

Diastereo- and Regioisomeric Bicyclic Thiohydantoins from Chiral 1,3-Thiazolidine-2,4-dicarboxylic Acids

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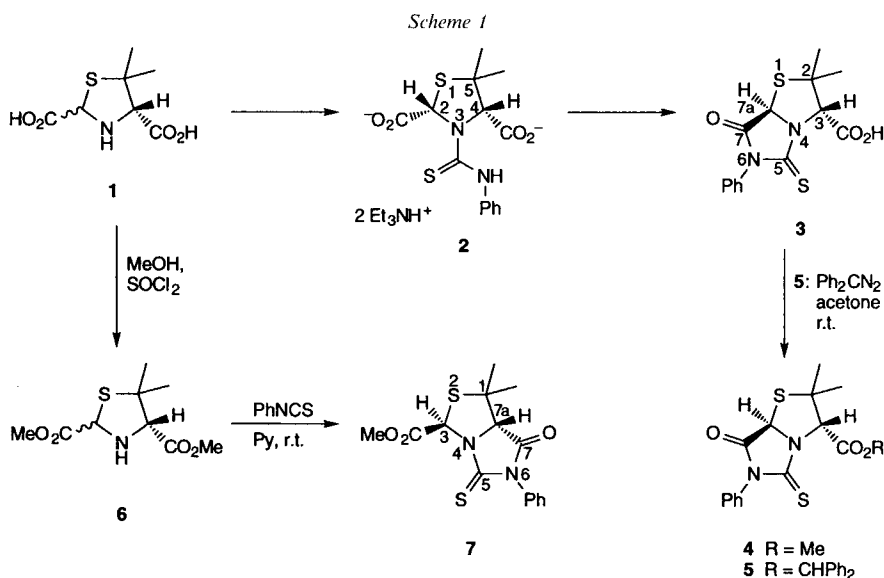
Bicyclic thiohydantoins were synthesized in a stereoselective manner by reacting (2*R*)/(2*S*)-diastereoisomer mixtures of 1,3-thiazolidine-2,4-dicarboxylic acids or their dimethyl diesters with PhNCS. 5,5-Dimethyl-1,3-thiazolidine-2,4-dicarboxylic acid with PhNCS led to a cyclization involving the C=O group at the C(2) center of the thiazolidine ring, while the acid's dimethyl diester gave cyclization involving the C=O group at C(4). In contrast, reactions involving unsubstituted 1,3-thiazolidine-2,4-dicarboxylic acid or its dimethyl diester led to thiohydantoins in which the ring closure had taken place only with the COO group at C(4). Independently of the direction of the ring closure, all reactions produce exclusively products with the (*R*)-configuration at C(2). The configurational assignments were based on ¹H- and ¹³C-NMR studies, and confirmed by X-ray crystallographic analyses.

1. Introduction. – Sulfur-containing cyclic α -amino acids, such as 1,3-thiazolidine-4-carboxylic acids, are well-known as building blocks of natural penicillins [1], and are also attracting increasing interest as chiral heterocycles [2].

The existing chiral center(s) in 1,3-thiazolidine-4-carboxylic acids offers the opportunity for diastereoselective reactions, and these possibilities have been widely used for the synthesis of 1,3-thiazolidin-2-yl analogues of pseudo-uridine [3], mesoionic 5*H*,7*H*-thiazolo[3,4-*c*]oxazol-1-ones [4][5], thiazolo[3,2-*a*]pyridines [6], 1*H*-thieno[3,4-*b*]pyrroles [7], for the total synthesis of chiral di- and tetrahydropyridines [8] and (+)-latrunculin A and B [9], for the stereochemical assignments of pyochelins [10] in the synthesis of antagonists of the Platelet Activating Factor (PAF) [11], for the production of thiazolidines with medium-size lactam rings [12], as dual metalloprotease inhibitors [13], as β -turn mimetics [14], and for the synthesis of cytotoxic thiazolo[4,3-*c*][1,4]benzothiazepines [15] and (*R*)-3-[(*S*)-5-oxopyrrolidin-2-yl]carboxy]thiazolidine-4-carboxylic acid, which is the immunostimulator *Pidotimod* [16].

