Synthesis of Endothiopeptides and Their Cyclization to 1,3-Thiazol-5(4*H*)-imines

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Further investigations of the synthesis of endothio analogues of the segment 1–10 (**8**) of an apolar analogon of zervamicin IIA are described. The endothiodecapeptide Boc-Trp-Ile-Ala-Aib-Ile-Val-Aib-Leu-Aib-Ψ(CS)-Pro-OMe (**10**) has been prepared in good yield by our novel methodology. On the other hand, all attempts to prepare endothio analogues of **8** with the thioamide group at position 3 (Ala^t) gave not the expected linear endothiopeptides but led to epimerized 1,3-thiazol-5(4*H*)-imine derivatives as the main products. The mixture of epimers of the thiazolimines **27**, **30**, and **31** have been separated by means of preparative HPLC, and their structures have been established by 2D-NMR experiments.

Introduction. – Peptides with backbone modifications have attracted considerable interest in recent years [1]. Among them, endothiopeptides with one or more thioamide groups replacing amide groups within the peptide chain play an important role for several reasons (*cf.* refs. cited in [2–4]). Endothiopeptides have hitherto been prepared by the use of thionating reagents [5–8] or *via* thioacylation [9–16]. Unfortunately, most of these methods are accompanied by low yields or epimerization. Other backbone-modified peptides of considerable interest are those containing α-alkylated α-amino acids, *e.g.*, α-aminoisobutyric acid (Aib) and isovaline (Iva). Representatives are the naturally occurring peptaibols, which show antibiotic properties [17][18]. The twofold substitution at the C(α)-atom of these amino acids restricts the conformational flexibility and stabilizes or induces helices (*cf.* [19–24] and refs. cited therein). With the 'azirine/oxazolone method', we developed a convenient synthetic access to such peptides, and 3-amino-2*H*-azirines proved to be useful synthons for the introduction of α-alkylated α-amino acids (*cf.* [25–28] and refs. cited therein). Recently, we succeeded in combining these two types of backbone modifications by a variation of the 'azirine/oxazolone method' [2–4] (*Scheme 1*).

Reaction of a *N*-protected α-amino thio *S*-acid **1** with 2,2-dimethyl-3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**2**) yields a thiodipeptide amide of type **3**. With $ZnCl_2$ and HCl in AcOH, **3** undergoes an unprecedented isomerization to give **4** without epimerization (*ca.* 90% yield) [2]. The acid-catalyzed conversion of the endothiodipeptide **4** to 1,3-thiazol-5(4*H*)-one **5** and direct coupling with an amino compound **6** (*e.g.*, a *C*-protected α-amino acid) leads to endothiopeptides of type **7** in satisfactory yields without epimerization [3]. We have already demonstrated the usefulness of this novel methodology by the synthesis of Boc-Trp-Ile-Ala-Aib-Ile-Val-Ψ(CS)-Aib-Leu-

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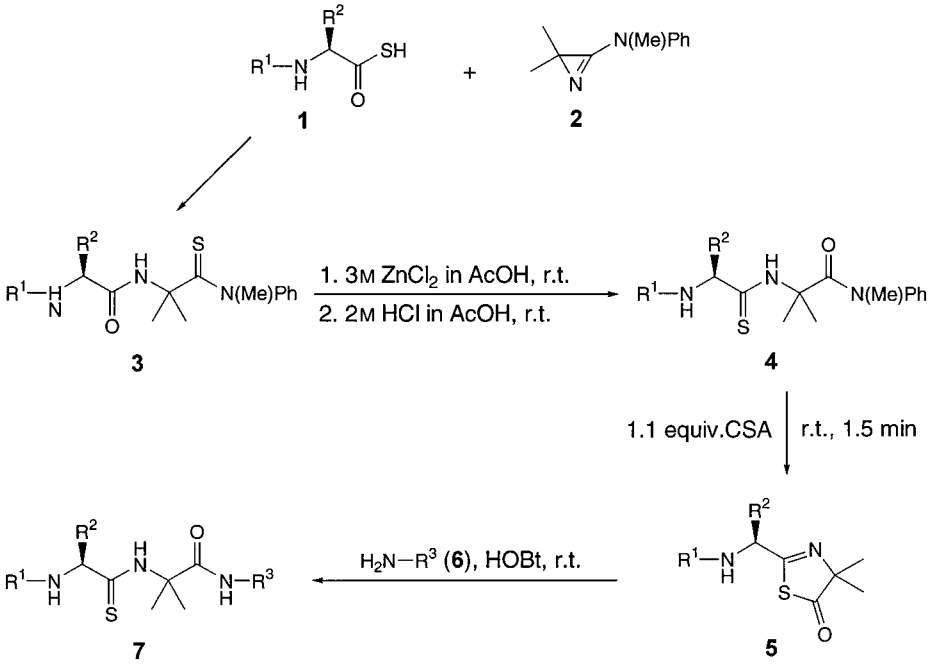
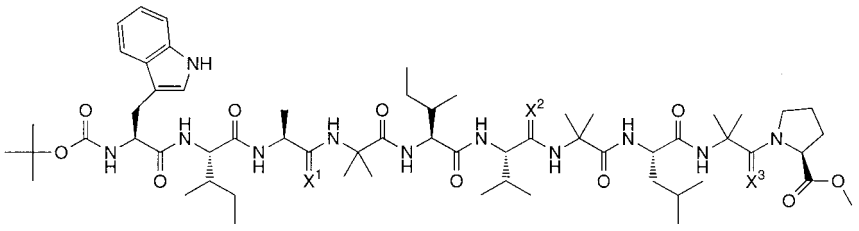
[1]) Part of the Ph. D. thesis of *J.L.*, Universität Zürich, 1998; present address: Department of Chemistry, University of California at Berkeley, CA 94720 (USA).

Scheme 1



CSA = (±)-Camphor-10-sulfonic acid



8 $X^1 = X^2 = X^3 = O$
9 $X^1 = O$, $X^2 = S$, $X^3 = O$
10 $X^1 = X^2 = O$, $X^3 = S$
11 $X^1 = S$, $X^2 = O$, $X^3 = O$
12 $X^1 = X^2 = S$, $X^3 = O$

Fig. 1. *Apolar analogues of segment 1–10 of Zervamicin IIA*

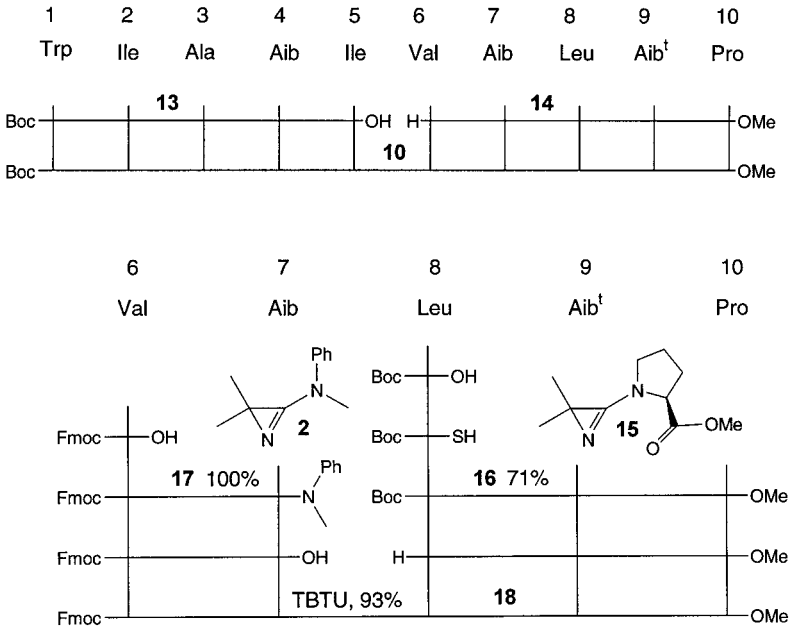
Aib-Pro-OMe (**9**) [4], an endothio derivative of the apolar segment 1–10 of the zervamicin IIA-analogue **8** [29] (*Fig. 1*).

In the present work, we describe our further investigations in preparing other endothio derivatives of **8**. We intended to synthesize endothiodecapeptides **10**–**12** to show, on the one hand, the usefulness of our methodology and, on the other hand, to solve their crystal structures, with the aim of further understanding the influence of the

replacement of an amide group by a thioamide group with respect to the conformation of the peptide.

Results and Discussion. – The endothiodecapeptide **10** was prepared by coupling of segment 1–5 (**13**) with segment 6–10 (**14**; *Scheme 2*).

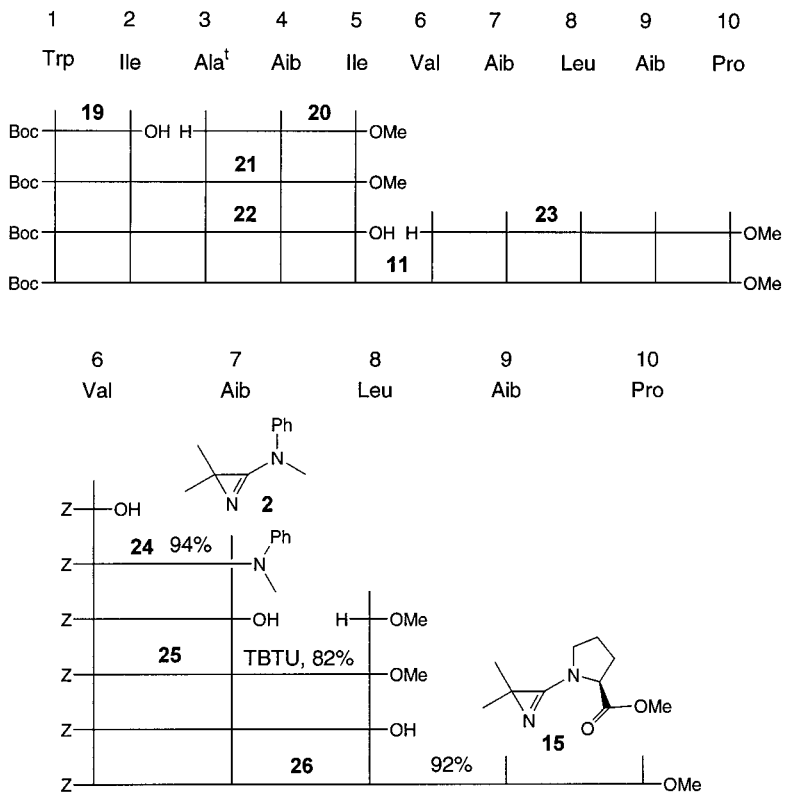
Scheme 2



Segment 1–5 (**13**) was synthesized by standard solution peptide methodology, by which the Aib group was introduced *via* the 'azirine/oxazolone method' [2–4], and segment 6–10 (**18**) was prepared as shown in *Scheme 2:* the *N*-protected amino acid Boc-Leu-OH was transformed into the corresponding thioacid *via* reaction of its mixed anhydride with H_2S. The crude Boc-Leu-SH was then treated with the Aib-Pro synthon methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**15**) to afford the endothiotripeptide **16** in 71% yield, with respect to Boc-Leu-OH. The dipeptide Fmoc-Val-Aib-N(Me)Ph (**17**) was prepared in quantitative yield by the reaction of Fmoc-Val-OH and 3-amino-2*H*-azirine **2**. After the hydrolysis of **17** under the standard conditions of the 'azirine/oxazolone method' (3M HCl, THF/H_2O 1:1), Fmoc-Val-Aib-OH was coupled with the terminal-*N*-deprotected **16** (2M HCl in THF/H_2O 1:1) using 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) as the coupling reagent in the presence of 1-hydroxy-1*H*-benzotriazole (HOBt) and EtN(i-Pr)$_2$, leading to the endothiopentapeptide **18** in 93% yield, with respect to **16**. Finally, coupling of the pentapeptide **13** with the endothiopentapeptide **14**, which was obtained by treatment of **18** with Et_2NH, with [(benzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) as the coupling reagent in the presence of EtN(i-Pr)$_2$, yielded the endothiodecapeptide **10** in 90% yield.

