  Bull. Chem. Soc. Jpn., 55, 1568—1573 (1982) [Vol. 55, No. 5

Optical Resolution of 2-Amino-1,2-diphenylethanol by Preferential Crystallization and Its Utilization in Fractional Crystallization and Enantioselective Reduction of Prochiral Ketones

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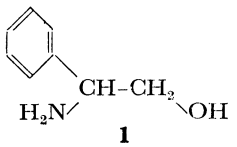
(Received October 8, 1981)

(±)-*erythro*-2-Amino-1,2-diphenylethanol prepared from benzoin oxime by catalytic reduction was successfully resolved into a pair of optically active forms by preferential crystallization. The optically active amino alcohol was found to be useful as a basic resolving agent for the optical resolution of tartaric acid, *trans*-2,3-oxiranedicarboxylic acid, 2-hydroxy-2-phenylpropionic acid, and 3-*endo*-benzamido-5-norbornene-2-*endo*-carboxylic acid. Chiral hydrides prepared from lithium aluminium hydride and optically active *threo*- or *erythro*-2-amino-1,2-diphenylethanol derivatives were applied to the enantioface differentiating reduction of prochiral ketones to give the corresponding optically active alcohols in 26—72% optical purities.

In contrast to ephedrine which is widely used in fractional crystallization as a resolving agent[1] and in asymmetric synthesis as a chiral source,[2] *erythro*-2-amino-1,2-diphenylethanol having similar configuration to ephedrine is little applied to fractional crystallization and asymmetric synthesis except for the synthesis of optically active asparic acid.[3] The preparation of optically active *erythro*-2-amino-1,2-diphenylethanol in a preparative quantity was considered to be troublesome because it is obtained by the fractional crystallization of diastereomeric salts with L-glutamic acid.[4] These prompted us to study on the optical resolution of *erythro*-2-amino-1,2-diphenylethanol by preferential crystallization, which gives preparatively both enantiomers by simple operation, and on the application of itself or its derivative to fractional crystallization of chiral carboxylic acids as a resolving agent and to asymmetric reduction of prochiral ketones as a modifier for lithium aluminium hydride.

In the previous papers, it was reported that 2-amino-2-phenylethanol (**1**)[5] and cinnamic acid salts of 1-phenylethylamine (**2**) and 1-phenyl-2-(*p*-tolyl)ethylamine (**3**)[6] were successfully resolved into pairs of enantiomers by preferential crystallization. Based on these results, *erythro*-2-amino-1,2-diphenylethanol (**4**) was considered to be also resolvable by preferential crystallization of itself or its cinnamic acid salt because **4** has α-aminobenzyl group in the structure in analog with **1**, **2**, and **3**.



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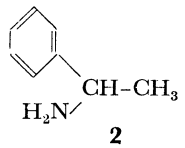

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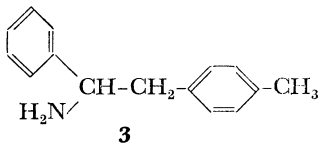

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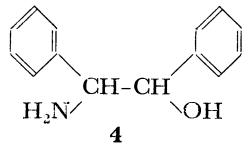

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Comparing physical properties such as melting point and solubility, infrared spectrum, and X-ray diffraction pattern of optically active form with those of racemate is efficient and appropriate to ensure the possibility of optical resolution by preferential crystallization. Then, to obtain optically active **4**, the fractional crystallization of diastereomeric salts of (±)-**4** with L-glutamic acid was initially tried according to the method described in the literature.[4] The fractional crystallization of diastereomeric salts of (±)-**4** with optically active *trans*-2-benzamidocyclohexanecarboxylic acid (**5**)[7] was found to be more convenient. Thus, the fractional crystallization of the diastereomeric salts of (±)-**4** with (+)-**5** gave (−)-**4**·(+)-**5** salt in a high optical purity, and a similar treatment of **4** recovered from the mother liquor with (−)-**5** gave highly optically pure (+)-**4**·(−)-**5** salt.

Table 1. Properties of **4** and its salts

		Optically active form		Racemate
4	Mp θ_m/°C	142—143		163—164
	Solubility[a]	5.64		3.73
	IR Spectrum		Different	
4·6 Salt	Mp θ_m/°C	172—173		172—173
	Solubility[a]	0.25		0.41
	IR Spectrum		Identical	
	X-Ray Diffraction Pattern		Identical	
4·7 Salt	Mp θ_m/°C	159—160		162—163
	Solubility[a]	0.71		1.71
	IR Spectrum		Different	
4·8 Salt	Mp θ_m/°C	131—132		165—167
	Solubility[a]	1.38		0.92
	IR Spectrum		Different	

a) g/100 ml of 99% EtOH at 15 °C.

