The 'Azirine/Oxazolone Approach' to the Synthesis of Aib-Pro Endothiopeptides

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The reaction of methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2a**) with thiobenzoic acid at room temperature gave the endothiopeptide Bz-AibΨ[CS]-Pro-OMe (**7**) in high yield. In an analogous manner, (benzyloxy)carbonyl (Z)-protected proline was transformed into the thioacid, which was reacted with **2a** to give the endothiotripeptide Z-Pro-AibΨ[CS]-Pro-OMe (**12**). The corresponding thioacid of **7** was prepared *in situ via* saponification, formation of a mixed anhydride, and treatment with H_2S. A second reaction with **2a** led to the endodithiotetrapeptide **9**, but extensive epimerization at Pro^2 was observed. Similarly, saponification of **12** and coupling with either **2a** or H-Phe-OMe and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate/1-hydroxy-1*H*-benzotriazole (TBTU/HOBt) gave the corresponding endothiopeptides as mixtures of two epimers. The synthesis of the pure diastereoisomer BzΨ[CS]-Aib-Pro-AibΨ[CS]-N(Me)Ph (**21**) was achieved *via* isomerization of **7** to BzΨ[CS]-Aib-Pro-OMe (**16**), transformation into the corresponding thioacid, and reaction with *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**). The structures of **12** and **21** were established by X-ray crystallography.

Introduction. – Peptides with modified backbones are of considerable pharmaceutical interest [1]. The concept of peptidomimetics, *i.e.*, compounds with different chemical structure but maintained ability to interact with specific peptide receptors, proved to be a successful approach in the design of novel inhibitors of enzymes. For example, the stabilization of β-turns and helical peptide conformations can be achieved by the replacement of protein amino acids by α,α-disubstituted α-amino acids [2], while *N*-methylated α-amino acids can disrupt helices, and direct secondary and tertiary structures [3], thereby enhancing the hydrophobicity [4] and improving the stability towards proteolytic enzymes [5]. The substitution of proteolyzable amide bonds by thioamides also leads to increased proteolytic stability, while other biological effects remain unaltered [6].

The 'azirine/oxazolone method', which was developed in our laboratory [7], has proven to be a powerful tool for the synthesis of such modified peptides. Thus, 2*H*-azirin-3-amines **1** are useful synthons for sterically demanding α,α-disubstituted α-amino acids in peptides. The reaction of the most widely applied reagent **1a** with peptide acids leads to elongated peptides containing an α-aminoisobutyric acid (Aib) and a terminal amide bond [8][9]. Moreover, a family of dipeptide synthons **2a**–**2g** has been prepared for the same purpose. The synthon **2a** has been successfully applied for

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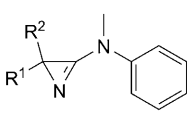
the elongation at the C-terminus of various peptides with the Aib-Pro fragment [10–12]. Thus, the 'azirine/oxazolone method' has proven to be successful in the solution-phase synthesis of naturally occurring antibiotic peptaibols [10][12–14]. Recently, the method has been applied for the synthesis of Aib-containing peptides on solid phase [15].

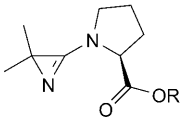


1a $R^1 = R^2 = Me$

1b $R^1–R^2 = –(CH_2)_4–$

1c $R^1–R^2 = –(CH_2)_2\text{-}O\text{-}(CH_2)_2–$

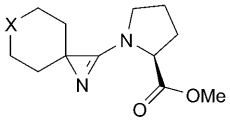
1d $R^1 = Me$, $R^2 = PhCH_2$



2a R = Me

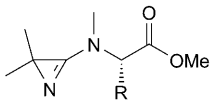
2b $R = PhCOCH_2$

2c $R = CH_2{=}CH{-}CH_2$



2d X = O

2e X = S



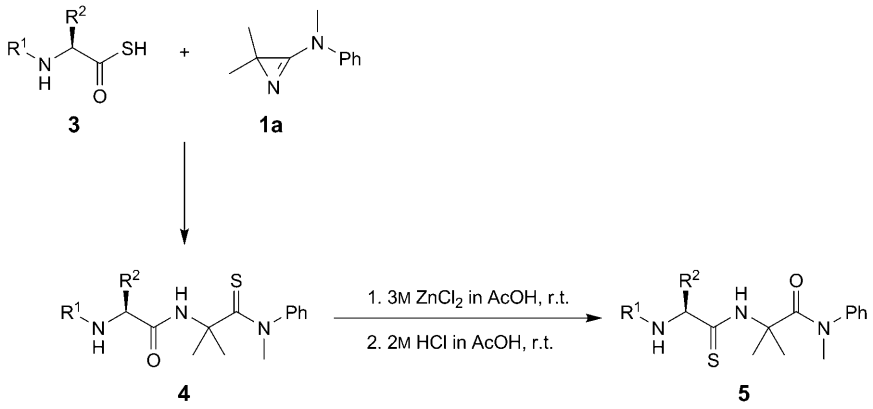
2f R = Me

2g R = i-Pr

Peptides containig α,α-disubstituted α-amino acids (2,2-disubstituted glycines) show restricted conformational flexibility, and secondary structures such as helices or β-turns are stabilized [2][16]. For most of the peptaibols, which adopt helical structures, the presence of Aib-Pro fragments is characteristic [5][17]. The first total synthesis of alamethicin I, one of the most well-known peptaibols, which contains the starting sequence Ac-Aib-Pro-Aib, was accomplished by the traditional coupling (with *N,N′*-dicyclohexylcarbodiimide (DCC)) of the amino acids in solution [18], as well as on solid phase [19]. Other approaches involved the use of Fmoc-Aib chloride and the potassium salt of 1-hydroxy-1*H*-benzotriazole (HOBt) [20] or 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (CIP) as coupling reagents [21]. The structural studies on the peptaibols suggested that the alternating Pro and Aib residues might be responsible for adopting a 3_{10}-helix by the peptide chain. Thus, a series of model compounds with terminally blocked -(Pro-Aib)$_n$- units have been synthesized [22]. The conformational analysis has shown that the formation of the 'β-bend ribbon spiral' starts to form already at the -Aib-Pro-Aib- tripeptide level. In that paper, some problems with the instability of the Aib-Pro linkage under acidic condition were also reported.

The methods for the incorporation of the C=S group into the peptide chain so far involved direct thionation, *e.g.*, with *Lawesson* reagent (LR) [6a][23], thioacylation with activated amino thioacid derivatives, *e.g.*, thio- or dithioesters [24], or combined protocols involving thionation of an amide intermediate with P_4S_{10} or LR with subsequent transacylation [25]. However, most of these methods have certain limitations, *e.g.*, they are accompanied by epimerization or side reactions. Very recently, it has been shown that endothiopeptides can be obtained *via* the *Ugi* reaction with thioacids as acid components [26]. A different approach developed in our laboratory is based on the 'azirine/oxazolone method' [27][28]. The reactions of the building blocks **1** or **2** with α-amino thioacids **3**, which are prepared from protected α-amino acids *via* mixed anhydrides, leads to products **4** containing an AibΨ[CS] fragment. On treatment with $ZnCl_2$ and HCl in AcOH, the peptides **4**, with a C-terminal thioamide group, isomerize to give the endothiodipeptides **5** without epimerization (*Scheme 1*). The reaction mechanism for the azirine coupling has been

Scheme 1



discussed earlier [7], that of the isomerization involves the formation of an 1,3-oxazole-5(4*H*)-thione, which is transformed to the isomeric 1,3-thiazol-5(4*H*)-one *via* spirocyclic intermediates or dipolar nitrilium ions [27b][28a].

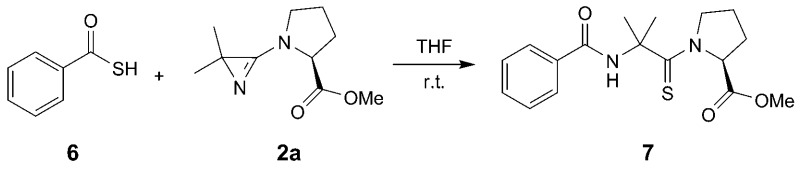
Only a few examples concerning the preparation of endothiopeptides with more than one C=S group are known. Attempts at synthesizing a dithio analogue of zervamicin IIA, *e.g.*, by coupling of the two monothiopeptides Boc-Trp-Ile-AlaΨ[CS]-Aib-Ile-OH and H-ValΨ[CS]-Aib-Leu-OMe using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)/HOBt led to an endothiooctapeptide with a 1,3-thiazol-5(4*H*)-imine residue as the main product (60%) instead of the endodithiooctapeptide with the AlaΨ[CS]-Aib fragment [27d]. An additional problem was the extensive epimerization, the obtained ratio of the epimers being 66:34. A similar coupling of Z-ValΨ[CS]-Aib-Ile-OH with H-ValΨ[CS]-Aib-N(Me)Ph afforded an analogous cyclized product, but without detectable epimerization [28b]. Some model 1,3-thiazol-5(4*H*)-imine derivatives reacted with H_2S in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give peptides containing two thioamide bonds, *e.g.*, Z-AlaΨ[CS]-AibΨ[CS]-Ile-Aib-N(Me)Ph; however, epimerization occurred at the Ala residue.

In the present work, we report new results of the application of the 'azirine/oxazolone method' in endothiopeptide synthesis.

Results and Discussion. – The aim of this work was to develop synthetic procedures for the preparation of endothiopeptides, containing Aib-Pro units and more than one thioamide group, which can serve as model compounds for structural and conformational studies.

