

Optical Resolution by Preferential Crystallization of (*RS*)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid and Its Use in Synthesizing Optically Active 2-Amino-2-methyl-3-phenylpropanoic Acid

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To synthesize optically active 2-amino-2-methyl-3-phenylpropanoic acid (**1**), (*RS*)-2-benzoylamino-2-benzyl-3-hydroxypropanoic acid [(*RS*)-**2**] was first optically resolved using cinchonidine as a resolving agent to yield optically pure (*S*)- and (*R*)-**2** in yields of about 70%, based on half of the starting amount of (*RS*)-**2**. Next, the racemic structure of (*RS*)-**2** was examined based on melting point, solubility, IR spectrum, and binary and ternary phase diagrams, with the aim of optical resolution by preferential crystallization of (*RS*)-**2**. Results indicated that the (*RS*)-**2** exists as a conglomerate at room temperature, although it forms a racemic compound at the melting point. The optical resolution by preferential crystallization yielded (*S*)- and (*R*)-**2** with optical purities of about 90%, which were fully purified by recrystallization. After *O*-tosylation of (*S*)- and (*R*)-**2**, reduction by zinc powder and sodium iodide gave (*R*)- and (*S*)-**1**, respectively.

Key words α -methylphenylalanine; *N*-benzoyl- α -benzylserine; optical resolution; preferential crystallization

α,α -Disubstituted α -amino acids, such as 2-amino-2-methyl-3-phenylpropanoic acid (**1**; α -methylphenylalanine) and 2-amino-2-benzyl-3-hydroxypropanoic acid (α -benzylserine), are known as enzyme inhibitors and as conformational modifiers in physiologically important peptides.¹⁾ For example, the dipeptide that is synthesized from optically active **1** and *N*-benzoylglycine is a substrate for carboxypeptidase A.²⁾ (*R*)- and (*S*)-**1** have been synthesized by conversion of optically active 2-methylaziridine-2-carboxylic acid,³⁾ by reduction of optically active *N*-benzoyl derivative (**2**) of α -benzylserine,⁴⁾ and by alkylation of the Schiff's base, formed from benzaldehyde and DL-alanine ester, using enantiopure 2-hydroxy-2'-amino-1,1'-binaphthyl as the catalyst.⁵⁾ Among the reagents which are employed in the above syntheses, optically active **2** is seemed to be easily obtained by optical resolution of its racemate, which is synthesized from L-phenylalanine (L-Phe).^{4,6)} Therefore, we attempted to obtain optically active **1** via optical resolution of (*RS*)-**2**.

Preferential crystallization and separation of a diastereoisomeric mixture have been well employed for optical resolution.⁷⁾ Although (*RS*)-**2** has been optically resolved by separation of the diastereoisomeric salts with quinine to obtain optically active **2**,⁴⁾ the optical resolution by preferential crystallization of (*RS*)-**2** have not yet been reported. Racemates exist in the forms of racemic compounds, racemic solid solutions, and conglomerates (racemic mixtures), among which only conglomerates can be optically resolved by preferential crystallization.⁷⁾ Since we found that (*RS*)-**2** exists as a conglomerate at room temperature, (*RS*)-**2** was subjected to optical resolution by preferential crystallization. The obtained (*R*)- and (*S*)-**2** were attempted to be reduced by zinc powder and sodium iodide to give optically active **1** (Chart 1).^{4,6,8)}

Results and Discussion

(*RS*)-5-Benzoylamino-5-benzyl-4-oxo-1,3-dioxane [(*RS*)-**3**] was synthesized starting from L-Phe by *N*-benzoylation of L-Phe, followed by dehydration of the *N*-benzoyl-DL-phenyl-

alanine (DL-**4**) to the corresponding oxazolone [(*RS*)-**5**], and then treatment of (*RS*)-**5** with aqueous formaldehyde in the presence of pyridine.⁶⁾ When (*RS*)-**3** was refluxed for 15—30 min in 5 mol dm⁻³ hydrochloric acid, (*RS*)-2-amino-3-benzoyloxy-2-benzylpropanoic acid hydrochloride [(*RS*)-**6**] was obtained in yields of 65—83%. (*RS*)-**3** was hydrolyzed under alkaline conditions to give (*RS*)-**2**.

We first attempted the optical resolution of (*RS*)-**2** by separation of the diastereoisomeric salts with optically active amines such as cinchonidine (**7**), α -methylbenzylamine, and 2-amino-1-(4-nitrophenyl)-1,3-propanediol. Of these amines, only **7** formed a good crystalline salt with **2**. The salt of (*S*)-**2** with **7** [(*S*)-**2**·**7** salt] was crystallized as a less-soluble diastereoisomeric salt and the more-soluble (*R*)-**2**·**7** salt was obtained from the filtrate. After treating these salts with hydrochloric acid, the obtained (*S*)- and (*R*)-**2** were recrystallized from ethanol to give optically pure (*S*)- and (*R*)-**2** in yields of about 70%, based on half of the starting amount of (*RS*)-**2**.

