

Preparations of Optically Active Homocysteine and Homocystine by Asymmetric Transformation of (*RS*)-1,3-Thiazane-4-carboxylic Acid

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(Received August 11, 1992)

DL-Homocysteine [DL-Hcy] from (*RS*)-homocysteine thiolactone hydrochloride [(*RS*)-HTL·HCl] was subjected to reaction with formaldehyde in acetic acid to give (*RS*)-1,3-thiazane-4-carboxylic acid monohydrate [(*RS*)-THA·H₂O]. An asymmetric transformation of (*RS*)-THA·H₂O was achieved via salt formation with optically active tartaric acid in the presence of salicylaldehyde in acetic acid. The (*R*)- and (*S*)-THA obtained, respectively, from the salt of (*R*)-THA with (2*R*, 3*R*)-tartaric acid and its enantiomeric salt were treated with hydroxylamine hydrochloride to give D- and L-Hcy of 100% optical purity, respectively, in 50% yield from (*RS*)-HTL·HCl. Oxidation of D- and L-Hcy with hydrogen peroxide gave D- and L-homocystine, respectively, in 47% yield.

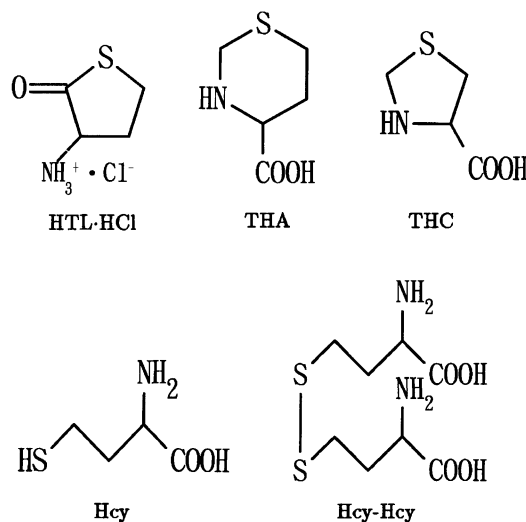
L-Homocysteine [abbreviated as L-Hcy] and L-homocystine [L-Hcy-Hcy] are not amino acids constituting proteins. L-Hcy, however, plays an important role as an intermediate product in the metabolic pathway converting L-methionine to L-cysteine *in vivo*.¹ Although optically active amino acids, such as cysteine [Cys] and cystine, are useful as chiral reagents in asymmetric syntheses, Hcy and Hcy-Hcy have not been studied as the chiral reagents because both D- and L-Hcy and Hcy-Hcy are not easily available in large quantity. D- and L-Hcy are obtained by treatment of corresponding enantiomers of homocysteine thiolactone hydrochloride [HTL·HCl], respectively, in aqueous solution of sodium hydroxide.² Although HTL is obtained by refluxing methionine in hydroiodic acid,³ the HTL hydroiodide obtained from L-methionine was the racemate. This paper, therefore, describes a possibility for efficiently obtaining optically active Hcy and Hcy-Hcy.

Although an optical resolution by diastereomeric procedure gives both enantiomers by a good choice of resolving agent, the yield does not theoretically go to over 50% of a starting racemate. On the other hand, an asymmetric transformation has been carried out in heterogeneous system by combination of selective crystallization of a less soluble diastereomeric salt with epimerization of a more soluble one in a solution and has a possibility for converting efficiently a racemate to a desired enantiomer. One of major problems in the asymmetric transformation is a choice of resolving agent. α -Amino acids, such as Hcy and Hcy-Hcy, do not form salts with ordinary carboxylic acids and amines. In addition, the salts of Hcy and Hcy-Hcy with (1*S*)-10-camphorsulfonic acid did not give the proper crystals. 4-Thiazolidinecarboxylic acid [THC] has been synthesized by reaction of Cys with formaldehyde^{4,5} and reported to regenerate Cys by treatment with hydroxylamine hydrochloride.^{5,6} We also reported the optical resolution and asymmetric transformation, by using aldehydes as catalysts, of (*RS*)-THC,^{5,7} DL-proline⁸ [DL-Pro], and (*RS*)-2-piperidinecarboxylic acid⁸ [(*RS*)-Pia] via salt

