J. prakt. Chem. 338 (1996) 251–256

Journal für praktische Chemie
Chemiker-Zeitung

Dithio and Thiono Esters. 61 [1]

Synthesis of α-Amino Dithioesters and Endothiodipeptides

Klaus Hartke and Stephan Barrmeyer

Marburg, Institut für Pharmazeutische Chemie, Universität

Received September 20th, 1995 respectively November 24th, 1995

Dedicated to Prof. Dr. Dr. E. Mutschler on the Occasion of his 65th Birthday

Abstract. The α-amino ester hydrochlorides (**1**) are converted into N-protected α-amino amides (**3**), α-amino thioamides (**4**) and α-amino dithiomethylesters (**5**). Condensation of **5** with the alkali salts of α-amino acids gives rise to the endothiodipeptide alkali salts (**7**).

Chemically modified peptides have attracted considerable attention in recent years. Among them endothiopeptides with one or more CS-NH groups instead of CO-NH groups play an important role [2]. The geometry of such endothiopeptides is similar to that of peptides [3]. Differences in bond length and torsion angles, however, may alter the secondary structure of endothiopeptides in comparison to peptides and consequently influence their biological activity [3]. Thus the binding to specific cellular receptors can be altered accompanied by enhancement or reduction of biological activity [4]. In general, enzymatic hydrolyses of endothiopeptides by proteases is slowed down considerably [5].

Suitable building blocks for the thiopeptide bond are N-protected α-amino dithioesters. Without any activation of the dithioester function they will condense at room temperature with primary amines to form thioamides. With this approach, however, two main problems are connected:

- simple preparation of optically active N-protected α-amino dithioesters.
- convenient formation of the thioamide bond *without* racemisation.

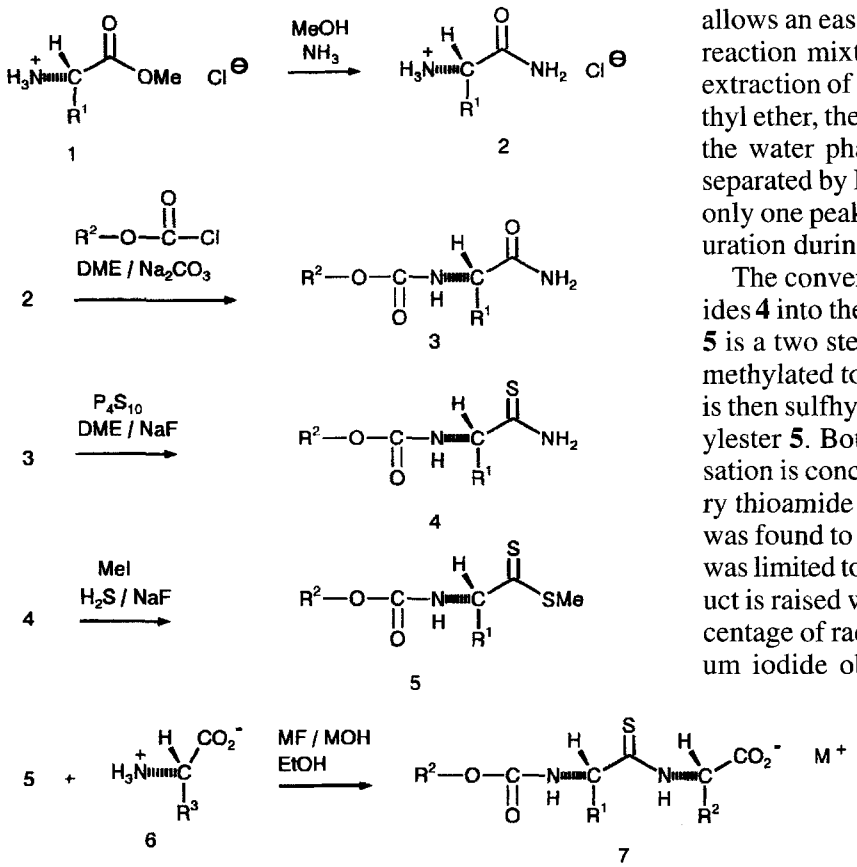
Lawesson and his group were the first to prepare optically active, N-protected α-amino dithioesters by the following route: L-amino acid → *tert*-amide →*tert*-thioamide → thioliminium salt → dithio ester. They postulated retention of configuration without any experimental proof. Our group has been able to obtain N-protected α-amino dithioesters from optically active Z-substituted α-amino nitriles (Z = benzyloxycarbonyl) and from optically active BOC-substituted α-amino amides (BOC = *tert*-butoxycarbonyl) with high retention of configuration (90-99 % ee) [2]. Thus the first problem mentioned has been solved, at least in principle.

The second problem, however, still remains to be solved. The reaction rate to form the thiopeptide bond from N-protected α-amino dithioesters with α-amino esters, sterically more hindered than alkyl glycinates, is rather slow. Reaction times of 24 hours are necessary with phenylalanine esters or leucine esters. Due to the rather high pK_s values of N-protected α-amino dithioesters (pK_s about 9) [2, 6] long reaction times lead to partial or complete racemisation [4, 5, 7, 8]. Recently Høeg-Jensen et al. [9] reported the transformation of N-protected α-amino monothio acids with benzotriazol-1-yl-tripyrrolidinophosphonium hexafluorophosphate into activated N-protected α-amino dithioesters and their condensation to thiopeptides within 5 hours. The formation of the thiopeptide bond is said to occur without racemisation. A side reaction, however, gives rise to about 20% of a by-product with a normal peptide bond.

