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Synthesis of Four Stereoisomers of 1,4-Thiazane-3-carboxylic Acid 1-Oxide *via* the Asymmetric Transformation (combined isomerization-preferential crystallization) of 1,4-Thiazane-3-carboxylic Acid

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In order to synthesize four stereoisomers of 1,4-thiazane-3-carboxylic acid 1-oxide (TCA·SO), (*S*)-1,4-thiazane-3-carboxylic acid [(*S*)-TCA], which is one of the precursors, was prepared by the asymmetric transformation (combined isomerization-preferential crystallization) of (*RS*)-TCA. This asymmetric transformation was used (2*R*, 3*R*)-tartaric acid [(*R*)-TA] as a resolving agent and salicylaldehyde as the epimerization catalyst in propanoic acid at 110°C to afford a salt of (*S*)-TCA with (*R*)-TA in 100% de with a yield of over 90%. Optically pure (*S*)-TCA was obtained by treating the salt with triethylamine in methanol in a yield of over 80%, based on (*RS*)-TCA as the starting material. In addition, asymmetric transformation of (*R*)-TCA gave (*S*)-TCA in a yield of 60–70%. (*S*)-TCA was oxidized by hydrogen peroxide in dilute hydrochloric acid to selectively crystallize (1*S*, 3*S*)-TCA·SO. (1*R*, 3*S*)-TCA·SO of 70% de from the filtrate was allowed to form a salt with (*R*)-TA after a treatment with triethylamine to give (1*R*, 3*S*)-TCA·SO as a single diastereoisomer. (1*R*, 3*R*)- and (1*S*, 3*R*)-TCA·SO were also prepared by starting from (*R*)-TCA that had been synthesized from L-cysteine.

Key words: 1,4-thiazane-3-carboxylic acid 1-oxide; 1,4-thiazane-3-carboxylic acid; asymmetric transformation; tartaric acid

(1*S*, 3*R*)-1,4-Thiazane-3-carboxylic acid 1-oxide [(1*S*, 3*R*)-TCA·SO], the sulfoxide amino acid "chondrine", has been isolated from the red alga, *Chondria crassicaulis*, and the brown alga, *Undaria pinnatifida*.[1-3] Four stereoisomers are possible for TCA·SO because of the existence of two chiral centers, an asymmetric sulfur and carbon atoms. (1*R*, 3*R*)- and (1*S*, 3*R*)-TCA·SO have been synthesized from L-cystine *via* (*R*)-2-amino-3-[(2-hydroxyethyl)-sulfanyl]propanoic acid, (*R*)-2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride [(*R*)-ACS·HCl], and (*R*)-1,4-thiazane-3-carboxylic acid [(*R*)-TCA] as intermediate,[4,5] however, (1*S*, 3*S*)- and (1*R*, 3*S*)-TCA·SO have not previously been synthesized. Although (1*S*, 3*S*)- and (1*R*, 3*S*)-TCA·SO can be synthesized from D-cystine or D-cysteine (D-Cys),[4-6] these D-α-amino acids are more expensive than the corresponding L-α-amino acids, and hence are difficult to obtain in quantity. Therefore, we have prepared (*S*)-TCA from (*S*)-ACS·HCl that had been obtained by optical resolution with the preferential crystallization of (*RS*)-ACS·HCl.[6] However, this procedure did not provide desired (*S*)-ACS·HCl in a yield of more than 50%. In this paper, we describe the preparation of (*S*)-TCA based upon the so-called "asymmetric transformation", which is defined as the transformation of a mixture of stereoisomers into a single stereoisomer, or into a mixture with a different ratio of stereoisomers, by an equilibrium process.[7] Asymmetric transformation of the second type can be achieved by preferential crystallization of less-soluble diastereoisomeric salt combined with *in situ*-racemization of the undesired enantiomer to enrich the desired enantiomer in a yield approaching 100%.[7-9]

One major problem in asymmetric transformation is the choice of resolving agent. In general, α-amino acids do not form salts with (2*R*, 3*R*)- and (2*S*, 3*S*)-tartaric acid (TA). However, cyclic α-amino acids such as 1,3-thiazane-4-carboxylic acid (THA),[10] 4-thiazolidinecarboxylic acid (THC),[10,11] proline,[12] and 2-thiazolidinecarboxylic acid[13] have been optically resolved by separating the diastereoisomeric

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Abbreviations: ACS·HCl, 2-amino-3-[(2-chloroethyl)sulfanyl]propanoic acid hydrochloride; Cys, cysteine; TA, tartaric acid; TCA, 1,4-thiazane-3-carboxylic acid; TCA·SO, 1,4-thiazane-3-carboxylic acid 1-oxide; THA, 1,3-thiazane-4-carboxylic acid; THC, 4-thiazolidinecarboxylic acid