formation with (2*R*,3*R*)- or (2*S*,3*S*)-tartaric acid [(*R*)- or (*S*)-TA]. If optically active TA is used as a resolving agent in the asymmetric transformation, we can efficiently obtain both enantiomers because (*R*)- and (*S*)-TA are readily obtainable. (*RS*)-1,3-Thiazane-4-carboxylic acid [(*RS*)-THA] was synthesized by reacting DL-Hcy with formaldehyde to use as a racemic substance in the asymmetric transformation because (*RS*)-THA was also estimated to form a salt with TA.

Another problem in the asymmetric transformation is racemization rate of optically active substance. Optically active amino acids are easily racemized in the presence of catalytic aldehydes in carboxylic acids.^{9,10} In addition, optically active THA is estimated to be apt to be racemized by sulfur atom on a hetero ring similarly to the case of optically active THC.⁵

Based on the above suggestions, the asymmetric transformation of (*RS*)-THA was attempted by using (*R*)- and (*S*)-TA as resolving agents to obtain optically active Hcy and Hcy-Hcy (Scheme 1).



Scheme 1.

Results and Discussion

Racemization of Optically Active 1,3-Thiazane-4-carboxylic Acid. We reported that the racemization rate of optically active Pia with a six membered ring is extremely low even in the presence of aldehydes in carboxylic acids, though optically active Pro with a five membered ring is apt to racemize at 80°C.⁸⁾ Since THA has a six membered ring and THC a five membered one, the racemization rates of (*R*)-THA and (*R*)-THC were measured in the presence and absence of salicylaldehyde in acetic acid. The racemizations showed the first-order kinetics of

$$\ln \alpha_0 / \alpha_t = k_R \cdot t, \quad (1)$$

where α_t is the optical rotation at time t and α_0 that extrapolated to zero time. The rate constants (k_R/s^{-1}) and half-life periods ($t_{1/2}/s$) are summarized in Table 1.

Salicylaldehyde, as the catalyst, accelerates the racemization of (*R*)-THA. The acceleration, however, was not so dramatic as expected; the k_R value in the presence of salicylaldehyde was about 1.4 times that in the absence of the aldehyde. Although the k_R values of (*R*)-THA is about one fourth of those of (*R*)-THC, optically active THA is estimated to be racemized because (*R*)-THA is racemized only by heating in acetic acid. The above result, therefore, suggested a possibility of asymmetric transformation of (*RS*)-THA.

Asymmetric Transformation of (*RS*)-1,3-Thiazane-4-carboxylic Acid. As seen in Fig. 1,¹¹⁾ the asymmetric transformation of (*R*)-THC (20.0 mmol) into (*S*)-THC by use of (*R*)-TA was achieved only by heating to 110°C in 25 cm³ of propanoic acid to give (*S*)-THC of 94% optical purity in 75% yield from the (*S*)-THC·(*R*)-TA salts; the asymmetric transformation in acetic acid was not carried out because the formed salt dissolved at 80°C.

Next we attempted the asymmetric transformation of (*RS*)-THA·H₂O (10.0 mmol) at 80°C in 10 cm³ of acetic acid in the absence of salicylaldehyde; (*RS*)-THA·H₂O was used as the racemic substance because (*RS*)-THA was obtained as monohydrate from (*RS*)-HTL·HCl. The result is shown in Fig. 2; the yields were calculated on the basis of the starting (*RS*)-THA·H₂O.