In this paper we describe improved conditions for a simple transformation of optically active α-amino acids via its amides and thioamides into N-protected α-amino dithioesters with retention of configuration. Their subsequent condensation with the alkali salts of natural α-amino acids, catalyzed by alkali fluoride in ethanol, gives rise to endothiopeptides within 15–60 minutes. These mild conditions indicate, that the thioamide bond should be formed essentially without racemisation.

Results and Discussions

The α-amino ester hydrochlorides **1** were converted into the N-protected α-amino amides **3** in a one pot reac-



Scheme 1

tion. We used preferentially menthyloxycarbonyl (MOC) as a protecting group; it allows an easy control of the racemisation process by NMR spectroscopy or by HPLC analysis due to its three stereogenic centres: 1R, 3R, 4S [10]. **3a-k** were prepared in this way (scheme 2).

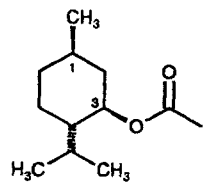
Nowadays the reagent of choice to convert carbonyl into thiocarbonyl groups is 2,4-bis(methoxyphenyl)-1,3-dithia-2,4-diphosphetan-2,4-disulfide (Lawesson reagent) [11]. The main disadvantages in using this reagent are higher reaction temperatures and the formation of by-products, that are often difficult to separate by simple column chromatography. In former times tetraphosphorus decasulfide (P_4S_{10}) had been used extensively for the same purpose. Meanwhile the suitability of mixtures of P_4S_{10} with mild bases has been studied. Thus Scheeren et al. [12] reported the conversion of ketones into thioketones with P_4S_{10}/$NaHCO_3$ at temperatures between 30–120 °C. Recently Brillon [13] obtained thioamides and thiolactams with an equimolar mixture of P_4S_{10}/$NaHCO_3$ in THF under very mild conditions (−20 to +50°C). In our hands a mixture of P_4S_{10} (2,5 mmol), sodium fluoride (4,75 mmol) and α-amino amide (1,67 mmol) in dimethoxyethane at room temperature gave optimum results (see Experimental, table 1). P_4S_{10}/NaF dissolves completely in DME and allows an easy work up procedure. After dilution of the reaction mixture with aqueous sodium carbonate and extraction of the α-amino thioamide with *tert*-butylmethyl ether, the thiophosphates formed are removed with the water phase. The diastereomeric mixture **4e** was separated by HPLC; under the same conditions **4d** gave only one peak, indicating complete retention of configuration during the thionation process.

The conversion of the N-protected α-amino thioamides **4** into the N-protected α-amino dithiomethylesters **5** is a two step process. First the thioamide must be S-methylated to form a methylthioiminium salt. This salt is then sulfhydrolyzed to yield the α-amino dithiomethylester **5**. Both steps are crucial ones as far as racemisation is concerned. For an S-methylation of the primary thioamide group in **4** the reactivity of methyl iodide was found to be sufficient. The reaction time, however, was limited to 2 hours. The yield of the methylated product is raised with longer reaction times but also the percentage of racemisation goes up. The methylthioiminium iodide obtained in the first step is hygroscopic. Therefore it was not isolated but rather sulfhydrolyzed immediately at room temperature for 30 min. This step requires a basic catalyst in order to increase the concentration of SH^- ions. Sodium fluoride was found to be sufficiently basic under the reaction conditions; stronger bases and longer reaction times will favour racemisation of the dithioesters **5**.

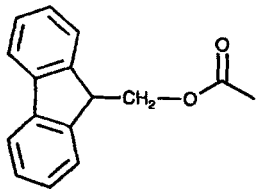
By this one pot reaction the N-protected α-amino dithiomethylesters **5**, summarized in table 1 (see Experimental), were obtained. The medium yields of **5** are to a certain extent due to an incomplete formation of the methylthioiminium iodides and to an incomplete sulfhydrolysis. Following, however, our reaction conditions (see Experimental) an enantiomeric excess of about 97% is found. This was confirmed by an HPLC seperation of **5a** and **5b.**

Endothiodipeptides are formed by condensation of N-protected α-amino dithioesters with α-amino acid derivatives. With esters of glycine, the sterically most favourable amino acid, this reaction is over within 1 hour. With esters of higher amino acids, e.g. phenyl alanine, the formation of the thiopeptide bond takes 24 hours and more. This long reaction time is accompanied by a high degree of racemisation and therefore not acceptable.