The first endothiopeptide Bz-AibΨ[CS]-Pro-OMe (**7**; Bz = benzoyl) was prepared according to the 'azirine/oxazolone method' from thiobenzoic acid (PhCOSH; **6**) and *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2a**). The reaction was carried out analogously to reactions of **2b** and **2c** with **6** [15c], and proceeded smoothly, to give **7** in almost quantitative yield (*Scheme 2*). The solid product **7** was fully characterized; most indicative were the signals in the ^{13}C-NMR spectrum at 205.8 (thioamide), 170.8

Scheme 2

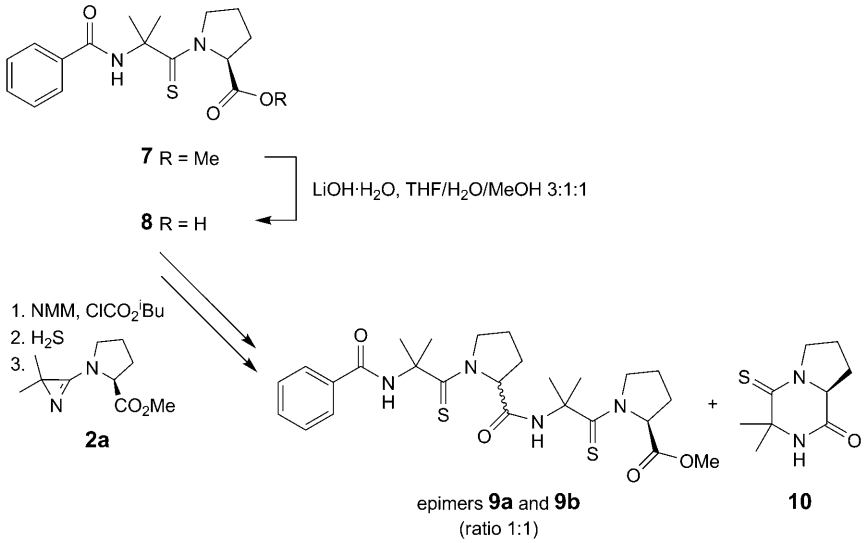


6 **2a** **7**

(ester), and 164.7 ppm (amide), and the corresponding IR absorptions (KBr) at 1425, 1740, and 1657 cm^{-1}.

The attempted direct conversion of the methyl ester **7** to the corresponding thioacid according to [29] failed, as **7** was resistant to the treatment with NaSH in THF solution even at reflux temperature. An alternative pathway was the saponification of **7** with subsequent conversion of the carboxylic acid into the thioacid *via* a mixed anhydride [30]. Thus, the reaction of **7** with LiOH afforded Bz-AibΨ[CS]-Pro-OH (**8**) in high yield (94%). The acid **8** was transformed to the thioacid by the reaction of the *in situ* prepared mixed anhydride with H_2S at $-20°$, and the crude mixture was instantly treated with an excess (2.5 equiv.) of the Aib-Pro synthon **2a** (*Scheme 3*). Surprisingly, two epimers of the expected product Bz-AibΨ[CS]-Pro-AibΨ[CS]-Pro-OH (**9**), *i.e.*, **9a** and **9b** were formed. Separation by means of prep. TLC gave the two epimers in poor yield (7% each). However, 2D-NMR techniques did not allow assignment of the configurations of Pro[2] for the samples **9a** and **9b**. The main product obtained from the reaction described above was (*S*)-perhydro-3,3-dimethyl-4-thioxopyrrolo[1,2-*a*]pyrazin-1-one (**10**), which also arose from the reaction of **2a** with H_2S. Our extensive studies on the reactions of **2a**, **2d**, and **2e** with H_2S have already been published [31].

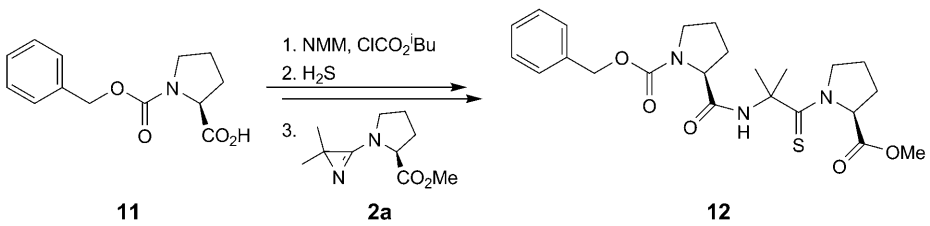
Scheme 3



Measurements of the optical rotation of samples of the acid **8** recovered from the reaction mixture unequivocally indicated complete racemization, although the above-mentioned protocol had been shown to give, *e.g.*, Boc-Val-AibΨ[CS]N(Me)Ph and Boc-Leu-AibΨ[CS]-Pro-OMe without epimerization [27]. Obviously, Pro-OH is more susceptible to enolization under the chosen conditions (see also [18]). Another explanation is the presence of the thioamide group in the precursor **7**. All attempts to optimize the reaction conditions, *e.g.*, by using pyridine as the base instead of *N*-methylmorpholine (NMM), or by replacing isobutyl chloroformate by 1,1′-carbonyldiimidazole (CDI) [32] in order to avoid the anhydride formation were unsuccessful, and the epimerization still occurred, and the yield of **9a**/**9b** was even lower.

With the intention of preparing an endothiopeptide with a Pro residue as the N-terminus, we converted (benzyloxy)carbonyl (Z)-protected proline (**11**) into the corresponding thioacid *via* the mixed anhydride under the conditions described above. Subsequent reaction with the Aib-Pro synthon **2a** afforded the desired product Z-Pro-AibΨ[CS]-Pro-OMe (**12**) in very good yield (89%, *Scheme 4*). The NMR spectrum of **12** in $CDCl_3$ was not conclusive, because all signals were very broad. In the ^{1}H-NMR spectrum in (D_6)DMSO, only some of the signals were broadened, but others appeared doubled. In a series of ^{1}H-NMR measurements at increased temperatures, most of these signals coalesced at 360 K, suggesting the presence of a single epimer of **12**, which exists as two rotamers at lower temperatures. However, it was not possible to observe the coalescence of all the broadened signals, since the sample decomposed at 380 K. Finally, crystallization from AcOEt gave suitable crystals, and the structure of **12** was unequivocally established by X-ray crystallography (*Fig. 1*).

Scheme 4



The compound in the crystal is enantiomerically pure, and the absolute configuration of the molecule (4*S*,10*S*) has been determined by the diffraction experiment. The asymmetric unit contains two symmetry-independent molecules of **12**, plus two molecules of AcOEt. The two peptide molecules have quite different conformations. First, the molecules differ by a small twist of *ca.* 14° about the C(8)–N(9) bond, then the central five-membered rings have an inverted puckering, and finally, the benzyloxy group is rotated by *ca.* 100° about the O(1)–C(14) bond in molecule A, compared with its orientation in molecule B. The amide NH group of molecule A forms an intermolecular H-bond with the amide O-atom of molecule B. In turn, molecule B has an identical interaction with a different molecule A. These interactions link the peptide molecules in an ···A···B···A···B··· sequence into extended chains which run