Physical properties, infrared spectrum, and X-ray diffraction pattern of optically active **4** obtained as above or of its salt with an achiral carboxylic acid such as cinnamic acid (**6**), benzoic acid (**7**), or *cis*-1,2-cyclohexanedicarboxylic acid (**8**) were compared with those of the corresponding racemate. As shown in Table 1, optically active **4·6** salt has the same melting point as the racemate and is less soluble in ethanol than the racemate, and their infrared spectra and X-ray diffraction patterns are identical. These results indicate that crystals of **4·6** salt are deposited as con-

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Table 2. Preferential crystallization of **4·6** salt on standing

Run	(±)-**4·6** Salt added (g)	Seed	Cooling		Yield g	$[\alpha]_{435}$[a]/°	Optical purity[b] %
			Temp °C	Time min			
1	—	(+)	7	250	0.32	+53.5	31
2	0.40	(−)	5	250	0.40	−97.6	57
3	0.50	(+)	6	250	0.48	+120.4	71
4	0.70	(−)	5	180	0.77	−167.8	98
5	0.70	(+)	6	160	0.45	+161.2	94
6	0.80	(−)	6	180	0.76	−162.1	95
7	0.90	(+)	5	180	0.84	+167.8	98

The initial composition of the mother liquor: (±)-**4·6** salt (4.30 g) and (±)-**4**·lactic acid salt (6.00 g) in 99% methanol (110 ml). In all runs, 0.02 g of seed was added.
a) (*c* 0.60, 99% MeOH). b) Based on $[\alpha]_{435}^{30}$ + and −170.7°.

Table 3. Preferential crystallization of **4·6** salt under stirring

Run	(±)-**4·6** Salt added (g)	Seed	Cooling		Yield g	$[\alpha]_{435}$[a]/°	Optical purity[b] %
			Temp °C	Time min			
1	—	(+)	8	75	5.11	+164.3	96
2	5.50	(−)	9	80	4.99	−161.6	95
3	5.00	(+)	6	60	4.99	+169.6	99
4	5.00	(−)	6	85	4.58	−167.7	98
5	6.00	(+)	6	35	4.80	+156.2	92
6	5.00	(−)	7	35	5.11	−166.8	98
7	5.00	(+)	8	35	4.78	+160.7	94
8	5.00	(−)	7	40	5.40	−155.7	91

The initial composition of the mother liquor: (±)-**4·6** salt (22.40 g), (+)-**4·6** salt (2.17 g), which was added to facilitate the preferential crystallization from the first stage, and (±)-**4**·lactic acid salt (30.00 g) in 99% methanol (550 ml). In all runs, 0.04 g of seed was added.
a) (*c* 0.60, 99% MeOH). b) Based on $[\alpha]_{435}^{30}$ + and −170.7°.

glomerate and that **4·6** salt is resolvable by preferential crystallization in a similar manner as **2·6** and **3·6** salts.

Actually, (+)-**4·6** salt was obtained from a supersaturated solution of (±)-**4·6** salt in methanol when (+)-**4·6** salt, which was prepared from equimolar amounts of (+)-**4** and **6** followed by recrystallizations for several times, was seeded to the solution, and the solution was stood for 2.5 h at around 5 °C. Alternate seeding of (−)- or (+)-**4·6** salt to the solution supersaturated in a similar magnitude gave (−)- or (+)-**4·6** salt in a moderate to high optical purity.

The procedure is inapplicable to the optical resolution of (±)-**4·6** salt in a preparative scale because it is difficult to obtain optically active **4·6** salt in a constant yield. The problem was overcome by coexisting the readily soluble (±)-lactic acid salt of (±)-**4** in the mother liquor, which decreased the concentration change of 2-hydroxy-1,2-diphenylethylammonium ion in the solution during crystallization to stabilize the preferential crystallization (Table 2). Moreover, gentle stirring of the supersaturated solution in the course of crystallization was found to be effective to shorten the cooling time. Stirring made the solution uniform and accelerated the crystal growth from seed surface. But, the nucleation of the unseeded antipode crystals of **4·6** salt occured when the solution was stirred too vigorously. The result is summarized in Table 3.

The crystals having the same sign of optical rotation were combined and recrystallized from methanol to give highly purified (+)- and (−)-**4·6** salts. They seemed to be almost optically pure because the values of their specific rotations were almost same to those of recrystallized **6** salts of (+)- and (−)-**4** obtained by the fractional crystallization with L-glutamic acid or *trans*-2-benzamidocyclohexanecarboxylic acid (**5**).