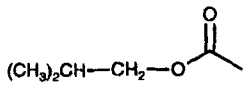
We observed that the condensation of **5** with the alkali salts of α-amino acids is much more rapid than with the corresponding esters. Furthermore the reaction time



menthyloxycarbonyl
MOC



fluoren-9-yl
methoxycarbonyl
FMOC



isobutyloxycarbonyl
ISOBOC

Scheme 2

3	α-amino amide	m.p [°C]	yield [%]
a	N-MOC-*L*-ala-NH_2	150	86
b	N-MOC-*D,L*-ala-NH_2	125	85
c	N-MOC-*L*-phe-NH_2	171	88
d	N-MOC-*D,L*-phe-NH_2	155	85
e	N-MOC-*L*-val-NH_2	130	87
f	N-MOC-*L*-leu-NH_2	125	83
g	N-MOC-*L*-pro-NH_2	110	88
h	N-ISOBOC-gly-NH_2	85	86
i	N-ISOBOC-*L*-ala-NH_2	105	89
j	N-ISOBOC-*D,L*-ala-NH_2	105	85
k	N-FMOC-*D,L*-ala-NH_2	170	87

can be shortened by a factor 4–5 with addition of alkali fluorides as catalysts. This means that the formation of the thiopeptide bond normally does not require more than 15–30 min. Even for sterically unfavourable α-amino acids such as valine or proline 60 min are sufficient to obtain up to 85% of pure endothiodipeptides. The condensation takes place in ethanol, and the α-amino acids are added in ethanolic solution with an equivalent amount of sodium hydroxide or potassium hydroxide. The alkali content should be controlled carefully in order to avoid racemisation. The alkali salts of the endothiopeptides formed can be purified by simple column chromatography on silica gel. By protonation of the alkali salts the free acids are formed, which were difficult to handle due to their tensidic properties. The analytical data of the endothiodipeptides **7** prepared by this method are summarized in table 2 (see Experimental)

The short reaction times for the formation of the thiopeptide bond suggests retention of configuration. This is confirmed by a careful study of the ^1H and ^{13}C NMR spectra of **7**. Unfortunately we have not been able so far to separate diastereomeric endothiodipeptides such as **7b, 7c** or **7k** by HPLC. Therefore a concluding answer to the extent of racemisation is still open.

Financial support from the Deutsche Forschungsgemeinschaft and from the Fonds der Chemischen Industrie is gratefully acknowledged.

Experimental

NMR (TMS as internal standard): Jeol JNM-GX 400 (probe temperature 25 C). – MS (70 eV): Vacuum Generators 70/70. – Melting points (uncorrected): Leitz heating microscope HM-Lux. – HPLC analysis: Silica gel 60 (5 μm) Merck, column length 150 mm, diameter 3 mm; pressure 25 bar, flowing rate 0,6 ml/min; solvent for **4d** and **4e**: *tert*-butylmethyl ether/*n*-hexane 1:1; solvent for **5a** and **5b**: CH_2Cl_2/*n*-hexane 1:1.

Preparation of the N-protected α-amino amides (3)

A solution of the α-amino acid methylester hydrochloride **1** (10 mmol) in methanol (20 ml), saturated with NH_3 gas, is stirred at room temperature for 72 h and then evaporated in vacuo. The solid residue is suspended in dimethoxyethane (20 ml) containing 10 mmol chlorocarbonic ester of the protecting group. With effective stirring an aqueous solution of Na_2CO_3 (0.5 M, 20 ml) is added. When the evolution of gas has ceased the reaction mixture is extracted with *tert*-butylmethyl ether (2×20 ml). The organic phase is dried with Na_2SO_4 and evaporated in vacuo. The residue is suspended in a small amount of *tert*-butylmethyl ether/*n*-pentane 1:1 and collected by filtration.

Preparation of the N-protected α-amino thioamides (4)

A suspension of P_4S_{10} (1,10 g, 2,5 mmol) and NaF (0,20 g, 4,75 mmol) in dry dimethoxyethane (10 ml) is stirred until a clear yellow solution results (about 30 min). Then the N-protected α-amino amide **3** (1,67 mmol) is added and stirring is continued for another 15 h. The reaction mixture is diluted with an aqueous solution of Na_2CO_3 (0,5 M, 10 ml) and extracted with *tert*-butylmethyl ether (2×10 ml). The organic phase is dried with Na_2SO_4, concentrated *in vacuo*, and the residue is chromatographed on silica gel with *tert*-butylmethyl ether/*n*-hexane 1:1.

Preparation of the N-protected α-amino acid dithiomethyl esters (5)

Methyl iodide (0,23 g, 1.6 mmol) is added to a stirred solution of the N-protected α-amino thioamide **4** (1 mmol) in dry dimethoxyethane (5 ml) at room temperature . After 2 h this solution is given to a stirred suspension of NaF (40 mg, 0.95 mmol) in dry dimethoxyethane (5 ml) saturated with dry H_2S. Bubbling of dry H_2S is continued for another 30 min. Then the reaction mixture is filtered, diluted with water (5 ml) and extracted with *tert*-butylmethyl ether (2×5 ml). The organic phase is dried with Na_2SO_4, concentrated *in vacuo*, and the residue is chromatographed on silica gel with CH_2Cl_2.

Preparation of the endothiodipeptides (7)

At room temperature a solution of the α-amino acid (1 mmol) and NaOH (or KOH) [1 mmol] in ethanol (10 ml) is added to a stirred suspension of the N-protected α-amino acid dithiomethylester **5** (1 mmol) and NaF (40 mg, 0,95 mmol) in ethanol (10 ml) . After 15-60 min the reaction mixture is filtered and the filtrate concentrated in vacuo without heating. The residue is chromatographed on silica gel with cyclohexane/ethanol 3:2.