A new approach to the synthesis of 2-alkylcysteins from *N*-acyl-1,3-thiazolidine-4-carboxylic acids has been developed [17]. Recently, these acids could be obtained by a convenient solid-phase synthesis [18], but if it is planned to synthesize the (2*R*,4*R*)- and (2*S*,4*R*)-isomers of (4*R*)-*N*-acyl-1,3-thiazolidine-4-carboxylic acids, these *cis*- and *trans*-derivatives are available only by the utilization of our procedures [5][19]. The acylating conditions [4b][19] (Ac₂O and pyridine, or Ac₂O and H₂O at 100°) result in the diastereoselective formation of the *cis*- and *trans*-(4*R*)-2-aryl-1,3-thiazolidine-4-car-

In the present article, we describe the regio- and stereochemical aspects of the cyclizations of 1,3-thiazolidine-2,4-dicarboxylic acids with isothiocyanates.



For details of $1 \rightarrow 2 \rightarrow 3 \rightarrow 4$, see [26]

NMR methods. To establish the structure and absolute configuration of **4**, which was a syrup, the crystalline diphenylmethyl ester **5** was prepared and studied by X-ray crystallography (*Fig. 1*).

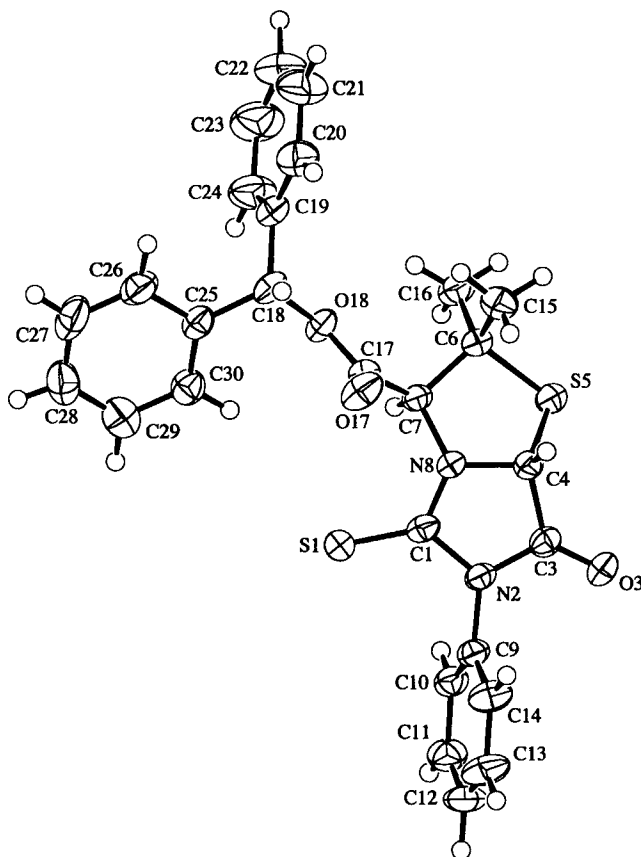
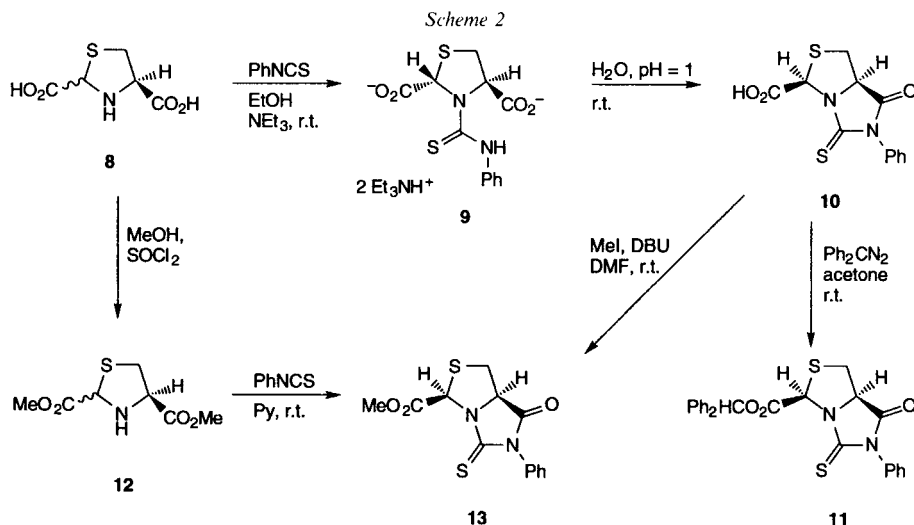


