Facile Preparation of Four Stereoisomers of 2,4-Thiazolidinedicarboxylic Acid

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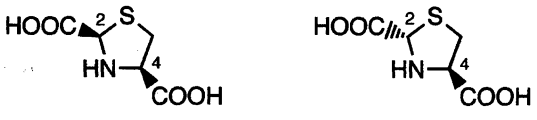
(2*R*,4*R*)-2,4-Thiazolidinedicarboxylic acid [(2*R*,4*R*)-TDA] was diastereoselectively synthesized in 100% *de* by condensation of L-cysteine (L-Cys) with an equimolar amount of glyoxylic acid monohydrate (GLA·H_2O) in acetic acid under reflux. The reaction employing a slight excess of GLA·H_2O afforded (2*S*,4*R*)-TDA, as a single diastereomer, at 80 °C. (2*S*,4*R*)-TDA was also synthesized by reaction of L-Cys with dichloroacetic acid under alkaline conditions. These reactions starting with D-Cys yielded (2*S*,4*S*)- and (2*R*,4*S*)-TDA.

Some 2-substituted 4-thiazolidinecarboxylic acids can be produced in vivo and may be of biological significance. Of such 4-thiazolidinecarboxylic acid derivatives, (4*R*)-2,4-thiazolidinedicarboxylic acid [(4*R*)-TDA] has been reported to be a hepatoprotective drug[1] and is known to be an excellent substrate for D-aspartate oxidase.[2] Further, L-cysteine (L-Cys) decreases oxalate production, which is a prime factor in formation of calcium oxalate stones, from glycollate via (4*R*)-TDA formation.[3] (4*R*)-TDA is obtained as mixture of two diastereomers, (2*R*,4*R*)-TDA (*cis*-form) and (2*S*,4*R*)-TDA (*trans*-form) (Scheme 1), by condensation of L-Cys with glyoxylic acid.[2—4] Although TDA exists as four stereoisomers, only (2*R*,4*R*)-TDA has been synthesized as a single diastereomer.[3] 2-Substituted 4-thiazolidinecarboxylic acids such as TDA are known to be subject to epimerization at the C-2 position in aqueous solutions under acidic, basic, and neutral conditions, but not in dimethyl sulfoxide (DMSO) solution.[3—7] The epimerization at the C-2 position has been explained by interconversion between the two diastereomers via a ring opening intermediate according to Scheme 2.[4—7]



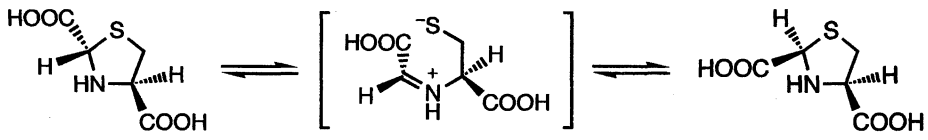
(2*R*,4*R*)-TDA **(2*S*,4*R*)-TDA**

Scheme 1. Structures of (2*R*,4*R*)- and (2*S*,4*R*)-2,4-thiazolidinedicarboxylic acids [(2*R*,4*R*)- and (2*S*,4*R*)-TDA].

Therefore, we first attempted to diastereoselectively synthesize thermodynamically stable TDA, as a single diastereomer, by reaction of L-Cys with glyoxylic acid monohydrate (GLA·H_2O) at an elevated temperature.

(*R*)-4-Thiazolidinecarboxylic acid has been synthesized by condensation of L-Cys with formaldehyde in acetic acid, as described in our previous paper.[8] Therefore, TDA was synthesized by reacting L-Cys with an equimolar amount of GLA·H_2O in acetic acid at 30—100 °C and under reflux (110 °C) for 2 h under heterogeneous conditions. The results are shown in Fig. 1. The specific rotation and ^{1}H NMR and ^{13}C NMR spectra of the obtained TDA were measured in DMSO and DMSO-d_6, respectively.

