Properties and Reactions of Substituted 1,2-Thiazetidine 1,1-Dioxides: Chiral Mono- and Bicyclic 1,2-Thiazetidine 1,1-Dioxides from α-Amino Acids

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New chiral mono- and bicyclic β-sultams, valuable building blocks for drug synthesis, have been prepared from L-Ala, L-Val, L-Leu, L-Ile, L-Phe, L-Cys, L-Ser, L-Thr, and D-penicillamine by transformation of the COOH group into a methylsulfonyl chloride function, followed by cyclization under basic conditions. Selected properties, derivatives, and reactions of the β-sultams are described.

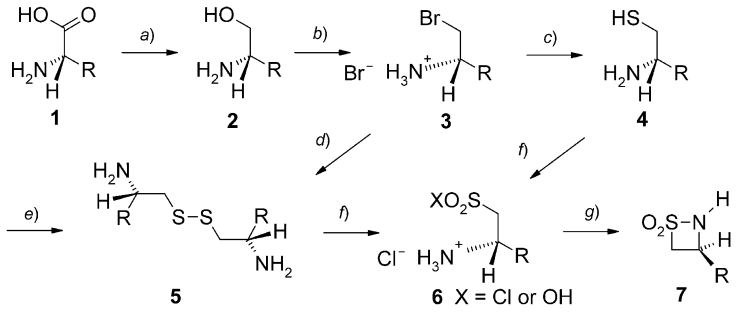
Introduction. – 1,2-Thiazetidine 1,1-dioxide (β-sultam) is a sulfone analogue (bioisoster) of the β-lactam moiety found in many important drugs [1]. It is known that the sultam ring is much more reactive than the β-lactam ring [2], and that β-sultams can interact with serine proteases such as elastase [3]. Therefore, β-sultams might be useful building blocks for new synthetic drugs and, therefore, should be available not only as racemic or diastereoisomeric mixtures, but as pure isomers [4]. Here, we report the synthesis and properties of chiral, stereochemically pure mono and bicyclic 3-substituted 1,2-thiazetidine 1,1-dioxides and their substitution products.

A few examples of chiral β-sultams have been described in the literature [5]. For example, (*R*)-1,2-thiazetidine-3-carboxylic acid was obtained from L-Cys, and (*R*)-1,2-thiazetidine-3-methanol from L-Ser. In both cases, compounds from the natural 'chiral pool' were used as starting materials, a general approach that has also been followed in the present paper.

Results and Discussion. – To obtain the 3-alkyl-substituted 1,2-thiazetidine 1,1-dioxides **7a**–**e**, the amino acids L-Ala, L-Val, L-Leu, L-Ile, and L-Phe (**1a**–**e**) were reduced with $LiAlH_4$ in THF, forming the parent 2-aminoethanols **2a**–**e** [6], which were then transformed into the Br compounds **3**, either by reaction with HBr (48%) [7], with a mixture of HBr and PBr_3 [8], or by reaction with thionylbromide (*Scheme 1*).

Compounds **3** were isolated as their crystalline hydrobromides. These salts were transformed into the thiols **4** by reaction with thiourea and tetraethylenepentamine [9] in *ca.* 40% yield, or they were transformed into the disulfides **5**. Compounds **4** were purified by sublimation; their high air sensitivity afforded immediate oxidation to the stable sulfonyl chloride hydrochlorides **6** with Cl_2/HCl in a mixture of EtOH and CCl_4. Finally, compounds **6** were cyclized with NH_3 in $CHCl_3$ at 0°, whereby the thiazetidine 1,1-dioxides **7a**–**e** were obtained in crystalline form. In the **a**-series of compounds, we isolated not the sulfonylchloride, but the sulfonic acid **6a** (X = CH), which was

Scheme 1



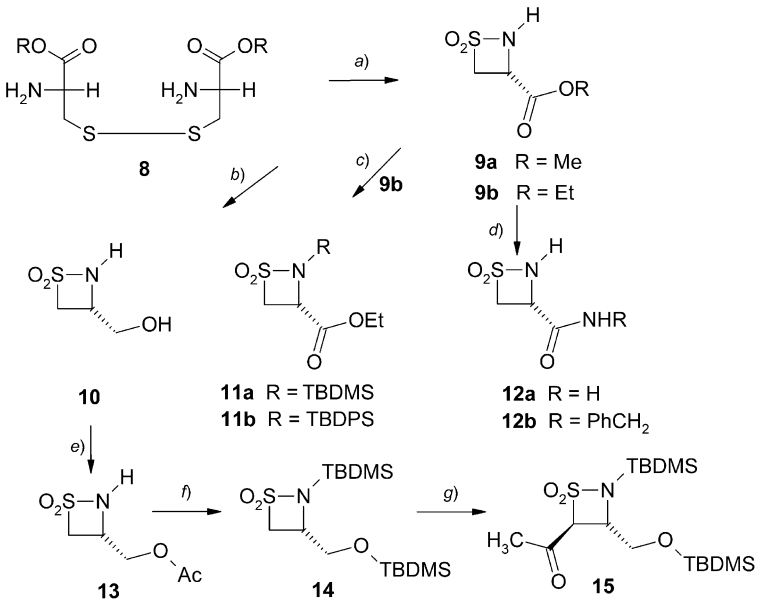
a R = Me, **b** R = i-Pr, **c** R = i-Bu, **d** R = *s*-Bu, **e** R = $PhCH_2$

a) $LiAlH_4$, THF. *b*) HBr, Ph_3P or $SOBr_2$. *c*) Thiourea, EtOH. *d*) $Na_2S_2O_3$, I_2, EtOH. *e*) I_2, EtOH. *f*) HCl, Cl_2, CCl_4, EtOH. *g*) NH_3, $CHCl_3$, CCl_4, THF.

transformed into the β-sultam **7a** in a one-pot reaction. Alternatively, **7a** was prepared from the disulfide **5a**.

L-Cystine dialkyl ester hydrochlorides **8**, obtained from L-Cys, were transformed into the parent β-sultams **9a** and **9b** [10] by oxidative chlorination (*Scheme 2*). By

Scheme 2



TBDMS = (*t*-Bu)Me_2Si, TBDPS = (*t*-Bu)Ph_2Si

a) 1. HCl, Cl_2, CCl_4, EtOH; 2. NH_3, $CHCl_3$, CCl_4, THF. *b*) $LiBH_4$, THF. *c*) BuLi, R_3SiCl, THF, $-78°$. *d*) RNH_2, $CHCl_3$, 0°. *e*) Ac_2O, 0°. *f*) BuLi, R_3SiCl, THF, $-78°$. *g*) BuLi, AcCl, THF, HMPA, $-78°$.

silylation of **9b**, we obtained the *N*-protected β-sultams **11a** and **11b**. Compounds **9** also allow simple modifications of the ester group. By reduction with $LiBH_4$, we obtained the free alcohol **10** [5]. Finally, by aminolysis of **9**, the amides **12** were obtained. Remarkably, **12a** is soluble only in DMSO or DMF/MeOH. Next, the acetate **13** was first transformed into the diprotected β-sultam **14**, which was then acetylated to **15**, which was obtained as a colorless liquid, and, as established by ^{1}H-NMR spectroscopy, present as the *trans* isomer only. Synthons **14** and **15** allow further reactions, such as cyclization to different bicyclic β-sultams [11].

N-Substituted β-sultams may be synthesized by deprotonation (Et_3N, NaOH, or $NaNH_2$) at low temperature, followed by alkylation or acylation [2]. An example is the synthesis of (*RS*)-**16** from (*RS*)-**7e**. However, since deprotonation may lead to (partial) racemization, it seems more appropriate to introduce the *N*-substituent into the starting material. Hence, we used *N*-benzoyl-L-Leu (**17a**) as the starting material for the synthesis of (*S*)-**24a**. Reduction with $LiAlH_4$ in THF yielded the *N*-benzylated derivative (*S*)-**18a**, which was reacted with Ph_3P in MeCN to yield the optically active aziridine derivative **19** in 71% yield. When **19** was reacted with $PhCH_2SH$, the mixed sulfide **21** was obtained. Oxidative chlorination and cyclization yielded (*S*)-**23a** and, finally, (*S*)-**24a**. By a similar sequence, the racemic (*RS*)-**17b** was reduced to (*RS*)-**18b**, then transformed into the bromo compound **20**, from which, in the presence of $Na_2S_2O_3$, the disulfide **22** and then the sulfonyl chloride (*RS*)-**23b** were obtained. Cyclization yielded the racemic (*RS*)-**24b** in 81% yield.

The 4,4-disubstituted 1,2-thiazetidine-3-carboxylate **27** was synthesized stereospecifically from the hydrochloride of D-penicillamine benzyl ester (**25**) [12]. As reported [13] for similar compounds, the oxidative chlorination of **25** was not possible. Therefore, **25** was oxidized with Br_2 in dilute AcOH to the sulfonic acid **26**, a taurine derivative, which, after chlorination with Cl_3PO in MeCN/sulfolane was cyclized by treatment with Et_3N to afford **27** as a yellow, viscous liquid in *ca.* 40% yield. The (*S*)-configuration of **27** was confirmed by ^{1}H- and ^{13}C-NMR experiments, including a ^{1}H-NMR dilution study with Pr(hfc)$_3$[1]), and by its circular-dichroism spectrum, giving rise to a minimum at $\lambda = 227$ nm, while the (*R*)-enantiomer of **27** has a maximum at this wavelength [14].

The bicyclic β-sultams **37a** and **37b** were prepared from *N*-benzylated L-Thr (**28a**) and L-Ser (**28b**) resp. By reaction with chloroacetyl chloride, they were transformed into the crystalline morpholine derivatives **29a** and **29b**, which, after esterification to **30a** and **30b**, were reduced with $LiAlH_4$ to the methanol derivatives **31a** and **31b**. The latter were transformed *via* the bromo compounds **32a** and **32b** into the benzyl sulfides **33a** and **33b**. Then, the *N*-Bn group was replaced by the (2,2,2-trichloroethoxy)carbonyl group. The resulting compounds **34a** and **34b** were transformed with Zn in glacial AcOH to the morpholine derivatives **35a** and **35b**. Oxidative chlorination gave the sulfonyl chlorides **36a** and **36b**. Cyclization with NH_3 in $CHCl_3$ finally resulted in the bicyclic β-sultams **37a** and **37b**. By an alternative route, the Bn group of **31a** was removed by hydrogenolysis in the presence of Pd/C to afford **38**. Furthermore, we transformed **31a** *via* the methanesulfonate **39** and the acetylthio derivative **40** into the

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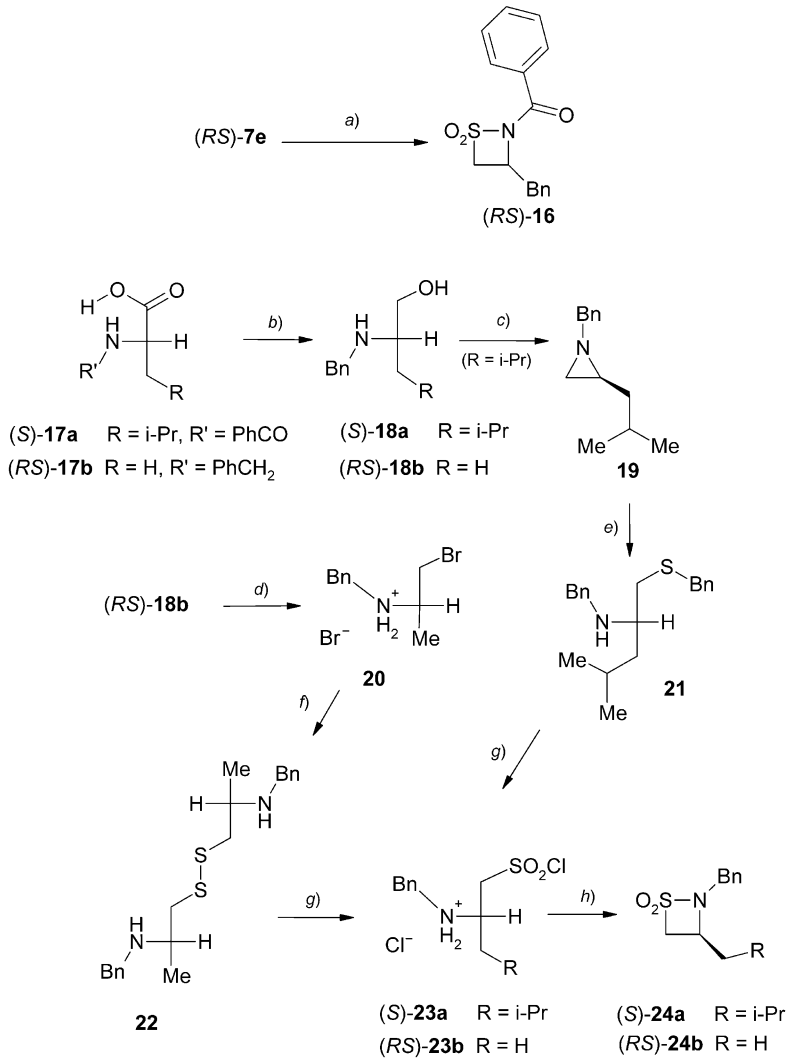
[1]) Chiral shift reagent 'tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]prasedymium(III)'.