Decomposition of purified (+)- and (−)-**4·6** salts with an alkali solution gave (+)- and (−)-**4**, of which the specific rotations at 589 nm in absolute ethanol were +7.7° and −7.6°, respectively. Weijland *et al.* reported that the specific rotations were +10.2° and −10.1°, respectively.[4] Attempts to get (+)- and (−)-**4** which have the specific rotations of the values were unsuccessful. No drop of the specific rotations under the conditions of the liberation of (+)- or (−)-**4** was observed. Recent literatures reported that the specific rotations were +6.8°[3] and −6.4°,[8] respectively. Based on the data, (+)- and (−)-**4** obtained as above were considered to be almost optically pure.

Then, we applied optically active **4** to the optical resolution of chiral carboxylic acids such as tartaric acid (**9**), *trans*-2,3-oxiranedicarboxylic acid (**10**), 2-hydroxy-2-phenylpropionic acid (**11**), and 3-*endo*-5-nor-

Table 4. Resolution of chiral carboxylic acids using **4**

Salt	Recrystallization: Solvent	Recrystallization: Time	Yield[a] %	Specific rotation
(−)-**9**·(+)-**4**	H_2O	1	64	$[\alpha]_{435}^{32}$ +155.9° (*c* 0.30, H_2O)
(+)-**9**·(−)-**4**	H_2O	1	69	$[\alpha]_{435}^{34}$ −157.1° (*c* 0.30, H_2O)
(−)-**10**·(−)-**4**	90% EtOH[b]	2	56	$[\alpha]_{435}^{24}$ −190.9° (*c* 0.68, 2 M HCl)
(−)-**11**·(−)-**4**	99% MeOH	2	63	$[\alpha]_{435}^{22}$ −235.4° (*c* 0.51, 99% MeOH)
(−)-**12**·(+)-**4**	95% EtOH	3	41	$[\alpha]_{435}^{33.5}$ −56.3° (*c* 0.61, 99% MeOH)

The specific rotations of (+)- and (−)-**4** used as resolving agent: $[\alpha]_{589}^{30}$ +7.4° and −7.1° (*c* 0.60, abs. EtOH), respectively.
a) Based on half the amount of (±)-carboxylic acid used. b) Extraction of more soluble salt under refluxing.

Table 5. Liberation of carboxylic acids resolved

Acid	Total yield[a]/%	Mp θ_m/°C	Specific rotation	Optical purity/%
(−)-**9**	54	167.5—168	$[\alpha]_{589}^{24}$ −14.4° (*c* 1.04, H_2O)	91[b]
(+)-**9**	60	166—167	$[\alpha]_{589}^{29}$ +14.1° (*c* 1.02, H_2O)	89[b]
(−)-**10**	40	177—178	$[\alpha]_{589}^{24}$ −117.4° (*c* 2.58, 99% EtOH)	100[c]
(−)-**11**	52	116.5—117	$[\alpha]_{589}^{30.5}$ −49.3° (*c* 1.00, H_2O)	92[d]
(−)-**12**	36	179—180	$[\alpha]_{435}^{33}$ −251.3° (*c* 1.00, 99% MeOH)	99[e]

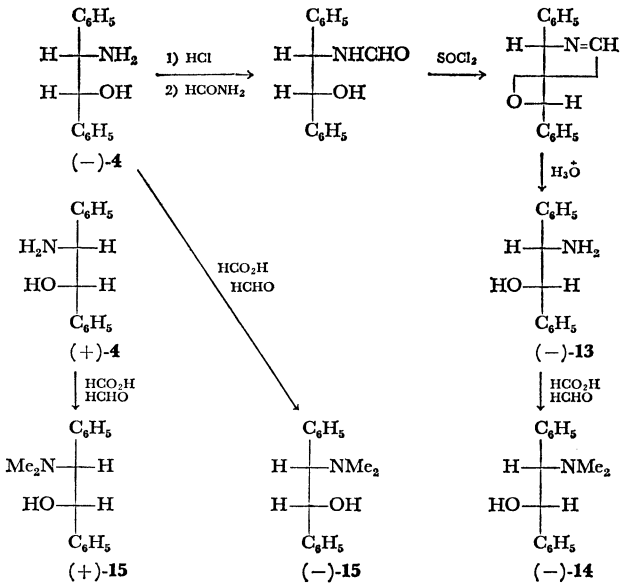
a) Based on half the amount of (±)-carboxylic acid used. b) Based on the specific rotation of commercial (+)-tartaric acid: $[\alpha]_{589}^{25}$ +15.9° (*c* 1.01, H_2O). c) Based on $[\alpha]_{589}^{25}$ +117.8° (*c* 2.6, EtOH).[1c] d) Based on $[\alpha]_{589}^{20}$ +53.5° (*c* 1.591, H_2O).[10] e) Based on $[\alpha]_{435}^{20}$ −254° (*c* 1.00, 99% MeOH).[11]