The specific rotations of the TDA obtained at 30—70 °C decreased with increase in temperature, whereas the TDA at 80—110 °C showed approximately constant specific rotation (about −180°). In the ^{1}H NMR spectrum of the mixture of (2*R*,4*R*)- and (2*S*,4*R*)-TDA, methine protons at the C-2 positions appeared at 5.00 and 4.85 ppm, respectively.[3,4] When the reaction was carried out at 30—70 °C, the intensity of the methine proton observed at 4.88 ppm decreased with increasing reaction temperature, whereas that at 4.99 ppm increased. The intensity ratios of the methine protons suggested that (2*S*,4*R*)-TDA was obtained in 12% *de* at 30 °C and (2*R*,4*R*)-TDA in 20% *de* at 70 °C. The TDA obtained under reflux (110 °C) did not show any proton signals due to (2*S*,4*R*)-TDA and showed ^{1}H NMR, ^{13}C NMR, and IR spectra identical to those of authentic (2*R*,4*R*)-TDA;[3,4] the ^{1}H NMR spectra of the TDA obtained at 80—100 °C



Scheme 2. Epimerization in aqueous solutions under acidic, neutral, and basic conditions.

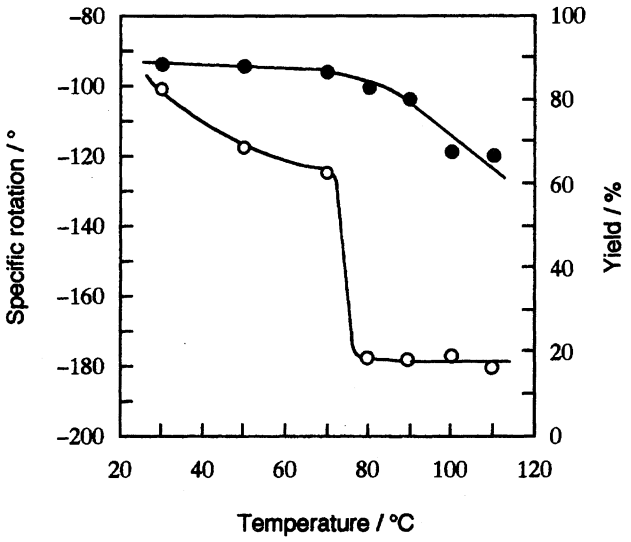


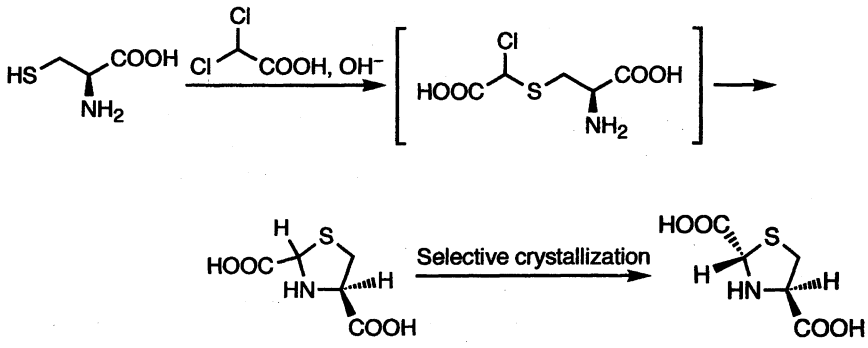
Fig. 1. Synthesis of 2,4-thiazolidinedicarboxylic acid by reaction of L-cysteine with glyoxylic acid. Conditions: L-Cys 20.0 mmol; GLA·H_2O 20.0 mmol; acetic acid 40 cm^3; temperature 30—110 °C; reaction period 2 h. ○: Specific rotation; $[\alpha]_D^{20}$ (*c* 1.00, DMSO). ●: Yield.

showed the presence of a small amount of (2*S*,4*R*)-TDA. These results indicated that the reaction under reflux (110 °C) diastereoselectively yielded (2*R*,4*R*)-TDA in 100% *de* with a yield of 66%; $[\alpha]_D^{20}$ −180° (*c* 1.00, DMSO). (2*S*,4*S*)-TDA was also obtained by the condensation of D-Cys and GLA·H_2O in 100% *de* with a yield of 66%, in a manner similar to that of (2*R*,4*R*)-TDA; $[\alpha]_D^{20}$ +180° (*c* 1.00, DMSO). We estimated from the above results that the reactions at 80—110 °C proceeded under thermodynamic control to afford thermodynamically stable (2*R*,4*R*)- and (2*S*,4*S*)-TDA.