Fig. 1. The molecular structure and absolute configuration of 5 (arbitrary numbering of the atoms, 50% probability ellipsoids)

In the case of the reaction of the dimethyl diester **6** with PhNCS in pyridine at room temperature (*Scheme 1*), cyclization occurred which involved the COO group at C(4) and gave the thiohydantoin derivative **7** in a regio- and stereoselective manner. The structure of **7** was also confirmed by X-ray crystallography (*Fig. 2*).

The reaction of a mixture of the (2*R*,4*R*)- and (2*S*,4*R*)-diastereoisomers of 1,3-thiazolidine-2,4-dicarboxylic acid **8** (obtained from L-cysteine and glyoxylic acid by condensation) with PhNCS led to the final product **13** by both of the routes depicted in *Scheme 2*, and the stereospecific cyclization occurred solely with the COO group at C(4). For NMR studies, the corresponding diphenylmethyl ester **11** was also synthesized.

For all of the synthesized products, the direction of cyclization and the correct configurational assignments were deduced from the ^1H - and ^{13}C -NMR data, and the



X-ray crystallographic studies. Remarkably, the configuration at C(2) was (*R*) in all products, even though the starting materials were (*2R*)/(*2S*)-mixtures, and even when the cyclization had taken place at C(4).

2.2. NMR Studies. The ^1H - and ^{13}C -NMR assignments for the compounds depicted in Schemes 1 and 2 were based on simple chemical-shift considerations and our previous study [26]. The relevant ^1H and ^{13}C chemical shifts for the new compounds reported herein are given in the *Exper. Part*. Note that, in the following discussion, the numbering of the atoms of both the mono- and bicyclic molecules corresponds to that of the thiazolidine ring in order to allow a unified presentation of the NMR data.

The relative configuration of the chirality centers, C(2) and C(4), in the 5,5-dimethylthiazolidine derivatives (compounds **5** and **7**) was established by selective, steady-state NOE experiments (for compounds **2** and **3**, see [26]). The large, *ca.* 20–30%, NOE enhancement observed on $\text{H}-\text{C}(2)$ and $\text{H}-\text{C}(4)$ upon irradiation of the high-field and low-field $\text{Me}-\text{C}(5)$ protons, respectively, indicated that the $\text{H}-\text{C}(2)$ and $\text{H}-\text{C}(4)$ protons in compounds **5** and **7** were in the *trans*-position. For compounds **10**, **11** and **13** (Scheme 2), the *cis*-configuration of the substituents of the stereogenic C-atoms was deduced from the sum of the coupling constants between the geminal protons $\text{CH}_2(5)$ and $\text{H}-\text{C}(4)$. The large values for the sum of $J(\text{H}-\text{C}(4), \text{H}-\text{C}(5))$ and $J(\text{H}-\text{C}(4), \text{H}'-\text{C}(5))$ (16–17 Hz; see *Exper. Part*) unambiguously indicate that compounds **10**, **11** and **13** have the *cis*-configuration, while the low value for this sum (12.1 Hz) in the case of compound **9** indicates that this derivative has the *trans*-configuration. The arguments for this reasoning have been discussed previously [19a].

In our earlier study [26], the direction of cyclization on formation of compound **3** was established by a combined selective heteronuclear NOE and solvent-dependence study. The upfield shift (–2.5 ppm) of the $\text{C}=\text{O}$ signal at 168.6 ppm in **3** upon esterification to diphenylmethyl ester **5** also corroborated the assignment of the ^{13}C resonances, and gave further evidence to support our earlier structure determination [26]. Simple chemical-shift considerations allowed us to assign the structure of compound **7** as shown in

Scheme 1. The distinctly different chemical shifts of the corresponding C-atoms in compounds **7** and **4** (see *Exper. Part*) unambiguously indicate that the cyclization in **7** took place in the direction involving the COO group at C(4).