The asymmetric transformation of (*RS*)-THA gave

Table 1. Kinetic Data for Racemization^{a)}

Compound	Salicylaldehyde mmol	k_R ^{b)} $10^{-5} s^{-1}$	$t_{1/2}$ ^{c)} $10^4 s$
(<i>R</i>)-THA	—	4.48	1.55
	0.34	6.17	1.12
(<i>R</i>)-THC	—	19.7	0.352
	0.34	25.7	0.270

a) Conditions: (*R*)-THA and (*R*)-THC 3.40 mmol; acetic acid 50 cm³; temperature 80°C. b) k_R : Racemization rate constant. c) $t_{1/2}$: Half-life period.

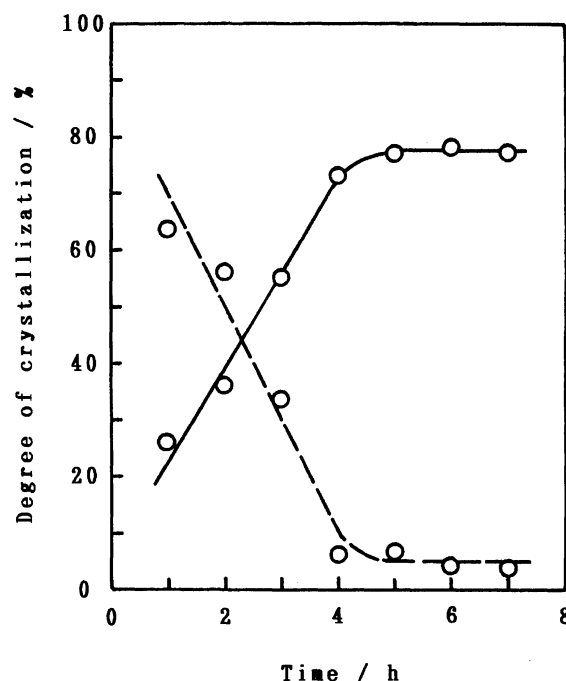


Fig. 1. Asymmetric transformation of (*R*)-4-thiazolidinecarboxylic acid into (*S*)-form. Conditions: (*R*)-THC 20.0 mmol; (*R*)-TA 20.0 mmol; propanoic acid 25 cm³; temperature 110°C. Degree of crystallization (see Ref. 11): — (*S*)-THC·(*R*)-TA salt; --- (*R*)-THC·(*R*)-TA salt.

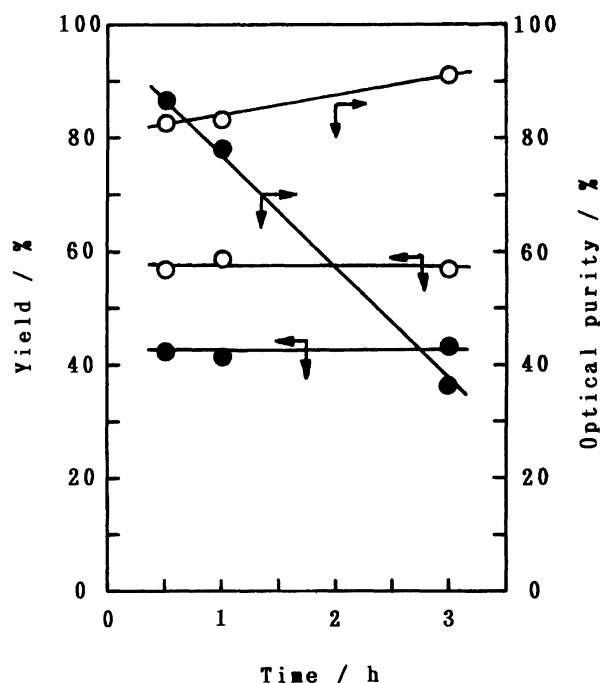


Fig. 2. Asymmetric transformation of (*RS*)-1,3-thiazane-4-carboxylic acid monohydrate in the absence of salicylaldehyde. Conditions: (*RS*)-THA·H₂O 10.0 mmol; (*R*)-TA 10.0 mmol; acetic acid 10 cm³; temperature 80°C. ○: The (*R*)-THA·(*R*)-TA salt crystallized from the reaction mixture. ●: The (*S*)-THA obtained from the filtrate.