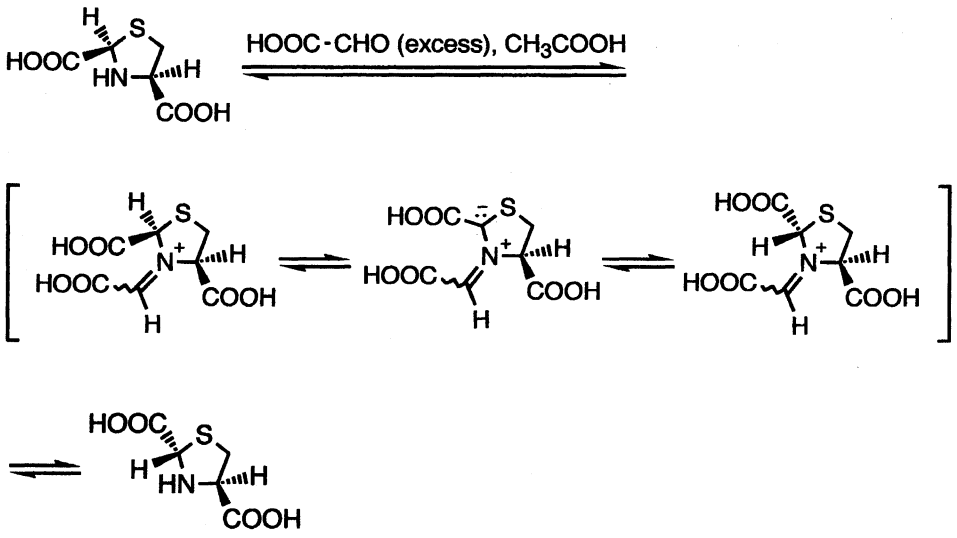
Next, we attempted to synthesize TDA by intramolecular condensation of 2-amino-3-[(carboxychloromethyl)thio]-propanoic acid (ACC). In order to synthesize ACC as a diastereomer mixture, followed by obtaining both diastereomers by separation from the mixture, L-Cys was reacted with dichloroacetic acid in aqueous sodium hydroxide. However, ACC was not obtained and TDA was crystallized from the reaction solution. The obtained TDA was washed with water to remove small amounts of sodium chloride; yield 12.6%; $[\alpha]_D^{20}$ −37.2° (*c* 1.00, DMSO). In its ^{1}H NMR spectrum, proton signals due to (2*S*,4*R*)-TDA were observed, but not those of (2*R*,4*R*)-TDA. In addition, the obtained TDA showed a ^{13}C NMR spectrum identical to that of (2*S*,4*R*)-TDA; the spectrum of a mixture of (2*R*,4*R*)- and (2*S*,4*R*)-TDA was measured and the signals due to (2*S*,4*R*)-TDA were assigned.[4] Therefore, the ^{1}H NMR and ^{13}C NMR spectra indicated that the TDA sample obtained here was the single diastereomer, (2*S*,4*R*)-TDA. The formation of the unexpected (2*S*,4*R*)-TDA can be explained as follows: The ACC formed as a mixture of two diastereomers immediately underwent intramolecular condensation to give TDA and then (2*S*,4*R*)-TDA was selectively crystallized as a less soluble diastereomer, as shown in Scheme 3. (2*R*,4*S*)-TDA was also synthesized starting with D-Cys in 12.1% yield, in a manner similar to that of (2*S*,4*R*)-TDA; $[\alpha]_D^{20}$ +37.2° (*c* 1.00, DMSO). To our knowledge, these are the first syntheses of optically pure (2*S*,4*R*)- and (2*R*,4*S*)-TDA, though the reactions did not give satisfactory yields.