The synthesis of the isomeric endothiodecapeptide **11**, in which the amide group of Ala is replaced by a thioamide group, was planned as depicted in *Scheme 3*.

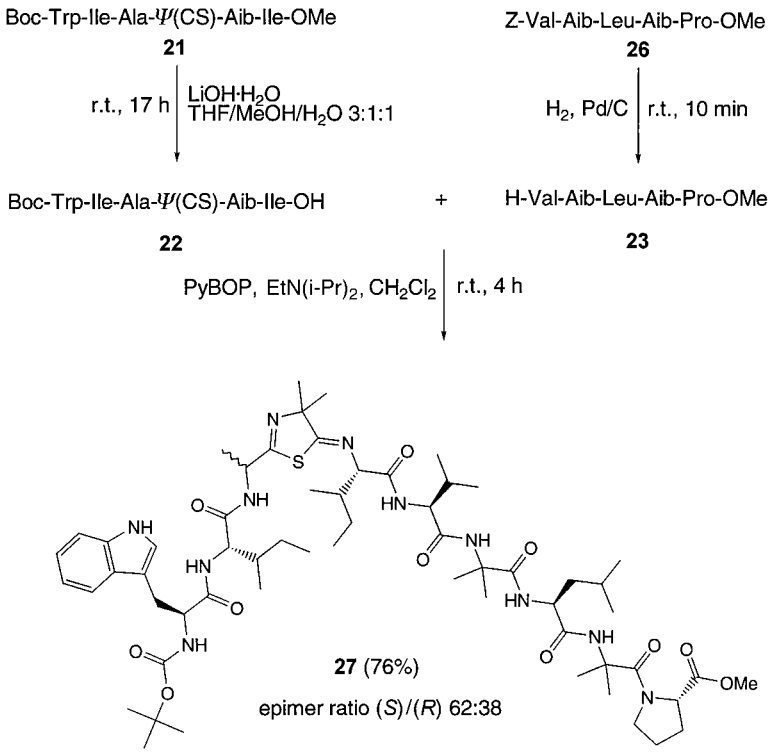
Scheme 3



Segment 3–5 (**20**), containing a N-terminal Fmoc protecting group, was synthesized by our novel methodology, which has been described earlier [2][3]. Reaction of Boc-Trp-OH and H-Ile-OMe with TBTU, in the presence of HOBt and EtN(i-Pr)$_2$, gave the corresponding dipeptide in 99% yield. Base-catalyzed hydrolysis led to **19**, and its coupling with **20** (TBTU, HOBt, and EtN(i-Pr)$_2$) gave the endothiopentapeptide **21** in 71% yield. Segment 6–10 (**26**) was prepared as shown in *Scheme 3*: treatment of Z-Val-OH with the Aib synthon **2** yielded dipeptide **24** (94%). Hydrolysis of **24** under the conditions of the 'azirine/oxazolone method', followed by coupling of the crude product with H-Leu-OMe, gave tripeptide **25** in 82% yield. Base-catalyzed hydrolysis of **25** with LiOH, followed by the reaction with 3-amino-2*H*-azirine **15**, led to pentapeptide **26** in 92% yield, with respect to **24**.

Unexpectedly, the coupling of peptide acid **22** with pentapeptide **23**, which was obtained *via* Pd-catalyzed hydrogenolytic cleavage of the Z protecting group of **26**, with PyBOP as the coupling reagent, did not lead to the endothiodecapeptide **11**. Rather, an epimeric mixture of 1,3-thiazol-5(4*H*)-imine derivative **27** was obtained in 76% yield (*Scheme 4*).

Scheme 4

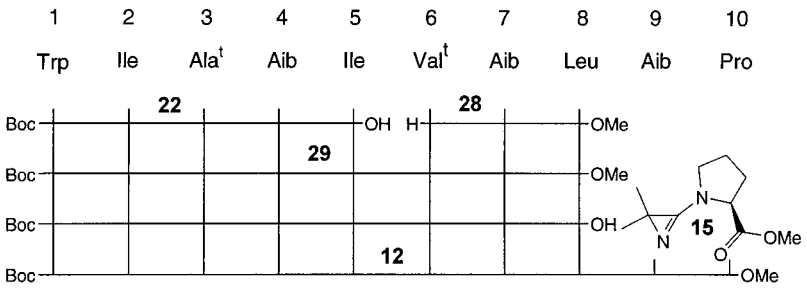


That the isolated product was the epimerized thiazolimine derivative **27** and not the desired linear endothiodecapeptide **11** has been inferred from the following observations: *i*) The ESI-MS showed the $[M + Na]^+$ peak at m/z 1201, *i.e.*, 18 mass units below that of **11**. *ii*) In the NMR spectra, peak doubling was observed, which did not disappear at elevated temperature (100°), *i.e.*, a mixture of conformers can be excluded. Moreover, ROESY spectra showed no exchange of doubled peaks. *iii*) Analytical HPLC showed two peaks in a ratio of 62 : 38, which were separated by preparative HPLC. *iv*) The NMR spectra of the two separated substances display following characteristics: in the ^{13}C-NMR spectra, no peak at *ca.* 200 ppm, typical for the linear endothiodecapeptide **11**, could be detected. Furthermore, in the region of the amide C-atoms, two *singlets* at too low and too high chemical shift, respectively, were observed: the *singlet* at 165.1 ppm of the main epimer showed a long-range coupling with the H-atoms at C(α) and C(β) of Ala, and the *singlet* at 179.5 ppm with the H-atoms of Aib(2). In the ^{1}H-NMR spectra, the signal of H-C(α) (Ile(2)) at 3.28 ppm appears as a sharp *singlet* and, in addition, only eight NH groups could be evidenced. *v*) That a mixture of epimers of **27** has been formed and not, as also conceivable, a mixture of (*Z*)/(*E*)-isomers around the double bond between C(5) of the thiazole ring, and the N-atom of the imine group, is supported by the following experiment: after separating the two peaks by means of preparative reversed-phase HPLC, an aliquot of the

evaporated fractions of the main peak was dissolved in MeCN, and (±)-camphor-10-sulfonic acid (CSA) was added. Even after only a few minutes, the second isomer could be detected again by means of analytical HPLC. After 1 h, both peaks were present in a 50 : 50 ratio. From this result, we concluded that the major compound of the original epimeric mixture (62%) has the (*S*)-configuration at C(α) of Ala; under acid catalysis the (*S*)/(*R*) ratio settled down to 50 : 50. *vi*) There is no prove whether the (*Z*) or the (*E*)-configured imino group has been formed. However, as a result of the steric interactions with the geminal Me groups at C(4) of the thiazole ring, it can be assumed that the (*Z*)-configuration is preferred, as shown for simpler but comparable 1,3-thiazol-5(4*H*)-imines (*cf.* [30][31]).

The preparation of the endothiopeptide **12**, in which two different amide groups are replaced by thioamide groups, was attempted according to *Scheme 5:* coupling of the two endothiopeptides **22** and **28** was expected to give the endothiooctapeptide **29**, which, after C-terminal deprotection and treatment with the Aib-Pro synthon **15**, should lead to **12**.

Scheme 5



The synthesis of segment 6–8 (**28**) has already been published [4]. In a first attempt, **22** and **28** were coupled using TBTU, HOBt, and EtN(i-Pr)$_2$. After the usual workup, the crude product could not be dissolved anymore and, therefore, could not be purified and analyzed. Thus, the crude product was directly hydrolyzed (LiOH) and treated with the Aib-Pro synthon **15**. Again, we did not obtain the expected linear **12** but a mixture of epimers of the 1,3-thiazol-5(4*H*)-imine **30** (*Fig. 2*) in 48% yield with

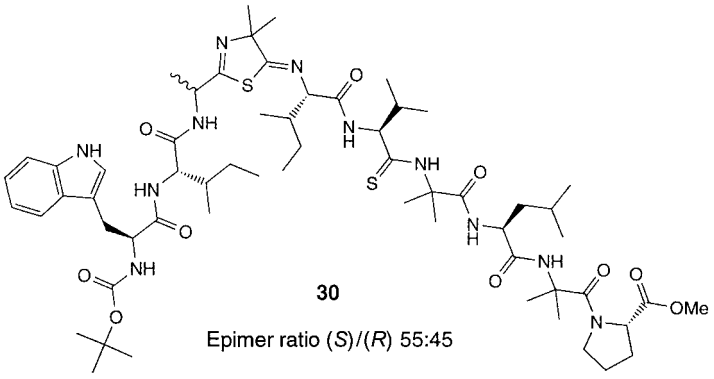
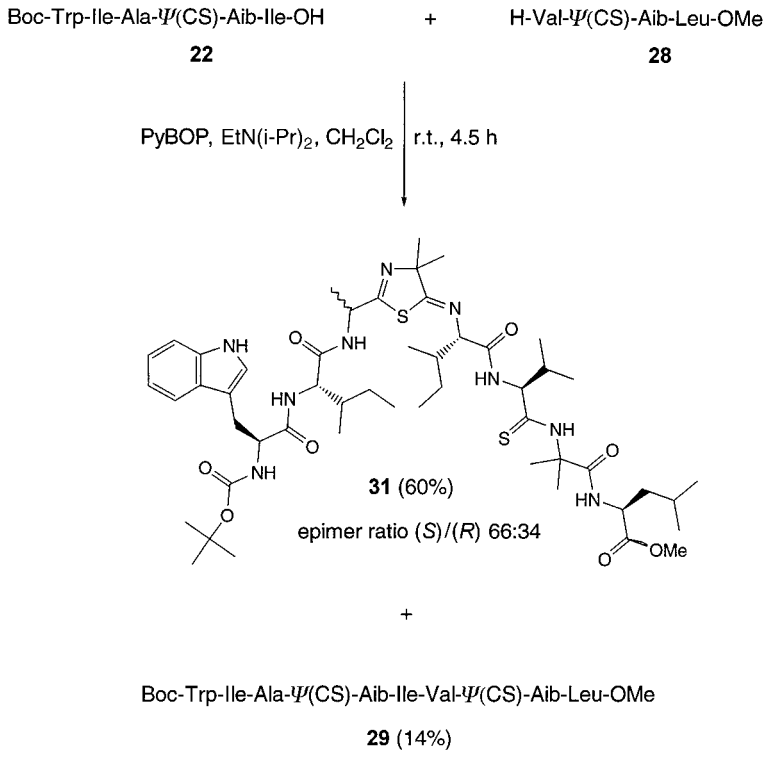


Fig. 2. *1,3-Thiazol-5(4*H*)-imine* **30** *of the endodithiodecapeptide* **12**

respect to Boc-Trp-Ile-Ala-Ψ(CS)-Aib-Ile-OMe (**21**). The two epimers were detected in a ratio of 55 : 45 (HPLC) and could be separated by preparative HPLC. In analogy to the case of **27**, it can be assumed that the major epimer, which has been formed in more than 50% yield, contains Ala with the (*S*)-configuration.

In a second experiment, **22** and **28** were coupled with PyBOP as the coupling reagent in the presence of $EtN(i\text{-}Pr)_2$ (*Scheme 6*). After the usual workup, no solubility problems arose, in contrast to the first attempt. A mixture of epimers of the 1,3-thiazol-5(4*H*)-imine **31** was isolated in 60% yield with a (*S*)/(*R*) ratio of 66 : 34. In addition, a third product, presumably the desired linear endothiooctapeptide **29**, was obtained in 14% yield[2]).

