Synthesis of Thiazolidine-2-thione Derivatives and Evaluation of Their Hepatoprotective Effects

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A series of *N*-(mercaptoalkyl)thiazolidine-2-thiones and their derivatives were synthesized and evaluated for hepatoprotective activities against *Propionibacterium acnes*-lipopolysaccharide (*P. acnes*-LPS)-induced liver injury in mice and *in vitro* lipid peroxide (LPO) formation in rat liver microsomes. Reaction of *N*-(*p*-methoxybenzylthioalkyl)cysteine methyl ester (11) with 1,1′-thiocarbonyldiimidazole followed by deprotection gave the corresponding thiazolidine-2-thione derivatives. Among the compounds synthesized, 1a and 2a showed the most potent hepatoprotective activities against *P. acnes*-LPS-induced liver injury. Compounds 1a—f and 4 inhibited LPO formation *in vitro*. Compounds 1a and 2a were chosen for further pharmacological evaluations.

Keywords thiazolidine-2-thione; radical scavenger; liver injury; *P. acnes*-LPS; lipid peroxide

In the course of our recent studies on the development of hepatoprotective agents, we found a novel cyclic disulfide, SA3443,[1] which showed a potent protective effect against immunologically induced liver injury in an *in vivo* model. In addition to immunological dysfunctions, lipid peroxidation is thought to be one of the causes of liver injury.[2] Therefore, for the purpose of developing a new hepatoprotective agent, we have designed compounds which possess dual actions, namely inhibitory actions on both immunologically induced liver injury and lipid peroxide (LPO) formation.

Initially, we designed *N*-(mercaptoacyl)thiazolidine-2-thione (A) (Chart 1). Compound A could be unstable, because the *N*-acyl bond of *N*-acylthiazolidine-2-thione is easily cleaved in the presence of base or nucleophile.[3] Accordingly, we designed a series of *N*-(mercaptoalkyl)-thiazolidine-2-thiones (**1a**—**f**). We incorporated in the chemical structures of these compounds a partial structure of bucillamine,[4] an immunomodulator developed in our laboratories, in the expectation that the products would have immunological effects. In addition, the thioamide moiety, which could have an oxygen radical-scavenging action,[5] was included in the bucillamine structure. We also designed **2a**, **2d** and **2e** which have a thioester group constructed from ester and mercapto groups in **1a**, **1d** and **1e**. To examine the roles of the thiazolidine-2-thione structure and the functional groups of the thiazolidine-2-thione ring, analogues (**3** and **4**) were designed. In this paper, we describe the preparation of *N*-(mercaptoalkyl)-thiazolidine-2-thione derivatives. The effects of these compounds on immunologically induced liver injury and on LPO formation are also discussed.

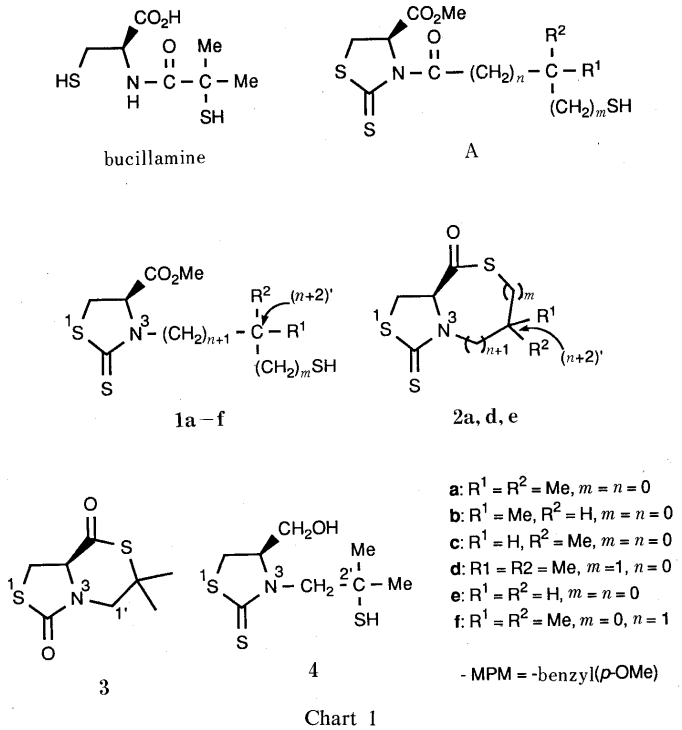
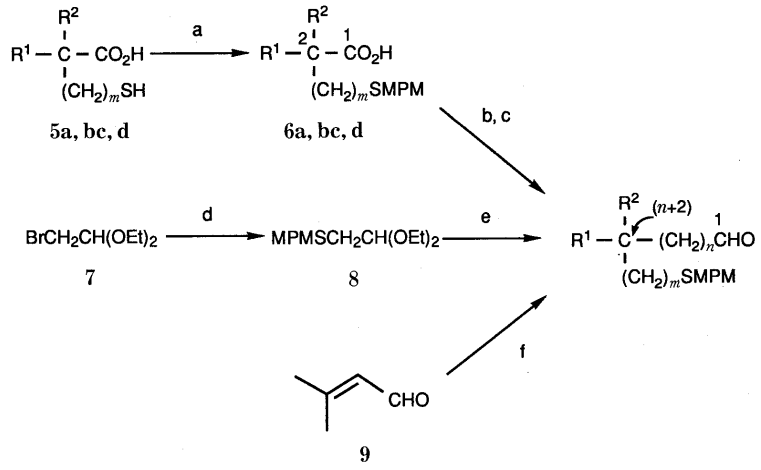