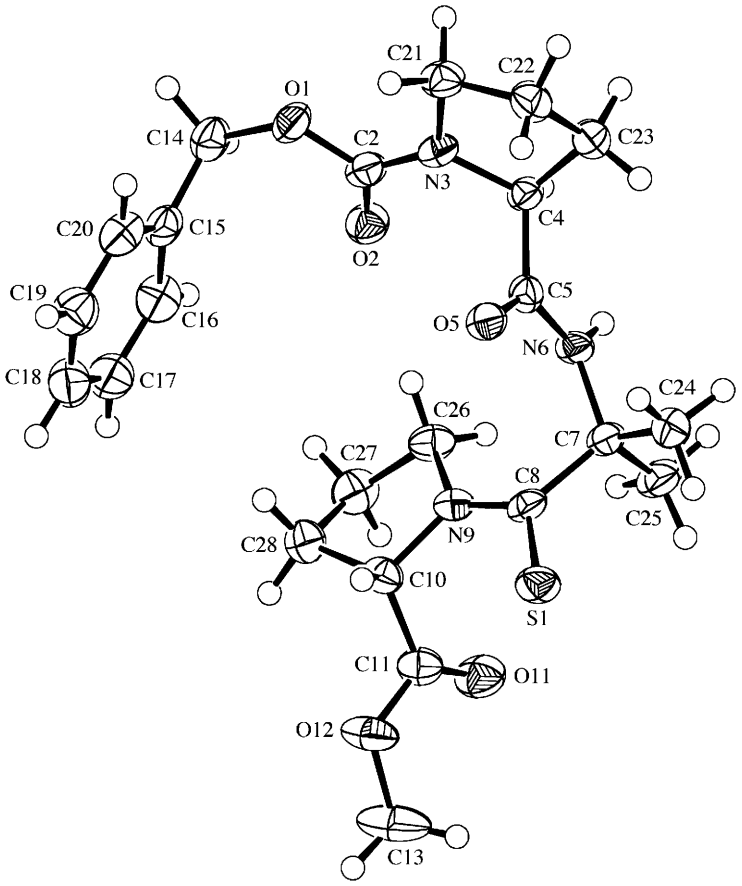


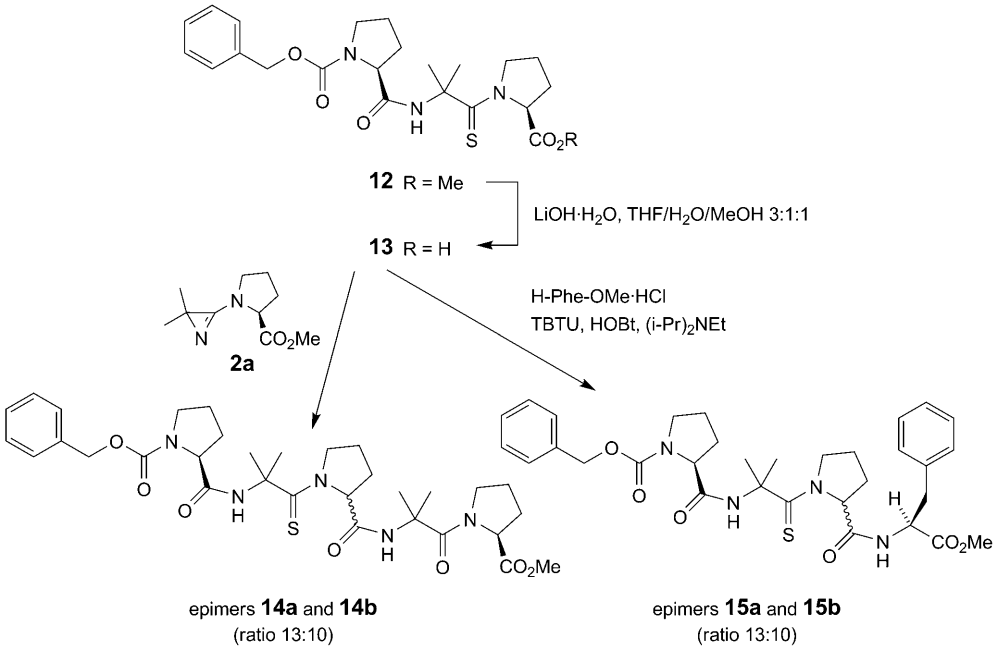
Fig. 1. *ORTEP Plot* [33] *of the molecular structure of one of the crystallographically independent molecules of* **12** (50% probability ellipsoids, arbitrary numbering of the atoms)

parallel to the [0 1 0] direction and have a graph set motif [34] of $C_2^2(8)$. In both molecules, the five-membered ring containing N(3) and N(33) has an envelope conformation with C(22) and C(52), respectively, as the envelope flap, while that containing N(9) and N(39) has a half-chair conformation twisted on C(27)–C(28) and C(57)–C(58), respectively. The Et group of one of the AcOEt molecules is disordered over two orientations with the major conformation existing in *ca.* 66% of the molecules.

The methyl ester **12** was hydrolyzed by treatment with LiOH according to the standard procedure. The yield of the acid **13** was good (80%), but the NMR spectra of the product showed two sets of signals, indicating extensive epimerization. However, the ratio of the epimers could not be determined due to the overlap of the broad signals. To characterize **13** appropriately, it was submitted directly to further reactions. We chose the standard reactions with the dipeptide synthon **2a** without previous thionation and the traditional coupling (TBTU/HOBt) with phenylalanine methyl ester (H-Phe-OMe). In both cases, diastereoisomeric mixtures of products were obtained

(*Scheme 5*). The reaction of **13** with **2a** at room temperature afforded a mixture of the epimers **14a** and **14b** in a ratio of 13 : 10, and in a total yield of 69%. After separation by column chromatography, 30% of **14a** and 12% of **14b** were isolated. The coupling of **13** with H-Phe-OMe gave a mixture of **15a** and **15b** in the same ratio of 13 : 10, and in a total yield of 51%. Again, the products were separated by column chromatography affording 26% of **15a** and 8% of **15b**.

Scheme 5

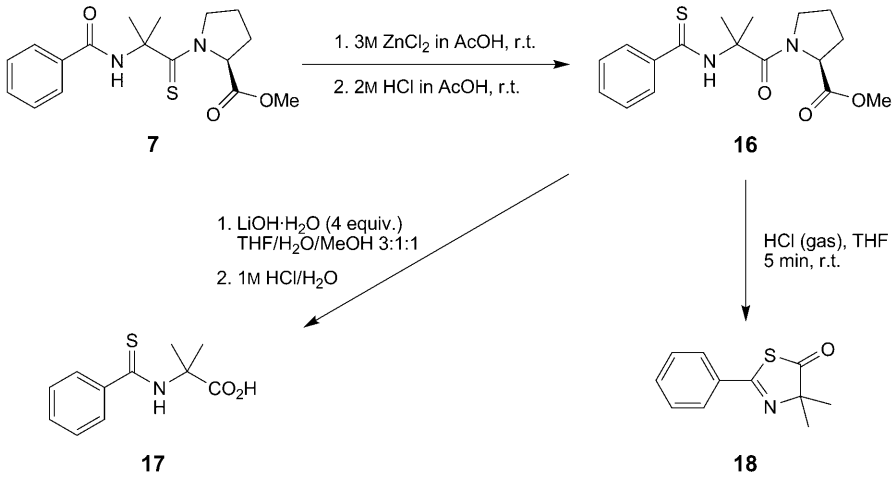


Control experiments showed that the partial epimerization occurred during the base-promoted hydrolysis of **12**. The small excess of one epimer of **13** let us hope for successful optimization of the reaction conditions. But, unfortunately, preliminary experiments revealed that the conversion of **13** to the corresponding thioacid, and subsequent treatment with **2a** did not provide the expected endothiopeptide analogue of **14** with an additional C=S function.

Our study on the synthesis of proline-containing endothiopeptides described above has shown that the peptides with the C=S group adjacent to the Pro residue, *i.e.*, with the –CS-Pro– unit, are particularly susceptible to epimerization. To circumvent this problem, we decided to prepare analogous endothiopeptides with the C=S group not adjacent to Pro. Therefore, we used the optimized protocol for the isomerization of Aib-containing thiopeptides, which was elaborated in our laboratory [27][28] (*Scheme 1*). The acid-catalyzed shift of the S-atom from the terminal position to the penultimate one has been shown to occur *via* the formation of an intermediate 1,3-oxazole-5(4*H*)-thione and its rearrangement into the isomeric 1,3-thiazol-5(4*H*)-one. So, a sample of **7**, which had been additionally purified by crystallization from *t*-

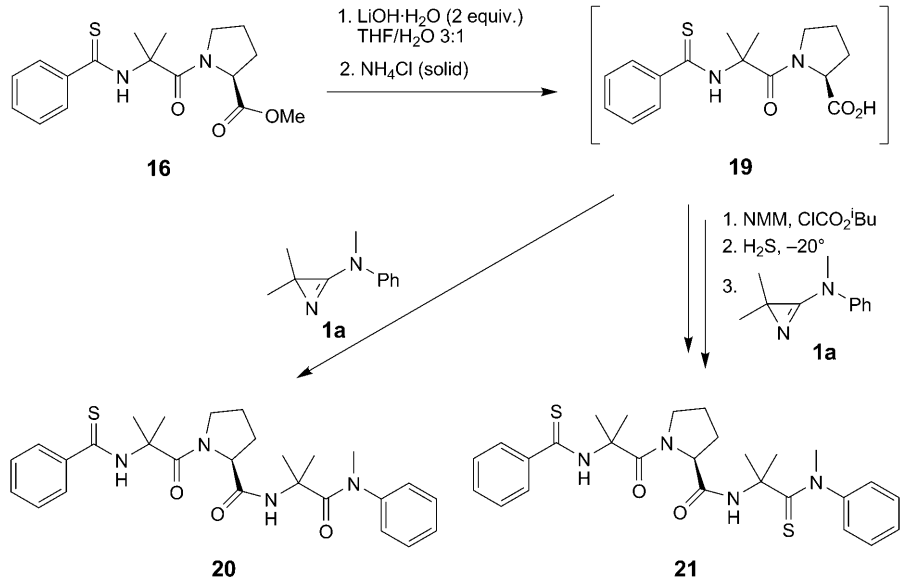
BuOMe, was treated with $ZnCl_2$ in AcOH solution and then with a saturated solution of HCl in AcOH. The isomerization proceeded smoothly at room temperature to afford product **16**, with the C=S group shifted to the benzamide linkage, in 78% yield (*Scheme 6*). The endothiopeptide **16** was then submitted to saponification with LiOH under standard conditions, but the product was destroyed during acidic workup with 1M HCl. The acid-promoted cleavage of the Aib-Pro unit in aqueous solution afforded Ph-CS-Aib-OH (**17**) almost quantitatively (99%); the proline methyl ester was identified in the filtrates. We assumed that the formation of a 1,3-thiazol-5(4*H*)-one was responsible for the cleavage. Therefore, in a control experiment, HCl gas was bubbled through a solution of **16** in THF affording 4,4-dimethyl-2-phenyl-1,3-thiazol-5(4*H*)-one (**18**) in 73% yield (*Scheme 6*). The spectroscopic data of **18** were in full agreement with those in [35].

Scheme 6



Since the product of the hydrolysis of **16** was sensitive to traces of acid, the procedure had to be modified. After the saponification with a smaller excess of LiOH (2 equiv.), the mixture was gradually saturated with solid NH_4Cl (see *Exper. Part*). Extraction with CH_2Cl_2 and evaporation of the solvent without heating afforded *ca.* 60% of the crude compound **19** (*Scheme 7*). The samples were also unstable, and slow decomposition occurred even at 0°. With the aim of characterizing the deprotected acid **19**, the crude material was reacted with the Aib synthon **1a**. The coupling at room temperature proceeded slowly, and the resulting product, Ph-CS-Aib-Pro-Aib-N(Me)Ph (**20**), was obtained only in moderate yield (48%). This positive result encouraged us to perform the transformation of the unstable intermediate **19** to the mixed anhydride and subsequently to the corresponding thioacid, which was immediately treated with **1a**. The Aib synthon **1a** has been chosen again, in order to avoid the formation of side products, such as **10**, in the presence of H_2S. The desired endothiopeptide **21** with two thioamide groups was isolated in 37% yield (*Scheme 7*). The final product **21** was a single stereoisomer, *i.e.*, no detectable epimerization had

Scheme 7



occurred, and the obtained sample was analytically pure. After crystallization from CH_2Cl_2/*t*-BuOMe by slow evaporation of the solvent, its structure was additionally confirmed by an X-ray crystal-structure determination (*Fig. 2*).