Since the (*S*)- and (*R*)-**2** partially resolved by the diastereoisomeric method were recrystallized from ethanol to give optically pure (*S*)- and (*R*)-**2**, (*RS*)-**2** was postulated to exist as a conglomerate. (*RS*)-**2** has a lower melting point than (*S*)-**2**; (*RS*)-**2**, 161 °C; (*S*)-**2**, 173 °C. Although the melting-point binary phase diagram suggested that (*RS*)-**2** forms a racemic compound, as shown in Fig. 1,⁷⁾ its IR spectrum was identical to that of (*S*)-**2**. In addition, (*RS*)-**2** was more soluble than (*S*)-**2** at 10 °C; solubility of (*RS*)-**2**, 10.773 g (100 ml of ethanol)⁻¹; solubility of (*S*)-**2**, 6.025 g (100 ml of ethanol)⁻¹. The solubility ternary phase diagram at 10 °C (Fig. 2) suggests that (*RS*)-**2** can exist as a conglomerate at room temperature, even a racemic compound at the melting point.

Thus, (*RS*)-**2** was tried to optically resolve by preferential crystallization at 10 °C in ethanol. To optimize conditions, the optical resolution was conducted by stirring 140—170% supersaturated solutions for 20—60 min, as shown in Figs. 3 and 4 and summarized in Table 1; (*S*)-**2** (0.050 g) was em-

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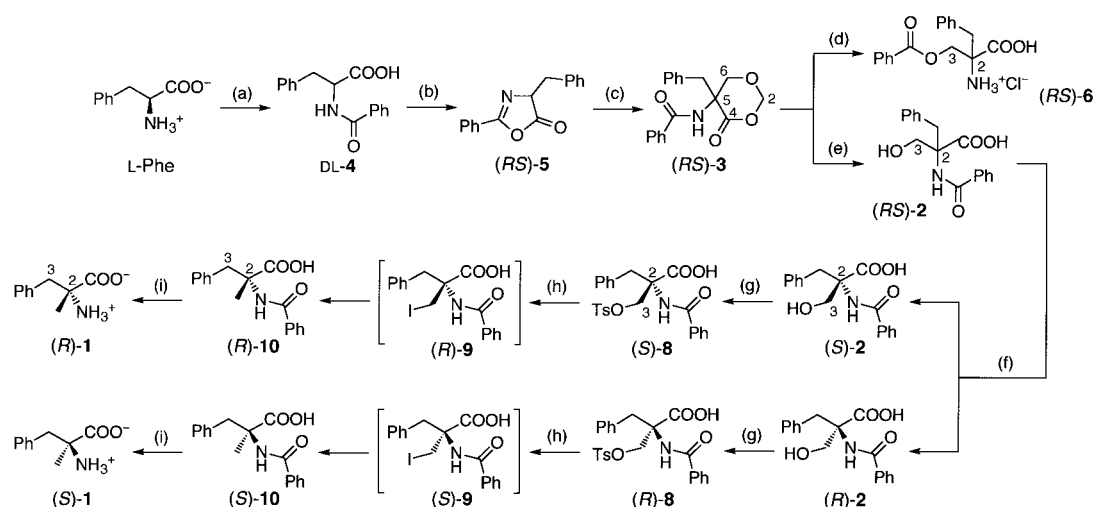


Chart 1. Synthetic Route to Optically Active 2-Amino-2-methyl-3-phenylpropanoic Acid (1)

(a) benzoyl chloride, OH^- ; (b) acetic anhydride, 95°C ; (c) pyridine, 37 wt% aq. formaldehyde; (d) 5 mol dm^{-3} hydrochloric acid, reflux; (e) i) 2 mol dm^{-3} aqueous sodium hydroxide, dioxane, ii) 2 mol dm^{-3} hydrochloric acid; (f) optical resolution; (g) i) tosyl chloride, pyridine; (h) zinc powder, sodium iodide, dimethylformamide, 120°C ; (i) i) 5 mol dm^{-3} hydrochloric acid, reflux, ii) triethylamine (pH 7), methanol.

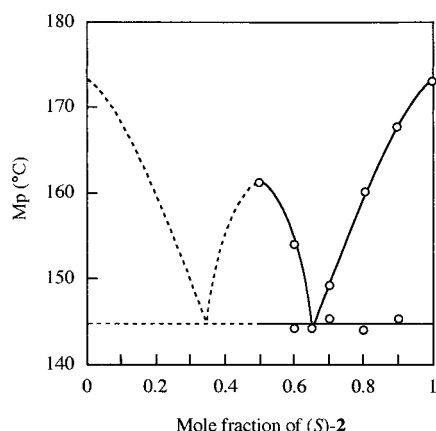


Fig. 1. Melting-Point Binary Phase Diagram of 2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid (**2**)

