Scope and Limitation of the Acid-Catalyzed Isomerization of Aib-Containing Thiopeptides

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The use of amino thio *S*-acids in the 'azirine/oxazolone method' and a novel isomerization led to Aib-containing endothiopeptides. With the aim of generalizing this method, a variety of Aib-containing dipeptide thioanilides have been prepared. By their treatment with $ZnCl_2$ in AcOH, followed by HCl-saturated AcOH, the C=S group was shifted from the last to the penultimate amino acid in high yield and without epimerization. As this methodology is very useful for the specific introduction of a thioamide group, it was extended to Aib-containing tripeptides. In addition, it could be shown that a mechanism *via* spirocyclic intermediates (*cf. Scheme 4*) is most likely for this isomerization. To establish the proposed neighboring-group participation of the *N*-acyl group, model dipeptide thioanilides containing no N-terminal C=O group were synthesized. These derivatives did not undergo rearrangement.

Introduction. – Peptides with backbone modifications are of considerable interest. Among them are endothiopeptides with one or more peptide bonds replaced by thioamide groups within the peptide chain[2]). These thioamides offer an almost isologous substitution of an amide linkage [5] that often leaves biological effects unaltered. However, computational studies show that this may not be generally the case, namely not in N-terminal thioamide replacements [6]. Endothio analogues of biologically active peptides can show an increased proteolytic stability [7], thus allowing higher bioavailability [8]. Moreover, enhanced biological activity and receptor selectivity can be expected but not predicted [9]. In addition, the thioamide-replacement strategy has also been applied to inhibition studies of proteases and peptidases [10]. A selection of recently published synthetic approaches to endothiopeptides provides further insights into the current synthetic developments of these modified peptides [1–4] [11–15].

Another interesting group of backbone-modified peptides contain α-alkylated α-amino acids. The introduction of a second alkyl group at the C(α)-atom of α-amino acids results in a restriction of the conformational flexibility (*cf.* [16], and refs. cit. therein), and stabilizes or induces helices. Two of these amino acids, Aib (= α-aminoisobutyric acid) and Iva (isovaline) characterize the peptaibols, a family of natural antibiotics, which show bactericidal and hemolytic activity [17][18]. Due to the severe steric hindrance, the synthesis of related peptides is difficult [19–21], but with the 'azirine/oxazolone method', we developed a convenient synthetic access to such peptides, of which 3-amino-2*H*-azirines proved to be useful synthons for the introduction of α-alkylated α-amino acids [22–26].

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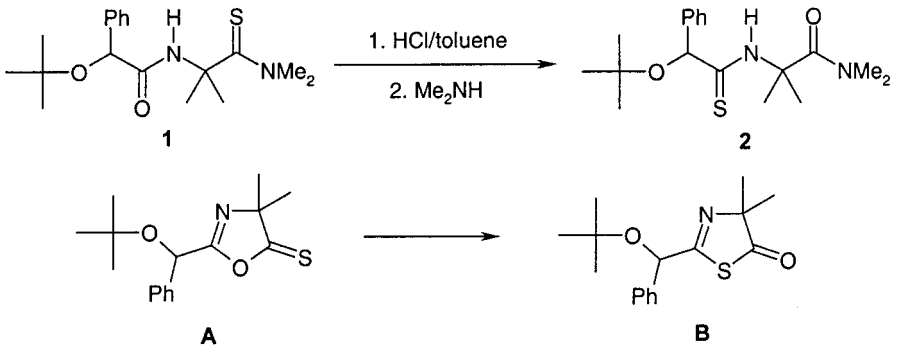
[1]) Part of the planned Ph.D. thesis of *R. A. B.*, Universität Zürich.

[2]) For our own work in this field, see [1–4].

We have shown that the reaction of 3-amino-2*H*-azirines with α-amino thio *S*-acids followed by a novel isomerization offers a convenient synthetic access to peptides with a combination of these two backbone modifications. First experiments were carried out by treatment of thiobenzoic acid [27] and later of *O*-(tert-butyl) DL-thiomandelic *S*-acid [28] (*cf.* also [29]) with 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine. In the latter case, thioamide **1** was obtained in 74% yield, and sequential treatment with HCl (gas) and Me_2NH gave the isomeric thioamide **2** in 53% yield [28] (*Scheme 1*). Control experiments established that the isomerization occurred *via* an intermediate 1,3-oxazole-5(4*H*)-thione **A** that underwent a spontaneous rearrangement to the 1,3-thiazole-5(4*H*)-one **B**.

Scheme 1



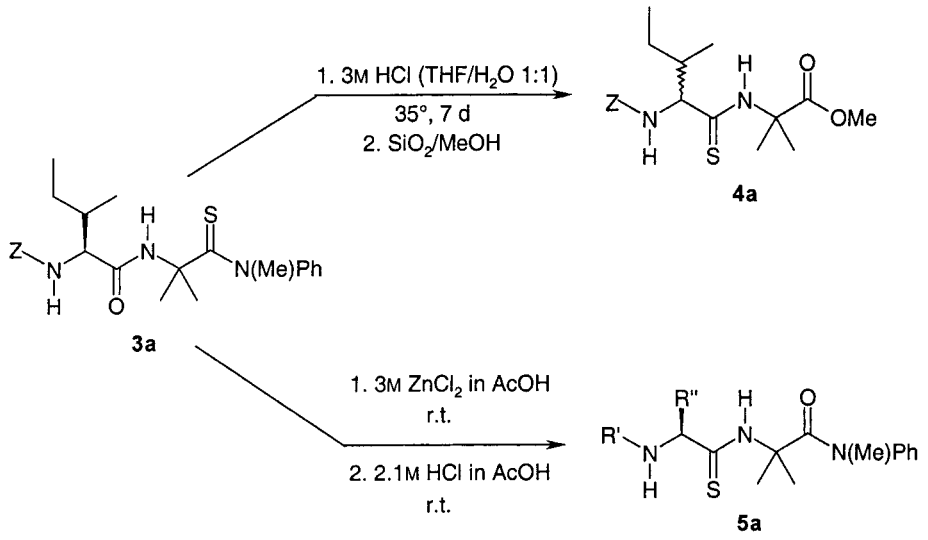
In more recent experiments [2], **3a** was hydrolyzed under the standard conditions of the 'azirine/oxazolone method' (3M HCl, THF/H_2O 1:1, 35°) and, after 7 days and chromatography with MeOH, **4a** with complete epimerization at the C(α)-atom of Ile was isolated as the only product in 87% yield (*Scheme 2*). On the other hand, treatment of **3a** with 3M $ZnCl_2$ in AcOH for 20 min, addition of 2.1M HCl in AcOH (HCl-saturated AcOH), and stirring the mixture for 30 min at room temperature led to the isomeric endothiopeptide **5a** (*Scheme 2*) in 88% yield without epimerization [2].

Two mechanisms for this isomerization are conceivable (*cf.* [2]). In the present work, these mechanistic doubts are clarified through experiments with dipeptide thioanilides having different N-terminal groups. In addition, we demonstrate that this isomerization is of general use.

Results and Discussion. – With the aim of either emphasizing the general synthetic value of this isomerization or underlining the feasibility of our mechanistic approach, different series of peptide thioamides were synthesized. To show that this method is not limited to the synthesis of endothiodipeptides, the model tripeptide **8** was synthesized as depicted in *Scheme 3*. After treatment of **6**[3]) with 3M HCl (THF/H_2O 1:1), the resulting crude *N*-deprotected dipeptide thioamide **7** was coupled with Z-Phe-OH using [(1*H*-benzotriazol-1-yl)oxy]tris[pyrrolidin-1-yl]phosphonium hexafluorophos-

[3]) Synthesized according to [2][30].