Scheme 6



A plausible mechanism for the formation of the thiazolimines **27**, **30**, and **31** is shown in *Scheme 7*: nucleophilic attack of the S-atom of the thioamide group in **A** at the C-atom of the neighboring amide group leads to the zwitterionic heterocycle **B**, which yields the thiazolimine **D** after elimination of H_2O.

To clarify whether the cyclization to the thiazolimines occurred after the formation of the linear endothiopeptide, a solution of **29** in MeCN was stirred at 40° for several

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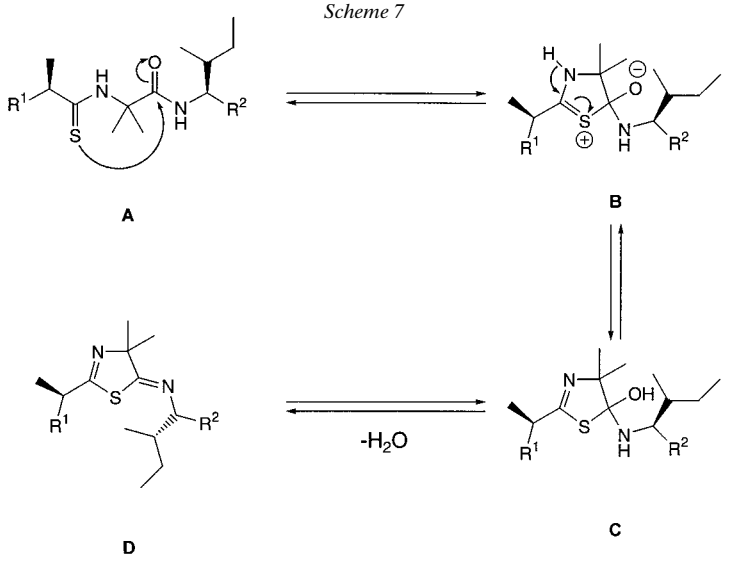
[2]) The structure of this product has not yet been established. The ESI-MS shows the $[M + Na]^+$ peak at *m*/*z* 1053, in accordance with structure **29**.

Scheme 7



days, but no thiazolimine could be detected by HPLC. Then, the coupling reagent PyBOP was added to the solution. Surprisingly, after stirring for several days, even under these conditions no cyclization occurred. Thus, it can be concluded that thiazolimine formation must take place before or during the coupling of the two segments. It is conceivable that, during the coupling, a conformation of the endothiopeptide is formed that favors cyclization according to *Scheme 7*.

In conclusion, we described further attempts to synthesize endothio derivatives of the segment 1–10 of the apolar zervamicin IIA analogue **8**. Surprisingly, in the two cases with Ala^t, we obtained not the expected linear endothiopeptides, but a mixture of epimers of thiazolimine derivatives. In our future work, we will try to answer several questions in connection with this cyclization, *e.g.*, which structure elements are required for the thiazolimine formation, and is there a possibility to prevent this cyclization or the epimerization of the thiazolimine derivatives.

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.

Experimental Part

1. *General. See* [2].

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

General Procedure 2 (*GP 2*). To a soln. of 1 equiv. of *N*-protected amino acid or *N*-protected peptide, 1.1 equiv. of terminal-*C*-protected amino acid or peptide, and 1 equiv. of [1*H*-benzotriazol-1-yl)oxy]tris-

(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) in CH_2Cl_2, 2 equiv. of EtN(i-Pr)$_2$ (3 equiv., when the hydrochloride of the terminal-*C*-protected amino acid was used) were added. The mixture was stirred at r.t. until the starting material was consumed (TLC). Then, the soln. was diluted with CH_2Cl_2 and extracted 3 × with 5% $NaHCO_3$ and $KHSO_4$ soln. The combined aq. phase was washed with CH_2Cl_2 and the combined org. phase dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography (SiO_2).

General Procedure 3 (*GP 3*). To a soln. of 1 equiv. of *N*-protected amino acid or *N*-protected peptide in CH_2Cl_2, 1 equiv. of 2,2-dimethyl-3-(*N*-methyl-*N*-phenylamino)-2*H*-azirine (**2**) or methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**15**) was added slowly. The soln. was allowed to reach r.t. and stirred until the starting material was consumed (TLC). The mixture was washed with $KHSO_4$ soln., the org. phase was dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by chromatography (SiO_2) or recrystallization.

General Procedure 4 (*GP 4*). To a soln. of 1 equiv. of terminal-*C*- and terminal-*N*-protected peptide in THF/MeOH/H_2O 3:1:1, 2–5 equiv. of $LiOH \cdot H_2O$ were added, and the mixture was stirred at r.t. until the starting material was consumed. The mixture was diluted with CH_2Cl_2 and washed with 5% $KHSO_4$ soln. The combined org. phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was dried under high vacuum and used in the next reaction without further purification.

General Procedure 5 (*GP 5*). A soln. of 1 equiv. of peptide anilide in 3M HCl (THF/H_2O 1:1) was stirred at r.t. until the starting material was consumed. Then, the mixture was diluted with H_2O and extracted 3 × with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$), filtered, and evaporated. The crude product was dried under high vacuum and used in the next reaction without further purification.

2. *Methyl (2S)-1-{2-[(2S)-2-(2-{(2S)-2-[(2S,3S)-2-(2-{(2S)-2-[(2S,3S)-2-((2S)-{[(*tert*-Butoxy)carbonyl]amino}-3-(indol-3-yl)propanamido)-3-methylpentanamido]propanamido}-2-methylpropanamido)-3-methylpentanamido]-3-methylbutanamido}-2-methylpropanamido)-4-methylpentanamido]-2-methylthiopropanoyl}pyrrolidine-2-carboxylate* (*Boc-Trp-Ile-Ala-Aib-Ile-Val-Aib-Leu-Aib-Ψ(CS)-Pro-OMe*; **10**). *(9*H*-Fluoren-9-yl)methyl 1-{(2S)-2-Methyl-1-[({1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)carbonyl]propyl}carbamate* (*Fmoc-Val-Aib-N(Me)Ph*; **17**). According to the *GP 3* with Fmoc-Val (1.022 g, 3.012 mmol), CH_2Cl_2 (25 ml), and **2** (0.528 g, 3.029 mmol); reaction time: 3 d. Chromatography (SiO_2; AcOEt/hexane 1:1) gave 1.560 g (100%) of **17** as a colorless, viscous oil, which solidified slowly. $[\alpha]_D = -9.9$ ($c = 1.06$). IR: 3430*m*, 3355*m*, 3070*m*, 3010*m*, 2965*m*, 1875*w*, 1720*s*, 1680*s*, 1630*s*, 1595*s*, 1495*s*, 1455*s*, 1390*m*, 1370*m*, 1320*m*, 1270*m*, 1250*m*, 1170*m*, 1130*m*, 1025*m*, 860*w*. ^{1}H-NMR (300 MHz): 7.77–7.17 (*m*, 13 arom. H); 6.59 (*s*, NH); 5.52 (*d*, $J = 8.6$, NH); 4.45–4.38 (*m*, CHC*H*$_2$O); 4.24 (*t*, $J = 7.0$, C*H*CH$_2$O); 3.80–3.78 (*m*, H–C(α) (Val)); 3.26 (*s*, MeN); 1.49, 1.43 (2*s*, 2 Me (Aib)); 0.93–0.87 (*m*, 2 Me (Val)). ^{13}C-NMR (75.5 MHz): 173.0, 169.4 (2*s*, 2 CO); 156.1 (*s*, urethane-CO); 144.0, 143.8, 141.2, 129.4, 128.1, 127.6, 127.0, 125.0, 119.9 (18 arom. C); 66.8 (*t*, CH*C*H$_2$O); 59.9 (*d*, C(α) (Val)); 58.5 (*s*, C(α) (Aib)); 47.1 (*d*, *C*HCH$_2$O); 41.4 (*q*, MeN); 31.7 (*d*, C(β) (Val)); 25.9, 25.5 (2*q*, 2 Me (Aib)); 19.0, 17.5 (2*q*, 2 Me (Val)). ESI-MS: 536 ([M + Na]$^+$). Anal. calc. for $C_{31}H_{35}N_3O_4$ (513.63): C 72.49, H 6.87, N 8.18; found: C 72.20, H 6.87, N 7.70.

*Methyl (2S)-1-{2-[(2S)-2-{[(*tert*-Butoxy)carbonyl]amino}-4-methylpentanamido]-2-methylthiopropanoyl}-pyrrolidine-2-carboxylate (Boc-Leu-Aib-Ψ(CS)-Pro-OMe*; **16**). A soln. of Boc-Leu (3.088 g, 12.386 mmol) in THF (25 ml) was cooled to $-10°$ in an ice/salt bath. Then, *N*-methylmorpholine (NMM; 2.52 g, 24.91 mmol) was added, followed by isobutyl carbonochloridate (1.697 g, 12.425 mmol). The mixture was stirred for 10 min, then a slow stream of H_2S was bubbled through the soln. for 1 h, and the resulting suspension was stirred for another 2 h at $-10°$. The mixture was diluted with Et_2O and washed with 0.1M H_3PO_4 soln. The org. phase was dried ($MgSO_4$), filtered, and evaporated. The crude Boc-Leu-SH (0.102 g, *ca*. 0.412 mmol) was treated at 0° with **15**, dissolved in CH_2Cl_2 (2.5 ml). The mixture was allowed to reach r.t., was stirred for 75 min, diluted with CH_2Cl_2, and extracted with 5% $KHSO_4$ soln. The combined aq. phase was washed with CH_2Cl_2, the combined org. phase was dried ($MgSO_4$), filtered, and evaporated. Chromatography (SiO_2; AcOEt/hexane 1:3) gave **16** (0.121 g, 71%) as a colorless, thick oil, which solidified slowly. $[\alpha]_D = -110.0$ ($c = 0.992$). IR: 3670*w*, 3435*w*, 3235*w*, 2985*s*, 1960*s*, 1870*w*, 1700*s*, 1500*s*, 1440*s*, 1385*m*, 1365*s*, 1165*s*, 1090*w*, 1050*m*, 1020*w*, 1005*w*, 970*m*, 915*w*, 870*w*. ^{1}H-NMR (300 MHz): 7.78 (br. *s*, NH); 5.21–5.18 (*d*, NH); 5.12–5.09 (*m*, H–C(2) (Pro)); 4.14–4.07 (*m*, H–C(α) (Leu)); 4.01–3.84 (*m*, 2 H–C(5) (Pro)); 3.72 (*s*, MeO); 2.24–1.96 (*m*, 2 H–C(3) (Pro), 2 H–C(β) (Leu)); 1.79, 1.67 (2*s*, 2 Me (Aib^t)); 1.75–1.39 (*m*, 2 H–C(4) (Pro) H–C(γ) (Leu)); 0.95–0.91 (*m*, 2 Me (Leu)). ^{13}C-NMR (75.5 MHz): 204.5 (*s*, CS (Aib^t)); 171.0, 170.7 (2*s*, 2 CO); 155.6 (*s*, urethane CO); 79.7 (*s*, Me$_3$*C*); 68.5 (*d*,C(2) (Pro)); 60.8 (*s*, C(α) (Aib^t)); 53.2 (*d*, C(α) (Leu)); 52.7 (*t*, C(5) (Pro)); 52.1 (*q*, MeO); 41.1 (*t*, C(β) (Leu)); 28.2 (*q*, *Me*$_3$C); 27.7 (*t*, C(3) (Pro)); 25.9 (*t*, C(4) (Pro)); 24.6 (*q*, 2 Me (Aib^t)); 22.7, 22.0 (2*q*, 2 Me (Leu)). ESI-MS: 466 ([M + Na]$^+$). Anal. calc. for $C_{21}H_{37}N_3O_5S$ (443.60): C 56.86, H 8.41, N 9.41, S 7.23; found: C 56.36, H 7.99, N 9.33, S 7.18.