bornene-2-*endo*-carboxylic acid (**12**) by fractional crystallization. As shown in Tables 4 and 5, they were resolved in moderate to high optical purities, and optically active **4** was found to be useful as a resolving agent. The results indicate that **4** is as effective as 2-amino-2-phenylethanol (**1**)[5] in the resolution of **9** and **11** and is superior to **1** with regard to the resolution of **10** which could not be resolved with **1**.

Next stage, derivatives of **4** were applied to asymmetric reduction of prochiral ketones as modifiers of lithium aluminium hydride. (−)-*threo*-2-Amino-1,2-diphenylethanol ((−)-**13**) was obtained from (−)-**4** *via* *N*-formylation, cyclization, and hydrolysis according to the procedure in the literatures.[4,9] The Eschweiler-Clarke reaction of (−)-**13** gave (−)-*threo*-2-dimethylamino-1,2-diphenylethanol ((−)-**14**). The reaction of (+)- and (−)-**4** also yielded (+)- and (−)-*erythro*-2-dimethylamino-1,2-diphenylethanol ((+)- and (−)-**15**), respectively (Scheme 1).

Acetophenone was chosen as a model substrate, and the reduction with lithium aluminium hydride modified by (−)-**14** or (+)-**15** was carried out in ether at −78 °C. As shown in Table 6 (Exp. 1 and 2), lithium aluminium hydride treated with 2.2 molar amounts of (+)-**15** was found to be more effective than that treated with (−)-**14**.

Contrary to the reduction with lithium aluminium hydride–(−)-**14** complex, which gave (*R*)-(+)-1-phenylethanol, the reduction with lithium aluminium hydride–(+)-**15** complex yielded (*S*)-(−)-1-phenylethanol. The result was considered to indicate that the configuration of the product was influenced by the configuration of C2 (the carbon atom carrying amino group) of 2-amino-1,2-diphenylethanol. The consideration is supported by the fact that the absolute configuration of (−)-**14** and (+)-**15**, derived from



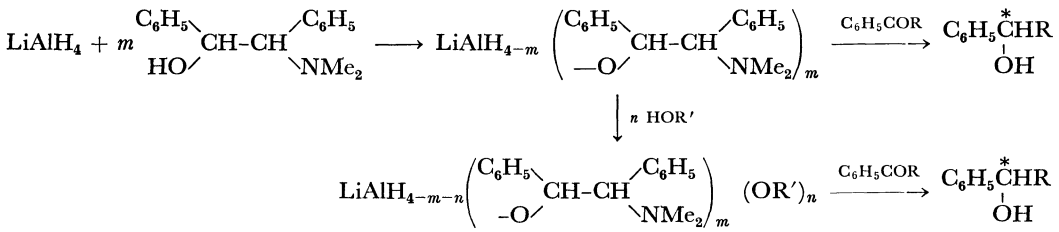
Scheme 1.

(*1S,2S*)-(−)-**13**[4,9] and (*1S,2R*)-(+)-**4**,[4] are (*1S,2S*) and (1*S*,2*R*), respectively.

A similar optical purity was achieved when lithium aluminium hydride was treated with 1.1 molar amount of (+)-**15** and 2.2 molar amounts of ethanol (Table 6. Exp. 10), but in the other cases no improvement was obtained by adding an achiral alcohol such as 2,4-xylenol and ethanol in several molar ratios (Table 6. Exp. 5—9). Moreover, lithium aluminium hydride modified with (+)-**15** and ethanol as mentioned above was found to be less effective for the asymmetric reduction of propiophenone (Table 6. Exp. 11).