Scheme 3

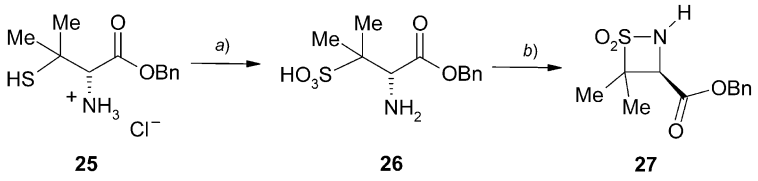


a) $PhCOBr$, Et_3N, THF. *b*) $LiAlH_4$, THF. *c*) Ph_3P, Et_3N, CCl_4, MeCN. *d*) HBr, PBr_3. *e*) Na/EtOH, $PhCH_2SH$. *f*) $Na_2S_2O_3$, I_2. *g*) HCl, Cl_2, $CHCl_3$, CCl_4, 0°. *h*) NH_3, $CHCl_3$, THF, CCl_4.

thiol **41**. However, the analogous transformation of the *N*-unprotected **38**, *via* the bromo- or mercapto analogs into a bicyclic sultam, failed.

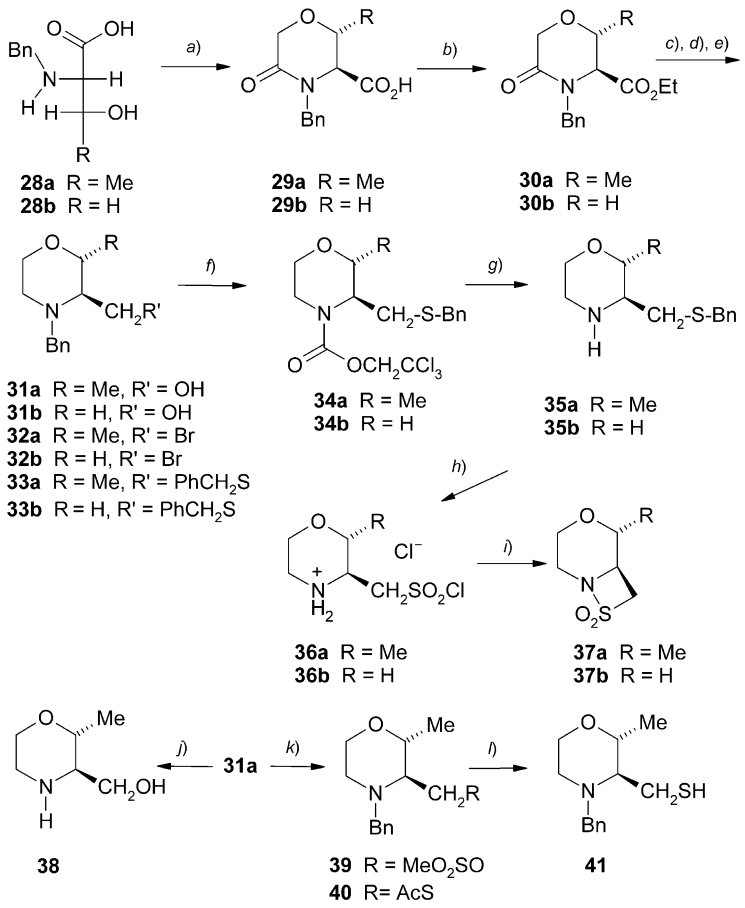
Finally, we prepared the spirotype-β-sultam **47** from 1-aminocyclohexanecarboxylic acid (**42**). Reduction with $LiAlH_4$ yielded the parent alcohol **43**, which was transformed to the bromide **44** [9], which, by reaction with $Na_2S_2O_3$ and I_2, gave the disulfide **45**. The latter was immediately transformed by oxidative chlorination into the stable

Scheme 4



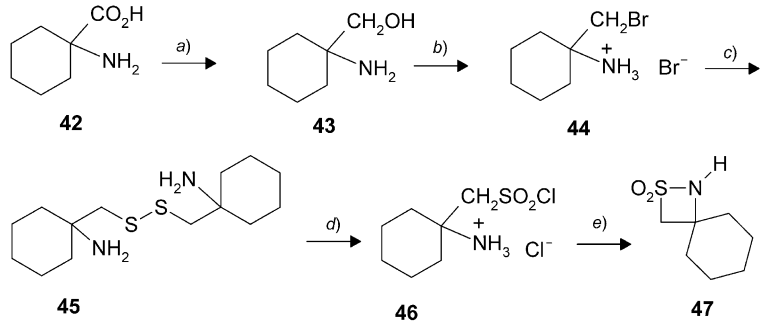
a) Br_2, H_2O, AcOH, 50°. *b*) 1. Cl_3PO, sulfolane, MeCN; 2. NH_3, $CHCl_3$.

Scheme 5



a) $CH_2ClCOCl$, NaOH. *b*) $SOCl_2$, EtOH. *c*) $LiAlH_4$, THF. *d*) Ph_3P, CBr_4, MeCN. *e*) NaOH, $PhCH_2SH$, EtOH. *f*) Cl_3CCH_2OCOCl, K_2CO_3. *g*) Zn, AcOH. *h*) HCl, Cl_2, $CHCl_3$, CCl_4. *i*) NH_3, $CHCl_3$. *j*) H_2, Pd/C, EtOH. *k*) 1. $MeSO_2Cl$, NH_3; 2. MeCOSK, DMF, $CHCl_3$. *l*) NH_3, EtOH.

Scheme 6



a) $LiAlH_4$. *b*) HBr, PBr_3. *c*) $Na_2S_2O_3$, I_2, H_2O. *d*) HCl, Cl_2, CCl_4, EtOH. *e*) NH_3, $CHCl_3$.

chlorosulfonyl derivative **46**. Cyclization in the usual manner yielded **47** in more than 80% yield, demonstrating the general utility of our synthetic route towards β-sultams.

In conclusion, we have demonstrated that differently substituted β-sultams, either optically active or racemic, can be synthesized from α-amino acids. Many of these compounds, which are often stable products, should be useful synthons, especially for drug synthesis.

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Experimental Part

General. THF was stored over KOH, refluxed over Na/benzophenone, and distilled prior to use. Other solvents were dried and purified according to literature procedures. Lithium diisopropylamide (LDA) was freshly prepared by mixing equimolar amounts of $(i\text{-}Pr)_2NH$ and BuLi (15% in hexane) in THF at $-78°$. TLC: silica-gel *60-F*$_{254}$ plates; *Merck*. Column and flash chromatography (CC, FC): silica gel *60*, 0.063–0.200 mm; *Merck*. M.p.: *Linström* apparatus, uncorrected. IR Spectra (KBr; cm^{-1}): *Perkin-Elmer 1310*. ^1H- and ^{13}C-NMR Spectra: *Varian T-60* (^1H, 60 MHz), *Bruker WP-80* (^1H, 80 MHz), and *Varian Unity-300* (300/75.43 MHz for ^1H and ^{13}C, resp.); δ in ppm rel. to $SiMe_4$ ($\delta = 0$ ppm), J in Hz; in $CDCl_3$, if not otherwise noted. MS: *Finnigan MAT-312*, *MAT-44S*. Elemental analyses: Institute of Pharmacy or Chemisches Laboratorium of the Universität Freiburg (Germany), or Institute of Pharmacy, University of Basel (Switzerland). All compounds gave satisfactory elemental analyses or were analyzed by MS and/or HR-MS; in *m/z* (rel. %).

Syntheses of 2-Amino Alcohols **2**. *(*S*)-2-Aminopropan-1-ol* (**2a**), *(*S*)-2-amino-4-methylpentan-1-ol* (**2c**), and *(*S*)-2-amino-3-phenylpropan-1-ol* (**2e**) were prepared according to [6]. *General Procedure* for the synthesis of **2b** and **2d**. $LiAlH_4$ (11.1 g, 0.29 mol) was suspended in THF (500 ml). The amino acid (200 mmol) was added in small portions at 0°. The mixture was refluxed for 4 h, then cooled to r.t. Then, an aq. soln. of KOH (10%, 12 ml) and H_2O (10 ml) were added dropwise. The precipitate was separated, washed with THF (50 ml), and extracted with boiling THF (250 ml) for 2 h. The combined org. filtrates (if necessary, CH_2Cl_2 was added to obtain a clear soln.) were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by distillation.

*(*S*)-2-Amino-3-methylbutan-1-ol* (**2b**) [6]. From L-Val (23.4 g, 0.2 mol): 17.0 g (83%). Yellow liquid. B.p. 100° (10 mbar). ^1H-NMR: 0.88, 0.89 (2*d*, $J = 2.7$, each 2 Me); 1.54 (*m*, H–C(3)); 2.51 (*m*, *ABM*, $J_{AM} = 3.7$, $J_{BM} = 8.4$, H–C(2)); 2.66 (*s*, NH_2, OH); 3.25 (*dd*, *ABM*, $J_{AB} = 10.6$, $J_{BM} = 8.5$, H–C(1)); 3.57 (*dd*, *ABM*, $J_{AB} = 10.6$, $J_{AM} = 3.7$, H′–C(1)). $[\alpha]_D^{20} = +16.7$ ($c = 1$, EtOH).

*(*S*)-2-Amino-3-methylpentan-1-ol* (**2d**). From L-Ile (26.2 g, 0.2 mol): 18.9 g (81%). Yellow liquid. B.p. 110° (10 mbar). $[\alpha]_D^{20} = +4.8$ ($c = 1$, EtOH). ^1H-NMR: 0.84 (*m*, 2 Me); 1.10 (*m*, CH); 1.33, 1.45 (2*m*, CH_2); 2.66 (*m*,

H–C(2), NH_2, OH); 3.28 (*dd*, *ABM*, J_{AB} = 10.4, J_{BM} = 8.4, 1 H of CH_2OH); 3.58 (*dd*, *ABM*, J_{AB} = 10.4, J_{AM} = 3.4, 1 H of CH_2OH).

General Procedures for the Synthesis of Bromoalkanamine Hydrobromides of Type **3**. *Method A* [8]: A mixture of **2** (0.1 mol) and HBr (48%, 50 ml) was refluxed at 170–175° for 5 h. The mixture was diluted with H_2O (100 ml), charcoal was added, and the filtrate was evaporated. The residue was recrystallized from AcOEt/EtOH.

Method B [8]: With cooling, HBr (48%, 10 ml) was added to **2** (0.1 mol). The mixture was evaporated *in vacuo* at r.t., and PBr_3 (10 ml) was added to the residue. When the reaction was complete, all volatile compounds were evaporated. The residue was precipitated by adding Et_2O and recrystallized from AcOEt/EtOH.

Method C [9]: To a cooled soln. of **2** (0.1 mol) in MeOH (20 ml), HBr (48%, 12 ml) was added. Volatile parts were evaporated, the residue was recrystallized from AcOEt and carefully added to hot PBr_3 (10 ml). This mixture was heated to 70° with vigorous stirring for 1.5 h. After cooling to 35°, Et_2O (50 ml) was slowly added. The supernatant was decanted, and the residue was recrystallized from a 1:1 mixture of AcOEt/Et_2O or AcOEt/EtOH.

Method D: $SOBr_2$ (15.6 g) in CH_2Cl_2 (20 ml) was added to **2** (66 mmol) in CH_2Cl_2 (50 ml) at 0°. The mixture was carefully warmed, until no more gas was produced. The residue was concentrated and dissolved in EtOH. Charcoal was added, and after heating, the charcoal was filtered off, the filtrate was concentrated, and the residue was recrystallized from EtOH/acetone.

*(*S*)-1-(Bromo(methyl)ethylammonium Bromide* (**3a**). From *a*) **2a** (8 g, 106 mmol) in MeOH (30 ml) with HBr (48%, 18 g, 110 mmol), *Method B*; or *b*) from **2a** (5 g, 66 mmol) in CH_2Cl_2 (50 ml), *Method D: a*) 8 g (34%); *b*) 6 g (44%). Yellow crystals. M.p. 117° (EtOH/acetone). IR: 3280–2200 (NH_3^+), 1570 (NH_3^+), 680 (C–Br).

