

## Synthesis of Optically Active 1,4-Thiazane-3-carboxylic Acid via Optical Resolution by Preferential Crystallization of (*RS*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochloride

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Optically active 1,4-thiazane-3-carboxylic acid [TCA] was synthesized from cysteine via optical resolution by preferential crystallization. The intermediate (*RS*)-2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride [(*RS*)-ACS·HCl] was found to exist as a conglomerate based on its melting point, solubility and IR spectrum. (*RS*)-ACS·HCl was optically resolved by preferential crystallization to yield (*R*)- and (*S*)-ACS·HCl. (*R*)- and (*S*)-ACS·HCl thus obtained were recrystallized from a mixture of hydrochloric acid and 2-propanol, taking account of the solubility of (*RS*)-ACS·HCl, efficiently yielding both enantiomers in optically pure forms. (*R*)- and (*S*)-TCA were then respectively synthesized by the cyclization of (*R*)- and (*S*)-ACS·HCl in ethanol in the presence of triethylamine.

**Key words:** 1,4-thiazane-3-carboxylic acid; 2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride; conglomerate; optical resolution; preferential crystallization

(*R*)-1,4-Thiazane-3-carboxylic acid [(*R*)-TCA] was isolated from the brown alga, *Undaria pinnatifida*, and is a precursor of chondrine [(1*S*, 3*R*)-3-thiomorphoricarboxylic acid 1-oxide] from the red alga, *Chondria crassicaulis*.<sup>1,2)</sup> (*R*)-TCA has been synthesized from L-cystine via (*R*)-2-amino-3-[(2-hydroxyethyl)sulfanyl]propanoic acid [(*R*)-AHS] and (*R*)-2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride [(*R*)-ACS·HCl] as intermediates<sup>3)</sup> and by the condensation of L-cysteine (L-Cys) with 1,2-dibromoethane,<sup>4)</sup> although the latter method did not give (*R*)-TCA in a good yield. (*R*)- and (*S*)-TCA can also be synthesized from benzyl (*S*)- and (*R*)-*N*-benzoyloxycarbonyl-2-aziridinecarboxylate, respectively.<sup>5)</sup> Of the foregoing methods, optically active TCA seemed to be most conveniently and efficiently obtained by the method<sup>3)</sup> starting with cystine. Therefore, we attempted to synthesize optically active TCA from Cys, instead of from cystine, as shown in Scheme 1. This approach, however, raised the problem that D-Cys is much more expensive than DL-

and L-Cys and hence is difficult to obtain in quantity. Therefore, we attempted to obtain optically active TCA via the optical resolution of (*RS*)-AHS, ACS·HCl or TCA.

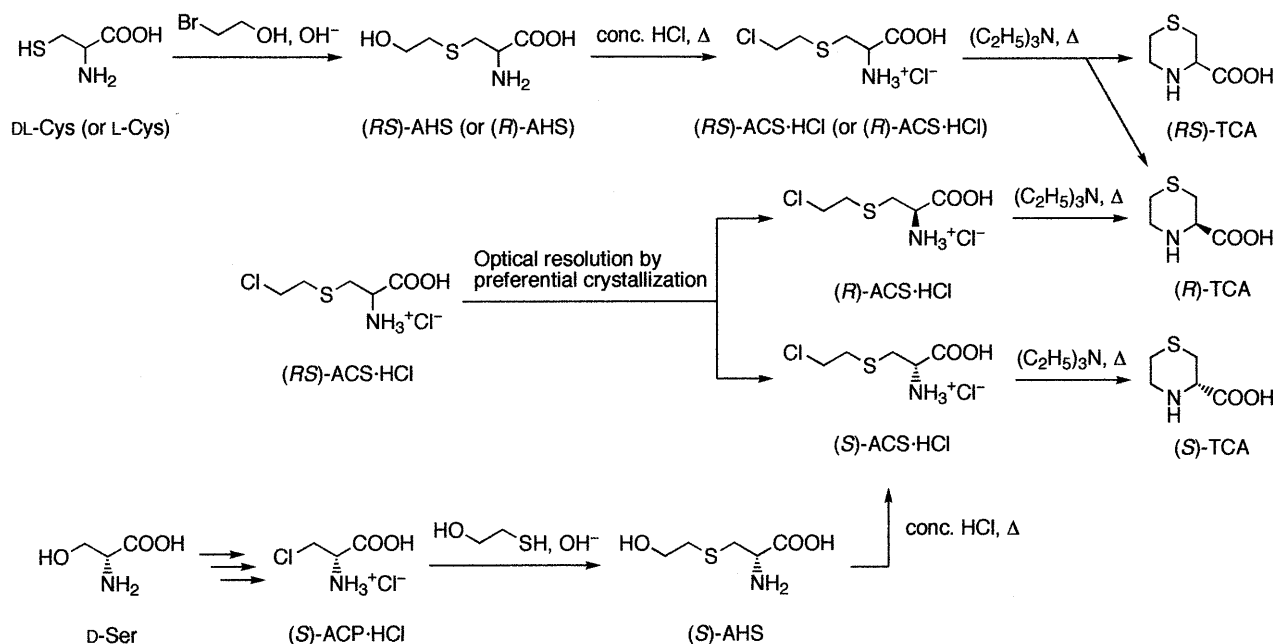
Since  $\alpha$ -amino acids such as AHS and ACS do not form salts with ordinary resolving agents like optically active tartaric acid and 1-phenylethylamine, (*RS*)-AHS and ACS cannot be optically resolved by separating diastereoisomeric salts unless they are first transformed into derivatives such as *N*-acyl compounds and esters. Therefore, we designed an optical resolution method using preferential crystallization. Although racemates exist in the form of racemic compounds, racemic solid solutions and conglomerates, only conglomerates which are defined as mechanical mixtures of crystals of both enantiomers can be optically resolved by preferential crystallization. These racemic structures have been distinguished by a comparison of melting points, solubilities and IR spectra of racemates and enantiomers.<sup>6,7)</sup> In addition, optical resolution by preferential crystallization requires small amounts of both enantiomers as seed crystals. Therefore, we first synthesized (*RS*)- and (*R*)-AHS, ACS·HCl and TCA from DL- and L-Cys.

