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Stereoselective follow-up reactions of (*S*)-2-sulfanyl nitriles[1]

Sebastian Gaupp † and Franz Effenberger *

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

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Abstract

Follow-up reactions of (*S*)-2-acetylthionitriles (*S*)-**2** and (*S*)-2-benzylthionitriles (*S*)-**4**, respectively, are described. (*S*)-2-Acetylthionitriles were converted via Pinner reaction to ethyl (*S*)-2-mercaptocarboxylates (*S*)-**3** almost without racemization. Two routes for the stereoselective preparation of 1,2-amino thiols (*S*)-**5** have been investigated. Hydrogenation of (*S*)-**2** with $BH_3 \cdot THF$ gave (*S*)-**5** which, however, could not be isolated directly under the reaction conditions, but, by reaction with phosgene in an alkaline medium, the 1,2-amino thiols (*S*)-**5** could be trapped as (*S*)-5-alkylthiazolidinones (*S*)-**7** in good yields without racemization. (*S*)-Benzylthioamines (*S*)-**6**, derived from (*S*)-**4** by hydrogenation with $LiAlH_4$, were debenzylated with sodium in NH_3 to give (*S*)-**5** which were isolated as hydrochlorides with high enantiomeric excesses. Optically active thiomorpholines (*S*)-**12** are accessible starting from (*S*)-2-(2-hydroxyethylthio)nitriles (*S*)-**10** which are first chlorinated with $SOCl_2$ to yield (*S*)-2-(2-chloroethylthio)nitriles (*S*)-**11** which after hydrogenation with $LiAlH_4$ cyclize to give thiomorpholines (*S*)-**12**.

1. Introduction

In the preceding publication[1] we have described the stereoselective preparation of various (*S*)-2-sulfanyl nitriles which have been obtained in high enantiomeric excesses starting from sulfonyl-activated (*R*)-cyanohydrins by enzyme-catalyzed addition of HCN to aldehydes and ketones, respectively, and subsequent sulfonylation. 2-Sulfanyl nitriles represent *S*-protected thiocyanohydrins whose synthetic potential is assumed to be nearly as high as that of cyanohydrins.[2] While follow-up reactions of optically active cyanohydrins have been investigated extensively in recent years,[2] nothing is known about reactions of chiral thiocyanohydrins.

In the present publication we report on follow-up reactions of (*S*)-2-sulfanyl nitriles especially with regard to stereoselectivity of the transformations.

* Corresponding author. E-mail: franz.effenberger@po.uni-stuttgart.de

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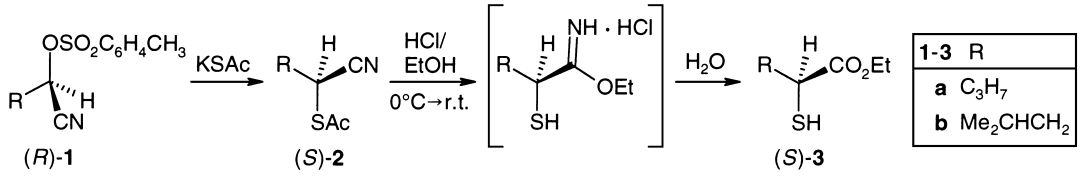
2. Preparation of optically active 2-mercaptocarboxylic acid esters (*S*)-3

2-Mercaptocarboxylic acids and their esters are of particular interest as components of pharmacologically active oligopeptides (e.g., ACE[3] or renin inhibitors[4]). Chiral 2-mercaptocarboxylic acids are accessible starting from either naturally occurring amino acids[4,5] or from 2-hydroxycarboxylic acid derivatives.[6]

We now describe an alternative route to optically active 2-mercaptocarboxylates starting from (*R*)-2-(sulfonyloxy)nitriles (*R*)-**1** by reaction with potassium thioacetate to yield the corresponding (*S*)-2-acetylthionitriles (*S*)-**2** which can be converted directly under conditions analogous to the Pinner reaction[7] to give (*S*)-2-mercaptocarboxylates (*S*)-**3** as outlined in Scheme 1.



Scheme 1.

As can be seen from the results summarized in Table 1, the reaction proceeds almost without racemization. It was not possible to decide whether removal of the acetyl group or Pinner reaction occurs first.

With the conversion of compounds (*R*)-**1** to (*S*)-**3** it could also be proved that the reaction of (*R*)-**1** with KSAc to 2-acetylthionitriles (*S*)-**2**, described in the preceding publication,[1] proceeded with complete inversion of configuration. A comparison of the optical rotation sign of (*S*)-**3b** with literature data[4] unambiguously confirms its (*S*)-configuration.

