A Novel Acid-Catalyzed Isomerization of Aib-Containing Thiodipeptides[1])

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Dedicated to Prof. *André S. Dreiding* on the occasion of his 80th birthday

The use of amino thioacids in the 'azirine/oxazolone method' led to completely epimerized Aib-containing endothiodipeptides (Aib = 2-aminoisobutyric acid). It could be established that the epimerization occurred during the acidic hydrolysis of the primarily formed dipeptide thioanilides in which the thiocarbonyl group was shifted from the last to the penultimate amino-acid residue. Several conditions for the hydrolysis were tested, and, in some of them, the degree of epimerization could be reduced. By treatment of the Aib-containing dipeptide thioanilides **21** with $ZnCl_2$ in AcOH followed by HCl in AcOH, the isomeric endothiodipeptide anilides **25** were formed, *i.e.*, the thiocarbonyl group was again shifted from the last to the penultimate amino acid residue. Under optimized reaction conditions, this novel isomerization proceeded in high yields and without any epimerization. Two conceivable mechanisms are proposed in *Scheme 12*. X-Ray diffraction analyses were performed for Z–Gly–Aib-Ψ(CS)–N(Me)Ph (**21f**) and the isomeric Z–Gly-Ψ(CS)–Aib–N(Me)Ph (**25f**).

Introduction. – Peptides containing α-alkylated α-amino acids are of considerable interest because the twofold substitution at the C(α)-atom in these amino acids restricts the conformational flexibility and stabilizes or induces helices (*cf.* [1–4] and refs. cit. therein). For instance, the peptaibols, an important family of natural antibiotics that alter the ion permeability of biological membranes by forming channels, are characterized by a high content of two of these amino acids, namely Aib (2-aminoisobutyric acid) and Iva (isovaline) [5][6]. Due to the severe steric hindrance in these α-alkylated α-amino acids, the synthesis of related peptides is difficult [7–9]. With the 'azirine/oxazolone method', we developed a convenient synthetic access to such peptides, and 2*H*-azirin-3-amines proved to be useful synthons for the introduction of α-alkylated α-amino acids (*cf.* [10–13] and refs. cit. therein).

Other backbone-modified peptides of considerable interest are the endothiopeptides with one or more thioamide groups instead of amide groups within the peptide chain. Endothio analogues of biologically active peptides can show protease resistance, thus allowing higher bioavailability [14]. In addition, enhanced biological activity [15] and receptor selectivity [16] can be expected. A series of recently published synthetic approaches to endothiopeptides document the significance and current interest in these modified peptides [17–26].

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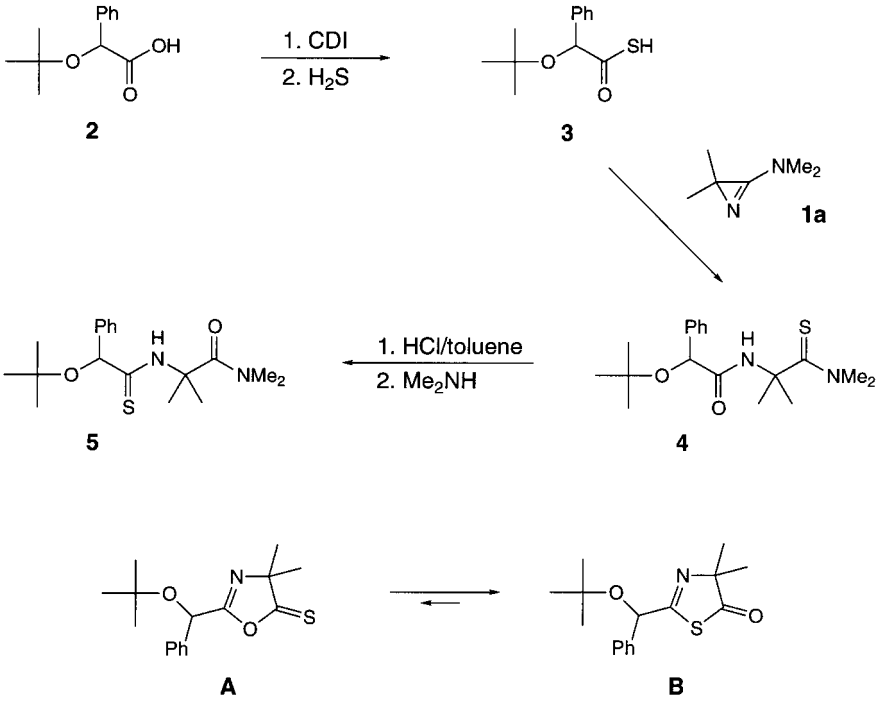
[1]) Presented as a short lecture at the 'Fall Meeting 1997 of the New Swiss Chemical Society' in Lausanne and as a poster at the '10th European Symposium on Organic Chemistry 1997' in Basel.

[2]) Part of the Ph. D. Thesis of *J.L.*, Universität Zürich, 1998; present address: Department of Chemistry, University of California at Berkeley, CA 94720, USA.

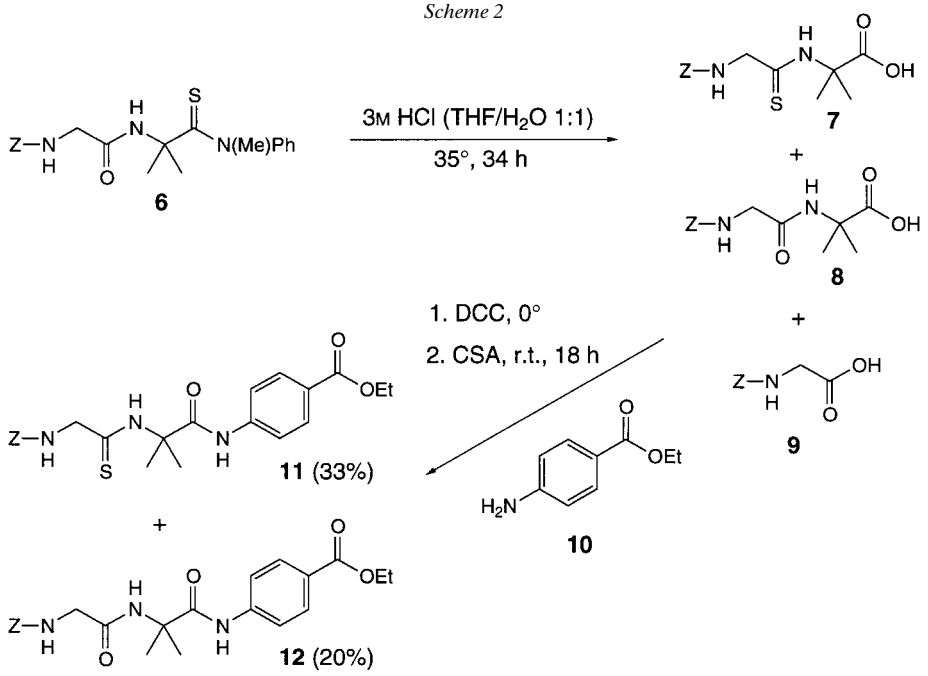
The reaction of 2*H*-azirin-3-amines with amino thiocarboxylic acids could offer a possibility to prepare peptides with a combination of these two backbone modifications. First attempts in this field were made by the treatment of thiobenzoic acid with *N*,*N*,2,2-tetramethyl-2*H*-azirin-3-amine (**1a**) [27]. Further experiments were carried out with *O*-(*tert*-butyl) DL-thiomandelic acid (**3**), prepared from *O*-(*tert*-butyl)-DL-mandelic acid (**2**) by activation with 1,1′-carbonyldiimidazole (= 1,1′-carbonylbis[1*H*-imidazole]; CDI) and subsequent treatment with H_2S (*Scheme 1*) [28]. Reaction of crude **3** with **1a** in MeCN at 0° → room temperature led to the thioamide **4** in 74% yield with respect to **2**. Sequential treatment of a solution of **4** in toluene with HCl (gas) and Me_2NH gave the isomeric thioamide **5** in 53% yield. Several control experiments have shown that the isomerization of **4** to **5** occurred *via* initial formation of 1,3-oxazole-5(4*H*)-thione **A** which rearranged to the 1,3-thiazol-5(4*H*)-one **B** [27][28]. The latter could be isolated in 60% yield; ring opening with Me_2NH then yielded **5**.

Scheme 1



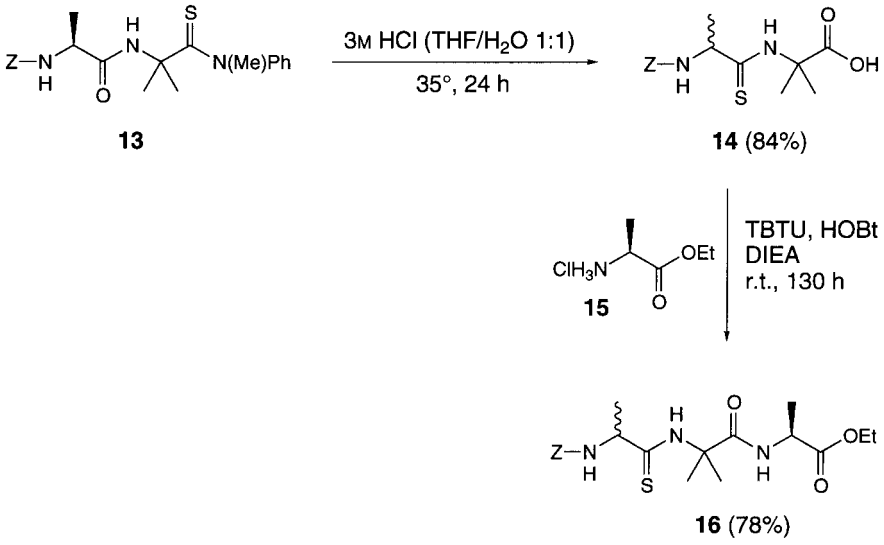
In addition, Z–Gly–Aib-Ψ(CS)–N(Me)Ph (**6**), which was obtained by the reaction of Z-thioglycine with *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1b**), was hydrolyzed under the standard conditions of the 'azirine/oxazolone method' (3M HCl, THF/H_2O 1:1, 35°) [29] (*Scheme 2*; Z = (benzyloxy)carbonyl). After 34 h, a mixture of endothiodipeptide **7**, dipeptide **8**, and Z-glycine (**9**) was isolated in a ratio of *ca.* 10:3:1. Treatment of the crude mixture with *N*,*N*′-dicyclohexylcarbodiimide (DCC) followed by the addition of benzocaine (**10**) and (±)-camphor-10-sulfonic acid (CSA) led to the endothiotripeptide **11** in 33% yield and to **12** in 20% yield.

Scheme 2



Finally, hydrolysis of Z–Ala–Aib-Ψ(CS)–N(Me)Ph (**13**) under the standard conditions of the 'azirine/oxazolone method' gave the endothiodipeptide **14** in 84% yield [30] (*Scheme 3*). The reaction of **14** and **15** with 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as the coupling reagent in the presence

Scheme 3

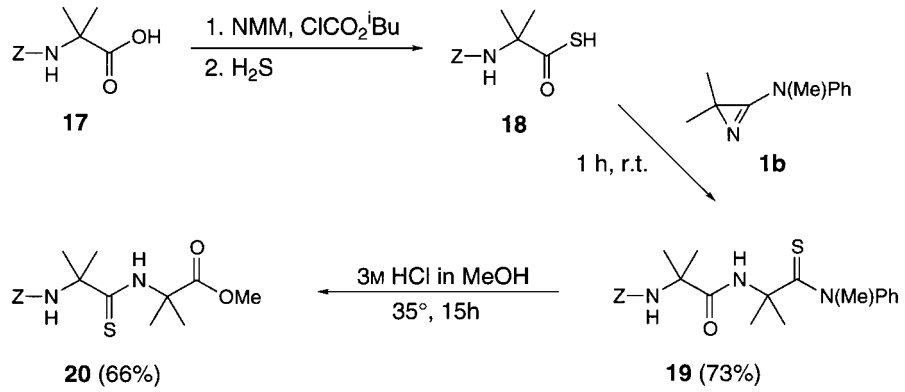


of 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIEA) gave the endothiotripeptide **16** in a yield of 78% after 130 h. As most of the peaks in the NMR spectra of **16** were doubled (even at 95°), it was presumed that two epimers of **16** were formed. Most likely, the hydrolysis of **13** took place with racemization, but also the coupling of **14** and **15** could occur with epimerization (*cf.* [19] and refs. cit. therein).

The present work clarifies these observations, especially the shift of the thiocarbonyl group and the complete racemization during the acidic hydrolysis. In addition, conditions for the specific synthesis of diastereomerically pure endothiopeptides of the type **16** are elaborated.

Results and Discussion. – With the aim of establishing the shift of the thioamide group from the last to the penultimate amino acid residue during the hydrolysis under the standard conditions of the 'azirine/oxazolone method', a methanolysis of Z–Aib–Aib-Ψ(CS)–N(Me)Ph (**19**), prepared from thioacid **18**[3]) and **1b**, was carried out (*Scheme 4*). The dipeptide Aib–Aib was chosen because in this sequence no epimerization during the hydrolysis can occur.