The results described above indicate that (2*S*,4*R*)- and (2*R*,4*S*)-TDA are less soluble diastereomers and (2*R*,4*R*)- and (2*S*,4*S*)-TDA are more soluble ones. Therefore, if (2*R*,4*R*)- and (2*S*,4*S*)-TDA are subject to selective epimerization at the C-2 positions, but not at the C-4 positions, (2*S*,4*R*)- and (2*R*,4*S*)-TDA are selectively crystallized by asymmetric transformation of (2*R*,4*R*)- and (2*S*,4*S*)-TDA, respectively. Therefore, we further attempted to obtain (2*S*,4*R*)- and (2*R*,4*S*)-TDA by asymmetric transformation. Carbonyl compounds accelerate racemization at α-position of optically active α-amino acids in carboxylic acid, such as acetic acid, via Schiff base formation.[8—11] Therefore, asymmetric transformation was performed by reacting 20.0 mmol of L-Cys with 24.0 mmol of GLA·H_2O in acetic acid at 80 °C, because excess GLA·H_2O was expected to act as the epimerization catalyst. The results are shown in Fig. 2.

The specific rotation of the TDA obtained at 0.5—4 h increased with reaction time and the TDA obtained at 5—7 h showed an approximately constant value (about −40°). The ^{1}H NMR spectra of the TDA obtained at 5 and 6 h showed the presence of small amounts of (2*R*,4*R*)-TDA. The specific rotation of the TDA obtained at 7 h agreed with that of the (2*S*,4*R*)-TDA obtained by reaction of L-Cys with dichloroacetic acid; $[\alpha]_D^{20}$ −37.2° (*c* 1.00, DMSO). In addition, the ^{1}H NMR, ^{13}C NMR, and IR spectra were identical to those



Scheme 3. Synthesis of (2*S*,4*R*)-2,4-thiazolidinedicarboxylic acid by reaction of L-cysteine with dichloroacetic acid under basic conditions.



Scheme 4. Epimerization in the presence of excess glyoxylic acid.

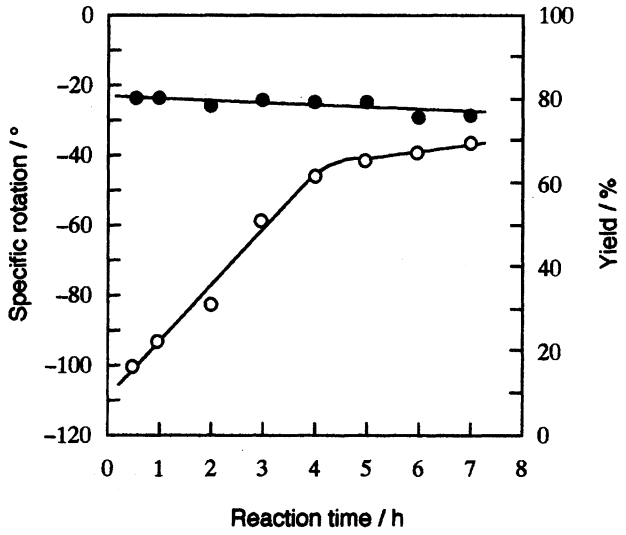


Fig. 2. Preparation of (2*S*,4*R*)-2,4-thiazolidinedicarboxylic acid by asymmetric transformation. Conditions: L-Cys 20.0 mmol; GLA·H_2O 24.0 mmol; acetic acid 40 cm^3; temperature 80 °C; reaction period 0.5—7 h. ○: Specific rotation; $[\alpha]_D^{20}$ (*c* 1.00, DMSO). ●: Yield.

of (2*S*,4*R*)-TDA obtained by reaction of L-Cys with dichloroacetic acid, respectively. Therefore, we concluded that TDA was subject to selective epimerization only at the C-2 position by excess GLA·H_2O to give (2*S*,4*R*)-TDA, as the single diastereomer, in 76% yield by asymmetric transformation for 7 h. (2*R*,4*S*)-TDA in 100% *de* was also obtained from D-Cys in 75% yield, in a manner similar to that described above; $[\alpha]_D^{20}$ +37.2° (*c* 1.00, DMSO).

