Studies on Amino Acid Derivatives. IX.[1] Synthesis of Chiral Penam-3-carboxylic Acid and Its Substituted Derivatives

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Methyl penam-(3*S*)-carboxylate (methyl 7-oxo-1-thia-4-azabicyclo[3.2.0]heptane-(3*S*)-carboxylate), the basic skeleton of penicillin-type β-lactams, has been synthesized from D-cysteine methyl ester and *tert*-butyl formylacetate in three steps through the formation of the thiazolidinylacetic acid followed by cyclization by Mukaiyama–Ohno's procedure. Use of D-penicillamine methyl ester as well as the dimethyl derivative of *tert*-butyl formylacetate in the above method provides a general synthetic route to a variety of methyl penam-(3*S*)-carboxylates having methyl groups at the 2 and/or 6-positions.

The yields as well as stereoselectivity at C-5 in the cyclization step are shown to be strongly dependent upon the patterns of substituents on the thiazolidinylacetic acid skeleton, and the reason for this is discussed from the mechanistic viewpoint.

Keywords penicillanic acid; penam-3-carboxylate; chiral penam; D-cysteine; D-penicillamine; chemoselective reduction; calcium borohydride; (4-methoxycarbonylthiazolidin-2-yl)acetic acid derivative; thiazolidinylacetic acid; crystal structure

In the previous paper of this series, we have established a general synthetic method for penam[2] (7-oxo-1-thia-4-azabicyclo[3.2.0]heptane; D: R, R′=H), the basic skeleton of penicillin-type β-lactams, and its alkylated derivatives from appropriately substituted thiazolidinylacetic acid (C) derived from an appropriate β-ketoester (*e.g.* A) and cysteamine.[3] The key step in these syntheses was the formation of the β-lactam ring by using Mukaiyama–Ohno's procedure (triphenylphosphine, 2,2′-dipyridyl disulfide in acetonitrile). Among several methods elaborated in the above work, the best method is to use the *tert*-butyl thiazolidinylacetate (B: R, R′=H) as the key intermediate from which the final compound (D) is obtained by two successive reactions [deblocking of the *tert*-butyl group under appropriate acidic condition followed by cyclization of the free acid thus obtained] (Chart 1).

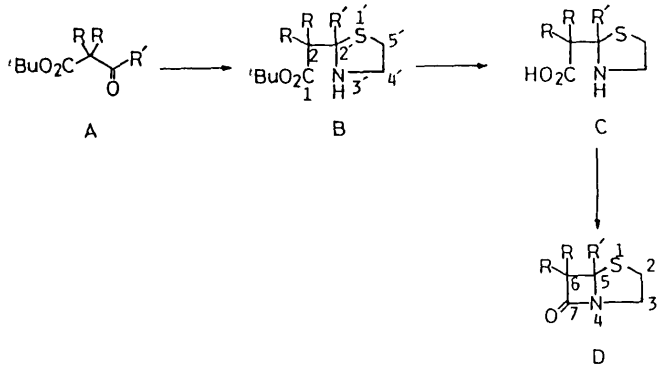

Chart 1

By using the corresponding methyl esters of D-cysteine (**3**) and D-penicillamine (**4**) instead of cysteamine in the above method, we now have succeeded in the synthesis of chiral penams having a carboxy group at the 3-position and some of their derivatives. This paper reports these results in detail. Though total synthesis of penicillins has been accomplished by Sheehan *et al.*[4] and Vanderhaeghe and coworkers[5] by essentially the same methodology, the present work differs from their methods in the following three points. These are: (i) since they intended to synthesize penicillins, an appropriately protected aminoformylacetate was used as the starting material and, hence, any stereochemical problem at the cyclization step concerning the substituted pattern of the side chain in the thiazolidinylacetic acid has never been examined, (ii) they employed dicyclohexylcarbodiimide instead of Mukaiyama–Ohno's reagents for the cyclization step (which was ineffective for the synthesis of penam itself[3]), and (iii) since D-cysteine has now become available in a large quantity,[6] the present work would provide a practicable synthetic route to a variety of 2,2-bisnor derivatives of penicillins.

Results and Discussion

tert-Butyl formylacetate (**1**)[7] and D-cysteine methyl ester (**3**) hydrochloride in methanol in the presence of an equimolar amount of triethylamine afforded the thiazolidinylacetate in 88% yield as a mixture of diastereomers (**5a**-*trans* and **5a**-*cis*) in *ca.* 1 : 1 ratio. Though these two isomers could be separated partially by medium-pressure column chromatography into each diastereoisomer, they isomerized gradually to the same mixture (*ca.* 1 : 1) when each isomer was merely kept standing in deuteriochloroform ($CDCl_3$) at room temperature (equilibration was complete within a few hours). Treatment of **5a** with 25% hydrobromic acid at room temperature, followed by evaporation of the solvent *in vacuo*, gave the corresponding thiazolidinylacetic acid (**6a**) as the readily crystallizable hydrobromide in an almost quantitative yield. Though the free acid (**6a**) was found to suffer ready decarboxylation,[8,9] the hydrobromide was surprisingly stable during the above hydrolysis[10–12] and could be recrystallized from methanol–ether as colorless crystals (mp 141—142 °C) without any decomposition.

With a satisfactory route to the thiazolidinylacetic acid (**6a**: HBr salt) in hand, our attention was then turned to the preparation of the penam derivative by using Mukaiyama–Ohno's procedure.[13] After thorough investigation to accomplish this aim, it was found that the best result was obtained when Mukaiyama's reagents (triphenylphosphine and 2,2′-dipyridyl disulfide) were added first to a suspension of the salt in acetonitrile, followed by the addition of