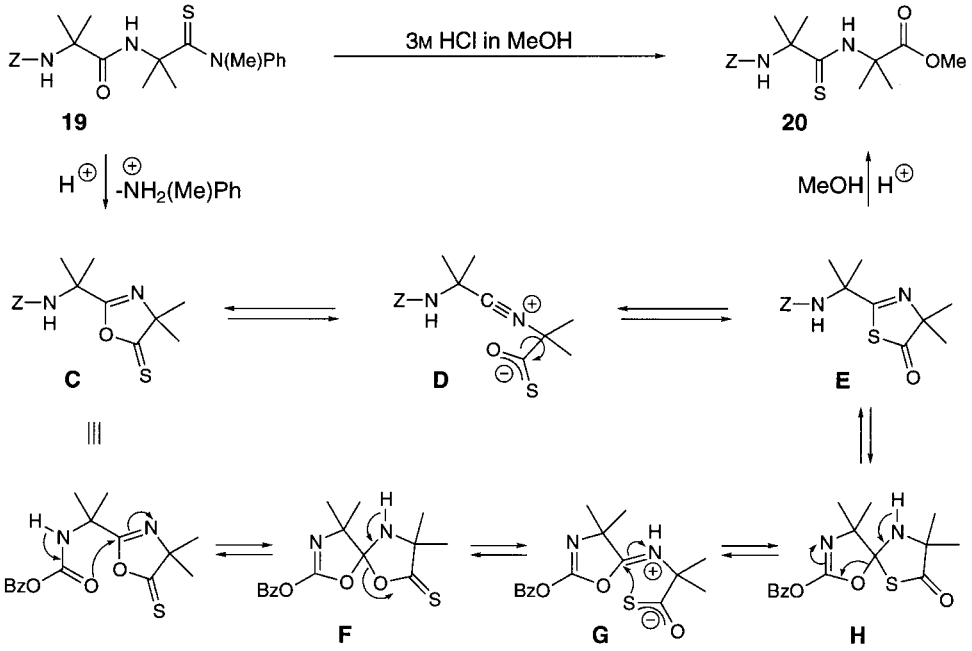
Scheme 4



Treatment of **19** with 3M HCl in MeOH led to **20** as the only product in 66% yield. The long-range HMBC NMR experiments on **20** showed a coupling of the thiocarbonyl C-atom (203.8 ppm) with the Me protons of one of the Aib units (1.69 ppm), however none with the Me protons of the ester group (3.70 ppm). On the other hand, the carbonyl C-atom (171.7 ppm) showed a coupling with the Me protons of an Aib unit (1.62 ppm) and with those of the ester. Therefore, the thiocarbonyl group is situated at the position shown in *Scheme 4*. This exchange of the S- and O-atoms can be explained as proposed in *Scheme 5:* nucleophilic attack of the amide O-atom at the C-atom of the activated thioamide group and elimination of *N*-methylaniline yields the unstable 1,3-oxazole-5(4*H*)-thione **C** (*cf.* [27]), which, *via* ring opening, gives the dipolar, open-chain species **D**. Rotation around the former C(4)–C(5) bond of **C** and ring closure by

[3]) The acid Z–Aib (**17**) was transformed into the thioacid **18** *via* the reaction of the mixed anhydride of **17** and isobutyl chloroformate (= isobutyl carbonochloridate) with H_2S. The crude **18** was then treated with 2*H*-azirin-3-amine **1b** to yield thioamide **19** in 73% yield with respect to **17**.

Scheme 5



nucleophilic attack of the S-atom at the nitrilium group gives the more stable 1,3-thiazol-5(4*H*)-one **E**. Finally, nucleophilic addition of MeOH and ring opening leads to **20**. The isomerization of **C** to **E** may also conceivably proceed *via* the spirocyclic intermediates **F** and **H**, formed by participation of the (benzyloxy)carbonyl group[4]).

To support the assumption of an epimerization during the acid-catalyzed hydrolysis, Z–Ile–Aib-Ψ(CS)–N(Me)Ph (**21a**) was treated under the standard conditions used in the hydrolysis by the 'azirine/oxazolone method'. Because there are two chiral C-atoms in Ile, the epimerization could be directly observed by NMR spectroscopy. The dipeptidethioamide **21a** was prepared analogously to the procedure illustrated in *Scheme 4* in 71% yield with respect to Z–Ile. The acid-catalyzed hydrolysis (3M HCl, THF/H_2O 1:1) at 35° required seven days for completion (*Scheme 6*). As expected, a complete epimerization at the C(α)-atom of Ile was observed by the doubling of most of the peaks in the ^{1}H-NMR spectrum. Furthermore, the two epimers could be partly separated by reversed-phase HPLC. Unfortunately, the splitting of the two peaks was not good enough for a preparative separation. Finally, we succeeded in separating the two epimers preparatively, after converting the endothiopeptides **22** into the corresponding 1,3-thiazol-5(4*H*)-ones **23** *via* formation of the mixed anhydrides and intramolecular attack of the S-atom at the carboxy C-atom (*Scheme 6*).

Presumably, the epimerization involves the intermediate 1,3-thiazol-5(4*H*)-one **23** *via* the mechanism shown in *Scheme 7:* the primarily formed 1,3-thiazol-5(4*H*)-one **23a**

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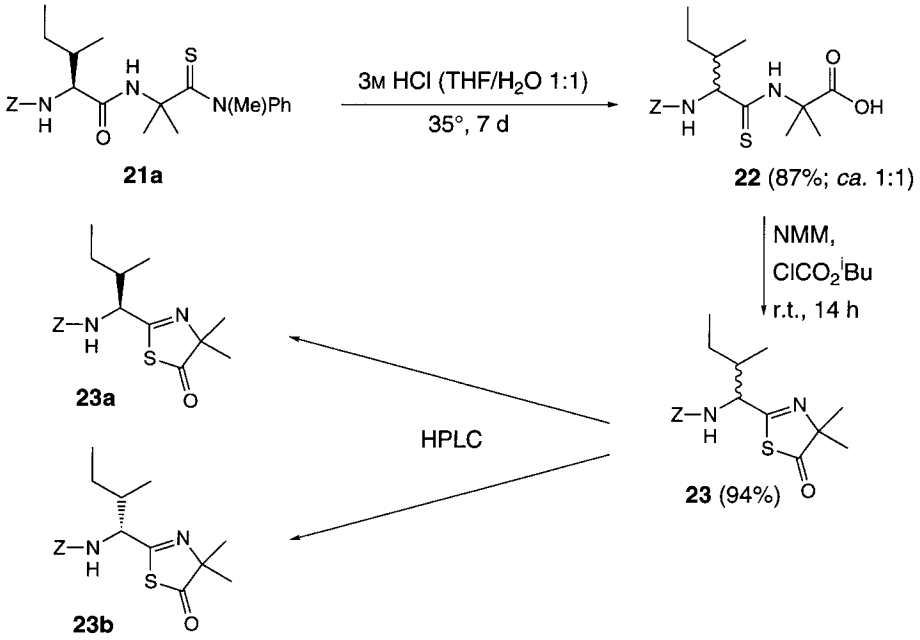
4) Other mechanisms for this transformation can also be formulated. With the aim of establishing the detailed mechanism, further experiments are in progress.

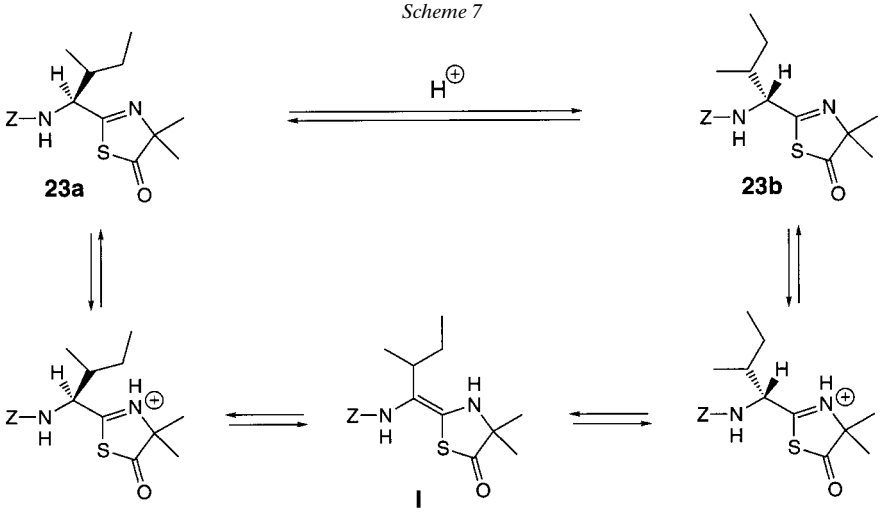
Scheme 6



with the (*S*)-configuration at the C(α) atom of Ile is protonated at the ring N-atom. Abstraction of the α-proton leads to the 2-alkylidene-1,3-thiazolidinone **I**, which affords the epimeric (*R*)-1,3-thiazol-5(4*H*)-one **23b** by reprotonation of the C(α) atom of Ile.

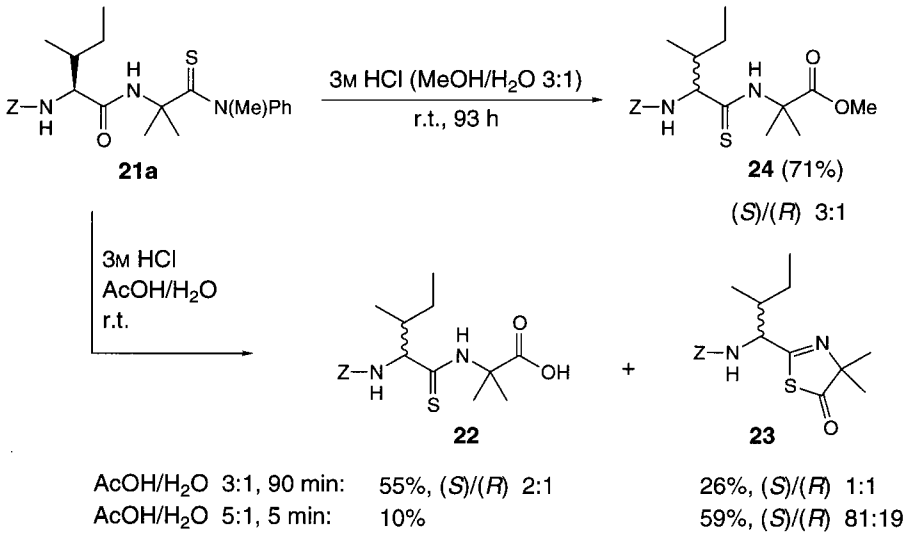
With the intention of finding a way to prevent or to reduce, at least, this epimerization, different reaction conditions were tested for the hydrolysis of thioanilide **21a**. For instance, treatment of Z–Ile–Aib-Ψ(CS)–N(Me)Ph (**21a**) with

Scheme 7



3M HCl (MeOH/H_2O 3:1) led, after 93 h, to the methyl ester **24** in 71% yield (*Scheme 8*). The ratio (*S*)/(*R*) of **24** was determined to be 3:1 (^{1}H-NMR). The shorter reaction time and the lower degree of epimerization compared with the hydrolysis under standard conditions can be explained by the better nucleophilic properties of MeOH and, therefore, faster attack at the primarily formed 1,3-thiazol-5(4*H*)-one.

Scheme 8

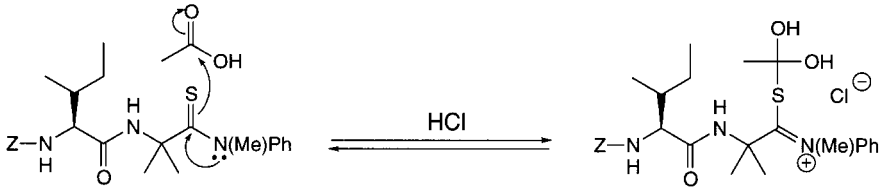


The reaction times were dramatically reduced when the reactions were carried out in the presence of AcOH. Thus, when **21a** was treated with 3M HCl (AcOH/H_2O 3:1), no starting material could be detected after just 90 min. Workup gave Z–Ile–Aib-Ψ(CS)–N(Me)Ph (**22**) in 55% yield as a mixture of epimers (ratio (*S*)/(*R*) 2:1; HPLC) and the completely epimerized 1,3-thiazol-5(4*H*)-one (**23**) in 29% yield. With 3M HCl in AcOH/H_2O 5:1, the reaction time could be shortened to 5 min. Under these conditions, the epimerization was also reduced. Thus, **23** was isolated in 59% yield as a mixture of epimers with a (*S*)/(*R*) ratio of 81:19 (HPLC). In addition, **22** was obtained in 10% yield[5]). A conceivable explanation for the catalytic effect of AcOH is shown in *Scheme 9:* reaction of the thioamide group with AcOH to give **K** results in an increase of the electrophilicity and, therefore, in an easier attack by the O-atom of the amide group.

When a thiopeptide **21** was first treated with 3M $ZnCl_2$ in AcOH and then with AcOH saturated with HCl, the isomeric endothiopeptide **25** was formed in which the thiocarbonyl group had been shifted from the last to the penultimate amino acid (*Table 1*). Depending on the reaction conditions, this reaction also resulted in the epimerization of the penultimate amino acid. For example, if **21a** was first treated with 3M HCl in AcOH for 23 h (t_1), then 2M HCl in AcOH (HCl-saturated AcOH) was added, and the mixture was stirred for 30 min (t_2) at room temperature, the

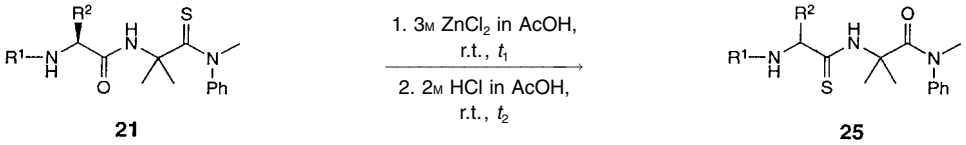
[5]) In this case, the ratio of epimers was not determined.

Scheme 9



endothiopeptide **25a** was isolated in 84% yield as a 100:44 mixture of epimers. Fortunately, the epimerization could be reduced by shortening the reaction time t_1. For instance, in the case of **21a**, no epimerization could be detected (HPLC) when t_1 was 20 min and t_2 30 min (*Table 1*).