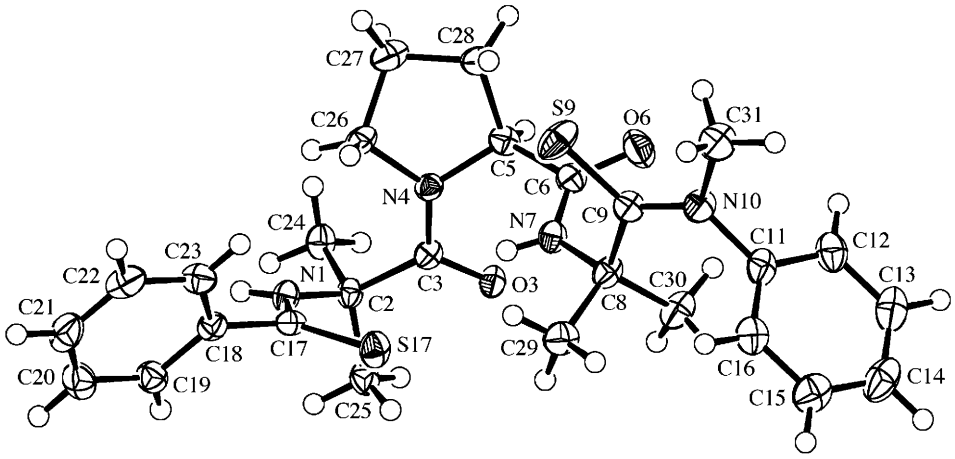


Fig. 2. *ORTEP Plot* [33] *of the molecular structure of* **21** (50% probability ellipsoids, arbitrary numbering of the atoms)

The compound **21** in the crystal is enantiomerically pure, and the absolute configuration has been determined independently by the diffraction experiment. The molecule has the expected (5*S*)-configuration. The asymmetric unit contains one

peptide molecule **21** and one H_2O molecule. The peptide molecule has one intramolecular N–H···S H-bond between N(7)–H and S(17). This interaction serves to maintain the helical conformation of the molecule and has a graph set motif [34] of S(10). N(1)–H forms an intermolecular H-bond with O(3) of an adjacent peptide molecule and links the molecules **21** into extended chains which run parallel to the [0 1 0] direction and have a graph set motif of C(5). The H_2O molecule donates one H-bond to S(9) in one peptide molecule and to O(6) in another peptide molecule, and thereby links the peptide and H_2O molecules into extended chains which run parallel to the [1 0 0] direction and have a graph set motif of $C_2^2(9)$. The intermolecular interactions combine to link the moieties in the structure into a three-dimensional framework.

In summary, new applications and limitations of the 'azirine/oxazolone method' in the synthesis of proline-containing endothiopeptides are described. Whereas the introduction of AibΨ[CS]-Pro units was possible, the results demonstrate the extraordinary lability of these thiopeptides towards epimerization of the Pro unit. The use of the acid-catalyzed isomerization protocol for thiopeptides and the optimization of some reaction conditions allowed the synthesis of an optically pure peptide fragment with two thioamide groups. However, this attractive site-selective incorporation of more thioamide groups into endothiopeptides by using the 'azirine/oxazolone method' still needs improvement, especially for avoiding epimerization.

We thank the analytical units of our institute for spectra and elemental analyses. Financial support of this work by the Dr. *Helmut Legerlotz-Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

1. *General*. See [12b][36]. *Abbreviations.* Aib, 2-aminoisobutyric acid (2-methylalanine); DCC, *N,N′*-dicyclohexylcarbodiimide; HOBt, 1-hydroxy-1*H*-benzotriazole; i-BuOCOCl, isobutyl carbonochloridate; NMM, *N*-methylmorpholine; TBTU, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate. M.p.: *Mettler FP-5* or *Büchi B-450* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 781* or *Perkin-Elmer 1600-FT-IR* spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AC-300* or *Bruker ARX-300* instrument (300 and 75.5 MHz, resp.), and *Bruker DRX-600* instrument (600 and 150.9 MHz, resp.), in $CDCl_3$; multiplicity of C-atoms from DEPT spectra. MS: *Finnigan MAT-90* or *Finnigan SSQ-700* instrument (EI, 70 eV, or CI (NH_3)). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich.

2. *General Procedures. General Procedure A* (*GP A*). To a soln. of 1 equiv. of a *N*-protected peptide or a thiocarboxylic acid in dry CH_2Cl_2, a soln. of 1.02–1.3 equiv. of *methyl* N-*(2,2-dimethyl-2*H*-azirin-3-yl)*-L-*prolinate* (Aib-Pro synthon; **2a**) in dry CH_2Cl_2 was added slowly at 0°. The mixture was stirred at 0° for 0.5 h, then at r.t. until the starting material was consumed (TLC). The soln. was diluted with CH_2Cl_2, washed with 5% aq. $KHSO_4$, the org. layer was dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography (CC) or prep. TLC (SiO_2).

General Procedure B (*GP B*). To a soln. of 1 equiv. of a *N*-terminal-protected peptide ester in THF/MeOH/H_2O 3:1:1, 4 equiv. of $LiOH \cdot H_2O$ were added, and the mixture was stirred at r.t. until the starting material was consumed (TLC). Then, the mixture was slowly acidified with 1M HCl until pH 3 was reached, and the org. solvent was evaporated. The precipitated solid was collected by filtration, washed with H_2O, and dried *in vacuo*.

General Procedure C (*GP C*). To a soln. of 1 equiv. of a *N*-terminal-protected amino acid or peptide in dry THF or THF/DMF, 2.4 equiv. of NMM, and, after 15 min, 1.2 equiv. of i-BuOCOCl were added slowly at –20°, and a white solid precipitated. After stirring for 1 h, a slow stream of H_2S was bubbled

through the mixture for 2 h, and then N_2 for 1 h, while the temp. was kept below $-20°$. A soln. of 2–2.5 equiv. of **2a** or **1a** in THF was added dropwise, the mixture was stirred at $-10°$ for 2 h, and at r.t. overnight. Then, the mixture was diluted with Et_2O, washed with 5% aq. $KHSO_4$, dried ($MgSO_4$), and evaporated. The crude products were purified by chromatography (CC or prep. TLC; SiO_2).

General Procedure D (*GP D*). To a soln. of 1 equiv. of a *N*-terminal-protected amino acid or peptide, 2 equiv. (3 equiv. when the hydrochloride of the protected amino acid was used) of $EtN(i\text{-}Pr)_2$, 1 equiv. of TBTU, and 1 equiv. of HOBt in MeCN, 1.1 equiv. of an amino acid ester were added. The mixture was stirred at r.t. until the starting material was consumed (TLC). Then, the soln. was diluted with CH_2Cl_2, and extracted 3 × with 5% aq. $NaHCO_3$ and $KHSO_4$ soln. The combined aq. phase was washed with Et_2O, and the combined org. phase dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by CC or prep. TLC (SiO_2) or recrystallization.

General Procedure E (*GP E*). A soln. of a thiopeptide in AcOH was treated with $ZnCl_2$ and stirred vigorously at r.t. for 20 min; $ZnCl_2$ only partially dissolved. Then, AcOH saturated with HCl (2.1M) was added to the mixture. After 30 min of stirring, the mixture was carefully added to 5% aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$), evaporated, and the residue was purified by CC or prep. TLC (SiO_2).

3. *Starting Materials. Methyl* N-*(2,2-dimethyl-2*H*-azirin-3-yl)*-L-*prolinate* (**2a**)[2]) [10a] and N,*2,2-trimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**1a**) [37] were synthesized according to the procedures described in the literature.

4. *Synthesis of Endothiopeptides.* 4.1. *Methyl (2*S*)-1-[2-(Benzoylamino)-2-methyl-1-thioxopropyl]-pyrrolidine-2-carboxylate* (*Bz-AibΨ[CS]-Pro-OMe*; **7**). According to *GP A*, PhCOSH (**6**; 276 mg, 2.0 mmol) in CH_2Cl_2 (20 ml), **2a**[2]) (435 mg, 2.04 mmol) in CH_2Cl_2 (9 ml); reaction time 30 h. CC (AcOEt) yielded 650 mg (97%) of **7**. Colorless solid. M.p. 149–152°. $[\alpha]_D^{23} = -150.4$ ($c = 1.00$, MeOH). IR (KBr): 3396*m*, 2985*m*, 2952*w*, 2880*w*, 1740vs, 1657v*s*, 1580*w*, 1515*s*, 1484*s*, 1425v*s*, 1389*m*, 1362*m*, 1352*w*, 1284*m*, 1263*w*, 1244*w*, 1198*s*, 1161*s*, 1149*m*, 1041*m*, 1000*w*, 970*m*. ^{1}H-NMR ($CDCl_3$): 8.58 (br. *s*, NH); 7.87–7.82 (*m*, 2 arom. H); 7.49–7.37 (*m*, 3 arom. H); 5.16 (*dd*, $J = 8.8, 4.2$, H–C(α)(Pro)); 4.03–3.89 (*m*, $CH_2(\delta)$(Pro)); 3.72 (*s*, MeO); 2.29–2.11 (*m*, $CH_2(\beta)$(Pro)); 2.07–1.98 (*m*, $CH_2(\gamma)$(Pro)); 1.93, 1.86 (2*s*, 2 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 205.8 (C=S); 170.8, 164.7 (2 C=O); 135.0 (arom. C); 131.2, 128.4, 126.8 (5 arom. CH); 68.8 (CH(α)(Pro)); 61.0 (C(α)(Aib)); 53.3 ($CH_2(\delta)$(Pro)); 52.2 (MeO); 27.8, 25.8 ($CH_2(\beta)$(Pro), $CH_2(\gamma)$(Pro)); 25.6, 24.8 (2 Me(Aib)). CI-MS: 335 (13, $[M+1]^+$), 303 (84), 300 (100), 286 (7), 234 (24), 200 (75), 198 (14), 172 (14), 165 (24), 139 (23), 130 (52). Anal. calc. for $C_{17}H_{22}N_2O_3S$ (334.43): C 61.05, H 6.63, N 8.38, S 9.59; found: C 61.15, H 6.84, N 8.35, S 9.38.