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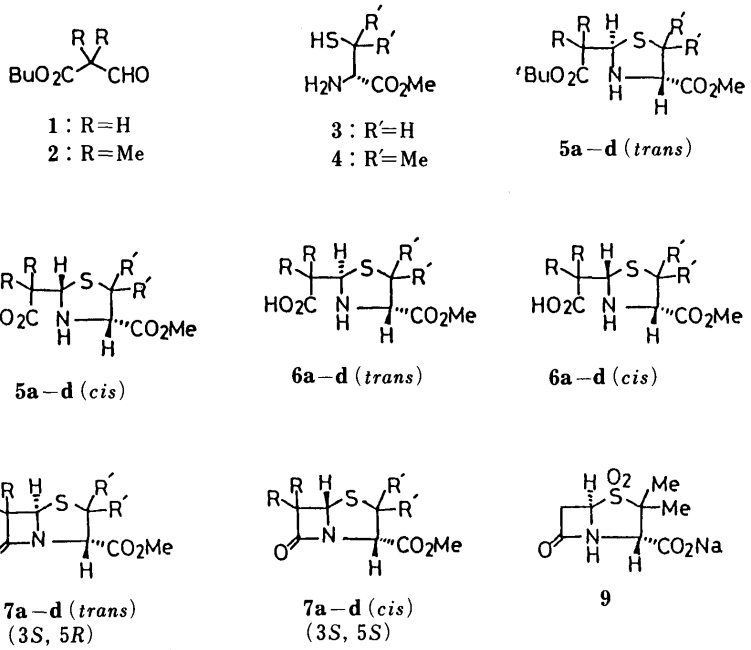

	R	R'
a	H	H
b	Me	H
c	H	Me
d	Me	Me

Chart 2

triethylamine under stirring (condition A). As expected from the facile decarboxylation reaction of the free acid **6a** (*vide supra*), if the above order was reversed (condition B: addition of triethylamine first to the suspension followed by addition of Mukaiyama's reagents), formation of the β-lactam was supressed with an appreciable increase of the decarboxylation product: methyl 2-methylthiazolidine-(4*S*)-carboxylate (**8a**). Hence, throughout this paper, we used condition A for the β-lactam formation reaction from **6a** (HBr salt) and its related compounds. When the above cyclization condition (A) was applied to **6a**·HBr, the β-lactam (**7a**) and the simple decarboxylated product (**8a**) were obtained in 17 and 10% yields, respectively.

Inspection of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of the β-lactam (**7a**) obtained after silica gel column chromatography revealed that the product was a mixture of diastereomers in *ca.* 12:1 ratio as evidenced by the C_3-H signals at δ 3.96 and 4.96 ppm, respectively. Recrystallization of the above mixture from chloroform–hexane gave the major isomer as a pure crystalline compound (C_3-H at δ 3.96 ppm). Since the proton (C_3-H) of 7-*trans* type compounds is known to appear at a lower field than that of the other isomer (7-*cis* type ones) owing to deshielding by the β-lactam carbonyl group,[14] it is evident that the minor product is **7a**-*trans* and the major one is its diastereoisomer (**7a**-*cis*). In addition to the ^{1}H-NMR spectrum mentioned above, the sign of the specific rotation ($[\alpha]_D$ −272.5°) of the major product is also in good accordance with the assigned (3*S*,5*S*) structure.[14] It should be noted that in contrast to the almost stereoselective formation of **7a**-*cis*, the NMR spectrum of **8a** shows the presence of both the *cis*- and *trans*-isomers in *ca.* 3:1 ratio.

In the same manner, the thiazolidine ester (**5b**: a mixture of *cis*- and *trans*-isomers in *ca.* 2:1 ratio) prepared in 83% yield from *tert*-butyl 2,2-dimethylformylacetate[3] (**2**) and D-cysteine methyl ester (**3**) was subjected to the above two-step reaction (treatment with HBr–AcOH and cyclization by Mukaiyama–Ohno's procedure under condition A) to give the desired β-lactam (**7b**) in 79% yield. As in the cyclization reaction to the 3-nor series,[3] the yield of the β-lactam increased dramatically, indicating again that introduction of two methyl groups at the side chain of the thiazolidinylacetic acid (**6b**) enhances the cyclizing ability. It should also be noted that the product is a mixture of diastereomers (*ca.* 5:3) and the major one is the 3,5-*trans* isomer (**7b**-*trans*) as evidenced by the chemical shifts of the C_3-H signals (δ 4.92 ppm for **7b**-*trans* and δ 3.86 ppm for **7b**-*cis*). In order to examine the effect of 5′,5′-dimethyl groups of the thiazolidinylacetic acid in the cyclization reaction, we then applied our two-step cyclization method to **5c** and **5d**, both of which could be readily prepared by the reactions of the corresponding formylacetates with D-penicillamine methyl ester (**4**). When the thiazolidinylacetate (**5c**) was subjected to the above two-step reaction, the β-lactam (**7c**) was obtained in 9% yield as a mixture of diastereoisomers (*ca.* 1:2 ratio). The major isomer was determined as having 3,5-*cis* configuration (**7c**-*cis*), as judged from the chemical shift (δ 3.78 ppm) of the C_3-H signal. The structure of the minor product was confirmed as **7c**-*trans* by the comparison of all instrumental data [^{1}H-NMR spectrum (δ 4.46 ppm of the C_3-H signal), infrared (IR) spectrum, and $[\alpha]_D$ with those of an authentic sample synthesized from 6-aminopenicillanic acid (6-APA)[15]]. Since the latter compound has already been transformed to sulbactam[16] (**9**: sodium penicillanate 1,1-dioxide), a β-lactamase inhibitor, the above synthesis provides a formal total synthesis of this

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β-lactam.

The two-step β-lactam formation reaction, if applied to **5d**, gave the corresponding lactam (**7d**) in 55% yield. In this case, the 3,5-*trans* isomer predominates over the 3,5-*cis* isomer (**7d**-*trans*/**7d**-*cis* = *ca.* 8).

Finally, we have investigated the synthesis of 3-hydroxymethyl derivatives (**11a** and **11b**), in order to see whether another substituents at the 4′-position in the thiazolidinylacetic acid has any effect on the facility of the cyclization step. Chemoselective reduction of the two ester groups in **5** has been realized readily by using calcium borohydride[17] as the reducing reagent. Thus, when **5a** and its 2,2-dimethyl derivative (**5b**) were treated with this reagent in methanol at room temperature, only the methyl ester group was reduced selectively to give **10a** and **10b**. These alcohols were subjected to the above two-step method to give the corresponding β-lactams (**11a,b**) with concomitant acetylation of the hydroxy group at the first step (Chart 3).

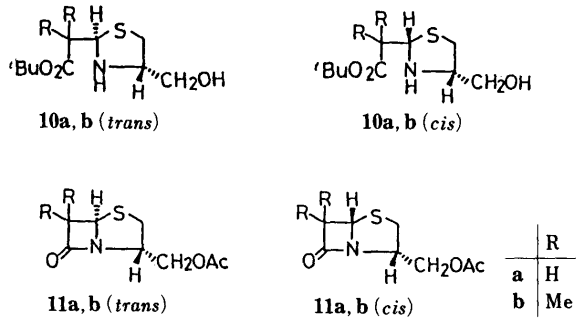

Chart 3

Though the yield of β-lactam (**11a**) was poor (*ca.* 13%), the yield of the 6,6-dimethyl derivative (**11b**) was 46%. In both cases, the cyclization reactions resulted in the predominant formation of the 3,5-*trans* isomers, though the *cis*-isomers were also obtained in significant amounts.