Utilizing lithium aluminium hydride treated with 2.2 molar amounts of (+)- or (−)-**15**, the reduction

Table 6. Asymmetric reduction of prochiral ketones with $LiAlH_4$-chiral amino alcohol complex



Exptl	R of ketone	Amino alcohol	Achiral alcohol	Molar ratio[a]	Reaction[b] time/h	Yield %	$[\alpha]_{589}$/° (c, solvent, T/°C)	Optical purity/%
1	CH_3	(−)-**14**	—	A	5	55	+19.3 (6.71, C_5H_{10}, 23)	45[c]
2	CH_3	(+)-**15**	—	A	5	92	−29.0 (7.21, C_5H_{10}, 30)	67[c]
3	C_2H_5	(+)-**15**	—	A	5	83	−32.5 (5.14, $CHCl_3$, 32)	72[d]
4	n-C_3H_7	(−)-**15**	—	A	5	94	+29.9 (4.28, C_6H_6, 33)	69[e]
5	CH_3	(+)-**15**	Xylenol	B	5	83	−17.9 (7.31, C_5H_{10}, 32)	42[c]
6	CH_3	(+)-**15**	Xylenol	C	10	54	−16.3 (3.94, C_5H_{10}, 26)	38[c]
7	CH_3	(+)-**15**	Xylenol	D	10	94	−11.8 (7.22, C_5H_{10}, 35)	27[c]
8	CH_3	(+)-**15**	Ethanol	B	5	91	−11.1 (7.20, C_5H_{10}, 28)	26[c]
9	CH_3	(+)-**15**	Ethanol	C	10	52	−14.4 (5.60, C_5H_{10}, 27)	33[c]
10	CH_3	(+)-**15**	Ethanol	D	10	82	−26.6 (7.11, C_5H_{10}, 32)	62[c]
11	C_2H_5	(+)-**15**	Ethanol	D	10	99	−16.6 (5.19, $CHCl_3$, 34)	37[d]

a) $LiAlH_4$: Amino alc. : Achiral alc. : Ketone

A	2.0	4.4	0	1.0
B	2.0	2.2	2.0	1.0
C	2.0	4.4	2.0	1.0
D	2.0	2.2	4.0	1.0

b) The reactions were carried out in ether at −78 °C. c) Based on $[\alpha]_{589}^{21}$ −43.1° (c 7.19, cyclopentane).[12] d) Based on $[\alpha]_{589}$ −45.45° (c 5.15, $CHCl_3$).[13] e) Based on $[\alpha]_{589}$ +43.6° (c 4.18, C_6H_6).[14]

of propiophenone and butyrophenone was carried out to give 1-phenyl-1-propanol in 72% optical purity and 1-phenyl-1-butanol in 69% optical purity, respectively.

In conclution, it is noteworthy that both enantiomers of **4** become obtainable in high optical purities by the preferential crystallization of (±)-**4**·**6** salt and that it or its derivative is useful as a synthetic basic resolving agent for the optical resolution of chiral carboxylic acids or as a modifier of lithium aluminium hydride for asymmetric reduction of prochiral ketones.

Experimental

The melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The values of specific rotation were measured on JASCO DIP-181 digital polarimeter. The ^{1}H-NMR spectra were recorded in $CDCl_3$ solution at 60 MHz on Varian A-60 Spectrometer using TMS as an internal standard. The IR spectra were determined on JASCO IR-2A Spectrophotometer.

Synthesis of (±)-erythro-*2-Amino-1,2-diphenylethanol* ((±)-**4**). To a solution of benzoin α-oxime (50.30 g, 0.22 mol) in 90% ethanol (530 ml) was added 5% palladium–chacoal catalyst (5.00 g), and the suspension was stirred at 51—52 °C under a hydrogen atmosphere using an ordinary pressure hydrogenation apparatus. After the required amount of hydrogen (about 10 l) has been absorbed, hydrogen absorption abruptly slowed. At this point, the hydrogenation was stopped, and concd HCl (40 ml) was added to the reaction mixture. After the mixture was stirred at around 60 °C for 1.5 h, the solvent was evaporated. To the residue was added boiling water (500 ml), and the catalyst was filtered off from the hot aqueous solution. The catalyst was washed twice with boiling water (500 ml). The filtrate and the washings were combined, basified with concd aqueous ammonia, and cooled with ice bath to give white precipitates. The precipitates were collected by filtration and recrystallized from 99% methanol to yield 41.81 g of (±)-**4**: mp 163—164 °C (lit,[4] 163 °C).

Optical Resolution of (±)-**4** *with Optically Active* trans-*2-Benzamidocyclohexanecarboxylic Acid* (**5**) *by Fractional Crystallization.* A clear solution of (±)-**4** (7.64 g) and (+)-**5**[7] (9.51 g) in a mixture of 99% ethanol and ethyl acetate (1:1) (200 ml) at an elevated temperature was allowed to cool slowly at room temperature and stood overnight. The white precipitates were collected by filtration to give 5.76 g (67%) of crude (−)-**4**·(+)-**5** salt: $[\alpha]_{435}^{30}$ −68.6° (c 1.01, 99% MeOH). The mother liquor was reserved for later use. Recrystallization of the crude salt (5.66 g) from a 99% ethanol–ethyl acetate (1:1) mixture (150 ml) gave 3.85 g (46% total yield) of pure (−)-**4**·(+)-**5** salt: mp 187.5—188 °C; $[\alpha]_{435}^{26}$ −80.9° (c 1.17, 99% MeOH).