For compounds **10**, **11** and **13**, the direction of cyclization was established by selective, long-range INEPT [27] experiments. Both H–C(2) and the Ph₂CH proton (compound **11**) showed long-range correlations with the ester carbonyl C-atom, indicating that the ester group is attached to C(2), whereas the ring closure took place in the direction of C(4). Furthermore, also in accordance with the structure depicted in *Scheme 2*, two signals corresponding to the C=S and C=O of the newly formed ring were exclusively observed in the long-range INEPT spectrum obtained upon selective excitation of H–C(4). Thus, the observed long-range ¹H, ¹³C correlations clearly indicate that the direction of cyclization is towards the COO group at C(4). In a similar way to the 5,5-dimethyl derivative **5**, esterification of compound **10** resulted in a significant upfield shift (–1.2 and –2.9 ppm in **13** and **11**, resp.) of the carbonyl ¹³C signals assigned to the ester group. Accordingly, the chemical shift of the other C=O signal belonging to the ring C-atom attached to C(4) was not significantly affected by esterification.

2.3 X-Ray Crystallographic Studies. The molecular structures of **5** and **7** are depicted in *Figs. 1* and *2*, respectively. The bond lengths and angles generally have normal values, and the trends in the C–S and C=S bond lengths correspond closely with those in a compound similar to **7** in which the ester group has been replaced by a thienyl substituent [26]. The thiazolidine ring in **5** has the envelope conformation with S(5) as the envelope flap, while that in **7** has a half-chair conformation twisted on C(4)–C(5). In each compound, the imidazole ring makes an angle of *ca.* 73° with the Ph substituent at N(2) and is quite planar due to delocalisation effects between the N-atoms and the C=S and C=O bonds. The mean planes of the two fused five-membered rings in **5** and **7** enclose angles of 29° and 40°, respectively. The absolute configuration of **5** was determined successfully (see *Exper. Part*) and confirmed that **5** has the (2*R*,4*S*)-configuration. Although the relative configuration of **7** has been unambiguously elucidated, the determination of the absolute configuration gave results which suggested that the crystals were racemic twins, and a data collection performed using a second crystal yielded very similar results. However, as **7** is derived from D-penicillamine, it is unlikely that a racemic product would ensue, and optical rotation measurements confirmed the presence of optical activity. It is, therefore, assumed that the absolute-configuration determination is yielding inconclusive results, and the enantiomer used in the refinement and depicted in *Fig. 2* was chosen to agree with the known absolute configuration of the D-penicillamine precursor.

3. Conclusion. – The reaction of (2*R*)/(2*S*) diastereoisomeric mixtures of 5,5-dimethyl-1,3-thiazolidine-2,4-dicarboxylic acid [26] or its dimethyl diester with PhNCS yielded bicyclic thiohydantoin in a stereoselective manner involving the COO group at C(2) (in the case of the free acid) or C(4) (in the case of the diester). In contrast, reactions involving 1,3-thiazolidine-2,4-dicarboxylic acid or its dimethyl diester led to thiohydantoin in which the ring closure had taken place only in the direction of the COO group at C(4) of the thiazolidine ring.

This phenomenon may originate from the electron-donor character of the Me group and from the different ‘allylic 1,3-strains’ in the *cis*- and *trans*-products [28][29]. Accord-