It is evident from the above results that the high stereoselectivity in the cyclization step was realized only in two cases (*i.e.* formations of **7a** and **7d**) and not in the other cases.

Knowing that only **5a** and **5d** afforded readily crystallizable hydrobromides (**6a**·HBr and **6d**·HBr) having sharp melting points in the deblocking reaction with HBr–AcOH, we consider the following mechanism as the most reasonable to account for the high stereoselectivity in these two cyclization reactions. Supposing that the hydrobromides of **6a** and **6d** have single stereostructures, one can explain nicely the high stereoselectivity by assuming that the cyclization to the lactams (**7a** and **7d**) *via* the free acid (**6a** and **6d**) proceeds much faster than the isomerization between *cis*- and *trans*-isomers of the free acids. Accordingly, we have carried out X-ray crystallographic analysis of both salts (**6a**·HBr and **6d**·HBr). Though the crystalline form of **6a**·HBr was found to be inadequate for this analysis, **6d**·HBr was found to have the *trans*-configuration at the C-2′ and C-4′ centers.

Since the above working hypothesis has now been confirmed as correct (at least for the tetramethyl derivative), it is obvious that the free acid (E: R = Me) does not isomerize to any significant extent to the other isomer (G: R = Me) *via*

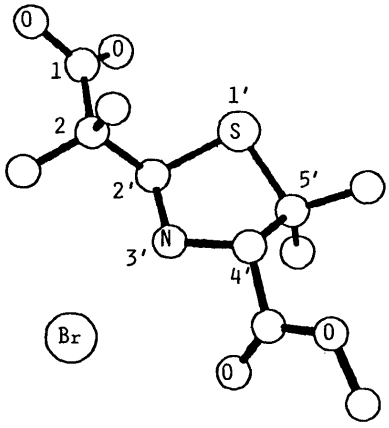

Fig. 1. Molecular Structure of the Hydrobromide Salt of **6d** (Br^- Anions at Positions of Smaller Occupancy are Omitted)

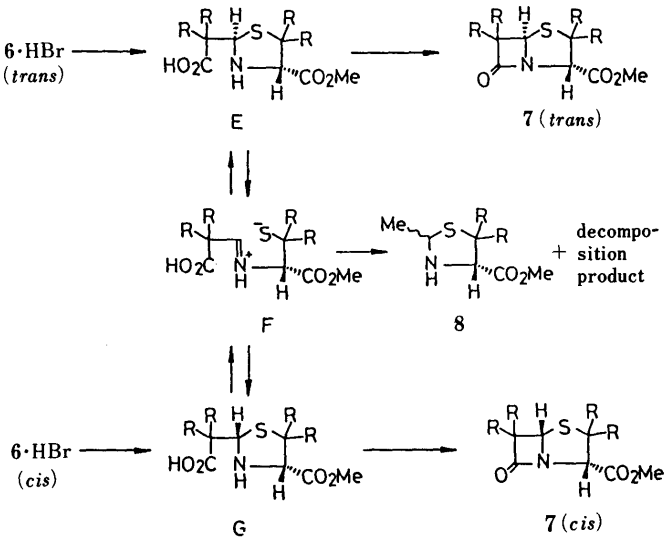

Chart 4

the imine (F) during the cyclization reaction (Chart 4).

This is probably because the imine species (F) mostly suffers decarboxylation to give **8d** (through concomitant recyclization) or decomposition under these conditions (acetonitrile containing triethylamine and Mukaiyama's reagents) and, hence, only a minor amount of it isomerizes to the other isomer (G: R = Me). Though X-ray crystallographic analysis of **6a**·HBr was not possible (*vide supra*), the same argument can also be made to account for the almost selective formation of the *cis*-β-lactam (**7a**-*cis*) by assuming that the salt (**6a**·HBr) has the *cis*-configuration.

Knowing that the proportion of **5a**-*cis* and **5a**-*trans* is nearly equal (*vide supra*), it is evident that the salt formation with hydrobromic acid not only causes rapid isomerization between these two isomers (E and G) but also changes the proportion significantly so as to give a single isomer (G for **6a** and E for **6d**) as the hydrobromide.

The lack of significant stereoselectivity in other cases (formations of **7b**, **7c**, **11a**, and **11b**) is probably due to the fact that all of these salts are composed from both *cis*- and *trans*-isomers. Actually, in accordance with this explanation, none of the hydrobromides of these acids gave pure crystals on recrystallization from a variety of solvents.

In conclusion, the following can be said concerning the

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effect of substituents in the cyclization reaction of thiazolidinylacetic acids having an ester or a hydroxymethyl group at the 4′-position by Mukaiyama–Ohno's procedure: 1) the presence of 2-substituents in the thiazolidinylacetic acids is essential in order to attain high-yield formation of the β-lactams; 2) though the introduction of a substituent at the 5′-position in thiazolidinylacetic acid rather lowers the yield of the β-lactams, it enhances the stereoselectivity so as to increase the 3,5-*trans* isomer/3,5-*cis* isomer ratio of the β-lactam, as compared to the corresponding 5′-unsubstituted series; 3) as evidenced by the almost complete stereoselective conversion of **6a**·HBr to **7a**-*cis* and that of **6d**·HBr to **7d**-*trans*, the ratio of diastereomers of the final β-lactams (**7a** and **7d**) is determined by the stereostructure of the precursors (**6**) in their hydrobromides, based on X-ray crystallographic analysis of **6d**-hydrobromide (*trans*-isomer).

Use of some other acid such as hydrochloric acid or trifluoroacetic acid as the deblocking reagent is currently being investigated in order to confirm the above explanation.

Experimental

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. IR spectra were measured on a JASCO A-102 spectrometer and ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 SI or JEOL JNM-GX 500 spectrometer with tetramethylsilane (TMS) as an internal standard, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublets of doublets; br, broad. Low- and high-resolution mass spectra (MS) were obtained on Hitachi M-52G and JEOL DX-303 spectrometers, respectively. Wakogel (C-200) and Merck Kiesel-gel 60 F254 were employed for silica gel column and preparative thin layer chromatography (TLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume/volume.