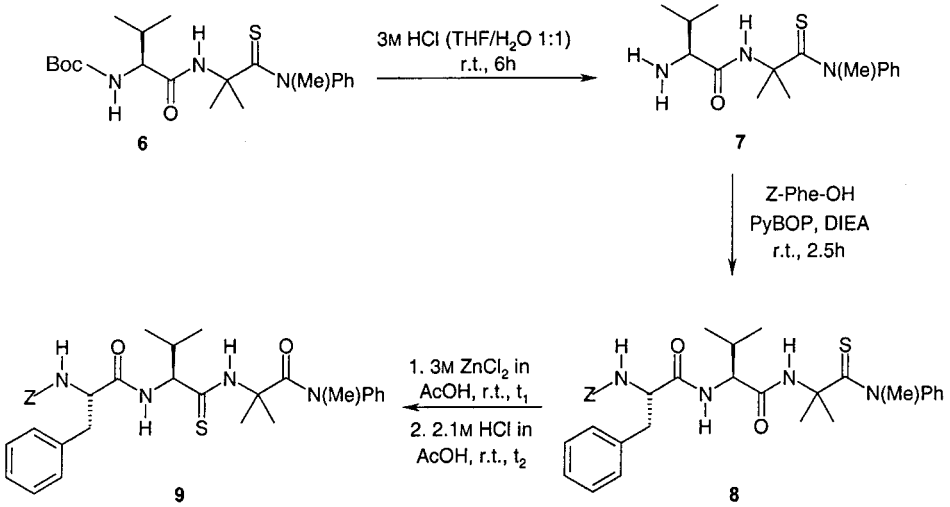
Scheme 2



phate (PyBOP) as the coupling reagent in the presence of $EtN(i\text{-}Pr)_2$, leading to the tripeptide thioamide **8** in 69% yield.

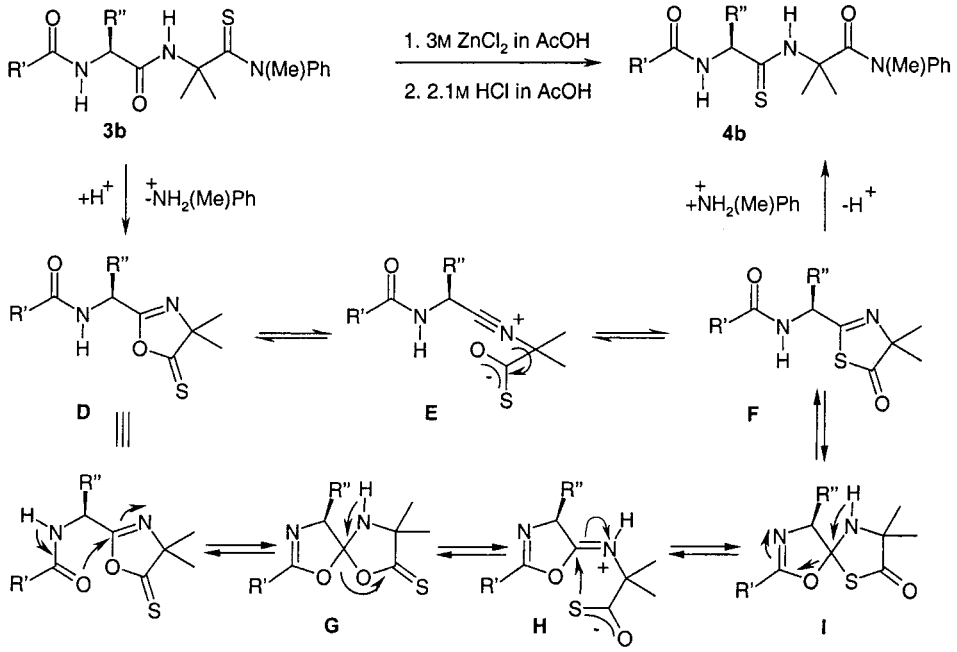
Then, **8** was treated with 3M $ZnCl_2$ in AcOH for 30 min (t_1), 2.1M HCl in AcOH was added, and the mixture was stirred for 20 min (t_2) at room temperature (previously [30] optimized reaction times; *Scheme 3*). The isomeric endothiotripeptide **9** was isolated in 91% yield as stereochemically homogenous material. No epimerization could be detected by ^{1}H-NMR spectroscopy.

Scheme 3



The exchange of the S- and O-atoms can be explained as proposed earlier (*Scheme 4*). Nucleophilic attack of the amide O-atom at the C-atom of the activated thioamide group and elimination of *N*-methylaniline leads to the unstable 1,3-oxazol-5(4*H*)-thione[4]) **D**, which, *via* attack of the amide or carbamate O-atom, yields the spirocyclic intermediate **G**. Ring opening leads to the dipolar species **H**, and ring closure by nucleophilic attack of the S-atom at the iminium group gives the isomeric spirocyclic intermediate **I**. Anew, ring opening leads to the more stable 1,3-thiazol-5(4*H*)-one **F**, and, after nucleophilic attack of *N*-methylaniline and ring opening, **4b** is obtained. A more simple mechanism without neighboring-group participation can be formulated *via* the nitriliumion **E**.

Scheme 4



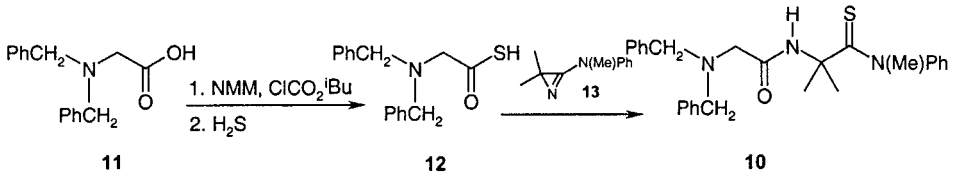
With the intention of establishing the occurrence of spirocyclic intermediates, corresponding dipeptide thioamides without an N-terminal amide or carbamate group were synthesized. According to the proposed mechanism, these dipeptide thioamides should not be able to undergo the shift of the S-atom of the thioamide group from the last to the penultimate amino acid under the standard isomerization conditions. On the other hand, the isomerization *via* intermediate **E** should still be possible.

As the first example, we selected the *N*,*N*-dibenzylated dipeptide thioamide **10** (*Scheme 5*). In analogy to the previously reported procedure, *N*,*N*-dibenzylglycine (**11**, (*cf.* [31]) was transformed into the thio *S*-acid **12** *via* the reaction of the mixed

[4]) The elimination of *N*-methylaniline also occurs under ESI-MS and CI-MS conditions. The peak corresponding to the ($[M-(\mathrm{Me(Ph)N})]^+$ ion was always detected, sometimes as the most intense peak.

anhydride of **11** with H_2S. The crude **12** was then treated with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**13**) to afford thioamide **10** in 18% yield, with respect to **11**[5])[6]).

Scheme 5

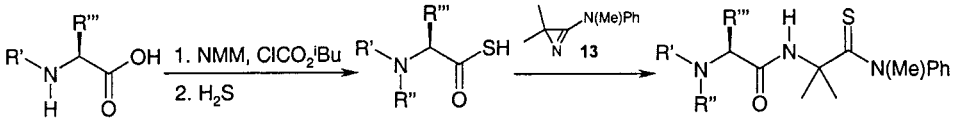


11 **12** **10**

When **10** was treated under standard isomerization conditions and previously optimized reaction times [30] ($t_1 = 10$ min, $t_2 = 5$ min), no isomerization could be detected; 87% of the starting material **10** was recovered.

Control experiments led to the conclusion that the failure of isomerization was not due to an influence of the $PhCH_2$ group, but has to be put down to the absence of an amide or carbamate group. For this purpose, the model dipeptide thioamides **16a**–**c** were prepared according to *Scheme 6*, starting from *N*-benzylglycine (**14a**), *N*-methylalanine (**14b**), and *N*-benzoylphenylalanine (**14c**), respectively. Simultaneously with the formation of the thio *S*-acids *via* the mixed anhydrides, the isobutyl carbamates were formed in the case of **14a** and **14b**. The crude thio *S*-acids **15a**–**c** were then reacted with **13** to afford the thioamides **16** (*Table 1*).