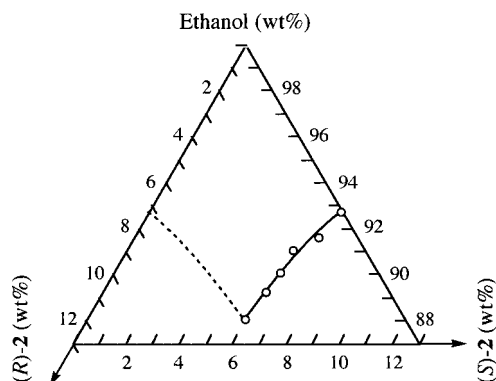


Fig. 2. Solubility Ternary Phase Diagram of 2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid (**2**)

Conditions: temperature, 10 °C; solvent, ethanol.

played as seed crystals. The yield of enantiomer [YE (g)], degree of resolution [DR (%)] of (*S*)-**2** obtained, and the amounts of crystallization [$AC_{(S)}$ and $AC_{(R)}$ (g)] were calculated from

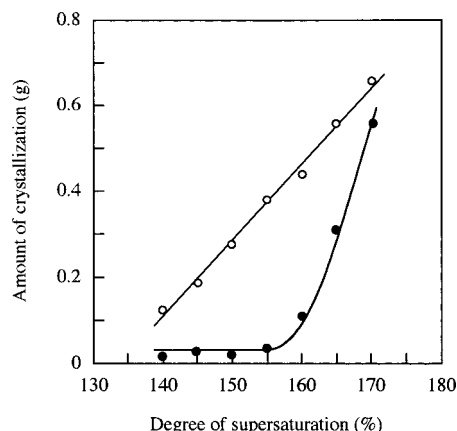


Fig. 3. Relationship between the Amount of Crystallization and Degree of Supersaturation in the Optical Resolution of 2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid [(*RS*)-2]

Conditions: (*RS*)-**2**, 3.016–3.663 g (140–170% supersaturation); seed crystals, 0.050 g of (*S*)-**2**; solvent, 20 ml of ethanol; stirring time, 30 min; temperature, 10 °C. Amount of crystallization: ○ (*S*)-**2**; ● (*R*)-**2**.

$$YE \text{ (g)} = [Yield \text{ (g)} \times OP \text{ (\%)} / 100] - 0.050,$$

$$DR(\%) = YE(g) \times 100 / (1/2)[\text{amount of (RS)-2 (g)} - 2.155],$$

$$AC_{(R)} \text{ (g)} = (1/2)[Yield \text{ (g)} - YE \text{ (g)} - 0.050],$$

$$AC_{(S)}(g) = YE(g) + AC_{(R)}(g),$$

where the solubility of (*RS*)-**2** is 2.155 g in 20 cm³ of ethanol at 10 °C and *Yield* is the sum of the amounts of the crystallized **2** and seed crystals (0.050 g). *OP* is the optical purity of the obtained (*S*)-**2** and was calculated on the basis of the reported specific rotation of (*R*)-**2**; (*R*)-**2**, [α]_D²⁰ + 70.0° (*c* = 1, methanol);⁴⁾ (*S*)-**2**, [α]_D²⁰ − 69.5° (*c* = 1, methanol).⁴⁾ The yield of enantiomer [*YE* (g)] is the amount of crystallized optically pure (*S*)-**2** and corresponds to the theoretical yield of optically pure (*S*)-**2** obtained by separation from partially resolved (*S*)-**2**.

When the 140—170% supersaturated solutions were employed, the amount of crystallization of the seeded (*S*)-2 in-

creased with increasing degree of supersaturation, after a resolution time of 30 min (Fig. 3). On the other hand, rapid crystallization of the unseeded (*R*)-**2** was not observed in the optical resolutions for the 140–155% supersaturated solutions (Fig. 3), although (*R*)-**2** crystallized rapidly from the 160 and 170% supersaturated solutions. Thus, the optical resolution for the 155% supersaturated solution at 30 min gave (*S*)-**2** with an optical purity of 85% in the highest degree of resolution (58%). Furthermore, the optical resolution for the 155% supersaturated solution was carried out at resolution times of

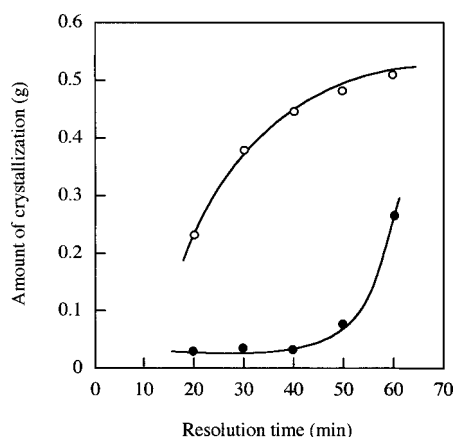


Fig. 4. Relationship between the Amount of Crystallization and Resolution Time in the Optical Resolution of (*RS*)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid [(*RS*)-**2**]

Conditions: (*RS*)-**2**, 3.340 g (155% supersaturation); seed crystals, 0.050 g of (*S*)-**2**; solvent, 20 ml of ethanol; stirring time, 20–60 min; temperature, 10 °C. Amount of crystallization: ○ (*S*)-**2**; ● (*R*)-**2**.

20–60 min (Fig. 4). The unseeded (*R*)-**2** began to crystallize rapidly at 50 min, but did not during the first 40 min. Therefore, the optical resolution at 40 min gave (*S*)-**2** with an optical purity of 89% in the highest degree of resolution (70%).