***tert*-Butyl 2-[(4*S*)-4-Methoxycarbonylthiazolidin-2-yl]acetate (5a)** A solution of *tert*-butyl formylacetate (**1**) (3.17 g, 22 mmol), D-cysteine methyl ester hydrochloride (**3**·HCl) (3.78 g, 22 mmol) and triethylamine (2.22 g, 22 mmol) in methanol (100 ml) was stirred for 4 h at room temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography [hexane–ethyl acetate (8 : 1)] to give **5a** (5.05 g, 88%) as a colorless oil. $[\alpha]_D^{27}$ +70.2° (c=3.0, $CHCl_3$). High-resolution MS m/z Calcd $C_{11}H_{19}NO_4S$ (M^+): 261.1034. Found: 261.1041. Calcd $C_7H_{10}NO_4S$ ($M^+ - tert$-Bu): 204.0330. Found: 204.0332. IR ($CHCl_3$): 3300, 1735, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s, *tert*-Bu), 2.46—3.48 (5H, m, C_2-2H, $C_{5'}$-2H, NH), 3.77 (3H, s, CO_2Me), 3.85—4.21 (1H, m, $C_{4'}$-H), 4.70 (1H×1/2, t, J=6.2 Hz, $C_{2'}$-H), 4.96 (1H×1/2, t, J=6.2 Hz, $C_{2'}$-H).

***tert*-Butyl 2-[(4*S*)-4-Methoxycarbonylthiazolidin-2-yl]-2-methylpropanoate (5b)** A solution of *tert*-butyl 2-formyl-2-methylpropanoate (**2**) (861 mg, 5 mmol), compound **3**·HCl (858 mg, 5 mmol) and triethylamine (506 mg, 5 mmol) in methanol (40 ml) was stirred for 4 h at room temperature. The residue obtained by evaporation of the methanol was purified by silica gel column chromatography [hexane–ethyl acetate (10 : 1)] to give **5b** (1.19 g, 82%) as a colorless oil. $[\alpha]_D^{28}$ +37.2° (c=3.0, $CHCl_3$). High-resolution MS m/z Calcd $C_{13}H_{23}NO_4S$ (M^+): 289.1346. Found: 289.1390. Calcd $C_9H_{14}NO_4S$ ($M^+ - tert$-Bu): 232.0643. Found: 232.0654. IR ($CHCl_3$): 3300, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H×1/3, s, Me), 1.23 (3H×1/3, s, Me), 1.27 (3H×2/3, s, Me), 1.37 (3H×2/3, s, Me), 1.46 (9H×1/3, s, *tert*-Bu), 1.49 (9H×2/3, s, *tert*-Bu), 2.68 (1H×2/3, t, J=11.5 Hz, $C_{5'}$-H), 3.09 (2H×1/3, d, J=5.9 Hz, $C_{5'}$-2H), 3.27 (1H×2/3, dd, J=11.5, 7.0 Hz, $C_{5'}$-H), 3.77 (3H×1/3, s, CO_2Me), 3.72—3.78 (1H×2/3, m, $C_{4'}$-H), 3.79 (3H×2/3, s, CO_2Me), 4.22 (1H×1/3, t, J=5.9 Hz, $C_{4'}$-H), 4.60 (1H×2/3, br d, J=11.8 Hz, $C_{2'}$-H), 4.90 (1H×1/3, s, $C_{2'}$-H).

***tert*-Butyl 2-[(4*S*)-5,5-Dimethyl-4-methoxycarbonylthiazolidin-2-yl]-acetate (5c)** A mixture of compound **1** (854 mg, 5.93 mmol), D-penicillamine methyl ester hydrochloride (**4**·HCl) (1.18 g, 5.93 mmol) and triethylamine (599 mg, 5.93 mmol) in methanol (50 ml) was stirred for 10 h at room temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography [hexane–ethyl acetate (5 : 1)] to give **5c** (1.34 g, 78%) as colorless needles, mp 43—45.5 °C (hexane). $[\alpha]_D^{26}$ +7.45° (c=2.2, $CHCl_3$). High-resolution MS m/z Calcd $C_{13}H_{23}NO_4S$ (M^+): 289.1348. Found: 289.1354. Calcd $C_9H_{14}NO_4S$ ($M^+ - tert$-Bu): 232.0642. Found: 232.0635. IR ($CHCl_3$): 3320, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, s, Me), 1.47 (9H, s, *tert*-Bu), 1.65 (3H, s, Me), 2.72 (1H, dd, J=16.8, 6.8 Hz, C_2-H), 2.82 (1H, dd, J=16.8, 5.7 Hz, C_2-H), 3.61 (1H, s, $C_{4'}$-H), 3.78 (3H, s, CO_2Me), 4.87 (1H, dd, J=6.8, 5.7 Hz, $C_{2'}$-H).

***tert*-Butyl 2-[(4*S*)-5,5-Dimethyl-4-methoxycarbonylthiazolidin-2-yl]-2-methylpropanoate (5d)** A mixture of compound **2** (2.1 g, 12.2 mmol), compound **4**·HCl (2.44 g, 12.2 mmol) and triethylamine (1.24 g, 12.2 mmol) in methanol (50 ml) was stirred for 10 h at room temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography [hexane–ethyl acetate (7 : 1)] to give **5d** (2.74 g, 71%) as colorless needles, mp 64—67 °C (hexane). $[\alpha]_D^{25}$ +4.98° (c=3.1, $CHCl_3$). High-resolution MS m/z Calcd $C_{15}H_{27}NO_4S$ (M^+): 317.1659. Found: 317.1654. Calcd $C_7H_{12}NO_2S$ ($M^+ - C_8H_{15}O_2$): 174.0587. Found: 174.0581. IR ($CHCl_3$): 3320, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s, Me), 1.22 (3H, s, Me), 1.35 (3H, s, Me), 1.48 (9H, s, *tert*-Bu), 1.64 (3H, s, Me), 3.58 (1H, br d, J=12.0 Hz, $C_{4'}$-H), 3.77 (3H, s, CO_2Me), 4.75 (1H, br d, J=10.8 Hz, $C_{2'}$-H).