In this study, four stereoisomers of TDA were diastereoselectively synthesized by reacting D- and L-Cys with equimolar and 1.2 molar amounts of GLA·H_2O in acetic acid. When an equimolar amount of GLA·H_2O was employed, the formed TDA was subject to epimerization at the C-2 position by interconversion between the two diastereomers via a ring opening intermediate[4—7] and thermodynamically stable (2*R*, 4*R*)- and (2*S*,4*S*)-TDA were diastereoselectively yielded at over 80 °C because of the reaction under thermodynamic control. On the other hand, when 1.2 molar amount of GLA·H_2O was employed, epimerization at the C-2 position was estimated to proceed without ring opening and by the same mechanism as racemization of cyclic α-amino acids, such as L-proline,[9] as shown in Scheme 4. Therefore, (2*R*, 4*R*)- and (2*S*,4*S*)-TDA, which are thermodynamically stable forms, are easily transformed into (2*S*,4*R*)- and (2*R*,4*S*)-TDA via formation of Schiff bases with excess GLA·H_2O, respectively, and (2*S*,4*R*)- and (2*R*,4*S*)-TDA are selectively crystallized as less soluble diastereomers.

Experimental

General. Specific rotations were measured at 589 nm with a Horiba Seisakusho SEPA-300 auto polarimeter equipped with a quartz cell with 5.00 cm path length. Infrared 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. ^1H NMR and ^{13}C NMR spectra were recorded on a JNM-FX270 FT NMR System and tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are reported in δ units downfield from TMS.

L-Cys was purchased from Kokusan Chemical Works, Ltd. D-Cys was prepared from L-Cys by asymmetric transformation via formation of a salt of 2,2,-dimethyl-4-thiazolidinecarboxylic acid with (2*R*,3*R*)-tartaric acid;[5] $[\alpha]_D^{20}$ −6.50° (*c* 2.00, 5 mol dm^{-3} HCl). Found: C, 29.77; H, 5.82; N, 11.47%. Calcd for $C_3H_7NO_2S$: C, 29.74; H, 5.82; N, 11.56%.

(2*R*,4*R*)- and (2*S*,4*S*)-2,4-Thiazolidinedicarboxylic Acid. A mixture of L-Cys (2.42 g, 20.0 mmol) and GLA·H_2O (1.84 g, 20.0 mmol) in 40 cm^3 of acetic acid was stirred for 2 h at 30—100 °C and under reflux (110 °C). After cooling the reaction mixture to room temperature, the formed TDA was collected by filtration and then stirred for 1 h in 200 cm^3 of ethanol at room temperature. TDA was filtered off, washed with diethy ether, and dried. (2*R*,4*R*)-TDA was obtained in 100% *de* under reflux and (2*S*,4*S*)-TDA from D-Cys.

TDA obtained at 80 °C; Yield 2.95 g (83.3%); mp 185—186 °C (decomp); $[\alpha]_D^{20}$ −178° (*c* 1.00, DMSO). Found: C, 33.95; H, 3.99; N, 7.87%. Calcd for $C_5H_7NO_4S$: C, 33.89; H, 3.98; N, 7.91%.

(2*R*,4*R*)-TDA obtained under reflux: Yield 2.34 g (66.1%); mp 186—187 °C (decomp) (lit,[4] 186 °C (decomp)); $[\alpha]_D^{20}$ −180° (*c* 1.00, DMSO). Found: C, 34.00; H, 4.06; N, 7.88%. IR (KBr) 3140, 2995, 1694, 1542, 1335, 1139, 1027, and 798 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ =4.99 (1H, s), 4.22 (1H, t, J=6.3 Hz), 3.14 (1H, dd, J=6.6, 9.9 Hz), 2.91 (1H, dd, J=5.9, 9.9 Hz). ^{13}C NMR (270 MHz, DMSO-d_6) δ = 172.3 (4-COOH), 172.2 (2-COOH), 65.6 (C-2), 65.5 (C-4), 37.1 (C-5).

(2*S*,4*S*)-TDA obtained under reflux: Yield 2.34 g (66.1%); mp 186—187 °C (decomp); $[\alpha]_D^{20}$ +180° (*c* 1.00, DMSO). Found: C, 33.78; H, 3.85; N, 7.95%. The IR, ^1H NMR, and ^{13}C NMR spectra were virtually identical to those of (2*R*,4*R*)-TDA.