the (*R*)-THA·(*R*)-TA salt, as the less soluble diastereomeric salt, in 56–58% yield and anhydrous (*S*)-THA was obtained in 41–43% yield from the filtrate after filtering off the (*R*)-THA·(*R*)-TA salt. The optical purity of the (*R*)-THA·(*R*)-TA salt increased gradually from 82% (0.5 h) to 91% (3 h) with the elapse of reaction time, whereas that of (*S*)-THA fell from 86% (0.5 h) to 36% (3 h). This result suggested that (*S*)-THA was also apt to be racemized in acetic acid. The yield of the (*R*)-THA·(*R*)-TA salt, however, was not so high as expected. Although the asymmetric transformation was also carried out by stirring for 3–7 h at 80°C in 2 cm³ of acetic acid, the (*R*)-THA·(*R*)-TA salts of 84–90% optical purity were obtained in low yield (51–56%). This poor result was seemed to be due to slower epimerization than that of THC.

The asymmetric transformation of (*RS*)-THA·H₂O by use of (*R*)- and (*S*)-TA, therefore, was carried out in the presence of an equimolar amount of salicylaldehyde at 80°C. The result is summarized in Table 2.

The asymmetric transformation gave the (*R*)-THA·(*R*)-TA and (*S*)-THA·(*S*)-TA salts of 87–99% optical purity in 85–90% yield for 4–9 h; (*R*)- and (*S*)-THA of 86–97% optical purity were obtained from these salts. In comparing the results in the absence and presence of salicylaldehyde, salicylaldehyde was estimated not only to accelerate the epimerization, but also to lower solubilities of the diastereomeric salts. The findings in the absence of salicylaldehyde, however, suggested that the resulting salt was easily purified by washing with acetic acid. (*R*)- and (*S*)-THA of 100% optical purity were obtained in 80% yield from the salts purified by this procedure.

Preparation of Optically Active Homocysteine and Homocystine. D- and L-Hcy and Hcy-Hcy were prepared from the (*R*)- and (*S*)-THA, which were obtained by the asymmetric transformation. The results are summarized in Table 3.

(*R*)- and (*S*)-THA gave D- and L-Hcy, respectively, in over 90% yields. Specific rotation of optically active Hcy has not been reported. The (*R*)-THA·(*R*)-TA salt, therefore, was subjected to repetition of purification by washing with acetic acid to obtain optically pure D-Hcy until the specific rotation revealed the constant value. Since the specific rotation of the *S*-benzyl-D-homocysteine obtained from the D-Hcy agreed with the specific rotation reported (Table 3), the specific rotation of D-Hcy was determined to be $[\alpha]_D^{20} - 26.8^\circ$ (*c* 1.00, 1 mol dm⁻³ HCl). Even when THA of 96 or 97% optical purity was used, treatment of the THA with hydroxylamine hydrochloride gave optically pure D- or L-Hcy.

Although oxidation of (*R*)-THA with hydrogen peroxide gave D-Hcy-Hcy of 100% optical purity in low yield (49%), D- and L-Hcy-Hcy were obtained from D- and L-Hcy, respectively, in 95% yield.

D- and L-Hcy and Hcy-Hcy were obtained in 50 and

47% yield, respectively, from (*RS*)-HTL·HCl.

Experimental

Materials. (*RS*)-HTL·HCl was purchased from Aldrich Chemicals Co., Ind., (*R*)-TA from Wako Pure Chemicals Ind., (*S*)-TA from Tokyo Kasei Kogyo Co., Ltd., and L-Cys from Kokusan Chemical Works, Ltd. (*R*)-THA was obtained by the asymmetric transformation and (*R*)-THC by reaction of L-Cys with formaldehyde in acetic acid;⁵⁾ $[\alpha]_D^{20} - 141^\circ$ (*c* 0.500, water); lit.⁴⁾ $[\alpha]_D^{20} - 141^\circ$ (water).