Scheme 6



14 **15** **16**

Table 1. *Preparation of Dipeptide Thioamides* **16**

16	R′	R″	R‴	Yield [%][a])
a	$PhCH_2$	^{i}BuOCO	H	24
b	Me	^{i}BuOCO	Me	11
c	PhCO	H	$PhCH_2$	25

[a]) With respect to **14**.

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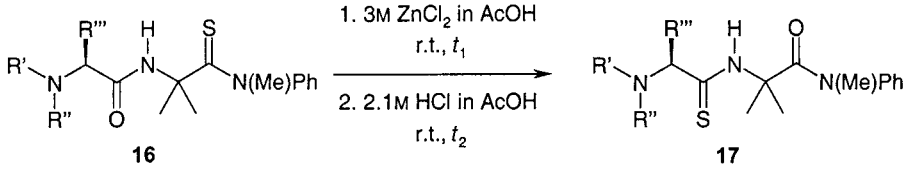
[5]) Usually, the preparation of the thio *S*-acid is carried out in THF. In the present case, the solubility of **11** in THF is rather low, and no dipeptide **10** was obtained after the reaction with **13**. Therefore, a mixture of THF/DMSO 1:1 was used to increase solubility and the yield. However, the yield of **10** was still low, possibly due to the influence of DMSO as solvent.

[6]) The analogous reactions with *N*,*N*-dimethylglycine and *N*,*N*-dimethylalanine failed because of the very low solubility of the starting materials.

The peptide thioamides **16** were first treated with 3M $ZnCl_2$ in AcOH (t_1), then 2.1M HCl in AcOH was added, and the mixture was stirred at room temperature (t_2). The isomeric endothiodipeptides **17** were isolated in good yields (*Table 2*).

Table 2. *Isomerization of Dipeptide Thioamides* **16**

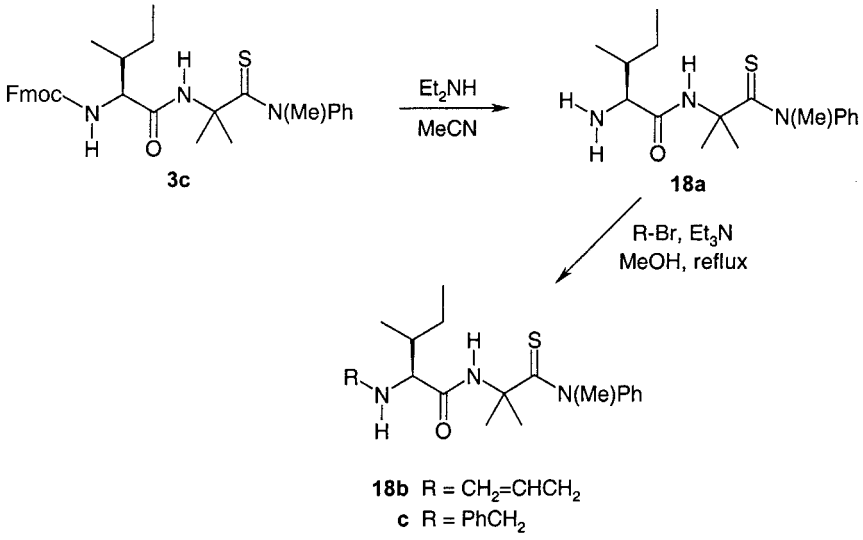


16/17	R′	R″	R‴	t_1 [min]	t_2 [min]	Yield [%]
a	$PhCH_2$	^{i}BuOCO	H	10	5	81
b	Me	^{i}BuOCO	Me	1.5[a])	1[a])	96
c	PhCO	H	$PhCH_2$	10	5	94

[a]) The reaction times had previously been optimized, and no epimerization could be detected under these conditions [30].

As additional models, we selected the dipeptide thioamides **18a–c**, which were prepared from **3c** obtained earlier [30] (*Scheme 7*). Treatment of the Fmoc (=(9*H*-fluoren-9-yl)methoxycarbonyl)-protected **3c** with Et_2NH gave **18a** in 82% yield, which was then alkylated with benzyl or allyl bromide in refluxing MeOH in the presence of Et_3N, leading to **18b** and **18c**, respectively, in 19 and 25% yield. The low yields are presumably due to the reaction of the alkyl bromide with the thioamide, leading to desulfurized peptide analogues after hydrolysis. The formation of bad-smelling thiols

Scheme 7



during the reaction confirms this hypothesis, as does the higher yield for the alkylation of an analogue of **18a**[7]) that does not contain sulfur.

When the dipeptide thioanilides **18a**–**c** were treated under standard isomerization conditions with previously optimized reaction times [2][30][8]), no isomerization occurred. The starting materials were recovered in 61–86% yield.

In summary, we showed that the modified 'azirine/oxazolone method' in combination with the acid-catalyzed isomerization of the resulting peptide thioamides is a versatile protocol for the synthesis of epimerically pure endothiopeptides containing the thiocarbonyl group next to the bulky Aib. This procedure is applicable as long as the N-atom of the penultimate amino acid bears a C=O group. In peptide synthesis, this is only a minor limitation. Moreover, it could be established that a mechanism *via* spirocyclic intermediates is conceivable for this isomerization in which the thiocarbonyl group is shifted from the last to the penultimate amino acid in high yields.

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Experimental Part

1. *General*. See [2]. M.p. *Büchi B-540*.

General Procedure A (*GP A*). To a soln. of 1 equiv. of *N*-terminal-protected amino acid in THF, THF/DMSO or CH_2Cl_2/DMSO, 2 equiv. of *N*-methylmorpholine (NMM) and 1 equiv. of isobutyl carbonochloridate (^{i}BuOCOCl) were added at $-10°$; immediately a white solid precipitated. The mixture was stirred for *ca*. 5 min, then a slow stream of *in situ* generated H_2S (a 50% H_2SO_4 soln. was dropped slowly onto 10–20 equiv. $Na_2S \cdot H_2O$) was bubbled through the soln. After stirring for 1 h at $-10°$, the suspension was transferred into a separatory funnel, diluted with Et_2O, and extracted 3 × with 0.1M H_3PO_4 soln. The combined org. phase was dried ($MgSO_4$) and evaporated, and the residue was dried under high vacuum. The crude amino thio *S*-acid formed was dissolved in CH_2Cl_2 and cooled to 0°, and 1 equiv. of 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine **13** was added slowly. The mixture was allowed to reach r.t. and stirred until the starting material was completely consumed (TLC). Then, the solvent was evaporated, and the residue was dried under high vacuum (h.v.). The crude products were purified by chromatography (SiO_2).

General Procedure B (*GP B*). The intensely yellow soln. of thiopeptide in AcOH was treated with $ZnCl_2$ and stirred at r.t.; the $ZnCl_2$ dissolved only slowly. After t_1, AcOH saturated with HCl (2.1M) was added to the mixture. After t_2, the pale yellow mixture was carefully added to a 5% $NaHCO_3$ soln., and the resulting mixture was extracted with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and evaporated, and the residue was chromatographed (SiO_2) if necessary.

2. *Benzyl* N-*((*S*)-1-Benzyl-2-{[(*S*)-2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)-1-(1-methylethyl)-2-thioxoethyl]amino}-2-oxoethyl)carbamate* (Z-Phe-Val-ψ(CS)-Aib-N(Me)Ph, **9**). *Benzyl* N-*((*S*)-1-Benzyl-2-{[(*S*)-2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino)-1-(1-methylethyl)-2-oxoethyl]amino}-2-oxoethyl)carbamate* (Z-Phe-Val-Aib-ψ(CS)-N(Me)Ph, **8**). A soln. of Boc-Val-Aib-ψ(CS)-N(Me)Ph (**6** [2], 212 mg, 0.52 mmol) in 10 ml of 3M HCl (THF/H_2O 1:1) was stirred at r.t. After 6 h, the mixture was transferred to a separatory funnel, diluted with 5% $NaHCO_3$ soln., and extracted with CH_2Cl_2

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[7]) When Val-Aib-N(Me)Ph was treated with $PhCH_2Br$ under the same conditions as **18a**, the monoalkylated product was isolated in 56% yield. In addition, 9% of the dibenzylated product and 10% of the starting material were isolated as well.

