary in optical resolutions1) and asymmetric syntheses.1,2) Optically active **1** can be obtained by the fractional crystallization of the diastereomeric salts of racemic **1** with D-glutamic acid3) or with (+)-10-camphorsulfonic acid,4) by the preferential crystallization of the enantiomeric salts of racemic **1** with cinnamic acid,1) and by chromatographic separation of diastereomeric 2-oxazolidinone derivative of racemic **1**.5) The fractional crystallization, however, requires several recrystallization to get (+)- and (−)-**1** in high optical purities. The resolution efficiency of the preferential crystallization is not so high as observed in usual one although (+)- and (−)-**1** are obtained in high optical purities by simple operation. Moreover, the chromatographic separation includes multiple step and has a limitation in a quantity per one operation. We therefore examined another method to prepare optically active **1** more efficiently and easily.

Treatment of (+)- and (−)-**1**, which was prepared by preferential crystallization,1) with an equimolar amount of (−)-mandelic acid (**2**) gave a pair of diastereomeric salts. Between the solubilities of these two salts in methanol and ethanol, there was little difference, meaning that it is impossible to resolve simply these diastereomeric salts by fractional crystallization. Actually a mixture of both diastereomeric salts with ethanol of crystallization deposited on cooling a hot clear ethanol solution of the mixture. By contrast, (+)-**1**·(−)-**2**·EtOH salt deposited preferentially when the supersaturated solution was cooled to about 40 °C by standing at room temperature and seeded with a small amount of diastereomerically pure (+)-**1**·(−)-**2**·EtOH salt. Moreover, seeding of (−)-**1**·(−)-**2**·EtOH salt to the filtrate gave (−)-**1**·(−)-**2**·EtOH salt preferentially. On the basis of specific rotations, these salts were found to be highly diastereomerically pure. This result means that racemic **1** can be resolved by "reciprocal crystallization of diastereomeric salts on alternate seeding," which is very rare in the optical resolution of diastereomers.

By repeating alternate seeding of (+)-**1**·(−)-**2**·EtOH and (−)-**1**·(−)-**2**· EtOH salts in this order to the mother liquor, which was supersaturated in a similar magnitude on addition of (±)-**1**·(−)-**2**·salt, both diastereomeric salts were reciprocally obtained in high diastereomeric purities. The result is shown in the Table. This procedure could be carried out in 0.10—0.05 mol scale to give both of diastereomeric salts in large quantities with high diastereomeric purities.

The recrystallized diastereomeric salts were dissolved in hot water and treated with aqueous ammonia to give white precipitates, respectively. Recrystallization of them from ethanol gave optically pure (+)- and (−)-**1**.



Experimental

All melting points were measured by a Laboratory Devices MEL-TEMP apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-360 Digital Polarimeter.

Table 1. Reciprocal Crystallization of (±)-**1**·(−)-**2** Salt on Alternate Seeding

Run^a)	(±)-**1**·(−)-**2** Salt Supplied (g)	Signs of Seed **1**·**2**·EtOH	Yield g	Diastereomeric Purity/%
1	—	(+) (−)	1.37	94
	—	(−) (−)	1.37	99
2	2.32	(+) (−)	1.33	96
	—	(−) (−)	0.99	97
3	2.13	(+) (−)	1.09	96
	—	(−) (−)	1.37	99

a) The initial composition of the mother liquor: (±)-**1**·(−)-**2** salt (3.65 g) in ethanol (60 ml).

(±)-*erythro*-2-Amino-1,2-diphenylethanol (**1**) was synthesized by hydrogenation of commercially available benzoin oxime.[1,3] A pair of optically active **1** was prepared by the preferential crystallization of enantiomeric salts of racemic **1** with cinnamic acid salt.[1] (−)-Mandelic acid (**2**) is of commercial origin and was used without any purification.

Preparation of (+)-1·(−)-2·EtOH and (−)-1·(−)-2·EtOH Salts for Seeds. The reaction of (+)- or (−)-**1** with (−)-**2** in ethanol, followed by recrystallization from ethanol, gave the corresponding diastereomeric salts in pure state, respectivively. The salts, dried at room temperature for 12 h over P_2O_5 in vacuo, contained an equimolar amount of ethanol of crystallization. They were used as seeds for the reciprocal crystallization of diastereomeric salts on alternate seeding.

(+)-**1**·(−)-**2**·EtOH salt: Mp 167—168.5 °; $[\alpha]^{17}_{435}$ +93.9° (*c* 1.00, MeOH). (−)-**1**·(−)-**2**·EtOH salt: Mp 162—163.5 °; $[\alpha]^{15}_{435}$ −259.7° (*c* 1.00, MeOH).