Preparation of (*RS*)-1,3-Thiazane-4-carboxylic Acid Monohydrate. After stirring a solution of (*RS*)-HTL·HCl 0.100 mol (15.4 g) and sodium hydroxide 0.30 mol (12 g) in 40 cm³ of water for 30 min at room temperature, the solution was adjusted to pH 6 by concentrated hydrochloric acid and then was evaporated to dryness under reduced pressure at 70°C; the residue was a mixture of sodium chloride and DL-Hcy.¹²⁾ To a mixture of the residue in 30 cm³ of acetic acid was added 8.7 cm³ of 37% aqueous formaldehyde; 8.7 cm³ of 37% aqueous formaldehyde correspond to 0.12 mol of formaldehyde. After stirring the mixture for 5 h at 45°C and cooling to 15°C, followed by removing sodium chloride by filtration, the filtrate was evaporated to dryness under reduced pressure. Acetic acid (30 cm³) was added to the syrupy residue to precipitate further sodium chloride. After removing sodium chloride by filtration, followed by evaporating acetic acid from the filtrate, 100 cm³ of ethanol was added to the residue to precipitate (*RS*)-THA·H₂O. Crude (*RS*)-THA·H₂O was collected by filtration and then was recrystallized from water.

(*RS*)-THA·H₂O: Yield 10.3 g (62.4%); mp 218–219°C (decomp). Found: C, 36.20; H, 6.69; N, 8.50%. Calcd for C₅H₁₁NO₃S: C, 36.35; H, 6.71; N, 8.48%.

Preparation of Standard Salt of (*R*)-1,3-Thiazane-4-carboxylic Acid with (2*R*, 3*R*)-Tartaric Acid. After stirring a suspension of 10.0 mmol (1.47 g) of (*R*)-THA and 10.0 mmol (1.50 g) of (*R*)-TA in 15 cm³ of acetic acid for 2 h at room temperature, the (*R*)-THA·(*R*)-TA salt formed was collected by filtration, washed with diethyl ether, and dried.

The (*R*)-THA·(*R*)-TA salt: Yield 2.68 g (90.2%); mp 188–191°C (decomp); $[\alpha]_D^{20} + 24.8^\circ$ (*c* 1.00, water). Found: C, 36.39; H, 5.11; N, 4.65%. Calcd for C₉H₁₅NO₈S: C, 36.36; H, 5.09; N, 4.71%.

The optical purities of the salts obtained by the asymmetric transformation were estimated on the basis of the specific rotation of the (*R*)-THA·(*R*)-TA salt and that ($[\alpha]_D^{20} + 9.4^\circ$ (*c* 1.00, water)) of the equimolar mixture of (*RS*)-THA and (*R*)-TA.

Asymmetric Transformation of (*RS*)-1,3-Thiazane-4-carboxylic Acid by Heating in Acetic Acid.

After stirring a mixture of 10.0 mmol (1.65 g) of (*RS*)-THA·H₂O and 10.0 mmol (1.50 g) of (*R*)-TA in 10 cm³ of acetic acid for 0.5–3 h at 80°C, followed by cooling to room temperature, the precipitated (*R*)-THA·(*R*)-TA salt was collected by filtration, washed with a small amount of acetic acid and diethyl ether, and dried. On the other hand, the filtrate, after filtering off the (*R*)-THA·(*R*)-TA salt, was evaporated to dryness under reduced pressure. After adding 10 cm³ of ethanol to the syrupy residue, followed by stirring the mixture for 15 min at room temperature, (*S*)-THA was collected by filtration, washed with ethanol, and dried.

