Epimerization at C-2 of 2-Substituted Thiazolidine-4-carboxylic Acids

H. T. Nagasawa, D. J. W. Goon and F. N. Shirota

Medical Research Laboratories, Veterans Administration Medical Center and the Department of Medicinal Chemistry, University of Minnesota, Minneapolis, Minnesota 55417

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2(*R,S*)-5,5-Trimethylthiazolidine-4-(*S*)-carboxylic acid (**1a**), with a 3.3 to 1 predominance of the 2*S* (*cis*) isomer, was shown to epimerize at the C-2 position in neutral, protic solvents. This was manifested by mutarotation concomitant to changes in the ratios of the C-4 methine proton resonances in the nmr spectrum. Compound **1a** was stable in dilute sodium carbonate solution, but underwent rapid equilibration in 1*N* hydrochloric acid.

Acetylation of **1a** gave an acetyl derivative (**2a**) with exclusively 2*S*,4*S* stereochemistry. Chiral integrity at C-2 was proved by conversion of both **2a** and its enantiomer **2b** *via* their munchnone derivatives to enantiomeric dimethyl 1,1,3,5-tetramethyl-1*H*,2*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylates (**4a** and **4b**).

Acetylation of 2-(*R,S*)-phenyl-5,5-dimethylthiazolidine-4(*S*)-carboxylic acid, afforded both the 2*S*,4*S* (**6a**) and 2*R*,4*S* (**6b**) epimers. Epimerization of **6a** at C-4 gave the 2*S*,4*R* isomer (**6c**) which was enantiomeric with **6b**.

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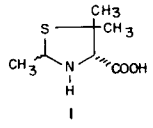
Although thiazolidine-4-carboxylic acids derived from the condensation of aldehydes and/or ketones with the naturally-occurring chiral amino acid, L-cysteine, have been known for some time (1), the stereochemistry of the 2-substituent relative to the 4-carboxyl group has been totally neglected until only recently (2). The observation that these thiazolidine-4-carboxylic acids can be produced *in vivo*, (3,4) underscores their growing biological importance, thus mandating a detailed knowledge of their stereochemistry.

As the chiral α-position of the sulfhydryl amino acid is unaffected during this condensation, the absolute chirality at the C-2 position of the formed 2-substituted thiazolidine-4-carboxylic acid has been assigned on the basis of ^{1}H-nmr measurements by relating it to the known chirality at C-4 (2a-c,4). In these studies, the stability of the C-2 position in solution has been tacitly assumed, and the compounds have generally been purified by recrystallizations, often from protic solvents such as ethanol. Occasionally, the thiazolidine-4-carboxylic acids have been converted to the more stable *N*-acyl derivatives for stereochemical analysis (6,2a).

While investigating the apparent stereoselectivity at C-2 in the formation of 2-substituted thiazolidine-4-carboxylic acids (3b), we have observed that these compounds mutarotate in water or methanol solutions at room temperature, suggesting that this C-2 position can epimerize in neutral, protic solvents. That such epimerizations can take place at elevated *p*H or at elevated temperatures has been shown by Carroll, *et al.* (5), who observed that a *trans*-thiazolidine-4-carboxylic acid (penicic acid) obtained by solvolysis of the β-lactam ring of 6-aminopenicillanic acid was rapidly converted to the C-2 *cis* epimer under these conditions.

Results.

When D(−)penicillamine and a slight excess of acetaldehyde were condensed in an aqueous solution at ice bath temperature, a crystalline product precipitated within 15-20 minutes. This product, obtained in 32% yield, was the expected 2,5,5-trimethylthiazolidine-4-carboxylic acid (**1a**) and not a thiohemiacetal or a Schiff base, the possible intermediates in this reaction. Further workup of the mother liquor afforded an additional 65% of a water-soluble equilibrium product **1b**, which was isomeric with **1a**. Identical results were obtained with L(+)penicillamine in place of the D-isomer in the above reaction, except for the optical rotations of the products which were equal but opposite in sign.