Next, successive optical resolution was attempted by stirring the 155% supersaturated solution as the initial solution for 40 min (Table 2). The degrees of resolution [*DR* (%)] of (*S*)- and (*R*)-**2** obtained were calculated from

$$DR(\%) = YE(g) \times 100 / [\text{operation amount of } (S)\text{- or } (R)\text{-2}(g) - 1.077],$$

where the operation amount is the amount of (*S*)- or (*R*)-**2** in the solution used in the optical resolution and those in runs 2–4 in Table 2 were calculated based on the yields and optical purities of the (*S*)- or (*R*)-**2** obtained in runs 1–3, respectively. The half amount for solubility of (*RS*)-**2** is 1.077 g in 20 cm³ of ethanol at 10 °C.

The optical resolution afforded (*S*)- and (*R*)-**2** with optical purities of about 90% in degrees of resolution of 70–81% and the partially resolved (*S*)- and (*R*)-**2** could be purified by simple recrystallization.

The *O*-tosyl derivatives of (*S*)- and (*R*)-**2** [(*S*)- and (*R*)-**8**] were subjected to reductive removal of their tosyloxy groups with zinc powder and sodium iodide, *via* the iodide intermediates (**9**), to give the *N*-benzoyl derivative of optically active **1** (**10**).^{4,8)} Thus (*R*)- and (*S*)-**1** were afforded from (*S*)- and (*R*)-**2**, after hydrolysis of (*R*)- and (*S*)-**10**, respectively, as shown in Chart 1.

Experimental

General Specific rotations were measured at 589 nm and 20 °C with a Horiba Seisakusho SEPA-300 auto polarimeter equipped with a quartz cell with a 5.00 cm path length. IR spectra were obtained in the range of 4000–

Table 1. Preferential Crystallization of (*RS*)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid^{a)}

Degree of supersaturation (%)	(<i>RS</i>)- 2 (g)	Resolution time (min)	(<i>S</i>)- 2 obtained		
			Yield ^{b)} (g)	Specific rotation ^{c)} (°)	<i>DR</i> ^{d)} (%)
140	3.016	30	0.183	−62.3	26
145	3.124	30	0.267	−53.2	32
150	3.232	30	0.343	−61.8	47
155	3.340	20	0.302	−57.0	33
155	3.340	30	0.463	−59.7	58
155	3.340	40	0.527	−62.0	70
155	3.340	50	0.611	−51.9	68
155	3.340	60	0.823	−25.3	41
160	3.447	30	0.593	−45.0	51
165	3.555	30	0.918	−22.6	35
170	3.663	30	1.257	−8.5	14

^{a)} Conditions: seed crystals, 0.050 g of (*S*)-**2**; solvent, 20 ml of ethanol; temperature, 10 °C. ^{b)} The Yield is the sum of the amounts of crystallized **2** and seed crystals. ^{c)} [α]_D²⁰ (*c* = 1.00, methanol). ^{d)} *DR*: degree of resolution.

Table 2. Successive Optical Resolution by Preferential Crystallization of (*RS*)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid^{a)}

Run	Added amount of (<i>RS</i>)- 2 (g)	Operation amounts of (<i>S</i>)- and (<i>R</i>)- 2 ^{b)} (g)		Resolution time (min)	(<i>S</i>)- or (<i>R</i>)- 2 obtained		
		(<i>S</i>)- 2	(<i>R</i>)- 2		Yield ^{c)} (g)	Specific rotation ^{d)} (°)	<i>DR</i> ^{e)} (%)
1	3.340	1.670	1.670	40	(<i>S</i>) 0.527	−62.0	70
2	0.480	1.463	1.880	40	(<i>R</i>) 0.733	+65.5	79
3	0.680	1.779	1.561	30	(<i>S</i>) 0.689	−63.1	81
4	0.640	1.494	1.847	20	(<i>R</i>) 0.682	+62.8	73

^{a)} Conditions: seed crystals, 0.050 g of (*S*)- or (*R*)-**2**; solvent, 20 ml of ethanol; temperature, 10 °C. ^{b)} The operation amounts in runs 2–4 were calculated from the results in runs 1–3. ^{c)} The Yield is the sum of the amounts of crystallized **2** and seed crystals. ^{d)} [α]_D²⁰ (*c* = 1.00, methanol). ^{e)} *DR*: degree of resolution.

400 cm⁻¹ with a Perkin-Elmer Model 1600 FT-IR spectrometer by the KBr disk method. ¹H- and ¹³C-NMR spectra were recorded on a JNM-FX270 FT NMR system (270 MHz for ¹H and 67.5 MHz for ¹³C) in deuterium oxide (D₂O), 0.5 mol dm⁻³ solution of sodium deuteroxide (NaOD) in D₂O, or deuterium chloroform-*d* (CDCl₃) with sodium 3-(trimethylsilyl)propane-1-sulfonate (DSS) or tetramethylsilane (TMS) as an internal standard. Chemical shifts were reported in δ units downfield from DSS or TMS. Melting points were measured with a Yanaco MP-500 D micro melting point apparatus.