Chart 1

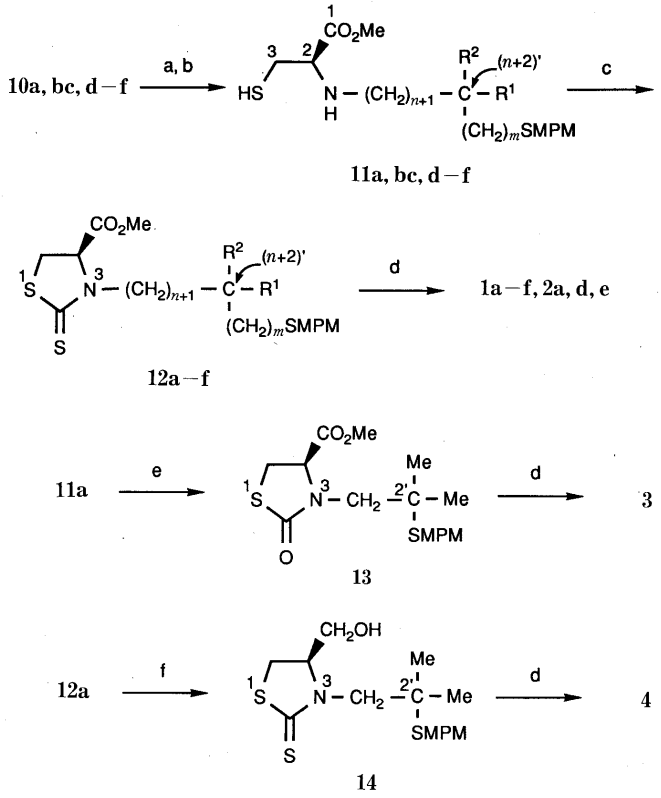
Chemistry The *N*-(mercaptoalkyl)thiazolidine-2-thiones and their derivatives were prepared by the following methods. Aldehydes (**10a**—**d**) were prepared by protection of SH groups of **5a**—**d** with *p*-methoxybenzyl chloride (MPMCl),[6] followed by a reduction to alcohol using lithium aluminum hydride ($LiAlH_4$) and Swern oxidation.[7] Aldehyde **10e** was prepared by introduction of an S group at the acetal (**7**) with *p*-methoxybenzylmercaptan (MPMSH), followed by deprotection of the diethyl acetal. Aldehyde **10f** was prepared by Michael-type addition of MPMSH to the α,β-unsaturated aldehyde (**9**) by the use of a catalytic amount of 4-dimethylaminopyridine (DMAP) (Chart 2).

N-Alkylcysteines (**11a**—**f**) were prepared by reductive amination[8] of the aldehydes (**10a**—**f**) with cystine dimethylester dihydrochloride in MeOH using $NaBH_3CN$ in the presence of Molecular sieves (M.S.) 3A, followed by S–S cleavage using $(n\text{-}Bu)_3P$.[9] Reaction of **11a**—**f** with 1,1′-thiocarbonyldiimidazole in $CHCl_3$ gave the ring closed products (**12a**—**f**). The diastereoisomers (**12b** and **12c**) could be separated by column chromatography. The deblocking of the *p*-methoxybenzyl (MPM) group was carried out in trifluoroacetic acid (TFA) using trifluoromethanesulfonic acid (TFMSA) in the presence of thioanisole.[10] The conditions of run 1 (Table I) gave two products (**1a** and **2a**), which could easily be separated by column chromatography. Depending on the deprotection conditions, **1a** or **2a** was obtained selectively (runs 2 and 3).



a: MPMCl, NaOH / EtOH - H_2O b: $LiAlH_4$ / THF - Et_2O c: Swern oxidation
d: MPMSH, NaOH / EtOH - H_2O e: HCl / acetone - H_2O f: MPMSH, 4-DMAP / MeOH

Chart 2



a: cystine dimethyl ester dihydrochloride, $NaBH_3CN$, M.S. 3A / MeOH
b: $(n\text{-}Bu)_3P$ / EtOH - H_2O c: 1, 1'-thiocarbonyldiimidazole / $CHCl_3$
d: CF_3SO_3H, thioanisole / CF_3CO_2H e: 1, 1'-carbonyldiimidazole / DMF
f: $LiAlH_4$ / THF - Et_2O

Chart 3

A thiazolidin-2-one derivative (**3**) was synthesized by ring construction with an *N*-alkylcysteine (**11a**) and 1,1'-carbonyldiimidazole in *N*,*N*-dimethylformamide (DMF), followed by deprotection under the same reaction conditions as used in run 3.

A 4-hydroxymethyl derivative (**4**) was synthesized by $LiAlH_4$ reduction of the methyl ester in **12a**, followed by deprotection under the same reaction conditions as used in run 2.

Table I. Deprotection of S-*p*-Methoxybenzyl (S-MPM) Group

Run	Temp. (°C)	Time (min)	CF_3SO_3H (eq)	C_6H_5SMe (eq)	**1a** (%)	**2a** (%)
1	25	15	2	2	49	13
2	0	15	2	2	62	0
3	25	30	4	4	3	60

Table II. Effects of Thiazolidine-2-thione Derivatives on the Mortality of Mice with Acute Hepatic Failure Induced by *P. acnes*-LPS

Compd. No.	Mortality (No. dead/total)	
	0—48 h	
Control	4/6	67%
1a	0/5	0%
1b	5/6	83%
1c	4/6	67%
1d	2/6	33%
1e	3/6	50%
1f	4/5	80%
2a	0/6	0%
2d	4/6	67%
2e	3/6	50%
3	2/5	40%
4	4/5	80%

Biological Results and Discussion

The compounds synthesized above were initially examined for hepatoprotective activities against *Propionibacterium acnes*-lipopolysaccharide (*P. acnes*-LPS)-induced liver injury in mice.[11] The results are summarized in Table II. Compound **1a** and the bicyclic compound **2a** showed remarkable hepatoprotective activity. On the other hand, the activities of **1b**—**f**, **2d** and **2e** were rather weak. These results clearly indicate that the substitution pattern and the N–SH length of the *N*-alkyl chain in **1a**—**f** profoundly influenced the hepatoprotective activity. In the bicyclic compounds **2a**, **2d** and **2e**, the substitution pattern and the size of the thiolactone ring profoundly influenced the activity. Furthermore, the thiazolidin-2-one derivative (**3**) and the derivative (**4**) having a hydroxymethyl group

TABLE III. Effects of Thiazolidine-2-thione Derivatives on the Formation of Lipid Peroxide by ADP–Fe^{2+}–Ascorbic Acid in Rat Liver Microsomes (*in Vitro*)

Compd. No.	Inhibition of LPO formation (%)	
Conc. (M)	10^{-3}	10^{-4}
1a	97.0	11.2
1b	97.8	11.1
1c	82.2	10.5
1e	95.3	14.7
2a	29.6	17.5
2d	15.9	NT
3	9.4	NT
4	95.2	19.5
Bucillamine	16.1	NT

NT, represents not-tested.

instead of the methoxycarbonyl group did not show the activity. These results suggest that the 2-thioxo group of the thiazolidine moiety and the ester group on the thiazolidine-2-thione ring considerably influence the hepatoprotective activity.

We next examined the inhibitory action on LPO formation by ADP–Fe^{2+}–ascorbic acid in rat liver microsomes. The results are shown in Table III. While compounds **1a**—**e** and **4** having an SH group in the *N*-alkyl chain showed an inhibitory action on the formation of LPO, bicyclic compounds in which the SH group is protected by a thioester construction did not show the activity in spite of the presence of the thiazolidine-2-thione ring. On the other hand, the parent compound, bucillamine, and the 2-one compound (**3**) did not show inhibitory action on the formation of LPO. From these results, we can conclude that the existence of both the thiazolidine-2-thione ring and the SH group in the molecule is necessary for inhibitory activity on LPO formation *in vitro*.