(*RS*)- and (*R*)-AHS were respectively synthesized in yields of 74 and 81% by the condensation of DL- and L-Cys with 2-bromoethanol in aqueous sodium hydroxide. The structures of (*RS*)- and (*R*)-AHS were determined by their <sup>1</sup>H-NMR spectra and elemental analyses. Although authentic (*R*)-AHS has been reported to show specific rotation  $[\alpha]_D^{20}$  of  $-53.3^\circ$  (*c* 2, water),<sup>3)</sup> the (*R*)-AHS sample obtained here showed a value of  $-27.2^\circ$ . Therefore, (*R*)-AHS seemed to have undergone partial racemization during the condensation of L-Cys with 2-bromoethanol. The specific rotation reached a constant value ( $-37.7^\circ$ ) after repeated recrystallization of (*R*)-AHS from water-ethanol, although its yield was reduced to 27%. Therefore, recrystallized (*R*)-AHS was employed without further purification to synthesize (*R*)-ACS·HCl.

(*RS*)- and (*R*)-ACS·HCl were respectively synthe-

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Abbreviations: ACP·HCl, 2-amino-3-chloropropanoic acid hydrochloride; ACS·HCl, 2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride; AHS, 2-amino-3-[(2-hydroxyethyl)sulfanyl]propanoic acid; TCA, 1,4-thiazane-3-carboxylic acid



Scheme 1. Synthetic Routes to Optically Active 1,4-Thiazane-3-carboxylic Acid.

sized in yields of 66 and 60% by stirring (RS)- and (R)-AHS in concentrated hydrochloric acid at 90–95°C, before recrystallizing from 2-propanol according to the method previously reported.<sup>3,8)</sup> The specific rotation of (R)-ACS·HCl obtained was unchanged by recrystallization from 2-propanol;  $[\alpha]_D^{20} -4.6^\circ$  (*c* 1.00, water);  $[\alpha]_D^{20} -23.6^\circ$  (*c* 1.00, 0.1 M NaOH). The specific rotation in aqueous sodium hydroxide was confirmed to undergo no changes after standing the solution for 3 h at 20°C. (R)-ACS·HCl was treated with triethylamine in ethanol in an ice bath to compare the specific rotation of the obtained (R)-ACS with that of authentic (R)-ACS ( $[\alpha]_D^{25} -2.0^\circ$  (*c* 1.0, 1 M HCl)),<sup>5)</sup> because the specific rotation of (R)-ACS·HCl has not been reported. The (R)-ACS sample obtained here showed a specific rotation which agreed with that of authentic (R)-ACS;  $[\alpha]_D^{20} -2.0^\circ$  (*c* 1.00, 1 M HCl),  $[\alpha]_D^{20} -1.97^\circ$  (*c* 5.00, 1 M HCl). Therefore, the result just described indicates that (R)-ACS·HCl had been obtained in optically pure form. The (R)-AHS obtained was not an optically pure enantiomer, and hence a mixture of (R)- and (S)-ACS·HCl was obtained by heating in concentrated hydrochloric acid, (R)-ACS·HCl being estimated to have been preferentially crystallized from the mixture by recrystallization. This suggested that (RS)-ACS·HCl would exist as a conglomerate that could be optically resolved by preferential crystallization. (RS)- and (R)-ACS·HCl were thus refluxed in the presence of triethylamine in ethanol to give (RS)- and (R)-TCA in yields of 53 and 64%, respectively. The (R)-TCA sample obtained here showed a specific rotation which agreed with that of authentic (R)-TCA;  $[\alpha]_D^{20} -54.5^\circ$  (*c* 1.00, water) (lit.<sup>3)</sup>  $[\alpha]_D^{25.5} -54.03^\circ$  (*c* 1.6, water)). This result also indicates that (R)-TCA had been synthesized from optically pure (R)-ACS·HCl.

Next, aiming at optical resolution by preferential crys-

tallization, (S)-2-amino-3-chloropropanoic acid hydrochloride<sup>9,10)</sup> [(S)-ACP·HCl] from D-serine (D-Ser) was condensed with 2-mercaptoethanol in aqueous sodium hydroxide to give partially racemized (S)-AHS in a yield of 63%;  $[\alpha]_D^{20} +30.3^\circ$  (*c* 2.00, water) (Scheme 1). However, optically pure (S)-ACS·HCl was obtained from (S)-AHS in a yield of 49%;  $[\alpha]_D^{20} +4.6^\circ$  (*c* 1.00, water);  $[\alpha]_D^{20} +23.6^\circ$  (*c* 1.00, 0.1 M NaOH).