Cinchonidine (**7**) was purchased from Wako Pure Chemicals Ind.; [α]_D²⁰ = -109° (*c* = 1.00, ethanol). Compound DL-**4** was prepared reacting L-Phe with benzoyl chloride under alkaline conditions; mp 187–189°C (lit.⁹) 187–188°C). L-Phe was purchased from Wako Pure Chemicals Ind.

(RS)-5-Benzoylamino-5-benzyl-4-oxo-1,3-dioxane [(RS)-3] A solution of DL-**4** (202 g, 750 mmol) in acetic anhydride (650 g, 6.37 mol) was stirred at 95°C for 1 h. After evaporation of the solution *in vacuo* at 75°C, followed by addition of pyridine (90 ml) and 380 ml of 37 wt% aqueous formaldehyde to the residue, the mixture was stirred at room temperature for 12 h and was then poured into 1 l of water. The precipitated (RS)-**3** was collected by filtration, washed with water, and dried. After dissolving the crude (RS)-**3** (190 g) in 500 cm³ of methanol on heating, followed by being allowed to stand the solution at 5°C overnight, the precipitated (RS)-**3** was collected by filtration and dried. Yield, 121 g (51.8%); mp 176–179°C (lit.⁶) 176–178°C). IR ν_{max} (KBr) cm⁻¹: 3404, 1726, 1651, 1522, 1489, 1458, 1227, 996, 734, 704. ¹H-NMR (CDCl₃) δ : 7.66–7.63 (2H, m, aromatic H), 7.52–7.26 (8H, m, aromatic H), 6.63 (1H, s, -NH-), 5.67 (1H, d, *J* = 5.1 Hz, 2-HH), 5.48 (1H, d, *J* = 5.1 Hz, 2-HH), 4.27 (1H, d, *J* = 11.4 Hz, 6-HH), 4.17 (1H, d, *J* = 11.4 Hz, 6-HH), 3.55 (1H, d, *J* = 13.9 Hz, Ph-CHH-), 3.23 (1H, d, *J* = 13.9 Hz, Ph-CHH-). ¹³C-NMR (CDCl₃) δ : 169.5 (4-C=O), 166.8 (Ph-CO-NH-), 133.6 (aromatic C), 132.7 (aromatic C), 132.3 (aromatic C), 130.4 (aromatic C), 129.3 (aromatic C), 128.7 (aromatic C), 128.2 (aromatic C), 127.0 (aromatic C), 94.9 (2-C), 87.5 (6-C), 57.9 (5-C), 41.1 (Ph-CH₂-). Anal. Calcd for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.22; H, 5.47; N, 4.47.

(RS)-2-Amino-3-benzoyloxy-2-benzylpropanoic Acid [(RS)-6] After refluxing (RS)-**3** (6.28 g, 20.0 mmol) in 50 ml of 5 mol dm⁻³ hydrochloric acid for 15 min, the precipitated (RS)-**6** was collected by filtration, washed with small amounts of water and then methanol, and dried.¹¹ Yield, 4.87 g (83.0%); mp 191–194°C. ¹H-NMR (NaOD) δ : 7.90–7.83 (2H, m, aromatic H), 7.60–7.24 (8H, m, aromatic H), 3.89 (1H, d, *J* = 10.7 Hz, 3-HH), 3.54 (1H, d, *J* = 10.8 Hz, 3-HH), 3.04 (1H, d, *J* = 13.3 Hz, Ph-CHH-), 2.69 (1H, d, *J* = 13.3 Hz, Ph-CHH-). Anal. Calcd for C₁₇H₁₈NO₄Cl: C, 60.81; H, 5.40; N, 4.17. Found: C, 60.77; H, 5.33; N, 4.17.

(RS)-2-Benzyloxy-2-benzyl-3-hydroxypropanoic Acid [(RS)-2] After adding 2 mol dm⁻³ aqueous sodium hydroxide (25 ml) to a suspension of (RS)-**3** (12.2 g, 38.7 mmol) in 25 ml of dioxane, followed by stirring the solution at room temperature for 1 h, the dioxane was evaporated *in vacuo* at 60°C. The aqueous layer was acidified with 2 mol dm⁻³ hydrochloric acid and then the mixture was stirred in an ice bath for 1 h. The precipitated (RS)-**2** was collected by filtration and then was recrystallized from ethanol (3.3 ml g⁻¹). Yield, 10.4 g (89.2%); mp 158–161°C (lit.⁴) 159–161°C). IR ν_{max} (KBr) cm⁻¹: 3379, 3194, 1729, 1635, 1527, 1417, 1239, 1204, 1093, 1073, 728, 694, 631. ¹H-NMR (NaOD) δ : 7.65–7.19 (10H, m, aromatic H), 4.51 (1H, d, *J* = 11.1 Hz, 3-HH), 4.10 (1H, d, *J* = 11.3 Hz, 3-HH), 3.51 (1H, d, *J* = 13.2 Hz, Ph-CHH-), 3.18 (1H, d, *J* = 13.2 Hz, Ph-CHH-). ¹³C-NMR (NaOD) δ : 161.8 (1-COOH), 154.2 (Ph-CO-NH-), 121.6 (aromatic C), 119.3 (aromatic C), 117.0 (aromatic C), 114.7 (aromatic C), 113.8 (aromatic C), 113.3 (aromatic C), 111.7 (aromatic C), 111.6 (aromatic C), 67.2 (3-C), 62.7 (2-C), 36.4 (Ph-CH₂-). Anal. Calcd for C₁₇H₁₇NO₄: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.07; H, 5.76; N, 4.64.