*(*S*)-1-(Bromomethyl)-2-methylpropylammonium Bromide* (**3b**). From **2b** (7.5 g, 0.1 mol): 12.3 g (50%). Colorless crystals. M.p. 177°. $[\alpha]_D^{20}$ = +4.49 (*c* = 1, EtOH). IR: 3200–2800 (NH_3^+), 2970 (CH), 1590 (NH_3^+). ^{1}H-NMR: 1.12, 1.20 (2*d*, *J* = 6.8, each 2 Me); 2.32 (*m*, H–C(2)); 3.36, 3.72, 3.87 (*ABM*, J_{AM} = 4.3, J_{BM} = 5.4, J_{AB} = 11.6, H–C(1), CH_2Br); 8.30 (br. *s*, NH_3^+). Anal. calc. for $C_5H_{13}Br_2N$ (246.98): C 24.32, H 5.30, Br 64.71, N 5.30; found: C 24.20, H 5.34, Br 64.24, N 5.59.

*(*S*)-1-(Bromomethyl)-3-methylbutylammonium Bromide* (**3c**) [15]. From **2c** (11.8 g, 0.1 mol), *Method C:* 16.0 g (61%). Colorless crystals. M.p. 181° (AcOEt/Et_2O; lit. 180° [15]). $[\alpha]_D^{20}$ = +3.56 (*c* = 1, EtOH). IR: 3160–2700, 1600 (NH_3^+), 2950 (CH). ^{1}H-NMR: 0.86, 0.88 (2*d*, *J* = 3.5 each, 2 Me); 1.45 (*t*, *J* = 7.1, CH_2); 1.67 (*m*, H–C(4)); 3.48, 3.68, 3.75 (*ABM*, J_{AM} = 3.75, J_{BM} = 4.4, J_{AB} = 11.4, H–C(2), BrCH_2); 8.15 (br. *s*, NH_3^+).

*(*RS*)-1-(Bromomethyl)-3-methylbutylammonium Bromide* ((*RS*)-**3c**). From (*RS*)-**2c**, *Method C:* 15.6 g (60%). Colorless crystals. M.p. 182°.

*(*S*)-1-(Bromomethyl)-2-methylbutylammonium Bromide* (**3d**). From **2d** (11.8 g, 0.1 mol): 15.2 g (57%). Colorless crystals. M.p. 187°. $[\alpha]_D^{20}$ = +7.69 (*c* = 1, EtOH). IR: 3200–2700, 1590 (NH_3^+), 2960 (CH). ^{1}H-NMR: 0.98 (*t*, *J* = 7.3, Me); 1.07 (*d*, *J* = 6.8, Me); 1.39, 1.68 (2*m*, 2 CH_2); 2.12 (*m*, H–C(3)); 3.46, 3.71, 3.83 (*ABM*, J_{AM} = 3.8, J_{BM} = 6.1, J_{AB} = 11.5, H–C(2), BrCH_2); 8.40 (br. *s*, NH_3^+). Anal. calc. for $C_6H_{15}Br_2N$ (261.01): C 27.61, H 5.79, Br 61.23, N 5.37; found: C 27.27, H 5.70, Br 61.04, N 5.46.

*(*S*)-1-(Bromomethyl)-2-phenylethylammonium Bromide* (**3e**). From *a*) **2e** (15.1 g, 0.1 mol), *Method C*; or *b*) **2e** (5 g, 0.33 mol), *Method D: a*) 18.0 g (61%), *b*) 5 g (51%). Colorless crystals. M.p. 168°. IR: 3000–2800, 1500 (NH_3^+), 2925 (CH), 745, 700 (arom.). ^{1}H-NMR ((D$_6$)DMSO): 2.86, 2.99 (*ABM*, J_{AM} = 8.6, J_{BM} = 5.8, J_{AB} = 13.7, H–C(3), H′–C(3)); 3.44, 3.67 (*ABM*, J_{AM} = 4.5, J_{BM} = 3.4, J_{AB} = 11.5, H–C(1), H′–C(1)); 3.77 (*m* (*ABM*), H–C(2)); 7.3 (*m*, 5 arom. H); 8.2 (br. *s*, NH_3^+). $[\alpha]_D^{20}$ = –3.9 (*c* = 1, EtOH). MS (70 eV): 214 (8.8, [M – HBr]$^+$), 162 (24.6); 91 (39).

Synthesis of Amino Thiols **4**. *General Procedure* [16]. A soln. of **3** (0.05 mol) and thiourea (4.2 g, 0.05 mol) in EtOH (80–100 ml) was refluxed for 15 h. Then, tetraethylenepentamine (7.5 g) was added, and the mixture was refluxed for 1 h. The solvent was removed *in vacuo*, and the residue was purified by sublimation and recrystallization from EtOH. Alternatively, the sublimate was dissolved in a few milliliters of CCl_4 and immediately used for the next reaction.

*(*S*)-2-Amino-3-methylbutane-1-thiol* (**4b**). From **3b** (12.3 g, 0.05 mol): 1.9 g (32%). Colorless crystals. M.p. 46°. $[\alpha]_D^{20}$ = +4.24 (*c* = 1, EtOH). IR: 2995 (CH), 2535 (SH), 1585 (NH). ^{1}H-NMR: 0.90, 0.92 (2*d*, *J* = 2.2 each, 2 Me); 1.48 (br. *s*, NH_2, SH); 1.69 (*m*, H–C(3)); 2.38, 2.69, 2.85 (*ABM*, J_{AB} = 12.8, J_{AM} = 8.7, J_{BM} = 3.4, H–C(2), H–C(1), H′–C(1)).

*(*S*)-2-Amino-4-methylpentane-1-thiol* (**4c**). From **3c** (13.0 g, 0.05 mol): 2.5 g (38%). Colorless crystals. M.p. 48°. $[\alpha]_D^{20}$ = +6.23 (*c* = 1, EtOH). IR: 3000 (CH), 2530 (SH), 1587 (NH). ^{1}H-NMR: 0.9 (*m*, 2 Me); 1.25 (*t*,

$J = 7.2$, H–C(3), H′–C(3)); 1.68 (*m*, H–C(4), NH_2, SH); 2.36, 2.65, 2.85 (*ABM*, $J_{AB} = 13.4$, $J_{AM} = 7.6$, $J_{BM} = 3.9$, H–C(2), H–C(1), H′–C(1)).

*(*RS*)-2-Amino-4-methylpentane-1-thiol* ((*RS*)-**4c**). From (*RS*)-**3c** (13.0 g, 0.05 mol): 2.7 g (41%). Colorless crystals. M.p. 48°.

*(*S*)-2-Amino-3-methylpentane-1-thiol* (**4d**). From **3d** (13.0 g, 0.05 mol): 2.3 g (35%). Colorless crystals. M.p. 52°. $[\alpha]_D^{20} = +7.2$ ($c = 1$, EtOH). IR: 2995 (CH), 2530 (SH), 1585 (NH). ^{1}H-NMR: 1.02 (*m*, 2 Me); 1.61 (*s*, CH_2); 1.68 (*m*, H–C(3), NH_2, SH); 2.34, 2.64, 2.85 (*ABM*, $J_{AB} = 13.2$, $J_{AM} = 7.1$, $J_{BM} = 3.7$, H–C(2), H–C(1), H′–C(1)).

*(*S*)-2-Amino-3-phenylpropane-1-thiol* (**4e**). From **3e** (14.7 g, 0.05 mol): 3.2 g (38.4%). Colorless crystals. M.p. 56°. $[\alpha]_D^{20} = -5.2$ ($c = 1$, EtOH). IR: 3350 (NH), 3030, 2920 (CH), 900, 730, 700 (Ar). ^{1}H-NMR: 2.54, 2.59 (*ABM*, $J_{AB} = 13.43$, $J_{AM} = 8.4$, $J_{BM} = 6.83$, H–C(3), H′–C(3)); 2.76, 2.78 (*ABM*, $J_{AB} = 13.30$, $J_{AM} = 7.1$, $J_{BM} = 4.4$, H–C(1), H′–C(1)); 2.96 (br. *s*, NH_2, SH); 3.29 (*m* (*ABM*), H–C(2)); 7.2 (*m*, 5 arom. H).

Synthesis of Disulfides **5**. *General Procedure* [16]. To a soln. of **3** (25 mmol) in H_2O (80 ml), $Na_2S_2O_3 \cdot 5\ H_2O$ (6.3 g, 25 mmol) was added. The soln. was refluxed for 1 h, and to the hot soln., a soln. of I_2 in EtOH was added dropwise, until the reaction was complete. The mixture was cooled, an aq. soln. of NaOH (20%) was added dropwise, until a pH of *ca.* 10 was reached. Then, the mixture was extracted 3–4 times with CH_2Cl_2, the combined org. layers were washed with sat. NaCl soln., dried (Na_2SO_4), and evaporated *in vacuo*. The residue was immediately used for the next reaction without further purification.

*(2*S*)-1-[((2*S*)-2-Aminopropyl)disulfanyl]propan-2-amine* (**5a**). From **3a** (5 g) and I_2 (3.2 g): 2.9 g (71%).

*(2*S*)-1-[((2*S*)-2-Amino-4-methylpentyl)disulfanyl]-4-methylpentan-2-amine* (**5c**). From **3c** (10 g, 38 mmol), $Na_2S_2O_3 \cdot 5\ H_2O$ (8.7 g, 38 mmol), and I_2 (4.6 g): 3.5 g (70%).

*(2*S*)-1-[((2*S*)-2-Amino-3-phenylpropyl)disulfanyl]-3-phenylpropan-2-amine* (**5e**). From **3e** (3 g, 10 mmol), $Na_2S_2O_3 \cdot 5\ H_2O$ (2.5 g, 10 mmol), and I_2 (1.2 g): 2 g (60%). Yellow viscous liquid.

*(*S*)-2-Aminopropane-1-sulfonic Acid* (**6a**). A refluxing soln. of **3a** (8 g, 37 mmol) in EtOH (95%, 20 ml) and H_2O (8 ml) was slowly treated with a soln. of $Na_2SO_3 \cdot 5\ H_2O$ (5 g) in H_2O (10 ml), and reflux was continued for 2 h. The solvents were evaporated, the inorg. salts were filtered off, and the product was extracted with boiling EtOH (95%, 40 ml). On cooling, **6a** crystallized: 3.2 g (54%). Colorless crystals. M.p. 302° (dec).

Synthesis of 2-(Aminoalkyl)sulfonylchloride Hydrochlorides **6b**–**6e**. *General Procedure.* A soln. of **4** (20 mmol) in CCl_4 (100 ml) was saturated with HCl. EtOH (50 ml) was added, and Cl_2 gas was bubbled through the soln. below 10°. When the reaction was complete (yellow soln.), N_2 was blown through the mixture, and the solvent was evaporated. A few milliliters of Et_2O were added to the residue, which was recrystallized from acetone.

*(*S*)-2-Amino-3-methylbutane-1-sulfonyl Chloride Hydrochloride* (**6b**). From **4b** (2.4 g, 20 mmol): 3.2 g (72%). Colorless crystals. M.p. 185°. $[\alpha]_D^{20} = +25.5$ ($c = 1$, EtOH). IR: 3300–2700 (CH, NH_3^+), 2895 (CH), 1570, 1470 (NH_3^+), 1380, 1170 (SO_2). ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*m*, 2 Me); 1.67 (*m*, H–C(3)); 2.55, 2.75, 3.38 (*ABM*, $J_{AB} = 14.2$, $J_{AM} = 10.2$, $J_{BM} = 2.4$, H–C(2), H–C(1), H′–C(1)); 7.9 (br. *s*, NH_3^+). Anal. calc. for $C_5H_{13}Cl_2NO_2S$ (222.13): C 27.04, H 5.90, N 6.30, S 14.43; found: C 27.21, H 5.87, N 6.16, S 14.38.

*(*S*)-2-Amino-4-methylpentane-1-sulfonyl Chloride Hydrochloride* (**6c**). From **4c** (2.6 g, 20 mmol): 3.2 g (69%). Colorless crystals. M.p. 197°. $[\alpha]_D^{20} = +11.74$ ($c = 1$, EtOH). IR: 3200–2800 (CH, NH_3^+), 1595 (NH_3^+), 1380, 1170 (SO_2). ^{1}H-NMR ((D$_6$)DMSO): 0.87 (*m*, 2 Me); 1.46 (*m*, H–C(3), H′–C(3)); 1.67 (*m*, H–C(4)); 2.59, 2.74, 3.34 (*ABM*, $J_{AB} = 14.3$, $J_{AM} = 10.1$, $J_{BM} = 2.7$, H–C(2), H–C(1), H′–C(1)); 7.95 (br. *s*, NH_3^+). Anal. calc. for $C_6H_{15}Cl_2NO_2S$ (236.16): C 30.52, H 6.40. N 5.93, S 13.58; found: C 30.31, H 6.31, N 5.91, S 13.67.

*(*RS*)-2-Amino-4-methylpentane-1-sulfonyl Chloride Hydrochloride* ((*RS*)-**6c**). From (*RS*)-**4c** (2.6 g, 20 mmol): 2.9 g (63%). Colorless crystals. M.p. 197°.