Based on the foregoing idea, the racemic structures of (RS)-AHS, (RS)-ACS·HCl, and (RS)-TCA were examined by taking advantage of the decomposition point or melting point, solubility and IR spectrum.<sup>6,7)</sup> Since partially racemized (R)-AHS could not be purified by recrystallization, as already mentioned, (RS)-AHS did not seem to be a conglomerate. Although (RS)- and (R)-AHS and TCA were decomposed by heating, (RS)-AHS and (RS)-TCA had approximately equal decomposition points to those of (R)-AHS and (R)-TCA, respectively. In addition, the IR spectra of (RS)-AHS and (RS)-TCA were different from those of (R)-AHS and (R)-TCA, respectively. Therefore, (RS)-AHS and (RS)-TCA were determined to have formed racemic compounds.<sup>6,7)</sup>

On the other hand, (RS)-ACS·HCl had a lower melting point than (R)-ACS·HCl and was more soluble than (R)-ACS·HCl, as described in the Experimental section. The IR spectrum of (RS)-ACS·HCl was identical to that of (R)-ACS·HCl. Conglomerates have such characteristics.<sup>6,7)</sup> In addition, in the binary melting point phase diagram, as shown in Fig. 1, the mole fraction of (R)-ACS·HCl at the eutectic point was 0.5 (racemic composition). Therefore, the phase diagram shows what was expected for a conglomerate.<sup>6,7)</sup> These results indicate that (RS)-ACS·HCl exists as a conglomerate.

Based on the foregoing results, (RS)-ACS·HCl was optically resolved by preferential crystallization at 10°C

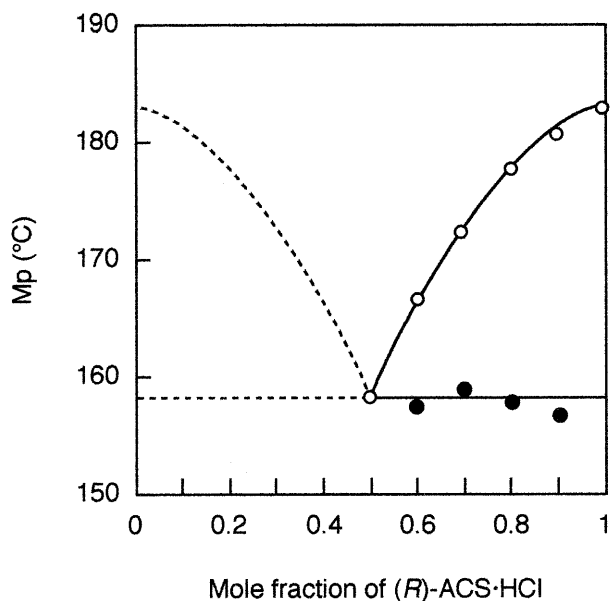


Fig. 1. Binary Melting Point Phase Diagram of 2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochloride.

in a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9. To optimize the conditions, optical resolution was conducted by stirring 110–140% supersaturated solutions for 10–40 min; (*R*)-ACS·HCl (0.050 g) was employed as seed crystals. The results are shown in Figs. 2 and 3.

When 110–130% supersaturated solutions were employed, the degree of crystallization of seeded (*R*)-ACS·HCl increased with increasing degree of supersaturation, whereas no rapid crystallization of unseeded (*S*)-ACS·HCl was observed after a resolution time of 30 min (Fig. 2). When a 140% supersaturated solution was employed, unseeded (*S*)-ACS·HCl crystallized rapidly. Based on these results, optical resolution of the 130% supersaturated solution was carried out for resolution times of 10–40 min (Fig. 3). Unseeded (*S*)-ACS·HCl began to crystallize rapidly at 40 min, but did not during the first 30 min. Therefore, the optical resolution at 30 min gave (*R*)-ACS·HCl at the highest degree of resolution (81%). Based on the foregoing results, successive optical resolution was attempted by stirring the 130% supersaturated solution as the initial solution for 30 min. These results are summarized in Table 1.

Optical resolution afforded (*R*)- and (*S*)-ACS·HCl at degrees of resolution of 44–81%. The (*R*)- and (*S*)-ACS·HCl samples obtained were recrystallized from a mixture of hydrochloric acid and 2-propanol to give both optically pure ACS·HCl enantiomers, as described in the Experimental section. For example, optically pure (*R*)-ACS·HCl (4.95 g) was obtained from 8.10 g of partially resolved (*R*)-ACS·HCl ( $[\alpha]_D^{20} -15.1^\circ$  (*c* 1.00, 0.1 M NaOH)), and optically pure (*S*)-ACS·HCl (3.82 g) from 5.57 g of partially resolved (*S*)-ACS·HCl ( $[\alpha]_D^{20} +16.7^\circ$  (*c* 1.00, 0.1 M NaOH)).