As a result, **1a** was found to inhibit both immunologically induced liver injury and LPO formation. Although compound **2a** did not show inhibitory activity on LPO formation *in vitro*, it might act as an equivalent of **1a** by being metabolized *in vivo*.

Consequently, compounds **1a** and **2a** were selected as candidates for further pharmacological evaluations. These studies are in progress.

Experimental

Melting points were determined in open glass capillaries with a Yamato MP-21 or Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed by a Yanagimoto MT-3 CHN Corder elemental analyzer. IR spectra were recorded on a JASCO A-302 or Perkin Elmer 1600 series FTIR infrared spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Hitachi M-80B spectrometer in the EI mode with samples introduced directly into the ion source for spectral determination. NMR spectra were measured by a JEOL GX-400 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are given in hertz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dq=doublet of quartets, dd=doublet of doublets and ddd=doublet of doublets of doublets. Fuji-Davison Silica gel BW-300 (200—325 mesh) was used for column chromatography. Rotations at the sodium D line were determined at 25 °C with a JASCO DIP-140 digital polarimeter (1-dm cells). Analytical thin layer chromatography (TLC) was peformed using precoated glass-backed plates (Merck Kieselgel 60 F_{254}) and bands were visualized under ultraviolet light.

2-(4-Methoxybenzylthio)-2-methylpropanal (10a) (General Procedure) A 2 N NaOH solution (597 ml, 1.19 mol) and MPMCl (86.9 ml, 0.64 mol) were added to a solution of 2-mercapto-2-methylpropanoic acid (**5a**) (70.0 g, 0.58 mol) in EtOH (600 ml) under ice cooling. The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo* followed by acidification with 6 N HCl. The mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was collected by filtration and washed with iso-Pr_2O to give **6a** (97.0 g, 69%), mp 92—93 °C (*n*-hexane–AcOEt). IR (KBr): 1685, 1610, 1515, 1302, 1294, 1254, 1173, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (6H, s, C_2-CH_3), 3.78 (3H, s, OCH_3), 3.86 (2H, s, SCH_2Ar), 6.82 (2H, d, J=8.8, aromatic protons), 7.24 (2H, d, J=8.8, aromatic protons). A solution of **6a** (80.0 g, 0.33 mol) in anhydrous tetrahydrofuran (THF) (50 ml) was added to a stirred suspension of $LiAlH_4$ (13.64 g, 0.34 mol) in anhydrous ether (350 ml) at room temperature. Stirring was continued at the same temperature overnight, then the reaction mixture was decomposed with AcOEt, H_2O and 6 N HCl, and the mixture was extracted with AcOEt. The organic layer was washed with 1 N HCl, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was oxidized using the Swern oxidation procedure.[7] A solution of the crude alcohol was added to a cold (−60 °C) stirred solution of $(COCl)_2$ (32.8 ml, 0.38 mol) and dimethyl sulfoxide (DMSO) (53.4 ml, 0.75 mol) in dry CH_2Cl_2 (730 ml). The solution was stirred for 10 min at −60 °C, and then Et_3N (238 ml, 1.71 mol) was added. The mixture was stirred at 20 °C for a period of 1.5 h, then the reaction was quenhced with H_2O and the whole was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **10a** (62.6 g, 83%) as a colorless oil.

2-(4-Methoxybenzylthio)-2-methylpropanal (**10a**): (57% overall yield). IR (neat): 2964, 2928, 1707, 1611, 1514, 1462, 1302, 1247, 1176, 1126, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (6H, s, C_2-CH_3 × 2), 3.47 (2H, s, SCH_2Ar), 3.78 (3H, s, OCH_3), 6.82 (2H, d, J=8.8, aromatic protons), 7.18 (2H, d, J=8.8, aromatic protons), 9.12 (1H, s, C_1-H). HRMS m/z (M^+): Calcd for $C_{12}H_{16}O_2S$: 224.0870. Found: 224.0900.

(±)-2-(4-Methoxybenzylthio)propanal (**10bc**): Compound **10bc** was prepared starting from **5bc** (enantiomeric mixture) by the same procedures as described for the synthesis of compound **10a** (37% overall yield). Colorless oil. IR (neat): 1710, 1611, 1514, 1245, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6.8, C_2-CH_3), 3.13 (1H, dq, J=4.4, 6.8, C_2-H), 3.52 (1H, d, J=13.2, SCHAr), 3.60 (1H, d, J=13.2, SCHAr), 3.80 (3H, s, OCH_3), 6.85 (2H, d, J=8.8, aromatic protons), 7.23 (2H, d, J=8.8, aromatic protons), 9.20 (1H, d, J=4.4, C_1-H). HRMS m/z (M^+): Calcd for $C_{11}H_{14}O_2S$: 210.0714. Found: 210.0710.

3-(4-Methoxybenzylthio)-2,2-dimethylpropanal (**10d**): Compound **10d** was prepared starting from **5d** by the same procedures as described for the synthesis of compound **10a** (23% overall yield). Colorless oil. IR (neat): 2928, 1723, 1681, 1609, 1510, 1460, 1245, 1174, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, s, C_2-CH_3 × 2), 2.57 (2H, s, C_3-H_2), 3.67 (2H, s, SCH_2Ar), 3.80 (3H, s, OCH_3), 6.85 (2H, d, J=8.3, aromatic protons), 7.22 (2H, d, J=8.3, aromatic protons), 9.41 (1H, s, C_1-H). HRMS m/z (M^+): Calcd for $C_{13}H_{18}O_2S$: 238.1027. Found: 238.1023.

2-(4-Methoxybenzylthio)acetaldehyde (10e) A 1 N NaOH solution (29 ml, 29 mmol) and 97% bromoacetaldehyde diethyl acetal (**7**) (2.06 ml, 13.3 mmol) were added dropwise to a solution of 90% MPMSH (2.06 ml, 13.3 mmol) in EtOH (30 ml) under ice cooling. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, and extracted with Et_2O. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **8** (1.74 g, 49%) as a colorless oil. IR (neat): 2980, 2928, 1611, 1513, 1465, 1301, 1246, 1175, 1122, 1053 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, t, CH_3CH_2O × 2), 2.58 (2H, d, J=5.4, MPMSCH_2), 3.59 (4H, m, OCH_2 × 2), 3.75 (2H, s, SCH_2Ar), 3.80 (3H, s, OCH_3), 4.55 (1H, t, J=5.4, $CH(OEt)_2$), 6.84 (2H, d, J=8.8, aromatic protons), 7.25 (2H, d, J=8.8, aromatic protons). A solution of **8** (1.14 g, 4.22 mmol) in acetone (10 ml) and 1 N HCl (1 ml) was stirred at room temperature overnight. The reaction mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **10e** (0.58 g, 70%) as a colorless oil. IR (neat): 3000, 2836, 1717, 1611, 1514, 1465, 1303, 1244, 1176, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (2H, d, J=3.4, C_2-H_2), 3.59 (2H, s, SCH_2Ar), 3.80 (3H, s, OCH_3), 6.86 (2H, d, J=8.8, aromatic protons), 7.22 (2H, d, J=8.8, aromatic protons), 9.41 (1H, t, J=3.4, C_1-H).