Drying at 80 °C for 24 h over P_2O_5 in vacuo gave the dastereomeric salts without ethanol of crystallization.

(+)-**1**·(−)-**2** salt: Mp 165—167 °C; $[\alpha]^{17}_{435}$ +105.7 ° $[\alpha]^{17}_{\mathrm{D}}$ +49.0° (*c* 1.00, MeOH).

Found: C, 72.49; H, 6.08; N, 3.96%. Calcd for $C_{22}H_{23}NO_4$: C, 72.31 H, 6.34; N, 3.83%.

(−)-**1**·(−)-**2** salt: Mp 156—158 °C; $[\alpha]^{15}_{435}$ −292.5°, $[\alpha]^{15}_{\mathrm{D}}$ −134.4° (*c* 1.00, MeOH).

Found: C, 72.39; H, 6.20; N, 3.62%. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83%.

The diastereomeric purities of the deposited precipitates by reciprocal crystallization on alternate seeding and the recrystallized diastereomeric salts were calculated on the basis of the specific rotations of the salts with or without ethanol of crystallization, respectively.

Optical Resolution by Reciprocal Crystallization of Diastereomeric Salts on Alternate Seeding. A solution of (±)-**1** (2.13 g, 10 mmol) and (−)-**2** (1.52 g. 10 mmol) in 99% ethanol (60 ml) was refluxed until the solution became clear. The solution was cooled to about 40 °C by standing at room temperature and then seeded with (+)-**1**·(−)-**2**·EtOH salt (10 mg), followed by standing overnight at room temperature. The white precipitate deposited was collected by filtration and dried over P_2O_5 at room temperature in vacuo to give (+)-**1**·(−)-**2**·EtOH salt (1.37 g, 67%): $[\alpha]^{13}_{435}$ +83.8° (*c* 1.00, MeOH); 94% diastereomeric purity.

The filtrate was again refluxed, cooled, and seeded with (−)-**1**·(−)-**2**·EtOH salt. On standing the solution overnight at room temperature, white precipitate deposited. The precipitate was collected by filtration and dried at room temperature for 12 h in vacuo to give (−)-**1**·(−)-**2**·EtOH salt (1.37 g, 67%): $[\alpha]^{16}_{435}$ −257.9° (*c* 1.00, MeOH); 99% diastereomeric purity.

To the mother liquor was added (±)-**1**·(−)-**2** salt (2.32 g) and the solution was similarly refluxed, cooled, and seeded with (+)-**1**·(−)-**2**·EtOH and (−)-**1**·(−)-**2**·EtOH salts, successively. The process was repeated in a similar manner supplying 2.1—2.3 g of (±)-**1**·(−)-**2** salt in each run to give (+)-**1**·(−)-**2**·EtOH and (−)-**1**·(−)-**2**·EtOH salts in high diastereomeric purities. The initial three runs are shown in the Table.

The crystals of the same diastereomer were combined, recrystallized from ethanol, and dried at about 80 °C for 24 h in vacuo to give optically pure (+)-**1**·(−)-**2** and (−)-**1**·(−)-**2** salts.

(+)-**1**·(−)-**2** salt: 84% recrystallization yield; mp 165—167 °C; $[\alpha]^{15}_{435}$ +105.6 ° (*c* 1.00, MeOH); 100% diastereomeric purity.

(−)-**1**·(−)-**2** salt: 84% recrystallization yield; mp 156—157 °C; $[\alpha]^{15}_{435}$ −292.5 °C (*c* 1.00, MeOH); 100% diastereomeric purity.

Decomposition of the Diastereomeric Salts. In 530 ml of water (+)-**1**·(−)-**2** salt (28.61 g) was dissolved at 70 °C and then treated with aqueous ammonia (28 ml). Recrystallization of the resulting precipitate from ethanol gave (+)-**1** (11.57 g, 86%): Mp 142.5—144 °C; $[\alpha]^{19}_{\mathrm{D}}$ +7.7° (*c* 0.60, EtOH); 100% optical purity (lit,[1] mp 143—144 °; $[\alpha]^{24}_{\mathrm{D}}$ +7.7° (*c* 0.63, EtOH)).

Similar treatment of (−)-**1**·(−)-**2** salt (22.40 g), followed by recrystallization, gave (−)-1 (10.16 g, 80%): Mp 143—144.5 °C; $[\alpha]^{16}_{\mathrm{D}}$ −7.5° (*c* 0.60, EtOH); over 99% optical purity (lit,[1] mp 143—144 °C; $[\alpha]^{32}_{\mathrm{D}}$ −7.6° (*c* 0.60, EtOH).

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