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The optical rotation of **1a** (or a similar product from the L-series) was found to visibly change with time in water or methanol solutions, reaching equilibrium essentially within 24 hours-to values for **1b**. That epimerization was occurring at C-2 was suggested by the reversal of intensities of the C-4 protons of the individual diastereomers at 4.12 ppm and 4.02 ppm in their ^{1}H-nmr spectra (Figure 1). Equilibration occurred rapidly (within 1 hour) in 1*N* hydrochloric acid, but optical rotations were constant in deuterium oxide/2% sodium carbonate solutions (**1a**: + 146°; **1b**: + 133°) and this was reflected by stability of the nmr spectra of **1a** and **1b** over 24 hours. These products were somewhat less stable in pyridine; moreover, the epimeric mixture at equilibrium (72 hours) was different

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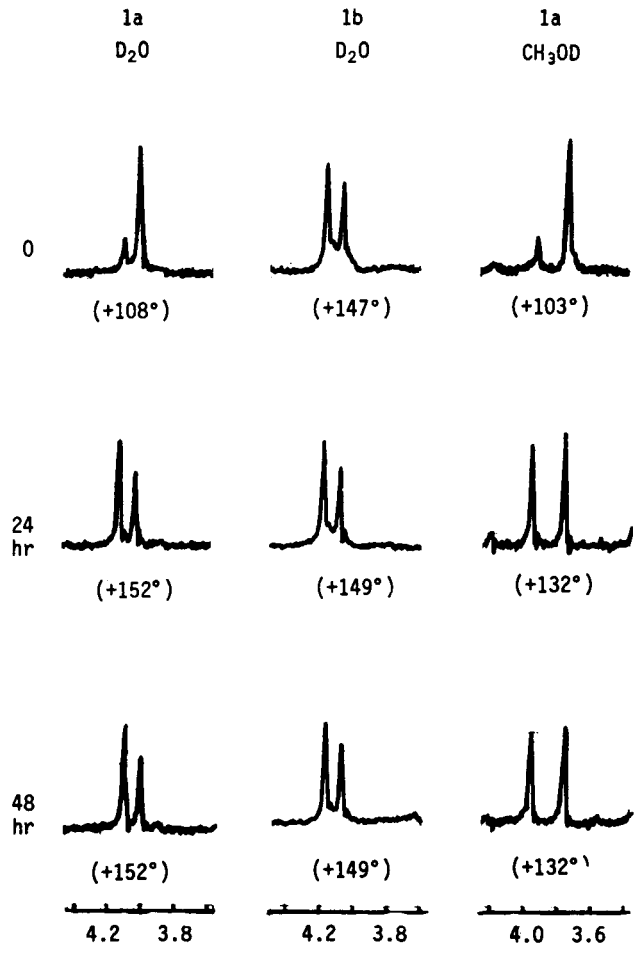


Figure 1. ^{1}H-nmr spectra of **1a** in deuterium oxide and in deuteriomethanol and **1b** in deuterium oxide correlated with their optical rotations (in water or methanol c ∿ 1.0) at various time intervals. The numbers below are in δ (from TMS).

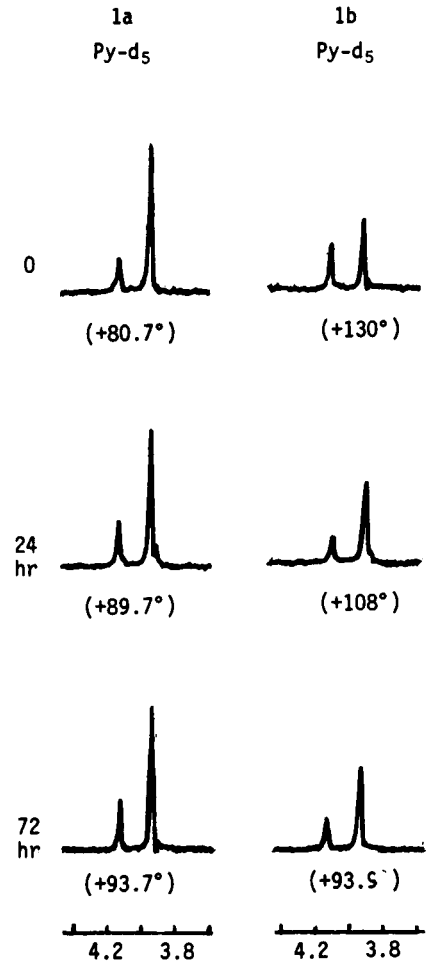


Figure 2. ^{1}H-nmr spectra of **1a** and **1b** in pyridine-d_5 correlated at different times with their optical rotations taken in the corresponding protic solvents.

from that obtained in water or methanol solutions (Figure 2).