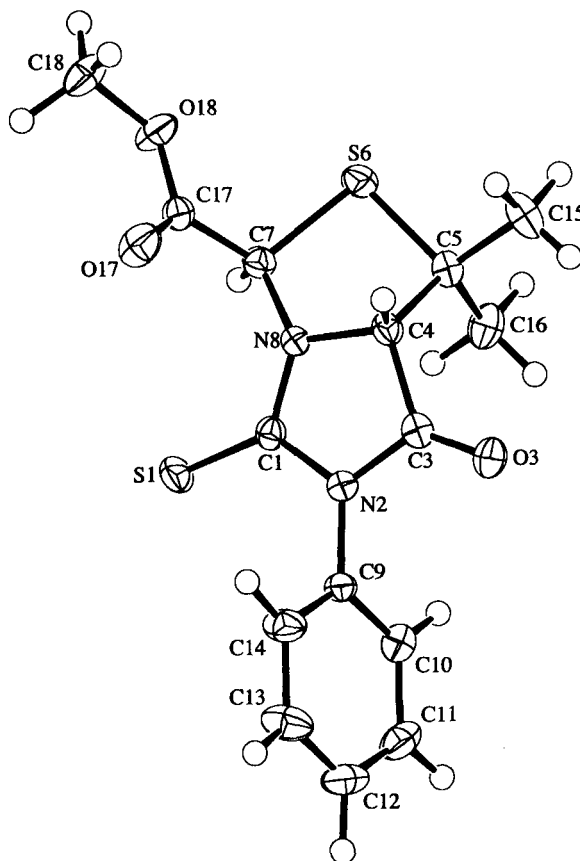


Fig. 2. The molecular structure of **7** (arbitrary numbering of the atoms, 50% probability ellipsoids)

ing to CD measurements [19], the conformation of the 1,3-thiazolidine ring is altered by the presence of the Me groups.

It is remarkable that the configuration at C(2) in each thiohydantoin is (*R*) and is independent of the configuration at C(4), the substituent at C(2), the initial configuration at C(2), and the direction of cyclization. This phenomenon has been shown previously to be attributable to an initial ring opening at C(2) and subsequent epimerization/ring closure, which can occur in a controlled way by employing the proper conditions during the acylation [19], and also occurs during the subsequent cyclization to yield the less strained fused ring system [26].

In the case of *N*-acyl- and *N*-(thio)carbamoyl-1,3-thiazolidine-4-carboxylic acids, the investigation of this complex phenomenon is in progress.

Experimental Part

1. *General*. TLC: Merck DC Alurolle Kieselgel 60F₂₅₄. M.p.: PHMK hot plate apparatus, uncorrected. Optical rotations: Perkin-Elmer 241 polarimeter. ¹H- and ¹³C-NMR: Bruker WP 200 SY (200.12 MHz for ¹H, 50.3 MHz for ¹³C) spectrometer at ambient temp. For ¹H measurements, 20–30 mg of samples were dissolved in 0.5 ml of

CDCl_3 or (D_6)DMSO 80–100 mg/0.05 ml (D_6)DMSO soln. were used for ^{13}C -NMR experiments. The chemical shifts were referenced to the DMSO solvent signal (2.49 ppm for ^1H , 39.5 ppm for ^{13}C), while TMS was used as an internal reference in CDCl_3 solutions. The selective, steady-state homonuclear NOE experiments were carried out in difference mode using the frequency jumping line selective saturation of proton transitions [25][26]. Selective proton pulses of 6–8 and 20–25 Hz were applied for the NOE and long-range INEPT experiments, respectively. The INEPT delay was optimized for the evolution of long-range couplings of 4–8 Hz. Microanalyses: Carlo Erba EA1108 Elemental Analyzer.

2. *Syntheses.* The mixture of the (2*R*,4*S*)- and (2*S*,4*S*)-diastereoisomers of 5,5-dimethyl-1,3-thiazolidine-2,4-dicarboxylic acid (**1**), bis(triethylammonium) (2*S*,4*S*)-5,5-dimethyl-3-(phenylthiocarbamoyl)-1,3-thiazolidine-2,4-dicarboxylate (**2**), (3*S*,7*aR*)-6-phenyl-2,2-dimethyl-7-oxo-5-thioxoimidazo[5,1-*b*]thiazole-3-carboxylic acid (**3**) the mixture of the (2*R*,4*R*)- and (2*S*,4*R*)-diastereoisomers of 1,3-thiazolidine-2,4-dicarboxylic acid (**8**) and the dimethyl diesters, (**6** and **12**), were prepared by known procedures [20 b, f, g][26].