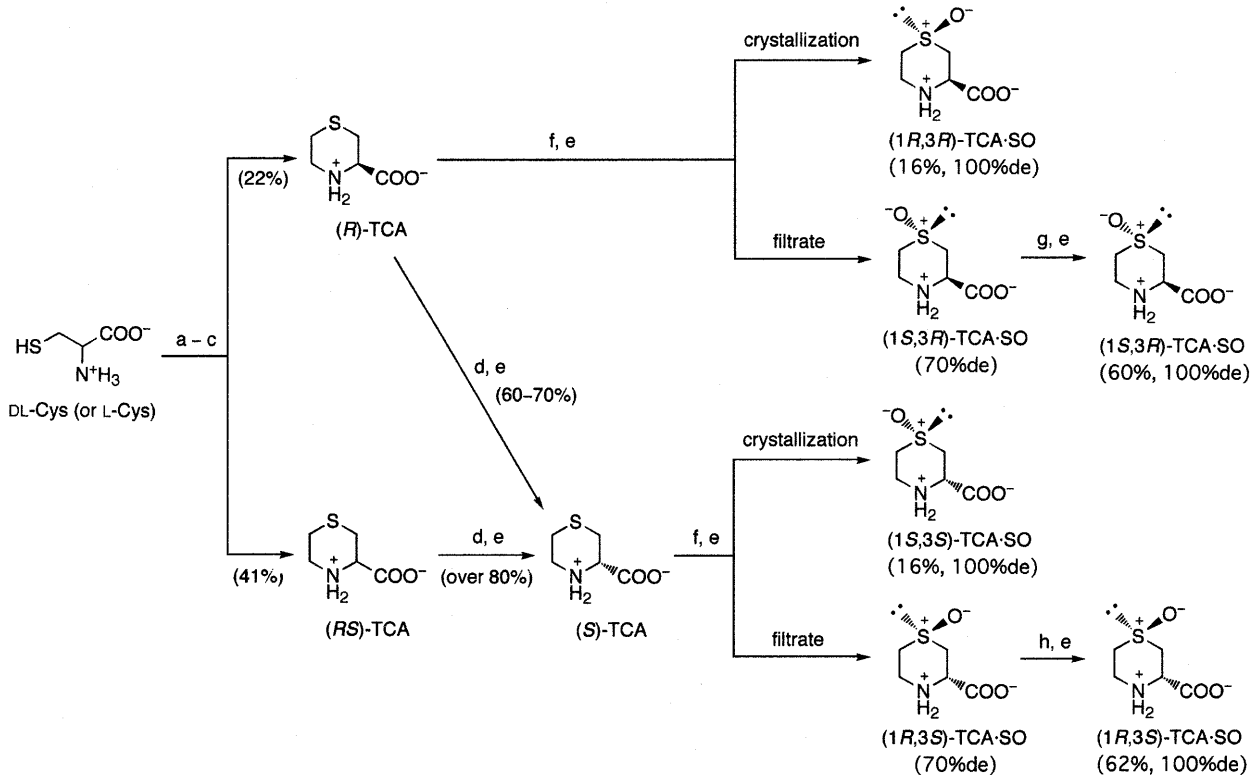

Chart 1. Synthetic Routes to the Four Stereoisomers of 1,4-Thiazane-3-carboxylic Acid 1-Oxide.
(a) 2-bromoethanol, OH^-; (b) conc. HCl, 90–95°C; (c) $(C_2H_5)_3N$, dimethylformamide, 90–95°C; (d) (*R*)-TA, salicylaldehyde, propanoic acid, 90–110°C; (e) $(C_2H_5)_3N$; (f) H_2O_2, dil. HCl; (g) (*S*)-TA; (h) (*R*)-TA.

salts with optically active TA. We therefore attempted to convert (*RS*)- and (*R*)-TCA into (*S*)-TCA by asymmetric transformation with optically active TA as the resolving agent. (*S*)-TCA obtained in this way and (*R*)-TCA, which had been separately synthesized from L-Cys,[4-6] were respectively oxidized with hydrogen peroxide to yield TCA·SO, and the resulting diastereoisomeric mixtures were separated into four stereoisomers of TCA·SO (Chart 1).

Results and Discussion

Racemization of (R)-1,4-thiazane-3-carboxylic acid [(R)-TCA]

Another important problem in asymmetric transformation is the epimerization rate; namely, the racemization rate of an optically active substance. Racemization of optically active α-amino acids is catalyzed by carbonyl compounds in carboxylic acids, such as acetic acid and propanoic acid.[8,11,14] Therefore, the racemization rate of (*R*)-TCA was measured in the presence of salicylaldehyde and an equimolar amount of (*RS*)-TA in acetic acid at 80°C, as shown in Fig. 1.

The racemization of (*R*)-TCA obeyed first-order kinetics. The rate constant [k_R (s^{-1})] was calculated as $1.06\times10^{-4}\,s^{-1}$, and the half-life period as 6.54×10^3 s. (*R*)-THA and THC showed k_R values of 6.17×10^{-5} and $2.57\times10^{-4}\,s^{-1}$, respectively, under similar conditions to those for (*R*)-TCA.[10] (*RS*)-THA and (*RS*)-THC were coverted into the (*R*)- and (*S*)-enantiomers *via* asymmetric transformation.[10,11] This result therefore suggests the possibility for asymmetric transformation of (*RS*)- or (*R*)-TCA into (*S*)-TCA.