[8]) Under these conditions, the Fmoc-protected analogue **3c** isomerized to the corresponding endothiodipeptide in 96% yield, and no epimerization could be detected [2].

(3×). The combined org. phase was dried ($MgSO_4$) and concentrated *in vacuo* to give 112 mg (70%) of Val-Aib-ψ(CS)-N(Me)Ph as a crude product. To a soln. of Z-Phe (109 mg, 0.364 mmol), Val-Aib-ψ(CS)-N(Me)Ph (112 mg, 0.364 mmol), PyBOP (189 mg, 0.364 mmol) in CH_2Cl_2 (10 ml), and EtN(i-Pr)$_2$ (0.06 ml, 0.37 mmol) were added. The mixture was stirred at r.t. until the starting material was completely consumed (TLC). After 2.5 h, the soln. was concentrated *in vacuo*. Chromatography (SiO_2; AcOEt/hexane, 1:2) gave 208 mg (69%) of **8**. Colorless, thick oil that solidified. IR (KBr): 3307*m*, 3062*w*, 3030*w*, 2963*m*, 2932*w*, 1706*s*, 1648*s*, 1594*w*, 1493*s*, 1455*m*, 1370*m*, 1257*m*, 1102*m*, 1028*w*, 1004*w*, 774*w*, 743*m*, 698*m*, 652*w*. ^{1}H-NMR: 7.43–7.13 (*m*, 15 arom. H); 7.07 (br. *s*, NH); 6.75 (*d*, J = 7.2, NH); 5.35 (*d*, J = 7.5, NH); 5.13–5.02 (*m*, CH_2O); 4.59–4.48 (*m*, CH(α)(Val)); 4.06–3.97 (*m*, CH(α)(Phe)); 3.67 (*s*, MeN); 3.19–3.11 (*m*, CH_2(β)(Phe)); 2.08–2.02 (*m*, CH(β)(Val)); 1.63, 1.55 (2*s*, Me_2C(Aib^r)); 0.84–0.79 (*m*, 2 Me(γ)(Val)). ^{13}C-NMR: 200.2 (*s*, CS(Aib^r)); 170.6, 168.3 (2*s*, CO(Phe), CO(Val)); 155.9 (*s*, CO(carbamate); 147.3, 136.1, 136.0 (3*s*, 3 arom. C); 129.6, 129.2, 128.6, 128.5, 128.3, 128.1, 127.9, 127.0, 126.3 (9*d*, 15 arom. C); 67.0 (*t*, CH_2O); 62.7 (*s*, C(α)(Aib^r)); 58.2, 56.2 (2*d*, CH(α)(Phe), CH(α)(Val)); 51.8 (*q*, MeN); 37.9 (*t*, CH_2(β)(Phe)); 31.3 (*d*, CH(β)(Val)); 28.9 (*q*, *Me*$_2$C(Aib^r)); 18.9, 17.7 (2*q*, 2 Me(γ)(Val)). ESI-MS: 611 ([M+Na]$^+$), 589 ([M+1]$^+$), 588 ($M^{+\cdot}$), 482 ([M−(Me(Ph)N)]$^+$). Anal. calc. for $C_{33}H_{40}N_4O_4S$ (588.78): C 67.32, H 6.85, N 9.52, S 5.45; found: C 67.15, H 7.15, N 9.24, S 5.38.

Z-Phe-Val-ψ(CS)-Aib-N(Me)Ph (**9**). According to the *GP B*, with **8** (0.678 g, 1.39 mmol), AcOH (14 ml), $ZnCl_2$ (5.724 g, 42.00 mmol), and 1.4 ml of 2.1M HCl in AcOH (t_1 = 20 min, t_2 = 30 min). Chromatography (SiO_2; AcOEt/CH_2Cl_2/hexane 1:1:2) gave 0.619 g (91%) of **9**. Thick oil that solidified under h.v. IR (KBr): 3253*m*, 3032*m*, 2963*m*, 2931*m*, 1715*s*, 1635*s*, 1593*m*, 1495*s*, 1454*m*, 1426*m*, 1389*m*, 1361*m*, 1251*m*, 1177*w*, 1090*m*, 1050*w*, 1028*w*, 911*w*, 740*m*, 701*m*. ^{1}H-NMR: 8.31 (br. *s*, NH); 7.4–7.15 (*m*, 15 arom. H, NH); 5.32 (br. *s*, NH); 5.32–5.01 (*m*, CH_2O); 4.58–4.46 (*m*, CH(α)(Val^t)); 4.38–4.22 (*m*, CH(α)(Phe)); 3.23 (*s*, MeN); 3.2–3.05 (*m*, CH_2(β)(Phe)); 2.12–1.98 (*m*, CH(β)(Val)); 1.70, 1.58 (2*s*, Me_2C(Aib)); 0.92–0.81 (*m*, 2 Me(γ)(Val)). ^{13}C-NMR: 200.2 (*s*, CS(Val^t)); 171.4, 170.3 (2*s*, CO(Phe), CO(Aib)); 155.9 (*s*, CO(carbamate)); 143.8, 135.9 (2*s*, 3 arom. C); 129.3, 129.2, 128.7, 128.5, 128.1, 128.0, 127.7, 127.0 (8*d*, 15 arom. C); 67.1 (*t*, CH_2O); 64.0 (*d*, CH(α)(Val^t)); 61.8 (*s*, C(α)(Aib)); 56.3 (*d*, CH(α)(Phe)); 40.6 (*q*, MeN); 37.7 (*t*, CH_2(β)(Phe)); 34.1 (*d*, CH(β)(Val^t)); 25.6, 24.0 (2*q*, *Me*$_2$C(Aib)); 19.2, 18.1 (2*q*, 2 Me(γ)(Val^t)). ESI-MS: 611 ([M+Na]$^+$), 482 ([M−(Me(Ph)N)]$^+$). Anal. calc. for $C_{33}H_{40}N_4O_4S \cdot 0.5\ H_2O$ (597.79): C 66.31, H 6.91, N 9.37, S 5.36; found: C 66.14, H 7.02, N 9.02, S 5.08.

3. *N′,N′-Dibenzyl-*N*-{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}glycinamide* (Bn_2Gly-Aib-ψ(CS)-N(Me)Ph, **10**). *N,N-Dibenzylglycine* (**11**). To a soln. of glycine (1.29 g, 17.17 mmol) in H_2O (10 ml), KOH (3.46 g, 61.13 mmol) and EtOH (10 ml) were added. $PhCH_2Br$ (2.04 ml, 17.17 mmol) was added dropwise, and the resulting soln. was stirred for 16 h at r.t., followed by heating under reflux for 30 min. After cooling and evaporation to 50% of the original volume, the soln. was acidified with AcOH to pH 6, and **11** precipitated immediately; after one night, 2.33 g (quant.) of **11** were obtained by filtration. Colorless solid. ^{1}H-NMR ((D$_6$)DMSO): 7.38–7.22 (*m*, 10 arom. H); 3.74 (*s*, 2 PhC*H*$_2$); 3.16 (*s*, CH_2(Gly). ^{13}C-NMR ((D$_6$)DMSO): 172.0 (*s*, CO); 138.9 (*s*, 2 arom. C); 128.4, 128.1, 126.9 (3*d*, 10 arom. C); 56.7 (*t*, 2 PhC*H*$_2$); 52.9 (*t*, CH_2(Gly)). CI-MS: 257 (17), 256 (100, ([M+1]$^+$). Anal. calc. for $C_{16}H_{17}N_3O_2 \cdot 0.25\ H_2O$ (259.82): C 73.96, H 6.91, N 5.39; found: C 74.23, H 6.73, N 5.40.