3. Preparation of optically active 1-amino-2-thiols (*S*)-5

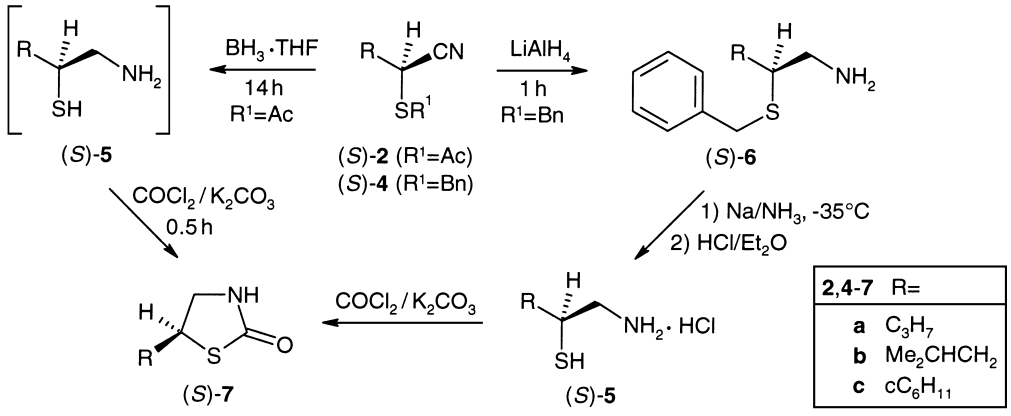
Optically active 1,2-amino thiols (*S*)-**5**, which are of increasing interest as N,S-chelate ligands[8] and as intermediates in the synthesis of chiral heterocycles, have been prepared so far from L-amino acids.[9] In recent times 1,2-amino thiols have been investigated especially with respect to their biological activities as aminopeptidase N-inhibitors.[9,10] The preparation of (*S*)-1-amino-2-thiols (*S*)-**5**, as illustrated in Scheme 2, starts from (*S*)-acetylthio- and benzylthionitriles (*S*)-**2** and (*S*)-**4**, respectively.[1]

Preliminary investigations have shown that 2-acetylthionitriles **2** could be reacted with $LiAlH_4$ in diethyl ether to give the corresponding amino thiols. The required aqueous workup, however, is di-

Table 1
Conversion of acetylthionitriles **2** to ethyl 2-mercaptocarboxylates **3** under Pinner reaction conditions

Acetylthionitriles		Ethyl 2-mercaptocarboxylates			
2	*ee* (%)	**3**	Yield (%)	$[\alpha]_D^{20}$ (*c*, solvent)	*ee* (%)[a]
(*RS*)-**2a**	–	(*RS*)-**3a**	58	–	–
(*S*)-**2a**	(96)	(*S*)-**3a**	68	n.d.	93
(*RS*)-**2b**	–	(*RS*)-**3b**	79	–	–
(*S*)-**2b**	(90)	(*S*)-**3b**[b]	69	-20.2 (2.18, Et_2O)	87

[a] Determined directly by gas chromatography on a Chiraldex B-TA phase. [b] See Ref.[4]



Scheme 2.

Table 2
5-Alkylthiazolidin-2-ones (*S*)-**7** from 2-acetylthionitriles (*S*)-**2** via 1,2-amino thiols (*S*)-**5** by reduction with $BH_3 \cdot THF$ and subsequent reaction with phosgene

2-Acetylthionitriles		5-Alkyl-1,3-thiazolidin-2-ones			
(*S*)-**2**	*ee* (%)	(*S*)-**7**	Yield (%)	*ee* (%)[a]	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)
a	96	**a**	42	96	-97.9 (1.4)
b	91	**b**	48	91	-91.7 (1.0)
c	89	**c**	46	–[b]	-92.9 (1.0)

[a] *ee*-Values determined directly by gas chromatography on a Chiraldex B-TA phase.

[b] Compound **7c** could not be detected on the used phase.

sadvantageous since amino thiols exist in aqueous media mainly in zwitterionic form,[11] resulting in an extremely difficult extraction and isolation in neutral form. Therefore, $LiAlH_4$ was replaced by $BH_3 \cdot THF$. In this case, the reduction could be terminated with methanol, whereby excess borane was converted to methyl borate which could be removed under vacuum. We first investigated this reaction by using racemic 2-acetylthiopentanenitrile (*RS*)-**2a**. After 14 h reaction time, neither the cyano nor the acetyl group were detected any more by NMR spectroscopy. The hydrogenation of (*RS*)-**2a** with $BH_3 \cdot THF$ afforded a product mixture from which the desired 1-aminopentane-2-thiol (*RS*)-**5a** could not be isolated by distillation, chromatography or recrystallization of the hydrochloride.

Analogous to the preparation of 1,3-oxazolidin-6-ones[12] we treated the crude amino thiol (*RS*)-**5a** with a solution of phosgene in toluene[13] in an alkaline medium to yield the stable 5-propyl-1,3-thiazolidin-2-one (*RS*)-**7a**. Compound **7a** could be purified by chromatography. By applying these reaction conditions to optically active 2-acetylthionitriles (*S*)-**2** the corresponding (*S*)-5-alkylthiazolidin-2-ones (*S*)-**7** were obtained without any racemization (Scheme 2, Table 2).