Table 1 Analytical data of N-protected α-amino thioamides (**4a–l**) and α-amino acid dithiomethylesters (**5a-j**)

No.	Name Molecular Formula [a]	m.p. yield	MS *m/z* (%)	^{1}H NMR [b] ($CDCl_3$ [c]), TMS) δ (ppm)	^{13}C NMR [b] ($CDCl_3$ [c]), TMS) δ (ppm)
4a	N-MOC-glycine- thioamide $C_{13}H_{24}N_2O_2S$ (272.4)	96 °C 90%,	272 (25), 198 (78), 138 (100)	8.1–8.0 (2s, 2H, NH_2), 5.65 (d, 1H, NH), 4.19 (d, 2H, 2-H)	204.8 (C=S), 157.0 (C=O), 51.3 (C-2)
4b	N-MOC-*L*-alanine- thioamide $C_{14}H_{26}N_2O_2S$ (286.4)	85°C 87%	286 (14), 226 (42), 182(21)	8.1–7.7 (2s, 2H, NH_2), 5.50 (d, 1H, NH), 1.50–1.45 (m, 4H, 3-H, 1'-H)	210.3 (C=S), 156.2 (C=O). 55.4 (C-2), 21.8 (C-3)
4c	N-MOC-*D,L*-alanine- thioamide $C_{14}H_{26}N_2O_2S$ (286.4)	60 °C 84%	286 (8,2) 226(31), 182(16)	8.0–7.6 (2s, 2H, NH_2), 5.44 (d, 1H, NH), 1.50–1.46 (m, 4H, 3-H, 1'-H)	210.3 (C=S), 156.2 (C=O), 55.3 (C-2), 21.8 (C-3)
4d	N-MOC-*L*-phenyl- alanine-thioamide $C_{20}H_{30}N_2O_2S$ (362.5)	130°C 88%	362 (30), 302 (62), 258 (21)	7.7–7.6 (2s, 2H, NH_2), 7.25 (m, 5H, arom. H), 5.53 (m, 1H, NH), 4.72 (m, 1H, 2-H), 3.12 (m, 2H, 3-H)	208.1 (C=S), 156.1 (C=O), 136.5, 129.3, 127.8, 127.1 (arom.C), 60.4 (C-2), 41.8 (C-3)
4e	N-MOC-*D.L*-phenyl- alanine-thioamide $C_{20}H_{30}N_2O_2S$ (362.5)	156 °C 85%	362 (29), 302 (52), 258 (18)	7.7–7.4 (2d, 2H, NH_2), 7.25 (1m, 5H, arom. H), 5.47 (2d, 1H, NH), 4.70 (m, 1H, 2-H), 3.10 (m, 2H, 3-H)	208.2, 208.1 (C=S), 156.0 (C=O), 36.5, 129.3, 128.7, 127.1(arom.C), 61.6, 61.2 (C-2), 42.0 (C-3)
4f	N-MOC-*L*-valine- thioamide $C_{16}H_{30}N_2O_2$ (314.5)	110 °C 90%	206 (27), 116 (12), 91 (27), 58 (100)	8.2, 7.9 (2s, 2H, NH_2), 5.45 (d, 1H, NH), 4.33 (m, 1H, 2- H), 2.48 (m, 1H, 3H), 1.1–0.9 (m, 8H, 4-, 5-, 2'-, 5'-H)	210.2 (C=S), 157.6 (C=O), 66.5 (C-2), 34.2, 20.5, 19.4 (C-4, C-5)
4g	N-MOC-*L*-leucine- thioamide $C_{17}H_{32}N_2O_2S$ (328.5)	120 °C 91%	328 (0.9), 272 (45), 224 (15), 138 (27)	8.2–7.7 (2s, 2H, NH), 5.31 (d, 1H, NH), 4.52 (m, 2H, 2-H, 3'- H), 1.65 (m, 3H, 4-, 5'-, 6'-H), 1.0–0.8 (m, 15H)	210.7 (C=S), 156.7 (C=O 58.3 (C-2), 44.5 (C-3), 24.9 (C-4), 22.9, 22.0 (C-5, -6, -7')
4h	N-MOC-L-proline- thioamide $C_{16}H_{28}N_2O_2S$ (312.5)	210 °C 93%	312 (23), 252 (91), 208(24), 70(100)	9.5–9.0 (2s, 2H, NH_2), 4.46 (m, 1H, 2-H), 3.5–3.3 (2m, 2H, 5-H), 1.9–1.8 (m, 8H, 3-, 4-, 2'-, 8'-H)	208.4 (C=S), 154.0–153.7 (C=O), 66.1 (C-2), 46.9–46.5 (C-5, C-4'), 32.5 (C-3), 23.5– 22.9 (C-4, C-5')
4i	N-ISOBOC-glycine- thioamide $C_7H_{14}N_2O_2S$ (190.3)	85 °C 91%	190 (80), 173 (12), 134 (21), 131 (19)	8.1–8.0 (2s, 2H, NH_2), 5.7–4.9 (2s, 1H, NH), 4.20 (d 2H, 2-H)	204.7 (C=S), 159.4 (C=O), 51.2 (C-2)
4j	N-ISOBOC-*L*- alanine-thioamide $C_8H_{16}N_2O_2S$ (204.3)	oil 93%	204 (26), 176 (47), 152 (12), 144(55)	8.3–8.0 (2s, 2H, NH_2), 5.69 (d, 1H, NH), 4.63 (m, 1H, 2-H), 1.49 (d, 3H, 3-H)	210.2 (C=S), 156.5 (C=O), 55.2 (C-2), 22.0 (C-3)
4k	N-ISOBOC-*D,L*- alanine-thioamide $C_8H_{16}N_2O_2S$ (204.3)	oil 90%	204 (6,3), 144 (18), 97 (13), 73 (100)	8.3–8.0 (2s, 2H, NH_2), 5.72 (d, 1H, NH), 4.64 (m, 1H, 2-H), 1.49 (d, 3H, 3-H)	210.1 (C=S), 156.4 (C=O), 55.3 (C-2), 21.8 (C-3)
4l	N-FMOC-*L*-alanine- thioamide $C_{18}H_{18}N_2O_2S$ (326.4)	100 °C 92%	178 (100), 166 (29), 165 (59)	9.6–9.1 (2s, 2H, NH_2), 7.42 (m, 3H, NH, 3'-, 6'-H), 4.4–4.2 (m, 4H, 2-, 9'-, 14'-H), 1.33 (d, 3H, 3-H)	209.2 (C=S), 156.4, 155.2 (C=O), 55.9 (C-2), 20.9 (C-3)
5a	N-MOC-*L*-alanine- dithiomethylester $C_{15}H_{27}NO_2S_2$ (317.5)	105 °C 63%	317 (1), 226 (36), 182 (15)	5.54 (d, 1H, NH), 4.96 (m, 1H, 2-H), 2.64 (s, 3H, SCH_3)	241.2 (C=S), 155.3 (C=O), 61.4 (C-2), 24.0 (C-3), 19.2 (SCH_3)
5b	N-MOC-*D,L*-alanine- dithiomethylester $C_{15}H_{27}NO_2S_2$ (317.5)	77 °C 58%	317 (1.1) 226 (63), 182 (20)	5.52 (d, 1H, N-H), 4.97 (m, 1H, 2-H), 2.64 (s, 3H, SCH_3)	241.2, 241.1 (C=S), 155.3, 155.2 (C=O), 61.3, 61.2 (C-2), 23.9 (C-3), 19.2 (SCH_3)
5c	N-MOC-*L*-phenylalanine- dithiomethylester $C_{21}H_{31}NO_2S_2$ (393,6)	138 °C 66%	393 (2), 302 (86), 258 (23), 237 (11)	7.3–7.1 (m, 5H, arom. H), 5.46 (d, 1H, NH), 5.17 (m, 1H, 2-H), 3.23 (m, 2H, 3-H), 2.59 (s, 3H, SCH_3)	238.7 (C=S), 155.3 (C=O), 136.2, 129.3, 128.4, 126.9 (arom. C), 66.4 (C-2), 43.7 (C-3), 19.4 (SCH_3)
5d	N-MOC-*D,L*- phenylalanine- dithiomethylester $C_{21}H_{31}NO_2S_2$ (393.6)	120 °C 61%	393 (1.6), 302 (90), 258 (27), 194 (12)	7.3–7.1 (m, 5H. arom. H), 5.46 (d, 1H, NH), 5.18 (m, 1H, 2-H), 3.3–3.0 (2d. 2H, 3-H), 2.59 (SCH_3)	238.7 (C=S), 155.2 (C=O) 136.2, 129.3, 128.3, 126.9 (arom. C), 66.4, 66.1 (C-2), 43.7 (C-3), 19.4 (SCH_3)
5e	N-MOC-*L*-valine- dithiomethylester $C_{17}H_{31}NO_2S_2$ (345.6)	65 °C 61%	345 (0.5), 254 (51), 210 (18), 139 (22)	5.44 (d, 1H, NH), 4.69 (m, 1H, 2-H), 2.63 (s, 3H, SCH_3), 2.32 (m, 1H, 3-H), 1.0–0.8 (m, 10H, 4-, 5-H)	239.8 (C=S),155.9 (C=O), 70.5 (C-2), 34.9 (C-3), 20.0 (SCH_3), 17.4 (C4)