(2*S*,4*R*)- and (2*R*,4*S*)-2,4-Thiazolidinedicarboxylic Acid. A solution of L-Cys (6.06 g, 50.0 mmol) in 5 mol dm^{-3} aqueous sodium hydroxide (70 cm^3) was added dropwise to a solution of dichloroacetic acid (6.45 g, 50.0 mmol) in water (10 cm^3) over a period of 1 h in an ice bath. After stirring the mixture for 1.5 h at 20 °C, 5 mol dm^{-3} hydrochloric acid (80 cm^3) was added to the mixture in an ice bath, followed by stirring the solution for 5 h in an ice bath. The precipitated (2*S*,4*R*)-TDA was collected by filtration, washed with diethyl ether, and dried; yield 1.74 g (19.6%); $[\alpha]_D^{20}$ −34.6° (*c* 1.00, DMSO). The obtained (2*S*,4*R*)-TDA was purified by stirring in 40 cm^3 of water for 30 min at 40 °C. (2*R*,4*S*)-TDA was obtained from D-Cys, in a manner similar to that used for (2*S*, 4*R*)-TDA.

(2*S*,4*R*)-TDA: Yield 1.12 g (12.6%); mp 188—190 °C (decomp); $[\alpha]_D^{20}$ −37.2° (*c* 1.00, DMSO). Found: C, 33.70; H, 3.83; N, 7.77%. IR (KBr) 3047, 2965, 1718, 1612, 1524, 1414, 1328, 1273, 1214, 1065, 947, 839, 806, 739, and 493 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ = 4.88 (1H, s), 3.81 (1H, dd, J = 6.3, 9.6 Hz), 3.30 (1H, dd, J = 6.4, 10.1 Hz), 2.72 (1H, t, J = 9.7 Hz). ^{13}C NMR (270 MHz, DMSO-d_6) δ = 171.8 (4-COOH), 171.7 (2-COOH), 65.8 (C-2), 64.8 (C-4), 37.4 (C-5).

(2*R*,4*S*)-TDA: Yield 1.07 g (12.1%); mp 188—190 °C (decomp); $[\alpha]_D^{20}$ +37.2° (*c* 1.00, DMSO). Found: C, 33.62; H, 3.84; N, 7.86%. The IR, ^1H NMR, and ^{13}C NMR spectra were virtually identical to those of (2*S*,4*R*)-TDA.

Asymmetric Transformation. A mixture of L-Cys (2.42 g, 20.0 mmol) and GLA·H_2O (2.21 g, 24.0 mmol) in 40 cm^3 of acetic acid was stirred for 0.5—7 h at 80 °C. After the reaction mixture was cooled to room temperature, the formed (2*S*,4*R*)-TDA was collected by filtration and then stirred for 1 h in 200 cm^3 of ethanol at room temperature. (2*S*,4*R*)-TDA was filtered off, washed with diethy ether, and dried. (2*R*,4*S*)-TDA was obtained from D-Cys by reacting for 7 h at 80 °C, in a manner similar to that used for (2*S*, 4*R*)-TDA.

(2*S*,4*R*)-TDA: Yield 2.70 g (76.3%); mp 188—190 °C (decomp); $[\alpha]_D^{20}$ −37.2° (*c* 1.00, DMSO). Found: C, 33.97; H, 4.04; N, 7.86%. The IR, ^1H NMR, and ^{13}C NMR spectra were virtually identical to those of (2*S*,4*R*)-TDA obtained by reaction of L-Cys with dichloroacetic acid.

(2*R*,4*S*)-TDA: Yield 2.67 g (75.4%); mp 188—190 °C (decomp); $[\alpha]_D^{20}$ +37.2° (*c* 1.00, DMSO). Found: C, 33.98; H, 4.03; N, 7.84%. The IR, ^1H NMR, and ^{13}C NMR spectra were virtually identical to those of (2*S*,4*R*)-TDA obtained by reaction of L-Cys with dichloroacetic acid.

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