Recrystallization of **1a** from ethyl acetate gave **1c**; likewise, **1b** gave **1c** when recrystallized from the same solvent. Both products had identical optical rotations ($[\alpha]_D^{24}$ 121° in methanol) and mutarotated *in concert* with each other, both samples reaching identical values after 24 hours. The change in their ^{1}H-nmr spectra paralleled this change in optical rotation. It appears that recrystallization, even from a non-protic solvent such as ethyl acetate, caused a shift in the relative epimer ratios. Based on nmr analysis in pyridine-d_5 (5a), **1a** represented a 3.3:1 predominance of the *cis* isomer, while **1b** had a *cis*-trans ratio of 1.8 to 1. The recrystallized product **1c**, consisted of an intermediate mixture, *viz.*, 69% *cis* and 31% *trans* isomers.

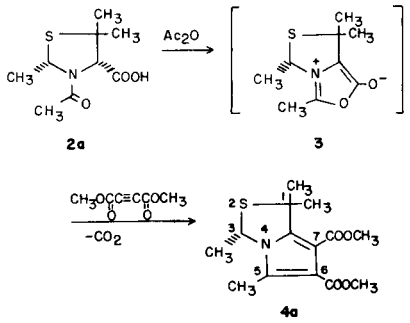
If the reaction of D(−)-penicillamine and AcH was allowed to continue at room temperature, the product that originally precipitated redissolved after 1 hour. Workup of the reaction mixture after this time gave, after recrystallization, an epimer mixture which was essentially identical to **1c**.

It is clear from the above results that the stereochemistry at C-2 of the thiazolidine-4-carboxylic acid produced in the condensation of acetaldehyde with chiral penicillamine is dependent on the nature of the solvent from which the product is isolated, the crystallization solvent, and the medium in which it is analyzed.

Acetylation of **1a** or **1c** with acetic anhydride/sodium carbonate gave a crystalline product which was the C-2,C-4 *cis* isomer (**2a**) (3b). Direct chemical evidence in support of **2a** being a single epimer was provided by racemizing the chiral C-4 carbon of **2a** without affecting the chirality at the 2-position. This was achieved by converting **2a** to its corresponding munchnone (7) in-

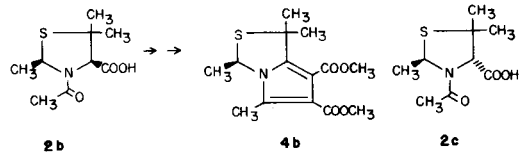
termediate (**3**) and effecting a 1,3-dipolar addition on the latter with dimethyl acetylenedicarboxylate. Concomitant elimination of carbon dioxide gave a dihydropyrrolo-[1,2-*c*]-thiazole (**4a**) wherein the chirality at the original C-4 position of **2a** had been destroyed (Scheme 1). This product had a specific rotation of -108° due to the original

Scheme 1



chirality at C-2 (now, C-3). The enantiomeric dihydropyrrolothiazole (**4b**) derived from the sequence starting from L(−)penicillamine *via* the *cis* isomer **2b** (Scheme 2) had a specific rotation of + 111°. The enantiomeric purities of **4a** and **4b** were both assessed by nmr using the chiral shift reagent, *tris*-(3-heptafluorobutyryl-*d*-camphorato)europium[Eu(hfbc)$_3$] (8), and were estimated to be greater than 90% optically pure.