To a solution of the salt (3.85 g) in 99% methanol (50 ml) was added 3 M NaOH solution at 0 °C to basify the solution. After evaporation of the solvent, water (50 ml) was added to the white mass remained, and the suspension was vigorously stirred for 1 h. The precipitates were collected by filtration to yield 1.62 g of (−)-**4**. Recrystallization from 95% ethanol gave 1.05 g (28% total yield based on half the amount of (±)-**4** used) of pure (−)-**4**: mp 141—142 °C; $[\alpha]_{589}^{30}$ −7.3° (c 0.63, abs. EtOH) (lit,[8] mp 141—144 °C; $[\alpha]_{589}^{24}$ −6.4° (c 1.25, abs. EtOH)).

The mother liquor from the original crystallization was

concentrated under reduced pressure, and a similar treatment of the remained residue gave 4.50 g of **4** which contained (+)-**4** in excess. The recovered amino alcohol (4.50 g) and (−)-**5**[7] (5.21 g) were dissolved in a 99% ethanol–ethyl acetate (1:1) mixture (210 ml) under refluxing, and the solution was allowed to cool slowly at room temperature to give 7.66 g of crude (+)-**4**·(−)-**5** salt. Recrystallization of the salt (7.66 g) from a 99% ethanol–ethyl acetate (1:1) mixture gave 5.54 g of the pure salt: mp 187—188 °C; $[\alpha]^{27}_{435}$ +79.0° (*c* 1.04, 99% MeOH).

Decomposition of the salt in a similar manner to the case of (−)-**4**·(+)-**5** salt yielded 2.28 g of (+)-**4**. Recrystallization from 95% ethanol gave 1.77 g (46% total yield based on half the amount of (±)-**4** used) of pure (+)-**4**: mp 142—143 °C; $[\alpha]^{30}_{589}$ +7.1° (*c* 0.60, abs. EtOH) (lit,[3] $[\alpha]^{22}_{589}$ +6.8° in abs. EtOH).

Preferential Crystallization of (±)-4·Cinnamic Acid (6) Salt. Racemic **4·6** salt was prepared from equimolar amounts of (±)-**4** and **6** in methanol. For instance, a boiled solution of (±)-**4** (19.20 g) and **6** (13.33 g) in 99% methanol was cooled slowly and stood overnight at room temperature to give 24.57 g (76%) of (±)-**4·6** salt: mp 172—173 °C; IR (KBr) 3425, 3250, 3050, 2925, 1640, 1500, 1395, 1380 (shoulder), and 700 cm^{-1}. Found: N, 3.60%. Calcd for $C_{23}H_{23}NO_3$: N, 3.88%.

Optically active **4·6** salts for seeds in the preferential crystallization were also prepared from (+)- and (−)-**4** in a similar manner followed by twice recrystallizations from 99% methanol: mp 172—173 °C; $[\alpha]^{30}_{435}$ + and −170.7° (*c* 0.60, 99% MeOH); IR (KBr) 3425, 3250, 3050, 2925, 1640, 1500, 1395, 1380 (shoulder), and 700 cm^{-1}.

A refluxed solution of (±)-**4·6** salt (22.40 g), (+)-**4·6** salt (2.17 g), which was added to facilitate the preferential crystallization from the first stage, and (±)-**4**·lactic acid salt (30.00 g) in 99% methanol (550 ml) was cooled at about 35 °C to give a supersaturated solution. To the solution was added (+)-**4·6** salt (0.04 g) as a seed, and the solution was stirred gently (about 25 rpm) by a mechanical stirrer for 75 min at about 8 °C. The white precipitates deposited were collected by filtration, washed with 99% methanol (8 ml), and dried over P_2O_5 to yield 5.11 g of (+)-**4·6** salt: $[\alpha]^{27.5}_{435}$ +164.3° (*c* 0.60, 99% MeOH); 96% optical purity.

To the filtrate was added (±)-**4·6** salt (5.50 g) and dissolved at an elevated temperature. In a similar manner, the solution was cooled, seeded with (−)-**4·6** salt, and stirred gently at about 9 °C for 80 min to give 4.99 g of (−)-**4·6** salt: $[\alpha]^{26}_{435}$ −161.5° (*c* 0.60, 99% MeOH); 95% optical purity.