Preparation of (S)-1,4-thiazane-3-carboxylic acid [(S)-TCA] by asymmetric transformation

(*R*)-TCA was reacted with (*R*)- or (*S*)-TA in water. The salt of (*R*)-TCA with (*S*)-TA [(*R*)-TCA·(*S*)-TA salt] was isolated by evaporating the water, but the (*R*)-TCA·(*R*)-TA salt was not obtained as crystals. The (*R*)-TCA·(*S*)-TA salt was demonstrated by ^{1}H-NMR spectral and elemental analysis data to be composed of equimolar amounts of (*R*)-TCA and (*S*)-TA: $[\alpha]_D^{20}$ −33.2° (*c* 1.00, water). This result indicated that (*R*)-TCA·(*S*)-TA and (*S*)-TCA·(*R*)-TA were the less-soluble diastereoisomeric salts, and that (*R*)-TCA·(*R*)-TA and (*S*)-TCA·(*S*)-TA were the more-soluble salts. Therefore, asymmetric transformation of (*RS*)-TCA was attempted by employing (*R*)-TA as the resolving agent in acetic acid at 80°C, as shown in Fig. 2; an equimolar amount of salicylaldehyde was employed to accelerate the epimerization rate.

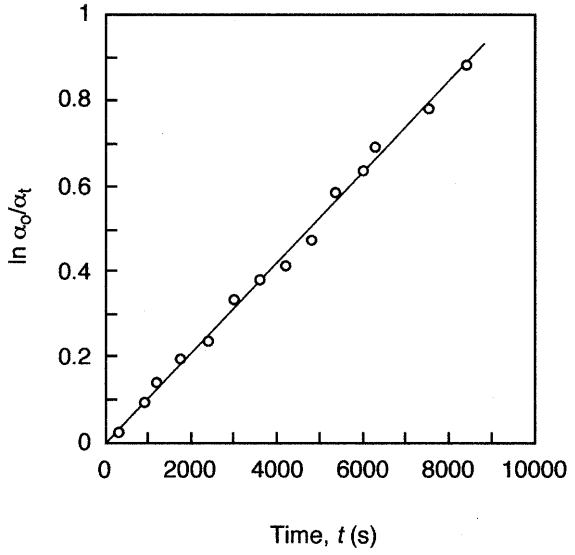

Fig. 1. Racemization of (*R*)-1,4-Thiazane-3-carboxylic Acid [(*R*)-TCA].

Conditions: (*R*)-TCA, 2.00 mmol; (*RS*)-TA, 2.00 mmol; acetic acid, 100 cm^3; temperature, 80°C; salicylaldehyde, 0.20 mmol. α_0, optical rotation extrapolated to time zero. α_t, optical rotation at time t (s).

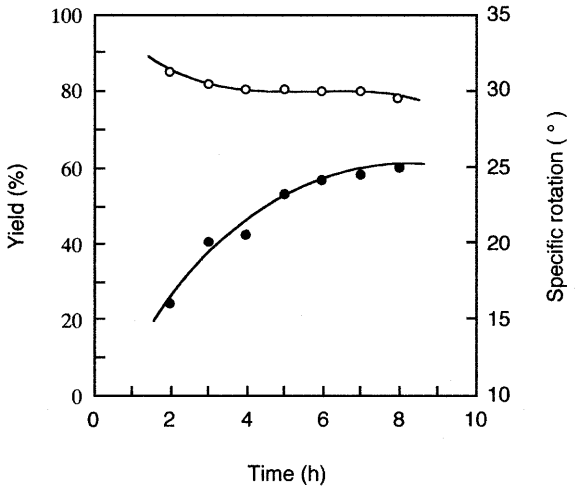

Fig. 2. Asymmetric Transformation of (*RS*)-1,4-Thiazane-3-carboxylic Acid [(*RS*)-TCA] in Acetic Acid.

Conditions: (*RS*)-TCA, 1.47 g (10.0 mmol); (*R*)-TA, 1.50 g (10.0 mmol); salicylaldehyde, 1.22 g (10.0 mmol); acetic acid, 10 cm^3; temperature, 80°C. ○ Yield. ● Specific rotation, $[\alpha]_D^{20}$ (*c* 1.00, water).

The asymmetric transformation reaction gave the (*S*)-TCA·(*R*)-TA salt in a yield of about 80%, whose specific rotation value was $[\alpha]_D^{20}$ +23.3–+25.0° (*c* 1.00, water), while that of an equimolar mixture of (*RS*)-TCA and (*R*)-TA was $[\alpha]_D^{20}$ +9.0° (*c* 1.0, water). The salt was washed with acetic acid at 80°C and then treated with triethylamine in ethanol to afford optically pure (*S*)-TCA in a yield of 52%, based on (*RS*)-TCA as the starting material: $[\alpha]_D^{20}$ +54.5° (*c* 1.00, water) [lit.,[6] $[\alpha]_D^{20}$ +54.5° (*c* 1.00, water)]. Although the yield was over 50%, the asymmetric transformation in acetic acid was not satisfactory in regard to the recovery of the desired product.