Methyl (2S)-1-[2-((2S)-2-{2-[(2S)-({[(9H-Fluoren-9-yl)methoxy]carbonyl}amino)-3-methylbutanamido]-2-methylpropanamido}-4-methylpentanamido)-2-methylthiopropanoyl]pyrrolidine-2-carboxylate (*Fmoc-Val-Aib-Leu-Aib-Ψ(CS)-Pro-OMe*; **18**). A soln. of **16** (42.6 mg, 0.096 mmol) in 2 ml of 2M HCl (THF/H_2O 1:1) was stirred at r.t. for 17 h. The mixture was diluted with 5% $NaHCO_3$ soln., and extracted 3 × with CH_2Cl_2. The combined org. phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was added to the crude product obtained from **17** (55.2 mg, 0.109 mmol) according to *GP 5*, and the mixture was treated according to *GP 1* with $EtN(i\text{-}Pr)_2$ (16.0 mg, 0.124 mmol), TBTU (31.3 mg, 0.103 mmol), and HOBt (16.1 mg, 0.105 mmol) in MeCN (2 ml); reaction time: 2 h. Chromatography (SiO_2; AcOEt/hexane 2:1) gave **18** (62.6 mg, 93%) as a colorless, viscous oil, which solidified under high vacuum. $[\alpha]_D = -39.2$ ($c = 1.00$). IR: 3690*w*, 3420*w*, 3345*w*, 3005*w*, 2960*m*, 2875*w*, 1710*s*, 1675*s*, 1515*s*, 1450*m*, 1425*m*, 1385*w*, 1365*w*, 1270*m*, 1165*m*, 1110*w*, 1045*w*, 1005*w*, 970*w*, 850*w*. ^{1}H-NMR (300 MHz): 7.78–7.27 (*m*, 10 arom. H, 1 NH); 6.92 (*d*, $J = 7.9$, NH); 6.63 (*s*, NH); 5.79 (br. *s*, NH); 5.07–5.03 (*m*, H–C(2) (Pro)); 4.48–3.58 (*m*, C*H*CH_2O, H–C(α) (Val), H–C(α) (Leu), 2 H–C(5) (Pro)); 3.80 (*s*, MeO); 2.18–0.75 (*m*, 2 H–C(4) and 2 H–C(3) (Pro), 2 H–C(β) (Leu), 2 Me (Val), 2 Me (Leu)); 1.78, 1.68, 1.57, 1.42 (4*s*, 2 Me (Aib), 2 Me (Aib^t)). ^{13}C-NMR (75.5 MHz): 204.8 (*s*, CS (Aib^t)); 173.5, 171.4, 170.7, 169.1 (4*s*, 4 CO); 157.6 (*s*, urethane-CO); 143.4, 143.2, 141.2, 127.9, 127.1, 124.7, 124.6, 120.1 (12 arom. C); 68.2 (*d*, C(2) (Pro)); 67.4 (*t*, CH*C*H_2O); 63.1 (*d*, C(α) (Val)); 61.2, 57.1 (2*s*, C(α) (Aib), C(α) (Aib^t)); 53.0 (*t*, C(5) (Pro)); 52.2 (*d*, C(α) (Leu)); 52.0 (*q*, MeO); 46.8 (*d*, *C*HCH_2O); 39.6 (*t*, C(β) (Leu)); 29.7, 25.1 (2*d*, C(β) (Val), C(γ) (Leu)); 27.8, 27.2 (2*t*, C(3) and C(4) (Pro)); 29.4, 27.0, 25.8, 23.7, 23.3, 20.6, 19.0, 18.8 (8*q*, 2 Me (Aib), 2 Me (Aib^t), 2 Me (Val), 2 Me (Leu)). ESI-MS: 722 ([*M* + Na]$^+$).

Boc-Trp-Ile(1)-Ala-Aib(1)-Ile(2)-Val-Aib(2)-Leu-Aib(3)-Ψ(CS)-Pro-OMe (**10**). According to *GP 4*, Boc-Trp-Ile-Ala-Aib-Ile-OMe[3]) (47.4 mg, 0.0676 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (15.1 mg, 0.360 mmol in THF/H_2O/MeOH 3:1:1 (5 ml) to give **13**; reaction time: 17 h. A soln. of **18** (50.4 mg, 0.0672 mmol) in MeCN (2 ml) was treated with Et_2NH (0.2 ml), yielding **14**. After stirring at r.t. for 1 h, the intensely yellow soln. was concentrated, and the residue dried under high vacuum. The two crude products were coupled according to *GP 2* with PyBOP (38.1 mg, 0.0732 mmol) and $EtN(i\text{-}Pr)_2$ (17.4 mg, 0.135 mmol) in CH_2Cl_2 (1 ml); reaction time: 4.5 h. Chromatography (SiO_2; AcOEt/hexane 10:1) gave 72.9 mg (90%) of **10** as a colorless, thick oil, which solidified. $[\alpha]_D = -14.3$ ($c = 1.00$). IR: 3660*w*, 3475*w*, 3315*s*, 2965*m*, 2875*w*, 1730*m*, 1660*s*, 1535*s*, 1460*m*, 1435*m*, 1385*m*, 1365*m*, 1275*m*, 1250*m*, 1165*m*, 1095*w*, 1045*w*, 1010*w*, 970*w*, 915*w*, 850*w*. ^{1}H-NMR (600 MHz, *cf. Figs. 3–6*): 9.29 (*s*, H–N(1) (Trp)); 7.77 (*s*, NH (Aib^t)); 7.71 (*d*, $J = 4.3$, NH (Ala)); 7.62 (*d*, $J = 4.8$, NH (Val)); 7.52 (*d*, $J = 7.9$, H–C(4) (Trp)); 7.46 (*d*, $J = 8.2$, H–C(7) (Trp)); 7.44 (*s*, NH (Aib(1))); 7.32 (*s*, NH (Aib(2))); 7.32 (*d*, $J = 6.2$, H–C(2) (Trp)); 7.24 (*d*, $J = 5.5$, NH (Ile(2))); 7.23 (*d*, $J = 8.1$, NH (Leu)); 7.20 (*t*, $J = 7.6$, H–C(6) (Trp)); 7.10 (*t*, $J = 7.6$, H–C(5) (Trp)); 6.30 (*s*, NH (Ile(1))); 5.48 (*s*, NH (Trp)); 5.07–5.05 (*m*, H–C(2) (Pro)); 4.40–4.36 (*m*, H–C(α) (Leu)); 4.25 (br. *s*, H–C(α) (Trp)); 4.08–4.02 (*m*, 1 H–C(5) (Pro), H–C(α) (Ala)); 3.95–3.88 (*m*, 1 H–C(5) (Pro), H–C(α) (Ile(2))); 3.68 (*s*, MeO); 3.61–3.59 (*m*, H–C(α) (Val)); 3.33–3.22 (*m*, 2 H–C(β) (Trp)); 2.23–2.19 (*m*, H–C(β) (Val)); 2.11–1.98 (*m*, 2 H–C(β) (Leu), H–C(γ) (Leu), 1 H–C(3) (Pro), 1 H–C(4) (Pro)); 1.83 (*s*, Me(1) (Aib^t)); 1.73 (*s*, Me(2) (Aib^t)); 1.615 (*s*, Me(1) (Aib(1))); 1.609 (*s*, Me(2) (Aib(2))); 1.64–1.41 (*m*, H–C(β) (Ile(1)), 2 H–C(γ) (Ile(2))); 1.55 (*s*, Me(2) (Aib(1)); 1.53 (*s*, Me(1) (Aib(2))); 1.45 (*d*, $J = 6.4$, Me (Ala)); 1.43 (*s*, Me_3C); 1.36–1.32 (*m*, 1 H–C(γ) (Ile(1))); 1.10–1.06 (*m*, 1 H-C(γ) (Ile(1))); 1.08 (*d*, $J = 6.7$, Me(2) (Val)); 1.04 (*d*, $J = 6.8$, Me(1) (Val)); 1.01 (*d*, $J = 6.9$, Me(β^1) (Ile(2))); 0.95 (*t*, $J = 7.3$, Me(δ) (Ile(2))); 0.95 (*d*, $J = 6.4$, Me(2) (Leu)); 0.88 (*d*, $J = 6.4$, Me(1) (Leu)); 0.85 (*t*, $J = 7.3$, Me(δ) (Ile(1))); 0.68–0.67 (*d*, $J = 6.8$, Me(β^1) (Ile(1))). ^{13}C-NMR (150.9 MHz, *cf. Figs. 3–6*): 205.2 (*s*, CS (Aib^t)); 176.0 (*s*, CO (Aib(1))); 175.0 (*s*, CO (Aib(2))); 174.1 (*s*, CO (Trp)); 173.9 (*s*, CO (Ile(2))); 173.6 (*s*, CO (Ala)); 172.7 (*s*, CO (Val)); 172.0 (*s*, CO (Ile(1))); 171.9 (*s*, CO (Leu)); 171.7 (*s*, CO (Pro)); 157.2 (*s*, urethane-CO); 136.8 (*s*, C(3a) (Trp)); 127.1 (*s*, C(7a) (Trp)); 124.4 (*d*, C(2) (Trp)); 122.4 (*d*, C(6) (Trp)); 119.7 (*d*, C(5) (Trp)); 118.3 (*d*, C(4) (Trp)); 111.9 (*d*, C(7) (Trp)); 108.4 (*s*, C(3) (Trp)); 81.7 (*s*, Me_3C); 68.3 (*d*, C(2) (Pro)); 63.4 (*d*, C(α) (Val)); 61.4 (*s*, C(α) (Aib^t)); 60.9 (*d*, C(α) (Ile(2))); 59.6 (*d*, C(α) (Ile(1))); 57.1 (*s*, C(α) (Aib(2))); 56.9 (*d*, C(α) (Trp)); 56.8 (*s*, C(α) (Aib(1))); 53.3 (*t*, C(5) (Pro)); 52.7 (*d*, C(α) (Leu)); 52.1 (*d*, C(α) (Ala)); 52.0 (*q*, MeO); 40.1 (*t*, C(β) (Leu)); 35.9 (*d*, C(β) (Ile(2))); 35.8 (*d*, C(β) (Ile(1))); 29.9 (*q*, Me(1) (Aib^t)); 29.1 (*d*, C(β) (Val)); 28.2 (*q*, *Me*$_3$C); 28.0 (2*t*, C(3) and C(4) (Pro)); 27.50 (*q*, Me(1) (Aib(1))); 27.49 (*q*, Me(1) (Aib(2))); 27.4 (*q*, Me(2) (Aib^t)); 27.3 (*t*, C(β) (Trp)); 26.0 (*t*, C(γ) (Ile(2))); 25.2 (*t*, C(γ) (Ile(1))); 25.1 (*d*, C(γ) (Leu)); 23.5 (*q*, Me(2) (Leu)); 23.4 (*q*, Me(2) (Aib(2))); 23.1 (*q*, Me(2) (Aib(1))); 20.9 (*q*, Me(1) (Leu)); 19.8 (*q*, Me(2) (Val)); 19.2 (*q*, Me(1) (Val)); 16.5

[3]) For the preparation of Boc-Trp-Ile-Ala-Aib-Ile-OMe, see [4].