Table 1. *Novel Acid-Catalyzed Isomerization* **21** → **25**



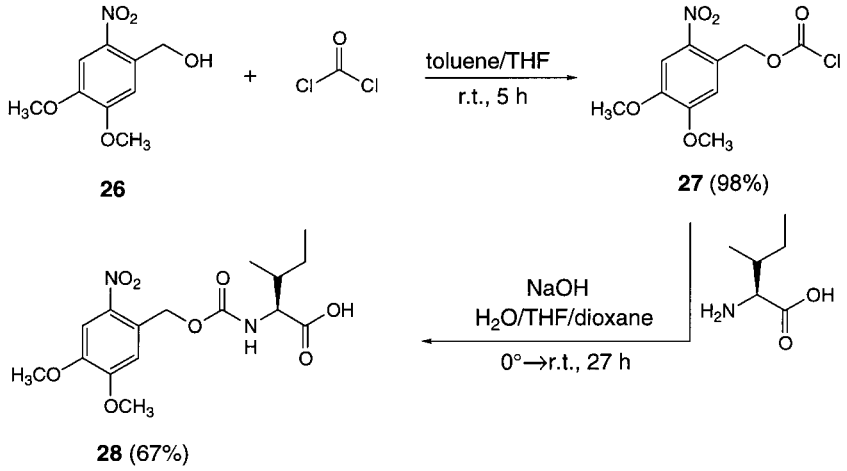
21 → **25**	R^1	R^2	t_1 [min]	t_2 [min]	Yield [%]	(*S*)/(*R*)[c])
a	Z	EtCH(Me)	1380	30	84	100:44
a	Z	EtCH(Me)	390	10	85	100:33
a	Z	EtCH(Me)	20	30	88	>100:1
b	Nvoc[a])	EtCH(Me)	20	30	92	>100:1
c	Fmoc[b])	EtCH(Me)	20	30	96	>100:1
d	Fmoc	Me_2CH	20	30	71	100:5[d])
d	Fmoc	Me_2CH	15	20	86	>100:1[d])
e	Fmoc	Me	5	7	91	100:16[d])
e	Fmoc	Me	2	3	87	100:5[d])
e	Fmoc	Me	1.5	2	94	100:2[d])
f	Z	H	30	15	96	
g	Z	$PhCH_2$	20	30	91	100:10[e])

[a]) Nvoc = [(6-Nitroveratryl)oxy]carbonyl (= [(4,5-dimethoxy-2-nitrobenzyl)oxy]carbonyl). [b]) Fmoc = [(9*H*-Fluoren-9-yl)methoxy]carbonyl. [c]) Determined by HPLC. [d]) Determined after coupling with Leu or Ile [30]. [e]) Determined by ^{1}H-NMR spectroscopy after coupling with Ala [30].

These reaction conditions were applied to several other thiodipeptides **21**, and the reaction times t_1 and t_2 were optimized with the aim of avoiding epimerization. Three different protecting groups R^1 were used. The thiopeptides **25a,b,f,g** were prepared by the procedure shown in *Scheme 4* in 71, 85, 90, and 55% yield, respectively. The photolabile Nvoc–Ile (**28**) was synthesized according to *Scheme 10:* treatment of 4,5-dimethoxy-2-nitrobenzyl alcohol (**26**) with $COCl_2$ at room temperature for 5 h gave Nvoc-Cl (**27**) in 98% yield, whose reaction with Ile led to Nvoc–Ile (**28**) in 67% yield.

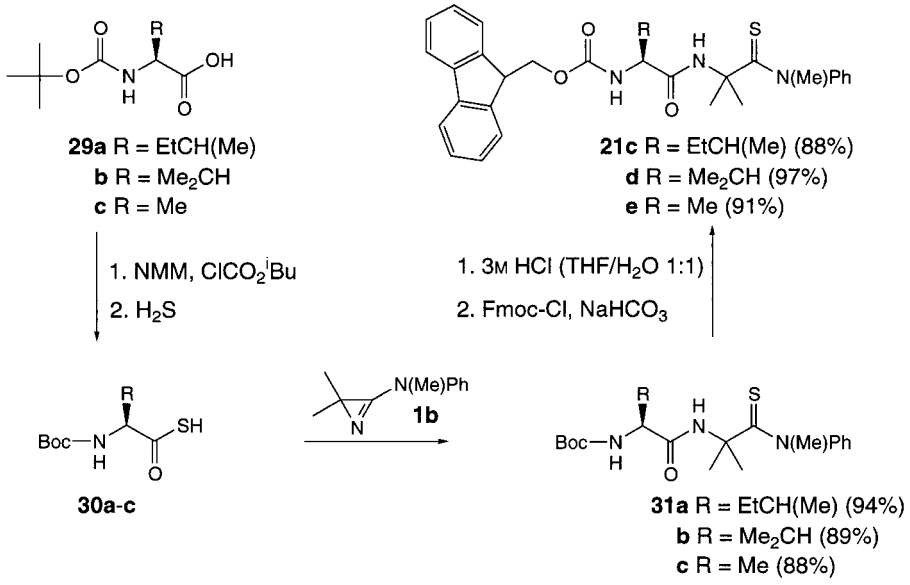
For the preparation of the Fmoc-thiodipeptides **21c–e**, an exchange of the protecting group was necessary, because the base-labile Fmoc protecting group was

Scheme 10



partly cleaved under the basic conditions (*N*-methylmorpholine, NMM) needed for the conversion of the carboxyl group into the thiocarboxyl group (*cf. Scheme 4*). Therefore, we started the synthesis with the Boc-protected amino acids **29a**–**c** which were transformed into the thioacids **30a**–**c** *via* the reaction of the mixed anhydrides of **29a**–**c** with H_2S (*Scheme 11*). The crude thioacids **29a**–**c** were then treated with **1b** to afford the thioamides **31a**–**c** in 94, 89, and 88% yield, respectively. Deprotection of the NH_2 groups with 3M HCl, subsequent basification with $NaHCO_3$, and treatment with Fmoc-Cl led to the Fmoc-thiopeptides **21c**–**e** in 88, 97, and 91% yield, respectively.

Scheme 11



The rearrangements of **21a–c** to **25a–c** (*cf. Table 1*) show that the different protecting groups influence neither the reaction times nor the yields or the degrees of epimerization. On the other hand, it has been established that the reaction times and the extent of epimerization depend on the size of the side chains of the penultimate amino acid: the larger R^2 is, the longer are the required reaction times. Thus, t_1 and t_2 decreased from the Ile- to the Val- and to the Ala-thiodipeptide (*e.g.*, $t_1 = 20$, 15, and 1.5 min, resp.). In the case of Ala ($R^2 = Me$, **21e**), the reaction was complete after 1.5 min, and already 2% of the (*R*)-enantiomer could be observed. With the Gly-

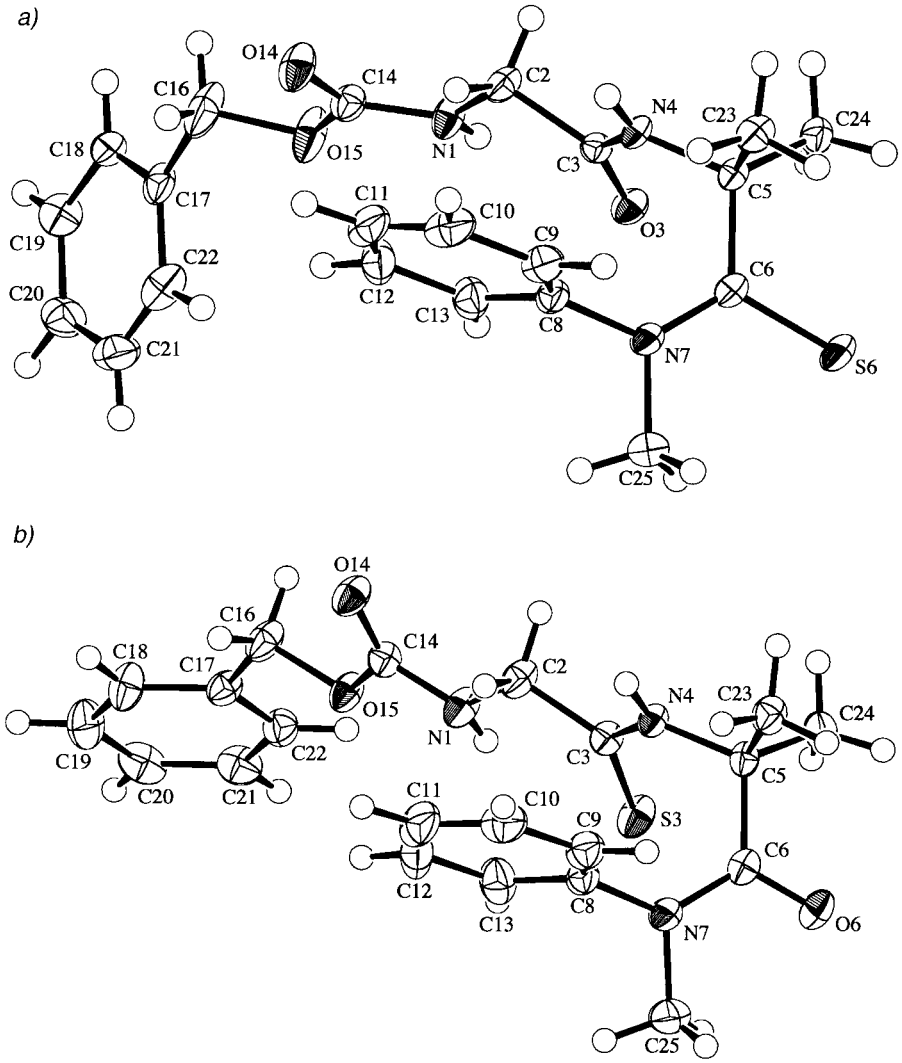


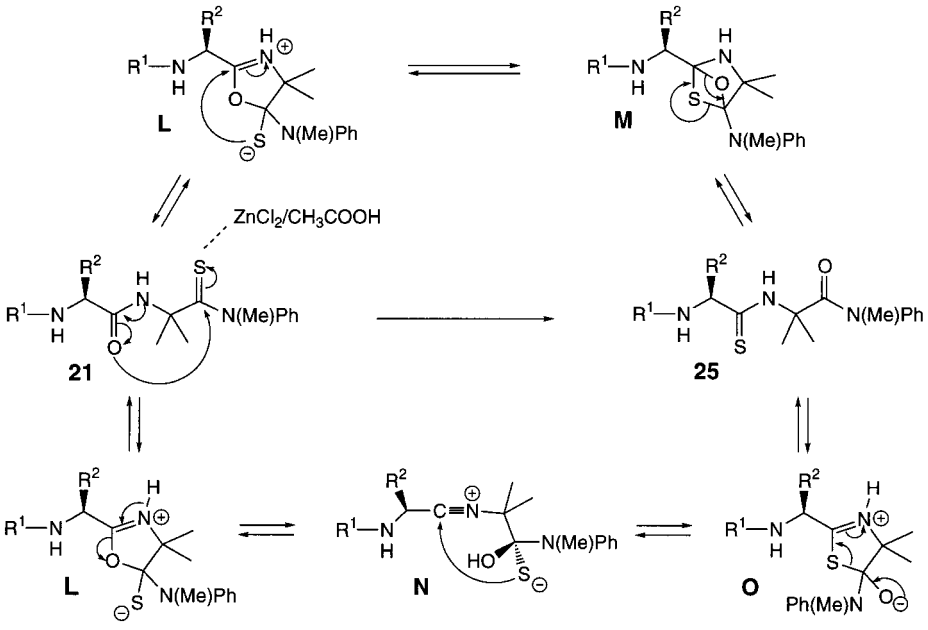
Fig. 1. *ORTEP Plot with 50% probability ellipsoids of the molecular structures of* a) *Z–Gly–Aib-Ψ(CS)–N(Me)Ph* (**21f**) *and* b) *Z–Gly-Ψ(CS)–Aib–N(Me)Ph* (**25f**)

thiodipeptide **21f**, the reaction time should be even shorter according to the observed trend, but as **21f** has no chiral center, there was no need to optimize the reaction time. In the case of the Phe-dipeptide **21g**, the reaction time was also not optimized; the reaction was carried out under the conditions optimized for **21a**, whereby 10% of the (*R*)-epimer was formed.

The structures of a pair of isomers of type **21** and **25** were established by X-ray crystallography. We succeeded in growing single crystals of the isomeric Gly-thiopeptides **21f** and **25f** which were suitable for X-ray diffraction analyses (*Fig. 1*). It is remarkable that the conformation of the backbone of the two peptides is almost identical; the structures differ only in the orientation of the Z-protecting group.

For the novel isomerization **21** → **25**, two mechanisms are conceivable (*Scheme 12*). In each of them, the thioamide group of **21** is activated by complexation with $ZnCl_2$ or AcOH, in analogy to *Scheme 9*. Then, cyclization yields the dipolar species **L**, in which an intramolecular attack of the S-atom at C(2) of the oxazolium ring gives the uncharged but highly strained bicycle **M**, which is converted to the isomeric endothiopeptide **25** by opening of the four-membered ring. In the second postulated mechanism, the initially formed **L** undergoes a ring opening to give the nitrilium ion **N**[6]). Intramolecular nucleophilic attack of the negatively charged S-atom at the nitrilium group leads to the isomeric zwitterion **O**, which is converted to the endothiopeptide **25** by ring opening.

Scheme 12



[6]) A mechanism *via* spirocyclic intermediates, similar to the one depicted in *Scheme 5*, is also conceivable.

In summary, we described a novel selective reaction leading to endothiodipeptides in high yields and without epimerization when the reaction times were optimized. The prepared endothiodipeptides of type **25**, with the thiocarbonyl group at the penultimate amino acid, can be used to generate longer epimerically pure endothiopeptides, which contain the thiocarbonyl group next to the bulky Aib unit [31].