*(*S*)-2-Amino-3-methylpentane-1-sulfonyl Chloride Hydrochloride* (**6d**). From **4d** (2.6 g, 20 mmol): 3.0 g (65%). Colorless crystals. M.p. 195°. $[\alpha]_D^{20} = +13.5$ ($c = 1$, EtOH). IR: 3200–2800 (CH, NH_3^+), 1500 (NH_3^+), 1375, 1165 (SO_2). ^{1}H-NMR ((D$_6$)DMSO): 0.82 (*m*, 2 Me); 1.16, 1.32 (2*m*, H–C(4), H′–C(4)); 1.74 (*m*, H–C(3)); 2.56, 2.68, 3.31 (*ABM*, $J_{AB} = 14.2$, $J_{AM} = 10.8$, $J_{BM} = 1.9$, H–C(2), H–C(1), H′–C(1)); 7.89 (br. *s*, NH_3^+). Anal. calc. for $C_6H_{15}Cl_2NO_2S$ (236.16): C 30.52, H 6.40, N 5.93, S 13.58; found: C 30.30, H 6.35, N 5.89, S 13.65.

*(*S*)-2-Amino-3-phenylpropane-1-sulfonyl Chloride Hydrochloride* (**6e**). From **4e** (3.3 g, 20 mmol): 4.1 g (77%). Colorless crystals. M.p. 184° (dec.). $[\alpha]_D^{20} = -12.0$ ($c = 1$, MeOH). IR: 3000–2800 (CH, NH_3^+), 1495 (NH_3^+), 1370, 1160 (SO_2), 760, 745, 700. ^{1}H-NMR ((D$_6$)DMSO): 2.57, 2.66 (*dd* (*ABM*), $J_{AB} = 14.2$, $J_{AM} = 3.2$, $J_{BM} = 9.6$, H–C(3), H′–C(3)); 2.80, 3.08 (*ABM*, $J_{AB} = 13.3$, $J_{AM} = 9.4$, $J_{BM} = 5.1$, H–C(1), H′–C(1)); 3.5 (*m* (*ABM*), H–C(2)); 7.2 (*m*, 5 arom. H); 8.1 (br. *s*, NH_3^+). MS (70 eV): 274 (17, M^+). Formula: $C_9H_{13}Cl_2NO_2S$ (270.17 g mol^{-1}).

(S)-3-Methyl-1,2-thiazetidine 1,1-Dioxide (**7a**). *Method A:* To a soln. of **6a** (3.2 g, 20 mmol) in Cl_3PO (60 ml), H_2O (4 ml) was added at 60°. Then, PCl_5 (27 g) was added, and the mixture was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$ (20 ml) and neutralized with 8N KOH at 0°. The org. layer was washed with ice-cold H_2O, dried (Na_2SO_4), and concentrated *in vacuo:* 0.8 g (33%).

Method B: **5a** (1 g, 11 mmol) was dissolved in a mixture of $CHCl_3$ (20 ml) and CCl_4 (20 ml). Then, HCl gas was passed at 0° through the mixture for a few minutes. EtOH (98%, 10 ml) was added, and the mixture was saturated with Cl_2 gas. After evaporation *in vacuo*, the residue was dissolved in anh. (!) $CHCl_3$ (30 ml), and NH_3-sat. $CHCl_3$ (50 ml) was added. After 24 h at r.t., NH_4Cl salts were separated by filtration over *Kieselgur*, and the filtrate was evaporated *in vacuo:* 0.8 g (61%). Colorless oily liquid. IR (film): 3290 (NH), 3040, 2870, 2930 (CH), 1300, 1155 (SO_2). ^{1}H-NMR: 1.48 (*d*, *J* = 6.0, Me); 3.83 (*m*, H–C(3)); 3.83 (*dd*, *J* = 14.0, 5.0, H–C(4)); 4.39 (*dd*, *J* = 14.0, 9.0, H′–C(4)); 5.95 (br. *s*, NH). Anal. calc. for $C_3H_7NO_2S$ (121.16): C 29.74, H 5.82, N 11.56; found: C 29.70, H 5.89, N 11.45.

Synthesis of 3-Alkyl-1,2-thiazetidine 1,1-Dioxides **7b**–**e**. *General Procedure*. To a cooled suspension of **6** (20 mmol) in THF (100 ml), a sat. soln. of NH_3 in $CHCl_3$ was added, until the mixture was pH-neutral. After a few hours, the precipitate was separated, and the solvent was evaporated *in vacuo*. A few milliliters of CCl_4 were added to the residue, and, after a short period of heating, the product crystallized on cooling.

(S)-3-Isopropyl-1,2-thiazetidine 1,1-Dioxide (**7b**). From **6b** (4.4 g, 20 mmol): 1.8 g (61%). Colorless crystals. M.p. 53°. $[\alpha]_D^{20} = +9.73$ (*c* = 1, EtOH). IR: 3335 (NH), 3047 (CH), 1340, 1150 (SO_2). ^{1}H-NMR: 0.92, 0.95 (2*d*, *J* = 6.7 each, 2 Me); 1.89 (*m*, CH); 3.29 (*m* (*ABM*), H–C(3)); 3.89, 4.18 (*ABM*, $J_{AB} = 12.6$, $J_{AM} = 11.6$, $J_{BM} = 6.1$, H–C(4), H′–C(4)); 5.4 (*s*, NH). ^{13}C-NMR: 17.86, 18.35 (2 Me); 33.55 (CH); 46.56 (C(3)); 63.03 (C(4)). Anal. calc. for $C_5H_{11}NO_2S$ (149.21): C 40.25, H 7.43, N 9.39, O 21.45; found: C 40.08, H 7.35, N 9.36, O 21.47.

(S)-3-(2-Methylpropyl)-1,2-thiazetidine 1,1-Dioxide (**7c**). *Method A:* From **6c** (4.7 g, 20 mmol): 1.2 g (37%). *Method B:* from **5c** (3.5 g, 26.5 mmol), as described for **7a**: 2.9 g (86%). Colorless crystals. M.p. 56° ($CHCl_3$/pentane). *A*) $[\alpha]_D^{20} = +11.5$ (*c* = 1, EtOH); *B*) $[\alpha]_D^{23} = +3.57$ (*c* = 2.41, $CHCl_3$). IR: 3290 (NH), 3030 (CH), 1370, 1160 (SO_2). ^{1}H-NMR: 0.89, 0.93 (2*d*, *J* = 5.3 each, 2 Me); 1.58 (*m*, CH_2); 1.69 (*m*, CH); 3.69 (*m* (*ABM*), H–C(3)); 3.83, 4.28 (*ABM*, $J_{AB} = 12.5$, $J_{AM} = 10.8$, $J_{BM} = 5.7$, H–C(4), H′–C(4)); 5.3 (br. *s*, NH). ^{13}C-NMR: 21.94, 22.59 (2 Me); 25.80 (CH); 44.95 (CH_2); 39.50 (C(3)); 65.18 (C(4)). Anal. calc. for $C_6H_{13}NO_2S$ (163.24): C 44.15, H 8.03, N 8.58, S 19.64; found: C 44.03, H 8.09, N 8.52, S 19.74.

(RS)-3-(2-Methylpropyl)-1,2-thiazetidine 1,1-Dioxide ((*RS*)-**7c**). From (*RS*)-**6c** (4.4 g, 20 mmol): 1.4 g (43%). Colorless crystals. M.p. 56°.

(S)-3-(1-Methylpropyl)-1,2-thiazetidine 1,1-Dioxide (**7d**). From **6d** (4.7 g, 20 mmol): 1.2 g (37%). Colorless crystals. M.p. 58°. $[\alpha]_D^{20} = +12.54$ (*c* = 1, EtOH). IR: 3330 (NH), 3048 (CH), 1385, 1165 (SO_2). ^{1}H-NMR: 0.9 (*m*, 2 Me); 1.1 (*m*, CH); 1.49, 1.65 (2*m*, 2 CH_2); 3.35 (*m* (*ABM*), H–C(3)); 3.89, 4.17 (*ABM*, $J_{AB} = 12.6$, $J_{AM} = 4.0$, $J_{BM} = 6.1$, H–C(4), H′–C(4)); 5.40 (*s*, NH). ^{13}C-NMR: 10.78, 14.02 (2 Me); 25.49 (CH_2); 39.83 (CH); 45.39 (C(3)); 63.03 (C(4)). Anal. calc. for $C_6H_{13}NO_2S$ (163.23): C 44.15, H 8.03, N 8.58; found: C 43.71, H 7.83, N 8.52.

(S)-3-(Phenylmethyl)-1,2-thiazetidine 1,1-Dioxide (**7e**). From **6e** (3.0 g, 11 mmol): 1.9 g (87%). Light yellow crystals. M.p. 68–70°. $[\alpha]_D^{23} = -19.96$ (*c* = 2.43, $CHCl_3$); $[\alpha]_D^{20} = -34.7$ (*c* = 1, EtOH). IR: 3270 (NH), 1385, 1165 (SO_2), 780, 740, 700. ^{1}H-NMR: 3.02 (*d*, CH_2); 3.85 (*m* (*ABM*), H–C(3)); 3.95, 4.26 (*ABM*, $J_{AB} = 12.5$, $J_{AM} = 7.6$, $J_{BM} = 5.3$, H–C(4), H′–C(4)); 5.21 (br. *s*, NH); 7.2 (*m*, 5 arom. H). ^{13}C-NMR: 41.79 (CH_2); 41.98 (C(3)); 64.31 (C(4)); 127.39, 128.86, 129.01, 136.04 (6 arom. C). Anal. calc. for $C_9H_{11}NO_2S$ (197.26): C 54.80, H 5.62, N 7.10, S 16.25; found: C 54.61, H 5.69, N 7.16, S 16.20.

(RS)-3-(Phenylmethyl)-1,2-thiazetidine 1,1-Dioxide ((*RS*)-**7e**) was prepared from D,L-Phe *via* the disulfide (*RS*)-**5e**. M.p. 69°.

Methyl (R)-1,2-Thiazetidine-3-carboxylate 1,1-Dioxide (**9a**). From L-cystine dimethyl ester hydrochloride (**8**; 5 g, 14.7 mmol)), as described for **9b** [10]: 2.3 g (50%). Colorless crystals. M.p. 72–73°. $[\alpha]_D^{23} = -58.15$ (*c* = 1.26, $CHCl_3$).

Ethyl (R)-1,2-Thiazetidine-3-carboxylate 1,1-Dioxide (**9b**): see [10].

(R)-1,2-Thiazetidine-3-methanol 1,1-Dioxide (**10**) [10]. From **9b** (1.8 g, 10 mmol) in THF (40 ml), and $LiBH_4$ (0.2 g, 10 mmol): 0.5 g (36%). Colorless crystals. M.p. 70° (CH_2Cl_2; lit. 70–71° [10]). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 3.58 (*m*, CH_2OH, H–C(3), NH); 3.88–4.50 (*m*, H–C(4), H′–C(4)). Formula: $C_3H_7NO_3S$ (137.16 g mol^{-1}).

Ethyl (R)-2-[(tert-Butyl)dimethylsilyl]-1,2-thiazetidine-3-carboxylate 1,1-Dioxide (**11a**). Under N_2 at –78°, BuLi (7.5 ml, 12 mmol) was added to **9b** (2.15 g, 12 mmol) dissolved in THF (100 ml). After stirring for 10 min, (*t*-Bu)Me_2SiCl (1.96 g, 13 mmol) was added. After stirring for 30 min at –78°, the mixture was warmed to r.t., and hydrolyzed with a sat. NaCl soln. The org. layer was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by CC (cyclohexane/AcOEt 5:7): 2.5 g (71%). Light yellow liquid. $[\alpha]_D^{23} = -64.22$ (*c* = 2.2,

$CHCl_3$). IR (film): 3030, 2950, 2920, 2850 (CH), 1745 (C=O), 1320, 1310, 1195, 1150 (SO_2). ^{1}H-NMR: 0.25, 0.31 (2*s*, $Si(Me)_2$); 1.00 (*s*, *t*-Bu); 1.35 (*t*, *J* = 7.0, Me); 4.15 (*dd*, *J* = 4.0, 8.0, H–C(3)); 4.25 (*q*, *J* = 7.0, OCH_2); 4.3 (*dd*, *J* = 12.0, 4.0, H–C(4)); 4.55 (*dd*, *J* = 12.0, 8.0, H′–C(4)). Anal. calc. for $C_{11}H_{23}NO_4SSi$ (293.46): C 45.02, H 7.90, N 4.77; found: C 44.74, H 7.71, N 4.91.