Table 1 continued

5f	N-MOC-*L*-leucine-dithiomethylester $C_{18}H_{33}NO_2S_2$ (359.6)	85 °C 64%	359 (0.7), 268 (49), 224 (20), 149 (17)	5.37 (d, 1H, NH), 4.94 (m, 1H, 2-H), 2.64 (s, 3H, SCH_3), 1.7–1.6 (m, 3-, 5'-, 6'-H), 0.9–0.8 (m, 15H, 3-, 5-, 6-H)	241.3 (C=S), 155.6 (C=O), 64.0 (C-2), 47.1 (C-3). 25.1 (C-4), 22.9 (C-6), 22.0 (C-5, -7'), 19.2 (SCH_3)
5g	N-MOC-*L*-proline-dithiomethylester $C_{17}H_{29}NO_2S_2$ (343.5)	70 °C 58%	343 (1.7), 252 (100), 208 (21), 149 (15)	5.05 (2d, 1H, 2-H), 3.6–3.5 (2m, 2H, 5-H), 2.61 (s, 3H, SCH_3), 2.5–2.3 (m, 1H, 3-H), 2.2–1.8 (m, 5H, 3-, 4-, 2'-, 8'-H)	242.6, 241.4 (C=S), 154.8, 154.5 (C=O), 73.1 (C-2), 47.4 (C-5), 31.4, 31.2 (C-3), 23.8, 23.7 (C-4). 19.1, 18.9 (SCH_3)
5h	N-ISOBOC-*L*-alanine-dithiomethylester $C_9H_{17}NO_2S_2$ (235.4)	50 °C 68%	235 (7.4), 204 (13), 157 115), 144 (100)	5.67 (d, 1H, NH), 4.99 (m, 1H, 2-H), 2.64 (s, 3H, SCH_3), 1.51(d, 3H, 3-H)	240.8 (C=S), 155.5 (C=O), 61.1(C-2), 24.0 (SCH_3), 19.2 (C-3)
5i	N-ISOBOC-*D,L*-alanine-dithiomethylester $C_9H_{17}NO_2S_2$ (235.4)	50 °C 64%	235 (9.8), 161 (21), 144 (100)	5.67 (d, 1H, NH), 4.99 (m, 1H, 2-H) 2.64 (s, 3H, SCH_3), 1.51(d, 3H, 3-H)	240.9 (C=S), 155.5 (C=O), 61.1 (C-2), 24.0 (SCH_3), 19.2 (C-3)
5j	N-FMOC-*L*-alanine-dithiomethylester $C_{19}H_{19}NO_2S_2$ (357.5)	135 °C 62%	357 (0.7), 178 (100), 165 (38)	5.75 (d, 1H, NH), 5.1–5.0 (m, 1H, 2-H), 2.64 (s, 3H, SCH_3), 1.53 (d, 3H, 3-H)	240.5 (C=S), 155.2 (C=O), 61.2 (C-2), 24.0 (SCH_3), 19.3 (C-3)

