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TETRAHEDRON

Site-Selective Incorporation of Thioamide-Linkages into a Growing Peptide

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Abstract

The use of endothiodipeptide anilides, which were obtained in high yields by a variation of the 'azirine/oxazolone method', for the synthesis of longer endothiopeptides is described. With this novel methodology, epimerically pure endothiopeptides with the thiocarbonyl group next to the bulky Aib were prepared in satisfactory yields. The structures of two endothiotripeptides and one endothiotetrapeptide were established by single-crystal X-ray crystallography. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: Thiopeptides; Azirines; X-ray crystal structures

INTRODUCTION

Peptides with backbone modifications have attracted considerable attention in recent years[1]. Among them, endothiopeptides, in which thioamide groups replace one or more amide bonds, play an important role. Endothio-analogues of biologically active peptides can show protease resistance, thus allowing better bioavailability[2]. In addition, enhanced receptor selectivity[3] and biological activity can be expected[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. Two of these amino acids, Aib (α-aminoisobutyric acid) and Iva (isovaline) characterize the peptaibols, an important family of natural antibiotics[17,18]. The twofold substitution at the α-carbon atom in these amino acids restricts the conformational flexibility and so can stabilize or induce helices[19-21]. Due to the severe steric hinderance in these α-alkylated α-amino acids, the synthesis of the related peptides is

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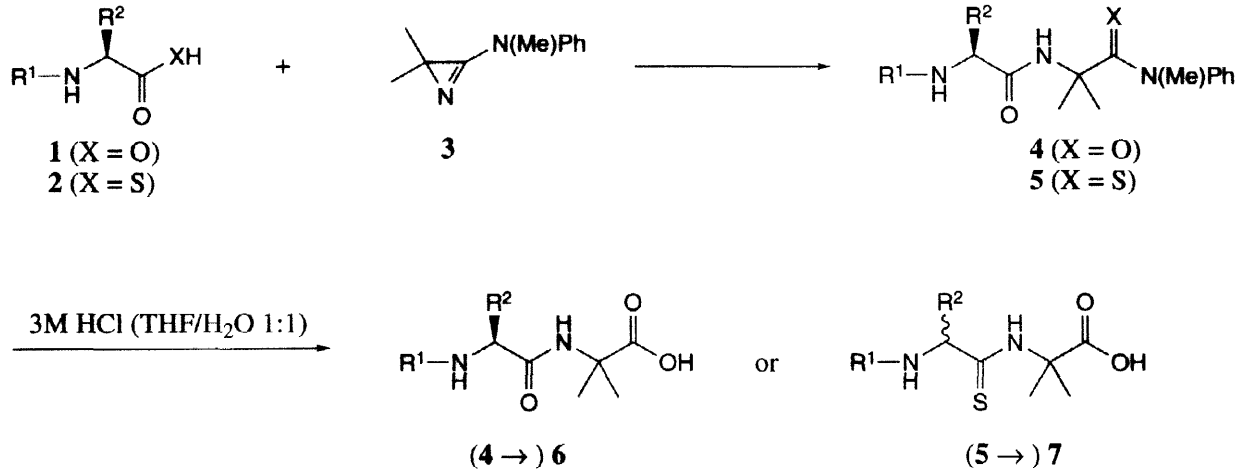
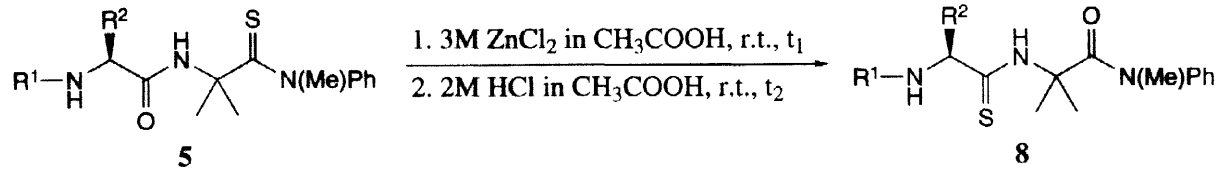
difficult[22-24]. With the 'azirine/oxazolone method' we developed a convenient access to such peptides. 3-Amino-2*H*-azirines **3** proved to be useful synthons for the introduction of α-alkylated α-amino acids [25-27] (Scheme 1, X = O).



Scheme 1

By using amino thioacids **2** in the 'azirine/oxazolone method' we potentially have a method in hand to synthesize peptides with a combination of these two backbone modifications. However, the acid catalyzed hydrolysis of the primarily formed thiodipeptide anilides **5** under the standard conditions (3M HCl, THF/H_2O 1:1) led to the completely epimerized endothiodipeptides **7**, in which the thiocarbonyl group has been shifted from the last to the penultimate amino acid (Scheme 1, X = S)[28]. During our further investigations with the aim of finding conditions under which no epimerization occurred, we discovered a novel and unprecedented isomerization: when the thiodipeptide amides **5** were initially treated with 3M $ZnCl_2$ in acetic acid and then with 2M HCl in acetic acid, the isomeric endothiodipeptide amides **8** were formed, in which the thiocarbonyl group has also been shifted from the last to the penultimate amino acid (Scheme 2).