Optical Resolution of (RS)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid [(RS)-2] by Separation of Diastereoisomeric Salts with Cinchonidine (7) (RS)-**2** (59.9 g, 0.200 mol) and **7** (58.9 g, 0.200 mol) were dissolved in 390 ml of ethanol on heating. After stirring the solution in an ice bath for 6 h, the precipitated (S)-**2**·**7** salt was collected by filtration; yield, 58.8 g; [α]_D²⁰ = -124° (*c* = 1.00, methanol). The filtrate was evaporated to dryness *in vacuo* at 30°C to give the (R)-**2**·**7** salt as the residue; yield, 56.6 g; [α]_D²⁰ = -11.0° (*c* = 1.00, methanol). After stirring each suspension of (S)-**2**·**7** salt (59.2 g) and (R)-**2**·**7** salt (56.3 g) in 1 mol dm⁻³ hydrochloric acid (3.4 ml g⁻¹) in an ice bath for 30 min, the precipitated (S)- and (R)-**2** were collected by filtration in yields of 28.5 and 27.1 g; (S)-**2**, [α]_D²⁰ = -65.0° (*c* = 1.00, methanol); (R)-**2**, [α]_D²⁰ = +61.8° (*c* = 1.00, methanol). The obtained, respectively, (S)- and (R)-**2** were recrystallization from ethanol (5.7 ml g⁻¹).

(S)-**2**: Yield, 22.1 g (73.8%); mp 172–173°C (lit.⁴) 176–177°C; [α]_D²⁰

= -70.0° (*c* = 1.00, methanol) (lit.⁴) [α]_D²⁰ = -69.5° (*c* = 1.00, methanol). Anal. Calcd for C₁₇H₁₇NO₄: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.15; H, 5.71; N, 4.65.

(R)-**2**: Yield, 20.5 g (68.4%); mp 171–173°C (lit.⁴) 176–177°C; [α]_D²⁰ = +70.0° (*c* = 1.00, methanol) (lit.⁴) [α]_D²⁰ = +70.0° (*c* = 1.00, methanol). Anal. Calcd for C₁₇H₁₇NO₄: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.16; H, 5.66; N, 4.70.

Optical Resolution by Preferential Crystallization of (RS)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid [(RS)-2] (RS)-**2** (3.016–3.663 g) was dissolved in 20 ml of ethanol at 40°C and the solution was gradually cooled to 10°C over a period of 1 h and then seeded with 0.050 g of (S)-**2**. After stirring the mixture with a blade (0.70 cm width; 2.0 cm length) at 100 rpm at 10°C for 30 min, the crystallized (S)-**2** was quickly collected by filtration and thoroughly dried.

Optical resolution was carried out for the 155% supersaturated solution (3.340 g of (RS)-**2** in 20 ml of ethanol) by stirring for 20–60 min at 10°C in a manner similar to that described above.

Successive Optical Resolution of (RS)-2-Benzoylamino-2-benzyl-3-hydroxypropanoic Acid [(RS)-2] (RS)-**2** (3.340 g) was dissolved in 20 ml of ethanol at 40°C. The solution was gradually cooled to 10°C over a period of 1 h and then seeded with 0.050 g of (S)-**2**. After stirring the mixture at 10°C for 40 min, (S)-**2** (0.527 g) was quickly collected by filtration and thoroughly dried (run 1 in Table 2). (RS)-**2** (0.480 g) was dissolved in the filtrate at 40°C and then the resulting solution was gradually cooled to 10°C. (R)-**2** (0.050 g) was added as seed crystals and then the mixture was stirred for 40 min. (R)-**2** (0.733 g) was collected by filtration and dried (run 2 in Table 2). The filtrate was treated in a manner similar to that described above; the detailed conditions for runs 3 and 4 are given in Table 2.

A mixture of (S)-**2** (2.30 g) with an optical purity of 64% in 8 ml of ethanol was vigorously stirred at 10°C for 5 h. Then the purified (S)-**2** (1.37 g) was collected by filtration and dried; [α]_D²⁰ = -70.0° (*c* = 1.00, methanol). (R)-**2** (2.31 g) with an optical purity of 67% was treated with 7 ml of ethanol, in a manner similar to that for (S)-**2**, to give optically pure (R)-**2** in a yield of 1.49 g; [α]_D²⁰ = +70.0° (*c* = 1.00, methanol).