After several stages of the preferential crystallization as shown in Table 3, the crystals having the same sign of optical rotation were combined and recrystallized from 99% methanol to yield almost optically pure (+)- and (−)-**4·6** salts, respectively. For example, recrystallization of (+)-**4·6** salt (36.78 g, 91% optical purity on the average) from 99% methanol (440 ml) gave 24.25 g (66%) of (+)-**4·6** salt: mp 172—173 °C; $[\alpha]^{25}_{435}$ +168.5° (*c* 0.60, 99% MeOH); 99% optical purity. Found: N, 3.68%. Calcd for $C_{23}H_{23}NO_3$: N, 3.88%.

Similar recrystallization of (−)-**4·6** salt (34.40 g, 90% optical purity on the average) from 99% methanol (400 ml) gave 21.12 g (61%) of (−)-**4·6** salt: mp 172—173 °C; $[\alpha]^{26}_{435}$ −169.6° (*c* 0.60, 99% MeOH), 99% optical purity. Found: N, 3.61%. Calcd for $C_{23}H_{23}NO_3$: N, 3.88%.

Liberation of (+)- and (−)-4 from the Cinnamic Salts. To a hot solution of (−)-**4·6** salt (10.65 g) in 99% methanol (200 ml) was added 10% NaOH solution (50 ml) to decompose the salt. After evaporation of the solvent, water (200 ml) was added to the remained residue and the suspension was stirred for 40 min. The precipitates were collected by filtration and recrystallized from 95% ethanol (50 ml) to give 4.89 g (78%) of (−)-**4**: mp 143—144 °C; $[\alpha]^{32}_{589}$ −7.6° (*c* 0.60, abs. EtOH) (lit,[8] mp 141—144 °C; $[\alpha]^{24}_{589}$ −6.4° (*c* 1.25, abs. EtOH)). Found: N, 6.28%. Calcd for $C_{14}H_{15}NO$: N, 6.57%.

In a similar manner, (+)-**4** (8.26 g) was obtained from (+)-**4·6** salt (19.16 g): mp 143—144 °C; $[\alpha]^{24}_{589}$ +7.7° (*c* 0.63, abs. EtOH) (lit,[3] $[\alpha]^{22}_{589}$ +6.8° in abs. EtOH). Found: 6.78%. Calcd for $C_{14}H_{15}NO$: N, 6.57%.

Resolution of (±)-Tartaric Acid ((±)-9) with (+)-4. A solution of (±)-**9** (1.50 g, 10 mmol) and (+)-**4** (2.13 g, 10 mmol) in water (75 ml) was refluxed to give a clear solution. The solution was allowed to cool and stood overnight at room temperature. The white precipitates were collected by filtration and dried over P_2O_5 to yield 1.16 g (64%) of (−)-**9**·(+)-**4** salt: $[\alpha]^{32}_{435}$ +155.9° (*c* 0.30, H_2O).

To a suspension of the salt (1.06 g) was added 2 M NaOH (5 ml), and the precipitates appeared were filtered off. The aqueous solution was charged on an ion exchange column (Amberlite IR 120B, 35 ml) and the product was eluted with water (200 ml). The eluate was concentrated under reduced pressure. The mass remained was ground to a powder and dried over P_2O_5 to give 0.37 g (54% total yield based on half the amount of (±)-**9** used) of (−)-**9**: mp 167.5—168 °C; $[\alpha]^{24}_{589}$ −14.4° (*c* 1.04, H_2O), 91% optical purity based on the specific rotation of commercial (+)-tartaric acid.

When (−)-**4** was used as a resolving agent instead of (+)-**4**, similar treatment gave 2.51 g of (+)-**9**·(−)-**4** salt $[\alpha]^{34}_{435}$ −157.1° (*c* 0.30, H_2O). The salt (1.26 g) was similarly decomposed with 2 M NaOH to yield 0.45 g of (+)-**9**: mp 166—167 °C; $[\alpha]^{29}_{589}$ +14.1° (*c* 1.02, H_2O); 89% optical purity.

In a similar fashion, *trans*-2,3-oxiranedicarboxylic acid (**10**), 2-hydroxy-2-phenylpropionic acid (**11**), and 3-*endo*-benzamido-5-norbornene-2-*endo*-carboxylic acid (**12**) were resolved by fractional crystallization using (+)- or (−)-**4** as a resolving agent as shown in Tables 4 and 5.