Experimental Part

1. *General*. Solvents were purified by standard procedures. Thin-layer chromatography (TLC): *Merck 60 F_{254}* SiO_2-coated glass plates, 0.25 mm. Column chromatography (CC): *Merck 60* 230–400 mesh SiO_2. HPLC: anal.: *Varian-2510*-HPLC pump, *Varian-2550* static mixer, *Varian λ*-detector; prep.: *Jasco-PU-987* pump, *Jasco-UV-975* detector; peak registration: *Burkard Instruments Linear 1200*, *Borwin 1.20*; columns: *Bischoff Spherisorb ODS2* (5 μm) and *Bischoff Nucleosil 100-7* (7 μm) (anal.: 250 × 4.6 mm; prep.: 250 × 20 mm). M.p.: *Mettler FP5/FP52*. Optical rotations: *Perkin-Elmer-241* polarimeter (*c* in g/100 ml $CHCl_3$, 18°). IR: *Perkin-Elmer-1600-FTIR* spectrometer, $CHCl_3$; in cm^{-1}. NMR: *Bruker-ARX-300* and *Bruker-AMX-600* spectrometer; in $CDCl_3$; chemical shifts δ (ppm) refer to residual $CHCl_3$ (7.27 ppm, ^1H) and to $CDCl_3$ (77.0 ppm, ^{13}C); *J* in Hz; amino thiocarboxylic acid residues are labelled with the superscript t, *e.g.*, Aib^t. MS: *Finnigan MAT SSQ-700* (CI) and *Finnigan MAT TSQ-700* (ESI) spectrometer; *m/z* (rel.%).

General Procedure A (*GP A*). To a soln. of 1 equiv. of N-terminal protected amino acid in THF, 2 equiv. of *N*-methylmorpholine (NMM) and 1 equiv. of isobutyl carbonochloridate 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 to 10 equiv. of $Na_2S \cdot H_2O$) was bubbled through the soln. After stirring for 1 h at −10°, the suspension was diluted with Et_2O and extracted 3 × with 0.1M H_3PO_4. The combined org. phase was dried ($MgSO_4$) and evaporated and the residue dried under high vacuum. The formed crude amino thiocarboxylic acid was dissolved in CH_2Cl_2 and cooled to 0°, and 1 equiv. of *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1b**) was added slowly. The mixture was allowed to reach r.t. and stirred until the starting material was completeley consumed (TLC). Then, the soln. was washed 3 × with 5% $NaHCO_3$ soln., the combined org. phase dried ($MgSO_4$) and evaporated, and the crude product purified by chromatography (SiO_2) or by recrystallization.

General Procedure B (*GP B*). The intense yellow soln. of thiodipeptide **21** 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 extracted with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (SiO_2).

2. *Methyl 2-{[2-{[(Benzyloxy)carbonyl]amino}-2-methyl-1-thioxopropyl]amino}-2-methylpropanoate* (Z–Aib-Ψ(CS)–Aib–OMe; **20**). *Benzyl* N-*{2-{[1,1-Dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl]amino}-1,1-dimethyl-2-oxoethyl}carbamate* (Z–Aib–Aib-Ψ(CS)–N(Me)Ph; **19**). According to the *GP A*, with Z–Aib (2.357 g, 9.935 mmol) in THF (25 ml), NMM (2.03 g, 20.1 mmol), isobutyl carbonochloridate (1.49 g, 10.91 mmol), $Na_2S \cdot H_2O$ (5.3 g, 58.9 mmol), CH_2Cl_2 (50 ml), and **1b** (1.71 g, 9.81 mmol) (reaction time 17 h). Chromatography (SiO_2, AcOEt/hexane 1:1.5) yielded 3.28 g (77%) of **19**. Colorless crystals. M.p. 126.5–127.2°. IR: 3280*s*, 3200*s*, 3070*w*, 3030*m*, 2990*m*, 2970*m*, 2930*m*, 1720*s*, 1660*s*, 1650*s*, 1590*w*, 1530*s*, 1510*s*, 1460*s*, 1430*m*, 1370*s*, 1360*s*, 1260*s*, 1210*m*, 1180*m*, 1160*w*, 1100*s*, 1070*s*, 1080*w*, 1000*w*, 990*w*, 970*w*, 960*w*, 940*m*, 910*w*, 860*w*, 830*w*, 800*m*, 780*m*, 740*m*, 710*m*, 690*m*, 670*m*, 660*m*. ^1H-NMR: 8.41 (br. *s*, NH); 7.44–7.20 (*m*, 10 arom. H); 5.49 (*s*, CH_2O); 5.06 (*s*, MeN); 1.51 (*s*, $Me_2C(Aib)$, $Me_2C(Aib^t)$). ^{13}C-NMR: 209.3 (*s*, $CS(Aib^t)$); 172.0 (*s*, CO(Aib)); 154.8 (*s*, CO(carbamate)); 147.3, 136.4, 129.4, 128.5, 128.4, 127.9, 126.7 (12 arom. C); 66.4 (*t*, CH_2O); 62.6 (*s*, C(α)(Aib^t)); 57.2 (*s*, C(α)(Aib)); 51.3 (*q*, MeN); 27.3, 25.2 (2*q*, $Me_2C(Aib)$, $Me_2C(Aib^t)$). ESI-MS: 452 ($[M+Na]^+$), 428 ($[M+1]^+$). Anal. calc. for $C_{23}H_{29}N_3O_3S$ (427.57): C 64.61, H 6.84, N 9.83, S 7.50; found: C 64.65, H 6.62, N 10.17, S 7.79.

Z–Aib-Ψ(CS)–Aib–OMe (**20**). In 3M methanolic HCl soln. (10 ml; prepared by dilution of a HCl-sat. MeOH soln.), **19** (0.503 g, 1.176 mmol) was dissolved, and the soln. was stirred at 35°. After 14 h, the mixture was diluted with 2M HCl soln. and extracted 3 × with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (SiO_2, AcOEt/hexane 1:2): 0.272 g (66%) of **20**. Viscous oil which solidified under high vacuum. IR: 3420*w*, 3360*w*, 3300*w*, 3060*w*, 3020*m*, 3005*m*, 2940*w*, 1730*s*, 1505*s*, 1470*w*, 1455*s*, 1400*m*, 1385*m*, 1365*s*, 1285*s*, 1260*s*, 1155*s*, 1085*m*, 1075*m*, 1050*m*, 1030*w*, 1015*w*. ^1H-NMR: 8.69 (br. *s*, NH); 7.39–7.35 (*m*, 5 arom. H); 5.51 (br. *s*, NH); 5.13 (*s*, CH_2O); 3.70 (*s*, MeO); 1.69, 1.63 (*s*, $Me_2C(Aib)$, $Me_2C(Aib^t)$). ^{13}C-NMR: 203.8 (*s*, $CS(Aib^t)$); 171.7 (*s*, CO(Aib)); 153.5 (*s*, CO(carbamate)); 134.3, 126.7, 126.4,

126.3 (6 arom. C); 65.1 (*t*, CH_2O); 60.4, 58.1 (2*s*, C(α)(Aib), C(α)(Aib^t)); 50.7 (*q*, MeO); 26.5, 21.8 (2*q*, *Me*$_2$C(Aib), *Me*$_2$C(Aib^t)). ESI-MS: 374 ([M+Na]$^+$), 352 ([M+1]$^+$). Anal. calc. for $C_{17}H_{23}N_2O_4S$ (351.45): C 58.10, H 6.60, N 7.97, S 9.12; found: C 57.74, H 6.72, N 7.93, S 9.14.

3. *Benzyl* N-*{(1S,2S)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}thioxomethyl}-butyl}carbamate* (Z–Ile-Ψ(CS)–Aib–N(Me)Ph; **25a**). *Benzyl* N-*{(1S,2S)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}carbonyl}butyl}carbamate* (Z–Ile–Aib-Ψ(CS)–N(Me)Ph; **21a**). According to *GP A* with Z–Ile (2.02 g, 7.63 mmol) in THF (15 ml), NMM (1.57 g, 15.5 mmol), isobutyl carbonochloridate (1.10 g, 0.81 mmol), $Na_2S\cdot H_2O$ (4.9 g, 54.4 mmol), CH_2Cl_2 (50 ml), and **1b** (1.380 g, 7.920 mmol) (reaction time 135 min). Chromatography (SiO_2, AcOEt/hexane 1:1) gave 2.47 g (71%) of **21a**. Yellow, thick oil which solidified under high vacuum. $[\alpha]_D = -59.5$ (c = 1.02). IR ($CHCl_3$): 3430*m*, 3210*w*, 3005*s*, 2970*s*, 2930*m*, 2880*w*, 1720*s*, 1675*s*, 1595*w*, 1370*s*, 1280*m*, 1220*s*, 1100*s*, 1040*m*, 1030*m*, 1005*w*, 975*w*, 920*w*, 705*m*, 660*w*. ^{1}H-NMR: 7.39–7.15 (*m*, 10 arom. H); 5.46 (*d*, J = 8.3, NH); 5.17–5.11 (*m*, CH_2O); 3.84–3.79 (*m*, H–C(α)(Ile)); 3.70 (*s*, MeN); 1.81–0.85 (*m*, H–C(β)(Ile), $CH_2(\gamma^1)$(Ile)); 1.63, 1.54 (2*s*, Me_2C(Aib^t)); 0.90–0.85 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 208.3 (*s*, CS(Aib^t)); 168.7 (*s*, CO(Ile)); 156.0 (*s*, CO (carbamate)); 147.2, 136.4, 129.5, 128.5, 128.4, 128.0, 126.9, 126.3 (12 arom. C); 66.8 (*t*, CH_2O); 62.8 (*s*, C(α)Aib^t)); 59.6 (*d*, CH(α)(Ile)); 51.2 (*q*, MeN); 38.1 (*d*, CH(β)(Ile)); 28.7, 28.5 (2*q*, *Me*$_2$C(Aib^t)); 24.7 (*t*, $CH_2(\gamma^1)$(Ile)); 15.3, 11.6 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). CI-MS: 456.3 ([M+1]$^+$). Anal. calc. for $C_{25}H_{33}N_3O_3S$ (455.62): C 65.90, H 7.30, N 9.22, S 7.04; found: C 65.43, H 7.11, N 9.06, S 7.04.

*2-{{(2*R*,3*S*)- and (2*S*,3*S*)-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-thioxopentyl}amino}-2-methylpropanoic acid* (Z–Ile-Ψ(CS)–Aib–OH; **22**). A soln. of **21a** (0.318 g, 0.698 mmol) in 10 ml of 3M HCl (THF/H_2O 1:1) was stirred at 35°. After 7 d, during which the soln. turned from yellow to colorless, the mixture was diluted with 2M HCl and extracted with Et_2O (3×). The combined org. phase was dried ($MgSO_4$) and evaporated. The crude product was chromatographed (SiO_2, AcOEt/hexane/AcOH 100:100:1): **22**. White solid. M.p. 149.2–150.2°. $[\alpha]_D = -12.7$ (c = 1.15). IR: 3390*m*, 3370*m*, 3280*s*, 3030*m*, 2960*s*, 2930*m*, 1730*s*, 1675*s*, 1540*m*, 1515*s*, 1455*m*, 1445*m*, 1430*s*, 1370*w*, 1305*w*, 1255*m*, 1235*s*, 1180*w*, 1150*m*, 1130*w*, 1090*m*, 1035*w*, 1015*w*. ^{1}H-NMR ((D$_6$)DMSO): 9.29, 9.42 (2*s*, NH); 7.34–7.27 (*m*, 5 arom. H); 6.61–6.51 (*m*, NH); 5.06–5.05 (*m*, CH_2O); 4.41–4.26 (*m*, H–C(α)(Ile^t)); 1.98–1.61 (*m*, H–C(β)(Ile^t)); 1.59, 1.58 (2*s*, Me_2C(Aib)); 1.56-1.13 (*m*, $CH_2(\gamma^1)$(Ile^t)); 0.91–0.82 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR ((D$_6$)DMSO): 202.8, 202.3 (2*s*, CS(Ile^t)); 173.23, 173.16 (2*s*, COOH); 155.4 (*s*, CO(carbamate)); 137.0, 128.2, 127.6, 127.4 (4*s*, 6 arom. C); 65.4 (*d*, CH(α)(Ile^t)); 65.4, 65.3 (2*t*, CH_2O); 59.13, 59.05 (2*s*, C(α)(Aib)); 38.0, 37.8 (2*d*, CH(β)(Ile^t)); 25.4, 24.3 (2*t*, $CH_2(\gamma^1)$(Ile^t)); 24.0, 23.7 (2*q*, *Me*$_2$C(Aib)); 14.8, 14.0 (2*q*, Me(γ^2)(Ile^t)); 11.4, 10.6 (2*q*, Me(δ)(Ile^t)). ESI-MS: 389 ([M+Na]$^+$). Anal. calc. for $C_{18}H_{26}N_2O_4S$ (366.48): C 58.99, H 7.15, N 7.64; found: C 59.36, H 6.99; N 7.65.

Benzyl N-*[(1S,2S)-2-Methyl-1-(4,5-dihydro-4,4-dimethyl-5-oxo-1,3-thiazol-2-yl)butyl]carbamate* (Z–Ile-Ψ(cyclo)-Aib; **23a**): A soln. of **22** (0.195 g, 0.532 mmol) in THF (5 ml) was treated with NMM (0.106 g, 1.05 mmol) and isobutyl carbonochloridate (0.081 g, 0.593 mmol); a white solid precipitated. After 14 h stirring at r.t., the mixture was diluted with Et_2O and extracted 3× with 0.1M H_3PO_4 soln. The combined org. layer was dried ($MgSO_4$) and evaporated and the crude product chromatographed (SiO_2, AcOEt/hexane 5:1): **23** (0.174 g, 94%). Colorless, thick oil. The two epimers were separated by prep. normal-phase HPLC (*Bischoff Nucleosil 100-7* (7.0 μm), hexane/AcOEt 88:12, 10 ml/min). (*S*)-Epimer **23a**: $[\alpha]_D = -16.4$ (c = 0.764). IR: 3430*w*, 2960*m*, 2930*m*, 2880*w*, 1720*s*, 1640*m*, 1500*s*, 1460*m*, 1455*m*, 1400*w*, 1380*w*, 1360*w*, 1330*m*, 990*m*, 920*m*. ^{1}H-NMR: 7.36–7.32 (*m*, 5 arom. H); 5.44–5.42 (br. *d*, NH); 5.14–5.13 (*m*, CH_2O); 4.80–4.76 (*m*, H–C(α)-(Ile^t)); 1.98–1.00 (*m*, H–C(β)(Ile^t), $CH_2(\gamma^1)$(Ile^t)); 1.39, 1.38 (2*s*, Me_2C); 0.98–0.87 (*m*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ^{13}C-NMR: 210.6 (*s*, CO(Aib)); 165.6 (*s*, C=N); 156.2 (*s*, CO(carbamate)); 136.1, 128.5, 128.2, 128.0 (6 arom. C); 83.2 (*s*, Me_2C(Aib)); 67.1 (*t*, CH_2O); 58.0 (*d*, CH(α)(Ile^t)); 38.0 (*d*, CH(β)(Ile^t)); 26.4 (*t*, $CH_2(\gamma^1)$(Ile^t)); 24.5, 24.2 (2*q*, *Me*$_2$C(Aib)); 13.4 (2*q*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ESI-MS: 371 ([M+Na]$^+$). Anal. calc. for $C_{18}H_{24}N_2O_3S$ (348.47): C 62.04, H 6.94, N 8.04, S 9.20; found: C 62.20, H 6.98, N 7.94, S 9.10.