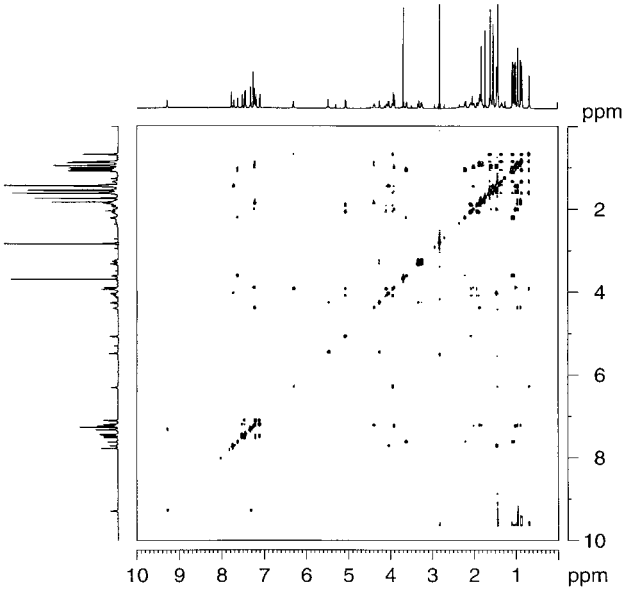


Fig. 3. *^{1}H-TOCSY Spectrum of* **10** ($CDCl_3$, 600 MHz; 10.0 – 0.0 ppm)

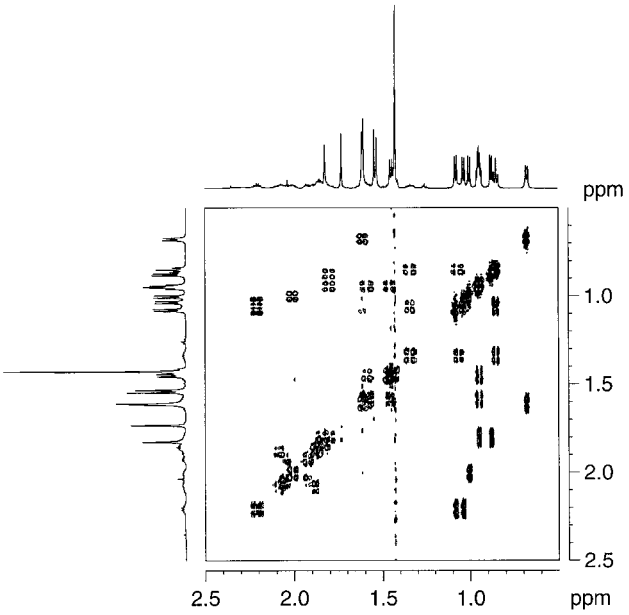


Fig. 4. *^{1}H-DQF-COSY Spectrum of* **10** ($CDCl_3$, 600 MHz; 2.5 – 0.0 ppm)

(q, Me (Ala)); 15.8 (q, Me(β^1) (Ile(2))); 15.6 (q, Me(β^1) (Ile(1))); 11.8 (q, Me(δ) (Ile(2))); 11.4 (q, Me(δ) (Ile(1))). ESI-MS: 1219 ($[M+Na]^+$), 621 ($[M+2Na]^{2+}$).

3. *Attempted Synthesis of Methyl (2*S*)-1-{2-[(2*S*)-2-(2-{(2*S*)-2-[(2*S*,3*S*)-2-(2-{(2*S*)-2-[(2*S*,3*S*)-2-((2*S*)-{[(tert-Butoxy)carbonyl]amino}-3-(indol-3-yl)propanamido)-3-methylpentanamido]propanethioamido}-2-methylpropan-*

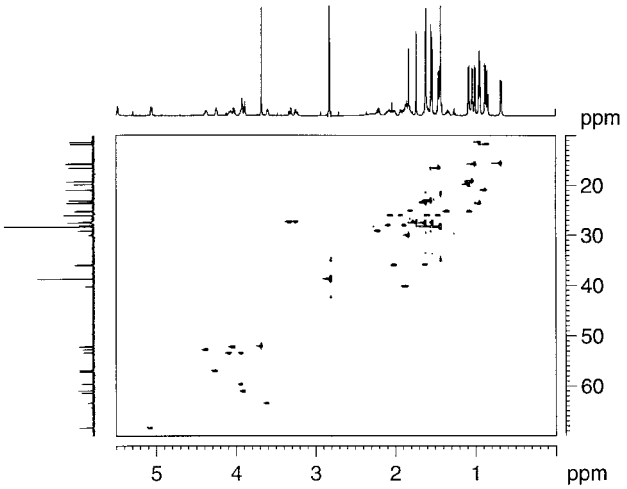


Fig. 5. *$^{13}C,^{1}H$-HSQC Spectrum of* **10** ($CDCl_3$, 600 MHz; 5.5 – 0.0 and 70.0 – 0.0 ppm, resp.)

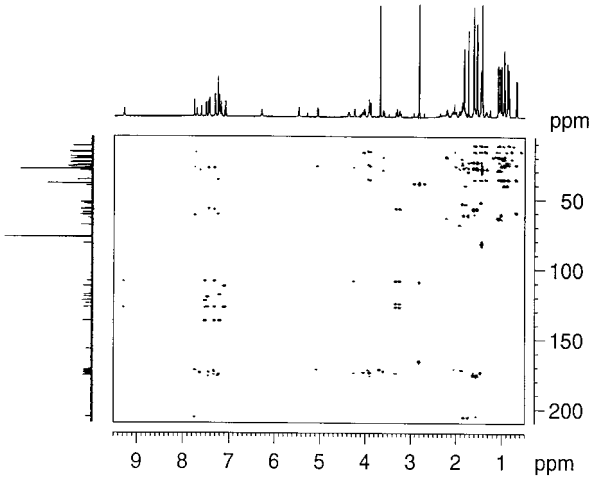


Fig. 6. *$^{13}C,^{1}H$-HMBC 'Longe-range' spectrum of* **10** ($CDCl_3$, 600 MHz; 9.5 – 0.5 and 210 – 5.0 ppm, resp.)

amido)-3-methylpentanamido]-3-methylbutanamido]-2-methylpropanamido)-4-methylpentanamido]-2-methylpropanoyl]pyrrolidine-2-carboxylate (*Boc-Trp-Ile-Ala-Ψ(CS)-Aib-Ile-Val-Aib-Leu-Aib-Pro-OMe*; **11**). *Methyl* N-*[(*tert-*Butoxy)carbonyl]*-L-*tryptophanyl*-L-*isoleucinate* (*Boc-Trp-Ile-OMe*; **19**). According to *GP 1* with Boc-Trp (2.020 g, 6.636 mmol), $EtN(i\text{-}Pr)_2$ (1.923 g, 14.878 mmol), TBTU (2.065 g, 6.858 mmol), HOBt (1.006 g, 6.575 mmol), and Ile-OMe · HCl (1.258 g, 6.925 mmol) in MeCN (50 ml); reaction time: 2.5 h. Chromatography (SiO_2; AcOEt/hexane 1:2) gave 2.818 g (99%) of **19** as a colorless, viscous oil, which solidified under high vacuum. $[\alpha]_D = +5.4$ ($c = 0.99$). IR: 3480*m*, 3425*m*, 3005*m*, 2970*m*, 2935*m*, 2880*w*, 1735*s*, 1705*s*, 1675*s*, 1490*s*, 1455*m*, 1440*m*, 1420*s*, 1390*m*, 1370*m*, 1340*m*, 1300*w*, 1165*s*, 1090*w*, 1060*w*, 1010*w*, 860*w*, 810*w*. ^{1}H-NMR (300 MHz): 8.39 (*s*, NH); 7.66 – 7.04 (*m*, 5 arom. H); 6.35 (*d*, NH); 5.22 (br. *s*, NH); 4.47 – 4.42 (*m*, H–C(α) (Trp), H–C(α) (Ile)); 3.61 (*s*, MeO); 3.32 – 3.14 (*m*, 2 H–C(β) (Trp)); 1.89 – 0.94 (*m*, H–C(β) (Ile), 2 H–C(γ) (Ile)); 1.43 (*s*, Me_3C); 0.86 – 0.81 (*t*, $J = 7.3$, Me(δ) (Ile)); 0.74 (*d*, $J = 6.9$, Me(β^1) (Ile)). ^{13}C-NMR (75.5 MHz): 171.6, 171.4, (2*s*, 2 CO); 155.5 (*s*, urethane-CO); 136.2, 127.4, 123.2, 122.1, 119.6, 118.7, 111.1, 110.4 (8 arom. C); 80.0 (*s*, Me_3C); 56.5, 55.2 (2*d*, C(α) (Trp), C(α) (Ile)); 51.8 (*q*, MeO); 37.7 (*d*, C(β) (Ile)); 28.2 (*q*, Me_3C); 28.0

(*t*, C(β) (Trp)); 25.0 (*t*, C(γ) (Ile)); 15.1, 11.4 (2*q*, Me(δ) (Ile), Me(β^1) (Ile)). CI-MS: 432 (89, $[M+1]^+$), 377 (6), 376 (33), 333 (19), 332 (100), 314 (6), 117 (5). Anal. calc. for $C_{23}H_{33}N_3O_5$ (431.52): C 64.17, H 7.49, N 9.76; found: C 63.50, H 7.65, N 9.67.

*Methyl (2S,3S)-2-(2-[(2S)-2-[(2S,3S)-2-((2S)-{[(*tert*-Butoxy)carbonyl]amino}-3-(indol-3-yl)propanamido)-3-methylpentanamido]propanethioamido}-2-methylpropanamido)-3-methylpentanoate* (*Boc-Trp-Ile-Ala-Ψ(CS)-Aib-Ile-OMe*; **21**). According to *GP 4*, **19** (75.1 mg, 0.174 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (15.1 mg, 0.360 mmol) in 4 ml of THF/MeOH/H_2O 3:1:1. To a soln. of Fmoc-Ala-Ψ(CS)-Aib-Ile-OMe[4]) (84.1 mg, 0.156 mmol), Et_2NH (0.3 ml) was added, and the mixture was stirred at r.t. After 45 min, the intensely yellow soln. was concentrated, and the residue was dried under high vacuum. The two crude products were coupled according to *GP 1* with EtN(i-Pr)$_2$ (21.7 mg, 0.168 mmol), TBTU (52.0 mg, 0.173 mmol), and HOBt (27.1 mg, 0.177 mmol) in MeCN (3 ml); reaction time: 2.5 h. Chromatography (SiO_2; AcOEt/hexane 3:1) gave **21** as a colorless, thick oil, which solidified under high vacuum. $[\alpha]_D = -10.1$ ($c = 0.971$. IR: 3675*w*, 3475*w*, 3315*m*, 2965*m*, 2935*w*, 2880*w*, 1735*m*, 1670*s*, 1515*s*, 1455*m*, 1435*m*, 1370*m*, 1275*m*, 1160*m*, 1095*w*, 1070*w*, 1010*w*, 920*w*, 850*w*. ^{1}H-NMR (300 MHz): 9.14 (*s*, NH); 8.47 (*s*, NH); 7.52–7.05 (*m*, 5 arom. H, 1 NH); 6.79 (*d*, $J = 8.0$, NH); 6.20 (*d*, $J = 5.2$, NH); 5.25 (*d*, $J = 2.6$, NH); 4.61–3.98 (*m*, 2 H–C(α) (Ile), H–C(α) (Ala^t)); 3.61 (*s*, MeO); 3.25–3.18 (*m*, 2 H–C(β) (Trp)); 1.99–0.58 (*m*, 2 H–C(β) (Ile), 4 H–C(γ) (Ile), 2 Me(δ) (Ile), 2 Me(β^1) (Ile)); 1.77, 1.73 (2*s*, 2 Me (Aib)); 1.35 (*s*, Me_3C). ^{13}C-NMR (75.5 MHz): 207.9 (*s*, CS (Ala^t)); 173.4, 173.3, 172.1, 170.8 (4*s*, 4 CO); 156.8 (*s*, urethane-CO); 136.6, 127.0, 123.9, 122.3, 119.6, 118.3, 111.7, 108.6 (8 arom. C); 81.4 (*s*, Me_3C); 60.9 (*s*, C(α) (Aib)); 59.3, 58.4, 57.4, 56.5 (4*d*, C(α) (Trp), C(α) (Ile), C(α) (Ala^t)); 51.7 (*q*, MeO); 40.2, 37.0 (2*d*, 2 C(β) (Ile)); 28.1 (*q*, Me_3C); 27.3 (*t*, C(β) (Trp)); 26.5, 23.8 (2*q*, 2 Me (Aib)); 25.3, 24.5 (2*t*, 2 C(γ) (Ile)); 20.5, 15.5, 15.5, 11.7, 11.2 (5*q*, 2 Me(γ) (Ile), 2 Me(β^1) (Ile), Me (Ala^t)). ESI-MS: 739 ($[M+Na]^+$). Anal. calc. for $C_{36}H_{56}N_6O_7S$ (431.52): C 60.31, H 7.87, N 11.72, S 4.47; found: C 59.89, H 7.76, N 11.29, S 4.49.