(S)- and (R)-2-Benzoylamino-2-benzyl-3-tosyloxypropanoic Acid [(S)- and (R)-8] Tosyl chloride (38.1 g, 0.200 mol) was added to a solution of (S)-**2** (5.99 g, 20.0 mmol) in 25 ml of pyridine at 0°C. After being allowed to stand at 5°C for 3 d, the solution was poured on ice-water (150 ml). The mixture was extracted with chloroform (4×50 ml) and then the organic layer was washed with water (3×50 ml), 1 mol dm⁻³ hydrochloric acid (3×50 ml), and then water (3×50 ml). After dried over magnesium sulfate, the organic layer was evaporated to dryness *in vacuo* to give crude the (S)-**8**, which was recrystallized from ethyl acetate (50 ml) and hexane (250 ml). (R)-**8** was prepared from (R)-**2**, in a similar manner to (S)-**8**.

(S)-**8**: Yield, 7.82 g (86.2%); mp 97–100°C (lit.⁴) 98–99°C; [α]_D²⁰ = -119° (*c* = 1.00, methanol) (lit.⁴) [α]_D²⁰ = -117.4° (*c* = 1.00, methanol). IR ν_{max} (KBr) cm⁻¹: 1826, 1657, 1359, 1182, 1004, 984, 756, 698, 670. ¹H-NMR (CDCl₃) δ : 7.79–7.10 (14H, m, aromatic H), 4.45 (1H, d, *J* = 9.9 Hz, 3-HH), 4.37 (1H, d, *J* = 10.0 Hz, 3-HH), 3.12 (1H, d, *J* = 13.2 Hz, Ph-CHH-), 3.04 (1H, d, *J* = 13.4 Hz, Ph-CHH-), 2.39 (3H, s, -CH₃). ¹³C-NMR (CDCl₃) δ : 176.0 (1-COOH), 161.4 (Ph-CO-NH-), 144.9 (aromatic C), 132.7 (aromatic C), 132.2 (aromatic C), 129.9 (aromatic C), 129.6 (aromatic C), 128.4 (aromatic C), 128.2 (aromatic C), 128.1 (aromatic C), 127.9 (aromatic C), 127.8 (aromatic C), 127.7 (aromatic C), 127.4 (aromatic C), 124.9 (aromatic C), 73.6 (3-C), 70.5 (2-C), 39.2 (Ph-CH₂-), 21.6 (-CH₃). Anal. Calcd for C₂₄H₂₃NO₆S: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.82; H, 4.94; N, 3.22.

(R)-**8**: Yield, 8.16 g (90.0%); mp 98–99°C; [α]_D²⁰ = +119° (*c* = 1.00, methanol). Anal. Calcd for C₂₄H₂₃NO₆S: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.91; H, 4.99; N, 3.12. The ¹H- and ¹³C-NMR and IR spectra of (R)-**8** were virtually identical to those of (S)-**8**.

(R)- and (S)-2-Benzoylamino-2-methyl-3-phenylpropanoic Acid [(R)- and (S)-10] After stirring a mixture of (S)-**8** (4.54 g, 10.0 mmol), sodium iodide (6.49 g, 50.0 mmol), and zinc powder (6.54 g, 100 mmol) in 50 ml of dimethylformamide at 120°C for 10 h, excess of sodium iodide and zinc powder was removed by filtration. The filtrate was evaporated to dryness *in vacuo* at 70°C and then the residue was dissolved in 100 ml of ethyl acetate. The solution was washed with 0.5 mol dm⁻³ hydrochloric acid (3×50 ml) and then water (3×50 ml). After dried over magnesium sulfate, the organic layer was evaporated to dryness *in vacuo* at 65°C to give (R)-**10** as the viscous residue. (S)-**10** was prepared from (R)-**8**, in a similar manner to (R)-**10**.

(R)-**10**: Yield, 2.12 g (74.9%). ¹H-NMR (CDCl₃) δ : 7.68–7.13 (10H, m, aromatic H), 3.63 (1H, d, *J* = 13.8 Hz, 3-HH), 3.41 (1H, d, *J* = 13.5 Hz, 3-HH), 1.80 (3H, s, -CH₃). ¹³C-NMR (CDCl₃) δ : 175.9 (1-COOH), 167.3 (Ph-CO-NH-), 136.1 (aromatic C), 134.2 (aromatic C), 131.1 (aromatic C),

129.5 (aromatic C), 128.6 (aromatic C), 127.9 (aromatic C), 127.7 (aromatic C), 126.5 (aromatic C), 126.3 (aromatic C), 61.2 (2-C), 40.4 (3-C), 23.0 (–CH₃).

(S)-**10**: Yield, 2.05 g (72.4%). The ¹H- and ¹³C-NMR spectra of (S)-**10** were virtually identical to those of (R)-**10**.

(R)- and (S)-2-Amino-2-methyl-3-phenylpropanoic Acid [(R)- and (S)-**1**] The crude (R)-**10** (5.67 g, 20.0 mmol) was refluxed in 100 ml of 5 mol dm^{−3} hydrochloric acid for 10 h. After removing benzoic acid by filtration, the filtrate was evaporated to dryness *in vacuo* at 70 °C to give (R)-**1** hydrochloride, which was dissolved in 100 ml of methanol and then the solution was adjusted with triethylamine to pH 7. The precipitated (R)-**1** was collected by filtration, washed with methanol, and dried. The obtained (R)-**1** (3.47 g) was recrystallized from 50 ml of water.