2-[(2*S*,4*S*)-4-Methoxycarbonylthiazolidin-2-yl]acetic Acid Hydrobromide (6a·HBr) The ester (**5a**) (261 mg, 1 mmol) was treated with 25% HBr–AcOH (25 ml) for 30 min at room temperature and the reaction mixture was concentrated under reduced pressure. The obtained crystalline residue was recrystallized from methanol–ether to give **6a**·HBr (263 mg, 92%) as colorless needles, mp 141—142 °C (dec.). $[\alpha]_D^{26}$ +72.0° (c=1.0, MeOH) (after 15 min). *Anal.* Calcd for $C_7H_{12}BrNO_4S$: C, 29.38; H, 4.23; Br, 27.93; N, 4.90; S, 11.20. Found: C, 29.36; H, 4.40; Br, 27.68; N, 4.84; S, 10.93. IR (Nujol): 1740, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.89—3.59 (4H, m, C_2-2H, $C_{5'}$-2H), 3.62—3.98 (1H, m, $C_{4'}$-H), 3.80 (3H, s, CO_2Me), 4.78—5.23 (1H, m, $C_{2'}$-H), 8.11—9.17 (3H, br, H_2N^+, OH).

2-[(2*R*,4*S*)-5,5-Dimethyl-4-methoxycarbonylthiazolidin-2-yl]-2-methylpropanoic Acid Hydrobromide (6d·HBr) The ester (**5d**) (317 mg, 1 mmol) was treated with 25% HBr–AcOH (25 ml) for 30 min at room temperature and the reaction mixture was concentrated under reduced pressure. The obtained crystalline residue was recrystallized from methanol–ether to give **6d**·HBr (291 mg, 85%) as colorless needles, mp 168 °C (sublimation from 122 °C). $[\alpha]_D^{26}$ +57.4° (c=1.0, MeOH) (after 15 min). *Anal.* Calcd for $C_{11}H_{20}BrNO_4S$: C, 38.60; H, 5.89; Br, 23.35; N, 4.09; S, 9.37. Found: C, 38.56; H, 6.03; Br, 23.46; N, 4.03; S, 9.37. IR (Nujol): 1745, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, s, Me), 1.30 (3H, s, Me), 1.36 (3H, s, Me), 1.58 (3H, s, Me), 3.81 (3H, s, CO_2Me), 4.14 (1H, s, $C_{4'}$-H), 5.19 (1H, s, $C_{2'}$-H), 8.40—8.93 (3H, br, H_2N^+, OH).

Crystallographic Measurement of 6d·HBr Colorless prismatic crystals of **6d**·HBr were grown in methanol–ether solution. A crystal, 0.25×0.1×0.05 mm^3 in size, was used for data collection on a Rigaku AFC-5R diffractometer with graphite-monochromated Cu $K\alpha$ radiation (λ=1.54184 Å). The crystal data are as follows: $C_{11}H_{19}NO_4S$·HBr, M_r 342.25, monoclinic, space group $P2_1$, a=9.503(3), b=8.778(2), c=9.606(3) Å, β=114.51(2)° and Z=2. Intensities were measured in the θ–2θ scan mode with a scanning speed of 4°(2θ)/min. Of 1174 independent reflections with 2θ<120°, 42 weak reflections below the background were considered to be zero reflections; the observational threshold value, F_{lim}, was 0.146. Corrections were made for Lorentz and polarization factors but not for absorption. The standard deviations were estimated by using the equation $\sigma(|F_O|)=\sigma_p^2(|F_O|)+q^2F_O^2$ where q, 0.048, was derived from the variation of 3 reflections monitored after every 50 reflections and σ_p was due to the counting statistics.[18]

The structure was solved by the direct method using the program MULTAN84[19] and the atomic parameters were refined by the block-diagonal least-squares method. The refinements were first isotropically and then anisotropically performed for non-hydrogen atoms. However, the convergence was sluggish and difference maps around the Br^- anion indicated the presence of scattering which was interpreted as a disordering of the Br^- anion. By introducing two additional Br^- anions, the R factor was remarkably improved. The site-occupancy factors were 0.8 for the central Br^- anion and 0.1 for each of the other two. Hydrogen atoms were placed in the calculated position, but not included in the refinement. The quantity minimized was $\sum\omega(|F_O|-|F_C|)^2$ with $\omega=1/\sigma(|F_O|)$. In the refinement, the zero reflections were assumed to be $F_O=F_{lim}$, but those for which $|F_C|<F_{lim}$ were omitted. The final R value was 0.060 (R_w=0.079) for reflections with $|F_O|>3(|F_O|)$. The final atomic parameters for non-

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hydrogen atoms, bond distances and angles have been deposited. The atomic scattering factors were taken from reference 20.

(3*S*,5*S*)-3-Methoxycarbonyl-7-oxo-1-thia-4-azabicyclo[3.2.0]heptane (7a) The ester (**5a**) (261 mg, 1 mmol) was treated with 25% HBr–AcOH (25 ml) for 30 min at room temperature and the reaction mixture was concentrated under reduced pressure. The crystalline residue was dissolved in acetonitrile (100 ml), and then triphenylphosphine (393 mg, 1.5 mmol), 2,2′-dipyridyl disulfide (330 mg, 1.5 mmol) and triethylamine (111 mg, 1.1 mmol) were added to this solution and the whole was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was extracted with CH_2Cl_2 (20 ml × 3) and dried over anhydrous $MgSO_4$. The oily residue obtained by evaporation of the CH_2Cl_2 layer was purified by silica gel column chromatography [hexane–ethyl acetate (5 : 1)] to give **7a** (31.8 mg, 17%) as a semisolid diastereomixture [**7a** (*trans*) : **7a** (*cis*) = 1 : 12]. Recrystallization of the mixture from $CHCl_3$–hexane afforded the major isomer as colorless needles. **7a** (*cis*): mp 128 °C, $[\alpha]_D^{24}$ −272.5° (*c* = 0.51, $CHCl_3$). High-resolution MS *m/z* Calcd $C_7H_9NO_3S$ (M^+): 187.0304. Found: 187.0309. Calcd $C_6H_9NO_2S$ ($M^+ - CO$): 159.0357. Found: 159.0362. Calcd $C_5H_7NO_2S$ ($M^+ - CH_2=C=O$): 145.0197. Found: 145.0202. Calcd C_5H_6NOS ($M^+ - CO_2Me$): 128.0168. Found: 128.0155. IR ($CHCl_3$): 1780, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.07 (1H, dd, *J* = 15.4, 2.7 Hz, $C_{6\alpha}$-H), 3.36 (1H, dd, *J* = 11.5, 5.8 Hz, C_2-H), 3.54 (1H, dd, *J* = 15.4, 4.2 Hz, $C_{6\beta}$-H), 3.57 (1H, dd, *J* = 11.5, 4.3 Hz, C_2-H), 3.86 (3H, s, CO_2Me), 3.96 (1H, dd, *J* = 5.8, 4.3 Hz, C_3-H), 5.01 (1H, dd, *J* = 4.2, 2.7 Hz, C_5-H).