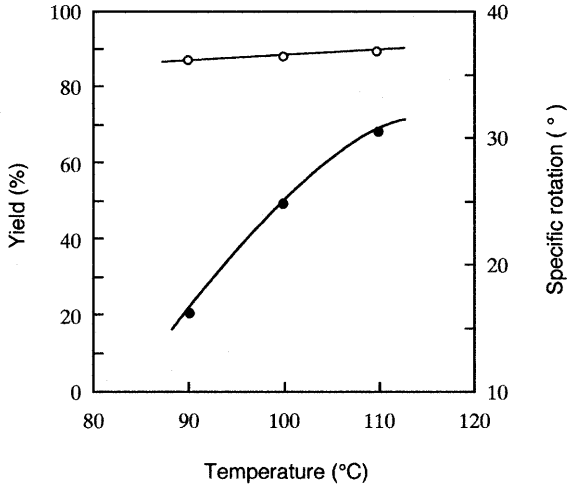

Fig. 3. Influence of Temperature on the Asymmetric Transformation.

Conditions: (*RS*)-TCA, 1.47 g (10.0 mmol); (*R*)-TA, 1.50 g (10.0 mmol); salicylaldehyde, 1.22 g (10.0 mmol); propanoic acid, 30 cm^3; reaction time, 2 h; temperature, 90, 100, and 110°C. ○ Yield. ● Specific rotation; $[\alpha]_D^{20}$ (*c* 1.00, water).

We found that the (*S*)-TCA·(*R*)-TA salt seemed to be less soluble in propanoic acid than in acetic acid. In addition, although the rate of racemization of (*R*)-TCA could not be measured in propanoic acid due to its poor solubility, it seemed to be faster than that in acetic acid, as described in our previous papers.[9,12] Therefore, the asymmetric transformation of (*RS*)-TCA was attempted by reacting for 2 h in propanoic acid at 90–110°C (Fig. 3).

The yield of the (*S*)-TCA·(*R*)-TA salt was slightly increased from 87.5% to 90% with increasing in temperature, and the specific rotation value rapidly increased. The specific rotation value of the (*S*)-TCA·(*R*)-TA salt obtained at 110°C was $[\alpha]_D^{20}$ +30.7° (*c* 1.00, water), and (*S*)-TCA with an optical purity of 86% was obtained from the salt in a yield of 82%: $[\alpha]_D^{20}$ +46.7° (*c* 1.00, water). Based on this result, the asymmetric transformation of (*RS*)-TCA was carried out by reacting for 1–6 h in propanoic acid at 110°C (Table 1).

The (*S*)-TCA·(*R*)-TA salt was obtained after 3–6 h in a yield of about 93% whose absolute value for specific rotation agreed with that of authentic the (*R*)-TCA·(*S*)-TA salt: $[\alpha]_D^{20}$ +33.2° (*c* 1.00, water). Therefore, this salt was treated with triethylamine in ethanol without purification to yield optically pure (*S*)-TCA in a yield of 83–85%: $[\alpha]_D^{20}$ +54.5° (*c* 1.00, water).

In addition, we attempted to convert (*R*)-TCA to

Table 1. Preparation of (*S*)-1,4-Thiazane-3-carboxylic Acid by Asymmetric Transformation[a]

Starting material	(*S*)-TCA·(*R*)-TA salt			(*S*)-TCA		
	Reaction time (h)	Yield (g) [%[b]]	Specific rotation[c] (°)	Yeild (g) [%[b]]	Specific rotation[c] (°)	Optical purity[d] (%)
(*RS*)-TCA[e]	1	2.62 [88.2]	+25.1	1.17 [79.6]	+34.4	63.1
	1[f]	1.93 [65.0]	+33.2	0.946 [64.4]	+54.5	100
	2	2.66 [89.6]	+30.7	1.20 [81.6]	+46.7	85.7
	2[f]	2.37 [79.8]	+33.2	1.07 [72.8]	+54.5	100
	3	2.80 [94.3]	+33.2	1.25 [85.0]	+54.5	100
	4	2.76 [92.9]	+33.2	1.22 [83.0]	+54.5	100
	6	2.77 [93.3]	+33.2	1.23 [83.7]	+54.5	100
(*R*)-TCA[g]	2	2.67 [89.9][h]	−10.7	1.22 [83.0][i]	−43.1	79.1
	4	2.68 [90.2][h]	+3.5	1.22 [83.0][i]	−4.4	8.1
	6	2.39 [80.5]	+17.4	1.10 [74.8]	+16.6	30.5
	7	2.36 [79.5]	+26.2	1.00 [68.0]	+35.5	65.1
	7[f]	1.97 [66.3]	+33.2	0.912 [62.0]	+54.5	100
	8	2.36 [79.5]	+28.2	1.06 [72.1]	+40.6	74.5
	8[f]	2.10 [70.7]	+33.2	0.967 [65.8]	+54.5	100
	9	2.34 [78.8]	+28.8	0.958 [65.1]	+44.1	80.9
	9[f]	2.12 [71.4]	+33.2	1.02 [69.4]	+54.5	100
	10	2.30 [77.4]	+29.0	0.954 [64.9]	+45.0	82.6
	10[f]	1.87 [63.0]	+33.2	0.882 [60.0]	+54.5	100