HRMS *m/z* (M^+): Calcd for $C_{10}H_{12}O_2S$: 196.0557. Found: 196.0558.

3-(4-Methoxybenzylthio)-3-methylbutanal (10f) A mixture of 97% 3-methyl-2-butenal (**9**) (7.71 ml, 77.5 mmol) and 90% MPMSH (8.00 ml, 51.7 mmol) in MeOH (10 ml) containing a catalytic amount of DMAP was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel to give **10f** (12.01 g, 98%) as a colorless oil. IR (neat): 2960, 2928, 1717, 1611, 1513, 1301, 1249, 1176, 1132, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (6H, s, C_3-$CH_3 \times 2$), 2.55 (2H, d, J=2.9, C_2-H_2), 3.74 (2H, s, SCH_2Ar), 3.78 (3H, s, OCH_3), 6.83 (2H, d, J=8.8, aromatic protons), 7.24 (2H, d, J=8.8, aromatic protons), 9.83 (1H, t, J=2.9, C_1-H). HRMS *m/z* (M^+): Calcd for $C_{13}H_{18}O_2S$: 238.1027. Found: 238.1029.

***N*-[2-(4-Methoxybenzylthio)-2-methylpropyl]-L-cysteine Methyl Ester (11a) (General Procedure)** L-Cystine dimethyl ester dihydrochloride (4.53 g, 13.3 mmol) and M.S. 3A (3 g) were added to a stirred solution of the aldehyde **10a** (5.95 g, 26.5 mmol) in MeOH (140 ml) at room temperature. The mixture was stirred at the same temperature for 30 min, then 95% $NaBH_3CN$ (1.75 g, 26.5 mmol) was added and the whole was stirred at room temperature overnight. The reaction was quenched by careful addition of saturated $NaHCO_3$ solution, and the mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. (n-Bu)$_3$P (6.61 ml) was added to a solution of the residue in MeOH (170 ml) and H_2O (20 ml) at room temperature. The reaction mixture was stirred at the same temperature for 2 h, concentrated *in vacuo* and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **11a** (4.96 g, 54%) as a pale yellow oil.

N-[2-(4-Methoxybenzylthio)-2-methylpropyl]-L-cysteine Methyl Ester (**11a**): IR (neat): 2956, 1736, 1611, 1514, 1249, 1175, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, s, $C_{2'}$-CH_3), 1.34 (3H, s, $C_{2'}$-CH_3), 2.38 (1H, d, J=11.7, $C_{1'}$-H), 2.72 (1H, d, J=11.7, $C_{1'}$-H), 2.78 (2H, t-like, J=5.9, C_3-H_2), 3.38 (1H, t, J=5.9, C_2-H), 3.66 (1H, d, J=12.0, SCHAr), 3.71 (1H, d, J=12.0, SCHAr), 3.76 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.78 (3H, s, CO_2CH_3 or $ArOCH_3$), 6.83 (2H, d, J=8.8, aromatic protons), 7.27 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −14.6° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{16}H_{25}NO_3S_2$: 343.1274. Found: 343.1285.

N-[2-(4-Methoxybenzylthio)propyl]-L-cysteine Methyl Ester (**11bc**) (inseparable diastereomixture): Compound **11bc** was prepared starting from **10bc** by the same procedures as described for the synthesis of compound **11a** (66% overall yield). Pale yellow oil. IR (neat): 2952, 1736, 1611, 1513, 1463, 1302, 1247, 1174, 1033 cm^{-1}. HRMS *m/z* (M^+): Calcd for $C_{15}H_{23}NO_3S_2$: 329.1118. Found: 329.1086.

N-[3-(4-Methoxybenzylthio)-2,2-dimethylpropyl]-L-cysteine Methyl Ester (**11d**): Compound **11d** was prepared starting from **10d** by the same procedures as described for the synthesis of compound **11a** (53% overall yield). Pale yellow oil. IR (neat): 2948, 1736, 1609, 1511, 1463, 1432, 1299, 1247, 1194, 1173, 1031 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, s, $C_{2'}$-CH_3), 0.94 (3H, s, $C_{2'}$-CH_3), 2.25 (1H, d, J=11.7, $C_{1'}$-H), 2.41 (1H, d, J=12.2, $C_{3'}$-H), 2.50 (1H, d, J=12.2, $C_{3'}$-H), 2.52 (1H, d, J=11.7, $C_{1'}$-H), 2.73 (2H, br s, C_3-H_2), 3.35 (1H, t, J=5.4, C_2-H), 3.66 (2H, s, SCH_2Ar), 3.75 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.80 (3H, s, CO_2CH_3 or $ArOCH_3$), 6.84 (2H, d, J=8.3, aromatic protons), 7.23 (2H, d, J=8.3, aromatic protons). $[\alpha]_D^{25}$ −13.8° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{17}H_{27}NO_3S_2$: 357.1431. Found: 357.1425.

N-[2-(4-Methoxybenzylthio)ethyl]-L-cysteine Methyl Ester (**11e**): Compound **11e** was prepared starting from **10e** by the same procedures as described for the synthesis of compound **11a** (23% overall yield). Pale yellow oil. IR (neat): 2951, 2835, 1735, 1610, 1584, 1512, 1464, 1302, 1248, 1175, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.85 (6H, m, C_3-H_2, $C_{1'}$-H_2, $C_{2'}$-H_2), 3.43 (1H, t, J=5.9, C_2-H), 3.75 (2H, m, SCH_2Ar), 3.76 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.80 (3H, s, CO_2CH_3 or $ArOCH_3$), 6.84 (2H, d, J=8.3, aromatic protons), 7.23 (2H, d, J=8.3, aromatic protons). $[\alpha]_D^{25}$ −33.8° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{14}H_{21}NO_3S_2$: 315.0962. Found: 315.0962.

N-[3-(4-Methoxybenzylthio)-3-methylbutyl]-L-cysteine Methyl Ester (**11f**): Compound **11f** was prepared starting from **10f** by the same procedures as described for the synthesis of compound **11a** (57% overall yield). Pale yellow oil. IR (neat): 2952, 2924, 1736, 1611, 1513, 1464, 1301, 1248, 1174, 1033 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s, $C_{3'}$-$CH_3 \times 2$), 3.43 (1H, t, J=5.4, C_2-H), 3.68 (2H, s, SCH_2Ar), 3.76 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.78 (3H, s, CO_2CH_3 or $ArOCH_3$), 6.83 (2H, d, J=8.8, aromatic protons), 7.25 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −12.1° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{17}H_{27}NO_3S_2$: 357.1431. Found: 357.1398.