Since the isolation of (*S*)-1-amino-2-thiols (*S*)-**5** failed by this method, we have investigated an alternative route starting from (*S*)-2-benzylthionitriles (*S*)-**4** as outlined in Scheme 2. The cyano group in (*S*)-**4** could easily be hydrogenated to the amino function with $LiAlH_4$ in diethyl ether within 1 h. The (*S*)-1,2-benzylthioamines (*S*)-**6**, which were obtained thereby in a GC purity of >96% and high chemical yields (Table 3), could be debenzylated without further purification.

The removal of the benzyl group by using sodium in NH_3 has already been described for racemic 2-benzylthioamines.[14] Based on the published method, sodium was added to (*S*)-2-benzylthioamines (*S*)-**6** in liquid NH_3 at −35°C, and the reaction was terminated with NH_4Cl. After nonaqueous workup,

Table 3
Hydrogenation of (*S*)-2-benzylthionitriles (*S*)-**4** with $LiAlH_4$ to (*S*)-2-benzylthioamines (*S*)-**6** and their conversion to (*S*)-1-amino-2-thiols (*S*)-**5** with sodium in NH_3

Benzylthionitriles		(*S*)-2-Benzylthioamines			(*S*)-1-Amino-2-thiol hydrochlorides			
(*S*)-**4**	*ee* (%)[a]	(*S*)-**6**	Yield (%)	$[\alpha]_D^{20}$ (*c*,CH_2Cl_2)	(*S*)-**5**	Yield (%)	$[\alpha]_D^{20}$ (*c*,solvent)	*ee* (%)[b]
a	97	**a**	89	-24.9 (1.4)	**a**	69	-10.4 (1.0,H_2O)	97
b	94	**b**	78	-39.9 (1.0)	**b**	66	-22.3 (1.0,MeOH)	92
c	91	**c**	78	-28.4 (1.0)	**c**	68	-26.1 (1.0,MeOH)	–[c]

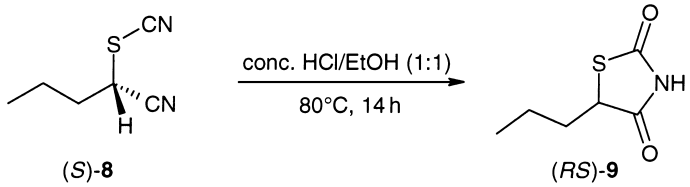
[a] ee-Values of starting (sulfonyloxy)nitriles (*R*)-**1**. [b] Determined by gc on Chiraldex B-TA phase after reaction with phosgene to 5-alkyl-2-thiazolidinones. [c] *ee*-Value could not be determined on the used phase; $[\alpha]_D^{20}$ = -93.2 (*c* 1.1, CH_2Cl_2).

(*S*)-1-amino-2-thiols (*S*)-**5** were precipitated as hydrochlorides (Scheme 2, Table 3). A direct gas chromatographic separation of the enantiomers of both **6** and **5** was not possible. Enantiomeric excesses of **5** were therefore determined again after cyclization to 5-alkyl-2-thiazolidinones **7**. As can be seen from Table 3, both reactions — hydrogenation of (*S*)-**4** and subsequent debenzylation of benzylthioamines (*S*)-**6** to (*S*)-**5** — proceed without racemization.

4. Preparation of 5-alkyl-2,4-thiazolidinediones 9

Numerous synthetic routes starting from thiocyano derivatives have been published for the preparation of thiazole, thiazoline and thiazolidine derivatives.[15] 2,4-Thiazolidinediones with substituents at the 5-position are known as components of a new class of antidiabetic agents.[16] Syntheses published so far afford, however, only racemic 2,4-thiazolidinediones.[16b–g]

(*S*)-2-Thiocyanatonitriles[1] appear to open an access to chiral sulfur–nitrogen heterocycles of this type. Therefore, we have investigated the preparation of 2,4-thiazolidinediones by intramolecular cyclization, using first racemic 2-thiocyanatopentanenitrile (*RS*)-**8** as outlined in Scheme 3.



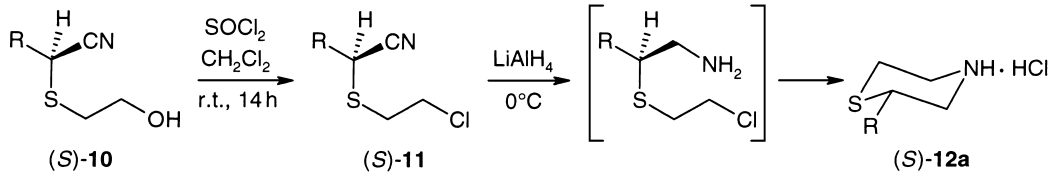
(*S*)-**8** (*RS*)-**9**

Scheme 3.

Owing to the high acidity of the proton at the 5-position of thiazolidinediones,[16g] the acid-catalyzed cyclization seems to be most suitable with respect to the preparation of optically active compounds **9**. Compound (*RS*)-**8** was heated in concentrated HCl/ethanol to 80°C for 14 h, and after chromatographic purification 5-propyl-2,4-thiazolidinedione (*RS*)-**9** was obtained in 57% yield. Under these reaction conditions, however, (*S*)-thiocyanatopentanenitrile (*S*)-**8** reacted with complete racemization. Neither shorter reaction times nor lower temperatures or replacement of conc. HCl by 10% HCl could prevent racemization. In all cases, conversion to **9** decreased and the formation of by-products became dominant. Obviously, racemization occurs by an acid-catalyzed keto–enol tautomerism. H–D exchange experiments also indicate deprotonation in acidic media. With increasing acidity of the medium, H–D exchange and racemization was accelerated.