[a] Conditions: (*RS*)- or (*R*)-TCA, 1.47 g (10.0 mmol); (*R*)-TA, 1.50 g (10.0 mmol); salicylaldehyde, 1.22 g (10.0 mmol); propanoic acid, 30 cm³.
[b] Yield was calculated on the basis of the amount of (*RS*)- or (*R*)-TCA as the starting material (1.47 g, 10.0 mmol).
[c] $[\alpha]_D^{20}$ (*c* 1.00, water).
[d] Optical purity was calculated on the basis of the specific rotation of authentic (*R*)-TCA; $[\alpha]_D^{20}$ −54.5° (*c* 1.00, water).
[e] Temperature, 110°C.
[f] The (*S*)-TCA·(*R*)-TA salt obtained was purified.
[g] Temperature, 100°C.
[h] (*R*)-TCA·(*R*)-TA salt.
[i] (*R*)-TCA.

(*S*)-TCA by asymmetric transformation. Asymmetric transformation could be carried out in propanoic acid at a lower temperature (100°C) than 110°C because it started from the more soluble diastereoisomeric salt, (*R*)-TCA·(*R*)-TA (Table 1).

The salt obtained after 4 h was nearly equimolar mixture of the diastereoisomeric salts. Although the yield of the (*S*)-TCA·(*R*)-TA salt obtained after 6–10 h decreased from 80.5% to 77% with reaction time, the specific rotation value increased: $[\alpha]_D^{20}$ +17.4–+29.0° (*c* 1.00, water). The salt obtained after 7–10 h was purified to afford enantiomerically pure (*S*)-TCA in a yield of 60–70%, based on (*R*)-TCA as the starting material.

Preparation of the four stereoisomers of 1,4-thiazane-3-carboxylic acid 1-oxide (TCA·SO)

The (*S*)-TCA obtained by asymmetric transformation was first oxidized by hydrogen peroxide in acetic acid according to the method reported by Carson *et al.*[4] to give a diastreoisomeric mixture of (1*S*, 3*S*)- and (1*R*, 3*S*)-TCA·SO in a yield of 77%: $[\alpha]_D^{20}$ +2.0° (*c* 1.0, water). In the ^{1}H-NMR spectrum of the mixture, methine protons at the C-3 positions appeared at 4.30 and 4.10 ppm.[5] Crude TCA·SO was washed with water to give TCA·SO whose specific rotation value was $[\alpha]_D^{20}$ −10.4° (*c* 1.00, water). However, this specific rotation value was unaffected by further washing with water: $[\alpha]_D^{20}$ −10.0° (*c* 1.00, water). In addition, the specific rotation value of TCA·SO obtained from the washings was $[\alpha]_D^{20}$ −10.4° (*c* 1.00, water). Although this (1*R*, 3*S*)-TCA·SO was estimated to be over 70%de from the specific rotation values[4,5] of (1*R*, 3*R*)- and (1*S*, 3*R*)-TCA·SO, it was difficult to obtain as a single diastereoisomer by washing with water.

In contrast, (*S*)-TCA was oxidized by hydrogen peroxide in dilute hydrochloric acid, and then the solution was treated with triethylamine and gradually allowed to crystallize TCA·SO in a yield of 16%, based on (*S*)-TCA as the starting material. The specific rotation value of the TCA·SO sample obtained was $[\alpha]_D^{20}$ +57.4° (*c* 1.00, water) [lit.:[5] (1*R*, 3*R*)-TCA·SO, $[\alpha]_D^{27}$ −55.1° (*c* 2, water)]. In addition, the methine proton at the C-3 position was observed at 4.10 ppm, but not at 4.30 ppm. Thus, the peaks resonating at 4.10 and 4.30 ppm were assigned to the methine protons of (1*S*, 3*S*)- and (1*R*, 3*S*)-TCA·SO, respectively. This result indicates that (1*S*, 3*S*)-TCA·SO had been selectively crystallized and obtained as a single diastereoisomer.

The filtrate was evaporated to dryness to give TCA·SO as the residue in a yield of 78%, based on (*S*)-TCA as the starting material: $[\alpha]_D^{20}$ −8.4° (*c* 1.0, water). The intensity ratio of the methine protons at the C-3 position suggested that (1*R*, 3*S*)-TCA·SO

had been obtained in 70%de. An attempt was made to separate the obtained (1*R*, 3*S*)-TCA·SO by the formation of diastereoisomeric salts with (*R*)- and (*S*)-TA in acetic acid. When (1*R*, 3*S*)-TCA·SO was reacted with (*R*)-TA, the formed salt was obtained in over 99%de: $[\alpha]_D^{20}$ −0.89° (*c* 1.0, water). The ^{1}H-NMR spectral and elemental analysis data demonstrated that the salt was composed of equimolar amounts of TCA·SO and TA. Treatment of the salt with triethylamine in methanol gave (1*R*, 3*S*)-TCA·SO in a yield of 62%: $[\alpha]_D^{20}$ −20.1° (*c* 1.00, water). The (1*R*, 3*S*)-TCA·SO sample obtained was determined to be a single diastereoisomer because the methine proton at the C-3 position was observed at 4.30 ppm, but not at 4.10 ppm. When (1*R*, 3*S*)-TCA·SO (1.63 g, 10.0 mmol, 70%de) was reacted with (*S*)-TA (1.50 g, 10.0 mmol), the (1*R*, 3*S*)-TCA·SO·(*S*)-TA salt was obtained in a yield of 92.3% and 78%de, and its specific rotation value was $[\alpha]_D^{20}$ −11.4° (*c* 1.00, water). Although the obtained (1*R*, 3*S*)-TCA·SO·(*S*)-TA salt was washed by stirring in 30 cm^3 of acetic acid for 2 h at room temperature, the specific rotation value remained unchanged.