*Ethyl (*R*)-2-[(*tert*-Butyl)diphenylsilyl]-1,2-thiazetidine-3-carboxylate 1,1-Dioxide* (**11b**). From **9b** (1.1 g, 6 mmol), BuLi (3.8 ml, 6 mmol), and (*t*-Bu)Ph_2SiCl (1.6 ml, 6 mmol), as described for **11a**. CC (cyclohexane/AcOEt 1:1): 1.6 g (65%). Colorless crystals. M.p. 80–82° (CCl_4/pentane). $[\alpha]_D^{23} = -49.3$ (*c* = 1.1, $CHCl_3$). IR: 3080, 3050, 2980, 2950, 2900, 2860 (CH), 1750 (C=O), 1320, 1310, 1200, 1150 (SO_2). ^{1}H-NMR: 0.83 (*t*, Me); 1.15 (*s*, *t*-Bu); 3.35–3.8 (*m*, OCH_2); 3.88 (*dd*, *J* = 4.0, 8.0, H–C(3)); 4.21 (dd, *J* = 13.0, 4.0, H–C(4)); 4.48 (*dd*, *J* = 13.0, 8.0, H′–C(4)); 7.25–7.96 (*m*, 10 arom. H). Anal. calc. for $C_{21}H_{27}NO_4SSi$ (417.60): C 60.40, H 6.52, N 3.35; found: C 60.13, H 6.48, N 3.47.

*(*R*)-1,2-Thiazetidine-3-carboxamide 1,1-Dioxide* (**12a**). Compound **9b** (3 g, 16.7 mmol) was dissolved in an NH_2-sat. $CHCl_3$ soln. At 0°, NH_3 was passed through the soln. for 30 min. After 2 d, the crystals that had formed were separated: 1.5 g (60%). Colorless crystals. M.p. 147° (dec.). IR: 3430, 3340 (NH), 3080, 2980 (CH), 1660, 1600 (amide), 1305, 1155, 1140 (SO_2). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 3.0–4.75 (br. *s*, NH_2); 3.98 (*dd*, *J* = 8.0, 5.0, H–C(3)); 4.2 (*dd*, *J* = 12.0, 5.0, H–C(4)); 4.54 (*dd*, *J* = 12.0, 8.0, H′–C(4)); 7.41 (*d*, NH). Anal. calc. for $C_3H_6N_2O_3S$ (150.16): C 22.64, H 4.44, N 17.60, S 20.14; found: C 22.50, H 4.47, N 17.35, S 20.02.

*(*R*)-N-(Phenylmethyl)-1,2-thiazetidine-3-carboxamide 1,1-Dioxide* (**12b**). *Method A:* **11a** (2.3 g, 7.8 mmol) was dissolved in Et_2O, benzylamine (1 ml, 9 mmol) was added, and the mixture was refluxed for 8 h. After evaporation, a few drops of CCl_4 were added to the residue: 1.1 g (60%).

Method B: **9b** (1.9 g, 10.6 mmol), and benzylamine (1.13 g, 10.6 mmol) in CH_2Cl_2 (20 ml) were refluxed for 10 h. After evaporation, a few drops of CCl_4 were added to the residue: 1.4 g (55%). Colorless crystals. M.p. 140° (dec.). IR: 3350, 3100 (NH), 1650, 1530 (amide), 1315, 1185, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 2.75–3.63 (br. *s*, NH); 4.05 (*dd*, *J* = 6.0, 8.0, H–C(3)); 4.25–4.49 (*m*, H–C(4), PhCH_2); 4.55 (*dd*, *J* = 12.0, 8.0, H′–C(4)); 7.26 (*m*, 5 arom. H); 8.2 (br. *s*, NH). Anal. calc. for $C_{10}H_{12}N_2O_3S$ (240.28): C 49.99, H 5.03, N 11.66, S 13.34; found: C 49.97, H 5.12, N 11.76, S 13.36.

*(*R*)-(1,2-Thiazetidine-3-yl)methyl Acetate 1,1-Dioxide* (**13**) [10]. From **10** (5 g, 18.1 mmol), FC (AcOEt/cyclohexane 1:2 → 1:1): 1.45 g (45%). Colorless crystals. M.p. 49°. $[\alpha]_D^{25} = +7.9$ (*c* = 3.3, EtOH). Formula: $C_5H_9NO_4S$ (179.20 g mol^{-1}).

*(*R*)-2-[(*tert*-Butyl)dimethylsilyl]-3-([[(*tert*-butyl)dimethylsilyl]oxy]methyl)-1,2-thiazetidine 1,1-Dioxide* (**14**). Under N_2 at –78°, BuLi (5.6 ml, 8.96 mmol) was added to **13** (0.5 g, 2.79 mmol) in THF (20 ml), and after stirring for 15 min, (*t*-Bu)Me_2SiCl (1.5 g, 9.95 mmol) in THF (5 ml) was added. Stirring was continued at r.t. for 90 min, the mixture was hydrolyzed with sat. NH_4Cl soln. (50 ml). AcOEt (50 ml) was added, and the org. layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by FC (AcOEt/cyclohexane 1:9): 0.5 g (49%). Colorless needles. M.p. 25°. R_f 0.30 (AcOEt/cyclohexane 1:9). $[\alpha]_D^{23.2} = -31.5$ (*c* = 1.1, Et_2O). IR (film): 2975, 2935, 2863 (CH), 1470 (Me), 1312, 1199, 1153, (SO_2), 1257 (MeSi). ^{1}H-NMR: 0.07, 0.08, 0.27, 0.28 (4*s*, 4 MeSi); 0.90, 0.99 (2*s*, 2 *t*-Bu); 3.60–3.69 (*m*, 1 H of CH_2, H–C(3)); 3.86 (*dd*, *J* = 8.0, 11.0, 1 H of CH_2); 3.97 (*dd*, *J* = 1.0, 13.0, H–C(4)); 4.30 (*dd*, *J* = 7.0, 14.0, H′–C(4)). ^{13}C-NMR: –5.6, –5.4, –4.3 (SiMe); 18.1, 18.3, 25.8, 26.1 (*t*-Bu); 43.7 (C(3)); 63.2 (C(4)); 65.6 (CH_2O). Anal. calc. for $C_{15}H_{35}NO_3SSi_2$ (365.69): C 49.27, H 9.65, N 3.83; found: C 49.43, H 9.47, N 3.56.

*(3*R*,4*S*)-4-Acetyl-2-[(*tert*-Butyl)dimethylsilyl]-3-([[(*tert*-butyl)dimethylsilyl]oxy]methyl)-1,2-thiazetidine 1,1-Dioxide* (**15**). Under N_2 at –78°, BuLi (1.03 ml, 1.65 mmol) was added to a soln. of **14** (0.4 g, 1.1 mmol) in a mixture of THF (5 ml) and HMPA (1 ml). After 10 min, acetyl chloride (0.15 ml, 2.2 mmol) was added with stirring, the mixture was warmed to r.t., AcOEt (50 ml) was added, and the mixture was washed with sat. NH_4Cl soln. (3 × 50 ml). The org. layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (AcOEt/cyclohexane 1:9): 42 mg (9.3%). Colorless liquid. R_f 0.3 (AcOEt/cyclohexane 1:9). $[\alpha]_D^{25} = -8.3$ (*c* = 0.3, acetone). ^{1}H-NMR: 0.15, 0.257 (2*s*, 2 SiMe); 0.263 (*s*, 2 MeSi); 0.94, 0.97 (*s* and m_c, 2 *t*-Bu); 2.07 (*s*, Ac); 3.60 (*ddd*, *J* = 4.0, 5.0, 6.0, H–C(3)); 3.86 (*d*, *J* = 4.0, H–C(4)); 4.16 (*dd*, *J* = 6.0, 12.0, 1 H, C(3)CH_2); 4.31 (*dd*, *J* = 5.0, 12.0, 1 H, C(3)CH_2). Anal. calc. for $C_{16}H_{37}NO_4SSi_2$ (407.72): C 50.08, H 9.15, N 3.44; found: C 50.50, H 9.39, N 2.99.

*(*RS*)-2-Benzoyl-3-(phenylmethyl)-1,2-thiazetidine 1,1-Dioxide* ((*RS*)-**16**). To a soln. of (*RS*)-**7e** (1.2 g, 6 mmol) in THF (40 ml), Et_3N (0.6 g, 6.1 mmol) was added at 0°, followed dropwise by PhCOBr (1.0 g, 5.8 mmol) in THF (10 ml). The mixture was stirred for 1.5 h at 5°, the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue solidified, when stored for 3 d at –20°: 1.3 g (74%). Colorless crystals. M.p. 89° (98% EtOH). IR: 3060, 3020, 2960, 2920 (CH), 1670 (C=O), 1600, 1580, 1490, 1445 (arom.), 1345, 1320, 1195, 1160 (SO_2). ^{1}H-NMR: 3.0 (*dd*, *J* = 14.4, 8.0, 1 H of PhCH_2); 3.5 (*dd*, *J* = 14.4, 4.0, 1 H of PhCH_2); 3.88

(*dd*, *J* = 13.0, 6.0, H–C(4)); 4.15 (*dd*, *J* = 13.0, 8.0, H′–C(4)); 4.38–4.8 (*m*, H–C(3)); 7.05–8.15 (*m*, 10 arom. H). Anal. calc. for $C_{16}H_{15}NO_3S$ (301.36): C 63.77, H 5.02, N 4.64, S 10.64; found: C 63.76, H 5.11, N 5.11, S 10.72.

N-*Benzoyl*-L-*leucine* ((S)-**17a**) [15]. From L-Leu (13.1 g, 100 mmol) and benzoyl chloride (11 ml, 100 mmol): 23 g (98%).

N-*(Phenylmethyl)*-D,L-*alanine* ((*RS*)-**17b**). See [18].

*(*S*)-4-Methyl-2-[(phenylmethyl)amino]pentan-1-ol* ((*S*)-**18a**). From (*S*)-**17a** (23 g, 98 mmol), and $LiAlH_4$ (20 g, 540 mmol), as described for **2**, after 3 h of heating. The residue solidified on cooling: 19.8 g (97%). Colorless crystals. M.p. 70° (toluene). $[\alpha]_D^{23} = -22.4$ (*c* = 3.6, EtOH). IR: 3280 (NH), 3200–2500 (OH, CH). ^{1}H-NMR (60 MHz): 0.97 (*d*, 2 Me); 1.1–1.8 (*m*, $CHCH_2$); 1.93–2.3 (*m*, OH, NH); 2.5–3.07 (*m*, CHN); 3.8 (*s*, PhCH_2); 3.17–3.9 (*m*, CH_2O); 7.33 (*m*, 5 arom. H). Anal. calc. for $C_{13}H_{21}NO$ (207.32): C 75.32, H 10.21, N 6.76; found: 75.09, H 10.10, N 6.68.

(RS)-*2-[(Phenylmethyl)amino]propan-1-ol* ((*RS*)-**18b**). From (*RS*)-**17b** (11.1 g, 62 mmol), and $LiAlH_4$ (5 g) in THF (200 ml), as described for **2**, after 5 h of heating. The residue solidified on cooling: 7.9 g (77%). Colorless crystals. M.p. 64° (Et_2O). IR: 3280 (NH), 3260–2500 (OH, CH). ^{1}H-NMR: 1.08 (*d*, Me); 2.5 (br. *s*, OH, NH); 2.83 (*m*, H–C(2)); 3.28 (*dd*, *J* = 11.0, 6.0, H–C(1)); 3.55 (*dd*, *J* = 11.0, 4.0, H′–C(1)); 3.75 (*AB*, CH_2); 7.26 (*m*, 5 arom. H). Formula: $C_{10}H_{15}NO$ (165.24 g mol^{-1}).

*(*S*)-2-(2-Methylpropyl)-1-(phenylmethyl)aziridine* (**19**). Ph_3P (15.5 g, 59 mmol), Et_3N (5.2 g, 52 mmol), and CCl_4 (8 g, 2 mmol) were added to a soln. of (*S*)-**18a** (10.8 g, 52 mmol) in MeCN (40 ml). The mixture was stirred for 4 h at *ca.* 8°, and was then stored at 5–8° for 12–24 h. The precipitate ($Et_3N \cdot HCl$) was filtered off, the filtrate was concentrated *in vacuo*, and the residue was extracted with petroleum ether (4 × 50 ml). The combined org. extracts were stored for 12–24 h at −18°. The precipitate (Ph_3PO) was separated, the solvent was concentrated, and the residue was purified by bulb-to-bulb distillation: 7 g (71%). Colorless liquid. B.p. 70° (0.8 mbar), 135° (15 mbar). $[\alpha]_D^{23} = +12.1$ (*c* = 2.98, $CHCl_3$). IR (film): 3080, 3060, 3015, 2950, 2860 (CH), 1490, 1460, 1450, 730, 695 (arom.). ^{1}H-NMR: 0.75, 0.80 (2*d*, 2 Me); 1.02–1.9 (*m*, CH, CH_2, H–C(2), H–C(3), H′–C(3)); 3.38 (*s*, $PhCH_2$). Anal. calc. for $C_{13}H_{19}N$ (189.30): C 82.48, H 10.12, N 7.40; found: C 82.20, H 10.01, N 7.27.