Scheme 2

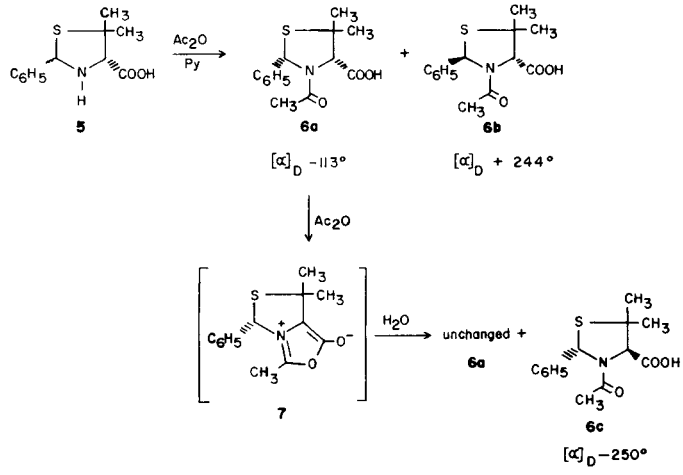


All attempts to obtain the C-2,C-4 *trans* epimer **2c** by acetylation of the *trans* enriched isomer **1b**, were uniformly unsuccessful. The presence of small amounts of **2c** was indicated by tlc, but this product − a low, wide-melting solid − could not be isolated in sufficient quantities and/or completely free from **2a** for characterization.

Isolation of the *N*-acetylated *trans* epimer was successful in the 2-phenyl series. Thus, condensation of benzaldehyde with D(−)-penicillamine gave a 3:1 *cis*-enriched **5** (9) which already represented an equilibrium mixture when isolated. Recrystallization of **5** from acetonitrile resulted in further *cis*-enrichment to a 5:1 epimeric mixture, **5a**. Acetylation of **5** with acetic anhydride/sodium carbonate gave the *N*-acetylated **cis** epimer **6a** as the only isolable product; however, acetylation of **5** using acetic anhydride/pyridine gave, in addition to **6a**, sufficient quantities of the *trans* epimer **6b** to permit its isolation as a crystalline solid.

Proof that **6b** was in fact the C-2 epimer of **6a** and not the epimer produced from **6a** by inversion at C-4, *viz.*, **6c**, was provided by deliberately racemizing the C-4 position of the pure *cis* isomer **6a** with acetic anhydride *via* its munchnone **7** (Scheme 3). Solvolysis of intermediate **7** gave unchanged **6a** plus a *trans* isomer which was clearly **6c**, enantiomeric with **6b** on the basis of its chiroptical properties. The absolute configurations at C-2 of **6a** and **6b** are *S* and *R*, respectively. This is based on the rule that the 2,4-*cis* isomers of *N*-acetylated 2-aryl-1,3-thiazolidine-4-carboxylic acids in the 4*S* series have the more negative rotation (2c). It follows that the chirality of **6c** is 2*S*,4*R*.

Scheme 3

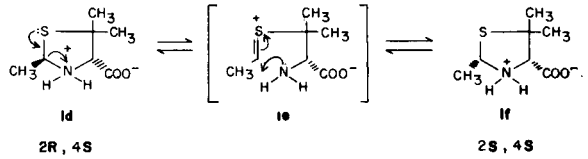


Discussion.

Although diverse and sometimes conflicting mechanisms have been advanced for the reaction of aldehydes with cysteine or penicillamine (10), it is quite clear that ring-to-chain reversal is favored in strongly basic solutions (11,10a). The stability of **1a** in a weak base (dilute sodium carbonate) as evidenced by its stable optical rotation and nmr spectrum, contrasted to its rapid equilibration in dilute acid suggests that the epimerization is acid catalyzed.

A mechanism involving a zwitterion of **1**, *viz.*, **1d**, is proposed for this epimerization at C-2 in neutral solvents (Scheme 4). Since tlc does not show the presence of the fully dissociated penicillamine or other ring *seco* intermediates, and exchange of ^{2}H for ^{1}H on the methyl

Scheme 4



group at C-2 during the epimerization of **1** in deuterium oxide was not observed (by nmr), the sulfonium ion intermediate **1e** must have only a transient existence.

These results strongly suggest that the previously

assumed chiral stability of the C-2 position of a 2-substituted thiazolidine-4-carboxylic acid must be completely reassessed.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are corrected to reference standards. Optical rotations were measured in a Perkin-Elmer model 141 polarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Spectrometers used were: nmr, Varian T-60 spectrophotometer with tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DDS) as internal standard; uv, Beckman Acta VI; and ir, Beckman ir-10 infrared spectrophotometer. Thin layer chromatography (tlc) was performed on silica gel GF-254 plates (Anal Tech, Inc., Newark, DE) and the plates viewed under a 254 nm lamp and/or developed in an iodine chamber. The D- and L-penicillamines were purchased from Aldrich Chemical Co., Milwaukee, WI. All solvent evaporations were carried out using a rotary evaporator under reduced pressure.