(1*R*, 3*R*)-TCA·SO was obtained from (*R*)-TCA, which had been separately synthesized from L-Cys,[4-6] in a yield of 16%, by a method similar to that described for the (1*S*, 3*S*)-isomer: $[\alpha]_D^{20}$ −57.4° (*c* 1.00, water). Crude (1*S*, 3*R*)-TCA·SO from the filtrate formed the salt with (*S*)-TA to give (1*S*, 3*R*)-TCA·SO as a single diastereoisomer in a yield of 60%: $[\alpha]_D^{20}$ +20.1° (*c* 1.00, water) [lit., $[\alpha]_D^{16}$ +20.9° (*c* 2, water),[1] $[\alpha]_D^{16}$ +19.0° (*c* 1, water),[4] and $[\alpha]_D^{16}$ +20.0° (*c* 2.0, water)[5]].

This study has demonstrated the asymmetric transformation to be an efficient means for obtaining enantiomerically pure (*S*)-TCA from (*RS*)- and (*R*)-TCA. (*S*)- and (*R*)-TCA were respectively oxidized by hydrogen peroxide in dilute hydrochloric acid to selectively crystallize (1*S*, 3*S*)- and (1*R*, 3*R*)-TCA·SO. (1*R*, 3*S*)- and (1*S*, 3*R*)-TCA·SO could be obtained as single diastereoisomers by treating the respective diastereoisomeric mixtures with optically active TA.

Experimental

General. Specific rotation values were measured at 589 nm with a Horiba SEPA-300 auto-polarimeter equipped with a quartz cell with a 5.00-cm path length. IR spectra were obtained in the range of 4000–400 cm^{-1} with a Perkin-Elmer model 1600 FT-IR spectrometer by the KBr disk method. ^{1}H- and ^{13}C-NMR spectra were recorded with a JNM-FX270 FT NMR system (270 MHz for ^{1}H and 67.5 MHz for ^{13}C) in deuterium oxide with sodium 3-(trimethylsilyl)propanesulfonate (DSS) as an internal standard (0 ppm). Chemical shift values are reported in δ units downfield from DSS.

(*RS*)- and (*R*)-TCA were synthesized by starting with DL- and L-Cys, respectively;[4,6] (*R*)-TCA, $[\alpha]_D^{20}$ −54.5° (*c* 1.00, water). L-Cys was purchased from Kokusan Chemical Works. DL-Cys was prepared from DL-Cys hydrochloride monohydrate purchased from Tokyo Kasei Kogyo Co. (*R*)-TA was purchased from Wako Pure Chemical Ind., and (*S*)- and (*RS*)-TA from Tokyo Kasei Kogyo Co.

Preparation of the authentic salt of (R)-1,4-thiazane-3-carboxylic acid [(R)-TCA] with (2S, 3S)-tartaric acid. A solution of (*R*)-TCA (1.47 g, 10.0 mmol) and (*S*)-TA (1.50 g, 10.0 mmol) in 10 cm^3 of water was evaporated to dryness *in vacuo* at 60°C. The (*R*)-TCA·(*S*)-TA salt was obtained as a residue.

(*R*)-TCA·(*S*)-TA salt: Yield, 2.89 g (97.3%); mp 175–177°C (decomp.); $[\alpha]_D^{20}$ −33.2° (*c* 1.00, water). ^{1}H-NMR δ: 4.75 [2H, s, -CH(OH)COOH], 3.96 [1H, dd, *J*=3.4, 10.0 Hz, -NHCH(COOH)-], 3.77–3.69 (1H, m), 3.39–3.29 (1H, m), 3.18–2.78 (4H, m). *Anal.* Found: C, 36.40; H, 4.94; N, 4.77%. Calcd. for $C_9H_{15}NO_8S$: C, 36.36; H, 5.09; N, 4.71%.

An equimolar mixture of (*RS*)-TCA and (*R*)-TA: $[\alpha]_D^{20}$ +9.0° (*c* 1.0, water).

Asymmetric transformation of (RS)- and (R)-1,4-thiazane-3-carboxylic acids (TCA). To a mixture of (*RS*)-TCA (1.47 g, 10.0 mmol) and (*R*)-TA (1.50 g, 10.0 mmol) in acetic acid (10 cm^3) or propanoic acid (30 cm^3) was added salicylaldehyde (1.22 g, 10.0 mmol) at 80, 90, 100, or 110°C. After vigorously stirring the mixture for 1–8 h at each temperature and then for 30 min in an ice bath, the resulting (*S*)-TCA·(*R*)-TA salt was collected by filtration, washed thoroughly with diethyl ether, and dried.