Bn_2Gly-Aib-ψ(CS)-N(Me)Ph (**10**). According to the *GP A*, with **11** (180 mg, 0.71 mmol) in THF/DMSO 1:1 (10 ml), *N*-methylmorpholine (NMM; 0.16 ml, 1.41 mmol), ^{i}BuOCOCl (0.18 ml, 0.74 mmol), $Na_2S \cdot H_2O$ (2.26 g, 14.1 mmol), CH_2Cl_2 (20 ml), and **13** (120 mg, 0.71 mmol); reaction time: 16 h. Chromatography (SiO_2; AcOEt/hexane 1:1) gave 55 mg (18%) of **10**. Yellow, thick oil that solidified under h.v. IR (KBr): 3361*s*, 3026*w*, 2982*w*, 2935*w*, 2914*w*, 2836*m*, 2810*w*, 1671*s*, 1594*w*, 1586*w*, 1506*s*, 1490*s*, 1453*m*, 1437*m*, 1383*m*, 1366*s*, 1356*w*, 1284*w*, 1257*m*, 1210*w*, 1166*w*, 1099*s*, 1073*m*, 1024*w*, 1004*w*, 993*w*, 968*w*, 919*w*, 772*m*, 744*s*, 736*m*, 704*s*, 696*s*. ^{1}H-NMR: 7.76 (br. *s*, NH); 7.35–7.13 (*m*, 15 arom. H); 3.66 (*s*, MeN); 3.50 (*s*, 2 PhC*H*$_2$); 2.87 (*s*, CH_2(Gly)); 1.57 (*s*, Me_2C(Aib^t)). ^{13}C-NMR: 208.5 (*s*, CS(Aib^t)); 169.5 (*s*, CO(Gly)); 147.7, 137.9 (2*s*, 3 arom. C); 129.1, 129.0, 128.4, 128.1, 127.3, 125.9 (6*d*, 15 arom. C); 62.4 (*s*, C(α)(Aib^t)); 58.9, 58.8 (2*t*, 2 PhC*H*$_2$), CH_2(Gly)); 50.9 (*q*, MeN); 29.8 (*q*, *Me*$_2$C(Aib^t)). CI-MS: 448 (8), 447 (31), 446 (100, [M+1]$^+$). Anal. calc. for $C_{27}H_{31}N_3OS \cdot 0.25\ H_2O$ (450.13): C 72.05, H 7.05, N 9.34, S 7.12; found: C 72.08, H 7.16, N 9.32, S 7.12.

Attempted Isomerization. According to the *GP B*, with **10** (55 mg, 0.12 mmol), AcOH (1.5 ml), $ZnCl_2$ (520 mg, 3.82 mmol), and 2.1M HCl in AcOH (0.35 ml) (t_1 = 10 min, t_2 = 5 min). Chromatography (SiO_2; AcOEt/hexane 1:1) yielded 48 mg (87%) of **10**. No other product could be detected.

4. *Isobutyl* N-*Benzyl*-N-*[2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)-2-thioxoethyl]carbamate* (*N*-Bn-*N*-^{i}BuOCO-Gly-ψ(CS)-Aib-N(Me)Ph, **17a**). *Isobutyl* N-*Benzyl*-N-*[2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino)-2-oxoethyl]carbamate* (*N*-Bn-*N*-^{i}BuOCO-Gly-Aib-ψ(CS)-N(Me)Ph, **16a**). According to the *GP A*, with Bn-Gly (180 mg, 0.89 mmol), THF/DMSO 2:1 (15 ml), NMM (0.32 ml,

2.67 mmol), ^{i}BuOCOCl (0.23 ml, 1.69 mmol), $Na_2S \cdot H_2O$ (2.18 g, 14.88 mmol), CH_2Cl_2 (10 ml), and **13** (155 mg, 0.89 mmol); reaction time: 3 h. Chromatography (SiO_2; AcOEt/hexane 1:1) gave 83 mg (24%) of **16a**. Yellow, thick oil that solidified under h.v. IR (KBr): 3650*w*, 3629*w*, 3324*m*, 3062*w*, 3029*w*, 2960*m*, 2934*m*, 2873*w*, 1703*s*, 1594*w*, 1509*m*, 1493*s*, 1464*s*, 1431*s*, 1387*m*, 1368*s*, 1283*m*, 1232*s*, 1185*m*, 1119*m*, 1102*s*, 1074*w*, 1004*m*, 958*w*, 773*m*, 733*w*, 701*m*, 652*w*, 628*w*. ^{1}H-NMR: 7.68 (br. *s*, NH); 7.44–7.19 (*m*, 10 arom. H); 4.56 (*s*, PhCH_2); 4.11 (*d*, $J = 7.1$, CH_2O); 3.71 (*s*, MeN); 3.62 (*s*, CH_2(Gly)); 1.99–1.88 (*m*, Me_2CH); 1.55 (br. *s*, Me_2C(Aib^t)); 0.91 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 208.7 (*s*, CS(Aib^t)); 170.0 (*s*, CO(Gly)); 155.1 (*s*, CO(carbamate)); 147.3, 136.9 (2*s*, 2 arom. C); 129.4, 128.6, 128.4, 127.5, 126.4 (5*d*, 10 arom. C); 72.2 (*t*, CH_2O); 62.6 (*s*, C(α)(Aib^t)); 51.3, 50.8 (2*t*, CH_2(Gly)), PhCH_2); 29.1 (*q*, Me_2C(Aib^t)); 27.9 (*d*, Me_2CH); 19.0 (*q*, Me_2CH); MeN could not be detected (probably hidden by CH_2(Gly) or PhCH_2). ESI-MS: 933 ($[2M + Na]^+$), 510 ($[M + Na + MeOH]^+$), 494 ($[M + K]^+$), 483, 478 ($[M + Na]^+$), 456 ($[M + 1]^+$, 349 ($[M - (Me(Ph)N)]^+$). Anal. calc. for $C_{25}H_{33}N_3O_3S \cdot 0.25\ H_2O$ (460.12): C 65.26, H 7.34, N 9.13, S 6.97; found: C 65.21, H 7.45, N 8.93, S 6.74.

N-*Bn*-N-*^{i}BuOCO-Gly-ψ(CS)-Aib-N(Me)Ph* (**17a**). According to the *GP B*, with **16a** (88 mg, 0.248 mmol), AcOH (7 ml), $ZnCl_2$ (1040 mg, 7.64 mmol), and 0.7 ml of 2.1M HCl in AcOH ($t_1 = 10$ min, $t_2 = 5$ min). Chromatography (SiO_2; AcOEt/hexane 1:1) gave 71 mg (81%) of **17a**. Thick oil that solidified under h.v. IR (KBr): 3434*w*, 3229*s*, 3050*m*, 2960*m*, 2873*m*, 2658*w*, 1706*s*, 1627*s*, 1591*s*, 1553*m*, 1494*s*, 1439*s*, 1414*s*, 1392*s*, 1359*s*, 1331*m*, 1229*s*, 1157*w*, 1117*s*, 1091*s*, 1002*m*, 978*w*, 932*w*, 908*w*, 876*w*, 806*w*, 767*m*, 754*m*, 704*s*, 644*w*, 619*w*. ^{1}H-NMR: 8.41 (br. *s*, NH); 7.40–7.22 (*m*, 10 arom. H); 4.49 (*s*, PhCH_2); 3.93–3.91 (*m*, CH_2(Gly^t)), CH_2O); 3.25 (*s*, MeN); 1.92 (*sept.*, $J = 6.7$, Me_2CH); 1.61 (*s*, Me_2C(Aib)); 0.90 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 197.2 (*s*, CS(Gly^t)); 171.5 (*s*, CO(Aib)); 156.9 (*s*, CO(carbamate)); 144.2, 136.7 (2*s*, 2 arom. C); 129.2, 128.6, 128.0, 127.6, 127.4 (5*d*, 10 arom. C); 72.5 (*t*, CH_2O); 61.4 (*s*, C(α)(Aib)); 60.0 (*t*, CH_2(Gly^t)); 51.5 (*t*, PhCH_2); 41.0 (*q*, MeN); 28.0 (*d*, Me_2CH); 25.2, 24.4 (2*q*, Me_2C(Aib)); 19.0 (*q*, Me_2CH). ESI-MS: 478 ($[M + Na]^+$), 349 ($[M - (Me(Ph)N)]^+$). Anal. calc. for $C_{25}H_{33}N_3O_3S \cdot 0.25\ H_2O$ (460.12): C 65.26, H 7.23, N 9.13, S 6.97; found: C 65.37, H 7.63, N 9.15, S 6.76.