The other isomer was detected in the mother liquor by ^{1}H-NMR spectroscopy. **7a** (*trans*): ^{1}H-NMR ($CDCl_3$) δ: 3.03 (1H, dd, *J* = 15.4, 3.1 Hz, $C_{6\beta}$-H), 3.35—3.62 (3H, m, C_2-2H, $C_{6\alpha}$-H), 3.78 (3H, s, CO_2Me), 4.96 (1H, dd, *J* = 7.7, 4.2 Hz, C_3-H), 5.07 (1H, dd, *J* = 4.6, 3.1 Hz, C_5-H).

By continuous column chromatography, the decarboxylated product **8a** (16.1 mg, 10%) was obtained as a diastereomixture [**8a** (*cis*)/**8a** (*trans*) = *ca.* 2]. The same mixture was obtained from D-cysteine methyl ester hydrochloride (**3**·HCl) and acetaldehyde.[21] **8a**: an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H × 1/3, d, *J* = 6.2 Hz, Me), 1.61 (3H × 2/3, d, *J* = 6.2 Hz, Me), 2.11 (1H, br s, NH), 2.90—3.41 (2H, m, C_5-H), 3.77 (3H × 1/3, s, OMe), 3.80 (3H × 2/3, s, OMe), 3.85 (1H × 2/3, dd, *J* = 9.0, 6.8 Hz, C_4-H), 4.21 (1H × 1/3, t, *J* = 7.0 Hz, C_4-H), 4.58 (1H × 2/3, q, *J* = 6.2 Hz, C_2-H), 4.78 (1H × 1/3, q, *J* = 6.2 Hz, C_2-H).

(3*S*)-6,6-Dimethyl-3-methoxycarbonyl-7-oxo-1-thia-4-azabicyclo[3.2.0]-heptane (7b) In a procedure similar to that described for the synthesis of **7a**, **5b** (300 mg, 1.04 mmol) was treated with 25% HBr–AcOH (30 ml). The reaction of the evaporated residue with triphenylphosphine (408 mg, 1.56 mmol), 2,2′-dipyridyl disulfide (340 mg, 1.56 mmol) and triethylamine (110 mg, 1.04 mmol) in acetonitrile (100 ml) gave **7b** (126 mg, 79%) as a diastereomixture [**7b** (*trans*) : **7b** (*cis*) = 5 : 3]. Each diastereoisomer was separated by additional preparative TLC [silica gel; hexane–ethyl acetate (10 : 1)] to give the more polar compound **7b** (*trans*) and the less polar one **7b** (*cis*).[22] **7b** (*trans*): colorless oil, $[\alpha]_D^{28}$ +174.8° (*c* = 2.1, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{13}NO_3S$ (M^+): 215.0615. Found: 215.0605. IR ($CHCl_3$): 1770, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, Me), 1.50 (3H, s, Me), 3.25 (1H, dd, *J* = 11.5, 6.9 Hz, C_2-H), 3.45 (1H, dd, *J* = 11.5, 3.5 Hz, C_2-H), 3.78 (3H, s, CO_2Me), 4.92 (1H, dd, *J* = 6.9, 3.5 Hz, C_3-H), 4.94 (1H, s, C_5-H). **7b** (*cis*): colorless needles, mp 102 °C (*n*-pentane), $[\alpha]_D^{25}$ −217.9° (*c* = 0.78, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{13}NO_3S$ (M^+): 215.0615. Found: 215.0608. IR ($CHCl_3$): 1770, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, Me), 1.45 (3H, s, Me), 3.25 (1H, dd, *J* = 11.5, 6.9 Hz, C_2-H), 3.31 (1H, dd, *J* = 11.5, 9.2 Hz, C_2-H), 3.85 (3H, s, CO_2Me), 3.86 (1H, dd, *J* = 9.2, 6.9 Hz, C_3-H), 4.82 (1H, s, C_5-H).

(3*S*)-2,2-Dimethyl-3-methoxycarbonyl-7-oxo-1-thia-4-azabicyclo[3.2.0]-heptane (Methyl Penicillanate) (7c) In a procedure similar to that described for the synthesis of **7a**, **5c** (289 mg, 1 mmol) was treated with 25% HBr–AcOH (20 ml) and the reaction of the evaporated residue with triphenylphosphine (314 mg, 1.2 mmol), 2,2′-dipyridyl disulfide (264 mg, 1.2 mmol) and triethylamine (101 mg, 1 mmol) in acetonitrile (100 ml) gave the less polar product **7c** (*trans*) (6.45 mg, 3%) and the more polar one **7c** (*cis*) (12.9 mg, 6%), which were separated by silica gel column chromatography [hexane–ethyl acetate (5 : 1)]. **7c** (*trans*): colorless needles, mp 52 °C (*n*-pentane) (lit.[15] mp 52—53 °C), $[\alpha]_D^{27}$ +304.7° (*c* = 0.38, acetone). High-resolution MS *m/z* Calcd $C_9H_{13}NO_3S$ (M^+): 215.0615. Found: 215.0613. Calcd $C_8H_{13}NO_2S$ ($M^+ - CO$): 187.0666. Found: 187.0677. IR ($CHCl_3$): 1775, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, s, Me), 1.67 (3H, s, Me), 3.06 (1H, dd, *J* = 15.9, 1.8 Hz, $C_{6\beta}$-H), 3.56 (1H, dd, *J* = 15.9, 4.3 Hz, $C_{6\alpha}$-H), 3.77 (3H, s, CO_2Me), 4.46 (1H, s, C_3-H), 5.29 (1H, dd, *J* = 4.3, 1.8 Hz, C_5-H). **7c** (*cis*): colorless oil, $[\alpha]_D^{24}$ −132.1° (*c* = 0.33, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{13}NO_3S$ (M^+): 215.0615. Found: 215.0599. Calcd $C_8H_{13}NO_2S$ ($M^+ - CO$): 187.0666. Found: 187.0670. IR ($CHCl_3$): 1780, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s, Me), 1.64 (3H, s, Me), 3.20 (1H, dd, *J* = 14.2, 2.8 Hz, $C_{6\alpha}$-H), 3.42 (1H, ddd, *J* = 14.2, 4.4, 1.2 Hz, $C_{6\beta}$-H), 3.76 (1H, d, *J* = 1.2 Hz, C_3-H), 3.82 (3H, s, CO_2Me), 5.08 (1H, dd, *J* = 4.4, 2.8 Hz, C_5-H).