(*S*)-TCA·(*R*)-TA salt obtained after 2 h in acetic acid at 80°C: Yield, 2.51 g (84.5%); $[\alpha]_D^{20}$ +16.0° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 3 h in acetic acid at 80°C: Yield, 2.42 g (81.5%); $[\alpha]_D^{20}$ +20.2° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 4 h in acetic acid at 80°C: Yield, 2.38 g (80.1%); $[\alpha]_D^{20}$ +20.8° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 5 h in acetic acid at 80°C: Yield, 2.38 g (80.1%); $[\alpha]_D^{20}$ +23.3° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 6 h in acetic acid at 80°C: Yield, 2.36 g (79.5%); $[\alpha]_D^{20}$ +24.1° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 7 h in acetic acid at 80°C: Yield, 2.37 g (79.8%); $[\alpha]_D^{20}$ +24.5° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 8 h in acetic acid at 80°C: Yield, 2.32 g (78.1%); $[\alpha]_D^{20}$ +25.0° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 2 h in propanoic acid at 90°C: Yield, 2.60 g (87.5%); $[\alpha]_D^{20}$ +16.2° (*c* 1.00, water). (*S*)-TCA·(*R*)-TA salt obtained after 2 h in propanoic acid at 100°C: Yield, 2.62 g (88.2%); $[\alpha]_D^{20}$ +24.9° (*c* 1.00, water). The

other results are summarized in Table 1.

Asymmetric transformation was also carried out by reacting (*R*)-TCA (1.47 g, 10.0 mmol) with (*R*)-TA (15.0 g, 10.0 mmol) in propanoic acid (30 cm^3) for 2–10 h at 100°C, in a manner similar to that just described (Table 1).

The (*S*)-TCA·(*R*)-TA salt obtained was stirred for 2 h in acetic acid (5 $cm^3\ g^{-1}$) at 80°C and then the suspension was cooled to room temperature. The purified salt was collected by filtration, washed with diethyl ether, and dried. After stirring an equimolar mixture of the (*S*)-TCA·(*R*)-TA salt and triethylamine in ethanol (4 $cm^3\ g^{-1}$) for 1 h at room temperature and then for 30 min in an ice bath, (*S*)-TCA liberated was collected by filtration, washed with methanol, and dried. The results are summarized in Table 1.

Four stereoisomers of 1,4-thiazane-3-carboxylic acid 1-oxide (TCA·SO). To a solution of (*S*)-TCA (2.94 g, 20.0 mmol) in water (10 cm^3) and 5 mol dm^{-3} hydrochloric acid (4.40 cm^3) was added five portions of 30 wt% hydrogen peroxide (0.6 $cm^3 \times 5$) at 30 min intervals at room temperature. After stirring the solution for 4 h at room temperature, methanol (40 cm^3) and triethylamine (2.25 g, 22.2 mmol) were successively added to the solution, and then the solution was stirred for 30 min at 100 rpm at room temperature. After allowing the solution to stand overnight at room temperature, the precipitated (1*S*, 3*S*)-TCA·SO was collected by filtration, washed with a small amount of methanol, and dried. The filtrate was evaporated to dryness *in vacuo* at 60°C and then the residue was washed thoroughly with methanol to give crude (1*R*, 3*S*)-TCA·SO in a yield of 2.55 g; $[\alpha]_D^{20}$ −8.4° (*c* 1.0, water). After stirring a suspension of (1*R*, 3*S*)-TCA·SO (2.55 g, 15.6 mmol) and (*R*)-TA (2.34 g, 15.6 mmol) in 80 cm^3 of acetic acid for 2 h at room temperature, the formed salt (4.10 g, 13.1 mmol) was collected by filtration, washed with a small amount of methanol, and dried. Triethylamine (1.34 g, 13.1 mmol) was added to a suspension of the salt in 130 cm^3 of methanol. After stirring the suspension for 1 h at room temperature, the liberated (1*R*, 3*S*)-TCA·SO was collected by filtration, washed with methanol, and dried.

(1*R*, 3*R*)- and (1*S*, 3*R*)-TCA·SO were obtained from (*R*)-TCA in a manner similar to that used for (1*S*, 3*S*)- and (1*R*, 3*S*)-TCA·SO. Crude (1*S*, 3*R*)-TCA·SO was purified by salt formation with (*S*)-TA.

(1*S*, 3*S*)-TCA·SO: Yield, 0.522 g (16.0%); mp 211–212°C (decomp.); $[\alpha]_D^{20}$ +57.4° (*c* 1.00, water). IR ν_{max} (KBr) cm^{-1}: 2992, 2970, 2923, 2359, 2341, 1614, 1587, 1424, 1411, 1391, 1374, 1172, 1090, 1038, 999, 962, 895, 861, 778, 671, 634, 526, 487. ^{1}H-NMR δ: 4.10 [1H, dd, *J*=3.4, 9.9 Hz, -NHC<u>H</u>(COOH)-], 4.01–3.92 (1H, m), 3.88–3.81 (1H, m), 3.67–3.58 (1H, m), 3.49–3.39 (1H, m), 3.34–3.23 (1H, m), 3.15–3.05 (1H, m). ^{13}C-NMR δ: 172.5 (-COOH), 56.5 (C-3), 49.5, 47.0, 39.5. *Anal.* Found: C, 36.95; H, 5.55; N, 8.49%. Calcd. for $C_5H_9NO_3S$: C, 36.80; H, 5.56; N, 8.58%.