(*R*)- and (*S*)-ACS·HCl obtained were cyclized in the presence of triethylamine in ethanol to give (*R*)- and (*S*)-

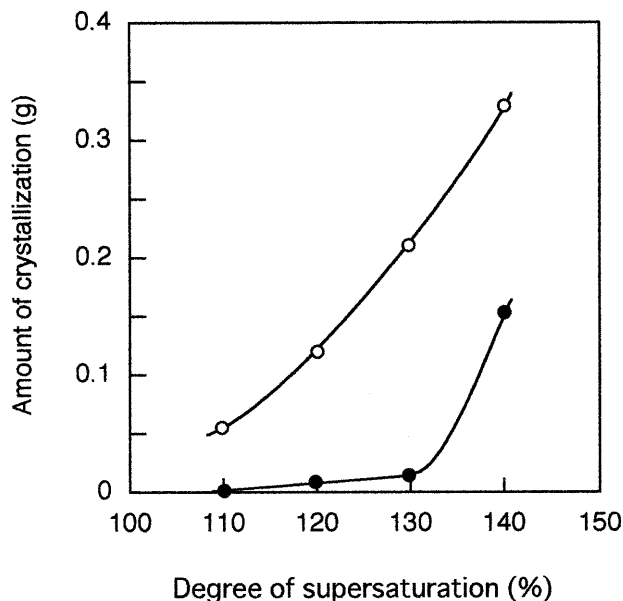


Fig. 2. Relationship between the Amount of Crystallization and Degree of Supersaturation in the Optical Resolution of (*RS*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochloride.

ACS·HCl: 2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride. Conditions: (*RS*)-ACS·HCl, 1.800 (110% supersaturation), 1.963 (120%), 2.126 (130%), and 2.290 (140%); seed crystals, 0.050 g of (*R*)-ACS·HCl; solvent, 25 cm<sup>3</sup> (the solvent consisted of a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9); stirring time, 30 min; temperature, 10°C. Amount of crystallization: ○ (*R*)-ACS·HCl; ● (*S*)-ACS·HCl.

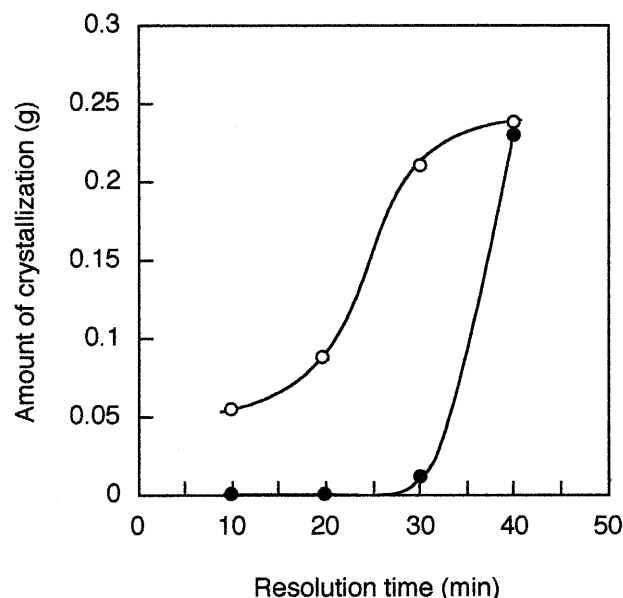


Fig. 3. Relationship between the Amount of Crystallization and Resolution Time in the Optical Resolution of (*RS*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochloride.

ACS·HCl: 2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride. Conditions: (*RS*)-ACS·HCl, 2.126 (130% supersaturation); seed crystals, 0.050 g of (*R*)-ACS·HCl; solvent, 25 cm<sup>3</sup> (the solvent consisted of a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9); stirring time, 10–40 min; temperature, 10°C. Amount of crystallization: ○ (*R*)-ACS·HCl; ● (*S*)-ACS·HCl.

**Table 1.** Successive Optical Resolution by Preferential Crystallization of (*RS*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochloride<sup>a)</sup>

Run	Added amount of ( <i>RS</i> )-ACS·HCl (g)	Operation amounts of ( <i>R</i> )- and ( <i>S</i> )-ACS·HCl <sup>b)</sup> (g)		Resolution time (min)	ACS·HCl obtained		
		( <i>R</i> )-ACS·HCl	( <i>S</i> )-ACS·HCl		Yield <sup>c)</sup> (g)	Specific rotation <sup>d)</sup> (°)	DR <sup>e)</sup> (%)
1	2.126	1.063	1.063	30	( <i>R</i> )0.272	−21.6	81
2	0.222	0.964	1.162	10	( <i>S</i> )0.322	+17.3	54
3	0.272	1.057	1.069	40	( <i>R</i> )0.162	−22.8	44
4	0.112	1.004	1.122	25	( <i>S</i> )0.307	+22.4	79
5	0.156	1.074	0.951	20	( <i>R</i> )0.250	−20.0	63
6	0.200	0.993	1.032	15	( <i>S</i> )0.271	+14.3	53

<sup>a</sup> Conditions: seed crystals, 0.050 g of (*R*)- or (*S*)-ACS·HCl; solvent, 25 cm<sup>3</sup> (the solvent consisted of a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9); temperature, 10°C.

<sup>b</sup> The operation amounts in runs 2–6 were calculated from the results in runs 1–5.

<sup>c</sup> The Yield is the sum of the amounts of crystallized ACS·HCl and seed crystals.