5. *Isobutyl* N-*Methyl*-N-*[(S)-1-methyl-(2-{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)-2-thioxoethyl]carbamate* (*N*-Me-*N*-^{i}BuOCO-Ala-ψ(CS)-Aib-N(Me)Ph, **17b**). *Isobutyl* N-*Methyl*-N-*[(S)-1-methyl-(2-{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino)-2-oxoethyl]carbamate* (*N*-Me-*N*-^{i}BuOCO-Ala-Aib-ψ(CS)-N(Me)Ph, **16b**). According to the *GP A*, with Me-Ala (328 mg, 3.17 mmol), THF/DMSO 1:1 (20 ml), NMM (0.72 ml, 6.36 mmol), ^{i}BuOCOCl (0.88 ml, 6.67 mmol), $Na_2S \cdot H_2O$ (7.78 g, 53 mmol), CH_2Cl_2 (25 ml), and **13** (550 mg, 3.17 mmol); reaction time: 20 h. Chromatography (SiO_2; AcOEt/hexane 1:3) gave 134 mg (11%) of **16b**. Yellow, thick oil that solidified under h.v. IR ($CDCl_3$): 3667*w*, 3442*w*, 3226*w*, 3007*m*, 2967*m*, 2875*m*, 1686*s*, 1594*m*, 1493*s*, 1464*s*, 1403*m*, 1386*m*, 1370*s*, 1317*m*, 1297*m*, 1170*m*, 1100*m*, 1004*w*, 986*w*, 972*w*, 919*w*, 838*w*, 693*w*, 658*w*. ^{1}H-NMR: 7.46–7.19 (*m*, 5 arom. H); 7.11 (br. *s*, NH); 4.37 (*q*, $J = 7.0$, CH(α)(Ala)); 3.95–3.86 (*m*, CH_2O); 3.72 (*s*, MeN); 2.78 (*s*, MeN(Ala)); 1.95 (*sept.*, $J = 6.8$, Me_2CH); 1.63, 1.52 (2*s*, Me_2C(Aib^t)); 1.26 (*d*, $J = 7.0$, Me(β)(Ala)); 0.94 (*d*, $J = 6.8$, Me_2CH). ^{13}C-NMR: 209.0 (*s*, CS(Aib^t)); 169.2 (*s*, CO(Ala)); 157.0 (*s*, CO(carbamate); 147.6 (*s*, 1 arom. C); 129.3, 128.3, 126.2 (3*d*, 5 arom. C); 71.9 (*t*, CH_2O); 62.7 (*s*, C(α)(Aib^t)); 54.6 (*q*, CH(α)(Ala)); 51.0 (*q*, MeN); 29.2 (*q*, Me_2C(Aib^t)); 27.9 (*d*, Me_2CH); 18.9 (*q*, Me_2CH); 13.2 (*q*, Me(β)(Ala)); MeN(Ala) could not be detected. ESI-MS: 432 ($[M + K]^+$), 425 ($[M + MeOH]^+$), 416 ($[M + Na]^+$), 394 ($[M + 1]^+$), 287 ($[M - (Me(Ph)N)]^+$), 185. Anal. calc. for $C_{20}H_{31}N_3O_3S \cdot 0.25\ H_2O$ (398.05): C 60.35, H 7.98, N 10.56, S 8.06; found: C 60.42, H 8.16, N 10.46, S 7.53.

N-*Me*-N-*^{i}BuOCO-Ala-ψ(CS)-Aib-N(Me)Ph* (**17b**). According to the *GP B*, with **16b** (29 mg, 0.074 mmol), AcOH (0.8 ml), $ZnCl_2$ (366 mg, 2.69 mmol), and 0.08 ml of 2.1M HCl in AcOH ($t_1 = 1.5$ min, $t_2 = 1$ min) gave, without further purification, 28 mg (96%) of **17b**. Thick oil which solidified under h.v. IR (KBr): 3233*s*, 3061*m*, 2963*m*, 2875*w*, 1696*s*, 1631*s*, 1592*m*, 1560*m*, 1493*s*, 1465*s*, 1436*s*, 1283*m*, 1262*w*, 1238*w*, 1167*s*, 1094*m*, 1078*m*, 1042*m*, 1002*w*, 986*w*, 774*m*, 739*w*, 712*m*. ^{1}H-NMR: 8.18 (br. *s*, NH); 7.39–7.18 (*m*, 5 arom. H); 4.36 (br. *m*, CH(α)(Ala^t)); 3.94–3.75 (*m*, CH_2O); 3.25 (*s*, MeN); 2.76 (*s*, MeN(Ala^t)); 1.91 (*sept.*, $J = 6.7$, Me_2CH); 1.69, 1.59 (2*s*, Me_2C(Aib)); 1.39 (*d*, $J = 7.0$, Me(β)(Ala^t)); 0.91 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 200.7 (*s*, CS(Ala^t)); 171.2 (*s*, CO(Aib)); 157.1 (*s*, CO(carbamate)); 147.3 (*s*, 1 arom. C); 129.0, 127.9, 127.1 (3*d*, 5 arom. C); 72.1 (*t*, CH_2O); 60.9 (*s*, CH(α)(Ala^t)); 41.2 (*q*, MeN); 29.1 (*q*, MeN(Ala^t)); 27.9 (*d*, Me_2CH); 24.4 (*q*, Me_2C(Aib)); 18.9 (*q*, Me_2CH); 16.1 (*q*, Me(β)(Ala^t)). ESI-MS: 809 ($[2M + Na]^+$), 432 ($[M + K]^+$), 416 ($[M + Na]^+$), 287 ($[M - (Me(Ph)N)]^+$). Anal. calc. for $C_{25}H_{33}N_3O_3S \cdot 0.2\ H_2O$ (397.15): C 60.49, H 7.97, N 10.58, S 8.07; found: C 60.77, H 7.89, N 10.13, S 8.13.

6. N-*{(S)-1-Benzyl-[2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)-2-thioxoethyl]}benzamide* (Bz-Phe-ψ(CS)-Aib-N(Me)Ph, **17c**). N-*{(S)-1-Benzyl-[2-({1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino)-2-oxoethyl]}benzamide* (Bz-Phe-Aib-ψ(CS)-N(Me)Ph, **16c**). According to the *GP A*, with Bz-Phe (173 mg, 0.64 mmol), THF (10 ml), NMM (0.23 ml, 1.28 mmol), ^{i}BuOCOCl (0.18 ml, 1.34 mmol),