Methyl (4*R*)-3-[2-(4-Methoxybenzylthio)-2-methylpropyl]-2-thioxothiazolidine-4-carboxylate (12a) (General Procedure) 1,1′-Thiocarbonyldiimidazole (90%, 3.03 g, 15.3 mmol) was added to a solution of **11a** (5.00 g, 14.6 mmol) in $CHCl_3$ (90 ml) at room temperature. The reaction mixture was stirred at the same temperature for 1 h, washed with 3 N HCl, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was collected by filtration and washed with iso-Pr_2O. Recrystallization from AcOEt gave **12a** (5.10 g, 91%) as colorless needles.

Methyl (4*R*)-3-[2-(4-Methoxybenzylthio)-2-methylpropyl]-2-thioxothiazolidine-4-carboxylate (**12a**): mp 125—127 °C. IR (KBr): 2964, 1743, 1609, 1514, 1443, 1408, 1303, 1242, 1217, 1177, 1130, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s, $C_{2'}$-CH_3), 1.48 (3H, s, $C_{2'}$-CH_3), 3.23 (1H, d, J=15.1, $C_{1'}$-H), 3.37 (1H, d, J=11.7, C_5-H), 3.64 (1H, dd, J=7.8, 11.7, C_5-H), 3.70 (1H, d, J=12.7, SCHAr), 3.77 (1H, d, J=12.7, SCHAr), 3.79 (6H, s, $ArOCH_3$, CO_2CH_3), 4.81 (1H, d, J=15.1, $C_{1'}$-H), 5.70 (1H, d, J=7.8, C_4-H), 6.84 (2H, d, J=8.8, aromatic protons), 7.21 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −63.7° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{23}NO_3S_3$: C, 52.96; H, 6.01; N, 3.63. Found: C, 52.89; H, 5.84; N, 3.55.

Methyl (4*R*)-3-[2-(4-Methoxybenzylthio)propyl]-2-thioxothiazolidine-4-carboxylate (**12b** and **12c**): Compounds **12b** and **12c** were prepared starting from a mixture of **11bc** by the same procedures as described for the synthesis of compound **12a**. Diastereomeric compounds **12b** and **12c** were easily separated by column chromatography. **12b**: (41% yield). Colorless needles, mp 60—62 °C (*n*-hexane–AcOEt). TLC *Rf* 0.40, *n*-hexane–AcOEt 2:1. IR (KBr): 2972, 1731, 1610, 1514, 1406, 1287, 1253, 1210, 1173, 1115, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.8, $C_{2'}$-CH_3), 3.02 (1H, dd, J=10.3, 14.2, $C_{1'}$-H), 3.29 (1H, m, $C_{2'}$-H), 3.36 (1H, dd, J=1.5, 11.7, C_5-H), 3.54 (1H, dd, J=8.8, 11.7, C_5-H), 3.66 (1H, d, J=13.2, SCHAr), 3.75 (1H, d, J=13.2, SCHAr), 3.80 (6H, s, $ArOCH_3$, CO_2CH_3), 4.48 (1H, dd, J=4.4, 14.2, $C_{1'}$-H), 5.06 (1H, dd, J=1.5, 8.8, C_4-H), 6.85 (2H, d, J=8.3, aromatic protons), 7.21 (2H, d, J=8.3, aromatic protons). $[\alpha]_D^{25}$ −76.9° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_3S_3$: C, 51.72; H, 5.70; N, 3.77. Found: C, 51.62; H, 5.60; N, 3.69. **12c**: (44% yield). Colorless oil. TLC *Rf* 0.33, *n*-hexane–AcOEt 2:1. IR (neat): 2952, 1746, 1610, 1513, 1452, 1246, 1205, 1177, 1107, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.8, $C_{2'}$-CH_3), 3.12 (1H, m, $C_{2'}$-H), 3.24 (1H, dd, J=6.8, 14.2, $C_{1'}$-H), 3.39 (1H, dd, J=2.0, 11.7, C_5-H), 3.60 (1H, dd, J=8.8, 11.7, C_5-H), 3.73 (1H, d, J=13.2, SCHAr), 3.797 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.802 (3H, s, CO_2CH_3 or $ArOCH_3$), 3.82 (1H, d, J=13.2, SCHAr), 4.69 (1H, dd, J=6.8, 14.2, $C_{1'}$-H), 4.83 (1H, dd, J=2.0, 8.8, C_4-H), 6.84 (2H, d, J=8.8, aromatic protons), 7.26 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −94.4° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+ − MPM): Calcd for $C_8H_{12}NO_2S_3$: 250.0029. Found: 250.0009.

Methyl (4*R*)-3-[3-(4-Methoxybenzylthio)-2,2-dimethylpropyl]-2-thioxothiazolidine-4-carboxylate (**12d**): Compound **12d** was prepared starting from **11d** by the same procedures as described for the synthesis of compound **12a** (quantitative yield). Colorless oil. IR (neat): 2952, 1743, 1608, 1510, 1444, 1401, 1300, 1201, 1029 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (6H, s, $C_{2'}$-$CH_3 \times 2$), 2.34 (1H, d, J=12.2, $C_{3'}$-H), 2.41 (1H, d, J=12.2, $C_{3'}$-H), 3.01 (1H, d, J=14.2, $C_{1'}$-H), 3.16 (1H, d, J=11.7, C_5-H), 3.23 (1H, dd, J=7.8, 11.7, C_5-H), 3.58 (1H, d, J=13.7, SCHAr), 3.71 (1H, d, J=13.7, SCHAr), 3.81 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.82 (3H, s, CO_2CH_3 or $ArOCH_3$), 4.49 (1H, d, J=14.2, $C_{1'}$-H), 4.76 (1H, d, J=6.8, C_4-H), 6.87 (2H, d, J=8.3, aromatic protons), 7.19 (2H, d, J=8.3, aromatic protons). $[\alpha]_D^{25}$ −13.7° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{18}H_{25}NO_3S_3$: 399.0995. Found: 399.0975.

Methyl (4*R*)-3-[2-(4-Methoxybenzylthio)ethyl]-2-thioxothiazolidine-4-carboxylate (**12e**): Compound **12e** was prepared starting from **11e** by the same procedures as described for the synthesis of compound **12a** (79% yield). Colorless oil. IR (neat): 2952, 1747, 1609, 1511, 1462, 1247, 1175, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (1H, ddd, J=5.4, 6.4, 13.7, $C_{2'}$-H), 2.85 (1H, m, $C_{2'}$-H), 3.26 (1H, ddd, J=6.4, 7.3, 14.2, $C_{1'}$-H), 3.40 (1H, dd, J=2.0, 11.2, C_5-H), 3.64 (1H, dd, J=8.8, 11.2, C_5-H), 3.72 (2H, s, SCH_2Ar), 3.80 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.81 (3H, s, CO_2CH_3 or $ArOCH_3$), 4.53 (1H, ddd, J=5.4, 6.8, 14.2, $C_{1'}$-H), 4.89 (1H, dd, J=2.0, 8.8, C_4-H), 6.85 (2H, d, J=8.8, aromatic protons), 7.24 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −65.9° (c=1.0, $CHCl_3$). HRMS *m/z* (M^+): Calcd for $C_{15}H_{19}NO_3S_3$: 357.0526. Found: 357.0506.