*Synthesis of (−)-*threo*-2-Amino-1,2-diphenylethanol (13).* The compound was prepared from 8.54 g of (−)-**4**·HCl salt (mp 212—214 °C; $[\alpha]^{28}_{589}$ −61.3° (*c* 1.00, H_2O)) according to the procedure in the literature[4,9] without the purification of the products in each steps. Recrystallization of crude (−)-**13** from 70% ethanol gave pure (−)-**13**: yield 3.24 g (44% total yield); mp 115—116 °C; $[\alpha]^{28}_{589}$ −125° (*c* 1.00, 99% EtOH) (lit,[4] mp 115.2—115.8 °C; $[\alpha]^{22}_{589}$ −123.7° (*c* 1.2, abs. EtOH).

*The Eschweiler-Clarke Reaction of (−)-*threo*-, (+)-*erythro*-, and (−)-*erythro*-2-Amino-1,2-diphenylethanol ((−)-13, (+)-4, and (−)-4).* The reaction was carried as follows: To a solution of 2-amino-1,2-diphenylethanol (8.0 g, 37.5 mmol) in 99% formic acid (16.0 g, 342 mmol) was added dropwise 35% aq formalin (8.0 g, 93 mmol) in a period of 15 min, and the mixture was refluxed for 20 h with stirring. After cooling at room temperature, concd HCl solution (28 ml) was added to the reaction mixture. The solution was concentrated under reduced pressure, treated with 10% NaOH solution at 0 °C (pH≃10), and extracted with ether (3×180 ml). The ethereal extracts were combined, washed with saturated NaCl solution, and dried with $MgSO_4$. Concentration of the solution followed by recrystallization from hexane gave pure 2-dimethylamino-1,2-diphenylethanol.

(−)-*threo*- ((−)-**14**): yield 6.72 g (74%): mp 57—58 °C; $[\alpha]^{29}_{589}$ −124.7° (*c* 1.00, 99% EtOH); IR (KBr) 3450, 750, and 700 cm^{-1}; NMR ($CDCl_3$) δ=2.20 (s, 6H), 3.53

(d, 1H, J=10 Hz), 5.00 (d, 1H, J=10 Hz), 4.95 (s, 1H), and 6.9—7.4 (m, 10H). Found: N, 5.74%. Calcd for $C_{16}H_{19}NO$: N, 5.80%.

(+)-*erythro*- ((+)-**15**): yield 8.27 g (91%); mp 90—91 °C; $[\alpha]_{589}^{24}$ +123° (*c* 1.00, 99% EtOH); IR (KBr) 3510, 770, 750, and 700 cm^{-1}; NMR ($CDCl_3$) δ=2.30 (s, 6H), 3.20 (d, 1H, J=4.5 Hz), 3.30 (s, 1H), 5.27 (d, 1H, J=4.5 Hz), and 6.8—7.2 (m, 10H). Found: N, 6.01%. Calcd for $C_{16}H_{19}NO$: N, 5.80%.

(−)-*erythro*- ((−)-**15**): yield 7.84 g (87%); mp 90—91 °C; $[\alpha]_{589}^{27}$ −123° (*c* 1.01, 99% EtOH); IR (KBr) 3510, 770, 750, and 700 cm^{-1}; NMR ($CDCl_3$) δ=2.30 (s, 6H), 3.20 (d, 1H, J=4.5 Hz), 3.30 (s, 1H), 5.27 (d, 1H, J=4.5 Hz), and 6.8—7.2 (m, 10H). Found: N, 5.91%. Calcd for $C_{16}H_{19}NO$: N, 5.80%.

General Procedure for Asymmetric Reduction of Ketone. To a standardized ethereal solution of $LiAlH_4$ (8.90 ml, 4.0 mmol) were added successively dry ether (8.0 ml) and 2-dimethylamino-1,2-diphenylethanol (2123.8 mg, 8.8 mmol) in dry ether (8.0 ml) at room temperature in a period of 30 min, and the suspension was stirred for an additional hour. Ketone (2.0 mmol) in ether (8.0 ml) was added to the suspension, cooled at −78 °C, with stirring in a period of 1 h. After the reaction mixture was stirred for 5—10 h at that temperature, water (1 ml) was added to hydrolyze $LiAlH_4$ complex, and a cooling bath was removed. To the mixture was added 6 M HCl solution (20 ml) followed by ether (50 ml), and the precipitates appeared were filtered off and washed with ether (3×20 ml). The filtrate and washings were combined, and the ethereal layer was separated. The ethereal solution was dried with Na_2SO_4 and concentrated under reduced pressure to give crude product. The product was purified by preparative TLC to give the corresponding alcohol. Further, it was purified for the measurement of specific rotation by bulb to bulb distillation. The chiral amino alcohol was recovered by usual work up from the aqueous layer and the precipitates filtered off.

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