$Na_2S \cdot H_2O$ (1.57 g, 6.42 mmol), CH_2Cl_2 (10 ml), and **13** (112 mg, 0.64 mmol); reaction time: 18 h. Chromatography (SiO_2; AcOEt/hexane 1:2), followed by recrystallization from CH_2Cl_2/hexane gave 74 mg (25%) of **16c**. Yellow solid. M.p. 174–175°. IR (KBr): 3255*m*, 3062*m*, 2925*w*, 1664*s*, 1632*s*, 1602*m*, 1578*m*, 1538*s*, 1491*s*, 1455*m*, 1375*m*, 1360*m*, 1317*m*, 1279*m*, 1189*w*, 1103*m*, 1074*w*, 1061*w*, 1029*w*, 773*w*, 762*w*, 748*w*, 696*s*, 668*w*. ^{1}H-NMR: 7.72–6.98 (*m*, 15 arom. H, NH); 6.41 (br. *s*, NH); 4.30 (*q*, $J = 7.2$, CH(α)(Phe)); 3.57 (*s*, MeN); 3.14–2.86 (*m*, H_2C(β)(Phe)); 1.55, 1.34 (2*s*, Me_2C(Aib^t)). ^{13}C-NMR: 206.9 (*s*, CS(Aib^t)); 167.7 (*s*, CO(Phe)); 165.7 (*s*, CO(benzoyl)); 146.4, 135.8, 132.9 (3*s*, 3 arom. C); 130.8, 128.5, 127.6, 127.4, 126.0, 124.9 (6*d*, 15 arom. C); 61.7 (*s*, C(α)(Aib^t)); 53.8 (*d*, CH(α)(Phe)); 50.0 (*q*, MeN); 37.4 (*t*, CH_2(β)(Phe)); 28.9 (*q*, *Me*$_2$C(Aib^t). CI-MS: 462 (8), 461 (30), 460 (100, $[M+1]^+$), 353 (3, $[M-(Me(Ph)N)]^+$). Anal. calc. for $C_{27}H_{29}N_3O_2S \cdot H_2O$ (477.64): C 67.90, H 6.54, N 8.80, S 6.71; found: C 68.16, H 6.30, N 8.76, S 6.48.

Bz-Phe-ψ(CS)-Aib-N(Me)Ph (**17c**). According to the *GP B*, with **16c** (30 mg, 0.065 mmol), AcOH (2 ml), $ZnCl_2$ (274 mg, 2.01 mmol), and 0.2 ml of 2.1M HCl in AcOH ($t_1 = 10$ min, $t_2 = 5$ min). Chromatography (SiO_2; AcOEt/hexane 1:1) gave 28 mg (94%) of **17c**. Yellow solid. M.p. 176–177°. IR (KBr): 3218*m*, 3055*m*, 2927*w*, 1629*s*, 1592*m*, 1514*s*, 1490*s*, 1433*s*, 1396*m*, 1362*m*, 1286*m*, 1234*w*, 1173*w*, 1093*m*, 1072*w*, 1028*w*, 992*w*, 874*w*, 802*w*, 734*w*, 704*s*, 648*w*. ^{1}H-NMR: 7.77–7.09 (*m*, 15 arom. H, 2 NH); 4.51 (*m*, CH(α)(Phe^t)); 3.24–2.79 (*m*, H_2C(β)(Phe^t)); 3.11 (*s*, MeN); 1.44, 1.21 (2*s*, Me_2C(Aib)). ^{13}C-NMR: 199.8 (*s*, CS(Phe^t)); 170.7 (*s*, CO(Aib)); 165.9 (*s*, CO(benzoyl)); 143.8, 136.6, 133.9 (3*s*, 3 arom. C); 131.8, 129.4, 129.1, 128.6, 128.1, 127.2, 126.9 (7*d*, 15 arom. C); 61.4 (*s*, C(α)(Aib)); 60.6 (*d*, CH(α)(Phe^t)); 42.2 (*t*, CH_2(β)(Phe^t)); 40.7 (*q*, MeN); 26.6, 24.0 (2*q*, *Me*$_2$C(Aib). CI-MS: 353 (100, $[M-(Me(Ph)N)]^+$). ESI-MS: 941 ($[2M+Na]^+$), 867, 727, 482 ($[M+Na]^+$), 362.

7. *(2S,3S)-2-Amino*-N-*{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}-3-methylpentanamide* (Ile-Aib-ψ(CS)-N(Me)Ph, **18a**). A soln. of Fmoc-Ile-Aib-ψ(CS)-N(Me)Ph [30] (**3c**, 89 mg, 0.164 mmol) in MeCN (2 ml) was treated with Et_2NH (0.3 ml). After 17 h stirring at r.t., additional Et_2NH (0.2 ml) was added. After another 4 h, the intensely yellow soln. was concentrated and dried under h.v. Chromatography (SiO_2; AcOH/hexane 2:1) gave 43 mg (82%) of **18a**. Thick oil that solidified under h.v. IR (KBr): 3853*w*, 3259*m*, 2963*s*, 2931*m*, 2875*m*, 2360*w*, 1662*s*, 1593*m*, 1492*s*, 1463*s*, 1369*s*, 1281*m*, 1187*m*, 1168*m*, 1102*s*, 1074*m*, 1024*w*, 1004*w*, 972*w*, 776*w*, 706*m*, 652*w*, 617*w*. ^{1}H-NMR: 7.51 (*s*, NH); 7.43–7.15 (*m*, 5 arom. H, 2 NH); 3.71 (*s*, MeN); 2.90 (*d*, $J = 3.8$, CH(α)(Ile)); 1.89–0.75 (*m*, CH(β)(Ile), CH_2(γ^1)(Ile)); 1.78, 1.63 (2*s*, Me_2C(Aib^t)); 0.89–0.75 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 208.5 (*s*, CS(Aib^t)); 171.8 (*s*, CO(Ile)); 147.8 (*s*, 1 arom. C); 129.3, 128.0, 125.6 (3*d*, 5 arom. C); 62.5 (*s*, C(α)(Aib^t)); 59.5 (*d*, CH(α)(Ile)); 51.1 (*q*, MeN); 38.2 (*d*, CH(β)(Ile)); 30.1, 29.9 (2*q*, *Me*$_2$C(Aib^t)); 24.0 (*t*, CH_2(γ^1)(Ile)); 15.7, 11.7 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). ESI-MS: 376 ($[M+MeOH+Na]^+$), 322 ($[M+1]^+$).

Attempted Isomerization. According to the *GP B*, with **18a** (37 mg, 0.115 mmol), AcOH (2 ml), $ZnCl_2$ (650 mg, 4.77 mmol), and 2.1M HCl in AcOH (0.2 ml) ($t_1 = 30$ min, $t_2 = 20$ min). Chromatography (SiO_2, AcOEt/hexane 2:1) led to 34 mg (81%) recovered **18a**.

8. *(2S,3S)*-N-*{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}-3-methyl-2-(prop-2-enyl)pentanamide* (Allyl-Ile-Aib-ψ(CS)-N(Me)Ph, **18b**). To a soln. of **18a** (264 mg, 0.82 mmol) in MeOH (30 ml), allyl bromide (0.21 ml, 2.47 mmol) and Et_3N (0.34 ml, 2.47 mmol) were added. After 19 h stirring under reflux, the soln. was concentrated, dissolved in Et_2O and washed with H_2O. The org. phase was dried ($MgSO_4$), filtered, the solvent was evaporated, and the residue was dried under h.v. Chromatography (SiO_2; AcOEt/hexane 1:1) gave 71 mg (25%) of **18b**. Yellow, thick oil. In addition, 28 mg (11%) of the starting material **18a** was recovered. IR ($CHCl_3$): 3668*w*, 3325*w*, 3228*w*, 3080*w*, 2967*s*, 2933*m*, 2876*m*, 2463*w*, 2385*w*, 1716*s*, 1660*s*, 1594*w*, 1492*s*, 1464*s*, 1369*s*, 1261*m*, 1170*w*, 1155*w*, 1100*s*, 1004*m*, 994*m*, 924*w*, 811*w*, 658*w*. ^{1}H-NMR: 8.64 (*s*, NH); 7.45–7.23 (*m*, 5 arom. H, NH); 5.94–5.82 (*m*, CH_2=C*H*CH$_2$); 5.17–5.08 (*m*, C*H*$_2$=CHCH$_2$); 3.73 (*s*, MeN); 3.26–3.10 (*m*, CH_2=CHC*H*$_2$); 2.85 (*d*, $J = 4.5$, CH(α)(Ile)); 1.87–0.86 (*m*, CH(β)(Ile), CH_2(γ^1)(Ile)); 1.57, 1.54 (2*s*, Me_2C(Aib^t)); 0.94–0.86 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 209.5 (*s*, CS(Aib^t)); 171.8 (*s*, CO(Ile)); 147.6 (*s*, 1 arom. C); 136.5 (*d*, CH_2=*C*HCH$_2$); 129.3, 128.0, 125.6 (3*d*, 5 arom. C); 116.0 (*t*, *C*H$_2$=CHCH$_2$); 67.1 (*d*, CH(α)(Ile)); 62.7 (*s*, C(α)(Aib^t)); 51.5 (*t*, CH_2=CH*C*H$_2$); 51.1 (*q*, MeN); 38.0 (*d*, CH(β)(Ile)); 28.3 (*q*, *Me*$_2$C(Aib^t)); 25.1 (*t*, CH_2(γ^1)(Ile)); 15.9, 11.8 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). CI-MS: 362 (9, $[M+1]^+$), 272 (15, $[M-N(Me)Ph+NH_3]^+$), 271 (100), 255 (19, $[M-(Me(Ph)N)]^+$). Anal. calc. for $C_{20}H_{31}N_3OS \cdot 0.75\ H_2O$ (375.06): C 64.05, H 8.73, N 11.20, S 8.55; found: C 64.31, H 8.68, N 11.02, S 8.62.