Methyl (4*R*)-3-[3-(4-Methoxybenzylthio)-3-methylbutyl]-2-thioxothiazolidine-4-carboxylate (**12f**): Compound **12f** was prepared starting from **11f** by the same procedures as described for the synthesis of compound **12a** (73% yield). Colorless needles, mp 81—83 °C (*n*-hexane–AcOEt). IR (KBr): 2956, 1752, 1611, 1514, 1465, 1417, 1366, 1225, 1172, 1035 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s, $C_{3'}$-CH_3), 1.38 (3H, s, $C_{3'}$-CH_3), 1.77 (1H, ddd, J=4.9, 11.2, 13.7, $C_{2'}$-H), 1.95 (1H, ddd, J=5.4, 11.2, 13.7, $C_{2'}$-H), 3.38 (1H, dd, J=2.9, 11.7, C_5-H), 3.39 (1H, m, $C_{1'}$-H), 3.53 (1H, dd, J=8.8, 11.7, C_5-H), 3.70 (1H, d, J=12.7, SCHAr), 3.77 (1H, d, J=12.7, SCHAr), 3.79 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.84 (3H, s, CO_2CH_3 or $ArOCH_3$), 4.45 (1H, ddd, J=5.4, 11.2, 13.7, $C_{1'}$-H), 4.57 (1H, dd, J=2.9, 8.8, C_4-H), 6.83 (2H, d, J=8.8, aromatic protons), 7.28 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −36.8° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{25}NO_3S_3$: C, 54.10; H, 6.31; N, 3.51. Found: C, 54.10; H, 6.29; N, 3.45.

Methyl (4*R*)-3-[2-(4-Methoxybenzylthio)-2-methylpropyl]-2-thioxothiazolidine-4-carboxylate (13) A solution of 1,1'-carbonyldiimidazole (0.28 g, 1.46 mmol) and **11a** (0.50 g, 1.46 mmol) in DMF (10 ml) was heated for 2.5 h at 100—110 °C. The reaction mixture was poured into 1 N HCl and extracted with AcOEt. The organic layer was washed with 1 N HCl, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **13** (0.29 g, 54%). Colorless needles, mp 51—54 °C (*n*-hexane–iso-PrOH). IR (KBr): 2964, 1738, 1685, 1510, 1448, 1383, 1333, 1231, 1189, 1120, 1034 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, s, $C_{2'}$-CH_3), 1.39 (3H, s, $C_{2'}$-CH_3), 2.96 (1H, d, J=14.7, $C_{1'}$-H), 3.35 (1H, dd, J=1.0, 11.2, C_5-H), 3.64 (1H, dd, J=8.3, 11.2, C_5-H), 3.66 (1H, d, J=12.2, SCHAr), 3.74 (1H, d, J=12.2, SCHAr), 3.78 (3H, s, $ArOCH_3$ or CO_2CH_3), 3.79 (3H, s, CO_2CH_3 or $ArOCH_3$), 3.92 (1H, d, J=14.7, $C_{1'}$-H), 5.01 (1H, dd, J=1.0, 8.3, C_4-H), 6.83 (2H, d, J=8.3, aromatic protons), 7.21 (2H, d, J=8.3, aromatic protons). $[\alpha]_D^{25}$ −49.9° (c=0.25, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{23}NO_4S_2$: C, 55.26; H, 6.27; N, 3.79. Found: C, 55.30; H, 6.30; N, 3.77.

(*R*)-4-Hydroxymethyl-3-[2-(4-methoxybenzylthio)-2-methylpropyl]thiazolidine-2-thione (14) A solution of **12a** (2.00 g, 5.19 mmol) in anhydrous THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (145 mg, 3.6 mmol) in anhydrous ether (10 ml) under ice cooling. The reaction mixture was stirred at room temperature for 5 h, then decomposed with AcOEt and 1 N HCl, and the mixture was extracted with AcOEt. The organic layer was washed with 1 N HCl, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **14** (1.85 g, quantitative yield) as a colorless oil. IR (neat): 3396, 2960, 1610, 1512, 1456, 1247, 1177, 1129, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, s, $C_{2'}$-CH_3), 1.48 (3H, s, $C_{2'}$-CH_3), 3.14 (1H, dd, J=1.5, 11.7, C_5-H), 3.33 (1H, d, J=14.7, $C_{1'}$-H), 3.53 (1H, dd, J=7.8, 11.7, C_5-H), 3.76 (4H, m, C_4-CH_2, SCH_2Ar), 3.79 (3H, s, $ArOCH_3$), 4.75 (1H, d, J=14.7, $C_{1'}$-H), 5.07 (1H, m, C_4-H), 6.85 (2H, d, J=8.8, aromatic protons), 7.26 (2H, d, J=8.8, aromatic protons). $[\alpha]_D^{25}$ −31.5° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_{16}H_{23}NO_2S_2$: 357.0890. Found: 357.0910.

Deprotection of S-*p*-Methoxybenzyl Group (General Procedure) Method A Thioanisole (0.61 ml, 5.19 mmol) and CF_3SO_3H (0.46 ml, 5.19 mmol) were added to a solution of **12a** (1.00 g, 2.59 mmol) in CF_3CO_2H (4 ml) under ice cooling. The reaction mixture was stirred at 25 °C for 15 min, then poured into $NaHCO_3$ solution containing flakes of ice and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **1a** (0.34 g, 49%) and **2a** (0.08 g, 13%).

Methyl (4*R*)-3-(2-Mercapto-2-methylpropyl)-2-thioxothiazolidine-4-carboxylate (**1a**): Colorless needles, mp 126—127 °C (*n*-hexane–AcOEt). IR (KBr) 2964, 1736, 1449, 1412, 1326, 1233, 1129 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, s, $C_{2'}$-CH_3), 1.51 (3H, s, $C_{2'}$-CH_3), 1.84 (1H, s, SH), 3.20 (1H, d, J=14.2, $C_{1'}$-H), 3.43 (1H, dd, J=1.5, 11.7, C_5-H), 3.71 (1H, dd, J=8.3, 11.7, C_5-H), 3.84 (3H, s, CO_2CH_3), 4.89 (1H, d, J=14.2, $C_{1'}$-H), 5.77 (1H, dd, J=1.5, 8.3, C_4-H). $[\alpha]_D^{25}$ −100.2° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_9H_{15}NO_2S_3$: C, 40.73; H, 5.70; N, 5.28. Found: C, 40.61; H, 5.54; N, 5.12.