2.1. *Bis(triethylammonium) (2*S*,4*R*)-3-(Phenylthiocarbamoyl)-1,3-thiazolidine-2,4-dicarboxylate (9).* Compound **8** (5 mmol) was dissolved in the presence of 10 mmol of Et_3N in 20 ml of EtOH, and 5 mmol of PhNCS was added. After stirring for 3 h, a white powder precipitated. Yield: 78%. M.p. 143°. ^1H -NMR (DMSO): 9.53 (s, NH); 7.1–7.3 (m, 5 arom. H); 5.85 (s, H–C(2)); 5.28 (t, $J(\text{H}–\text{C}(4), \text{H}–\text{C}(5)) + J(\text{H}–\text{C}(4), \text{H}'–\text{C}(5)) = 12.1$, H–C(4)); 3.54 (m, H–C(5)); 3.26 (m, H'–C(5)). Anal. calc. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2 \cdot 2 \text{ C}_6\text{H}_{15}\text{N}$: C 69.69, H 10.23, N 6.77, S 15.50; found: C 69.58, H 10.17, N 6.65, S 15.47.

2.2. *(3*R*,7*aR*)-7-Oxo-6-phenyl-5-thioxo[1*H*,3*H*,6*H*,7*aH*]imidazo[1,5-*c*]thiazole-3-carboxylic Acid (10).* Compound **9** (5 mmol) was dissolved in 20 ml H_2O . The reaction mixture was acidified to pH 1 with 10% HCl. After stirring for 1 h, the product was filtered. Yield: 78%. M.p. 152°. $[\alpha]_{\text{D}} = -92.7$ ($c = 1.0$, MeOH). ^1H -NMR (DMSO): 7.1–7.5 (m, 5 arom. H); 6.05 (s, H–C(3)); 4.94 (t, $J(\text{H}–\text{C}(7\text{a}), \text{H}–\text{C}(1)) + J(\text{H}–\text{C}(7\text{a}), \text{H}'–\text{C}(1)) = 16.4$, H–C(7a)); 3.45 (m, H–C(1)); 3.23 (m, H'–C(1)). ^{13}C -NMR (DMSO): 183.7 (C=S); 170.4 (C=O); 169.7 (COOH); 133.2, 128.9, 128.4 (arom. C); 66.3 (C(3)); 60.9 (C(7a)); 31.1 (C(1)). Anal. calc. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3\text{S}_2$: C 48.95, H 3.42, N 9.51, S 21.78; found: C 49.02, H 3.38, N 9.47, S 21.63.

2.3. *Methyl (3*R*,7*aR*)-7-Oxo-6-phenyl-5-thioxo[1*H*,3*H*,6*H*,7*aH*]imidazo[1,5-*c*]thiazole-3-carboxylate (13).* Compound **10** (1 mmol) was dissolved in 1.5 ml of DMF and the soln. was stirred at r.t. To this soln., 0.15 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 0.07 ml of MeI were added. After 90 min, the mixture was diluted with H_2O , and the product was isolated by extraction with Et_2O . The org. soln. was washed with H_2O , dried (Na_2SO_4) and evaporated, and the product crystallized from EtOH. Yield: 78%. M.p. 165°. $[\alpha]_{\text{D}} = +176$ ($c = 1.0$, DMSO). ^1H -NMR (DMSO): 7.3–7.6 (m, 5 arom. H); 6.05 (s, H–C(3)); 5.18 (t, $J(\text{H}–\text{C}(7\text{a}), \text{H}–\text{C}(1)) + J(\text{H}–\text{C}(7\text{a}), \text{H}'–\text{C}(1)) = 16.8$, H–C(7a)); 3.78 (s, MeO); 3.6 (m, 2 H–C(5)). ^{13}C -NMR (DMSO): 184.0 (C=S); 170.3 (C=O); 168.5 (COOMe); 133.3, 129.1, 128.6 (arom. C); 66.5 (C(3)); 60.4 (C(7a)); 53.2 (MeO); 30.7 (C(1)). Anal. calc. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{S}_2$: C 50.62, H 3.92, N 9.08, S 20.79; found: C 50.58, H 3.87, N 9.12, S 20.65.