Attempted Isomerization. According to the *GP B*, with **18b** (69 mg, 0.191 mmol), AcOH (3 ml), $ZnCl_2$ (1080 mg, 7.92 mmol), and 2.1M HCl in AcOH (0.3 ml) ($t_1 = 30$ min, $t_2 = 20$ min). Chromatography (SiO_2; AcOEt/hexane 1:1) led to 59 mg (86%) recovered **18b**.

9. *(2S,3S)-2-Benzylamino*-N-*{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}-3-methylpentanamide* (Bn-Ile-Aib-ψ(CS)-N(Me)Ph, **18c**). To a soln. of **18a** (121 mg, 0.38 mmol) in MeOH (10 ml), $PhCH_2Br$

(0.06 ml, 0.47 mmol) and Et_3N (0.16 ml, 1.13 mmol) were added. After 18 h stirring under reflux, the soln. was concentrated, dissolved in Et_2O, and washed with H_2O. The org. phase was dried ($MgSO_4$), the solvent was evaporated, and the residue was dried under h.v. Chromatography (SiO_2; AcOEt/hexane 1:3) gave 29 mg (19%) of **18c**. Yellow thick oil. In addition, 30 mg (25%) of the starting material **18a** was recovered. IR ($CHCl_3$): 3684*w*, 3621*w*, 3020*s*, 2976*m*, 1661*s*, 1595*m*, 1515*m*, 1476*m*, 1426*m*, 1370*w*, 1334*w*, 1101*w*, 1046*m*, 928*m*, 877*w*, 626*m*. ^{1}H-NMR: 8.70 (*s*, NH); 7.45–7.23 (*m*, 10 arom. H, NH); 3.82–3.63 (*m*, PhCH_2); 3.73 (*s*, MeN); 2.89 (*d*, $J = 4.6$, CH(α)(Ile)); 1.87–0.83 (*m*, CH(β)(Ile), CH_2(γ^1)(Ile)); 1.56 (*s*, Me_2C(Aib^t)); 0.95–0.83 (*m*, Me(δ)-(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 209.5 (*s*, CS(Aib^t)); 171.9 (*s*, CO(Ile)); 147.6, 139.2 (*s*, 2 arom. C); 129.4, 128.4, 128.3, 127.1, 126.7 (5*d*, 10 arom. C); 67.4 (*d*, CH(α)(Ile)); 62.8 (*s*, C(α)(Aib^t)); 53.2 (*t*, PhCH_2); 51.4 (*q*, MeN); 38.0 (*d*, CH(β)(Ile)); 28.4, 28.3 (2*q*, Me_2C(Aib^t)); 25.2 (*t*, CH_2(γ^1)(Ile)); 15.8, 11.7 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). ESI-MS: 412 ($[M+1]^+$).

Attempted Isomerization. According to the *GP B*, with **18c** (28 mg, 0.0705 mmol), AcOH (1.0 ml), $ZnCl_2$ (400 mg, 2.94 mmol), and 2.1M HCl in AcOH (0.125 ml) ($t_1 = 30$ min, $t_2 = 20$ min). Chromatography (SiO_2; AcOEt/hexane 1:3) led to 17 mg (61%) recovered **18c**.

REFERENCES

[1] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1998**, *54*, 8721.
[2] J. Lehmann, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 888.
[3] J. Lehmann, A. Linden, H. Heimgartner, *Tetrahedron* **1999**, *55*, 5359.
[4] J. Lehmann, H. Heimgartner, *Helv. Chim. Acta* **1999**, *82*, 1899.
[5] M. Schutkowski, M. Jakob, G. Landgraf, I. Born, K. Neubert, G. Fischer, *Eur. J. Biochem*. **1997**, *245*, 381.
[6] D. R. Artis, M. A. Lipton, *J. Am. Chem. Soc*. **1998**, *120*, 12200.
[7] D. Krumme, H. Tschesche, *Tetrahedron* **1999**, *55*, 3007.
[8] T. Hoeg-Jensen, A. Spatola, A. Holm, *Int. J. Pept. Protein Res.* **1996**, *47*, 190.
[9] H.-T. Le, J.-F. Gallars, M. Mayer, E. Guittet, R. Michelot, *Bioorg. Med. Chem. Lett*. **1996**, *4*, 2201.
[10] S. Yao, R. Zutshi, J. Chmielewski, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 699.
[11] T. Sifferlen, M. Rueping, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2067.
[12] C. T. Brain, A. Hallett, S. Y. Ko, *Tetrahedron Lett*. **1998**, *39*, 127.
[13] S. Alibert, D. Crestia, F. Dujuls, M. Mulliez, *Tetrahedron Lett*. **1998**, *39*, 8844.
[14] M. A. Shalaby, C. W. Grote, H. Rapoport, *J. Org. Chem*. **1996**, *61*, 9045.
[15] C. T. Brain, A. Hallett, S. Y. Ko, *J. Org. Chem*. **1997**, *62*, 3008.
[16] S. Vijayalakshmi, R. Balaji Rao, I. L. Karle, P. Balaram, *Biopolymers* **2000**, *53*, 84.
[17] A. Jaworski, J. Kirschbaum, H. Brückner, *J. Pept. Science* **1999**, *5*, 341.
[18] S. J. Lee, W. H. Yeo, B. S. Yun, I. D. Yoo, *J. Pept. Science* **1999**, *5*, 374.
[19] W. Mayr, G. Jung, J. Stähle, *Liebigs Ann. Chem*. **1980**, 715.
[20] M. T. Leplawy, D. S. Jones, G. W. Kenner, R. C. Sheppard, *Tetrahedron* **1960**, *11*, 39.
[21] H. Wenschuh, M. Beyermann, H. Haber, J. K. Seydel, E. Krause, M. Bienert, *J. Org. Chem*. **1995**, *60*, 405.
[22] H. Heimgartner, *Angew. Chem., Int. Ed*. **1991**, *30*, 238.
[23] C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1995**, *78*, 935.
[24] C. B. Bucher, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 1903.
[25] R. Luykx, C. B. Bucher, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1996**, *79*, 527.
[26] C. Strässler, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **1997**, *80*, 1528.
[27] D. Obrecht, H. Heimgartner, *Chimia* **1982**, *36*, 78.
[28] A. Bärtsch, Diploma thesis, Universität Zürich, 1984.
[29] P. Wipf, Ph. D. thesis, Universität Zürich, 1987.
[30] J. P. Lehmann, Ph. D. thesis, Universität Zürich, 1998.
[31] G. L. Rowley, G. L. Kenyon, *J. Heterocycl. Chem*. **1972**, *9*, 203.

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