Table 2. Asymmetric Transformation of (*RS*)-1,3-Thiazane-4-carboxylic Acid^{a)}

Reaction time h	Configura- tion of TA	Salt obtained			THA obtained		
		Yield g[% ^{b)}]	Specific rotation ^{c)} °	Optical purity %	Configu- ration	Yield ^{d)} %	Optical purity %
0.5	(<i>R</i>)	1.84 [61.7]	+15.4	38.8	(<i>R</i>)	61.5	38.2
1	(<i>R</i>)	2.06 [69.1]	+19.4	64.9	(<i>R</i>)	68.2	66.8
2	(<i>R</i>)	2.31 [77.5]	+19.9	68.2	(<i>R</i>)	76.8	70.2
3	(<i>R</i>)	2.64 [88.6]	+21.9	81.2	(<i>R</i>)	88.3	81.7
4	(<i>R</i>)	2.55 [85.6]	+23.2	89.6	(<i>R</i>)	85.4	89.9
5	(<i>R</i>)	2.69 [89.6]	+23.8	93.5	(<i>R</i>)	88.9	95.0
6	(<i>R</i>)	2.67 [89.6]	+23.5	91.6	(<i>R</i>)	88.3	91.9
6 ^{e)}	(<i>R</i>)	2.41 [80.9]	+24.8	100	(<i>R</i>)	78.5	100
7	(<i>R</i>)	2.67 [89.6]	+23.3	90.3	(<i>R</i>)	87.9	90.7
9	(<i>R</i>)	2.64 [89.0]	+24.4	97.4	(<i>R</i>)	88.0	96.9
9 ^{e)}	(<i>R</i>)	2.50 [83.9]	+24.8	100	(<i>R</i>)	81.0	100
4	(<i>S</i>)	2.62 [87.9]	−22.9	87.7	(<i>S</i>)	86.4	86.6
5	(<i>S</i>)	2.63 [88.3]	−22.9	87.6	(<i>S</i>)	87.2	89.3
6	(<i>S</i>)	2.60 [87.2]	−24.6	98.7	(<i>S</i>)	86.5	96.5
6 ^{e)}	(<i>S</i>)	2.47 [82.9]	−24.8	100	(<i>S</i>)	80.2	100
9	(<i>S</i>)	2.62 [88.0]	−24.0	94.8	(<i>S</i>)	87.1	95.8

a) Conditions: (*RS*)-THA·H₂O 10.0 mmol; TA 10.0 mmol; salicylaldehyde 10.0 mmol; acetic acid 2.3 cm³; temperature 80°C.

b) The yield was calculated on the basis of 10.0 mmol (2.98 g) of the salt of THA with TA. c) $[\alpha]_D^{20}$ (c 1.00, water). d) The yield was calculated on the basis of 10.0 mmol (1.47 g) of THA. e) The obtained salt was purified by washing with acetic acid.

Table 3. Preparation of Optically Active Homocysteine and Homocystine

Starting material [Optical purity/%]	Product		
	Compound	Yield ^{a)} %	Specific rotation ^{b)} °
(<i>R</i>)-THA [96.9]	D-Hcy	91.5	−26.8
(<i>R</i>)-THA [100]	D-Hcy	92.6	−26.8
(<i>S</i>)-THA [95.8]	L-Hcy	89.6	+26.8
(<i>S</i>)-THA [100]	L-Hcy	91.9	+26.8
D-Hcy [100]	D-BzHcy ^{c)}	81.2	−27.2 ^{d)}
D-Hcy [100]	D-Hcy-Hcy	95.5	−76.9
(<i>R</i>)-THA [100]	D-Hcy-Hcy	49.0	−77.1
L-Hcy [100]	L-Hcy-Hcy	95.7	+77.1

a) The yield was calculated on the basis of the starting material. b) $[\alpha]_D^{20}$ (c 1.00, 1 mol dm^{−3} HCl). c) D-BzHcy: *S*-Benzyl-D-homocysteine. d) $[\alpha]_D^{20}$ (c 2.00, 2 mol dm^{−3} HCl).

Asymmetric Transformation of (*RS*)-1,3-Thiazane-4-carboxylic Acid in the Presence of Salicylaldehyde.