5. Preparation of optically active 2-alkylthiomorpholines (*S*)-12

A further interesting class of compounds available from 2-sulfanyl nitriles are thiomorpholines, which were investigated recently with respect to their biological and pharmacological properties.[17] Numerous synthetic approaches to racemic thiomorpholines have been described in the literature.[18] (*S*)-2-(2-Hydroxyethylthio)nitriles[1] should present suitable chiral starting compounds for the synthesis of optically active thiomorpholines. Scheme 4 illustrates the synthetic pathway to chiral thiomorpholines starting from (*S*)-2-(2-hydroxyethylthio)nitriles (*S*)-**10**.



10-12	a	b	c
R	C_3H_7	Me_2CHCH_2	cC_6H_{11}

Scheme 4.

In the first step, (*S*)-2-(2-hydroxyethylthio)nitriles (*S*)-**10** were converted with thionyl chloride to the corresponding (*S*)-2-(2-chloroethylthio)nitriles (*S*)-**11** in high chemical yields after chromatographic purification (Table 4). Compounds (*S*)-**11** should react, after hydrogenation of the cyano group to the amine, intramolecularly to give thiomorpholines **12**. Nonaqueous workup is favorable in order to prevent hydrolysis of (*S*)-**11** to starting (*S*)-**10**. The determination of enantiomeric excesses of (*S*)-**11** by gas chromatography has failed so far. The nearly constant optical rotation values, however, indicate a racemization-free reaction.

By hydrogenation of nitriles **11** at 0°C with $LiAlH_4$, the primarily formed 1,2-(2′-chloroethylthio)amines spontaneously cyclized to the desired 2-alkylthiomorpholines **12** (Scheme 4). Compound (*S*)-**11a** was reacted as a single enantiomer to (*S*)-**12a** while **11b**,**c** were reacted as racemates. The enantiomeric excess of (*S*)-**12a** could be determined by gas chromatography on a β-cyclodextrin phase after acetylation. Compound (*S*)-**12a** was obtained in 92% yield with only 62% *ee* (determined from crude free thiomorpholine). In order to achieve this result (*R*)-**1a** (88% *ee*) was reacted at room temperature with mercaptoethanol to give (*S*)-**10a**, and then (*S*)-**11a**, obtained from (*S*)-**10a** as described above, was hydrogenated directly with $LiAlH_4$ without further purification by distillation. While **12b** was obtained as the hydrochloride in analytically pure form with 62% yield, the cyclohexyl derivative **12c** could not be isolated as the hydrochloride or as the free thiomorpholine.

Table 4
(*S*)-2-(2-Chloroethylthio)nitriles (*S*)-**11** prepared from (*S*)-2-(2-hydroxyethylthio)nitriles (*S*)-**10** by reaction with $SOCl^2$

Educts		(*S*)-2-(2-Chloroethylthio)nitriles		
(*S*)-**10**	*ee* (%)[a]	(*S*)-**11**	Yield (%)	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)
a	96	**a**	91	-92.4 (1.0)
b	91	**b**	96	-79.0 (1.0)
c	89	**c**	97	-58.9 (1.05)

[a] *ee*-Values of starting 2-(sulfonyloxy)nitriles (*R*)-**1**.

6. Experimental

6.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) with TMS as an internal standard. Column chromatography was performed with glass columns of different sizes packed with silica gel S (Riedel–de Haen) or silica gel 60 (Merck), grain size 0.032–0.063 mm. Optical rotations were determined in a Perkin–Elmer polarimeter 241 LC. GC for determination of enantiomeric excess: Hewlett–Packard 6890 Series with FID, 0.9 bar hydrogen, column 30 m×0.32 mm, phase Chiraldex B-TA (ICT).

6.2. Preparation of ethyl (S)-2-mercaptocarboxylates (S)-*3* from 2-acetylthionitriles (S)-*2*; general procedure

To a solution of **2** (6.4–17.5 mmol) in diethyl ether (10–20 mL) at 0°C an ice-cooled 10% solution of HCl in ethanol (10–20 mL) (for **2a**) or a saturated solution of HCl in ethanol (20–40 mL) was slowly added dropwise. The stirred reaction mixture was allowed to warm to room temperature (14 h), hydrolyzed with ice-water and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate.

6.3. Preparation of (S)-5-alkyl-1,3-thiazolidin-2-ones (S)-*7* from (S)-*2*; general procedure

To a 1 M solution of **2** (3.2–10 mmol) in THF at 0°C was added dropwise within 10 min a 1 M solution of $BH_3 \cdot$THF (2 equiv.). After being stirred for 36 h, the reaction was terminated with methanol (2 mL/mmol **2**), and the solvent was removed in vacuo. The residue was taken up in water:toluene (1:1) (2 mL/mmol **2**), and K_2CO_3 (3 equiv. based on **2**) was added. The reaction mixture was cooled to 0°C, and a 2 M solution of phosgene in toluene (2 equiv.) was added. After being stirred vigorously for 0.5 h, the reaction mixture was extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate.