(6*S*)-1-Aza-3,3-dimethyl-4,8-dithiabicyclo[4.3.0]nonane-9-thioxo-5-one (**2a**): Colorless needles, mp 126—128 °C (*n*-hexane–AcOEt). IR (KBr): 2936, 1664, 1423, 1350, 1280, 1206, 1169, 1130, 1056, 1011 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.568 (3H, s, CH_3), 1.574 (3H, s, CH_3), 3.29 (1H, d, J=13.7, $C_{1'}$-H), 3.48 (1H, dd, J=11.2, 11.7, C_5-H), 3.65 (1H, dd, J=8.8, 11.7, C_5-H), 4.75 (1H, dd, J=8.8, 11.2, C_4-H), 5.14 (1H, d, J=13.7, $C_{1'}$-H). $[\alpha]_D^{25}$ −24.6° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_8H_{11}NOS_3$: C, 41.17; H, 4.75; N, 6.00. Found: C, 41.07; H, 4.71; N, 5.96.

Method B Thioanisole (0.61 ml, 5.19 mmol) and CF_3SO_3H (0.46 ml, 5.19 mmol) were added to a solution of **12a** (1.00 g, 2.59 mmol) in CF_3CO_2H (4 ml) under ice cooling. The reaction mixture was stirred at the same temperature for 15 min, poured into $NaHCO_3$ solution including flakes of ice and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **1a** (0.43 g, 62%).

Method C Thioanisole (1.22 ml, 10.38 mmol) and CF_3SO_3H (0.92 ml, 10.38 mmol) were added to a solution of **12a** (1.00 g, 2.59 mmol) in CF_3CO_2H (4 ml) under ice cooling. The reaction mixture was stirred at 25 °C for 30 min, poured into $NaHCO_3$ solution including flakes of ice and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel to give **1a** (21 mg, 3%) and **2a** (0.36 g, 60%).

Methyl (4*R*)-3-(2-Mercaptopropyl)-2-thioxothiazolidine-4-carboxylate (**1b**): Compound **1b** was prepared starting from **12b**, according to method B (42% yield). Colorless oil. IR (neat): 2952, 1744, 1456, 1404, 1206, 1179, 1150, 1062 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, d, J=6.8, $C_{2'}$-CH_3), 1.51 (1H, d, J=8.8, SH), 3.04 (1H, dd, J=10.8, 14.2, $C_{1'}$-H), 3.47 (1H, dd, J=1.5, 11.2, C_5-H), 3.54 (1H, m, $C_{2'}$-H), 3.77 (1H, dd, J=8.8, 11.2, C_5-H), 3.85 (3H, s, CO_2CH_3), 4.61 (1H, dd, J=4.4, 14.2, $C_{1'}$-H), 5.29 (1H, dd, J=1.5, 8.8, C_4-H). $[\alpha]_D^{25}$ −144.6° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_8H_{13}NO_2S_3$: 251.0108. Found: 251.0105.

Methyl (4*R*)-3-(2-Mercaptopropyl)-2-thioxothiazolidine-4-carboxylate (**1c**): Compound **1c** was prepared starting from **12c**, according to method B (25% yield). Colorless oil. IR (neat): 2956, 1745, 1456, 1405, 1209, 1150, 1109 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=6.8, $C_{2'}$-CH_3), 1.65 (1H, d, J=6.8, SH), 3.33 (1H, dd, J=7.3, 13.7, $C_{1'}$-H), 3.40 (1H, m, $C_{2'}$-H), 3.47 (1H, dd, J=2.0, 11.2, C_5-H), 3.71 (1H, dd, J=8.8, 11.2, C_5-H), 3.85 (3H, s, CO_2CH_3), 4.58 (1H, dd, J=7.3, 13.7, $C_{1'}$-H), 4.96 (1H, dd, J=2.0, 8.8, C_4-H). $[\alpha]_D^{25}$ −149.3° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_8H_{13}NO_2S_3$: 251.0108. Found: 251.0080.

Methyl (4*R*)-3-(3-Mercapto-2,2-dimethylpropyl)-2-thioxothiazolidine-4-carboxylate (**1d**): Compound **1d** was prepared starting from **12d**, according to method B (49% yield). Colorless oil. IR (neat): 2952, 1739, 1445, 1401, 1058 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.069 (3H, s, $C_{2'}$-CH_3), 1.071 (3H, s, $C_{2'}$-CH_3), 1.54 (1H, dd, J=7.8, 9.3, SH), 2.47 (1H, dd, J=9.3, 13.7, $C_{3'}$-H), 2.61 (1H, dd, J=7.8, 13.7, $C_{3'}$-H), 3.02 (1H, d, J=14.2, $C_{1'}$-H), 3.38 (1H, dd, J=1.0, 11.7, C_5-H), 3.65 (1H, dd, J=8.3, 11.7, C_5-H), 3.85 (3H, s, CO_2CH_3), 4.64 (1H, d, J=14.2, $C_{1'}$-H), 4.97 (1H, dd, J=1.0, 8.3, C_4-H). $[\alpha]_D^{25}$ −111.1° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_{10}H_{17}NO_2S_3$: 279.0420. Found: 279.0401.

Methyl (4*R*)-3-(2-Mercaptoethyl)-2-thioxothiazolidine-4-carboxylate (**1e**): Compound **1e** was prepared starting from **12e**, according to method B (45% yield). Colorless oil. IR (neat): 2950, 2530, 1747, 1611, 1462, 1350, 1304, 1226, 1071 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (1H, t, J=8.3, SH), 2.80 (1H, m, $C_{2'}$-H), 3.00 (1H, m, $C_{2'}$-H), 3.45 (1H, ddd, J=6.8, 7.8, 14.2, $C_{1'}$-H), 3.47 (1H, dd, J=2.0, 11.7, C_5-H), 3.74 (1H, dd, J=8.8, 11.7, C_5-H), 3.85 (3H, s, CO_2CH_3), 4.54 (1H, ddd, J=4.9, 7.3, 14.2, $C_{1'}$-H), 5.07 (1H, dd, J=2.0, 8.8, C_4-H). $[\alpha]_D^{25}$ −112.4° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_7H_{11}NO_2S_3$: 236.9951. Found: 236.9947.