To a mixture of 10.0 mmol (1.65 g) of (*RS*)-THA·H₂O and 10.0 mmol (1.50 g) of (*R*)- or (*S*)-TA in 2.3 cm³ of acetic acid was added 10.0 mmol (1.22 g) of salicylaldehyde at 80°C. After stirring the mixture for 1–9 h at 80°C and then for 1 h at room temperature, the resulting (*R*)-THA·(*R*)-TA or (*S*)-THA·(*S*)-TA salt was collected by filtration, washed with 1 cm³ of acetic acid and thoroughly with diethyl ether, and dried. The (*R*)-THA·(*R*)-TA or (*S*)-THA·(*S*)-TA salt of over 90% optical purity was stirred for 2 h at 80°C in acetic acid (5 cm³ g^{−1}) and then the suspension was cooled to room temperature. The salt was collected by filtration, washed with a small amount of methanol, and

dried.

To a suspension of the salt in ethanol (4 cm³ g^{−1}) was added equimolar amount of triethylamine. After stirring the mixture for 1 h at room temperature and then for 0.5 h in an ice bath, the anhydrous (*R*)- or (*S*)-THA liberated was collected by filtration, washed with a small amount of methanol, and dried.

(*R*)-THA of 100% optical purity: Mp 275–277°C (decomp); $[\alpha]_D^{20} +12.5^\circ$ (c 1.00, 1 mol dm^{−3} HCl). Found: C, 40.55; H, 6.21; N, 9.53%. Calcd for C₅H₉NO₂S: C, 40.80; H, 6.16; N, 9.52.

(*S*)-THA of 100% optical purity: Mp 275–278°C (decomp); $[\alpha]_D^{20} -12.5^\circ$ (c 1.00, 1 mol dm^{−3} HCl); lit.¹²⁾ $[\alpha]_D^{27} -12.5^\circ$ (c 1%, 1 mol dm^{−3} HCl). Found: C, 40.59; H, 6.29; N, 9.34%.

Preparation of Optically Active Homocysteine.

After adding 5 cm³ of ethanol solution of hydroxylamine hydrochloride (0.4 mol dm^{−3}) under refluxing to a suspension of 10.0 mmol (1.47 g) of (*R*)- or (*S*)-THA in 50 cm³ of ethanol, five portions of triethylamine (2 mmol) and four portions of the ethanol solution of hydroxylamine hydrochloride (5 cm³) were alternately added to the resulted solution at 10 min intervals to keep pH of the solution to 8. After further refluxing the mixture for 1 h, the solution was adjusted to pH 6 with triethylamine and then the mixture was cooled to room temperature. The precipitated D- or L-Hcy was collected by filtration, washed with a small amount of ethanol, and dried.

D-Hcy: Yield 1.25 g (92.6%); mp 246–249°C (decomp); $[\alpha]_D^{20} -26.8^\circ$ (c 1.00, 1 mol dm^{−3} HCl). Found: C, 35.29; H, 6.75; N, 10.38%. Calcd for C₄H₉NO₂S: C, 35.54; H, 6.71; N, 10.36%.

L-Hcy: Yield 1.24 g (91.9%); mp 245–247°C (decomp); $[\alpha]_D^{20} +26.8^\circ$ (c 1.00, 1 mol dm^{−3} HCl).

To a solution of D-Hcy (5.00 mmol, 0.676 g) of 100% optical purity in 5 cm³ of 1 mol dm⁻³ aqueous sodium hydroxide was gradually added 5.00 mmol (0.633 g) of benzyl chloride in an ice bath. After stirring the solution for 2 h in an ice bath, the precipitated *S*-benzyl-D-homocysteine was collected by filtration, washed with 5 cm³ of cold methanol, and dried.

S-Benzyl-D-homocysteine: Yield 0.918 g (81.2%); mp 250–252°C (decomp); lit.¹³ of D-form, mp 247–252°C; lit.¹⁴ of L-form, mp 210–211°C, 244–246°C (decomp); $[\alpha]_D^{20} - 27.2^\circ$ (*c* 2.00, 2 mol dm⁻³ HCl); lit.¹⁴ of L-form, $[\alpha]_D^{26} + 27.2^\circ$ (*c* 2, 2 mol dm⁻³ HCl). Found: C, 57.43; H, 6.72; N, 6.39%. Calcd for C₁₁H₁₅NO₂S: C, 58.64; H, 6.71; N, 6.22%.