Benzyl N-{(1S)-2-Methyl-1-[({1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino)carbonyl]propyl}carbamate (*Z-Val-Aib-N(Me)Ph*; **24**). According to *GP 3* with Z-Val (1.310 g, 5.27 mmol), CH_2Cl_2 (50 ml) and azirine **2** (1.00 g, 5.74 mmol). Chromatography (SiO_2; AcOEt/hexane 1:1.5) led to 2.081 g (94%) of **24** as a viscous oil, which solidified slowly. $[\alpha]_D = +10.0$ ($c = 1.00$). IR: 3690*w*, 3430*m*, 3360*m*, 2970*m*, 2875*w*, 1720*s*, 1680*s*, 1630*s*, 1595*s*, 1495*s*, 1455*s*, 1390*m*, 1370*m*, 1270*m*, 1170*w*, 1120*m*, 1095*m*, 1025*m*, 925*w*. ^{1}H-NMR (300 MHz): 7.39–7.17 (*m*, 10 arom. H); 6.55 (*s*, NH (Aib)); 5.46 (*d*, $J = 8.2$, NH (Val)); 5.14–5.12 (*m*, CH_2O); 3.79–3.75 (*m*, H–C(α) (Val)); 3.25 (*s*, MeN); 2.06–2.01 (*m*, H–C(β) (Val)); 1.47, 1.43 (2*s*, 2 Me (Aib)); 0.90 (2*d*, $J = 6.8$, 2 Me (Val)). ^{13}C-NMR (75.5 MHz): 173.0, 169.5 (2*s*, 2 CO); 156.2 (*s*, urethane CO); 144.2, 136.5, 129.4, 128.4, 128.1, 128.0, 127.9 (12 arom. C); 66.9 (*t*, CH_2O); 60.0 (*d*, C(α) (Val)); 58.6 (*s*, C(α) (Aib)); 41.4 (*q*, MeN); 31.6 (*d*, C(β) (Val)); 25.9, 25.6 (2*q*, 2 Me (Aib)); 19.1, 17.5 (2*q*, 2 Me (Val)). ESI-MS: 448 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{31}N_3O_4$ (425.52): C 67.69, H 7.29, N 9.87; found: C 67.82, H 7.36, N 9.82.

Methyl (2S)-2-[2-((2S)-{[(Benzyloxy)carbonyl]amino}-3-methylbutanamido)-2-methylpropanamido]-4-methylpentanoate (*Z-Val-Aib-Leu-OMe*; **25**). According to *GP 4*, **24** (1.00 g, 2.35 mmol) was hydrolyzed in 30 ml of 3M HCl (THF/H_2O 1:1). The crude product was treated according to *GP 1* with Leu-OMe·HCl (0.500 g, 2.590 mmol), EtN(i-Pr)$_2$ (0.909 g, 7.033 mmol), TBTU (0.750 g, 2.490 mmol), and HOBt (0.370 g, 2.418 mmol) in MeCN (20 ml); reaction time: 17 h. Chromatography (SiO_2; AcOEt/hexane 1:1.5) gave 0.895 g (82%) **25** as a colorless, thick oil, which solidified slowly. $[\alpha]_D = -8.6$ ($c = 1.03$). IR: 3695*w*, 3430*m*, 3360*m*, 3010*m*, 2965*m*, 2875*w*, 1715*s*, 1680*s*, 1630*s*, 1595*s*, 1495*s*, 1455*s*, 1390*m*, 1370*m*, 1270*m*, 1170*m*, 1120*m*, 1090*m*, 1025*m*, 910*m*, 845*w*. ^{1}H-NMR (300 MHz): 7.35–7.32 (*m*, 5 arom. H); 6.93 (*d*, $J = 7.9$, NH); 6.59 (*s*, NH); 5.38 (*d*, $J = 8.0$, NH); 5.16–5.05 (*m*, CH_2O); 4.58–4.55 (*m*, H–C(α) (Leu)); 3.90–3.85 (*m*, H–C(α) (Val)); 3.70 (*s*, MeO); 2.11–1.52 (*m*, 2 Me (Val), 2 H–C(β) (Leu), H–C(γ) (Leu)); 1.57, 1.52 (2*s*, 2 Me (Aib)); 0.97–0.90 (*m*, 2 Me (Val), 2 Me (Leu)). ^{13}C-NMR (75.5 MHz): 173.7, 173.2, 170.9 (3*s*, 3 CO); 156.4 (*s*, urethane CO); 136.0, 128.4, 128.1, 127.9 (6 arom. C); 67.0 (*t*, CH_2O); 60.9 (*d*, C(α) (Val)); 57.3 (*s*, C(α) (Leu)); 52.0 (*q*, MeO); 41.1 (*t*, C(β) (Leu)); 30.7 (*d*, C(β) (Val)); 24.7 (*d*, C(γ) (Leu)); 25.6, 24.4, 22.7, 21.8, 19.0, 17.9 (6*q*, 2 Me (Aib), 2 Me (Leu), 2 Me (Val)). ESI-MS: 486 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{37}N_3O_6$ (463.57): C 62.18, H 8.04, N 9.06; found: C 62.04, H 8.13, N 8.89.

Methyl (2S)-1-(2-[(2S)-2-[2-((2S)-{[(Benzyloxy)carbonyl]amino}-3-methylbutanamido)-2-methylpropanamido]-4-methylpentanamido}-2-methylpropanoyl)pyrrolidine-2-carboxylate (*Z-Val-Aib-Leu-Aib-Pro-OMe*; **26**). According to *GP 4*, **25** (0.203 g, 0.437 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (41.3 mg, 0.984 mmol) in 5 ml of THF/MeOH/H_2O 3:1:1; reaction time: 15 h. The crude product was treated according to *GP 3* with

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[4]) For the preparation of Fmoc-Ala-Ψ(CS)-Aib-Ile-OMe, see [3].

azirine **15** (94.7 mg, 0.483 mmol) in 5 ml of CH_2Cl_2. Chromatography (SiO_2; AcOEt) led to 0.259 g (92%) of **26** as a colorless, viscous oil, which solidified under high vacuum. $[\alpha]_D = -58.5$ ($c = 1.00$). IR: 3690*w*, 3425*m*, 3350*s*, 3010*m*, 2960*s*, 2930*m*, 2875*m*, 1740*s*, 1715*s*, 1595*s*, 1675*s*, 1630*s*, 1515*s*, 1470*s*, 1455*s*, 1440*s*, 1415*s*, 1385*m*, 1365*s*, 1270*s*, 1170*s*, 1095*m*, 1005*w*, 910*w*, 825*w*. ^{1}H-NMR (300 MHz): 7.60 (*s*, NH); 7.37–7.27 (*m*, 5 arom. H); 7.13 (*d*, $J = 8.3$, NH); 7.05 (*s*, NH); 6.50 (*d*, $J = 2.9$, NH); 5.15–5.03 (*m*, CH_2O); 4.50–3.47 (*m*, H–C(α) (Val), H–C(α) (Leu), H–C(2) (Pro), 2 H–C(5) (Pro)); 3.67 (*s*, MeO); 2.32–1.20 (*m*, H–C(β) (Val), H–C(γ) (Leu), 2 H–C(3) and 2 H–C(4) (Pro)); 1.59, 1.56, 1.50, 1.42 (4*s*, 4 Me (Aib)); 1.07–0.82 (*m*, 2 Me (Val), 2 Me (Leu)). ^{13}C-NMR (75.5 MHz): 174.0, 173.3, 172.4, 172.0, 171.4 (5*s*, 5 CO); 157.7 (*s*, urethane CO); 135.9, 128.2, 127.6 (6 arom. C); 66.9 (*t*, CH_2O); 63.8, 60.4 (2*d*, C(2) (Pro), C(α) (Val)); 57.0, 56.5 (2*s*, C(α) (Aib)); 52.0 (*d*, C(α) (Leu)); 51.8 (*q*, MeO); 48.2 (*t*, C(5) (Pro)); 39.7 (*t*, C(β) (Leu)); 29.5 (*d*, C(β) (Val)); 27.8, 25.7 (2*t*, C(3) and C(4) (Pro)); 25.1 (*d*, C(γ) (Leu)); 27.3, 24.9, 24.3, 23.5, 23.3, 20.6, 19.3, 19.0 (8*q*, 4 Me (Aib), 2 Me (Val), 2 Me (Leu)). ESI-MS: 668 ($[M + Na]^+$). Anal. calc. for $C_{33}H_{51}N_5O_8$ (645.79): C 61.37, H 7.96, N 10.84; found: C 61.29, H 8.23, N 10.02.