6.4. Preparation of (S)-2-benzylthioamines (S)-*6* from (S)-2-benzylthionitriles (S)-*4*; general procedure

A solution of **4** (**4a**,**c**: 10 mmol, **4b**: 13 mmol) in diethyl ether (15 mL (**4a**) or 40 mL) was added dropwise within 1 h to $LiAlH_4$ (1.3 equiv.) in diethyl ether (15–40 mL) at 0°C, and the reaction mixture was stirred for 14 h at room temperature. Water was added until Al–Li-hydroxides coagulated. The organic phase was decanted, dried ($MgSO_4$), and concentrated. The remaining colorless to light yellow oils (GC purity >96%) were distilled in vacuo. Compounds **6** were reacted to **5** without further purification.

6.5. Preparation of (S)-1-amino-2-thiols (S)-*5* from (S)-*6*; general procedure

According to Carroll et al.[14] sodium metal was added in small portions to **6** (5.4–7.7 mmol) in liquid NH_3 at −35°C until a permanent blue color remained for 45 min. Then NH_4Cl was added to decompose excess sodium, and the reaction mixture was allowed to warm up for removal of NH_3. After addition of

diethyl ether (50 mL), the remaining NH_3 was removed by heating the solution on a hot water bath. The reaction mixture was cooled to 0°C, HCl saturated ethanol (2 mL/mmol **6**) was added, and the reaction mixture stirred for at least 2 h at 0°C. The solid was filtered off and extracted with isopropanol. The combined extracts were concentrated in vacuo, diethyl ether was added, and the hydrochlorides were allowed to precipitate at −20°C.

6.6. *Determination of enantiomeric excesses by conversion to 1,3-thiazolidin-2-ones **7***

To a solution of **5** (20 mg) in concentrated K_2CO_3 solution (1 mL) toluene (1 mL) and a 2 M solution of phosgene in toluene (20 μL) were added, and the reaction mixture was shaken for 10 min. The reaction was extracted with ethyl acetate (2 mL). The extract was filtered through a silica gel column (3×0.5 cm) with ethyl acetate (2 mL). The enantiomeric excess was determined directly from the filtrate.

*^{1}H NMR data and elemental analyses of compounds **3**, **5**-**7***

	bp (°C/Torr)	^{1}H NMR ($CDCl_3$, δ)
3a	–	0.93 (t, *J*=7.3 Hz, 3H, CH_3), 1.29 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 1.29-1.56 (m, 2H, CH_2CH_3), 1.61-1.98 (m, 2H, CH_2CH), 2.02 (d, *J*=9.2 Hz, 1H, SH), 3.31 (dt, *J*=7.2, 9.2 Hz, 1H, CH), 4.19 (q, *J*=7.2 Hz, 2H, OCH_2CH_3)
5a[a,b]	–	0.96 (t, *J*=6.9 Hz, 3H, CH_3), 1.41-1.76 (m, 4H, CH_2CH_3, CH_2CH), 2.85-3.32 (m, 3H, CH, CH_2NH_2)
5b[a]	–	0.91 and 0.97 (each d, *J*=6.6 Hz, 3H, CH_3), 1.40-1.58 (m, 2H, CH_2CH), 1.86-2.05 (m, 1H, $(CH_3)_2CH$), 2.85-3.31 (m, 3H, CH, CH_2NH_2), 4.92 (broad s, 3H, NH_3^+)
5c[a]	–	1.09-1.99 (m, 11H, C_6H_{11}), 2.84-3.38 (m, 3H, CH, CH_2NH_2)
6a[b]	78/0.005	0.86 (t, *J*=7.1 Hz, 3H, CH_3), 1.24-1.54 (m, 6H, CH_2CH_3, CH_2CH, NH_2), 2.47-2.57 (m, 1H, CH), 2.62-2.83 (m, 2H, CH_2NH_2), 3.70 (d, *J*=1.1 Hz, 2H, CH_2Ph), 7.18-7.37 (m, 5H, Ph)
6b	84/0.005	0.77 and 0.85 (each d, *J*=6.5 Hz, 3H, CH_3), 1.24-1.46 (m, 4H, CH_2CH, NH_2), 1.71-1.92 (m, 1H, $(CH_3)_2CH$), 2.33-2.85 (m, 3H, CH, CH_2NH_2), 3.69 (d, *J*=0.9 Hz, 2H, CH_2Ph), 7.20-7.35 (m, 5H, Ph)
6c	121/0.001	1.02-1.79 (m, 13H, C_6H_{11}, NH_2), 2.28-2.35 (m, 1H, CH), 2.59-2.85 (m, 2H, CH_2NH_2), 3.71 (d, *J*=2.7 Hz, 2H, CH_2Ph), 7.29-7.37 (m, 5H, Ph)
7a	–	0.94 (t, *J*=7.3 Hz, 3H, CH_3), 1.34-1.52 (m, 2H, CH_2CH_3), 1.67-1.86 (m, 2H, CH_2CH), 3.25-3.32 (m, 1H, CH), 3.58-3.93 (m, 2H, CH_2NH), 6.48 (broad s, 1H, NH)
7b	75[c]	0.93 (t, *J*=6.6 Hz, 6H, CH_3), 1.54-1.79 (m, 3H, $(CH_3)_2CH$, CH_2CH), 3.22-3.30 (m, 1H, CH), 3.65-3.99 (m, 2H, CH_2NH), 6.42 (broad s, 1H, NH)
7c	–	0.95-1.31 and 1.55-1.83 (each m, 11H, C_6H_{11}), 3.37 (t, *J*=8.9 Hz, 1H, CH), 3.60-3.79 (m, 2H, CH_2NH), 6.44 (broad s, 1H, NH)