Z–Ile-Ψ(CS)–Aib–N(Me)Ph (**25a**). According to the *GP B*, with **21a** (0.128 g, 0.281 mmol), AcOH (4.0 ml), $ZnCl_2$ (1.64 g, 12.00 mmol), and 2.1M HCl in AcOH (0.4 ml) (t_1 20 min, t_2 30 min). Chromatography (SiO_2, AcOEt/hexane/CH_2Cl_2 1:1:2) led to 112 mg (88%) **25a**. White solid. $[\alpha]_D = +61.3$ (c = 1.03). IR: 3380*w*, 3250*w*, 3020*m*, 3005*m*, 2970*m*, 2930*m*, 2880*w*, 1715*s*, 1640*s*, 1595*m*, 1505*s*, 1455*m*, 1425*m*, 1390*m*, 1365*m*, 1305*w*, 1280*w*, 1215*s*, 1170*w*, 1120*m*, 1090*w*, 1070*w*, 1040*w*, 1025*m*, 1000*w*. ^{1}H-NMR: 8.38 (br. *s*, NH); 7.56–7.39 (*m*, 10 arom. H); 5.93 (br. *d*, NH); 5.30 (*s*, CH_2O); 4.12–4.07 (*m*, H–C(α)(Ile^t)); 3.41 (*s*, MeN); 2.17–1.21 (*m*, H–C(β)(Ile^t), $CH_2(\gamma^1)$(Ile^t)); 1.87, 1.78 (2*s*, Me_2C(Aib)); 1.07–1.02 (*m*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ^{13}C-NMR: 201.1 (*s*, CS(Ile^t)); 171.6 (*s*, CO(Aib)); 155.7 (*s*, CO(carbamate)); 143.7, 136.3, 129.3, 128.4, 128.1, 127.9, 127.8 (12 arom. C); 66.8 (*t*, CH_2O); 66.2 (*d*, CH(α)(Ile^t)); 61.9 (*s*, C(α)(Aib)); 40.9 (*q*, MeN); 40.3 (*q*, CH(β)(Ile^t)); 25.2 (*q*, 1 Me(Aib)); 24.6 (*t*, $CH_2(\gamma^1)$(Ile^t)); 23.7 (*q*, 1 Me(Aib)); 15.5, 11.2 (2*q*, Me(δ)(Ile^t),

Me(γ^2)(Ile^t)). ESI-MS: 478 ([M + Na]$^+$). Anal. calc. for $C_{25}H_{33}N_3O_3S$ (455.62): C 65.90, H 7.30, N 9.22; found: C 65.72, H 7.13, N 9.13.

4. *4,5-Dimethoxy-2-nitrobenzyl N-{(1S,2S)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}-amino}thioxomethyl}butyl}carbamate* (Nvoc-Ile-Ψ(CS)–Aib–N(Me)Ph; **25b**). *4,5-Dimethoxy-2-nitrobenzyl Carbonochloridate* (= *6-Nitroveratryl Carbonochloridate*; Nvoc–Cl; **27**). 4,5-Dimethoxy-2-nitrobenzyl alcohol (2.036 g, 0.550 mmol) was treated at 0° with $COCl_2$ in toluene (20% soln.). Because the alcohol was not completely dissolved, THF (30 ml) was added. After 4 h stirring at 0°, a stream of N_2 was bubbled through the soln. for 16 h to remove the excess $COCl_2$. Then, the mixture was evaporated and the residue dried *i.v.:* 2.58 g (98%) of **27**. Pale yellow solid. IR: 3020*m*, 2970*w*, 2940*w*, 2910*w*, 1775*s*, 1640*w*, 1585*m*, 1530*s*, 1465*m*, 1440*m*, 1400*w*, 1380*m*, 1360*m*, 1340*s*, 1280*s*, 1140*s*, 1070*s*, 1030*w*, 1010*w*, 990*w*, 960*w*, 925*w*, 890*w*, 875*m*, 845*w*. ^{1}H-NMR: 7.76 (*s*, H–C(3)); 7.28 (*s*, H–C(6)); 5.73 (*s*, CH_2O); 4.02, 3.98 (2*s*, 2 MeO). ^{13}C-NMR: 153.7 (*s*, CO); 150.3 (*s*, C(5)); 148.9 (*s*, C(4)); 139.8 (*s*, C(2)); 124.1 (*s*, C(1)); 110.4, 108.3 (2*d*, C(4), C(6)); 69.8 (*t*, CH_2O); 56.5, 56.4 (2*q*, 2 MeO). CI-MS: 295 (26), 294 (9), 293 (80, [M + NH_4]$^+$), 231 (11), 214 (10), 213 (100), 197 (8), 196 (75), 182 (7), 180 (8). Anal. calc. for $C_{10}H_{10}ClNO_6$ (275.64): C 43.57, H 3.66, N 5.08; found: C 43.49, H 3.68, N 5.08.

N-*[(4,5-Dimethoxy-2-nitrobenzyloxy)carbonyl]*-L-*isoleucine* (Nvoc–Ile; **28**). To a soln. of Ile (0.964 g, 7.623 mmol) in 2M NaOH (10 ml) and dioxane (5 ml) at 0°, a soln. of **27** (2.148 g, 7.793 mmol) in dioxane/THF 1:1 (10 ml) was added slowly by means of a syringe. The mixture was kept basic by simultaneous addition of 2M NaOH. Then, the mixture was warmed to r.t. and stirred for another 27 h. The dark-brown soln. was washed 3 × with CH_2Cl_2, the combined org. phase dried ($MgSO_4$) and evaporated, and the residue dried under high vacuum: 1.89 g (67%) of **28**. Orange solid. $[\alpha]_D$ = + 10.3 (c = 1.10). IR: 3440*w*, 3020*m*, 2970*m*, 2940*m*, 2880*m*, 1720*s*, 1620*m*, 1585*m*, 1520*s*, 1465*m*, 1440*m*, 1425*m*, 1380*m*, 1330*s*, 1280*s*, 1170*m*, 1130*w*, 1090*m*, 1070*s*, 1040*m*, 1010*w*, 990*w*, 925*w*, 875*m*, 850*w*. ^{1}H-NMR: 8.94 (br. *s*, COOH); 7.70 (*s*, arom. H–C(3)); 6.99 (*s*, arom. H–C(6)); 5.54–5.52 (*m*, CH_2O); 5.47 (br. *d*, NH); 4.41–4.37 (*m*, H–C(α)(Ile)); 3.97, 3.95 (2*s*, 2 MeO); 2.08–1.89 (*m*, H–C(β)(Ile)); 1.56–1.16 (*m*, CH_2(γ^1)(Ile)); 1.00–0.92 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 176.6 (*s*, COOH); 155.8 (*s*, CO(carbamate)); 153.6 (*s*, arom. C(5)); 148.0 (*s*, arom. C(4)); 139.6 (*s*, arom. C(2)); 127.9 (*s*, arom. C(1)); 109.8, 108.1 (2*d*, arom. C(3), C(6)); 63.9 (*t*, CH_2O); 58.3 (*d*, CH(α)(Ile)); 56.3 (*q*, 2 MeO); 37.5 (*d*, CH(β)(Ile)); 24.8 (*t*, CH_2(γ^1)(Ile)); 15.5, 11.5 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). CI-MS: 388 (100, [M + NH_4]$^+$), 327 (9), 231 (13), 213 (30), 196 (30), 175 (5). Anal. calc. for $C_{16}H_{25}N_2O_8$ (370.35): C 51.89, H 6.80, N 7.56; found: C 51.19, H 6.10, N 7.30.

4,5-Dimethoxy-2-nitrobenzyl N-*{(1S,2S)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxo-ethyl}amino}carbonyl}butyl}carbamate* (Nvoc–Ile–Aib-Ψ(CS)–N(Me)Ph; **21b**). According to the *GP A*, with **28** (1.014 g, 2.730 mmol), THF (20 ml), NMM (0.550 g, 5.437 mmol), isobutyl carbonochloridate (0.411 g, 3.009 mmol), $Na_2S \cdot H_2O$ (3.0 g, 33.3 mmol), CH_2Cl_2 (50 ml), and **1b** (0.476 g, 2.732 mmol). Chromatography (SiO_2, AcOEt/hexane 1:1) led to 1.304 g (85%) of **21b**. Orange, viscous oil which solidified under high vacuum. $[\alpha]_D$ = – 60.9 (c = 0.933). IR: 3420*w*, 3210*w*, 3020*m*, 3010*m*, 2970*m*, 2930*m*, 2880*w*, 1730*s*, 1675*m*, 1620*w*, 1585*m*, 1525*s*, 1495*s*, 1465*s*, 1440*m*, 1370*m*, 1330*m*, 1280*s*, 1170*w*, 1100*m*, 1070*m*, 1045*w*, 1005*w*, 990*w*, 925*w*, 875*w*, 850*w*. ^{1}H-NMR: 7.72 (*s*, H–C(3)(Nvoc)); 7.44–7.18 (*m*, PhN); 7.06 (*s*, H–C(6)(Nvoc)); 5.66–5.61 (*m*, NH); 5.56–5.54 (*m*, CH_2O); 3.99, 3.95 (2*s*, 2 MeO); 3.91–3.86 (*m*, H–C(α)(Ile)); 3.71 (*s*, MeN); 1.62, 1.54 (2*s*, 2 Me_2C-(Aib^t)); 1.83–0.96 (*m*, H–C(β)(Ile), $CH_2\gamma^1$)(Ile)); 0.94–0.88 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 208.4 (*s*, CS(Aib^t)); 168.6 (*s*, CO(Ile)); 155.6 (*s*, CO (carbamate)); 153.7 (*s*, C(5)(Nvoc)); 148.0 (*s*, C(4) (Nvoc)); 147.2 (*s*, C(1)(Ph)); 139.6 (*s*, C(2)(Nvoc)); 129.7, 128.7, 128.57, 128.55 (C(1)(Nvoc), 5 arom. C(Ph)); 109.6, 108.2 (2*d*, C(3)(Nvoc), C(6)(Nvoc)); 63.7 (*t*, CH_2O); 62.9 (*s*, C(α)(Aib^t)); 59.8 (*d*, CH(α)(Ile)); 56.5, 56.4 (2*q*, 2 MeO); 51.4 (*q*, MeN); 38.4 (*d*, CH(β)(Ile)); 28.6, 28.3 (2*q*, *Me*$_2$C(Aib^t)); 24.9 (*t*, CH_2(γ^1)(Ile)); 15.5, 11.7 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). ESI-MS: 583 ([M + Na]$^+$). Anal. calc. for $C_{27}H_{36}N_4O_7S$ (560.67): C 57.84, H 6.47, N 9.99, S 5.72; found: C 57.48, H 6.61, N 9.80, S 5.53.

Nvoc–Ile-Ψ(CS)–Aib–N(Me)Ph (**25b**). According to the *GP B*, with **21b** (0.842 g, 1.501 mmol), AcOH (50 ml), and $ZnCl_2$ (20.5 g, 0.150 mol) (t_1 20 min, t_2 30 min). Chromatography (SiO_2, AcOEt/hexane/CH_2Cl_2 1:2:1) gave 0.791 g (94%) of **25b**. White solid. $[\alpha]_D$ = + 12.1 (c = 0.953). IR: 3680*w*, 3370*w*, 3250*w*, 3010*m*, 3005*m*, 2970*m*, 2930*m*, 2880*w*, 1725*s*, 1640*s*, 1595*m*, 1585*m*, 1525*s*, 1505*s*, 1465*s*, 1440*m*, 1425*m*, 1380*m*, 1360*m*, 1330*s*, 1280*s*, 1170*m*, 1120*m*, 1090*m*, 1070*s*, 1035*m*, 990*w*, 925*w*, 875*w*, 850*w*. ^{1}H-NMR: 8.40 (br. *s*, NH); 7.71 (*s*, H–C(3)(Nvoc)); 7.36–7.22 (*m*, PhN); 7.04 (*s*, H–C(6)(Nvoc)); 5.95 (br. *d*, NH); 5.65–5.48 (*m*, CH_2O); 3.98, 3.94 (2*s*, 2 MeO); 3.26 (*s*, MeN); 1.83–1.10 (*m*, H–C(β)(Ile^t), CH_2(γ^1)(Ile^t)); 1.69, 1.62 (2*s*, Me_2C(Aib)); 0.96–0.86 (*m*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ^{13}C-NMR: 201.0 (*s*, CS(Ile^t)); 171.7 (*s*, CO(Aib)); 155.2 (*s*, CO-(carbamate)); 153.7 (*s*, C(5)(Nvoc)); 147.9 (*s*, C(4)(Nvoc)); 143.6, 139.3, 129.4, 128.7, 128.3, 128.0 (6 C(Ph), C(2)(Nvoc), C(1)(Nvoc)); 109.1, 108.1 (2*d*, C(3)(Nvoc), C(6)(Nvoc)); 66.1 (*d*, CH(α)(Ile^t)); 63.5 (*t*, CH_2O); 62.1 (*s*, C(α)(Aib)); 56.5, 56.3 (2*q*, 2 MeO); 41.1 (*q*, MeN); 40.4 (*d*, CH(β)(Ile^t)); 24.8 (*q*, 1 Me(Aib)); 24.6

(*t*, $CH_2(\gamma^1)$(Ile^t)); 23.4 (*q*, 1 Me(Aib)); 15.5, 11.2 (2*q*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ESI-MS: 583 ([*M* + Na]$^+$). Anal. calc. for $C_{27}H_{36}N_4O_7S$ (560.67): C 57.84, H 6.47, N 9.99, S 5.72; found: C 57.22, H 6.45, N 10.06, S 5.78.