2.4. *Derivatives 5 and 11: General Procedure.* Compound **3** or **10** (5 mmol) was dissolved in acetone (50 ml). To this soln., 6 mmol of Ph_2CN_2 was added (until a continuous red color was observed). After stirring for 3 h, the mixture was evaporated *in vacuo*. The products were crystallized from a mixture of acetone/ Et_2O 1:2 (v/v).

*Diphenylmethyl (3*S*,7*aR*)-7,7-Dimethyl-7-oxo-6-phenyl-5-thioxo[1*H*,3*H*,6*H*,7*aH*]imidazo[5,1-*b*]thiazole-3-carboxylate (5).* Yield: 78%. M.p. 182°. $[\alpha]_{\text{D}} = +245.5$ ($c = 1.0$, DMSO). ^1H -NMR (CDCl_3): 7.1–7.6 (m, 5 arom. H); 7.02 (s, $\text{CH}(\text{Ph})_2$); 5.89 (s, H–C(7a)); 5.29 (s, H–C(3)); 1.62, 1.29 (s, 2 Me). ^{13}C -NMR (DMSO): 185.6 (C=S); 170.4 (C=O); 166.1 (COOR); 126–140 (arom. C); 78.0 ($\text{CH}(\text{Ph})_2$); 73.1 (C(7a)); 64.8 (C(3)); 59.6 (C(2)); 30.1, 25.2 (2 Me). Anal. calc. for $\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_3\text{S}_2$: C 66.36, H 4.95, N 5.73, S 13.12; found: C 66.42, H 4.87, N 5.68, S 13.20.

*Diphenylmethyl (3*R*,7*aR*)-7-Oxo-6-phenyl-5-thioxo[1*H*,3*H*,6*H*,7*aH*]imidazo[1,5-*c*]thiazole-3-carboxylate (11).* Yield: 76%. M.p. 189°. $[\alpha]_{\text{D}} = +190$ ($c = 1.0$, DMSO). ^1H -NMR (CDCl_3): 7.3–7.7 (m, 5 arom. H); 6.96 (s, $\text{CH}(\text{Ph})_2$); 6.44 (s, H–C(3)); 4.99 (t, $J(\text{H}–\text{C}(7\text{a}), \text{H}–\text{C}(1)) + J(\text{H}–\text{C}(7\text{a}), \text{H}'–\text{C}(1)) = 16.2$, H–C(7a)); 3.49 (m, H–C(1)); 3.23 (m, H'–C(1)). ^{13}C -NMR (DMSO): 183.9 (C=S); 170.2 (C=O); 166.8 (COOR); 126–140 (arom. C); 78.2 ($\text{CH}(\text{Ph})_2$); 66.4 (C(3)); 60.7 (C(7a)); 30.7 (C(1)). Anal. calc. for $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_3\text{S}_2$: C 65.19; H 4.37, N 6.08, S 13.92; found: C 65.23, H 4.38, N 6.13, S 13.87.

2.5. *Derivatives 7 and 13: General Procedure.* Compound **6** or **12** (5 mmol) was dissolved in pyridine (5 ml), and 5 mmol of PhNCS were added. After stirring at r.t. for 24 h, the mixture was poured into ice-water, and the product was isolated by extraction with CH_2Cl_2 . The products were crystallized from EtOH.

*Methyl (3*R*,7*aS*)-1,1-Dimethyl-7-oxo-6-phenyl-5-thioxo[1*H*,3*H*,6*H*,7*aH*]imidazo[1,5-*c*]thiazole-3-carboxylate (7).* Yield: 89%. M.p. 138–142° $[\alpha]_{\text{D}} = +191$ ($c = 1.0$, DMSO). ^1H -NMR (DMSO): 7.1–7.6 (m, 5 arom. H); 6.09 (s, H–C(3)); 4.98 (s, H–C(7a)); 3.80 (s, MeO); 1.62, 1.37 (s, 2 Me). ^{13}C -NMR (DMSO): 183.2 (C=S); 168.5

(C=O); 167.9 (COOR); 132.7, 129.2, 128.3 (arom. C); 74.1 (C(3)); 59.4 (C(7a)); 54.5 (C(1)); 53.2 (MeO); 25.1, 23.9 (2 Me). Anal. calc. for $C_{15}H_{16}N_2O_3S_2$: C 53.55, H 4.79, N 8.33, S 19.06; found: C 53.34, H 5.13, N 9.00, S 19.08.