	Mol. formula (Mol. weight)	Calculated/found C	H	N	S	Cl		Mol. formula (Mol. weight)	Calculated/found C	H	N	S
5b	$C_6H_{16}ClNS$[d]	42.46	9.50	8.25	18.89	20.89	**7a**	$C_6H_{11}NOS$	49.63	7.63	9.65	22.08
	(169.7)	42.63	9.47	8.21	18.68	20.93		(145.2)	49.87	7.72	9.59	22.24
6b	$C_{13}H_{21}NS$	69.89	9.48	6.27	14.35		**7b**	$C_7H_{13}NOS$	52.80	8.23	8.80	20.14
	(223.4)	69.38	9.32	5.96	14.27			(159.3)	52.91	8.24	8.72	20.24
6c	$C_{15}H_{23}NS$	72.24	9.29	5.62	12.85		**7c**	$C_9H_{15}NOS$	58.34	8.16	7.56	17.30
	(249.4)	72.37	9.15	5.38	12.86			(185.3)	58.58	8.15	7.47	17.25

[a] In methanol-d_4. [b] See Ref.[14] [c] mp. [d] As hydrochloride.

6.7. 5-Propyl-2,4-thiazolidinedione **9** by acid-catalyzed cyclization of 2-thiocyanatopentanenitrile **8**

A solution of **8** (1.0 g, 7.13 mmol) in ethanol was added dropwise to a solution of conc. HCl in ethanol (30:30 mL), and the reaction mixture was heated to 80°C for 14 h. Then it was set to pH 5–6 with $NaHCO_3$ and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate to give 0.64 g (57%) **9** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.99 (t, *J*=7.3 Hz, 3H, CH_3), 1.33–1.61 (m, 2H, CH_2CH_3), 1.83–2.23 (m, 2H, CH_2CH), 4.29 (dd, *J*=9.3, 4.2 Hz, 1H, CH). Anal. calcd for $C_6H_9NO_2S$ (159.2): C, 45.27; H, 5.69; N, 8.80; S, 20.14. Found: C, 45.36; H, 5.70; N, 8.55; S, 20.14.

*Physical and spectroscopic data as well as elemental analyses of compounds **11,12***

	bp (°C/Torr)	^{1}H NMR (250 MHz, $CDCl_3$, δ)
11a	72-74/0.005	0.98 (t, *J*=7.2 Hz, 3H, CH_3), 1.48-1.96 (m, 4H, CH_2CH_3, CH_2CH), 2.90-3.23 (m, 2H, CH_2S), 3.61-3.67 (dd, *J*=6.5, 8.3 Hz, 1H, CH), 3.68-3.83 (m, 2H, CH_2Cl)
11b	–	0.97 and 0.98 (each d, *J*=6.5 Hz, 3H, CH_3), 1.56-1.98 (m, 3H, $(CH_3)_2CHCH_2$), 3.02-3.24 (m, 2H, CH_2S), 3.64-3.70 (dd, *J*=6.8, 9.0 Hz, 1H, CH), 3.68-3.84 (m, 2H, CH_2Cl)
11c	–	1.10-1.36 (m, 5H, C_6H_{11}), 1.68-2.17 (m, 6H, C_6H_{11}), 3.00-3.20 (m, 2H, CH_2S), 3.50 (d, *J*=6.2 Hz, 1H, CH), 3.66-3.82 (m, 2H, CH_2Cl)
12a[a]	–	0.94 (t, *J*=6.7 Hz, 3H, CH_3), 1.25-1.58 (m, 4H, $(CH_2)_2$), 2.67-2.74 (m, 1H), 2.86 (dd, *J*=11.3, 12.6 Hz, 1H), 3.07 (dt, *J*=2.6, 12.4 Hz, 1H), 3.26-3.38 (m, 2H), 3.60-3.76 (m, 2H)
12b	–	0.94 (dd, *J*=6.7, 2.4 Hz, 6H, 2 CH_3), 1.36 (t, *J*=7.3 Hz, 2H, CH_2CH), 1.78 (s, 1H, CH), 2.66-2.73 (m, 1H), 2.83 (dd, *J*=11.2, 12.6 Hz, 1H), 3.07 (dt, *J*=2.6, 12.4 Hz, 1H), 3.28-3.47 (m, 2H), 3.59 (dd, *J*=2.5, 12.7 Hz, 1H), 3.61-3.75 (dt, *J*=2.8, 12.6 Hz, 1H)