2-(*R,S*), 5,5-Trimethylthiazolidine-4(*S*)-carboxylic Acid (**1**).

The condensation of D(−)penicillamine (11.95 g., 0.081 mole) and acetaldehyde (3.76 g., 0.085 mole) followed the procedure already described (4). Stirring was continued in the cold for 15 minutes after the initial precipitation of **1a** (total reaction time: 30 minutes) before its collection, giving 4.32 g. (after drying in a vacuum desiccator for 48 hours) of product, mp sublimes > 150°, 168.5-169° dec. (corrected) with gas evolution. The mother liquor after removal of **1a** was stirred for an additional 2 hours at room temperature and the solvent was evaporated to incipient dryness *in vacuo*. After further drying in a vacuum desiccator, 10.11 g. of **1b** was obtained, mp sublimes > 150°, 165-166.5° dec. Tlc of **1a** and **1b** on silica gel plates with *n*-butyl alcohol:acetic acid:water (50:11:25) showed identical R*f* values and indicated no contamination with starting D(−)penicillamine. Compound **1b** was recrystallized from ethyl acetate by repeated digestion with fresh quantities of ethyl acetate to give **1c** in two crops, 8.01 g. (57.1% yield), mp sublimed > 140°, 165-166° dec with gas evolution, and 0.97 g (6.9% yield), mp identical to above. Compound **1a** was similarly recrystallized from ethyl acetate to give 3.77 g (26.9% yield) of product, mp sublimes > 140°, 166.5-167.5° dec with gas evolution. Compound **1c** had $[\alpha]_D^{24}$ + 120.9° (c 1.00, methanol) initially which drifted to 137.1° at 24 hours and remained at this value at 47 hours. The recrystallized **1a** had $[\alpha]_D^{24}$ + 121.7° (c 1.00, methanol) initially, + 137.8° at 24 hours and + 138.5° at 47 hours. Their nmr spectra (in deuterium oxide) were identical to each other when examined at the above time periods.

3-Acetyl-2-(*S*),5,5-trimethylthiazolidine-4-(*S*)-carboxylic Acid (**2a**).

1a (or **1c**) dissolved in dilute sodium carbonate solution was acetylated with acetic anhydride as previously described (3b) to give in each case the *cis* isomer **2a** with the properties described.

Dimethyl 1,1,3(*S*),5-Tetramethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4a**).

3-Acetyl-2(*S*),5,5-trimethylthiazolidine-4-(*S*)-carboxylic acid (**2a**, 1.52 g, 7.00 mmoles) was heated on a steam bath with acetic anhydride (25 ml) until dissolved and dimethyl acetylenedicarboxylate (0.924 g, 8.39 mmoles) was added. The solution was then heated at 100-105° for 6 hours. The reaction mixture progressively darkened during heating. After standing overnight at room temperature, the solvent was removed and the residual dark yellow oil was dissolved in chloroform (25 ml). The chloroform solution was washed with saturated sodium chloride (3 x 24 ml), dried (anhydrous sodium sulfate) and the solvent was removed. The dark yellow oil which was obtained (2.05 g) was distilled to give 4a (1.16 g, 55.8% yield) as a pale yellow oil, bp 180-184°/2 mm; uv (methanol): λ max 263 nm (log ε 3.84); $[\alpha]_D^{24}$ - 108.1° (c 0.98, methanol); nmr (deuteriochloroform): δ 1.70 (d, J = 6 Hz, 3H, 3-CH_3), 1.73, 1.88 (2s, 6H, 1-CH_3's), 2.33 (s, 3H, 5-CH_3), 3.75 (s, 6H, ester-CH_3's), 5.33 (q, J = 6 Hz, 1H, H-3).

Anal. Calcd. for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.20; H, 6.58; N, 4.64; S, 10.57.

Dimethyl 1,1,3(*R*),5-Tetramethyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate (**4b**).