(1*R*, 3*S*)-TCA·SO: Yield, 2.01 g (61.7%); mp 255–258°C (decomp.); $[\alpha]_D^{20}$ −20.1° (*c* 1.00, water). IR ν_{max} (KBr) cm^{-1}: 2996, 2906, 2360, 2344, 1654, 1604, 1495, 1463, 1418, 1377, 1287, 1231, 1130, 1103, 1086, 1044, 1026, 991, 956, 929, 859, 808, 780, 661, 636, 554, 488. ^{1}H-NMR δ: 4.30 [1H, dd, *J*=2.6, 12.8 Hz, -NHC<u>H</u>(COOH)-], 3.85–3.59 (3H, m), 3.34–3.26 (1H, m), 3.17–3.01 (2H, m). ^{13}C-NMR δ: 173.9 (-COOH), 50.9 (C-3), 46.5, 42.7, 36.7. *Anal.* Found: C, 36.58; H, 5.45; N, 8.42%.

(1*R*, 3*R*)-TCA·SO: Yield, 0.515 g (15.8%); mp 210–212°C (decomp.); $[\alpha]_D^{20}$ −57.4° (*c* 1.00, water) [lit.,[5] $[\alpha]_D^{27}$ −55.1° (*c* 2, water)]. *Anal.* Found: C, 36.66; H, 5.40; N, 8.46%. The ^{1}H- and ^{13}C-NMR and IR spectra of (1*R*, 3*R*)-TCA·SO were virtually identical to those of (1*S*, 3*S*)-TCA·SO.

(1*S*, 3*R*)-TCA·SO: Yield, 1.97 g (60.4%); mp 255–258°C (decomp.) [lit., mp 210°C (decomp.) and 255–257°C (melting with decomp.),[1] 252°C (decomp.)[4]]; $[\alpha]_D^{20}$ +20.1° (*c* 1.00, water) [lit., $[\alpha]_D^{16}$ +20.9° (*c* 2, water),[1] $[\alpha]_D^{16}$ +19.0° (*c* 1, water),[4] $[\alpha]_D^{16}$ +20.0° (*c* 2.0, water)[5]]. *Anal.* Found: C, 36.58; H, 5.39; N, 8.42%. The ^{1}H- and ^{13}C-NMR and IR spectra of (1*S*, 3*R*)-TCA·SO were virtually identical to those of (1*R*, 3*S*)-TCA·SO.

(1*R*, 3*S*)-TCA·SO·(*R*)-TA salt: Yield, 4.10 g; mp 188–190°C (decomp.); $[\alpha]_D^{20}$ −0.89° (*c* 1.0, water). ^{1}H-NMR δ: 4.72 [2H, s, -C<u>H</u>(OH)COOH], 4.36 [1H, dd, *J*=2.7, 13.0 Hz, -NHC<u>H</u>(COOH)-], 3.86–3.60 (3H, m), 3.35–3.26 (1H, m), 3.19–3.01 (2H, m). ^{13}C-NMR δ: 177.4 [-CH(OH)<u>C</u>OOH], 173.7 (-COOH), 74.7 [-<u>C</u>H(OH)COOH], 50.7 (C-3), 46.3, 42.7, 36.8. *Anal.* Found: C, 34.45; H, 4.87; N, 4.44%. Calcd. for $C_9H_{15}NO_9S$: C, 34.51; H, 4.83; N, 4.47%.

(1*S*, 3*R*)-TCA·SO·(*S*)-TA salt: yield, 4.07 g; mp 187–189°C (decomp.); $[\alpha]_D^{20}$ +0.90° (*c* 1.0, water). The ^{1}H- and ^{13}C-NMR spectra of the (1*S*, 3*R*)-TCA·SO·(*S*)-TA salt were virtually identical to those of the (1*R*, 3*S*)-TCA·SO·(*R*)-TA salt.

Rate constant for racemization. (*R*)-TCA (0.294 g, 2.00 mmol) and (*RS*)-TA (0.300 g, 2.00 mmol) were rapidly dissolved in acetic acid (100 cm^3) at 80°C. After adding salicylaldehyde (0.024 g, 0.20 mmol) to the solution while stirring at 80°C, 5 cm^3 portions of the solution were pipetted out at appropriate time intervals and rapidly cooled to room temperature. The optical rotation was then measured. The rate constant [k_R (s^{-1})] and half-life period were calculated by the least-squares method from

$$\ln \alpha_o / \alpha_t = k_R \cdot t,$$

where α_t is the optical rotation at time t (s) and α_o is the optical rotation extrapolated to time zero.

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