<sup>d</sup>  $[\alpha]_D^{20}$  (c 1.00, 0.1 M NaOH).

<sup>e</sup> DR: degree of resolution.

TCA in yields of over 60%; (*S*)-TCA,  $[\alpha]_D^{20} +54.5^\circ$  (c 1.00, water) (lit.<sup>5)</sup>  $[\alpha]_D^{25} +50.6^\circ$  (c 1.0, water)).

## Experimental

Specific rotation values were measured at 589 nm with a Horiba Seisakusho SEPA-300 auto-polarimeter equipped with a quartz cell with a 5.00- or 10.0-cm path length. IR spectra were obtained in the range of 4000–400 cm<sup>−1</sup> with a Perkin-Elmer model 1600 FT-IR spectrometer by the KBr disk method. <sup>1</sup>H-NMR spectra were recorded with a JNM-FX270 FT NMR system with sodium 3-(trimethylsilyl)propanesulfonate (DSS) as an internal standard. Chemical shift values are reported in  $\delta$  units downfield from DSS. Refractive index values were measured with a Shimadzu Abbe 3 L refractometer at 20°C.

D-Ser was purchased from Wako Pure Chemical Ind., and L-Cys from Kokusan Chemical Works. DL-Cys was prepared from DL-Cys hydrochloride monohydrate that had been purchased from Tokyo Kasei Kogyo Co.

(*RS*)- and (*R*)-2-Amino-3-[(2-hydroxyethyl)sulfanyl]propanoic Acids. DL- or L-Cys (400 mmol, 48.5 g) and 2-bromoethanol (400 mmol, 50.0 g) were dissolved in 160 cm<sup>3</sup> of 5 M aqueous sodium hydroxide and 200 cm<sup>3</sup> of methanol. After stirring for 1.5 h at room temperature, 5 M hydrochloric acid (160 cm<sup>3</sup>) was added to the solution. The mixture was concentrated *in vacuo* at 50°C to give a mixture of (*RS*)- or (*R*)-AHS hydrochloride and sodium chloride as the residue. After adding 800 cm<sup>3</sup> of ethanol to the residue and stirring the mixture for 0.5 h at room temperature, sodium chloride was removed by filtration. The filtrate was adjusted with triethylamine to pH 6–7, and then the precipitated (*RS*)- or (*R*)-AHS was collected by filtration, washed thoroughly with ethanol, and dried. After dissolving (*RS*)- or (*R*)-AHS in water (2 cm<sup>3</sup> g<sup>−1</sup>) at 60°C and adding ethanol (12 cm<sup>3</sup> g<sup>−1</sup>), the mixture was allowed to stand overnight at room temperature. The precipitated (*RS*)- or (*R*)-AHS was collected by filtration, washed with methanol, and dried. (*R*)-AHS ( $[\alpha]_D^{20} -27.2^\circ$  (c 2.00, water)) obtained in a yield of 53.7 g was further

recrystallized four times from water-ethanol by a method similar to that just described until there was no further change in the specific rotation.

(*RS*)-AHS: Yield 49.1 g (74.3%); mp 191–192 (decomp.). IR  $\nu_{\max}$ (KBr) cm<sup>−1</sup>: 2940, 1653, 1586, 1405, 1342, 1066, 1013, 910, 681, 548. <sup>1</sup>H-NMR (D<sub>2</sub>O)  $\delta$ : 3.94 (1H, dd, *J*=4.3, 7.3 Hz, −CH(NH<sub>2</sub>)COOH), 3.76 (2H, t, *J*=6.1 Hz, −CH<sub>2</sub>OH), 3.15 (1H, dd, *J*=4.3, 14.9 Hz, −CH(NH<sub>2</sub>)CHHS−), 3.05 (1H, dd, *J*=7.3, 14.9 Hz, −CH(NH<sub>2</sub>)CHHS−), 2.77 (2H, t, *J*=6.1 Hz, −SCH<sub>2</sub>CH<sub>2</sub>−). *Anal.* Found: C, 36.55; H, 6.62; N, 8.46%. Calcd. for C<sub>5</sub>H<sub>11</sub>NO<sub>3</sub>S: C, 36.35; H, 6.71; N, 8.48%.

(*R*)-AHS: Yield 17.5 g (26.5%); mp 190–191°C (decomp.) (lit.<sup>3)</sup> 189–189.5°C);  $[\alpha]_D^{20} -37.7^\circ$  (c 2.00, water) (lit.<sup>3)</sup>  $[\alpha]_D^{20} -53.3^\circ$  (c 2, water));  $[\alpha]_D^{20} +4.7^\circ$  (c 1.00, 0.1 M NaOH). IR  $\nu_{\max}$ (KBr) cm<sup>−1</sup>: 3135, 1648, 1619, 1508, 1393, 1348, 1120, 1051, 1016, 946, 902, 825, 771, 652, 541. *Anal.* Found: C, 36.20; H, 6.71; N, 8.37%. The <sup>1</sup>H-NMR spectrum of (*R*)-AHS was virtually identical to that of (*RS*)-AHS.