[a]) Correct elemental analyses were obtained: **4**: C ± 0.54, H ± 0.43, N ± 0.46, S ± 0.75; **5**: C ± 0.39 H ± 0.46 N ± 0.47 S ± 0.56
[b]) Signals for protecting groups are generally not given (exceptions: numbers with a dash and O-CO-NH)
[c]) **4h**: [D_6]DMSO as solvent

Table 2 Analytical data of endothiodipeptides (**7a-o**)

No.	Name [a]) Molecular Formula [b])	R.T. [c]) m.p. yield	^{1}H NMR [d]) ([D_6]DMSO [e]),TMS) δ (ppm)	^{13}C NMR [d]) ([D_6]DMSO [e]), TMS) d (ppm)
7a	N-MOC-L-alat-gly$^-$ Na^+ $C_{16}H_{27}N_2O_4S^-$ Na^+ (366,5)	15 min 180 °C 90%	6.44 (d, 1H, CS-NH), 4.77 (d, 1H, CO-NH), 4.25–4.13 (2m, 2H, 2-H-gly), 2.02–1.89 (m, 5H, 3-H-alat, 2'-, 8'-H)	206.8 (C=S), 178 (CO_2^-), 156.6 (C=O), 56.4 (C-2-alat), 51.7 C-2-gly), 22.8 (C-3-alat)
7b	N-MOC-*D,L*-alat-*L*-ala$^-$ Na^+ $C_{17}H_{29}N_2O_4S^-$ Na^+ (380.5)	15 min 190 °C 92%	9.56 (d, 1H, CS-NH), 7.4–7.3 (2d 1H, CO-NH), 4.4–4.3 (m, 2H, 2-H-alat, 2-H-ala), 1.30 (m, 7H, 3-H-alat, 3-H-ala, 4'-H)	201.5 (C=S), 174 (CO_2^-), 155.1 (C=O). 56.4, 55.9 (C-2-alat), 54.9 (C-2-ala), 21.2 (C-3-alat). 16.9 (C-3-ala)
7c	N-MOC-*D,L*-alat-*L*-val$^-$ Na^+ $C_{19}H_{33}N_2O_4S^-$ Na^+ (408,5)	30 min 130 °C 88%	9.5–9.3 (2m, 1H, CS-NH), 7.4–7.2 (2m, 1H, CO-NH), 4.69 (d, 1H, 2-H-alat), 4.50 (m, 1H, 2-H-val), 2.26 (m, 1H, 3-H-val), 1.3–1.2 (3-H-alat), 1.0–0.8 (m, 13H, 4-, 5-H-val)	203.7 (C=S). 173.5 (CO_2^-), 155.1 (C=O), 63.8 (C-2-val), 57.3 (C-2-alat), 30.5 (C-3-val), 20.5 (C-3-alat, 18.8–18.6 (C-4-, -5-val)
7d	N-ISOBOC-L-alat-gly$^-$ Na^+ $C_{10}H_{17}N_2O_4S^-$ Na^+ (284.3)	15 min 180 °C 88%	4.52 (m, 1H, 2-H-alat), 4.2–4.0 (m, 2H, 2-H-gly), 1.44 (d, 3H, 3-H-alat)	205.4 (C=S), 175.6 (CO_2^-), 158.6 (C=O), 58.4 (C-2-alat), 50.5 (C-2-gly), 21.8 (C-3-alat)
7e	N-ISOBOC-*D,L*-alat-gly$^-$ Na^+ $C_{10}H_{17}N_2O_4S^-$ Na^+ (284.3)	15 min 170 °C 86%	9.38 (m, 1H, CS-NH), 7.55 (d, 1H, CO-NH), 4.42 (m, 1H, 2-H-alat), 3.78 (m, 2H, 2-H-gly), 1.32 (m, 3H, 3-H-alat)	202.4 (C=S), 170.5 (CO_2^-), 155.6 (C=O), 56.0 (C-2-alat), 49.0 (C-2-gly), 21.2 (C-3-alat)
7f	N-ISOBOC-L-alat-L-ala$^-$ Na^+ $C_{11}H_{19}N_2O_4S^-$ Na^+ (298.3)	15 min 180 °C 90%	4.73 (m, 1H, 2-H-ala), 4.49 (m, 1H, 2-H-alat), 1.46–1.40 (2d, 6H, 3-H-alat, 3-H-ala)	204.6 (C=S), 179.8 (CO_2^-), 158.2 (C=O), 58.3 (C-2-alat), 56.7 (C-2-ala), 21.9 (C-3-alat), 17.7 (C-3-ala)
7g	N-ISOBOC-*D,L*-alat-*L*-ala$^-$ Na^+ $C_{11}H_{19}N_2O_4S^-$ Na^+ (298.3)	15 min 170 °C 87%	9.54 (d, 1H, CS-NH), 7.50 (d, 1H, CO-NH), 4.41 (m, 2H, 2-H-alat, 2-H-ala), 1.4–1.3 (m, 6H, 3-H-alat, 3-H-ala)	201.4 (C=S), 174.6 (CO_2^-). 155 (C=O), 57.1(C-2-alat), 54.9(C-2-ala), 21.3 (C-3alat), 16.9 (C-3-ala)
7h	N-ISOBOC-*L*-alat-*L*-phe$^-$ K^+ $C_{17}H_{23}N_2O_4S^-$ K^+ (390.5)	30 min 150 °C 87%	7.20 (m, 5H, arom. H), 4.45 (m, 1H, 2-H-alat), 3.8–3.7 (m, 3H, 2-H-phe, 1'-H), 3.5, 3.2 (2m, 2H, 3-H-phe), 1.4–1.3 (d, 3H, 3-H-alat)	205.0 (C=S), 178.0 (CO_2^-), 158.4 (C=O), 138.7, 130.8, 129.2, 127.5 (arom. C), 58.6 (C-2-alat), 36.9 (C-3-1phe), 21.6 (C-3-alat)