4.2. *(2*S*)-1-[2-(Benzoylamino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carboxylic Acid* (*Bz-Aib-Ψ[CS]-Pro-OH*; **8**). According to *GP B*, **7** (1.67 g, 5.0 mmol), $LiOH \cdot H_2O$ (0.84 g, 20.0 mmol), THF/MeOH/H_2O 3:1:1 (500 ml); reaction time 2 d: 1.51 g (94%) of **8**. Colorless crystals. M.p. 230–231°. $[\alpha]_D^{23} = -51.6$ ($c = 1.00$, MeOH). IR (KBr): 3343*w*, 3283*m*, 2977*m*, 2939*w*, 2877*w*, 2672*m*, 1741*s*, 1610*s*, 1572*m*, 1544*s*, 1494*w*, 1449*w*, 1425v*s*, 1390*s*, 1361*m*, 1339*w*, 1321*m*, 1265*m*, 1247*w*, 1223*m*, 1166*m*, 1148*w*, 1047*w*, 972*w*. ^{1}H-NMR ((D_6)DMSO): 12.31 (br. *s*, OH); 8.64 (br. *s*, NH); 7.88–7.84 (*m*, 2 arom. H); 7.57–7.44 (*m*, 3 arom. H); 4.86 (*dd*, $J = 8.2, 2.6$, H–C(α)(Pro)); 4.03–3.97, 3.60–3.43 (2*m*, $CH_2(\delta)$(Pro)); 2.08–1.82 (*m*, $CH_2(\beta)$(Pro), $CH_2(\gamma)$(Pro)); 1.75, 1.56 (2*s*, 2 Me(Aib)). ^{13}C-NMR ((D_6)DMSO): 203.9 (C=S); 171.2, 164.9 (2 C=O); 133.9 (arom. C); 131.6, 128.1, 127.4 (5 arom. CH); 67.8 (CH(α)(Pro)); 60.7 (C(α)(Aib)); 52.2 ($CH_2(\delta)$(Pro)); 29.8, 26.9 (2 Me(Aib)); 27.3, 25.3 ($CH_2(\beta)$(Pro), $CH_2(\gamma)$(Pro)). CI-MS: 321 (8, $[M+1]^+$), 305 (13), 303 (10), 287 (100), 190 (21), 116 (14). Anal. calc. for $C_{16}H_{20}N_2O_3S$ (320.40): C 59.98, H 6.29, N 8.74, S 10.01; found: C 59.91, H 6.46, N 8.75, S 10.18.

4.3. *Methyl (2*S*)-1-[2-({(2*S*/2*R*)-1-[2-(Benzoylamino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl}pyrrolidine-2-carboxylate* (*Bz-AibΨ[CS]-Pro-AibΨ[CS]-Pro-OMe*; **9a**) *and Methyl (2*S*)-1-[2-({(2*R*/S*)-1-[2-(Benzoylamino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carboxylate* (**9b**). According to *GP C*, **8** (320 mg, 1.0 mmol) in THF/DMF 5:2 (28 ml), NMM (242 mg, 2.4 mmol), i-BuOCOCl (164 mg, 1.2 mmol), **2a**[2]) (533 mg, 2.5 mmol) in THF (8 ml). CC (AcOEt/hexane 2:1 → 4:1) and separation of the

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[2]) Azirine **2a** was contaminated with 8% of methyl *N*-(2-methylpropanoyl)-L-prolinate, the starting material of its preparation [10a].

diastereoisomers by prep. TLC (SiO_2; AcOEt/hexane 1.8:1) gave 36 mg (7%) of **9a**, 36 mg (7%) of **9b**, and 173 mg of *(*S*)-perhydro-3,3-dimethyl-4-thioxopyrrolo[1,2-*a*]pyrazin-1-one* (**10**) [31].

Data for **9a**. Colorless solid. M.p. 260–263° (dec.). IR (KBr): 3355*m*, 3299*m*, 3000*w*, 2979*w*, 2946*w*, 1722*s*, 1669*s*, 1643v*s*, 1578*w*, 1525*s*, 1487*w*, 1428*s*, 1409*m*, 1388*m*, 1362*m*, 1304*w*, 1207*m*, 1164*m*, 1147*w*, 1047*w*, 1001*w*, 968*w*. ^{1}H-NMR ($CDCl_3$): 7.84–7.81 (*m*, 2 arom. H); 7.77 (br. *s*, NH); 7.59–7.47 (*m*, 3 arom. H); 7.11 (br. *s*, NH); 5.51 (*dd*, *J* = 8.2, 5.8, H–C(α)(Pro)); 5.10–5.06 (*m*, H–C(α)(Pro)); 4.32–4.24, 4.21–4.12, 3.96–3.88, 3.51–3.43 (4*m*, 2 CH_2(δ)(Pro)); 3.70 (*s*, MeO); 2.25–1.99 (*m*, 5 H of Pro); 1.97 (*s*, Me(Aib)); 1.97–1.88 (*m*, 3 H of Pro); 1.75, 1.73, 1.69 (3*s*, 3 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 205.6, 204.1 (2 C=S); 171.7, 169.1, 166.4 (3 C=O); 133.0 (arom. C); 132.4, 129.1, 127.1 (5 arom. CH); 69.5, 68.1 (2 CH(α)(Pro)); 62.3, 61.1 (2 C(α)(Aib)); 53.3, 53.0 (2 CH_2(δ)(Pro)); 51.9 (MeO); 32.1, 30.8 (2 Me(Aib)); 28.3, 27.8, 25.8, 25.4 (2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 26.9, 26.0 (2 Me(Aib)). ESI-MS: 555 (100, $[M+Na]^+$).

Data for **9b**. Colorless solid. IR (KBr): 3278*s*, 2984*m*, 2946*m*, 2876*w*, 1741*s*, 1642v*s*, 1578*w*, 1534*s*, 1488*m*, 1462*m*, 1419v*s*, 1387*m*, 1362*m*, 1302*m*, 1244*w*, 1200*m*, 1150*s*, 1088*w*, 1046*m*, 1002*w*, 967*w*. ^{1}H-NMR ($CDCl_3$): 7.87–7.83 (*m*, 2 arom. H); 7.68 (br. *s*, NH); 7.58–7.45 (*m*, 3 arom. H); 7.39 (br. *s*, NH); 5.36 (*dd*, *J* = 8.4, 6.1, H–C(α)(Pro)); 5.06 (*dd*, *J* = 8.6, 4.6, H–C(α)(Pro)); 4.22–4.12 (*m*, H–C(δ)(Pro)); 4.03–3.93 (*m*, 2 H–C(δ)(Pro)); 3.70 (*s*, MeO); 3.55–3.47 (*m*, H–C(δ)(Pro)); 2.32–1.84 (*m*, 2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 1.96, 1.82, 1.77, 1.72 (4*s*, 4 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 205.6, 204.8 (2 C=S); 171.4, 168.9, 166.1 (3 C=O); 133.3 (arom. C); 132.2, 128.9, 127.2 (5 arom. CH); 70.0, 68.3 (2 CH(α)(Pro)); 62.1, 61.6 (2 C(α)(Aib)); 53.3, 52.9 (2 CH_2(δ)(Pro)); 52.2 (MeO); 31.0, 28.41 (2 Me(Aib)); 28.37, 27.8 (2 CH_2(β)(Pro)); 27.1, 26.7 (2 Me(Aib)); 25.8, 25.6 (2 CH_2(γ)(Pro)). ESI-MS: 555 (100, $[M+Na]^+$).