(3*S*,5*R*)-3-Methoxycarbonyl-7-oxo-2,2,6,6-tetramethyl-1-thia-4-azabicyclo[3.2.0]heptane (7d) In a procedure similar to that described for the synthesis of **7a**, **5d** (292 mg, 0.921 mmol) was treated with 25% HBr–AcOH (10 ml) and the reaction of the evaporated residue with triphenylphosphine (290 mg, 1.11 mmol), 2,2′-dipyridyl disulfide (243 mg, 1.11 mmol) and triethylamine (93 mg, 0.921 mmol) in acetonitrile (92 ml) gave, after silica gel column chromatography [hexane–ethyl acetate (7 : 1)], the less polar product **7d** (*trans*) (109 mg, 49%) and the more polar one **7d** (*cis*) (14 mg, 6%), each as an oil. **7d** (*trans*): $[\alpha]_D^{26}$ +231.5° (*c* = 1.14, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{11}H_{17}NO_3S$ (M^+): 243.0927. Found: 243.0925. Calcd $C_{10}H_{17}NO_2S$ ($M^+ - CO$): 215.0981. Found: 215.0992. IR ($CHCl_3$): 1780, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, Me), 1.46 (3H, s, Me), 1.50 (3H, s, Me), 1.61 (3H, s, Me), 3.76 (3H, s, CO_2Me), 4.39 (1H, s, C_3-H), 5.13 (1H, s, C_5-H). **7d** (*cis*): $[\alpha]_D^{25}$ −166.7° (*c* = 0.3, $CHCl_3$). High-resolution MS *m/z* Calcd $C_9H_{13}NO_3S$ (M^+): 243.0927. Found: 243.0928. IR ($CHCl_3$): 1780, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, Me), 1.43 (3H, s, Me), 1.47 (3H, s, Me), 1.64 (3H, s, Me), 3.72 (1H, s, C_3-H), 3.79 (3H, s, CO_2Me), 4.87 (1H, s, C_5-H).

By continuing column chromatography, the decarboxylated product (**8d**) was obtained in a small amount. The hydrochloride of **8d** had mp 167 °C ($CHCl_3$–ether) and was identical with an authentic sample[23] prepared from D-penicillamine methyl ester hydrochloride (**4**·HCl) and isobutyraldehyde.

***tert*-Butyl 2-[(4*S*)-4-Hydroxymethylthiazolidin-2-yl]acetate (10a)** A solution of sodium borohydride (1.20 g, 27 mmol) in ethanol (100 ml) was dropped into a solution of calcium chloride dihydrate (1.98 g, 13.5 mmol) in ethanol (100 ml) at −10 °C and stirred for 30 min at the same temperature. A solution of **5a** (7.0 g, 27 mmol) in ethanol (250 ml) was added to the former prepared solution and stirred for 5 h at −10 °C. The reaction mixture was additionally stirred for 10 h at room temperature. After the evaporation of ethanol from the reaction mixture, the residue was extracted with ether. The ether layer was dried over anhydrous $MgSO_4$ and evaporated down. The residue was purified by silica gel column chromatography (ethyl acetate) to give **10a** (4.76 g, 76%). Colorless needles, mp 42.5—43 °C (hexane), $[\alpha]_D^{30}$ +21.5° (*c* = 5.0, $CHCl_3$) (after 3 h). High-resolution MS *m/z* Calcd $C_{10}H_{19}NO_3S$ (M^+): 233.1085. Found: 233.1055. Calcd $C_9H_{16}NO_2S$ ($M^+ - CH_3O$): 202.0901. Found: 202.0912. IR ($CHCl_3$): 3440, 3330, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, *tert*-Bu), 2.05 (2H, br, NH, OH), 2.60—4.22 (7H, m, C_2-2H, $C_{4'}$-H, $C_{5'}$-2H, CH_2O), 4.78 (1H × 1/2, t, *J* = 6.0 Hz, $C_{2'}$-H), 4.82 (1H × 1/2, t, *J* = 6.0 Hz, $C_{2'}$-H) (after 3 h).[24]

***tert*-Butyl 2-[(4*S*)-4-Hydroxymethylthiazolidin-2-yl]-2-methylpropanoate (10b)** In a procedure similar to that described for the synthesis of **10a**, the reduction of **5b** (2.89 g, 10 mmol) with calcium borohydride prepared from sodium borohydride (0.39 g, 10 mmol) and calcium chloride dihydrate (0.76 g, 5 mmol) in ethanol (200 ml) gave, after silica gel column chromatography [hexane–ethyl acetate (1 : 1)], **10b** (1.90 g, 73%). Colorless needles, mp 49—50 °C (hexane), $[\alpha]_D^{27}$ +0.9° (*c* = 3.17, $CHCl_3$) (after 3 h). High-resolution MS *m/z* Calcd $C_{12}H_{23}NO_3S$ (M^+): 261.1397. Found: 261.1443. Calcd $C_{11}H_{20}NO_2S$ ($M^+ - CH_3O$): 230.1214. Found: 230.1212. Calcd $C_8H_{14}NO_3S$ ($M^+ - tert$-Bu): 204.0694. Found: 204.0670. IR ($CHCl_3$): 3420, 3310, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, s, Me), 1.30 (3H × 2/5, s, Me), 1.33 (3H × 3/5, s, Me), 1.46 (9H, s, *tert*-Bu), 2.27 (2H, br, NH, OH), 2.46—4.03 (5H, m, $C_{4'}$-H, $C_{5'}$-2H, CH_2O), 4.56 (1H × 2/5, s, $C_{2'}$-H), 4.61 (1H × 3/5, s, $C_{2'}$-H) (after 3 h).[24]