*(*RS*)-*N*-Benzyl-2-bromo-1-methylethylammonium Bromide* (**20**). From (*RS*)-**18b** (7.9 g, 48 mmol), HBr (48%, 7.8 g), and PBr_3 (6.8 g), as described for **3**, *Method B:* 9 g (60%). Yellowish crystals. M.p. 115° (EtOH/Et_2O).

*(*S*)-*N*-Benzyl-1-[(benzylsulfanyl)methyl]-3-methylbutanamine* (**21**). Under N_2, $PhCH_2SH$ (4 g, 32 mmol) and Na (50 mg) were dissolved in EtOH (20 ml), and warmed to 40°. **19** (6 g, 32 mmol) was added, the mixture was stirred for 3 h at 40°, then for 2 d at r.t. The solvent was evaporated, and the residue was purified by CC ($CHCl_3$/acetone 9:1): 3 g (31%). Colorless viscous liquid. ^{1}H-NMR: 0.78 (*d*, 2 Me); 1.09–1.75 (*m*, $CHCH_2$, NH); 2.3–2.8 (*m*, $CHCH_2S$); 3.53 (*s*, CH_2N); 3.58 (*s*, CH_2S); 7.19 (*m*, 10 arom. H). Anal. calc. for $C_{20}H_{27}NS$ (313.51): C 76.62, H 8.68, N 4.47; found: 76.40, H 8.35, N 4.21.

*(*RS*)-2,2′-Dithiobis(*N*-benzyl-1-methylethanamine)* (**22**). From **20** (9 g, 29 mmol), $Na_2S_2O_3 \cdot 5\ H_2O$ (7.2 g, 29 mmol), and I_2 (3.8 g), as described for **5**: 2.5 g (48%). Yellow viscous liquid, which was immediately used for the next reaction without further purification.

*(*S*)-*N*-Benzyl-2-[(chlorosulfonyl)methyl]-3-methylbutylammonium Chloride* ((*S*)-**23a**). A soln. of **21** (3 g, 10 mmol) in a mixture of $CHCl_3$ (20 ml) and CCl_4 (40 ml) was saturated at 0° with HCl, EtOH (96%, 20 ml) was added, the mixture was saturated with Cl_2 gas, and then evaporated *in vacuo*. A few milliliters of an acetone/Et_2O 1:1 mixture were added to the residue: 2.3 g (70%). Colorless crystals. M.p. 202° (dec.; acetone/Et_2O). IR: 3100–2300 (NH^{2+}), 1570 (NH^{2+}), 1380, 1165 (SO_2). Formula: $C_{13}H_{21}Cl_2NO_2S$ (326.29 g mol^{-1}).

*(*RS*)-*N*-Benzyl-2-(chlorosulfonyl)-1-methylethylammonium Chloride* ((*RS*)-**23b**). From **22** (2 g) by oxidative chlorination, as described for **6** (*General Procedure*). The product was precipitated by adding Et_2O: 2.2 g (79%). Colorless crystals. M.p. 148° (acetone/Et_2O). IR: 3100–2300 (NH_2^+), 1370, 1170, 1140 (SO_2Cl). Formula: $C_{10}H_{15}Cl_2NO_2S$ (284.21 g mol^{-1}).

*(*S*)-3-(2-Methylpropyl)-2-(phenylmethyl)-1,2-thiazetidine 1,1-Dioxide* ((*S*)-**24a**). From (*S*)-**23a** (2 g, 6 mmol), as described for **7** (*General Procedure*): 0.5 g (29%). Colorless crystals. M.p. 50°. $[\alpha]_D^{23} = +59.87$ (*c* = 2.22, $CHCl_3$). IR: 3030, 2950, 2920, 2860 (CH), 1310, 1295, 1160, 1145 (SO_2). ^{1}H-NMR: 0.75, 0.78 (2 *d*, 2 Me); 1.2–1.7 (*m*, $CHCH_2$); 3.08–3.5 (*m*, H–C(3)); 3.7 (*dd*, *J* = 12.0, 6.0, H–C(4)); 3.9, 4.3 (2*d*, *J* = 15.0, PhCH_2); 4.1 (*dd*, *J* = 12.0, 8.0, H′–C(4)); 7.3 (*m*, 5 arom. H). Anal. calc. for $C_{13}H_{19}NO_2S$ (253.37): C 61.63, H 7.56, N 5.53, S 12.65; found: C 61.78, H 7.50, N 5.50, S 12.79.

*(*RS*)-3-Methyl-2-(phenylmethyl)-1,2-thiazetidine 1,1-Dioxide* (**24b**). From (*RS*)-**23b** (2.1 g, 8.3 mmol), as described for **7** (*General Procedure*). Yield: 1.5 g (81%). Colorless crystals. M.p. 35° ($CHCl_3$/pentane). IR: 3080,

3060, 3030, 2970, 2920, 1310, 1165, 1145 (SO_2). Anal. calc. for $C_{10}H_{13}NO_2S$ (211.28): C 56.85, H 6.20, N 6.63, S 15.18; found: C 56.81, H 6.20, N 6.70, S 15.06.

D-*Penicillamine Benzyl Ester Hydrochloride (= Phenylmethyl (*S*)-2-Amino-3-methyl-3-sulfanylbutanoate Hydrochloride*; **25**) [19]. From D-penicillamine (13 g, 87 mmol), polyphosphoric acid (32.5 g), and BnOH (160 ml, 1.42 mol): 10.2 g (43%). Colorless solid. M.p. 140–144° (Et_2O/MeOH). IR: 3100–2750 (NH_3^+, CH), 1743 (C=O), 1584 (NH_3^+), 1230 (C–O). ^{1}H-NMR ((D_6)DMSO, 80 MHz): 1.45, 1.50 (2*s*, 2 Me); 4.15 (*s*, H–C(2)); 5.25 (*s*, CH_2); 7.40 (*s*, 5 arom. H); 7.30–8.30 (br. *s*, NH_3^+).

*(*S*)-1-Amino-1-[(benzyloxy)carbonyl]-2-methylpropane-2-sulfonic Acid* (**26**). To a soln. of **25** (2 g, 7.25 mmol) in H_2O/AcOH 1:1 (20 ml) at 50°, Br_2 (5 g, 31.3 mmol) was added dropwise. The mixture was stirred for 45 min, the solvent was evaporated, the residue was dried (KOH), and washed with acetone (20 ml): 1.6 g (77%). Colorless crystals. M.p. 235–240° (96% i-PrOH). $[\alpha]_D^{25} = -9.0$ ($c = 0.1$, 1N HCl). IR: 3300–2700 (NH_3^+, CH), 1744 (C=O), 1597 (NH_3^+), 1465, 1203, 1104 (SO_2). ^{1}H-NMR ((D_6)DMSO): 1.20, 1.22 (2*s*, 2 Me); 4.05 (*s*, H–C(3)); 5.10 (*s*, CH_2); 7.33–7.45 (*m*, 5 arom. H); 8.20 (*s*, NH_3^+). FAB-MS: 575 (36, $[2M+1]^+$), 380 (75), 288 (100, $[M+1]^+$), 277 (84), 206 (82), 185 (100). Formula: $C_{12}H_{17}NO_5S$ (287.34 g mol^{-1}).

*Phenylmethyl (*S*)-4,4-Dimethyl-1,2-thiazetidine-3-carboxylate 1,1-Dioxide* (**27**). To a suspension of **26** (1 g, 3.48 mmol) in a mixture of MeCN (2 ml) and sulfolane (2 ml), Cl_3PO (1.5 ml, 5.9 mmol) was added, and the mixture was heated to 65° for *ca.* 1 h. The solvent was evaporated at 50°, the residue was dissolved in $CHCl_3$ (50 ml) and alkalized with a soln. of Et_3N in $CHCl_3$. After stirring for 2 h, the solvent was evaporated, the residue was dissolved in AcOEt, and washed with sat. aq. NH_4Cl soln. The org. layer was dried (Na_2SO_4), evaporated, and the residue was purified by FC (AcOEt/cyclohexane 1:1): 0.35 g (37%). Yellow viscous liquid. R_f 0.4 (AcOEt/cyclohexane 1:1). $[\alpha]_D^{25.6} = +39.3$ ($c = 3.5$, AcOEt). IR (film): 3288 (NH), 1753 (C–O), 1320, 1168, 1129 (SO_2). ^{1}H-NMR: 1.46, 1.76 (2*s*, 2 Me); 3.90 (*s*, H–C(3)); 5.20 (*AB*, $J = 9.0$, CH_2); 5.72 (br. *s*, NH); 7.35 (*s*, 5 arom. H). ^{13}C-NMR: 18.9, 23.3 (2 Me); 54.3 (CH_2); 68.3 (C(3)); 80.4 (C(4)); 128.8, 128.9, 129.0, 134.4 (6 arom. C); 167.9 (C=O). CI-MS (isobutane): 413 (4), 270 (6, $[M+1]^+$), 262 (4), 207 (14), 206 (100.0). Anal. calc. for $C_{12}H_{15}NO_4S$ (269.32): C 53.52, H 5.61, N 5.20; found: C 53.47, H 5.74, N 5.02.

N-*Benzyl-*L*-threonine (= (2*S*,3*R*)-3-Hydroxy-2-[(phenylmethyl)amino]butanoic Acid*; **28a**). From L-Thr (16.7 g, 140 mmol), as described for **28b** [20]: 21 g (72%). Colorless crystals. M.p. 238° (dec.; H_2O). IR: 3200 (OH), 3100–2500 (CH, COOH), 1625 (C=O), 1590, 1550 (NH_2^+).

N-*Benzyl-*L*-serine (= (*S*)-3-Hydroxy-2-[(phenylmethyl)amino]propanoic Acid*; **28b**) [20]. From L-Ser (14.7 g, 140 mmol): 19 g (69%). Colorless crystals. M.p. 235° (dec.; lit. 219° [20]).

*(2*R*,3*S*)-2-Methyl-5-oxo-4-(phenylmethyl)morpholine-3-carboxylic Acid* (**29a**). To a cooled soln. of **28a** (20 g, 91 mmol) in 2N aq. NaOH soln. (100 ml), $ClCH_2COCl$ (9.5 ml, 109 mmol) was added dropwise. The mixture was stirred for 30 min, an aq. soln. of NaOH (30 ml, 30%) was added, and stirring was continued for 2 h. After acidifying with conc. HCl to pH 1, the precipitate was dissolved in boiling i-PrOH, and filtered hot. The solvent was evaporated *in vacuo*, the residue was dissolved in $CHCl_3$, the soln. was dried (Na_2SO_4), and evaporated: 9.6 g (40%). Colorless crystals. M.p. 136°. $[\alpha]_D^{29} = +26°$ ($c = 2$, EtOH). IR: 3200–2400 (OH), 1725, 1600 (C=O), 1110 (C–O). ^{1}H-NMR: 1.2 (*d*, Me); 3.6 (*d*, $J = 4.0$, H–C(3)); 3.7 (*d*, $J = 15.0$, H–C(6)); 4.26 (*s*, PhCH_2); 4.26 (*m*, H–C(2)); 5.6 (*d*, $J = 15.0$, H′–C(6)); 7.28 (*m*, 5 arom. H); 10.8 (*s*, COOH). Anal. calc. for $C_{13}H_{15}NO_4$ (249.27): C 62.64, H 6.07, N 5.62; found: C 62.49, H 6.01, N 5.66.

*(*S*)-5-Oxo-4-(phenylmethyl)morpholine-3-carboxylic Acid* (**29b**) [20]. From **28b** (17.8 g, 91 mmol) in 2N aq. NaOH soln. (100 ml) and $ClCH_2COCl$ (8.7 g, 109 mmol), as described for **29a**: 8.6 g (40%). Colorless crystals. M.p. 156° (lit. 143–145° [20]). IR: 3100–2300 (OH), 1720, 1600 (C=O), 1485, 1450, 730, 700 (arom.).

*Ethyl (2*R*,3*S*)-2-Methyl-5-oxo-4-(phenylmethyl)morpholine-3-carboxylate* (**30a**). From **29a** (7 g, 28 mmol) in EtOH (150 ml), and $SOCl_2$ (2.2 ml, 30 mmol), as described for **30b**: 7.7 g (97%). Light yellow crystals. M.p. 39–40°. $[\alpha]_D^{23} = -34.18$ ($c = 4.11$, AcOEt). IR: 1730, 1650 (C=O); 1110 (C–O). ^{1}H-NMR: 1.23 (*d*, Me); 1.25 (*t*, Me); 3.65 (*d*, H–C(3)); 3.75 (*d*, $J = 15.0$, H–C(6)); 4.18 (*q*, OCH_2); 4.24 (*s*, $PhCH_2$); 4.05–4.36 (*m*, H–C(2)); 5.48 (*d*, $J = 15.0$, H′–C(6)); 7.26 (*m*, 5 arom. H). Anal. calc. for $C_{15}H_{19}NO_4$ (277.32): C 64.97, H 6.91, N 5.05; found: C 64.70, H 6.80, N 5.18.