4.4. *Methyl (2*S*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carboxylate* (*Z-Pro-AibΨ[CS]-Pro-OMe*; **12**). According to *GP C*, Z-Pro-OH (1.0 g, 4.0 mmol) in THF (100 ml), NMM (969 mg, 9.6 mmol), i-BuOCOCl (656 mg, 4.8 mmol), **2a**[2]) (1.87 mg, 8.8 mmol) in THF (20 ml). After CC (AcOEt), a yellow oil was isolated and triturated with *t*-BuOMe. Filtration and recrystallization from *t*-BuOMe gave 1.64 g (89%) of **12**. Colorless crystals. M.p. 138–140°. $[\alpha]_D^{23} = -114.4$ (*c* = 1.00, $CDCl_3$). IR (KBr): 3443*w*, 3303*w*, 2976*m*, 2950*w*, 2883*w*, 1745*s*, 1697v*s*, 1660*s*, 1543*w*, 1422v*s*, 1386*w*, 1360*s*, 1270*w*, 1241*w*, 1203*s*, 1163*s*, 1118*m*, 1086*m*, 1047*w*, 1004*w*, 967*w*. ^{1}H-NMR ((D_6)DMSO, 300 K): 8.41, 8.36 (2 br. *s*, NH); 7.37–7.29 (*m*, 5 arom. H); 5.16–4.98 (*m*, PhCH_2); 4.83–4.80, 4.73–4.68, 4.38–4.32, 4.26–4.21 (4*m*, 2 H–C(α)(Pro)); 4.16–4.07, 3.88–3.77 (2*m*, CH_2(δ)(Pro)); 3.57, 3.53 (2*s*, MeO); 3.49–3.36 (*m*, CH_2(δ)(Pro)); 2.28–2.04, 1.96–1.72, 1.57–1.48 (3*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.61, 1.59, 1.40, 1.38 (4*s*, 2 Me(Aib)). ^{1}H-NMR ((D_6)DMSO, 360 K): 8.01 (br. *s*, NH); 7.36–7.27 (*m*, 5 arom. H); 5.12, 5.03 (*AB*, *J* = 13.0, PhCH_2); 4.96–4.89 (*m*, H–C(α)(Pro)); 4.28 (*dd*, *J* = 8.5, 3.0, H–C(α)(Pro)); 4.04–3.95, 3.84–3.76 (2*m*, CH_2(δ)(Pro)); 3.59 (*s*, MeO); 3.48–3.42 (*m*, CH_2(δ)(Pro)); 2.21–2.09, 2.01–1.78 (2*m*, 2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 1.64 (*s*, 2 Me(Aib)); 1.49 (*s*, 2 Me(Aib)). ^{13}C-NMR ((D_6)DMSO, 360 K): 203.8, 203.6 (C=S); 170.6, 170.4, 170.3 (2 C=O); 154.0, 153.5 ($PhCH_2OCO$); 137.2, 137.0 (arom. C); 128.2, 128.1, 127.6, 127.3, 126.2 (5 arom. CH); 67.8, 67.6 (CH(α)(Pro)); 65.8, 65.4 (PhCH_2); 60.0, 59.8 (C(α)(Aib)); 59.1, 58.7 (CH(α)(Pro)); 52.0, 51.9 (CH_2(δ)(Pro)); 51.5 (MeO); 47.0, 46.4 (CH_2(δ)(Pro)); 30.0, 29.5, 26.5, 26.1 (2 Me(Aib)); 31.2, 29.8, 27.2, 26.9 (2 CH_2(β)(Pro)); 25.4, 25.1, 23.7, 22.6 (2 CH_2(γ)(Pro)). ESI-MS: 484 (100, $[M+Na]^+$). Anal. calc. for $C_{23}H_{31}N_3O_5S \cdot C_5H_{12}O$ (**13**·*t*-BuOMe; 549.72): C 61.18, H 7.88, N 7.64; found: C 61.11, H 8.08, N 7.60.

Suitable crystals for an X-ray crystal-structure determination were obtained from AcOEt by slow evaporation of the solvent.

4.5. *(2*S*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carboxylic Acid* (*Z-Pro-AibΨ[CS]-Pro-OH*; **13**). According to *GP B*, **12** (1.38 g, 3.0 mmol), $LiOH \cdot H_2O$ (0.504 g, 12.0 mmol), THF/MeOH/H_2O 3:1:1 (400 ml); reaction time 26 h. After collection of the precipitated solid, additional portions of the product were recovered by extraction of the filtrate with CH_2Cl_2, and crystallization from *t*-BuOMe. Total yield of **13**: 1.07 g (80%). Colorless solid. M.p. 161–164°. IR (KBr): 3254*m*, 3034*w*, 2979*m*, 2881*w*, 2861*w*, 1704v*s*, 1540*m*, 1424v*s*, 1360*s*, 1265*m*, 1245*m*, 1209*s*, 1167*s*, 1150*m*, 1121*m*, 1090*w*, 1046*w*, 972*w*. ^{1}H-NMR ((D_6)DMSO): 12.27 (br. *s*, OH); 8.39, 8.34, 8.32 (3 br. *s*, NH); 7.36–7.30 (*m*, 5 arom. H); 5.15–4.91 (*m*, PhCH_2); 4.82–4.79, 4.72–

4.69, 4.38 – 4.33, 4.28 – 4.23 (4*m*, 2 H–C(α)(Pro)); 4.20 – 4.07, 3.84 – 3.69, 3.47 – 3.38 (3*m*, 2 CH_2(δ)(Pro)); 2.24 – 2.03, 1.94 – 1.73 (2*m*, 2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 1.62, 1.60, 1.40, 1.38 (4*s*, 2 Me(Aib)). ^{13}C-NMR ((D_6)DMSO, 360 K): 203.8, 203.6 (C=S); 170.3, 169.8, 169.6 (2 C=O); 153.7, 153.6 (PhCH_2OCO); 136.5, 136.4 (arom. C); 127.5, 126.8, 126.5 (5 arom. CH); 67.2 (CH(α)(Pro)); 65.4 (PhCH_2); 60.2, 60.0 (C(α)(Aib)); 59.5, 59.3 (CH(α)(Pro)); 51.9, 46.4, 46.2 (2 CH_2(δ)(Pro)); 29.4, 27.2 (2 Me(Aib)); 28.7, 28.6 (2 CH_2(β)(Pro)); 24.1, 22.7 (2 CH_2(γ)(Pro)). ESI-MS: 486 (14, $[M+K]^+$), 470 (100, $[M+Na]^+$), 454 (8). Anal. calc. for $C_{22}H_{29}N_3O_5S$ (447.54): C 59.04, H 6.53, N 9.39; found: C 58.75, H 6.40, N 7.14.

4.6. *Methyl (2*S*)-1-[2-({(2*S*/2*R*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-2-methylpropanoyl]pyrrolidine-2-carboxylate* (*Z-Pro-AibΨ[CS]-Pro-Aib-Pro-OMe*; **14a**) *and Methyl (2*S*)-1-[2-({(2*R*/2*S*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-2-methylpropanoyl]pyrrolidine-2-carboxylate* (**14b**). According to *GP A*, **13** (233 mg, 0.5 mmol) in CH_2Cl_2 (30 ml), **2a**[2]) (138 mg, 0.65 mmol) in CH_2Cl_2 (8 ml); reaction time 36 h. Two diastereoisomers **14a** and **14b** were formed in a ratio 1.3 : 1 (^{1}H-NMR). CC (AcOEt/MeOH 20 : 1) yielded 95 mg (30%) of **14a**, 39 mg (12%) of **14b**, and 88 mg (27%) of a mixture of both.

Data for **14a**. ^{1}H-NMR ($CDCl_3$): 7.98, 7.59 (2 br. *s*, NH); 7.36 – 7.28 (*m*, 5 arom. H); 7.03 (br. *s*, NH); 5.45 – 5.39 (*m*, H–C(α)(Pro)); 5.16 – 5.07 (*m*, PhCH_2); 4.52 (*dd*, *J* = 8.8, 4.3, H–C(α)(Pro)); 4.40 – 4.36 (*m*, H–C(α)(Pro)); 4.08 – 4.01, 3.92 – 3.83 (2*m*, 2 CH_2(δ)(Pro)); 3.68 (*s*, MeO); 3.71 – 3.43 (*m*, CH_2(δ)(Pro)); 2.44 – 2.35, 2.23 – 1.72 (2*m*, 3 CH_2(β)(Pro), 3 CH_2(γ)(Pro)); 1.49, 1.47 (2*s*, 4 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 205.3 (C=S); 173.5, 171.9, 171.6, 169.7, 169.4, 168.6 (4 C=O); 154.0, 153.5 (PhCH_2OCO); 136.1 (arom. C); 128.4, 128.1, 127.8 (5 arom. CH); 69.2 (CH(α)(Pro)); 67.1 (PhCH_2); 61.3 (C(α)(Aib)); 60.3, 59.7, 58.8 (2 CH(α)(Pro)); 57.3, 56.2 (C(α)(Aib)); 51.7 (MeO); 52.6, 48.1, 46.9, 45.5 (3 CH_2(δ)(Pro)); 32.1, 27.2, 26.1, 25.8, 25.3, 23.6 (4 Me(Aib)); 29.3, 28.9, 28.7 (3 CH_2(β)(Pro)); 25.9, 25.3, 24.3, 22.2 (3 CH_2(γ)(Pro)). ESI-MS: 666 (100, $[M+Na]^+$).

Data for **14b**. ^{1}H-NMR ($CDCl_3$): 7.47 (br. *s*, NH); 7.39 – 7.31 (*m*, 5 arom. H, NH); 5.28 – 5.11 (*m*, H–C(α)(Pro), PhCH_2); 4.53 – 4.49, 4.37 – 4.33 (2*m*, 2 H–C(α)(Pro)); 4.03 – 3.94, 3.75 – 3.47 (2*m*, 3 CH_2(δ)(Pro)); 3.70 (*s*, MeO); 2.32 – 1.90 (*m*, 3 CH_2(β)(Pro), 3 CH_2(γ)(Pro)); 1.70, 1.52, 1.51, 1.45 (4*s*, 4 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 204.6 (C=S); 173.3, 172.0, 169.4 (4 C=O); 153.8 (PhCH_2OCO); 136.1 (arom. C); 128.5, 128.3, 127.8 (5 arom. CH); 69.4 (CH(α)(Pro)); 67.5 (PhCH_2); 61.5 (C(α)(Aib)); 60.3 (2 CH(α)(Pro)); 56.8 (C(α)(Aib)); 51.8 (MeO); 53.0, 47.6, 47.1 (3 CH_2(δ)(Pro)); 32.5, 26.8, 24.5, 24.4 (4 Me(Aib)); 28.5, 27.8 (3 CH_2(β)(Pro)); 25.8, 25.6 (3 CH_2(γ)(Pro)). ESI-MS: 666 (100, $[M+Na]^+$).