(*S*)-2-Amino-3-[(2-hydroxyethyl)sulfanyl]propanoic Acid. (*S*)-ACP·HCl was synthesized from D-Ser;<sup>9,10</sup> mp 193–194°C;  $[\alpha]_D^{20} -10.4^\circ$  (c 2.00, methanol). To a solution of (*S*)-ACP·HCl (160 mmol, 25.6 g) in 40 cm<sup>3</sup> of water was added 2-mercaptoethanol (320 mmol, 25.0 g) and 96 cm<sup>3</sup> of 5 M aqueous sodium hydroxide. After standing overnight at room temperature, 5 M hydrochloric acid (67.2 cm<sup>3</sup>) was added, before evaporating *in vacuo* at 50°C to give a mixture of (*S*)-AHS hydrochloride and sodium chloride as the residue. After adding 400 cm<sup>3</sup> of ethanol to the residue and stirring for 0.5 h at room temperature, sodium chloride was removed by filtration. The filtrate was adjusted with triethylamine to pH 6–7, and then (*S*)-AHS was collected by filtration, washed thoroughly with ethanol and dried.

(*S*)-AHS: Yield 16.6 g (62.9%); mp 189–191°C (decomp);  $[\alpha]_D^{20} +30.3^\circ$  (c 2.00, water);  $[\alpha]_D^{20} -3.8^\circ$  (c 1.00, 0.1 M NaOH). *Anal.* Found: C, 36.19; H, 6.51; N, 8.45%. The <sup>1</sup>H-NMR and IR spectra of (*S*)-AHS were virtually identical to those of (*RS*)-AHS.

(*RS*)-, (*R*)-, and (*S*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochlorides. After stirring a solution of (*RS*)-, (*R*)-, or (*S*)-AHS (90.8 mmol, 15.0 g) in 600 cm<sup>3</sup> of concentrated hydrochloric acid for 12 h at 90–95°C, the solution was concentrated *in vacuo* at 60°C; the specific rotation values of (*R*)- and (*S*)-AHS were –37.7 and +30.3°, respectively. (*RS*)-, (*R*)-, or (*S*)-ACS·HCl obtained as the residue was dissolved in 350 cm<sup>3</sup> of 2-propanol at 75°C. After standing overnight at 5°C, the precipitated (*RS*)-, (*R*)-, or (*S*)-ACS·HCl was collected by filtration, washed with a small amount of cold 2-propanol and dried.

(*RS*)-ACS·HCl: Yield 13.1 g (65.5%); mp 156–158°C (lit.<sup>3</sup> 157°C). IR  $\nu_{\max}$ (KBr) cm<sup>–1</sup>: 2983, 1738, 1586, 1483, 1437, 1220, 1197, 1053, 822, 696. <sup>1</sup>H-NMR (D<sub>2</sub>O)  $\delta$ : 4.30 (1H, dd, *J*=4.5, 7.4 Hz, –CH(NH<sub>2</sub>)COOH), 3.77 (2H, t, *J*=6.1 Hz, –CH<sub>2</sub>Cl), 3.26 (1H, dd, *J*=4.6, 15.1 Hz, –CH(NH<sub>2</sub>)CHHS–), 3.13 (1H, dd, *J*=7.4, 15.0 Hz, –CH(NH<sub>2</sub>)CHHS–), 2.79 (2H, t, *J*=6.0 Hz, –S–CH<sub>2</sub>CH<sub>2</sub>–). *Anal.* Found: C, 27.36; H, 4.83; N, 6.36%. Calcd. for C<sub>5</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>2</sub>S: C, 27.28; H, 5.04; N, 6.36%.

(*R*)-ACS·HCl: Yield 12.0 g (60.0%); mp 181–183°C (lit.<sup>3</sup> 181.5–182°C); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –4.6° (c 1.00, water); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –23.6° (c 1.00, 0.1 M NaOH). *Anal.* Found: C, 27.47; H, 5.08; N, 6.36%. The <sup>1</sup>H-NMR and IR spectra of (*R*)-ACS·HCl were virtually identical to those of (*RS*)-ACS·HCl.

(*S*)-ACS·HCl: Yield 9.70 g (48.5%); mp 181–182°C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +4.6° (c 1.00, water); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +23.6° (c 1.00, 0.1 M NaOH). *Anal.* Found: C, 27.37; H, 4.74; N, 6.30%. The <sup>1</sup>H-NMR and IR spectra of (*S*)-ACS·HCl were virtually identical to those of (*RS*)-ACS·HCl.

(*R*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid. To a solution of (*R*)-ACS·HCl (5.00 mmol, 1.10 g) in 20 cm<sup>3</sup> of methanol was added 5 cm<sup>3</sup> of triethylamine at pH 6. After stirring the mixture for 1 h in an ice bath, the precipitated (*R*)-ACS was collected by filtration, washed thoroughly with methanol and dried.