(S)-**1** was prepared from (S)-**10**, in a similar manner to (R)-**1**.

(R)-**1**: Yield, 3.16 g (82.1%); mp 277–279 °C (decomp) (lit.,⁴⁾ 262–263 °C (decomp); [α]_D²⁰ +20.2° (*c*=1.00, water) (lit., [α]_D²⁰ +19.0° (*c*=0.51, water);³⁾ [α]_D²⁰ +6.3° (*c*=1.03, water);⁴⁾ [α]_D +20.5° (*c*=1, water)¹⁰⁾. IR ν_{max} (KBr) cm^{−1}: 3034, 1624, 1583, 1455, 1398, 1367, 1266, 745, 702. ¹H-NMR (D₂O) δ : 7.40–7.36 (3H, m, aromatic H), 7.28–7.25 (2H, m, aromatic H), 3.30 (1H, d, *J*=14.3 Hz, 3-HH), 2.98 (1H, d, *J*=14.3 Hz, 3-HH), 1.55 (3H, s, –CH₃). ¹³C-NMR (D₂O) δ : 176.7 (1-COOH), 134.9 (aromatic C), 130.6 (aromatic C), 129.6 (aromatic C), 128.5 (aromatic C), 62.9 (2-C), 43.5 (3-C), 23.2 (–CH₃). Anal. Calcd for C₁₀H₁₃NO₂: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.14; H, 7.14; N, 7.53.

(S)-**1**: Yield, 3.09 g (80.3%); mp 276–279 °C (decomp); [α]_D²⁰ −20.1° (*c*=1.00, water). Anal. Calcd for C₁₀H₁₃NO₂: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.14; H, 7.14; N, 7.53. The ¹H-, ¹³C-NMR, and IR spectra of (S)-**1** were virtually identical to those of (R)-**1**.

Solubility and Phase Diagrams (RS)-**2** (5.395 g) or (S)-**2** (2.698 g) was dissolved in 20 ml of ethanol at 50 °C. After vigorously stirring the solution at 10 °C for 10 h, the precipitated **2** was rapidly collected by filtration and thoroughly dried. The solubility at 10 °C was calculated on the basis of the weight of **2**. Solubility: (RS)-**2**, 10.773 g (100 ml of ethanol)^{−1}; (S)-**2**, 6.025 g (100 ml of ethanol)^{−1}.

Preparing a solubility ternary phase diagram, the solubilities of mixtures

of (RS)- and (S)-**2** were measured at 10 °C similarly to the method described above. The solid **2** was filtered off, thoroughly dried, and the specific rotation was measured. The amounts of (R)- and (S)-**2** in the solution were calculated based on the solubility of **2** and the specific rotation of the solid **2**.

In preparation of the melting-point binary phase diagram, the melting points of the mixtures composed of (RS)- and (S)-**2** were measured; after dissolving (RS)- and (S)-**2** in an appropriate ratio in methanol, the mixtures were obtained by evaporating the solutions to dryness *in vacuo*. The melting-point binary phase diagram was prepared from the temperatures at the beginning and end of melting.

Acknowledgments This research was financially supported by the Kansai University Grant-in-Aid for the Faculty Joint Research Program, 2002.

References and Notes

- Ohfuné Y., Horikawa M., *J. Syn. Org. Chem.*, **55**, 982–993 (1997).
- Lee M., Kim D. H., *Bioorg. Med. Chem.*, **8**, 815–823 (2000).
- Davis F. A., Liu H., Reddy G. V., *Tetrahedron Lett.*, **37**, 5473–5476 (1996).
- Olma A., *Polish J. Chem.*, **70**, 1442–1447 (1996).
- Belokon Y., Kochetkov K. A., Churkina T. D., Ikonnikov N. S., Vyskocil S., Kagan H. B., *Tetrahedron; Asymmetry*, **10**, 1723–1728 (1999).
- Kaminski Z. J., Leplaw M. T., Zabrocki J., *Synthesis*, **1973**, 792–793 (1973).
- Elie E. L., Wilen S. H., Mander L. N., “Stereochemistry of Organic Compounds,” John Wiley and Sons, New York, 1994, pp. 297–464.
- Fujimoto Y., Tatsuno T., *Tetrahedron Lett.*, **1976**, 3325–3326 (1976).
- “Amino Acids and Peptides,” ed. Davies J. S., Chapman and Hall, London, New York, 1985, p. 261.
- Georg G. I., Guan X., Kant J., *Tetrahedron Lett.*, **29**, 403–406 (1988).
- (RS)-**6** obtained by refluxing for 20 min: Yield, 4.09 g (72.5%); mp 190–192 °C. (RS)-**6** obtained by refluxing for 30 min: Yield, 3.93 g (65.9%); mp 191–193 °C.