*Methyl (2*S*)-1-(2-{(2*S*)-2-[2-((2*S*)-2-{(2*S*,3*S*)-2-[(2-{(*R*/*S*)-1-[(2*S*,3*S*)-2-((2*S*)-{[(*tert*-Butoxy)carbonyl]-amino}-3-(indol-3-yl)propanamido)-3-methylpentanamido]ethyl}-4,5-dihydro-4,4-dimethyl-1,3-thiazol-5-yli-den)amino]-3-methylpentanamido}-3-methylbutanamido)-2-methylpropanamido]-4-methylpentanamido}-2-methylpropanoyl)pyrrolidine-2-carboxylate* (**27**). To a soln. of **26** (21.7 mg, 0.0336 mmol) in 2 ml of MeOH, 2 mg of Pd/C were added, and the suspension was stirred under H_2 (balloon) for 5 min to give **23**. Then, the mixture was filtered over *Celite*, concentrated, and dried under high vacuum. According to *GP 4*, **21** (21.2 mg, 0.0296 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (2.5 mg, 0.0596 mmol) in 0.5 ml of THF/H_2O/MeOH 3 : 1 : 1 yielding **22**; reaction time: 18 h. The two crude products were coupled according to *GP 2* with PyBOP (17.4 mg, 0.0334 mmol) and EtN(i-Pr)$_2$ (5 µl, 0.03 mmol) in CH_2Cl_2 (0.5 ml); reaction time: 4 h. Chromatography (SiO_2; AcOEt/MeOH 30 : 1) gave a mixture of two epimers of **27** in a (*S*)/(*R*) ratio of 62 : 38 (27.0 mg, 76%). The epimers were separated by prep. HPLC (*Bischoff*, *Spherisorb ODS2*, 5 µm, MeCN/H_2O 70 : 30, 3.6 ml/min). The following data are those of the epimer with the (*S*)-configuration of Ala. $[\alpha]_D = +4.5$ ($c = 0.730$). IR: 3475*w*, 3335*m*, 2995*w*, 2960*m*, 2935*w*, 2875*w*, 1740*m*, 1665*s*, 1500*s*, 1455*m*, 1440*m*, 1415*w*, 1365*m*, 1265*m*, 1170*s*, 1010*w*, 915*w*, 855*w*. ^{1}H-NMR (600 MHz; ^{1}H-TOCSY, ^{1}H-DQF-COSY, ^{13}C,^{1}H-HSQC, ^{13}C,^{1}H-HMBC): 8.59 (*s*, H–N(1) (Trp)); 7.55 (*d*, $J = 8.0$, H–C(4) (Trp)); 7.33 (*d*, $J = 8.1$, H–C(7) (Trp)); 7.23 (*s*, NH (Aib(3))); 7.13–7.03 (*m*, H–C(2), H–C(5), H–C(6) (Trp), NH (Val), NH (Leu)); 6.80 (*s*, NH (Ala)); 6.27 (*d*, $J = 8.2$, NH (Ile(1))); 6.21 (*s*, NH (Aib(2))); 5.04 (*s*, NH (Trp)); 4.73–4.68 (*m*, H–C(α) (Ala)); 4.47–4.45 (*m*, H–C(2) (Pro)); 4.33–4.30 (*m*, H–C(α) (Trp)); 4.20–4.18 (*m*, H–C(α) (Ile(1))); 3.67–3.57 (*m*, H–C(α) (Val), 1 H–C(5) (Pro)); 3.52–3.48 (*m*, 1 H–C(5) (Pro)); 3.28 (*d*, $J = 3.3$, H–C(α) (Ile(2))); 3.23–3.15 (*m*, 2 H–C(β) (Trp)); 2.13–2.08 (*m*, H–C(β) (Val)); 2.03–1.97 (*m*, 1 H–C(3) (Pro)); 1.93–1.64 (*m*, 2 H–C(4) (Pro), H–C(β) (Ile(1)), H–C(β) (Ile(2)), 2 H–C(β) (Leu)), 1 H–C(3) (Pro)); 1.58–1.41 (*m*, H–C(γ) (Leu), 1 H–C(γ) (Ile(2))); 1.48 (*s*, Me(2) (Aib(2))); 1.47 (*s*, Me(2) (Aib(3))); 1.45 (*s*, Me(1) (Aib(3))); 1.41 (*s*, Me(2) (Aib(1))); 1.39 (*s*, Me(1) (Aib(1))); 1.37 (*s*, Me(1) (Aib(2))); 1.35 (*s*, Me_3C); 1.34 (*d*, $J = 3.2$, Me (Ala)); 1.28–1.20 (*m*, 1 H–C(α) (Ile(1)), 1 H–C(γ) (Ile(2))); 0.97 (*d*, $J = 6.8$, Me(1) (Val)); 0.95–0.94 (*d*, $J = 6.8$, Me(2) (Val)); 0.94–0.84 (*m*, 1 H–C(γ) (Ile(1)), 1 H–C(γ) (Ile(2))); 0.88 (*d*, $J = 6.7$, Me(2) (Leu)); 0.82 (*d*, $J = 6.8$, Me(1) (Leu)); 0.81 (*t*, $J = 6.8$, Me(δ) (Ile(2))); 0.75 (*t*, $J = 7.3$, Me(δ) (Ile(1))); 0.70 (*d*, $J = 6.8$, Me(β^1) (Ile(1))). ^{13}C-NMR (150.9 MHz): 179.5 (*s*, thiazole C(5)); 173.8 (*s*, CO (Aib(2))); 173.7 (*s*, CO (Pro)); 173.6 (*s*, CO (Ile(2))); 172.5 (*s*, CO (Aib(3))); 172.0 (*s*, CO (Trp)); 171.3 (*s*, CO (Leu)); 170.9 (*s*, CO (Val)); 170.8 (*s*, CO (Ile(1))); 165.1 (*s*, thiazole C(2)); 156.4 (*s*, urethane CO); 136.6 (*s*, C(3a) (Trp)); 127.5 (*s*, C(7a) (Trp)); 123.6 (*d*, C(2) (Trp)); 122.5 (*d*, C(6) (Trp)); 119.9 (*d*, C(5) (Trp)); 118.8 (*d*, C(4) (Trp)); 111.7 (*d*, C(7) (Trp)); 110.0 (*s*, C(3) (Trp)); 83.3 (*s*, thiazole C(4)); 80.9 (*s*, Me_3C); 78.5 (*d*, C(α) (Ile(2))); 61.5 (*d*, C(α) (Val)); 60.8 (*d*, C(2) (Pro)); 58.1 (*d*, C(α) (Ile(1))); 57.6 (*s*, C(α) (Aib(2))); 56.8 (*s*, C(α) (Aib(3))); 55.9 (*d*, C(α) (Trp)); 53.0 (*d*, C(α) (Leu)); 52.2 (*q*, MeO); 49.0 (*d*, C(α) (Ala)); 48.3 (*t*, C(5) (Pro)); 40.2 (*d*, C(β) (Ile(2))); 39.6 (*t*, C(β) (Leu)); 36.5 (*d*, C(β) (Ile(1))); 29.7 (*d*, C(β) (Val)); 28.5 (*q*, Me_3C); 28.2 (*t*, C(3) (Pro)); 27.9 (*q*, Me(1) (Aib(1)); 27.3 (*t*, C(β) (Trp)); 27.0 (*q*, Me(1) (Aib(2))); 26.8 (*q*, Me(2) (Aib(1))); 26.2 (*t*, C(4) (Pro)); 25.8 (*t*, C(γ) (Ile(2))); 25.5 (*d*, C(γ) (Leu)); 25.4 (*q*, Me(1) (Aib(3))); 24.7 (*q*, Me(2) (Aib(3))); 24.6 (*q*, Me(2) (Aib(2))); 23.7 (*q*, Me(2) (Leu)); 21.3 (*q*, Me(1) (Leu)); 19.6 (*q*, Me(1) (Val)); 18.9 (*q*, Me (Ala)); 18.6 (*q*, Me(2) (Val)); 16.1 (*q*, Me(β^1) (Ile(2))); 15.8 (*q*, Me(β^1) (Ile(1))); 12.1 (*q*, Me(δ) (Ile(2))); 11.8 (*q*, Me(δ) (Ile(1))). ESI-MS: 1201 ($[M + Na]^+$).

4. *Attempted Synthesis of Methyl (2*S*)-1-{2-[(2*S*)-2-(2-{(2*S*)-2-[(2*S*,3*S*)-2-(2-{(2*S*)-2-[(2*S*,3*S*)-2-((2*S*)-{[(*tert*-Butoxy)carbonyl]amino}-3-(indol-3-yl)propanamido)-3-methylpentanamido]propanethioamido}-2-methylpropan-amido)-3-methylpentanamido]-3-methylbutanethioamido}-2-methylpropanamido)-4-methylpentanamido]-2-meth-ylpropanoyl}pyrrolidine-2-carboxylate (Boc-Trp-Ile-Ala-Ψ(CS)-Aib-Ile-Val-Ψ(CS)-Aib-Leu-Aib-Pro-OMe*;

12). *Methyl (2S)-2-[2-((2S)-2-[(2S,3S)-2-[(2-[(R/S)-1-[(2S,3S)-2-((2S)-[[(*tert*-Butoxy)carbonyl]amino]-3-(indol-3-yl)propanamido)-3-methylpentanamido]ethyl]-4,5-dihydro-4,4-dimethyl-1,3-thiazol-5-yliden)amino]-3-methylpentanamido]-3-methylbutanamido)-2-methylpropanamido]-4-methylpentanoate* (**31**). According to *GP 4*, **21** (33.6 mg, 0.0468 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (4.0 mg, 0.095 mmol) in 0.5 ml of THF/MeOH/H_2O 3 : 1 : 1 to give **22**; reaction time: 17 h. To a soln. of Fmoc-Val-Ψ(CS)-Aib-Leu-OMe[5]) in MeCN (2 ml), Et_2NH (0.2 ml) was added, and the soln. was stirred at r.t., yielding **28**. After 50 min, the intensely yellow soln. was concentrated, and the residue was dried under high vacuum. The two crude products were coupled according to *GP 2* with PyBOP (26.3 mg, 0.0505 mmol) and EtN(i-Pr)$_2$ (8.6 µl, 0.05 mmol) in CH_2Cl_2 (1 ml); reaction time: 4.5 h. Chromatography (SiO_2; AcOEt/hexane 3 : 1) gave 35.7 mg (74%) of a mixture of three substances in a ratio of 53 : 28 : 19 (HPLC), which were separated by prep. HPLC (*Bischoff*, *Spherisorb ODS2*, 5 µm, MeCN/H_2O 70 : 30, 10.0 ml/min). The physical data showed that the first two main products were the epimers of thiazolimine **31**, and that the last, smallest peak corresponds to the linear endothiooctapeptide **29**[6]). The following data are those of the epimer of **31** with (*S*)-configuration at Ala. $[\alpha]_D = +26.6$ ($c = 1.05$). IR: 3695*w*, 3480*w*, 3380*w*, 2965*s*, 2935*m*, 2875*w*, 1735*m*, 1665*s*, 1505*s*, 1455*s*, 1420*m*, 1370*m*, 1170*s*, 1095*w*, 1010*w*, 925*w*. ^{1}H-NMR (600 MHz; ^{1}H-TOCSY, ^{1}H-DQF-COSY, ^{13}C,^{1}H-HSQC, ^{13}C,^{1}H-HMBC): 8.37 (*s*, H–N(1) (Trp)); 8.25 (*s*, NH (Aib(2))); 7.65 (*d*, $J = 7.9$, H–C(4) (Trp)); 7.37 (*d*, $J = 8.4$, NH (Val^t)); 7.36 (*d*, $J = 8.5$, H–C(7) (Trp)); 7.19 (*t*, $J = 7.4$, H–C(6) (Trp)); 7.12 (*t*, $J = 7.4$, H–C(5) (Trp)); 7.07 (*d*, $J = 1.8$, H–C(2) (Trp)); 6.72 (*d*, $J = 6.9$, NH (Ala)); 6.48 (*d*, $J = 7.7$, NH (Leu)); 6.44 (*d*, $J = 8.3$, NH (Ile(1))); 5.10 (br. *d*, NH (Trp)); 4.79–4.75 (*m*, H–C(α) (Ala)); 4.55-4.51 (*m*, H–C(α) (Leu)); 4.44 (br. *d*, H–C(α) (Trp)); 4.25–4.23 (*m*, H–C(α) (Ile(1)), H–C(α) (Val^t)); 3.71 (*s*, MeO); 3.29–3.21 (*m*, H–C(α) (Ile(2)), 2 H–C(β) (Trp)); 2.22–2.16 (*m*, H–C(β) (Val^t)); 1.98–1.91 (*m*, H–C(β) (Ile(2))); 1.86–1.79 (*m*, H–C(β) (Ile(1))); 1.72 (*s*, Me(1) (Aib(2))); 1.68 (*s*, Me(2) (Aib(2))); 1.66–1.49 (*m*, 2 H–C(β) (Leu), H–C(γ) (Leu), 1 H–C(γ) (Ile(2))); 1.49 (*s*, Me(1) (Aib(1))); 1.45 (*s*, Me(2) (Aib(1))); 1.42 (*s*, Me_3C); 1.39 (*d*, $J = 6.9$, Me (Ala)); 1.36–1.22 (*m*, 1 H–C(γ) (Ile(1)), 1 H–C(γ) (Ile(2))); 1.00 (*d*, $J = 6.7$, Me(1) (Val^t)); 0.98 (*d*, $J = 6.7$, Me(2) (Val^t)); 1.00–0.94 (*m*, 1 H–C(γ) (Ile(1))); 0.91 (*t*, $J = 8.0$, Me(δ) (Ile(2))); 0.90 (*d*, $J = 7.3$, Me(β^1) (Ile(2))); 0.89 (*d*, $J = 4.9$, Me(1) (Leu)); 0.89 (*d*, $J = 6.2$, Me(2) (Leu)); 0.82 (*t*, $J = 7.3$, Me(δ) (Ile(1))); 0.77 (*d*, $J = 6.8$, Me(β^1) (Ile(1)). ^{13}C-NMR (75.5 MHz): 202.4 (*s*, CS (Val^t)); 177.4 (*s*, thiazole C(5)); 173.5 (*s*, CO (Leu)); 172.5 (*s*, CO (Aib(1))); 171.6 (*s*, CO (Aib(2))); 170.3 (*s*, CO (Ile(1))); 164.7 (*s*, thiazole C(2)); 156.4 (*s*, urethane CO); 136.4 (*s*, C(3a) (Trp)); 127.5 (*s*, C(7a) (Trp)); 123.3 (*d*, C(2) (Trp)); 122.3 (*d*, C(6) (Trp)); 119.9 (*d*, C(5) (Trp)); 118.9 (*d*, C(4) (Trp)); 111.3 (*d*, C(7) (Trp)); 110.5 (*s*, C(3) (Trp)); 83.9 (*s*, thiazole C(4)); 80.6 (*s*, Me_3C); 79.5 (*d*, C(α) (Ile(2))); 66.4 (*d*, C(α) (Val)); 60.5 (*s*, C(α) (Aib(2))); 57.9 (*d*, C(α) (Ile(1))); 55.3 (*d*, C(α) (Trp)); 52.3 (*q*, MeO); 51.3 (*d*, C(α) (Leu)); 48.9 (*d*, C(α) (Ala)); 41.2 (*t*, C(β) (Leu)); 39.8 (*d*, C(β) (Ile(2))); 36.8 (*d*, C(β) (Ile(1))); 33.2 (*d*, C(β) (Val)); 28.3 (*q*, Me_3C); 27.5 (*q*, Me(2) (Aib(1))); 27.5 (*t*, C(β) (Trp)); 27.0 (*q*, Me(1) (Aib(1))); 25.4 (*t*, C(γ) (Ile(2))); 25.2 (*q*, Me(2) (Aib(2))); 24.8 (*d*, C(γ) (Leu)); 24.6 (*t*, C(γ) (Ile(1))); 23.1 (*q*, Me(1) (Aib(2))); 22.9 (*q*, Me(2) (Leu)); 22.0 (*q*, Me(1) (Leu)); 19.6 (*q*, Me (Ala)); 19.3 (*q*, Me(2) (Val)); 18.8 (*q*, Me(1) (Val)); 16.0 (*q*, Me(β^1) (Ile(2))); 15.4 (*q*, Me(β^1) (Ile(1))); 11.9 (*q*, Me(δ) (Ile(2))); 11.4 (*q*, Me(δ) (Ile(1))). ESI-MS: 1035 ([$M + Na$]$^+$).