Methyl (4*R*)-3-(3-Mercapto-3-methylbutyl)-2-thioxothiazolidine-4-carboxylate (**1f**): Compound **1f** was prepared starting from **12f**, according to method B (37% yield). Colorless oil. IR (neat): 2956, 1745, 1466, 1415, 1368, 1284, 1209, 1152, 1064 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, s, $C_{3'}$-CH_3), 1.45 (3H, s, $C_{3'}$-CH_3), 1.79 (1H, s, SH), 1.86 (1H, ddd, J=4.9, 10.8, 13.7, $C_{2'}$-H), 2.02 (1H, ddd, J=5.9, 10.8, 13.7, $C_{2'}$-H), 3.44 (1H, dd, J=3.4, 11.2, C_5-H), 3.49 (1H, m, $C_{1'}$-H), 3.63 (1H, dd, J=8.8, 11.2, C_5-H), 3.86 (3H, s, CO_2CH_3), 4.53 (1H, ddd, J=5.9, 10.8, 13.7, $C_{1'}$-H), 4.87 (1H, dd, J=3.4, 8.8, C_4-H). $[\alpha]_D^{25}$ −84.9° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_{10}H_{17}NO_2S_3$: 279.0420. Found: 279.0408.

(*R*)-4-(Hydroxymethyl)-3-(2-mercapto-2-methylpropyl)thiazolidine-2-thione (**4**): Compound **4** was prepared starting from **14**, according to method B (47% yield). Colorless oil. IR (neat): 3384, 2964, 1449, 1409, 1388, 1249, 1194, 1131, 1036 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.83 (1H, br s, OH), 1.92 (1H, s, SH), 3.21 (1H, dd, J=1.5, 11.7, C_5-H), 3.31 (1H, d, J=14.2, $C_{1'}$-H), 3.59 (1H, dd, J=7.8, 11.7, C_5-H), 3.90 (2H, t-like, J=4.9, C_4-CH_2O), 4.81 (1H, d, J=14.2, $C_{1'}$-H), 5.13 (1H, ddd, J=1.5, 7.8, 12.2, C_4-H). $[\alpha]_D^{25}$ −73.3° (c=1.0, $CHCl_3$). HRMS m/z (M^+): Calcd for $C_8H_{15}NOS_3$: 237.0315. Found: 237.0329.

(7*S*)-1-Aza-3,3-dimethyl-5,9-dithiabicyclo[5.3.0]decane-10-thioxo-6-one (**2d**): Compound **2d** was prepared starting from **12d**, according to method C (24% yield). Colorless needles, mp 184—186 °C ($CHCl_3$). IR (KBr): 1659, 1449, 1402, 1264, 1199, 1166, 1050, 1039 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, s, CH_3), 1.25 (3H, s, CH_3), 2.76 (1H, d, J=15.3, $C_{3'}$-H), 3.27 (2H, m, $C_{1'}$-H, $C_{3'}$-H), 3.47 (1H, dd, J=7.3, 11.2, C_5-H),

3.84 (1H, dd, J=3.9, 11.2, C_5-H), 4.64 (1H, d, J=13.7, $C_{1'}$-H), 4.97 (1H, dd, J=3.9, 7.3, C_4-H). $[\alpha]_D^{25}$ +93.5° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_9H_{13}NOS_3$: C, 43.69; H, 5.30; N, 5.66. Found: C, 43.60; H, 5.28; N, 5.62.

(6*S*)-1-Aza-4,8-dithiabicyclo[4.3.0]nonan-9-thioxo-5-one (**2e**): Compound **2e** was prepared starting from **12e**, according to method C (22% yield). Colorless needles, mp 156—159 °C (*n*-hexane–AcOEt). IR (KBr): 2990, 2855, 1675, 1437, 1420, 1350, 1310, 1263, 1225, 1054, 1006 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.38 (1H, ddd, J=3.9, 8.8, 13.7, $C_{2'}$-H), 3.53 (1H, ddd, J=4.9, 6.4, 13.7, $C_{2'}$-H), 3.54 (1H, dd, J=9.3, 11.7, C_5-H), 3.83 (1H, dd, J=6.8, 11.7, C_5-H), 3.98 (1H, ddd, J=3.9, 6.4, 13.7, $C_{1'}$-H), 4.63 (1H, ddd, J=4.9, 8.8, 13.7, $C_{1'}$-H), 4.94 (1H, dd, J=6.8, 9.3, C_4-H). $[\alpha]_D^{25}$ +26.8° (c=0.35, $CHCl_3$). HRMS m/z (M^+-CO): Calcd for $C_5H_7NS_3$: 176.9740. Found: 176.9736.

(6*S*)-1-Aza-3,3-dimethyl-4,8-dithiabicyclo[4.3.0]nonane-5,9-dione (**3**): Compound **3** was prepared starting from **13**, according to method C (64% yield). Colorless needles, mp 137—138 °C (*n*-hexane–AcOEt). IR (KBr): 2972, 1685, 1386, 1355, 1306, 1275, 1212, 1123, 1082 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, s, CH_3), 1.57 (3H, s, CH_3), 3.17 (1H, d, J=14.2, $C_{1'}$-H), 3.43 (1H, dd, J=9.8, 11.7, C_5-H), 3.61 (1H, dd, J=8.3, 11.7, C_5-H), 4.26 (1H, d, J=14.2, $C_{1'}$-H), 4.37 (1H, dd, J=8.3, 9.8, C_4-H). $[\alpha]_D^{25}$ −124.1° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_8H_{11}NO_2S_3$: C, 44.22; H, 5.10; N, 6.45. Found: C, 44.09; H, 5.09; N, 6.43.

***P. acnes*-LPS-induced Liver Injury Model** Acute hepatic failure was produced according to the method of Ferluga and Allison.[11] In brief, 0.7 mg of heat-killed *P. acnes* was injected i.v. into each BALB/c mouse through a tail vein. Seven days later, 25 μg of LPS was injected i.v. and acute hepatic failure was thereby induced. Compounds were orally administered at a dose of 100 mg/kg 1 h before LPS injection, and the mortality rate was estimated. The mice were starved for 24 h before LPS injection.

Effect on the Formation of LPO *in Vitro* The hepatic microsomes were isolated from nine- or ten-week-old rats. The assay mixtures contained 0.30 ml of microsomal protein suspension (10 mg protein/ml (0.15 M KCl)) in 2.45 ml of buffer (0.15 M KCl : 0.1 M Tris = 3 : 2), 0.1 ml of ADP–$FeSO_4$ (0.12 M ADP/0.1 M Tris : 1.0 μM $FeSO_4$ = 1 : 1), 0.1 ml of ascorbic acid (0.015 M) and compounds in 0.05 ml of DMSO (10^{-3} or 10^{-4} M final concentration). The assay mixtures not containing iron and ascorbic acid were taken as blanks. Controls were run without any test compound. After 10 min at 37 °C, incubations were stopped by adding 6 ml of 10% trichloroacetic acid. LPO was measured by the thiobarbituric acid method.[12]

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