(3*S*)-3-Acetoxymethyl-7-oxo-1-thia-4-azabicyclo[3.2.0]heptane (11a) In a procedure similar to that described for the synthesis of **7a**, **10a** (300 mg, 1.29 mmol) was treated with 25% HBr–AcOH (10 ml) and the reaction of the evaporated residue with triphenylphosphine (507 mg, 1.94 mmol), 2,2′-dipyridyl disulfide (460 mg, 1.94 mmol) and triethylamine (131 mg, 1.29 mmol) in acetonitrile (130 ml) gave **11a** (43 mg, 13%) as a diastereomixture [**11a** (*trans*) : **11a** (*cis*) = 5 : 3]. Each diastereoisomer was separated by additional preparative TLC [silica gel, hexane–ethyl acetate (10 : 1)] to give the more polar product **11a** (*trans*) and the less polar one **11a** (*cis*).[22] **11a** (*trans*): colorless oil, $[\alpha]_D^{25}$ +248.9° (*c* = 0.18, $CHCl_3$). High-resolution MS *m/z* Calcd $C_8H_{11}NO_3S$ (M^+): 201.0459. Found: 201.0455. Calcd $C_7H_{11}NO_2S$ ($M^+ - CO$): 173.0510. Found: 173.0506. Calcd $C_6H_9NO_2S$ ($M^+ - CH_2=C=O$): 159.0353. Found: 159.0370. IR ($CHCl_3$): 1780, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, Me), 3.00 (1H, dd, *J* = 17.7, 2.7 Hz, $C_{6\beta}$-H), 3.11 (1H, dd, *J* = 13.5, 4.2 Hz, C_2-H),

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3.45 (1H, dd, J=13.5, 7.7 Hz, C_2-H), 3.52 (1H, dd, J=17.7, 4.6 Hz, $C_{6\alpha}$-H), 3.98 (1H, dd, J=11.5, 6.9 Hz, CHOAc), 4.10 (1H, dd, J=11.5, 7.7 Hz, CHOAc), 4.55—4.61 (1H, m, C_3-H), 4.99 (1H, dd, J=4.6, 2.7 Hz, C_5-H). **11a** (*cis*): colorless oil, $[\alpha]_D^{25}$ −283.4° (c=0.20, $CHCl_3$). High-resolution MS *m/z* Calcd $C_8H_{11}NO_3S$ (M^+): 201.0459. Found: 201.0445. Calcd $C_7H_{11}NO_2S$ (M^+-CO): 173.0510. Found: 173.0508. Calcd $C_6H_9NO_2S$ ($M^+-CH_2=C=O$): 159.0353. Found: 159.0375. IR ($CHCl_3$): 1780, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s, Me), 3.00 (1H, dd, J=17.7, 2.7 Hz, $C_{6\alpha}$-H), 3.12 (1H, dd, J=11.7, 9.6 Hz, C_2-H), 3.30 (1H, dd, J=11.7, 7.3 Hz, C_2-H), 3.46 (1H, dd, J=17.7, 4.6 Hz, $C_{6\beta}$-H), 3.56—3.62 (1H, m, C_3-H), 4.56 (1H, dd, J=11.9, 7.7 Hz, CHOAc), 4.83 (1H, dd, J=11.9, 7.5 Hz, CHOAc), 4.94 (1H, dd, J=4.6, 2.7 Hz, C_5-H).

(3*S*)-3-Acetoxymethyl-6,6-dimethyl-7-oxo-1-thia-4-azabicyclo[3.2.0]-heptane (11b) In a procedure similar to that described for the synthesis of **7a**, **10b** (100 mg, 0.38 mmol) was treated with 25% HBr–AcOH (10 ml) and the reaction of the evaporated residue with triphenylphosphine (121 mg, 0.46 mmol), 2,2′-dipyridyl disulfide (101 mg, 0.46 mmol) and triethylamine (42 mg, 0.42 mmol) in acetonitrile (40 ml) gave **11b** (40 mg, 46%) as a diastereomixture [**11b**(*trans*) : **11b**(*cis*) = 5 : 3]. Two diastereoisomers were separated by additional preparative TLC [silica gel, hexane–ethyl acetate (10 : 1)] to give the more polar product **11b**(*trans*) and the less polar one **11b** (*cis*).[22] **11b** (*trans*): colorless oil, $[\alpha]_D^{30}$ +138.3° (c=0.93, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{10}H_{15}NO_3S$ (M^+): 229.0772. Found: 229.0781. Calcd $C_9H_{15}NO_2S$ (M^+-CO): 201.0823. Found: 201.0852. Calcd $C_8H_{13}NO_2S$ ($M^+-CH_2=C=O$): 187.0666. Found: 187.0645. IR ($CHCl_3$): 1765, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, Me), 1.45 (3H, s, Me), 2.10 (3H, s, $COCH_3$), 3.02 (1H, dd, J=12.7, 2.7 Hz, C_2-H), 3.15 (1H, dd, J=12.7, 7.8 Hz, C_2-H), 3.96 (1H, dd, J=12.5, 7.5 Hz, CHOAc), 4.10 (1H, dd, J=12.5, 7.5 Hz, CHOAc), 4.46—4.58 (1H, m, C_3-H), 4.79 (1H, s, C_5-H). **11b** (*cis*): colorless oil, $[\alpha]_D^{25}$ −190.0° (c=0.28, $CHCl_3$). High-resolution MS *m/z* Calcd $C_{10}H_{15}NO_3S$ (M^+): 229.0772. Found: 229.0779. Calcd $C_9H_{15}NO_2S$ (M^+-CO): 201.0823. Found: 201.0847. Calcd $C_8H_{13}NO_2S$ ($M^+-CH_2=C=O$): 187.0666. Found: 187.0654. IR ($CHCl_3$): 1765, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, s, Me), 1.43 (3H, s, Me), 2.12 (3H, s, $COCH_3$), 2.85 (1H, dd, J=10.6, 8.8 Hz, C_2-H), 3.20 (1H, dd, J=10.6, 6.9 Hz, C_2-H), 3.45—3.53 (1H, m, C_3-H), 4.56 (1H, dd, J=11.5, 7.5 Hz, CHOAc), 4.76 (1H, s, C_5-H), 4.78 (1H, dd, J=11.5, 7.7 Hz, CHOAc).

Acknowledgements We are grateful to Misses Akiko Kamiyama and Mariko Kikuchi for their technical assistance and indebted to Drs. Chōzo Inoue and Taketoshi Naito of Showa Denko Co., Ltd. for providing D-cysteine. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

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