	Molecular formula (Molecular weight)	Calculated/found C	H	N	S	Cl
11a	$C_7H_{12}ClNS$ (177.7)	47.32 47.61	6.81 6.88	7.88 8.13	18.04 17.79	19.95 19.89
11b	$C_8H_{14}ClNS$ (191.7)	50.12 50.14	7.36 7.44	7.31 7.07	16.73 16.93	18.49 18.47
11c	$C_{10}H_{16}ClNS$ (217.8)	55.15 54.96	7.41 7.39	6.43 6.42	14.73 14.83	16.28 16.44
12a	$C_7H_{15}NS{\cdot}HCl$ (181.7)	46.26 46.14	8.87 9.02	7.71 7.81	17.64 17.60	19.51 19.24
12b	$C_8H_{17}NS{\cdot}HCl$ (195.8)	49.08 49.17	9.27 9.27	7.16 7.15	16.39 16.50	18.11 17.87

[a] See Ref.[18d]

6.8. Preparation of (S)-2-(2-chloroethylthio)nitriles (S)-**11** from (S)-2-(2-hydroxyethylthio)nitriles (S)-**10**; general procedure

To a solution of **10** (8.8–9.8 mmol) in dichloromethane (20–40 mL) at 0°C $SOCl_2$ (ca. 1.5 equiv. with respect to **10**) was slowly added dropwise, and the reaction mixture was stirred at room temperature for

12 h. Solvent and excess $SOCl_2$ were removed in vacuo, and the residue was chromatographed on silica gel with petroleum ether/dichloromethane.

*6.9. Preparation of 2-alkylthiomorpholines **12** from 2-(2-chloroethylthio)nitriles **11**; general procedure*

A solution of **11** (**11a**: 5.6 mmol, **11b**: 8.9 mmol) in diethyl ether (**11a**: 10 mL, **11b**: 20 mL) was slowly added dropwise to a suspension of $LiAlH_4$ (1.6 equiv. with respect to **11**) in diethyl ether (10 or 20 mL) at 0°C. After being stirred for 3 h, water was added until Li–Al salts coagulated. The organic phase was decanted, dried ($MgSO_4$), and concentrated in vacuo. In the case of **12a**, yield and enantiomeric excess were determined from the concentrate. Compound **12b** crystallized as the hydrochloride without addition of HCl, and was sonified in diethyl ether to result in analytically pure form.

*6.10. Determination of enantiomeric excess of **12a***

A solution of crude **12a** (10 μL), pyridine (10 μL) and acetic anhydride (50 μL) in dichloromethane (0.2 mL) was heated to 60°C for 3 h. The reaction mixture was filtered through a silica gel column (3×0.5 cm) with dichloromethane (2 mL). The enantiomeric excess was determined directly from the filtrate.

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References

1. Enzyme-catalyzed Reactions, Part 36. Part 35: Effenberger, F.; Gaupp, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1765–1775.
2. (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1555–1564. (b) Effenberger, F. *Chimia* **1999**, *53*, 3–10. (c) Kruse, C. G. In *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley: New York, 1992; pp. 279–299. (d) Jackson, W. R.; Jacobs, H. A.; Matthews, B. R.; Jayatilake, G. S.; Watson, K. G. *Tetrahedron Lett*. **1990**, *31*, 1447–1450. (e) Kanerva, L. T. *Acta Chem. Scand*. **1996**, *50*, 234–242. (f) Griengl, H.; Hickel, A.; Johnson, D. V.; Kratky, C.; Schmidt, M.; Schwab, H. *Chem. Commun*. **1997**, 1933–1940. (g) Zandbergen, P.; Brussee, J.; van der Gen, A.; Kruse, C. G. *Tetrahedron: Asymmetry* **1992**, *3*, 769–774.
3. Roark, W. H.; Tinney, F. J.; Cohen, D.; Essenburg, A. D.; Kaplan, H. R. *J. Med. Chem*. **1985**, *28*, 1291–1295.
4. Ashton, W. T.; Cantone, C. L.; Tolman, R. L.; Greenlee, W. J.; Lynch, R. J.; Schorn, T. W.; Strouse, J. F.; Siegl, P. K. S. *J. Med. Chem*. **1992**, *35*, 2772–2781.
5. Yankeelov, J. A.; Fok, K.-F.; Carothers, D. J. *J. Org. Chem*. **1978**, *43*, 1623–1624.
6. Strijtveen, B.; Kellogg, R. M. *J. Org. Chem*. **1986**, *51*, 3664–3671.
7. Pinner, A. *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 1643–1655.
8. (a) Kang, J.; Bum Kim, J.; Whan Kim, J.; Lee, D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 189–194. (b) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4478. (c) Jin, M.-J.; Ahn, S.-J.; Lee, K.-S. *Tetrahedron Lett*. **1996**, *37*, 8767–8770. (d) Anderson, J. C.; Harding, M. *Chem. Commun*. **1998**, 393–394.
9. Fournié-Zaluski, M.-C.; Coric, P.; Turcaud, S.; Bruetschy, L.; Lucas, E.; Noble, F.; Roques, B. P. *J. Med. Chem.* **1992**, *35*, 1259–1266.
10. Gordon, E. M.; Godfrey, J. D.; Delaney, N. G.; Asaad, M. M.; Von Langen, D.; Cushman, D. W. *J. Med. Chem*. **1988**, *31*, 2199–2211.
11. Crampton, M. R. In *The Chemistry of the Thiol Group*, part 1; Patai, S., Ed.; Wiley: New York, 1974; pp. 396–401.
12. Effenberger, F.; Jäger, J. *Chem. Eur. J*. **1997**, *3*, 1370–1374.
13. Fodor, G.; Stefanovsky, J.; Kurtev, B. *Monatsh. Chem*. **1967**, *98*, 1027–1042.