5. *(9*H*-Fluoren-9-yl)methyl* N*-{(1*S*,2*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}-amino}thioxomethyl}butyl}carbamate* (Fmoc–Ile-Ψ(CS)–Aib–N(Me)Ph; **25c**). tert-*Butyl* N*-{(1*S*,2*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}carbonyl}butyl}carbamate* (Boc–Ile–Aib-Ψ(CS)–N(Me)Ph; **31a**). According to the *GP A*, with Boc–Ile (3.073 g, 13.286 mmol), THF (70 ml), NMM (2.73 g, 26.99 mmol), isobutyl carbonochloridate (2.04 g, 14.94 mmol), CH_2Cl_2 (100 ml), and **1b** (2.30 g, 13.20 mmol) (reaction time 30 min). Chromatography (SiO_2, AcOEt/hexane 1:4) led to 5.29 g (94%) of **31a**. Yellow, thick oil which solidified under high vacuum. $[\alpha]_D = -61.4$ ($c = 1.09$). IR: 3680*w*, 3430*m*, 3220*w*, 3020*w*, 3000*m*, 2970*s*, 2930*m*, 2880*w*, 1710*s*, 1680*s*, 1640*s*, 1595*w*, 1515*s*, 1505*s*, 1495*s*, 1465*s*, 1455*s*, 1435*m*, 1385*m*, 1370*s*, 1315*w*, 1165*s*, 1120*m*, 1100*s*, 1075*w*, 1045*w*, 1020*w*, 1005*w*, 970*w*, 925*w*, 860*w*, 700*m*. ^{1}H-NMR: 7.43–7.18 (*m*, 5 arom. H); 5.14 (br. *d*, NH); 3.87–3.72 (*m*, H–C(α)(Ile)); 1.84–1.05 (*m*, H–C(β)(Ile), $CH_2(\gamma^1)$(Ile)); 1.63, 1.57 (2*s*, Me_2C(Aib^t)); 1.46 (*s*, Me_3C); 0.91–0.86 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 208.5 (*s*, CS(Aib^t)); 169.3 (*s*, CO(Ile)); 155.6 (*s*, CO(carbamate)); 147.3, 129.6, 128.6, 126.5 (6 arom. C); 79.5 (*s*, Me_3C); 62.8 (*s*, C(α)(Aib^t)); 59.2 (*d*, CH(α)(Ile)); 51.2 (*s*, MeN); 38.1 (*q*, CH(β)(Ile)); 29.0, 28.8 (2*q*, Me_2C(Aib)); 28.4 (*q*, Me_3C); 24.8 (*t*, $CH_2(\gamma^1)$(Ile)); 15.5, 11.7 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). CI-MS: 422 (100, [*M* + 1]$^+$), 366(9), 192(13), 178(13), 131(6). Anal. calc. for $C_{22}H_{35}N_3O_3S$ (421.60): C 62.67, H 8.37, N 9.97; found: C 62.48, H 8.39, N 9.27.

*(9*H*-Fluoren-9-yl)methyl* N*-{(1*S*,2*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}-amino}carbonyl}butyl}carbamate* (Fmoc–Ile–Aib-Ψ(CS)–N(Me)Ph; **21c**). A soln. of **31a** (0.524 g, 1.219 mmol) in 20 ml of 3M HCl (THF/H_2O 1:1) was stirred for 15 h at r.t. The mixture was cooled to 0°, basified with $NaHCO_3$, and diluted with H_2O/dioxane 1:1 (10 ml). The yellow suspension was treated with Fmoc–Cl (0.36 g, 1.39 mmol) dissolved in dioxane (10 ml). After 2.5 h, the mixture was diluted with H_2O and extracted with Et_2O (3×), the combined org. layer dried ($MgSO_4$) and evaporated, and the yellow residue chromatographed (SiO_2, AcOEt/hexane 1:3): 0.579 g (88%) of **21c**. Yellow, viscous oil which solidified. $[\alpha]_D = -64.5$ ($c = 1.00$). IR: 3680*w*, 3430*w*, 3220*w*, 3060*w*, 3020*m*, 3000*m*, 2970*m*, 2930*m*, 2880*w*, 1715*s*, 1680*s*, 1665*s*, 1595*w*, 1550*w*, 1505*s*, 1495*s*, 1465*s*, 1455*s*, 1435*m*, 1385*m*, 1340*w*, 1285*w*, 1170*w*, 1120*m*, 1100*s*, 1075*m*, 1040*m*, 1005*w*, 970*w*, 930*w*, 880*w*, 830*w*, 700*w*. ^{1}H-NMR: 7.77–7.15 (*m*, 13 arom. H); 5.50 (br. *d*, *J* = 8.4, NH); 4.41 (*d*, *J* = 7.1, $CHCH_2O$); 4.24 (*t*, *J* = 7.0, $CHCH_2O$); 3.84–3.70 (*m*, H–C(α)(Ile)); 3.70 (*s*, MeN); 1.88–1.03 (*m*, H–C(β)(Ile), $CH(\gamma^1)$(Ile)); 1.64, 1.55 (2*s*, Me_2C(Aib^t)); 0.93–0.89 (*m*, Me(δ)(Ile), Me(γ^2)(Ile)). ^{13}C-NMR: 208.4 (*s*, CS(Aib^t)); 168.7 (*s*, CO(Ile)); 156.0 (*s*, CO(carbamate)); 147.2, 143.9, 141.3, 129.6, 128.6, 127.7, 127.1, 126.5, 125.1, 120.0 (18 arom. C); 66.9 (*t*, $CHCH_2O$); 62.9 (*s*, C(α)(Aib^t)); 59.7 (*d*, CH(α)(Ile)); 51.2 (*q*, MeN); 47.3 (*d*, $CHCH_2O$); 38.3 (*d*, CH(β)(Ile)); 28.8, 28.5 (2*q*, Me_2C(Aib^t)); 24.9 (*t*, $CH_2(\gamma^1)$(Ile)); 15.4, 11.7 (2*q*, Me(δ)(Ile), Me(γ^2)(Ile)). ESI-MS: 566 ([*M* + Na]$^+$). Anal. calc. for $C_{32}H_{36}N_3O_3S$ (542.72): C 70.82, H 6.69, N 7.74; found: C 70.69, H 6.81, N 7.47.

Fmoc–Ile-Ψ(CS)–Aib–N(Me)Ph (**25c**). According to the *GP B*, with **21c** (1.006 g, 1.854 mmol), AcOH (25 ml), $ZnCl_2$ (10.4 g, 76.3 mmol), and 2.5 ml of 2.1M HCl in AcOH (t_1 20 min, t_2 30 min). Chromatography (SiO_2, AcOEt/CH_2Cl_2/hexane 1:1:3) gave 0.961 g (96%) of **25c**. White solid. M.p. 159.7–160.7°. $[\alpha]_D = +22.2$ ($c = 1.00$). IR: 3365*w*, 3240*w*, 3055*w*, 3040*w*, 2970*m*, 2925*m*, 2875*w*, 1720*s*, 1645*s*, 1595*m*, 1510*s*, 1450*m*, 1410*m*, 1390*m*, 1360*m*, 1310*m*, 1230*m*, 1170*m*, 1120*m*, 1105*m*, 1090*m*, 1070*w*, 1030*m*, 890*w*. ^{1}H-NMR: 8.29 (br. *s*, NHCS); 7.70–7.22 (13 arom. H); 5.82–5.79 (*d*, NH); 4.42–4.37 (*m*, $CHCH_2O$); 4.24 (*t*, *J* = 7.0, $CHCH_2O$); 3.96–3.94 (*m*, H–C(α)(Ile^t)); 3.24 (*s*, MeN); 1.98–1.09 (*m*, H–C(β)(Ile^t), $CH_2(\gamma^1)$(Ile^t)); 1.70, 1.61 (2*s*, Me_2C(Aib)); 0.88–0.86 (*m*, Me(δ)(Ile), Me(γ^2)(Ile^t)). ^{13}C-NMR: 201.3 (*s*, CS(Ile^t)); 171.8 (*s*, CO(Aib)); 155.9 (*s*, CO(carbamate)); 143.8, 141.3, 129.4, 128.2, 128.0, 127.7, 127.1, 125.1, 120.0 (18 arom. C); 67.0 (*t*, $CHCH_2O$); 66.2 (*d*, CH(α)(Ile^t)); 62.0 (*s*, C(α)Aib)); 47.2 (*d*, $CHCH_2O$); 41.1 (*q*, MeN); 40.4 (*d*, CH(β)-(Ile^t)); 25.2 (*q*, 1 Me(Aib)); 24.7 (*t*, $CH_2(\gamma^1)$(Ile^t)); 23.7 (*q*, 1 Me(Aib)); 15.6, 11.3 (2*q*, Me(δ)(Ile^t), Me(γ^2)(Ile^t)). ESI-MS: 566 ([*M* + Na]$^+$). Anal. calc. for $C_{32}H_{36}N_3O_2$ (542.72): C 70.82, H 6.69, N 7.74; found: C 70.90, H 7.24, N 7.87.

6. *(9*H*-Fluoren-9-yl)methyl* N*-{(1*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}-thioxomethyl}propyl}carbamate* (Fmoc–Val-Ψ(CS)–Aib–N(Me)Ph; **25d**). tert-*Butyl* N*-{(1*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}carbonyl}propyl}carbamate* (Boc–Val–Aib-Ψ(CS)–N(Me)Ph; **31b**). According to the *GP A*, with Boc–Val (5.003 g, 23.026 mmol), THF (50 ml), NMM (4.740 g, 48.861 mmol), isobutyl carbonochloridate (3.480 g, 25.480), $Na_2S \cdot H_2O$ (18.0 g, 0.2 mol), CH_2Cl_2 (100 ml), and **1b** (3.90 g, 22.38 mmol) (reaction time 2.5 h). Chromatography (SiO_2, AcOEt/hexane 1:3) led to 8.353 g (20.495 mmol) of **31b**. Yellow, thick oil which solidified under high vacuum. $[\alpha]_D = -74.8$ ($c = 1.10$). IR: 3675*w*, 3430*m*, 3225*w*, 3005*m*, 2970*m*, 2935*m*, 2875*w*, 2455*w*, 2360*w*, 1705*s*, 1680*s*, 1595*w*, 1490*s*,

1465*w*, 1435*m*, 1370*s*, 1100*s*, 1050*w*, 1015*w*, 1005*w*, 970*w*, 925*w*, 870*w*, 835*w*. ^{1}H-NMR: 7.43–7.18 (*m*, 5 arom. H); 7.07 (br. *s*, NH); 5.14 (br. *d*, NH); 3.74–3.69 (*m*, H–C(α)(Val)); 3.71 (*s*, MeN); 2.11 (*m*, H–C(β)(Val)); 1.64, 1.58 (2*s*, Me$_2$(Aib^t)); 1.47 (*s*, Me$_3$C); 0.92, 0.85 (2*d*, J = 6.8, Me(γ^1)(Val), Me(γ^2)(Val)). ^{13}C-NMR: 208.5 (*s*, CS(Aib^t)); 169.4 (*s*, CO(Val)); 155.7 (*s*, CO(carbamate)); 147.4, 129.6, 128.6, 126.4 (6 arom. C); 79.5 (*s*, Me$_3$*C*); 62.7 (*s*, C(α)(Aib^t)); 59.6 (*d*, CH(α)(Val)); 51.1 (*q*, MeN); 31.4 (*d*, CH(β)(Val)); 29.1, 28.9 (2*q*, *Me*$_2$C(Aib^t)); 28.4 (*q*, *Me*$_3$C); 19.3, 17.4 (2*q*, Me(γ^1)(Val), Me(γ^2)(Val)). ESI-MS: 430 ([M+Na]$^+$). Anal. calc. for $C_{21}H_{33}N_3O_3S$ (407.57): C 61.88, H 8.16, N 10.31; found: C 62.25, H 8.30, N 10.36.