Data for 13: See 2.3.

3. *Crystal-Structure Determinations of 5 and 7*¹⁾. The data collection and refinement parameters for each compound are summarized in the Table. All measurements were conducted on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation ($\lambda = 0.71069 \text{ \AA}$) and a 12-kW rotating anode generator. The intensity data included the *Friedel* opposites of all unique reflections for 5, and all those with $2\theta < 50^\circ$ for 7. Three standard reflections measured after every 150 reflections showed negligible variation in intensity. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections, other than *Friedel* pairs, were merged. Each structure was solved by direct methods using *SHELXS86* [30], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The H-atoms were located in difference electron-density maps and were refined together with individual isotropic displacement parameters. Corrections for secondary extinction were applied. All refinements were carried out on *F* using full-matrix least-squares procedures which minimized the function $\sum w(|F_o| - |F_c|)^2$, where $1/w = \sigma^2(F_o) + (0.005F_o)^2$. Neu-

Table. Crystallographic Data for Compounds 5 and 7

	5	7
Crystallised from	Et ₂ O	EtOH
Empirical formula	C ₂₇ H ₂₄ N ₂ O ₃ S ₂	C ₁₅ H ₁₆ N ₂ O ₃ S ₂
Formula weight	488.62	335.42
Crystal colour, habit	colourless, prism	colourless, prism
Crystal dimensions [mm]	0.30 × 0.30 × 0.45	0.20 × 0.35 × 0.45
Temp. [K]	273 (1)	173 (1)
Crystal system	orthorhombic	monoclinic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁
<i>Z</i>	4	2
Reflections for cell determination	21	25
2 θ Range for cell determination [°]	38–40	39–40
Unit cell parameters		
<i>a</i> [Å]	15.031 (1)	9.086 (1)
<i>b</i> [Å]	25.636 (5)	8.505 (2)
<i>c</i> [Å]	6.468 (2)	10.702 (1)
β [°]	90	105.74 (1)
<i>V</i> [Å ³]	2492.3 (8)	796.0 (2)
<i>D</i> _{calc} [g cm ⁻³]	1.302	1.404
$\mu(MoK_\alpha)$ [mm ⁻¹]	0.245	0.347
Scan type	ω	$\omega/2\theta$
Maximum 2 θ [°]	55	55
Total reflections measured	6610	3617
Symmetry-independent reflections	5726	3186
Reflections used [<i>I</i> > 2 σ (<i>I</i>)]	4495	3008
Variables	404	263
<i>R</i>	0.0378	0.0265
<i>wR</i>	0.0328	0.0269
Goodness of fit <i>s</i>	1.397	1.909
Secondary extinction coefficient	7.97×10^{-4}	6.72×10^{-4}
Final $\Delta_{\max}/\sigma$	0.001	0.0007
$\Delta\rho(\max; \min)$ [e Å ⁻³]	0.21; -0.20	0.25; -0.18

¹⁾ Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-101079. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: + 44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

tral-atom scattering factors were taken from [31 a][32]. Anomalous dispersion effects were included in F_c [31 b][33]. All calculations were performed using the TEXSAN [34] crystallographic software package and the figures were produced with ORTEPII [35].

For each structure, the absolute configuration was determined by refinement [36] of the completed model together with the absolute structure parameter [37]. For **5**, this parameter refined to a value of $-0.04(6)$, which confirmed that the refined coordinates represent the true enantiomorph. For **7**, a value of $0.67(6)$ was obtained. A data collection performed using a second crystal yielded very similar refinement results, and the absolute structure parameter was $0.42(6)$. These results suggest that the crystals of **7** are racemic twins. As **7** is derived from D-penicillamine, it is unlikely that a racemic product would ensue and it is, therefore, assumed that the result is inconclusive. The enantiomer used in the final refinement was chosen to agree with the known absolute configuration of the D-penicillamine precursor.

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