Table 2 continued

7i	N-ISOBOC-*L*-alat-*L*-pro$^-$ Na$^+$ $C_{13}H_{21}N_2O_4S^-$ Na$^+$ (324.4)	30 min 185 °C 91%	6.87 (m, 1H, NH), 4.45 (m, 1H, 2-H-alat), 4.37 (m, 1H, 2-H-pro), 3.8–3.6 (m, 4H, 5-H-pro, 1'-H), 2.3–2.0 (2m, 2H, 3-H-pro), 1.9–1.7 (m, 3H, 4-H-pro, 2'-H), 1.3–1.2 (m, 3H, 3-H-alat)	207.0 (C=S). 171.5 (CO_2^-). 154.4 (C=O), 63.1 (C-2-pro), 54.2 (C-2-alat), 52.1 (C-5-pro), 31.1 (C-3-pro), 22.4 (C-4-pro), 21.5 (C-3-alat)
7j	N-FMOC-*L*-alat-*L*-phe$^-$ K$^+$ $C_{27}H_{25}N_2O_4S^-$ K$^+$ (512.7)	30 min 155 °C 86%	9.6–9.2 (2s, CS-NH), 7.84 (m, 1H, CO-NH) 7.2–7.1 (m, 5H, arom. H), 4.2 (m, 2H, 2-H-alat, 2-H-phe), 3.50 (d, 1H, 3-H-phe), 3.13 (d, 1H, 3-H-phe), 1.32 (d, 3H, 3-H-alat)	201.6 (C=S), 172.0 (C02), 155.3 (C=O), 138.0, 130.0–128.5, 125.7 (arom. C), 59.9 (C-2-phe), 55.8 (C-2-alat), 34.8 (C-3-phe), 21.0 (C-3-alat)
7k	N-MOC-*D,L*-phet-*L*-phe$^-$ Na$^+$ $C_{29}H_{37}N_2O_4S^-$ Na$^+$ (541.7)	30 min 135 °C 85%	9.6–9.5 (2d, 1H, CS-NH), 7.5–7.3 (2d, 1H, CO-NH), 7.3–7.1 (m, 10H, arom. H), 4.8–4.5 (m, 2H, 2-H-phet, 2-H-phe), 3.5–3.2 (2m, 2H, 3-H-phet), 3.2–2.7 (2m, 2H, 3-H-phe)	200.7 (C=S), 172.4, 172.0 (CO_2^-), 155.5, 155.2 (C=O). 138.4, 138.1, 129.6–128.5, 128.2–127.5, 126.0–125.6 (arom. C), 60.2 (C-2-phet), 55.7 (C-2-phe), 40.4, 40.3 (C-3-phet), 35.3, 35.1 (C-3-phe)
7l	N-MOC-*L*-valt-gly$^-$ Na$^+$ $C_{18}H_{31}N_2O_4S^-$ Na$^+$ (394.5)	60 min 160 °C 86%	9.43 (m, 1H, CS-NH), 7.05 (d, 1H, CO-NH), 4.22 (m, 1H, 2-H-valt), 3.83 (m, 2-H-gly), 2.20 (m, 1H, 3-H-valt), 0.9–0.8 (m, 13H, 4-H-, 5-H-valt, 6'-, 7'-, 10'-H)	200.7 (C=S), 169.9 (CO_2^-), 156.0 (C=O), 67.3 (C-2-valt), 46.7 (C-2-gly), 32.5 (C-3-valt), 19.3, 17.3 (C-4-, 5-valt)
7m	N-MOC-*L*-leut-*L*-leu$^-$ K$^+$ $C_{23}H_{41}N_2O_4S^-$ K$^+$ (480.7)	30 min 140 °C 83%	9.57 (m, 1H1, CS-NH), 7.08 (m, 1H, CO-NH), 4.70 (m, 1H, 2-H-leut), 4.40 (m, 2H, 2-H-leu, 3'-H), 1.7–1.6 (m, 4H, 4-H-leu, 5'-, 6'-H), 1.0–0.8.(m, 23H)	206.8 (C=S), 166.0 H-, (CO_2^-), 155.6 (C=O), 59.5 (C-2-leut), 58.1 (C-2-leu), 43.6 (C-3-1eut), 41.1 (C-3-leu), 24.3 (C-4-leut, -leu), 23.2–21.5 (C-5-, -6-1eu, -leut)
7n	N-MOC-*L*-prot-gly$^-$ K$^+$ $C_{18}H_{29}N_2O_4S^-$ K$^+$ (408.6)	30 min 200 °C 88%	9.18 (2s, 1H, CS-NH), 4.63 (2d, 1H, 2-H-prot), 3.81 (m, 2H, 2-H-gly), 3.5–3.4 (m, 2H, 5-H-prot), 2.23 (m, 1H, 3-H-prot), 2.1–1.8 (m, 5H, 3-H-, 4-H-prot, 2'-, 8'-H)	201.4 (C=S), 170.4 (CO_2^-), 153.9 (C=O), 66.7 (C-2-prot). 49.5(C-2-gly), 47.2–46.6 (C-5-prot, C-4'), 29.5 (C-3-prot), 23.2–22.8 (C-4-prot, C-5')
7o	N-MOC-*L*-prot-*L*-phe$^-$ K$^+$ $C_{25}H_{35}N_2O_4S^-$ K$^+$ · 0.5 H_20 (507.7)	60 min 140 ° C 87%	9.4–9.2 (2s, 1H, CS-NH), 7.2–7.1 (m, 5H, arom. H), 4.6–4.5 (m, 2H, 2-H-prot, 2-H-phe), 3.6–3.5 (m, 2H, 5-H-prot), 3.17 (2d, 2H, 3-H-phe), 2.2–2.1 (m, 1H, 3-H-prot), 2.0–2.2 (m, 4H, 3-H-, 4-H-prot)	208.2 (C=S), 172.0 (CO_2^-), 153.8 (C=O), 138.2, 129.6, 127.6, 125.8 (arom. C), 59.6 (C-2-prot), 55.7 (C-2-phe), 46.9 (C-5-prot), 34.9 (C-3-phe), 30.8 (C-3-prot), 23.0 (C-4-prot)