*(9*H*-Fluoren-9-yl)methyl* N-*{(1*S*)-2-Methyl-1-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}-carbonyl}propyl}carbamate* (Fmoc–Val–Aib-Ψ(CS)–N(Me)Ph; **21d**). A soln. of **31b** (2.036 g, 4.996 mmol) in 60 ml of 3M HCl (THF/H$_2$O 1:1) was stirred for 16 h at r.t. The mixture was cooled to 0°, basified with NaHCO$_3$, and diluted with H$_2$O/dioxane 1:1 (60 ml). The yellow suspension was treated with Fmoc–Cl (1.355 g, 5.238 mmol) dissolved in dioxane (30 ml). After 14 h, the mixture was diluted with H$_2$O and extracted with Et$_2$O (3×), the combined org. layer dried (MgSO$_4$) and evaporated, and the yellow residue chromatographed (SiO$_2$, AcOEt/hexane 1:3): 2.579 g (97%) of **21d**. Yellow, viscous oil which solidified. [α]$_D$ = –68.3 (c = 1.03). IR: 3675*w*, 3430*m*, 3220*w*, 3070*w*, 3030*m*, 2970*m*, 2875*w*, 1790*s*, 1680*m*, 1595*w*, 1490*s*, 1465*s*, 1370*s*, 1320*m*, 1250*m*, 1165*w*, 1100*s*, 1045*m*, 1005*w*, 970*w*, 920*w*, 835*w*. ^{1}H-NMR: 7.77–7.15 (*m*, 13 arom. H); 4.50–4.47 (br. *d*, J = 7.3, CHC*H*$_2$O); 4.25 (*t*, J = 7.0, C*H*CH$_2$O); 3.81–3.80 (*m*, H–C(α)(Val)); 3.70 (*s*, MeN); 2.14–2.00 (*m*, H–C(β)(Val)); 1.65, 1.55 (2*s*, Me$_2$C(Aib^t)); 0.92, 0.89 (2*d*, J = 6.7, Me(γ^1)(Val), Me(γ^2)(Val)). ^{13}C-NMR: 208.4 (*s*, CS(Aib^t)); 168.8 (*s*, CO(Val)); 156.2 (*s*, CO(carbamate)); 147.2, 143.9, 141.3, 129.6, 128.6, 127.7, 127.1, 126.4, 125.1, 120.0 (18 arom. C); 67.0 (*t*, CHCH$_2$O); 62.9 (*s*, C(α)(Aib^t)); 60.1 (*d*, CH(α)(Val)); 51.3 (*q*, MeN); 47.3 (*d*, *C*HCH$_2$O); 31.7 (*d*, CH(β)(Val)); 28.9, 28.6 (2*q*, *Me*$_2$C(Aib^t)); 19.1, 17.6 (2*q*, Me(γ^1)(Val), Me(γ^2)-(Val)). ESI-MS: 552 ([M+Na]$^+$).

Fmoc–Val-Ψ(CS)–Aib–N(Me)Ph (**25d**). According to the *GP B*, with **21d** (0.204 g, 0.384 mmol), AcOH (5 ml), ZnCl$_2$ (2.05 g, 15.0 mmol), and 0.5 ml of 2.1M HCl in AcOH (t_1 15 min, t_2 20 min). Chromatography (SiO$_2$, AcOEt/hexane 1:1) led to 0.174 g (86%) of **25d**. Thick oil which solidified. [α]$_D$ = +27.3 (c = 1.04). IR: 3675*w*, 3375*w*, 3250*w*, 3005*m*, 2965*m*, 2875*w*, 1715*s*, 1640*s*, 1595*m*, 1505*s*, 1450*s*, 1420*m*, 1390*m*, 1365*m*, 1305*m*, 1250*m*, 1170*m*, 1120*m*, 1090*m*, 1035*m*, 1250*m*, 1170*m*, 1120*m*, 1090*m*, 1035*w*, 860*w*. ^{1}H-NMR: 8.19 (*s*, NHCS); 7.77–7.22 (*m*, 13 arom. H); 5.81 (br. *d*, NHCO); 4.47–4.37 (*m*, CHC*H*$_2$O); 4.25 (*t*, J = 7.1, C*H*CH$_2$O); 3.91–3.87 (*m*, H–C(α)(Val^t)); 3.25 (*s*, MeN); 2.18–2.07 (*m*, H–C(β)(Val^t)); 1.71, 1.62 (2*s*, Me$_2$C(Aib)); 0.96–0.86 (*m*, Me(γ^1)(Val^t), Me(γ^2)(Val^t)). ^{13}C-NMR: 201.4 (*s*, CS(Val^t)); 171.8 (*s*, CO(Aib)); 155.9 (*s*, CO(carbamate)); 143.8, 141.3, 129.4, 128.3, 128.0, 127.7, 127.1, 125.1, 120.0 (18 arom. C); 67.0 (*t*, CHCH$_2$O); 66.9 (*d*, H–C(α)(Val^t)); 61.9 (*s*, C(α)(Aib)); 47.1 (*d*, *C*HCH$_2$O); 41.0 (*q*, MeN); 34.1 (*d*, CH(β)(Val^t)); 25.1, 23.7 (2*q*, *Me*$_2$C(Aib)); 19.5, 18.0 (2*q*, Me(γ^1)(Val^t), Me(γ^2)(Val^t)). CI-MS: 424(13), 423(52), 201(31), 179(13), 109(7), 108(100). Anal. calc. for $C_{31}H_{35}N_3O_3S$ (529.70): C 70.29, H 6.66, N 7.93; found: C 69.91, H 6.57, N 7.69.

7. *(9*H*-Fluoren-9-yl)methyl* N-*{(1*S*)-2-{[1,1-Dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}-1-methyl-2-thioxoethyl}carbamate* (Fmoc–Ala-Ψ(CS)–Aib–N(Me)Ph; **25e**). tert-*Butyl* N-*{(1*S*)-2-{[1,1-Dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}-1-methyl-2-oxoethyl}carbamate* (Boc–Ala–Aib-Ψ(CS)–N(Me)Ph; **31c**). According to the *GP A*, with Boc–Ala (2.498 g, 13.202 mmol), THF (30 ml), NMM (2.70 g, 26.69 mmol), isobutyl carbonochloridate (1.99 g, 14.57 mmol), Na$_2$S·H$_2$O (10.0 g, 0.1 mol), CH$_2$Cl$_2$ (50 ml), and **1b** (2.28 g, 13.08 mmol) (reaction time 1.5 h). Chromatography (SiO$_2$, AcOEt/hexane 1:3) gave 4.412 g (88%) of **31c**. Yellow, viscous oil which solidified under high vacuum. [α]$_D$ = –65.5 (c = 1.10). IR: 3430*m*, 3225*w*, 2985*m*, 2935*m*, 1695*s*, 1595*w*, 1490*s*, 1465*s*, 1370*s*, 1325*m*, 1165*s*, 1105*s*, 1070*m*, 1025*w*, 1005*w*, 990*w*, 970*w*, 945*w*, 905*w*, 855*w*. ^{1}H-NMR: 7.42–7.18 (*m*, 5 arom. H); 6.99 (br. *s*, NH); 4.93 (br. *d*, NH); 3.81–3.71 (*m*, H–C(α)(Ala)); 3.71 (*s*, MeN); 1.62 (*s*, Me$_2$C(Aib^t)); 1.44 (*s*, Me$_3$C); 1.25 (*d*, J = 7.0, Me(β)(Ala)). ^{13}C-NMR: 208.3 (*s*, CS(Aib^t)); 170.4 (*s*, CO(Ala)); 155.3 (*s*, CO(carbamate)); 147.5, 129.4, 128.3, 126.0 (6 arom. C); 79.8 (*s*, Me$_3$*C*); 62.5 (*s*, C(α)(Aib^t)); 51.1 (*d*, CH(α)(Ala)); 50.0 (*q*, MeN); 29.7 (*q*, *Me*$_2$C(Aib^t)); 28.2 (*q*, *Me*$_3$C); 17.8 (*q*, Me(β)(Ala)). CI-MS: 382(20), 381(100), 324(26), 192(10), 89(8). Anal. calc. for $C_{19}H_{29}N_3O_3S$ (379.52): C 60.13, H 7.70, N 11.07; found: C 60.46, H 7.81, N 10.92.

*(9*H*-Fluoren-9-yl)methyl* N-*{(1*S*)-2-{{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}-1-methyl-2-oxoethyl}carbamate* (Fmoc–Ala–Aib-Ψ(CS)–N(Me)Ph; **21e**). A soln. of **31c** (0.524 g, 1.219 mmol) in 60 ml of 3M HCl (THF/H$_2$O 1:1) was stirred for 16 h at r.t. The mixture was cooled to 0°, basified with NaHCO$_3$, and diluted with H$_2$O/dioxane 1:1 (60 ml). The yellow suspension was treated with Fmoc–Cl (1.81 g, 7.00 mmol) dissolved in dioxane (30 ml). After 17 h, the mixture was diluted with H$_2$O and extracted with Et$_2$O (3×), the combined org. layer dried (MgSO$_4$) and evaporated, and the yellow residue chromatographed (SiO$_2$, AcOEt/hexane 1:2): 2.858 g (91%) of **21e**. Yellow, viscous oil which solidified. [α]$_D$ = –52.9 (c = 1.08). IR: 3425*w*, 3220*w*, 3070*w*, 3005*m*, 2360*w*, 1715*s*, 1685*s*, 1595*w*, 1490*s*, 1465*s*, 1450*s*, 1370*s*, 1320*m*, 1250*m*, 1105*s*, 1075*m*,

1005*w*, 970*w*. ^{1}H-NMR: 7.77–7.15 (*m*, 13 arom. H); 7.05 (br. *s*, NH); 5.34 (br. *d*, NH); 4.46–4.34 (*m*, CHCH_2O); 4.22 (*t*, *J* = 6.9, CHCH$_2$O); 3.95–3.82 (*m*, H–C(α)(Ala)); 3.70 (*s*, MeN); 1.62, 1.57 (2*s*, Me_2C(Aib^t)); 1.29 (*d*, *J* = 7.0, Me(β)(Ala)). ^{13}C-NMR: 208.3 (*s*, CS(Aib^t)); 170.0 (*s*, CO(Ala)); 155.6 (*s*, CO(carbamate)); 147.4, 143.7, 141.2, 129.5, 128.4, 127.7, 127.0, 126.1, 125.0, 119.9 (18 arom. C); 66.8 (*t*, CHCH_2O); 62.7 (*s*, C(α)(Aib^t)); 51.3 (*q*, MeN); 50.6 (*d*, CHCH$_2$O); 47.1 (*d*, CH(α)(Ala)); 29.4 (*q*, Me_2C-(Aib^t)); 18.6 (*q*, Me(β)(Ala)). ESI-MS: 524 ([*M* + Na]$^+$).

Fmoc–Ala-Ψ(CS)–Aib–N(Me)Ph (**25e**). According to the *GP B*, with **21e** (0.206 g, 0.411 mmol), AcOH (5 ml), $ZnCl_2$ (2.05 g, 15.5 mmol), and 0.5 ml of 2.1M HCl in AcOH (t_1 1.5 min, t_2 2 min). Chromatography (SiO_2, AcOEt/CH_2Cl_2/hexane 1:1:2) gave 0.193 g (94%) of **25e**. White solid. $[\alpha]_D = -4.2$ (*c* = 1.06). IR: 3690*w*, 3545*w*, 3375*w*, 3270*w*, 3030*w*, 2995*w*, 2945*w*, 2360*w*, 1730*s*, 1640*s*, 1595*s*, 1495*s*, 1450*s*, 1420*m*, 1375*m*, 1360*m*, 1320*w*, 1270*m*, 1250*m*, 1120*w*, 1035*w*, 1000*w*, 940*w*, 845*w*. ^{1}H-NMR: 8.21 (br. *s*, NH); 7.78–7.21 (*m*, 13 arom. H); 5.76–5.74 (br. *d*, NH); 4.41–4.11 (*m*, CHCH$_2$O, H–C(α)(Ala^t)); 3.24 (*s*, MeN); 1.66, 1.59 (2*s*, Me_2C-(Aib)); 1.35 (*d*, *J* = 6.8, Me(β)(Ala^t)). ^{13}C-NMR: 202.2 (*s*, CS(Ala^t)); 171.3 (*s*, CO(Aib)); 155.5 (*s*, CO(carbamate)); 144.0, 143.6, 141.2, 129.1, 128.0, 127.7, 127.6, 127.0, 125.0, 120.0 (18 arom. C); 67.1 (*t*, CHCH_2O); 61.5 (*s*, C(α)(Aib)); 56.4 (*d*, CHCH$_2$O); 47.0 (*d*, CH(α)(Ala^t)); 40.9 (*q*, MeN); 25.6, 24.8 (2*q*, Me_2C(Aib)); 22.0 (*q*, Me(β)(Ala^t)). ESI-MS: 524 ([*M* + Na]$^+$). Anal. calc. for $C_{29}H_{31}N_3O_3S$ (501.64): C 69.44, H 6.23, N 8.38; found: C 68.55, H 6.28, N 8.28.

8. *Benzyl* N-*{2-{{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}-2-thioxoethyl}carbamate* (Z–Gly-Ψ(CS)–Aib–N(Me)Ph; **25f**). *Benzyl* N-*{2-{{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}-amino}-2-oxoethyl}carbamate* (Z–Gly–Aib-Ψ(CS)–N(Me)Ph; **21f**). According to the *GP A*, with Z–Gly (0.280 g, 1.337 mmol), THF (5 ml), NMM (0.275 g, 0.272 mmol), isobutyl carbonochloridate (0.196 g, 1.434 mmol), $Na_2S \cdot H_2O$ (1.5 g, 1.7 mmol), CH_2Cl_2 (10 ml), and **1b** (0.262 g, 1.504 mmol) (reaction time 1 h). Crystallization from hexane/Et_2O gave 0.480 g (90%) of **21f**. Colorless crystals. Recrystallization from hexane/EtOH/AcOEt/CH_2Cl_2 led to single crystals suitable for X-ray diffraction analysis. M.p. 106.2–107.1°. IR: 3425*w*, 3335*w*, 3210*w*, 3010*w*, 3005*w*, 2940*w*, 1720*m*, 1690*m*, 1595*w*, 1495*s*, 1465*m*, 1455*m*, 1430*w*, 1385*w*, 1370*m*, 1360*m*, 1235*m*, 1165*w*, 1100*m*, 1050*w*, 1005*w*. ^{1}H-NMR: 7.40–7.16 (*m*, 10 arom. H); 6.73 (br. *s*, NH); 5.28 (br. *s*, NH); 5.11 (*s*, CH_2O); 3.70 (*s*, MeN); 3.52 (*d*, *J* = 5.5, CH_2(α)(Gly)); 1.64 (*s*, Me_2C(Aib^t)). ^{13}C-NMR: 204.2 (*s*, CS(Aib^t)); 168.1 (*s*, CO(Gly)); 156.6 (*s*, CO(carbamate)); 147.7, 136.1, 129.3, 128.6, 128.1, 128.0, 126.7 (12 arom. C); 67.1 (*t*, CH_2O); 62.1 (*s*, C(α)(Aib^t)); 51.2 (*q*, MeN); 45.9 (*t*, CH_2(α)(Gly)); 28.7 (*q*, Me_2C(Aib^t)). CI-MS: 400 (100, [*M* + 1]$^+$), 292 (13). Anal. calc. for $C_{21}H_{25}N_3O_3S$ (399.51): C 63.14, H 6.31, N 10.52, S 8.03; found: C 63.10, H 6.24, N 10.80, S 8.14.