(*R*)-ACS: Yield 0.830 g (90.4%); mp 155–156°C (lit.<sup>5</sup> 156.5–157.0°C); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –2.0° (c 1.00, 1 M HCl) (lit.<sup>5</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> –2.0° (c 1.0, 1 M HCl)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –1.97° (c 5.00, 1 M HCl). IR  $\nu_{\max}$ (KBr) cm<sup>–1</sup>: 3034, 1603, 1528, 1420, 1357, 1314, 1218, 1063, 847, 705. <sup>1</sup>H-NMR (D<sub>2</sub>O)  $\delta$ : 4.23 (1H, dd, *J*=4.5, 7.4 Hz, –CH(NH<sub>2</sub>)COOH), 3.77 (2H, t, *J*=5.9 Hz, –CH<sub>2</sub>Cl), 3.24 (1H, dd, *J*=4.5, 15.0 Hz, –CH(NH<sub>2</sub>)CHHS–), 3.11 (1H, dd, *J*=7.3, 15.0 Hz, –CH(NH<sub>2</sub>)CHHS–), 2.79 (2H, t, *J*=5.9 Hz, –S–CH<sub>2</sub>CH<sub>2</sub>–). *Anal.* Found: C, 32.74; H, 5.32; N, 7.66%. Calcd. for C<sub>5</sub>H<sub>10</sub>ClNO<sub>2</sub>S: C, 32.70; H, 5.49; N, 7.63%.

(*RS*)-, (*R*)-, and (*S*)-1,4-Thiazane-3-carboxylic Acids. Triethylamine (60.0 mmol, 6.07 g) was added to a solution of (*RS*)-, (*R*)-, or (*S*)-ACS·HCl (20.0 mmol, 4.40 g) in 160 cm<sup>3</sup> of ethanol. After refluxing the mixture for 2.5 h and standing overnight at room temperature, the precipitated (*RS*)-, (*R*)-, or (*S*)-TCA was collected by filtration, washed thoroughly with methanol and dried.

(*RS*)-TCA: Yield 1.57 g (53.4%); mp 255–257°C

(decomp.) (lit.<sup>3</sup> 263–264 (decomp.)). IR  $\nu_{\max}$ (KBr) cm<sup>–1</sup>: 3003, 1648, 1398, 1357, 1241, 1210, 1045, 933, 903, 810, 704, 692, 670, 554, 504. *Anal.* Found: C, 40.62; H, 5.88; N, 9.44%. Calcd. for C<sub>5</sub>H<sub>9</sub>NO<sub>2</sub>S: C, 40.80; H, 6.16; N, 9.52%.

(*R*)-TCA: Yield 1.89 g (64.3%); mp 250–251°C (decomp.) (lit.<sup>5</sup> 250.0–251.0°C (decomp.)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> –54.5° (c 1.00, water) (lit. [ $\alpha$ ]<sub>D</sub><sup>25.5</sup> –54.03° (c 1.6, water),<sup>3</sup>) [ $\alpha$ ]<sub>D</sub><sup>25</sup> –51.7° (c 1.0, water)<sup>5</sup>). IR  $\nu_{\max}$ (KBr) cm<sup>–1</sup>: 3067, 2885, 1602, 1470, 1410, 1389, 1363, 1323, 1296, 1209, 1175, 1090, 994, 959, 908, 844, 786, 672, 617, 583, 527. *Anal.* Found: C, 40.88; H, 6.04; N, 9.48%.

(*S*)-TCA: Yield 1.94 g (66.0%); mp 250–251°C (decomp.) (lit.<sup>5</sup> 248.0–249.0°C (decomp.)); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +54.5° (c 1.00, water) (lit.<sup>5</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +50.6° (c 1.0, water)). *Anal.* Found: C, 40.69; H, 6.02; N, 9.36%. The IR spectrum of (*S*)-TCA was virtually identical to that of (*R*)-TCA.

*Optical Resolution by Preferential Crystallization.* (*RS*)-ACS·HCl (1.800, 1.963, 2.126, and 2.290 g) was dissolved in 25 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol at 40°C to prepare 110, 120, 130 and 140% supersaturated solutions at 10°C, respectively. The solvent consisted of a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9. The solution was gradually cooled to 10°C over a period of 1 h and then seeded with 0.050 g of (*R*)-ACS·HCl. After stirring the mixture for 30 min with a blade (0.70 cm width; 2.0 cm length) at 100 rpm and 10°C, the crystallized (*R*)-ACS·HCl was quickly collected by filtration and thoroughly dried.

(*R*)-ACS·HCl obtained from the 110% supersaturated solution: yield 0.104 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –23.6° (c 1.00, 0.1 M NaOH). (*R*)-ACS·HCl obtained from the 120% supersaturated solution: yield 0.175 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –22.0° (c 1.00, 0.1 M NaOH). (*R*)-ACS·HCl obtained from the 130% supersaturated solution: yield 0.272 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –21.6° (c 1.00, 0.1 M NaOH). (*R*)-ACS·HCl obtained from the 140% supersaturated solution: yield 0.524 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –10.2° (c 1.00, 0.1 M NaOH).

Optical resolution was carried out for the 130% supersaturated solution by stirring for 10, 20 and 40 min at 10°C in a manner similar to that just described.

(*R*)-ACS·HCl obtained at 10 min: yield 0.105 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –23.6° (c 1.00, 0.1 M NaOH). (*R*)-ACS·HCl obtained at 20 min: yield 0.136 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –23.6° (c 1.00, 0.1 M NaOH). (*R*)-ACS·HCl obtained at 40 min: yield 0.517 g; [ $\alpha$ ]<sub>D</sub><sup>20</sup> –2.6° (c 1.00, 0.1 M NaOH).