[a]) Letter "t" indicates the amino acid with the thiopeptide bond
[b]) Correct elemental analyses obtained: C ± 0.43 H ± 0.35
[c]) R.T.: Reaction time in minutes
[d]) Signals for protecting groups are generally not given (exceptions: numbers with a dash and O-CO-NH)
[e]) Other solvents: [D6]acetone (**7a**), CD_3OD (**7d**, **7f**, **7h**)

References

[1] Dithio and Thiono Esters, 60: N. Rettberg, U. Wagner, K. Hartke, *Arch. Pharm. (Weinheim, Ger.)* **326** (1993) 977

[2] For leading references prior to 1991 see: A. Kohrt, K. Hartke, Liebigs Ann. Chem. **1992**, 595

[3] M. Hollósi, Zs. Majer, M. Zewdu, F. Ruff, M. Kajtár, K. E. Kövér, Tetrahedron **44** (1988) 195

[4] J. Jurayj, M. Cushman, Tetrahedron **48** (1992) 8601

[5] O. E. Jensen, A. Senning, Tetrahedron **42** (1986) 6555

[6] A .C. Storer, Can. J. Chem. **61** (1983) 1440

[7] A. Kohrt, Ph. D. thesis, University of Marburg, **1991**

[8] K. Hartke, Phosphorus, Sulfur and Silicon **1991**, 223

[9] T. Høeg-Jensen, C. E. Olsen, A. Holm, J. Org. Chem. **59** (1994)1257

[10] (a) J. W. Westly, B. Halpern, J. Org. Chem. **33** (1968) 3978; (b) W. H. Pirkle, J. R. Hauske, J. Org. Chem. **42** (1977) 2436; (c) J. F. Nicoud, C. Eskenazi, H. B. Kagan, J. Org. Chem. **42** (1977) 4270; (d) J. I. Seeman, C. G. Chardarian, H. V. Secor, J. Org. Chem. **50** (1985) 5419; (e) T. Marx, E. Breitmaier, Liebigs Ann. Chem. **1992**, 183

[11] (a) Review: M. P. Cava, M. I. Levinson, Tetrahedron **41** (1985) 5061; (b) For Thiocyclosporins, obtained from Cyclosporin A with Lawesson's reagent, see: D. Seebach, S. Y. Ko, H. Kessler, M. Köck, M. Reggclin, P. Schmieder, M. D. Walkinshaw, J. J. Bölsterli, Helv. Chim. Acta **74** (1991) 1953

[12] J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, Synthesis **1973**, 149

[13] D. Brillon, Synth. Commun. **20** (1992) 1397

Address for correspondence:
Prof. Dr. K. Hartke
Philipps-Universität Marburg
Institut für Pharmazeutische Chemie
Marbacher Weg 6
D-35032 Marburg, Germany