Using the above procedure and starting with 3-acetyl-2(*R*),5,5-trimethylthiazolidine-4(*R*)-carboxylic acid (**2b**) (3b), **4b** was obtained as a dark yellow oil (1.04 g, 50.5% yield) bp 200-204°/7-8 mm. It was partially decolorized by treatment with alumina (Woelm, neutral activity grade I); uv (methanol): λ max 263 nm (log ε 3.82); $[\alpha]_D^{23}$ + 110.7° (c 1.07, methanol); nmr (deuteriochloroform): δ 1.70 (d, J = 6 Hz, 3H, 3-CH_3), 1.72, 1.87 (2s, 6H, 1-CH_3's), 2.33 (s, 3H, 5-CH_3), 3.73 (s, 6H, ester CH_3's), 5.33 (q, J = 6 Hz, 1H, H-3).

Anal. Calcd. for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.44; H, 6.67; N, 4.69; S, 10.69.

Determination of the Chiral Purity of **4a** and **4b**.

Addition of the chiral shift reagent, *tris*-(3-heptafluorobutyryl-*d*-camphorato)europium [Eu(hfbc)$_3$] (8) to **4a** (deuteriochloroform, TMS) in five increment portions resulted in gradual resolution of the methyl singlets of the two positional esters at C-6 and C-7, and transformation of the nmr spectrum into simple first order (without overlap) with concomitant shift of all the signals to lower field. Similar results were obtained when **4b** was subjected to the same conditions, except that the differential chemical shifts of the methyl groups were not identical, *i.e.*, the $\triangle\delta$ for **4a** > **4b**.

A synthetic 4:1 mixture composed of 60.5 mg of **4a** and 19.4 mg of **4b** when subjected to this analysis showed a 4:1 intensity split of the C-3 methyl doublets as well as the signals due to the C-1 *gem*-dimethyl. It can therefore be estimated that **4a** and **4b** are at least 80% and probably > 90% optically pure.

2(*R,S*)-Phenyl-5,5-dimethylthiazolidine-4(*S*)-carboxylic Acid (**5**).

A solution of 7.47 g (0.05 mole) of D(−)penicillamine {$[\alpha]_D^{26}$ - 61.3°; c 2.5, 1*N* sodium hydroxide} in 90 ml of water was filtered to remove fines and cooled to 4°. Benzaldehyde (5.84 g, 0.055 mole) was added followed by 10 ml of absolute ethanol. A white precipitate formed immediately. The mixture was stirred at 4° for 0.5 hour, 25% aqueous ethanol (100 ml) was added and stirring was continued at room temperature for 2 hours. After dilution with water (100 ml), the solids were collected and washed with water (2 x) to give 8.53 g (71.7% yield) of **5** as fine needles, mp 158-159°; $[\alpha]_D^{27}$ + 73.8°, (c 1.0, ethanol) {lit. (14) mp 151.5-153°, $[\alpha]_D^{22}$ + 73°, c 1.0, ethanol}; nmr (pyridine-d_5): δ 1.61, 1.67 (2s, 3H, 5-CH_3), 1.82, 1.92 (2s, 3H, 5-CH_3), 4.08, 4.15 (2s, 1H, H-4), 5.92, 6.15 (2s, 1H, ratio = 3:1, H-2), 7.10, 7.77 (2m, 5H, phenyl); nmr (deuteriochloroform): essentially the same as reported (14b) except for the chemical shifts at 1.67 (sh at 1.63, s, 3H, 5-CH_3) 3.77, 3.97 (2s, 1H, H-4), and 5.67, 5.73 (2s, 1H, H-2) and no signal at 6.19. When the product which precipitated initially was isolated after 15 minutes, 6.05 g of white microcrystals, mp 163-165°, $[\alpha]_D^{26}$ + 73.9° (c 2.0, methanol) were obtained. Recrystallization from acetonitrile yielded fine crystals, mp 157-158° dec.; $[\alpha]_D^{22}$ + 81.2° (c 1.01, methanol); nmr (pyridine-d_5): *cis/trans* (H-2) = 5:1.

3-Acetyl-2(*S*)-phenyl-5,5-dimethylthiazoldine-4(*S*)-carboxylic Acid (**6a**).