14. Carroll, F. I.; White, J. D.; Wall, M. E. *J. Org. Chem*. **1963**, *28*, 1236–1239.
15. (a) Guy, R. G. In *Reactions of the Thiol Group*; Patai, S., Ed.; Wiley: New York, 1974; pp. 859–886. (b) Gregory, J. T.; Mathes, R. A. *J. Am. Chem. Soc*. **1952**, *74*, 1719–1720. (c) Wohl, R. A.; Headley, D. F. *J. Org. Chem*. **1972**, *37*, 4401–4406. (d) Berger, J. *Prakt. Chem*. **1969**, *311*, 549–562.
16. (a) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. *J. Med. Chem*. **1989**, *32*, 421–428. (b) Sohda, T.; Mizuno, K.; Imamiya, E.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull*. **1982**, *30*, 3580–3600. (c) Sohda, T.; Mizuno, K.; Imamiya, E.; Tawada, H.; Meguro, K.; Kawamatsu, Y.; Yamamoto, Y. *Chem. Pharm. Bull*. **1982**, *30*, 3601–3616. (d) Kees, K. L.; Cheeseman, R. S.; Prozialeck, D. H.; Steiner, K. E. *J. Med. Chem*. **1989**, *32*, 11–13. (e) Stille, J. R.; Ward, J. A.; Leffelman, C.; Sullivan, K. A. *Tetrahedron Lett*. **1996**, *37*, 9267–9270. (f) Zask, A.; Jirkovsky, I.; Nowicki, J. W.; McCaleb, M. L. *J. Med. Chem*. **1990**, *33*, 1418–1423.
17. (a) Suzuki, K.; Tatsuoka, T.; Ishihara, T.; Ohno, T.; Aisaka, K.; Ogino, R.; Kuroki, M.; Satoh, F.; Miyano, S.; Sumoto, K. *Chem. Pharm. Bull*. **1996**, *44*, 132–138. (b) Suzuki, K.; Tatsuoka, T.; Murakami, T.; Ishihara, T.; Aisaka, K.; Inoue, T.; Ogino, R.; Kuroki, M.; Miyazaki, T.; Satoh, F.; Miyano, S.; Sumoto, K. *Chem. Pharm. Bull*. **1996**, *44*, 139–144. (c) Hungate, R. W.; Chen, J. L.; Starbuck, K. E.; Vacca, J. P.; McDaniel, S. L.; Levin, R. B.; Dorsey, B. D.; Guare, J. P.; Holloway, M. K.; Whitter, W.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Emini, E. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Anderson, P. S.; Huff, J. R. *Bioorg. Med. Chem*. **1994**, *2*, 859–879. (d) Harada, H.; Morie, T.; Hirokawa, Y.; Yoshida, N.; Kato, S. *Chem. Pharm. Bull*. **1995**, *43*, 1364–1378. (e) Morie, T.; Kato, S.; Harada, H.; Yoshida, N.; Fujiwara, I.; Matsumoto, J. *Chem. Pharm. Bull*. **1995**, *43*, 1137–1147. (f) Dutta, A. S.; Giles, M. B.; Gormley, J. J.; Williams, J. C.; Kusner, E. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 111–120.
18. (a) Idson, B.; Spoerri, P. E. *J. Am. Chem. Soc*. **1954**, *76*, 2902–2906. (b) Cymerman-Craig, J.; Rogers, W. P.; Tate, M. E. *Aust. J. Chem*. **1956**, *9*, 397–405. (c) Harman, D.; Vaughan, W. E. *J. Am. Chem. Soc*. **1950**, *72*, 631–632. (d) Gallego, M. T.; Brunet, E.; Ruano, J. L. G.; Eliel, E. L. *J. Org. Chem*. **1993**, *58*, 3905–3911. (e) Asinger, F.; Offermanns, H.; Neuray, D.; Müller, P. *Monatsh. Chem*. **1970**, *101*, 1295–1308.