*Methyl (2S)-1-(2-[(2S)-2-[2-[(2S)-2-[(2S,3S)-2-[(2-[(R/S)-1-[(2S,3S)-2-((2S)-[[(*tert*-Butoxy)carbonyl]-amino]-3-(indol-3-yl)propanamido)-3-methylpentanamido]-1-methylethyl]-4,5-dihydro-4,4-dimethyl-1,3-thiazol-5-yliden)amino]-3-methylpentanamido]-3-methylbutanethioamido)-2-methylpropanamido]-4-methylpentanamido]-2-methylpropanoyl)pyrrolidine-2-carboxylate* (**30**). A soln. of Fmoc-Val-Ψ(CS)-Aib-Leu-OMe[5] (48.5 mg, 0.0855 mmol) in MeCN (2 ml) was treated with Et_2NH (0.2 ml) and stirred at r.t., yielding **28**. After 55 min, the intensely yellow soln. was concentrated and dried under high vacuum. According to *GP 4*, **21** (43.2 mg, 0.0602 mmol) was hydrolyzed with $LiOH \cdot H_2O$ (7.2 mg, 0.172 mmol) in 2 ml of THF/MeOH/H_2O 3 : 1 : 1 to give **22**; reaction time: 17 h. The two crude products were coupled according to *GP 1* with EtN(i-Pr)$_2$ (10.0 mg, 0.0774 mmol), TBTU (20.0 mg, 0.0663 mmol), and HOBt (10.6 mg, 0.0693 mmol) in MeCN (2 ml); reaction time: 19 h. Because the precipitated crude product could not be dissolved anymore, it was hydrolyzed without further purification according to *GP 4* with $LiOH \cdot H_2O$ (5.1 mg, 0.122 mmol) in 1.5 ml of THF/MeOH/H_2O 3 : 1 : 1; reaction time: 20 h. The crude product was treated according to *GP 3* with azirine **15** (15 mg, 0.076 mmol) in CH_2Cl_2 (2 ml); reaction time: 3.5 h. Chromatography (SiO_2; AcOEt) led to 35.2 mg (48%) of a mixture of epimers of **30** in a (*S*)/(*R*) ratio of 55 : 45. The two epimers were separated by prep. HPLC (*Bischoff*,

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[5]) For the preparation of Fmoc-Val-Ψ(CS)-Aib-Leu-OMe, see [3].

[6]) The ESI-MS of this product showed a peak at *m*/*z* 1053 ([$M + Na$]$^+$); the molecular weight of the linear octaendothiopeptide **29** is 1030.

Spherisorb ODS2, 5 μm, MeCN/H_2O 70:30, 8.0 ml/min). The following data are those of **30** with the (*R*)-configuration of Ala. $[\alpha]_D = +10.6$ ($c = 0.50$). IR: 3475*w*, 3340*m*, 3000*w*, 2960*m*, 2935*w*, 2870*w*, 1740*m*, 1670*s*, 1505*s*, 1415*m*, 1365*m*, 1280*w*, 1170*s*, 1005*w*, 925*w*, 855*w*. ^{1}H-NMR (600 MHz; ^{1}H-TOCSY, ^{1}H-DQF-COSY, ^{13}C,^{1}H-HSQC, ^{13}C,^{1}H-HMBC): 8.46 (br. *s*, H–N(1) (Trp)); 7.90 (br. *s*, NH (Aib(2))); 7.65 (*d*, $J = 8.0$, H–C(4) (Trp)); 7.40 (*d*, $J = 8.1$, H–C(7) (Trp)); 7.30 (br. *s*, NH (Val^t)); 7.20 (*t*, $J = 7.7$, H–C(6) (Trp)); 7.13 (*t*, $J = 7.8$, H–C(5) (Trp)); 7.11–7.06 (*m*, H–C(2) (Trp), NH (Ile(2)), NH (Aib(3)), NH (Ala)); 6.86 (br. *d*, $J = 7.7$, NH (Leu)); 6.32 (*d*, $J = 8.1$, NH (Ile(1))); 5.11 (*d*, $J = 5.3$, NH (Trp)); 4.82–4.77 (*m*, H–C(α) (Ala)); 4.54 (*dd*, $J =$ 3.4, 8.8, H–C(2) (Pro)); 4.40–4.37 (*m*, H–C(α) (Leu)); 4.29–4.27 (*m*, H–C(α) (Ile(1))); 4.23–4.21 (*m*, H–C(α) (Val^t)); 3.77–3.71 (*m*, 1 H–C(5) (Pro), MeO); 3.55–3.50 (*m*, 1 H–C(5) (Pro)); 3.31–3.25 (*m*, H–C(α) (Ile(2)), 2 H–C(β) (Trp)); 2.49–2.42 (*m*, H–C(β) (Val^t)); 2.11–1.97 (*m*, 1 H–C(3) (Pro), 1 H–C(4) (Pro)); 1.94–1.77 (*m*, H–C(β) (Ile(1)), H–C(β) (Ile(2)), 1 H–C(4) (Pro), 1 H–C(3) (Pro), 1 H–C(β) (Leu)); 1.77 (*s*, Me(1) (Aib(2))); 1.68–1.37 (*m*, 1 H–C(β) (Leu), H–C(γ) (Leu), 1 H–C(γ) (Ile(2)), 1 H–C(γ) (Ile(1))); 1.60 (*s*, Me(2) (Aib(2))); 1.56 (*s*, Me(1) (Aib(3))); 1.55 (*s*, Me(2) (Aib(3))); 1.51 (*s*, Me(1) (Aib(1))); 1.46 (*s*, Me(2) (Aib(1))); 1.44 (*d*, $J = 4.6$, Me (Ala)); 1.42 (*s*, Me_3C); 1.32–1.23 (*m*, 1 H–C(γ) (Ile(2))); 1.05 (*d*, $J = 6.8$, Me(1) (Val^t)); 0.99–0.93 (*m*, 1 H–C(γ) (Ile(1))); 0.93 (*d*, $J = 7.4$, Me(2) (Val^t)); 0.92 (*d*, $J = 6.8$, Me(2) (Leu)); 0.90 (*t*, $J = 7.5$, Me(δ) (Ile(2))); 0.88 (*d*, $J = 6.6$, Me(1) (Leu), Me(β^1) (Ile(2))); 0.83 (*t*, $J = 7.3$, Me(δ) (Ile(1))); 0.77 (*d*, $J = 6.9$, Me(β^1) (Ile(1))). ^{13}C-NMR (150.9 MHz): 201.8 (*s*, CS (Val^t)); 179.2 (*s*, thiazole C(5)); 173.5 (2*s*, CO (Pro), CO (Ile(2))); 172.4 (*s*, CO (Aib(2))); 172.1 (*s*, CO (Aib(3))); 171.9 (*s*, CO (Trp)); 171.0 (*s*, CO (Leu)); 170.8 (*s*, CO (Ile(1))); 164.6 (*s*, thiazole C(2)); 156.4 (*s*, urethane CO); 136.6 (*s*, C(3a) (Trp)); 127.5 (*s*, C(7a) (Trp)); 123.5 (*d*, C(2) (Trp)); 122.6 (*d*, C(6) (Trp)); 120.1 (*d*, C(5) (Trp)); 118.9 (*d*, C(4) (Trp)); 111.6 (*d*, C(7) (Trp)); 110.3 (*s*, C(3) (Trp)); 83.3 (*s*, thiazole C(4)); 81.0 (*s*, Me_3C); 79.0 (*d*, C(α) (Ile(2))); 68.2 (*d*, C(α) (Val^t)); 61.2 (*s*, C(α) (Aib(2))); 60.9 (*d*, C(2) (Pro)); 58.3 (*d*, C(α) (Ile(1))); 57.1 (*s*, C(α) (Aib(3))); 56.1 (*d*, C(α) (Trp)); 53.1 (*d*, C(α) (Leu)); 52.2 (*q*, MeO)); 49.3 (*d*, C(α) (Ala)); 48.4 (*t*, C(5) (Pro)); 40.6 (*t*, C(β) (Leu)); 40.2 (*d*, C(β) (Ile(2))); 36.8 (*d*, C(β) (Ile(1))); 32.1 (*d*, C(β) (Val^t)); 28.5 (*q*, Me_3C)); 28.1 (*t*, C(3) (Pro)); 27.9 (*q*, Me(2) (Aib(1))); 27.9 (*t*, C(β) (Trp)); 27.0 (*q*, Me(1) (Aib(1))); 26.8 (*q*, Me(2) (Aib(2))); 26.2 (*t*, C(4) (Pro)); 25.7 (*t*, C(γ) (Ile(2))); 25.3 (*d*, C(γ) (Leu)); 25.1 (*q*, Me(2) (Aib(1))); 24.7 (*t* and *q*, C(γ) (Ile(1)), Me(1) (Aib(3))); 23.6 (*q*, Me(2) (Leu), Me(1) (Aib(2))); 21.4 (*q*, Me(1) (Leu)); 20.2 (*q*, Me(1) (Val^t)); 18.9 (*q*, Me (Ala)); 17.5 (*q*, Me(2) (Val^t)); 16.1 (*q*, Me(β^1) (Ile(2))); 15.8 (*q*, Me(β^1) (Ile(1))); 12.1 (*q*, Me(δ) (Ile(2))); 11.9 (*q*, Me(δ) (Ile(1))). ESI-MS: 1217 ($[M + Na]^+$), 620 ($[M + 2Na]^{2+}$).

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