The yield of the enantiomer [*YE*(g)], degree of resolution [*DR*(%)] of (*R*)-ACS·HCl obtained, and the amounts of crystallization [*AC*<sub>(*S*)</sub> and *AC*<sub>(*R*)</sub> (g)] were calculated from the following equations:

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

$$DR(\%) = YE(g) \times 100 / (1/2)$$

$$\times [\text{Amount of } (RS)\text{-ACS}\cdot\text{HCl}(g) - 1.636]$$

$$AC_{(S)}(g) = (1/2)[Yield(g) - YE(g) - 0.050]$$

$$AC_{(R)}(g) = Yield(g) - AC_{(S)}(g) - 0.050$$

where *OP* is the optical purity of the obtained (*R*)-ACS·HCl, the solubility of (*RS*)-ACS·HCl being 1.636 g in 25 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol at 10°C, and *Yield* is the sum of the amounts of crystallized ACS·HCl and seed crystals (0.050 g). The optical purity of (*R*)-ACS·HCl obtained was calculated on the basis of its specific rotation in aqueous sodium hydroxide;  $[\alpha]_D^{20} - 23.6^\circ$  (*c* 1.00, 0.1 M NaOH). The yield of the enantiomer is the amount of crystallized optically pure (*R*)-ACS·HCl and corresponds to the theoretical yield of optically pure (*R*)-ACS·HCl obtained by separation from partially resolved (*R*)-ACS·HCl.

**Successive Optical Resolution by Preferential Crystallization.** (*RS*)-ACS·HCl (2.126 g) was dissolved in 25 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol 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 (*R*)-ACS·HCl. After stirring the mixture for 30 min at 10°C, (*R*)-ACS·HCl (0.272 g) was quickly collected by filtration and thoroughly dried (run 1 in Table 1). (*RS*)-ACS·HCl (0.222 g) was dissolved in the filtrate at 40°C and then the resulting solution was gradually cooled to 10°C. (*S*)-ACS·HCl (0.050 g) was added as seed crystals and then the mixture was stirred for 20 min. (*S*)-ACS·HCl (0.322 g) was collected by filtration and dried (run 2 in Table 1). The filtrate was treated in a manner similar to that just described; the detailed conditions for runs 3–6 are given in Table 1. The degrees of resolution [*DR*(%)] of (*R*)- and (*S*)-ACS·HCl obtained were calculated from the following equation:

$$DR(\%) = YE(g) \times 100 / [\text{Operation amount of } (R)\text{- or } (S)\text{-ACS}\cdot\text{HCl}(g) - 0.818]$$

where the operation amount is the amount of (*R*)- or (*S*)-ACS·HCl in the solution used in the optical resolution, and those in runs 2–6 in Table 1 were calculated from the yields and optical purities of (*R*)- or (*S*)-ACS·HCl obtained in runs 1–5, respectively. The half amount for the solubility of (*RS*)-ACS·HCl was 0.818 g in 25 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol at 10°C.

**Purification of Partially Resolved (*R*)- and (*S*)-2-Amino-3-[(2-chloroethyl)sulfanyl]propanoic Acid Hydrochlorides.** (*R*)-ACS·HCl (8.10 g;  $[\alpha]_D^{20} - 15.1^\circ$  (*c* 1.00, 0.1 M NaOH)) was dissolved in 45 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol at 40°C. The mixture was vigorously stirred for 5 h at 10°C, before the purified (*R*)-ACS·HCl was collected by filtration and dried. (*S*)-ACS·HCl (5.57 g;  $[\alpha]_D^{20} + 16.7^\circ$  (*c* 1.00, 0.1 M NaOH)) was recrystallized from 25 cm<sup>3</sup> of the solvent in a manner similar to that described for (*R*)-ACS·HCl.

(*R*)-ACS·HCl: yield 4.95 g; mp 182–183°C;  $[\alpha]_D^{20} - 23.6^\circ$  (*c* 1.00, 0.1 M NaOH). (*S*)-ACS·HCl: yield 3.82 g; mp 182–183°C;  $[\alpha]_D^{20} + 23.6^\circ$  (*c* 1.00, 0.1 M NaOH).

**Determination of Solubility and Preparation of Binary Melting Point Phase Diagram.** (*RS*)-ACS·HCl (2.700 g) or (*R*)-ACS·HCl (1.500 g) was dissolved in 25 cm<sup>3</sup> of a mixture of hydrochloric acid and 2-propanol at 40°C. The solution was vigorously stirred at 10°C, an appropriate portion of the solution was pipetted from the mixture, avoiding contamination with solid ACS·HCl, and the refractive index was measured at 20°C. The mixture was stirred at 10°C until the refractive index had reached a constant value. The solubility was determined according to calibration curves previously prepared. Solubility at 10°C: (*RS*)-ACS·HCl, 6.544 g (100 cm<sup>3</sup> solvent)<sup>−1</sup>; (*R*)-ACS·HCl, 2.701 g (100 cm<sup>3</sup> solvent)<sup>−1</sup>. The solvent consisted of a mixture of 5 M hydrochloric acid and 2-propanol in a volumetric ratio of 1:9.

Preparation of a binary melting point phase diagram of ACS·HCl enabled the melting points of the mixtures composed of (*RS*)- and (*R*)-ACS·HCl to be measured accurately. The binary phase diagram was prepared from their temperatures at the beginning and end of melting.

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