Anhydrous sodium carbonate (0.159 g, 1.50 mmoles) was added to a solution of 2(*R,S*)-phenyl-5,5-dimethylthiazolidine-4(*S*)-carboxylic acid (**5**, 0.237 g, 1.00 mmole) in water (10.0 ml). After the solids had all dissolved, the solution was cooled in an ice bath and acetic anhydride (0.204 g, 2.00 mmoles) was added dropwise over 1 minute with stirring. A white precipitate formed after about 0.5 hour of stirring. After another 0.5 hour the mixture was brought to *p*H 7 with concentrated hydrochloric acid and the solids were collected, washed with water and dried in a vacuum desiccator to give 0.25 g (94.3% yield) of **6a**, m.p. 215-216°; $[\alpha]_D^{25}$ - 113.1° (c 1.0, methanol); nmr (pyridine-d_5): δ 1.53, 1.67 (2s, 6H, 5-CH_3's), 1.97 (br s, 3H, CH_3CO), 5.10 (br s, 1H, H-4), 6.50 (br s, 1H, H-2), 7.30 8.13 (2m, 5H, phenyl); nmr (DMSO-d_6): δ 8.05 and 7.08 (2m, 5H, phenyl), 6.35 (br s, 1H, H-2), 4.52 (br s, 1H, H-4), 1.95 (br s, 3H, CH_3CO),

1.58 and 1.28 (2s, 6H, 5-CH_3's).

3-Acetyl-2(*R*)-phenyl-5,5-dimethylthiazolidine-4(*S*)-carboxylic Acid (**6b**).

To 2.96 g (12.5 mmoles) of **5** in 32.5 ml of pyridine was added 3.9 ml of acetic anhydride with stirring. The reaction was allowed to continue at room temperature for 2.0 hours and the solvent removed, the last traces by lyophilization, to yield 3.32 g of product. Separation of **6a** (*cis*) from **6b** (*trans*) was achieved by preparative tlc on silica gel using chloroform:acetic acid (5:1) as the developing solvent to give 0.25 g of **6b** after recrystallization from ethyl acetate-petroleum ether (30-60°), mp 177-179°, $[\alpha]_D^{26}$ + 244.2° (c 1.0, methanol) (15); nmr pyridine-d_5): 1.68 (s, 6H, 5-CH_3's), 1.88 (s, 3H, (CH_3CO), 5.28 (s, 1H, H-4, 6.05 (s, 1H, H-2), 7.32 (m, 5H, phenyl); nmr (DMSO-d_6): δ 7.38 (m, 5H, phenyl), 6.43 and 6.25 (2br s, 0.7H + 0.3H, H-2), 4.79 and 4.65 (2br s, 0.3H + 0.74, H-4), 2.03 and 1.68 (2br s, 0.3H + 0.74, CH_3CO), 1.55 and 1.38 (2s, 6H, 5-CH_3's); and 0.83 g of **6a** after recrystallization from ethanol-water, mmp 215-216°, $[\alpha]_D^{26}$ - 113.1° (c 1.0, methanol); nmr (pyridine-d_5): δ 1.58, 1.70 (2s, 6H, 5-CH_3's), 2.00 (s, 3H, CH_3CO), 5.13 (s, 1H, H-4), 6.55 (s, 1H, H-2), 7.32, 8.15 (2m, 5H, phenyl).

Epimerization of **6a** at C-4 to 3-Acetyl-2(*S*)-phenyl-5,5-dimethylthiazolidine-4(*R*)-carboxylic Acid (**6c**).

To 1.1 g of the *cis*-isomer **6a** (4.0 mmoles) was added 6.0 ml of acetic anhydride and the suspension heated on the stream bath for 20 minutes. The clear syrup was poured into 60 ml of cold water and the oil scratched until solids appeared. The solids were collected and recrystallized from ethanol-water to give 0.68 g (68% yield) of unchanged **6a**, mp 216-217°, $[\alpha]_D^{25}$ - 113.9° (c 1.0 methanol); nmr, identical to **6a** above. The filtrate which contained mainly the *trans* isomer was lyophilized to yield 0.11 g of solids, $[\alpha]_D^{25}$ - 207.5° (c 1.0, methanol). Further purification of this *trans* isomer by preparative tlc on silica gel GF using chloroform:acetic acid (5:1) as the developing solvent, and recrystallization of the isolated product from ethyl acetate:p-petroleum ether (30-60°) gave 30 mg of **6c**, mp 174-175°, $[\alpha]_D^{28}$ - 250.2° (c 1.0, methanol) (15).

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