Preparation of Optically Active Homocystine. A solution of 7.40 mmol (1.00 g) of optically pure D- or L-Hcy and 0.74 cm³ of 30 wt% hydrogen peroxide in 5 cm³ of water was stirred for 8 h in an ice bath. The precipitated D- or L-Hcy-Hcy was collected by filtration, washed with a small amount of cold water, and dried. After concentrating the filtrate to 3 cm³, followed by standing for 1 d at 5 °C, the precipitated D- or L-Hcy-Hcy further was filtered.

D-Hcy-Hcy: Yield 0.948 g (95.5%); mp 281–285°C (decomp); lit.¹⁵ mp 281–283°C (decomp); $[\alpha]_D^{20} - 76.9^\circ$ (*c* 1.00, 1 mol dm⁻³ HCl); lit.¹⁵ $[\alpha]_D^{26} - 77^\circ$ (1 mol dm⁻³ HCl). Found: C, 35.51; H, 5.88; N, 10.50%. Calcd for C₈H₁₆N₂O₄S₂: C, 35.81; H, 6.01; N, 10.50%.

L-Hcy-Hcy: Yield 0.950 g (95.7 %); mp 282–285°C (decomp); lit.¹⁵ mp 281–284°C (decomp); $[\alpha]_D^{20} + 77.1^\circ$ (*c* 1.00, 1 mol dm⁻³ HCl); lit.¹⁵ $[\alpha]_D^{26} + 77^\circ$ (*c* 1, 1 mol dm⁻³ HCl).

D-Hcy-Hcy was also prepared by oxidation of 10.0 mmol (1.47 g) of (*R*)-THA with 1.0 cm³ of hydrogen peroxide in 10 cm³ of water.

D-Hcy-Hcy: Yield 0.657 g (49.0%); mp 282–284°C (decomp); $[\alpha]_D^{20} - 77.1^\circ$ (*c* 1.00, 1 mol dm⁻³ HCl).

Asymmetric Transformation of (*R*)-4-Thiazolidinecarboxylic Acid into (*S*)-4-Thiazolidinecarboxylic Acid. A mixture of 20.0 mmol (2.66 g) of (*R*)-THC and 20.0 mmol (3.00 g) of (*R*)-TA in 25 cm³ of propanoic acid was stirred for 2–7 h at 110°C. After stirring the mixture for 20 min in an ice bath, the (*S*)-THC·(*R*)-TA salt was collected by filtration, washed with diethyl ether, and dried. The (*S*)-THC·(*R*)-TA salt was stirred for 1 h at room temperature in methanol (40 cm³ g⁻¹) and then the liberated (*S*)-THC was collected by filtration, washed with methanol, and dried.

Racemization Rate. (*R*)-THA or (*R*)-THC (3.40 mmol) was dissolved in 50 cm³ of acetic acid at 80°C. Af-

ter adding 0.34 mmol of salicylaldehyde to the solution with stirring at 80°C, five cm³ portions of the solution were pipetted out at an appropriate time intervals and rapidly cooled to room temperature. The optical rotations at 589 nm were measured by a Horiba Seisakusho SEPA-200 auto polarimeter with a quartz cell of 5.00 cm path length. The rate constant and half-life period were calculated by the least-squares method from Eq. 1. The racemization rates of (*R*)-THA and (*R*)-THC were similarly measured in the absence of salicylaldehyde at 80°C.

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$$DC_{(R)}/\% = (1/2)[\text{Yield}/\% \times (100 - OP/\%)]/100,$$

$$DC_{(S)}/\% = \text{Yield}/\% - DC_{(R)}/\%,$$
 where *OP* is optical purity.
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