*Ethyl (*S*)-5-Oxo-4-(phenylmethyl)morpholine-3-carboxylate* (**30b**). To an ice-cold soln. of **29b** (8 g, 33.9 mmol) in EtOH (200 ml) was added dropwise under stirring $SOCl_2$ (4.3 g, 36 mmol). Stirring was continued at r.t. for 1 h. The mixture was evaporated *in vacuo:* 8.4 g (94%). Colorless crystals. M.p. 62–64° (AcOEt). IR: 3080, 3060, 3020, 2980, 2920, 2870 (CH); 1735, 1635 (C=O). ^{1}H-NMR: 1.2 (*t*, Me); 3.6–3.95 (*m*, H–C(2), H–C(3)); 3.8 (*d*, $J = 15.0$, H–C(6)); 4.0–4.45 (*m*, OCH_2, H′–C(2)); 4.25 (*s*, $PhCH_2$); 5.5 (*d*, $J = 15.0$, H–C(6)); 7.3 (*m*, 5 arom. H).

*(2*R*,3*R*)-2-Methyl-3-(phenylmethyl)morpholine-3-methanol* (**31a**). From **30a** (8 g, 28 mmol) in THF (30 ml) and $LiAlH_4$ (5 g) in THF (100 ml), as described for **31b**: 5 g (80%). Colorless, air-sensitive crystals.

M.p. 64°. $[\alpha]_D^{23} = -57.75$ ($c = 2$, EtOH). IR: 3600–3100 (OH), 3060, 3020, 2970, 2940, 2870, 2810 (CH), 1115 (C–O); 745, 695 (arom.). ^{1}H-NMR: 1.25 (*d*, Me); 1.95–2.8 (*m*, OH, H–C(3); H–C(5), H′–C(5)); 3.13 (*d*, J = 13.0, 1 H, PhCH_2); 3.3–4.13 (*m*, H–C(2), CH_2, H–C(6), H′–C(6)); 4.15 (*d*, J = 13.0, 1 H, PhCH_2); 7.29 (*s*, 5 arom. H). Anal. calc. for $C_{13}H_{19}NO_2$ (221.30): C 70.56, H 8.65, N 6.33; found: C 70.28, H 8.52, N 6.54.

*(*R*)-3-(Phenylmethyl)morpholine-3-methanol* (**31b**). An ice-cold soln. of **30b** (10.5 g, 40 mmol) in THF (50 ml) was slowly added to a suspension of $LiAlH_4$ (3 g, 80 mmol) in THF (150 ml). The mixture was refluxed for 6 h, before being slowly (!) hydrolyzed by adding wet Et_2O (100 ml), and then H_2O (10 ml). After cooling, the precipitate was separated, and the filtrate was dried (Na_2SO_4) and evaporated. The precipitate was extracted with EtOH (50 ml), which was filtered, and the filtrate was combined with the first residue. The soln. was concentrated to 20 ml, Et_2O (100 ml) was added, the soln. was filtered (*Kieselgur*) and evaporated *in vacuo*. The product solidified on cooling: 7.5 g (90%). Colorless, air-sensitive crystals. M.p. 35°. IR: 3600–3200 (OH), 3070, 3040, 2950, 2900, 2860, 2820 (CH), 1125 (C–O), 745, 705 (arom.). ^{1}H-NMR: 2.13–2.87 (*m*, H–C(3), H–C(5), H′–C(5), OH); 3.25 (*d*, J = 14.0, 1 H, PhCH_2); 3.38–4.0 (*m*, H–C(2), H′–C(2), H–C(6), H′–C(6), CH_2); 4.1 (*d*, J = 14.0, 1 H, PhCH_2); 7.25 (*m*, 5 arom. H).

*(2*R*,3*S*)-3-(bromomethyl)-2-methyl-4-(phenylmethyl)morpholine* (**32a**). Under N_2, Ph_3P (3.9 g, 15 mmol) was added to a soln. of **31a** (3 g, 13.5 mmol) in MeCN (50 ml). After cooling to 5°, a soln. of CBr_4 (5 g, 15 mmol) in MeCN (15 ml) was added. The clear soln. was stirred under N_2 at r.t. for 16 h. The solvent was evaporated *in vacuo*, and the residue was dissolved with stirring in a mixture of 0.5N HBr (100 ml), and hexane (100 ml). The precipitate (Ph_3PO) was separated, and the aq. (!) layer was alkalized with dil. aq. NaOH soln., and extracted with Et_2O/petroleum ether 1:1 (3 × 50 ml). The org. layer was dried (Na_2SO_4), cooled for 12 h to −18°, filtered, and evaporated *in vacuo:* 2.6 g (68%). Yellow viscous liquid. IR (film): 3100, 3080, 3040, 2990, 2970, 2870, 2820 (CH), 1605, 1490, 1450, 745, 700 (arom.). ^{1}H-NMR: 1.29 (*d*, Me); 2.00–2.85 (*m*, H–C(3), H–C(5), H′–C(5)); 3.13 (*d*, J = 13.0, 1 H, PhCH_2); 3.30–4.28 (*m*, H–C(2), H–C(6), H′–C(6), $BrCH_2$); 4.1 (*d*, J = 13.0, 1 H, PhCH_2); 7.25 (*m*, 5 arom. H). Anal. calc. for $C_{13}H_{18}BrNO$ (284.20): C 54.94, H 6.38, N 4.93; found: C 55.07, H 6.42, N 4.84.

*(*S*)-3-(Bromomethyl)-4-(phenylmethyl)morpholine* (**32b**). From **31b** (8.8 g, 42 mmol), Ph_3P (13.9 g, 53 mmol), and CBr_4 (17.6 g, 53 mmol), as described for **32a**: 6.8 g (60%). Yellow viscous liquid. $[\alpha]_D^{23} = -48.5$ (c = 1.4, $CHCl_3$). IR (film): 3080, 3060, 3020, 2960, 2910, 2860, 2810 (CH), 1490, 1450, 1120 (C–O), 740, 700 (arom.). ^{1}H-NMR: 2.08–2.88 (*m*, H–C(3), H–C(5), H′–C(5)); 3.28–4.0 (*m*, H–C(2), H′–C(2), H–C(6), H′–C(6), CH_2); 3.75 (*s*, PhCH_2); 7.23 (*m*, 5 arom. H). Anal. calc. for $C_{12}H_{16}BrNO$ (270.18): C 53.35, H 5.97, N 5.19; found: C 53.26, H 5.90, N 5.05.

*(2*R*,3*S*)-2-Methyl-4-(phenylmethyl)-3-{[(phenylmethyl)sulfanyl]methyl}morpholine* (**33a**). Under N_2, phenylmethanethiol (1.4 g, 11 mmol), dissolved in a soln. of Na (250 mg) in EtOH (10 ml), was added to a soln. of **32a** (3.1 g, 11 mmol) in EtOH (30 ml). The mixture was refluxed for 4–5 h, and stirred at r.t. for 12 h. The precipitate (NaBr) was filtered off, and the filtrate was evaporated *in vacuo*. The residue was dissolved in a mixture of Et_2O and H_2O, and extracted with Et_2O (4×). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and the residue was purified by CC ($CHCl_3$/AcOEt 7:3): 1.6 g (44%). Yellow viscous liquid. IR (film): 3080, 3060, 3020, 2940, 2900, 2860 (CH), 1600, 1490, 1450, 745, 700 (arom.). ^{1}H-NMR: 1.0 (*d*, Me); 1.89–2.65 (*m*, H–C(5), H′–C(5), C(3)–CH_2); 2.73–3.08 (*m*, H–C(3)); 2.93 (*d*, J = 13.0, 1 H, PhCH_2N); 3.3–3.85 (*m*, H–C(2), H–C(6), H′–C(6)); 3.63 (*s*, PhCH_2S); 4.08 (*d*, J = 13.0, 1 H, PhCH_2N); 7.26 (*m*, 10 arom. H). Anal. calc. for $C_{20}H_{25}NOS$ (327.49): C 73.35, H 7.69, N 4.28, S 9.79; found: C 73.08, H 7.60, N 4.34, S 9.50.

*(*S*)-4-(Phenylmethyl)-3-{[(phenylmethyl)sulfanyl]methyl}morpholine* (**33b**). From **32b** (4.45 g, 16.5 mmol), Na (0.4 g), and phenylmethanethiol (2.1 g, 16.5 mmol), as described for **33a**: 3.2 g (62%). Yellow viscous liquid. ^{1}H-NMR: 2.13 (*m*, H–C(3)); 2.35–2.73 (*m*, H–C(5), H′–C(5), C(3)CH_2); 3.13 (*d*, J = 13.0, 1 H, PhCH_2); 3.34–4.0 (*m*, H–C(2), H′–C(2), H–C(6), H′–C(6), PhCH_2S); 3.83 (*d*, J = 13.0, 1 H, PhCH_2N); 7.21 (*m*, 10 arom. H). Anal. calc. for $C_{19}H_{23}NOS$ (313.46): C 72.80, H 7.40, N 4.47; found: C 71.55, H 7.29, N 4.40.

*2,2,2-Trichloroethyl (2*R*,3*S*)-2-Methyl-3-{[(phenylmethyl)sulfanyl]methyl}morpholine-4-carboxylate* (**34a**). Compound **33a** (1.5 g, 4.5 mmol), 2,2,2-trichloroethyl chloroformate (1.06 g, 5 mmol), and K_2CO_3 (0.5 g) in toluene (20 ml) were refluxed for 10–12 h. The mixture was filtered, and the solvent was evaporated. The residue was dissolved in Et_2O (50 ml) and washed with 3N aq. HCl soln. (50 ml) and H_2O (100 ml). The org. layer was dried (Na_2SO_4), evaporated, and the residue was purified by CC ($CHCl_3$/CCl_4 2:3): 1.2 g (64%). Yellow viscous liquid. IR (film): 3090, 3060, 3020, 2970, 2920, 2870 (CH), 1710 (CO), 1125 (C–O), 750, 715 (arom.). ^{1}H-NMR (60 MHz): 1.33 (*d*, Me); 2.83 (*d*, C(3)–CH_2); 3.05–4.3 (*m*, H–C(2), H–C(3), H–C(5), H′–C(5), H–C(6), H′–C(6)); 3.8 (*s*, PhCH_2S); 4.87 (*s*, Cl_3CCH_2); 7.3 (*s*, 5 arom. H). Anal. calc. for $C_{16}H_{20}Cl_3NOS$ (412.77): C 46.56, H 4.88, Cl 25.77, N 3.39, S 7.77; found: C 46.55, H 4.98, Cl 25.55, N 3.30, S 7.64.

*2,2,2-Trichloroethyl (*S*)-3-{[(phenylmethyl)sulfanyl]methyl}morpholine-4-carboxylate* (**34b**). From **33b** (5 g, 16 mmol), and 2,2,2-trichloroethyl chloroformate (3.4 g, 16 mmol), as described for **34a**: 4 g (63%). Light-brown, viscous liquid. IR (film): 3060, 3020, 2950, 2910, 2850 (CH), 1710 (C=O), 1490, 1450, 715, 700 (arom.), 1120 (C–O).

*(2*R*,3*S*)-2-Methyl-3-{[(phenylmethyl)sulfanyl]methyl}morpholine* (**35a**). Compound **34a** (3 g, 7.3 mmol) was dissolved in MeOH (20 ml). Glacial AcOH (10 ml), and Zn powder (1.6 g) were added, and the mixture was refluxed for 5 h. After cooling and filtration, the soln. was alkalized with aq. NaOH soln. (10%), and extracted with CH_2Cl_2 (2 × 50 ml). The org. layer was washed with a sat. aq. soln. of NaCl, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was immediately transformed into **36a**.

*(*S*)-3-{[(Phenylmethyl)sulfanyl]methyl}morpholine* (**35b**). From **34b** (6 g, 15 mmol), glacial AcOH (3 ml), and Zn powder (3 g) in MeOH (30 ml), as described for **35a**: 2.2 g (67%). Yellow, viscous liquid. ^{1}H-NMR: 2.04 (*m*, NH); 2.29 (*m*, H–C(3)); 2.44–2.95 (*m*, C(3) – CH_2S, H–C(5)); 3.0–3.95 (*m*, H–C(2), H′–C(2), H′–C(5), H–C(6), H′–C(6)); 3.65 (*s*, PhCH_2S); 7.26 (*m*, 5 arom. H).