Z–Gly-Ψ(CS)–Aib–N(Me)Ph (**25f**). According to the *GP B*, with **21f** (0.211 g, 0.527 mmol), AcOH (6 ml), $ZnCl_2$ (2.45 g, 18.0 mmol), and 0.6 ml of 2.1M HCl in AcOH (t_1 30 min, t_2 15 min). Chromatography (SiO_2, AcOEt/hexane 1:1) led to 0.202 g (96%) of **25f**. White solid. Crystallization from hexane/EtOH/Et_2O/CH_2Cl_2 led to single crystals which were suitable for X-ray diffraction analysis. M.p. 110.7–111.7°. IR: 3450*w*, 3380*w*, 3350*w*, 3270*w*, 3070*w*, 1600*m*, 1820*s*, 1460*m*, 1390*m*, 1370*m*, 1270*m*, 1220*s*, 1175*m*, 1150*w*, 1125*m*, 1090*w*, 1080*w*, 1050*w*, 1010*w*, 970*w*, 930*w*. ^{1}H-NMR: 8.11 (br. *s*, NH); 7.51–7.40 (*m*, 10 arom. H); 5.60 (br. *s*, NH); 5.22 (*s*, CH_2O); 3.90 (*d*, *J* = 4.7, CH_2(α)(Gly^t)); 3.35 (*s*, MeN); 1.78 (*s*, Me_2C(Aib)). ^{13}C-NMR: 197.0 (*s*, CS(Gly^t)); 171.0 (*s*, CO(Aib)); 156.3 (*s*, CO(carbamate)); 144.2, 136.0, 129.1, 128.5, 128.2, 127.9, 127.2 (12 arom. C); 67.1 (*t*, CH_2O); 61.2 (*s*, C(α)(Aib)); 52.5 (*t*, CH_2(α)(Gly^t)); 40.9 (*q*, MeN); 25.8 (*q*, Me_2C(Aib)). ESI-MS: 422 ([*M* + Na]$^+$). Anal. calc. for $C_{21}H_{25}N_3O_3S$ (399.51): C 63.14, H 6.31, N 10.52, S 8.03; found: C 62.53, H 6.23, N 10.32, S 7.62.

9. *Benzyl* N-*{(1S)-1-Benzyl-2-{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}-2-thioxoethyl}-carbamate* (Z–Phe-Ψ(CS)–Aib–N(Me)Ph; **25g**). *Benzyl* N-*{(1S)-1-Benzyl-2-{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-thioxoethyl}amino}-2-oxoethyl}carbamate* (Z–Phe–Aib-Ψ(CS)–N(Me)Ph; **21g**). According to the *GP A*, with Z–Phe (0.961 g, 3.209 mmol), THF (15 ml), NMM (0.660 g, 6.529 mmol), isobutyl carbonochloridate (0.443 g, 3.245 mmol), CH_2Cl_2 (25 ml), and **1b** (0.639 g, 3.670 mmol) (reaction time 3 h). Chromatography (SiO_2, AcOEt/hexane 1:2) led to 0.935 g (55%) of **21g**. Yellow, thick oil which solidified. $[\alpha]_D = -47.1$ (*c* = 1.00). IR: 3480*m*, 3250*m*, 3100*m*, 3060*m*, 3040*m*, 2980*m*, 2930*w*, 1720*s*, 1680*s*, 1640*s*, 1600*m*, 1550*w*, 1520*m*, 1500*s*, 1480*m*, 1440*m*, 1380*m*, 1370*s*, 1340*m*, 1290*m*, 1160*m*, 1100*s*, 1050*m*, 1030*m*, 1000*m*, 990*w*, 970*w*, 920*m*, 840*w*. ^{1}H-NMR: 7.36–7.08 (*m*, 15 arom. H); 6.47 (br. *s*, NH); 5.39 (*d*, *J* = 7.6, NH); 5.11–5.09 (*m*, CH_2O); 3.99–3.08 (*m*, H–C(α)(Phe)); 3.65 (*s*, MeN); 3.04–2.87 (*m*, CH_2(β)(Phe)); 1.56, 1.38 (2*s*, Me_2C-(Aib^t)). ^{13}C-NMR: 208.0 (*s*, CS(Aib^t)); 168.3 (*s*, CO(Phe)); 155.6 (*s*, CO(carbamate)); 147.3, 136.6, 136.3, 129.4, 129.3, 128.6, 128.4, 128.3, 128.1, 128.0, 126.9, 126.0 (18 arom. C); 66.8 (*t*, CH_2O); 62.6 (*s*, C(α)(Aib^t)); 56.2 (*d*, CH(α)(Phe)); 51.1 (*q*, MeN); 38.6 (*t*, CH_2(β)(Phe)); 29.4, 29.3 (2*q*, Me_2C(Aib^t)). ESI-MS: 512 ([*M* + Na]$^+$).

Z–Phe-Ψ(CS)–Aib–N(Me)Ph (**25g**). According to the *GP B*, with **21g** (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, AcOH/CH_2Cl_2/hexane 1:1:2) gave 0.619 g (91%) of **25g**. White solid. M.p. 177–178°. $[\alpha]_D = +98.3$ ($c = 1.00$). IR: 3050*m*, 1720*s*, 1690*m*, 1640*m*, 1600*m*, 1520*m*, 1500*s*, 1480*m*, 1460*w*, 1420*m*, 1390*m*, 1370*m*, 1280*m*, 1120*m*, 1070*m*, 1040*s*, 920*m*, 840*m*. ^{1}H-NMR: 7.36–7.13 (*m*, 15 arom. H); 5.89 (*d*, $J = 6.8$, NH); 5.16–5.05 (*m*, CH_2O); 4.12–4.06 (*m*, H–C(α)(Phe^t)); 3.16 (*s*, MeN); 3.11–2.83 (*m*, CH_2(β)(Phe^t)); 1.48, 1.29 (2*s*, Me_2C(Aib)). ^{13}C-NMR: 197.9 (*s*, CS(Phe^t)); 169.1 (*s*, CO(Aib)); 153.3 (*s*, CO(carbamate)); 142.0, 134.8, 134.5, 133.3, 127.8, 127.5, 127.3, 126.8, 126.7, 126.4, 126.3, 125.6, 125.4, 125.2 (18 arom. C); 65.1 (*t*, CH_2O); 61.0 (*s*, C(α)(Aib)); 59.6 (*d*, CH(α)(Phe^t)); 40.5 (*t*, CH_2(β)(Phe^t)); 39.1 (*q*, MeN); 24.3, 22.1 (2*q*, Me_2C(Aib)). ESI-MS: 512 ($[M+Na]^+$).

Crystal-Structure Determination of **21f** *and* **25f**[7]). The intensities were collected on a *Rigaku-AFC5R* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating-anode generator. The $\omega/2\theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Data collection and refinement parameters are given in *Table 2*,

Table 2. *Crystallographic Data of Compounds* **21f** *and* **25f**

	21f	**25f**
Crystallized from	hexane/EtOH/AcOEt/CH_2Cl_2	hexane/EtOH/Et_2O/CH_2Cl_2
Empirical formula	$C_{21}H_{25}N_3O_3S$	$C_{21}H_{25}N_3O_3S$
Formula weight	399.51	399.51
Crystal color, habit	colorless, prism	colorless, prism
Crystal dimensions [mm]	0.25 × 0.30 × 0.36	0.22 × 0.23 × 0.38
Temperature [K]	173(1)	173(1)
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Z	2	2
Reflections for cell determination	25	25
2θ range for cell determination [°]	38–40	38–40
Unit cell parameters a [Å]	9.762(2)	10.628(3)
b [Å]	12.690(2)	12.083(3)
c [Å]	9.221(1)	8.959(2)
α [°]	106.76(1)	90.55(2)
β [°]	90.65(2)	109.44(2)
γ [°]	105.32(2)	70.17(2)
V [Å^3]	1050.2(4)	1013.6(5)
D_x [g cm^{-3}]	1.263	1.309
μ(MoK_α) [mm^{-1}]	0.180	0.186
$2\theta_{(max)}$ [°]	60	60
Total reflections measured	6439	6194
Symmetry-independent reflections	6105	5904
Reflections used ($I > 2\sigma(I)$)	4752	4645
Parameters refined	353	354
Final R	0.0485	0.0426
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0501	0.0425
Goodness of fit	2.260	2.080
Secondary extinction coefficient	–	$1.9(1)\cdot10^{-6}$
Final Δ_{max}/σ	0.0009	0.0006
$\Delta\rho$ (max; min) [e Å^{-3}]	0.39; −0.49	0.32; −0.26

7) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Center* as deposition no. CCDC-115359 and 115360 for **21f** and **25f**, respectively. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

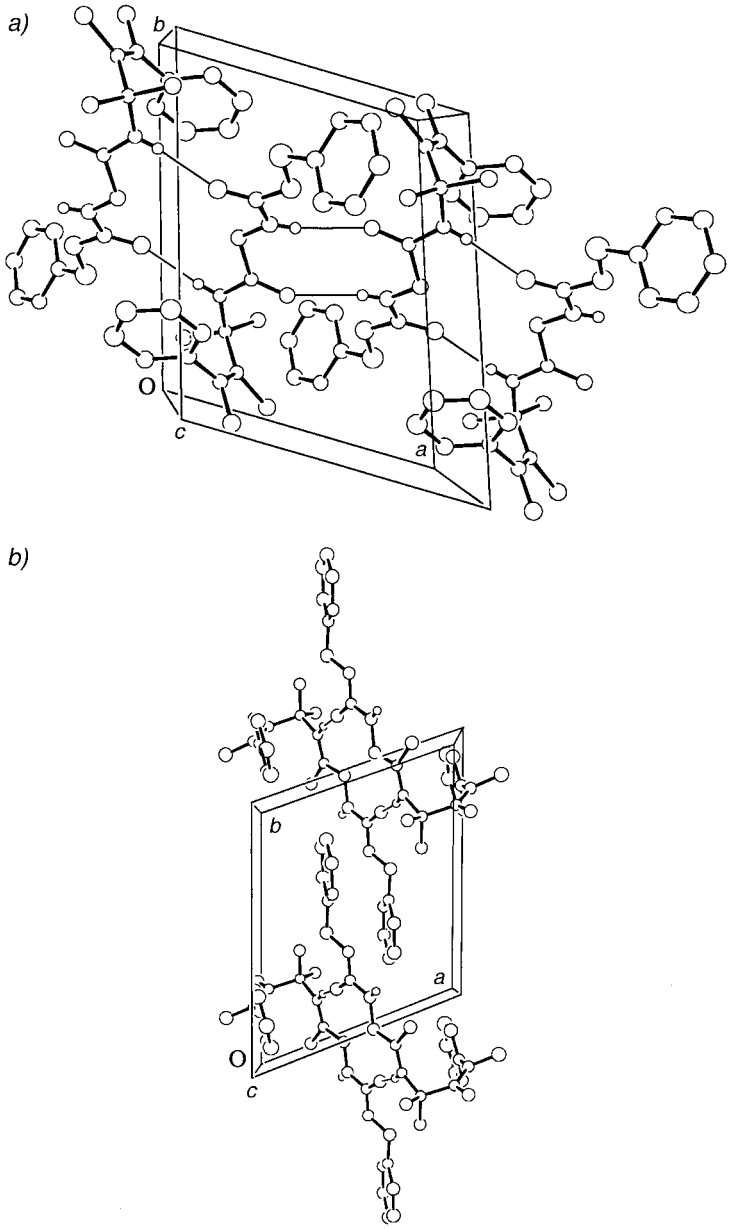


Fig. 2. *Molecular packing of* a) **21f** *and* b) **25f** *showing the H-bonding schemes* (arbitrary spheres for atoms; uninvolved H-atoms omitted for clarity)

views of the molecules are shown in *Fig. 1*. The structures were solved by direct methods using SHELXS86 [32], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anistropically. All of the H-atoms were located in difference electron-density maps, and their positions were allowed to refine together with individual isotropic displacement parameters. Refinement of each structure was carried out on *F* using full-

matrix least-squares procedures, which minimized the function $\sum w(|F_o|-|F_C|^2)$. A correction for secondary extinction was applied in the case of **25f**. Neutral-atom scattering factors for non-H-atoms were taken from [33], and the scattering factors for H-atoms from [34]. Anomalous dispersion effects were included in F_{calc} [35], the values for f' and f'' were those of [36]. All calculations were performed with the TEXSAN crystallographic software package [37].

Each NH group of **21f** acts as a donor for intermolecular H-bonds. The corresponding acceptor atoms are the carbonyl O-atoms of neighboring molecules that are related to the donor molecule by centers of inversion. This gives the unitary graph sets [38] $R_2^2(14)$ and $R_2^2(10)$ for the interactions involving N(1) and N(4), respectively. However, the donor molecule forms H-bonds with two different acceptor molecules, so that the combination of both interactions links the molecules into infinite one-dimensional zig-zag chains running parallel to the *x*-axis; binary graph set: $C_2^2(8)$ (*Fig. 2*). In **25f**, only one of the NH groups acts as a donor for H-bonds. The corresponding acceptor atom is the carbonyl O-atom of the carbamate group of a neighboring molecule. This intermolecular H-bond links the molecules across a center of inversion into dimers; graph set: $R_2^2(14)$ (*Fig. 2*).

We thank Dr. *G. Hopp-Rentsch*, Mrs. *N. Walch*, and Mr. *M. Binder* for NMR spectra, Mr. *N. Bild* and Dr. *L. Bigler* for mass spectra, and Mrs. *J. Kessler* for elemental analyses. Financial support of this work by the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

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Received March 6, 1999