4.7. *Methyl (2*S*)-2-({(2*S*/2*R*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-3-phenylpropionate* (*Z-Pro-AibΨ[CS]-Pro-Phe-OMe*; **15a**) *and Methyl (2*S*)-2-({(2*R*/2*S*)-1-[2-({(2*S*)-1-[(Benzyloxy)carbonyl]pyrrolidine-2-carbonyl}amino)-2-methyl-1-thioxopropyl]pyrrolidine-2-carbonyl}amino)-3-phenylpropionate* (**15b**). According to *GP D*, **14** (233 mg, 0.5 mmol) in MeCN (20 ml), EtN(i-Pr)$_2$ (194 mg, 1.5 mmol), TBTU (177 mg, 0.55 mmol), HOBt · H_2O (78 mg, 0.5 mmol), Phe-OMe · HCl (119 mg, 0.55 mmol); reaction time 48 h. Two diastereoisomers, **15a** and **15b**, were formed in a ratio 1.3 : 1 (^{1}H-NMR). CC (AcOEt/MeOH 20 : 1) yielded 80 mg (26%) of **15a**, 24 mg (8%) of **15b**, and 50 mg (17%) of a mixture of both.

Data for **15a**. ^{1}H-NMR ($CDCl_3$): 7.84 (br. *s*, NH); 7.66 (*d*, *J* = 6.0, NH); 7.48 – 7.12 (*m*, 10 arom. H); 5.31 – 5.08 (*m*, H–C(α)(Pro), PhCH_2); 4.69 – 4.58 (*m*, H–C(α)(Phe)); 4.41 – 4.37 (*m*, H–C(α)(Pro)); 4.15 – 4.04 (*m*, H–C(δ)(Pro)); 3.80 – 3.42 (*m*, 3 H–C(δ)(Pro), MeO); 3.23 – 2.92 (*m*, CH_2(β)(Phe)); 2.31 – 1.37 (*m*, 2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 1.80, 1.44 (*s*, 2 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 205.0, 204.4 (C=S); 172.6, 171.0, 170.3 (3 C=O); 156.2, 155.3 (PhCH_2OCO); 137.1, 136.3 (2 arom. C); 129.2, 129.1, 128.5, 128.2, 128.1, 127.5, 126.9, 126.4 (10 arom. CH); 69.4 (CH(α)(Pro)); 67.5, 67.3 (PhCH_2); 63.4, 61.4 (C(α)(Aib)); 60.1, 60.0 (CH(α)(Pro)); 52.4, 47.0 (2 CH_2(δ)(Pro)); 54.2, 53.7 (CH(α)(Phe)); 51.7 (MeO); 36.8, 36.7 (CH_2(β)(Phe)); 34.0, 30.0, 28.7, 27.3, 25.5, 24.4, 24.0, 21.3 (2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 31.7, 31.2, 26.6 (2 Me(Aib)).

Data for **15b**. ^{1}H-NMR ($CDCl_3$): 7.38 – 7.15 (*m*, 10 arom. H, 2 NH); 5.26 – 5.10 (*m*, H–C(α)(Pro), PhCH_2); 4.80 (*ddd*, *J* = 9.3, 8.5, 5.3, H–C(α)(Phe)); 4.37 – 4.33 (*m*, H–C(α)(Pro)); 3.87 – 3.76 (*m*, H–C(δ)(Pro)); 3.70 (*s*, MeO); 3.57 – 3.38 (*m*, 3 H–C(δ)(Pro)); 3.24 (*dd*, *J* = 14.0, 5.3, H–C(β)(Phe));

3.05 (*dd*, $J = 14.0$, 9.3, H–C(β)(Phe)); 2.38–2.29, 2.19–2.08, 1.99–1.85, 1.77–1.72, 1.63–1.53 (5*m*, 2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 1.70, 1.48 (*s*, 2 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 204.3 (C=S); 171.7, 170.4, 170.2 (3 C=O); 154.2 ($PhCH_2OCO$); 137.2, 135.2 (2 arom. C); 129.1, 128.5, 128.3, 128.1, 127.8, 126.6 (10 arom. CH); 69.4 (CH(α)(Pro)); 67.5 ($PhCH_2$); 61.4 (C(α)(Aib)); 60.5 (CH(α)(Pro)); 53.0, 47.2 (2 CH_2(δ)(Pro)); 52.8 (CH(α)(Phe)); 51.9 (MeO); 37.1 (CH_2(β)(Phe)); 28.4, 28.0, 25.5, 24.4 (2 CH_2(β)(Pro), 2 CH_2(γ)(Pro)); 27.3, 20.9 (2 Me(Aib)).

4.8. *Methyl (2S)-1-{2-Methyl-2-[(thiobenzoyl)amino]propanoyl}pyrrolidine-2-carboxylate* (*BzΨ[CS]-Aib-Pro-OMe*; **16**). According to *GP E*, **7** (167 mg, 0.5 mmol), $ZnCl_2$ (2.73 g, 20 mmol), 2.1M HCl in AcOH (0.65 ml). CC (AcOEt) and evaporation of the solvent gave 131 mg (78%) of **16**. Yellow crystals. M.p. 193–194°. $[\alpha]_D^{23} = -78.2$ ($c = 1.00$, $CDCl_3$). IR (KBr): 3442*w*, 3288*s*, 2986*w*, 2951*w*, 2875*w*, 1743*s*, 1726*s*, 1634v*s*, 1527*s*, 1446*s*, 1414*s*, 1357*m*, 1293*w*, 1247*w*, 1213*m*, 1181*m*, 1149*w*, 1092*w*, 1053*w*, 1007*w*, 927*w*. ^{1}H-NMR ($CDCl_3$): 8.41 (br. *s*, NH); 7.79–7.73 (*m*, 2 arom. H); 7.49–7.34 (*m*, 3 arom. H); 4.59 (*dd*, $J = 8.2$, 3.2, H–C(α)(Pro)); 3.82–3.74, 3.57–3.48 (2*m*, CH_2(δ)(Pro)); 3.73 (*s*, MeO); 2.16–2.01, 1.99–1.94 (2*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.93, 1.85 (2*s*, 2 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 196.6 (C=S); 172.7, 171.0 (2 C=O); 142.3 (arom. C); 130.9, 128.4, 126.4 (5 arom. CH); 60.9 (C(α)(Aib)); 60.8 (CH(α)(Pro)); 52.0 (MeO); 47.6 (CH_2(δ)(Pro)); 27.7, 25.8 (CH_2(β)(Pro)), CH_2(γ)(Pro)); 23.5, 22.2 (2 Me(Aib)). ESI-MS: 357 (100, $[M+Na]^+$). Anal. calc. for $C_{17}H_{22}N_2O_3S$ (334.43): C 61.05, H 6.63, N 8.38; found: C 60.82, H 6.62, N 8.31.

4.9. *(2S)-1-{2-Methyl-2-[(thiobenzoyl)amino]propanoyl}pyrrolidine-2-carboxylic Acid* (*BzΨ[CS]-Aib-Pro-OH*; **19**). To a soln. of **16** (334 mg, 1.0 mmol) in THF/H_2O 3:1 (80 ml), 2 equiv. of $LiOH \cdot H_2O$ (84 mg, 2.0 mmol) were added, and the mixture was stirred vigorously at r.t. for 24 h. Then, NH_4Cl (107 mg, 2.0 mmol) was added slowly, and N_2 was bubbled through the mixture until most of the NH_3 had evolved. The org. solvent was evaporated at r.t. under reduced pressure. The H_2O phase was treated again with small portions of NH_4Cl, and each time extracted with plenty of CH_2Cl_2. The combined yellow org. layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure at r.t. to afford 211 mg (66%) of **19**. Yellow gum. The unstable crude product was deep frozen (below −70°) or used directly for the next steps. ^{1}H-NMR ($CDCl_3$): 8.12 (br. *s*, NH); 7.77–7.73 (*m*, 2 arom. H); 7.50–7.36 (*m*, 3 arom. H); 4.63–4.61 (*m*, H–C(α)(Pro)); 3.72–3.64, 3.47–3.37 (2*m*, CH_2(δ)(Pro)); 2.25–2.15, 2.07–1.83 (2*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.82, 1.74 (2*s*, 2 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 197.4 (C=S); 173.7, 172.8 (2 C=O); 141.4 (arom. C); 131.3, 128.5, 126.4 (5 arom. CH); 61.7 (CH(α)(Pro)); 61.1 (C(α)(Aib)); 47.8 (CH_2(δ)(Pro)); 26.7, 25.9 (CH_2(β)(Pro), CH_2(γ)(Pro)); 24.6, 23.2 (2 Me(Aib)). ESI-MS (neg.): 639 (100, $[2M-H]^-$), 542 (7), 319 (37, $[M-H]^-$).