*((2*R*,3*S*)-2-Methylmorpholine-3-methanesulfonyl Chloride Hydrochloride* (**36a**). A soln. of **35a** (1.4 g, 5.9 mmol) in $CHCl_3$ (20 ml), and CCl_4 (10 ml) was cooled and saturated with gaseous HCl. Then, EtOH (96%, 10 ml) was added, and the mixture was saturated with Cl_2 gas (temp. < 10°). The excess of Cl_2 was removed by bubbling N_2 through the soln. The mixture was evaporated *in vacuo*, and a few milliliters of an acetone/Et_2O mixture were added to the residue: 1.1 g (75%). Colorless crystals. M.p. 100–101° (dec.). IR: 3200–2300 (NH_2^+, CH), 1580 (NH_2^+), 1380, 1170 (SO_2), 1120 (C–O).

*(*S*)-Morpholine-3-methanesulfonyl Chloride Hydrochloride* (**36b**). From **35b** (2 g, 10 mmol), as described for **36a**: 2 g (80%). Colorless crystals. M.p. 127° (dec.). IR: 3100–2500 (NH_2^+, CH), 1370, 1170 (SO_2), 1115 (C–O). Anal. calc. for $C_5H_{11}Cl_2NO_3S$ (236.12): C 25.43, H 4.70, Cl 30.03, N 5.93; found: C 25.28, H 4.60, Cl 30.24, N 5.85.

*(5*R*,6*S*)-5-Methyl-4-oxa-8-thia-1-azabicyclo[4.2.0]octane 8,8-Dioxide* (**37a**). To a suspension of **36a** (1 g, 4 mmol) in anh. $CHCl_3$ (20 ml), a sat. soln. of NH_3 in $CHCl_3$ was added, until the mixture was alkalized. After 24 h at r.t., the mixture was filtered (*Kieselgur*), and the filtrate was evaporated *in vacuo:* 0.5 g (70%). Colorless, viscous liquid. $[\alpha]_D^{23} = +24.74$ ($c = 1.17$, $CHCl_3$). IR (film): 3040, 2970, 2930, 2870 (CH), 1310, 1180, 1150 (SO_2), 1105 (C–O). ^{1}H-NMR (400 MHz): 1.20 (*d*, $J = 6.0$, Me); 3.15 (*ddd*, $J = 15.0$, 12.0, 4.5, H–C(2)); 3.33 (*ddd*, $J =$ 10.0, 7.5, 2.3, H–C(6)); 3.40 (*dd*-like, $J = 15.0$, 3.4, H′–C(2)); 3.63 (*dd*, $J = 12.0$, 2.3, H–C(7)); 3.70 (*dq*, $J = 10.0$, 6.0, H–C(5)); 3.76 (*dd*-like, $J = 12.0$, 4.5, H–C(3)); 3.91 (*dt*-like, $J = 12.0$, 12.0, 3.4, H′–C(3)); 4.25 (*dd*, $J =$ 12.0, 7.5, H′–C(7)). Anal. calc. for $C_6H_{11}NO_3S$ (177.22): C 40.66, H 6.26, N 7.90, S 18.09; found: C 40.89, H 6.34, N 7.75, S 18.00.

*(*S*)-4-Oxa-8-thia-1-azabicyclo[4.2.0]octane 8,8-Dioxide* (**37b**). From **36b** (2 g, 8 mmol), as described for **37a**: 1.1 g (85%). Colorless crystals. M.p. 91–92°. $[\alpha]_D^{23} = +13.1$ ($c = 1.32$, $CHCl_3$). IR: 3030, 2980, 2960, 2920, 2860 (CH), 1300, 1190, 1170 (SO_2), 1090 (C–O). ^{1}H-NMR (400 MHz): 3.24 (*ddd*, $J = 15.0$, 12.0, 4.5, H–C(2)); 3.46 (*dd*, $J = 15.0$, 3.0, H′–C(2)); 3.6 (*dd*, $J = 12.0$, 2.3, H–C(7)); 3.63 (*dd*-like, $J = 12.0$, 12.0, H′–C(5)); 3.72 (*dd*, $J = 12.0$, 4.5, H–C(3)); 3.78 (*ddd*-like, $J = 12.0$, 12.0, 3.0, H′–C(3)); 3.81 (*m*, H–C(6)); 4.12 (*ddd*, $J = 12.0$, 5.0, 1.5, H–C(5)); 4.28 (*dd*, $J = 12.0$, 7.5, H′–C(7)). Anal. calc. for $C_5H_9NO_3S$ (163.20): C 36.80, H 5.56, N 8.58, S 19.65; found: C 36.99, H 5.52, N 8.47, S 19.51.

*(2*R*,3*R*)-3-(Hydroxymethyl)-2-methylmorpholine Hydrochloride* (**38**). To a soln. of **31a** (4 g, 18 mmol) in anh. EtOH (80 ml), 10% Pd/C (1 g) was added, and the mixture was hydrogenated for *ca.* 3.5 h (1 atm of H_2). The catalyst was filtered off, the solvent was evaporated *in vacuo*, and the residue was dissolved in a mixture of EtOH (20 ml) and Et_2O (100 ml). The cooled soln. was saturated with gaseous HCl to complete precipitation: 2.4 g (78%). Colorless crystals. M.p. 176–179°. $[\alpha]_D^{23} = +18.4$. IR: 3400 (OH), 3100–2400, 1580 (NH_2^+, CH), 1115 (C–O). ^{1}H-NMR: 1.13 (*d*, Me); 2.68–3.30 (*m*, H–C(3), H–C(5), H′–C(5)); 3.43–4.13 (*m*, CH_2O, H–C(2), H–C(6), H′–C(6)); 5.46 (*s*, OH); 9.25 (*s*, NH_2^+). Anal. calc. for $C_6H_{14}ClNO_2$ (167.64): C 40.80, H 8.56, Cl 20.07, N 7.93; found: C 40.62, H 8.65, Cl 20.17, N 7.96.

*[(2*R*,3*S*)-2-Methyl-4-(phenylmethyl)morpholin-3-yl]methyl Methanesulfonate* (**39**). To a cooled soln. of **31a** (7.5 g, 34 mmol) in THF (50 ml), Et_3N (3.4 g, 34 mmol) was added. Over a period of 30 min, methanesulfonyl chloride (4 g, 35 mmol) was added dropwise with stirring. Stirring was continued for 16 h at r.t., the precipitate was separated, the filtrate was washed with a sat. aq. soln. of NaCl, the org. layer was dried (Na_2SO_4), and evaporated *in vacuo:* 2.7 g (26%). Colorless needles (turning red fast). M.p. 83–84° (EtOH). $[\alpha]_D^{23} = -34.52$ ($c = 1.99$, $CHCl_3$). IR: 3080, 3060, 3020, 3000, 2960, 2880, 2850, 2820 (CH), 1345, 1165 (OSO_2), 1125 (C–O), 750, 740, 700 (arom.). ^{1}H-NMR: 1.30 (*d*, Me); 2.05–2.85 (*m*, H–C(3), H–C(5), H′–C(5)); 2.96 (*s*, MeO_2S); 3.30 (*d*, $J = 14.0$, 1 H, PhCH_2); 3.40–3.95 (*m*, H–C(2), H–C(6), H′–C(6)); 4.12 (*d*, $J = 14.0$, 1 H,

PhCH_2); 4.20–4.69 (*dd*, $SOCH_2$); 7.28 (*m*, 5 arom. H). Anal. calc. for $C_{14}H_{21}NO_4S$ (299.39): C 56.17, H 7.07, N 4.68, S 10.71; found: C 56.01, H 7.00, N 4.60, S 10.83.

S-*[(2*R,*3*S*)-2-Methyl-4-(phenylmethyl)morphinan-3-yl] Ethanethioate* (**40**). Under N_2, potassium thioacetate (0.9 g, 7.9 mmol) in DMF (10 ml) was added to a soln. of **39** (2.2 g, 7.3 mmol) in $CHCl_3$ (20 ml) at r.t., and the mixture was stirred for 20 h. Then, the DMF was removed by washing with H_2O, the org. layer was dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The residue was purified by CC ($CHCl_3$/AcOEt 8:1): 1.4 g (69%). Light yellow, viscous liquid. $[\alpha]_D^{23} = 54.45$ ($c = 2.67$, $CHCl_3$). IR (film): 3080, 3060, 3020, 2960, 2850, 2800 (CH), 1680 (C=O), 1120, 1100 (C–O), 740, 700 (arom.). ^{1}H-NMR: 1.23 (*d*, Me); 2.0–2.75 (*m*, H–C(3), H–C(5), H′–C(5)); 2.3 (*s*, Ac); 3.05 (*d*, $J = 13.0$, 1 H, PhCH_2); 3.2–3.88 (*m*, H–C(2), H–C(6), H′–C(6), SCH_2); 4.06 (*d*, $J = 13.0$, 1 H, PhCH_2); 7.3 (*m*, 5 arom. H). Anal. calc. for $C_{15}H_{21}NO_2S$ (279.40): C 64.48, H 7.57, N 5.01; found: C 64.37, H 7.55, N 5.10.

*(2*R,*3*S*)-2-Methyl-4-(phenylmethyl)morpholine-3-methanethiol* (**41**). Under N_2, **40** (1.2 g, 4.3 mmol) was dissolved in EtOH, sat. with NH_3. After stirring for 3 h at r.t., the mixture was evaporated *in vacuo*, and the residue was purified by CC ($CHCl_3$/AcOEt 8:1): 0.8 g (79%). Light-yellow, viscous liquid. $[\alpha]_D^{23} = -46.2$ ($c = 2.26$, AcOEt). IR (film): 3090, 3060, 3020, 2960, 2860, 2800 (CH), 2550 (SH), 1125, 1105 (C–O), 1600, 1490, 1450, 740, 700 (arom.). ^{1}H-NMR: 1.21 (*d*, Me); 2.5–2.78 (*m*, H–C(3), H–C(5), H′–C(5), 1 H of CH_2S); 3.0 (*d*, $J = 13.0$, 1 H, PhCH_2); 2.94–3.31 (*m*, 1 H of CH_2S); 3.38–4.05 (*m*, H–C(2), H–C(6), H′–C(6)); 4.08 (*d*, $J = 13.0$, 1 H, PhCH_2); 7.3 (*m*, 5 arom. H). Anal. calc. for $C_{13}H_{19}NOS$ (237.37): C 65.78, H 8.07, N 5.90; found: C 65.99, H 8.00, N 5.80.

1-Aminocyclohexane-1-methanol (**43**). From *1-aminocyclohexane carboxylic acid* (**42**) (14.3 g, 100 mmol) and $LiAlH_4$ (10 g, 270 mmol), as described for **2**, reflux for 5 h: 9 g (70%). B.p. 117° (15 mbar) (lit. 68–69° (1 mbar)). IR (film): 3600–2400 (OH, NH_2), 1590 (NH_2), 1060 (C–O).

1-(Bromomethyl)cyclohexylammonium Bromide (**44**). HBr (48%, 11.4 g) was added to **43** (9 g, 70 mmol) in MeOH (40 ml) at 5°. The soln. was concentrated *in vacuo*, the aminium salt of **43** was precipitated by addition of acetone/Et_2O 1:1 , and then added to PBr_3 (14 g) at r.t. After heating for 1 h, all volatile compounds were evaporated, Et_2O was added, and the solid residue was recrystallized from AcOEt/Et_2O: 3 g (16%). Colorless crystals. M.p. 212° (AcOEt/Et_2O; lit. 214–216° [9]).

1,1′-Bis(dithiomethyl)cyclohexanamine (**45**). A mixture of **44** (3 g, 11 mmol) in H_2O (40 ml) and $Na_2S_2O_3 \cdot 5\ H_2O$ (2.7 g, 11 mmol) was refluxed for 1.5 h. At *ca.* 90°, I_2 (1.3 g) was added within 30 min. Workup as described for **5** (extraction with toluene (3×50 ml)): 1.7 g (47%). The crude product was used without further purification for the synthesis of **46**.

1-[(Chlorosulfonyl)methyl]cyclohexylammonium Chloride (**46**). Chlorination of **47** (1.7 g) in $CHCl_3$ (30 ml) and EtOH (96%, 10 ml) was carried out as described for **6**: 1.8 g (66%). Colorless crystals. M.p. 235° (dec.). Formula: $C_7H_{15}Cl_2NO_2S$ (248.18 g mol^{-1}).

2-Thia-1-azaspiro[3.5]nonane 2,2-Dioxide (**47**). According to the *General Procedure* described for **7**, **46** (1.8 g, 7 mmol), suspended in $CHCl_3$ (30 ml), was cyclized. The viscous residue was carefully dried, and crystallization started after some days: 1 g (81%). Colorless crystals. M.p. 52°. IR: 3270 (NH), 3020, 2930, 2860 (CH), 1320, 1290, 1165, 1140 (SO_2). ^{1}H-NMR (80 MHz): 1.25–2.0 (*m*, $(CH_2)_5$); 3.93 (*s*, H–C(4), H′–C(4)); 5.4 (br. *s*, NH). Anal. calc. for $C_7H_{13}NO_2S$ (175.25): C 47.97, H 7.48, N 7.99, S 18.29; found: C 47.71, H 7.52, N 7.89, S 18.44.

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