4.10. *N,2-Dimethyl-2-[((2S)-1-{2-methyl-2-[(thiobenzoyl)amino]propanoyl}pyrrolidine-2-carbonyl)-amino]*-N-*phenylpropanamide* (*BzΨ[CS]-Aib-Pro-Aib-N(Me)Ph*; **20**). To a soln. of crude **19** (39 mg, 0.122 mmol) in dry CH_2Cl_2 (10 ml), a soln. of 1.5 equiv. **1a** (32 mg, 0.183 mmol) in dry CH_2Cl_2 (4 ml) was added slowly at 0°. The mixture was stirred at 0° for 30 min, then at r.t. for 24 h, and evaporated. CC (SiO_2; AcOEt) and recrystallization from *t*-BuOMe yielded 29 mg (48%) of **20**. Pale yellow crystals. M.p. 205–206°. IR (KBr): 3443*m*, 3289*m*, 2986*w*, 2938*w*, 1641v*s*, 1593*m*, 1530*m*, 1493*m*, 1469*w*, 1450*m*, 1399*s*, 1360*s*, 1288*w*, 1251*w*, 1199*w*, 1176*w*, 1092*w*, 1011*w*, 924*w*. ^{1}H-NMR ($CDCl_3$): 8.37 (br. *s*, NH); 7.73 (*d*, $J =$ 7.4, 2 arom. H); 7.52–7.46 (*m*, 1 arom. H); 7.43–7.18 (*m*, 7 arom. H, NH); 4.39–4.34 (*m*, H–C(α)(Pro)); 3.60–3.52, 3.47–3.39 (2*m*, CH_2(δ)(Pro)); 3.29 (*s*, MeN); 2.18–2.10, 2.00–1.78 (2*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.78, 1.66, 1.46, 1.45 (4*s*, 4 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 197.4 (C=S); 173.0, 171.2, 170.1 (3 C=O); 145.2, 141.6 (2 arom. C); 131.2, 129.0, 128.4, 127.4, 127.1, 126.6 (10 arom. CH); 62.5 (CH(α)(Pro)); 61.5, 57.5 (2 C(α)(Aib)); 47.2 (CH_2(δ)(Pro)); 40.6 (MeN); 27.0, 25.6 (CH_2(β)(Pro), CH_2(γ)(Pro)); 26.4 (2 Me(Aib)); 24.7, 23.9 (2 Me(Aib)). ESI-MS: 533 (4, $[M+K]^+$), 517 (100, $[M+Na]^+$). Anal. calc. for $C_{27}H_{34}N_4O_3S$ (494.65): C 65.56, H 6.93, N 11.33; found: C 65.32, H 6.66, N 11.28.

4.11. *N,2-Dimethyl-2-[((2S)-1-{2-methyl-2-[(thiobenzoyl)amino]propanoyl}pyrrolidine-2-carbonyl)-amino]*-N-*phenylpropanethioamide* (*BzΨ[CS]-Aib-Pro-AibΨ[CS]-N(Me)Ph*; **21**). According to *GP C*, a soln. of crude **19** (211 mg, 0.66 mmol) in dry THF/DMF 10:1 (44 ml), NMM (160 mg, 1.58 mmol), i-BuOCOCl (1 equiv., 90.3 mg, 0.66 mmol), **1a** (229 mg, 1.32 mmol) in THF (10 ml). After stirring at −10° for 2 h and at r.t. overnight, the solvent was removed at r.t. under reduced pressure, the residue was treated with AcOEt, filtered, and the deep yellow filtrate purified by CC (SiO_2; AcOEt). The resulting oil was triturated with *t*-BuOMe, and **21** was collected by filtration: 125 mg (37%). Yellow

crystals. M.p. 190–192°. $[\alpha]_D^{23} = -35.1$ ($c = 1.00$, MeOH). IR (KBr): 3443*m*, 3301*m*, 2992*w*, 2937*w*, 1658v*s*, 1626*s*, 1530*s*, 1492*s*, 1450*s*, 1399*s*, 1368*s*, 1283*w*, 1246*m*, 1208*w*, 1181*w*, 1099*m*, 1005*w*, 923*w*. ^{1}H-NMR ($CDCl_3$): 8.10 (br. *s*, NH); 7.76–7.72 (*m*, 2 arom. H); 7.58 (br. *s*, NH); 7.51–7.45 (*m*, 1 arom. H); 7.42–7.13 (*m*, 5 arom. H); 7.22–7.17 (*m*, 2 arom. H); 4.32–4.28 (*m*, H–C(α)(Pro)); 3.70 (*s*, MeN); 3.55–3.50 (*m*, CH_2(δ)(Pro)); 2.22–2.14, 2.10–1.96, 1.91–1.78 (3*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.79, 1.75, 1.70, 1.59 (4*s*, 4 Me(Aib)). ^{13}C-NMR ($CDCl_3$): 208.6, 197.2 (2 C=S); 171.2, 169.4 (2 C=O); 141.7 (2 arom. C); 131.3, 129.3, 128.5, 127.9, 126.4, 126.0 (10 arom. CH); 62.6 (CH(α)(Pro)); 62.3, 61.4 (2 C(α)(Aib)); 47.4 (CH_2(δ)(Pro)); 30.6, 29.4 (2 Me(Aib)); 26.6, 25.7 (CH_2(β)(Pro), CH_2(γ)(Pro)); 24.2, 24.3 (2 Me(Aib)). ESI-MS: 549 (5, $[M + K]^+$), 533 (100, $[M + Na]^+$). Anal. calc. for $C_{27}H_{34}N_4O_2S_2$ (510.71): C 63.50, H 6.71, N 10.97; found: C 63.35, H 6.43, N 10.87.

5. *X-Ray Crystal-Structure Determination of* **12** *and* **21** (*Table*, and *Figs. 1* and *2*)[3]). All measurements were performed on a *Nonius KappaCCD* diffractometer [38] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream* 700 cooler. The data collection and refinement parameters are given in the *Table*, and views of the molecules are shown in *Figs. 1* and *2*. Data reduction was performed with *HKL Denzo* and *Scalepack* [39]. The intensities were corrected for *Lorentz* and polarization effects, and absorption corrections based on the multi-scan method [40] were applied. Each structure was solved by direct methods using SIR92 [41], which revealed the positions of all non-H-atoms. In the case of **12**, the asymmetric unit contains two symmetry-independent molecules of the peptide, plus two molecules of AcOEt. Substantial differences in the conformations of the two peptide molecules preclude the possibility of additional overlooked crystallographic symmetry. The Et group of one of the AcOEt molecules is disordered. Two positions were defined for each of the Et atoms, and refinement of the site occupation factors yielded a value of 0.66(2) for the major conformation. Bond-length and similarity restraints were applied to all chemically equivalent bond lengths and angles involving the disordered atoms. Furthermore, neighboring atoms within and between each disordered conformation were restrained to have similar and pseudo-isotropic atomic displacement parameters. A bond-length restraint was also applied to the C–C bond of the Et group in the ordered AcOEt molecule. In the case of **21**, the asymmetric unit contains one peptide and one H_2O molecule. In each structure, the non-H-atoms were refined anisotropically. The amide and H_2O H-atoms were placed in the positions indicated by a difference electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters, while restraining the H_2O O–H and H···H distances to suitable values. All remaining H-atoms in each structure were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me groups). The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied in the case of **12**. In the case of **21**, one reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement. Refinement of the absolute structure parameter [42] yielded values of $-0.02(7)$ for **12** and 0.12(7) for **21**, which confirms that the refined coordinates represent the true enantiomorph. Neutral atom scattering factors for non-H-atoms were taken from [43a], and the scattering factors for H-atoms were taken from [44]. Anomalous dispersion effects were included in F_c [45]; the values for f' and f'' were those of [43b]. The values of the mass attenuation coefficients are those of [43c]. All calculations were performed using the SHELXL97 [46] program.

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[3]) CCDC-683046–683047 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 1. *Crystallographic Data for Compounds* **12** *and* **21**

	12	**21**
Crystallized from	AcOEt	CH_2Cl_2/*t*-BuOMe
Empirical formula	$C_{23}H_{31}N_3O_5S \cdot C_4H_8O_2$	$C_{27}H_{34}N_4O_2S_2 \cdot H_2O$
Formula weight	549.68	528.73
Crystal color, habit	colorless, prism	colorless, needle
Crystal dimensions [mm]	$0.22 \times 0.25 \times 0.27$	$0.08 \times 0.10 \times 0.25$
Temp. [K]	160(1)	160(1)
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Z	8	4
Reflections for cell determination	69201	56524
2θ Range for cell determination [°]	4–50	4–55
Unit cell parameters a [Å]	14.4030(2)	8.3334(2)
b [Å]	18.5950(2)	10.1403(3)
c [Å]	21.8300(3)	32.6404(9)
V [Å^3]	5846.6(1)	2758.2(1)
D_x [g cm^{-3}]	1.249	1.273
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.158	0.228
Scan type	ϕ and ω	ϕ and ω
$2\theta_{(\max)}$ [°]	50	55
Transmission factors [min; max]	0.809; 0.970	0.820; 0.990
Total reflections measured	62916	33484
Symmetry independent reflections	10302	6286
Reflections with $I > 2\sigma(I)$	7870	4542
Reflections used in refinement	10302	6285
Parameters refined; restraints	724; 66	345; 3
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0465	0.0482
$wR(F^2)$ (all data)	0.1204	0.1059
Weighting parameters [a; b][a])	0.0660; 0.8380	0.0409; 0.7345
Goodness-of-fit	1.035	1.037
Secondary extinction coefficient	0.0032(4)	–
Final $\Delta_{\max}/\sigma$	0.001	0.002
$\Delta\rho$ (max; min) [e Å^{-3}]	0.69; −0.22	0.24; −0.29

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$

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