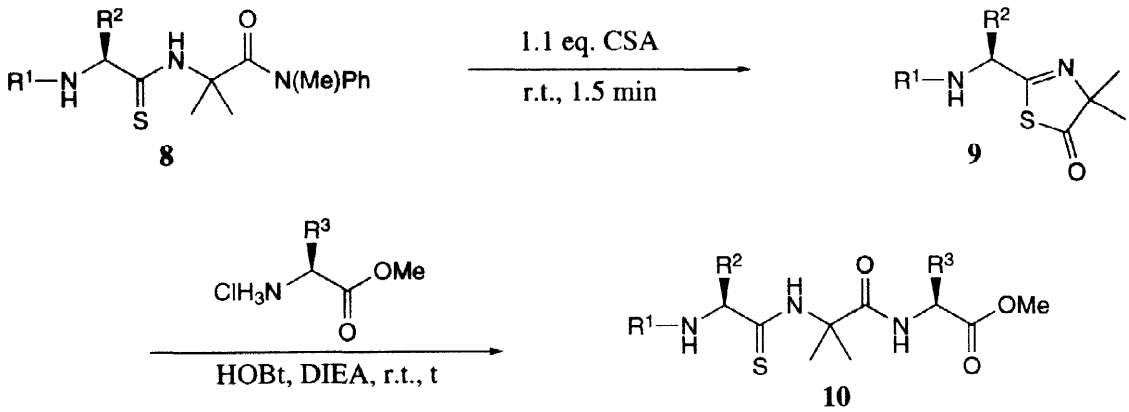
Scheme 2

This novel isomerization was carried out with different protecting groups R^1 and different amino acids (R^2). It has been shown that variations of R^1 have no influence on the reaction times. Conversely, the reaction times depend strongly on the steric hindrances introduced by R^2: the required reaction times increase with the size of R^2. This novel isomerization proceeds in high yields (ca. 90%) and without epimerization when the reaction times are optimised. The reaction times ($t_1 + t_2$) lie between 50 min (R^2 = CH(Et)Me) and ≤ 3.5 min (R^2 = Me).

The present work shows how the isomerized endothiodipeptides **8** can be incorporated into larger peptides to obtain endothiopeptides with the thiocarbonyl group at a position next to the bulky Aib.

RESULTS AND DISCUSSION

The endothiodipeptide amides of type **8** were easily converted into the corresponding endothiodipeptide acids *via* acidic hydrolysis analogous to that used in the 'azirine/oxazolone method' (3M HCl, THF/H_2O 1:1). For the next step, the C-terminal coupling of another amino acid, the acid functionality must be activated and is thereby converted spontaneously into the corresponding 1,3-thiazol-5(4*H*)-one by nucleophilic attack of the S-atom of the thioamide group. Therefore, the endothiodipeptide amides **8** were converted directly into the corresponding 1,3-thiazol-5(4*H*)-ones **9** by acid catalysis with (±)-camphor-10-sulfonic acid (CSA, Scheme 3). When the reaction times were kept short enough, the epimerization, which occurs easily with the thiazolones **9**, could be suppressed. Thus, no epimerization could be detected by HPLC when the reaction was quenched with $NaHCO_3$ solution after 1.5 min and **9** was extracted immediately. The coupling of thiazolones **9**, which are known to be only moderately reactive[29,30], with a C-terminal protected amino acid proceeded with satisfactory yields by catalysis with 1-hydroxybenzotriazole/*N*-ethyldiisopropylamine (HOBt/DIEA, Table 1).



8 **9** **10**

Scheme 3

The reaction times for the **9→10** step were quite long and increased with increasing bulkiness of R^2 and R^3. Thus, the reactions of 1,3-thiazol-5(4*H*)-ones **9a**, **c** and **d** with Gly-OMe led to the endothiotripeptides **10a**, **c** and **d** in 80-90% yield after 4-5 days. Coupling of Ala-OMe with the Phe-thiazolone **9b** gave **10b** in 72% yield after 3 days. Reaction of Val-thiazolone **9f** with Leu-OMe and Ala-thiazolone **9g** with Ile-OMe led to the corresponding endothiotripeptides **10f** and **10g** in 65 and 54%, yield, respectively, after 7 days. Finally, coupling of thiazolone **9d** with Phe-OMe gave, even after 14 days, the product **10e** in only 55% yield.

Table 1. Coupling of 1,3-thiazol-5(4*H*)ones **9** with C-terminal protected amino acids (Scheme 3)

9→10	R^1	R^2	R^3	t	Yield (%)
9a→10a	Z[a)]	CH(Et)Me	H	4 d	89
9b→10b	Z	CH_2Ph	CH_3	3 d	72
9c→10c	NVOC[b)]	CH(Et)Me	H	4 d	81
9d→10d	FMOC[c)]	CH(Et)Me	H	5 d	92
9d→10e	FMOC	CH(Et)Me	CH_2Ph	14 d	55
9f→10f	FMOC	$CHMe_2$	CH_2CHMe_2	7 d	65
9g→10g	FMOC	Me	CH(Et)Me	7 d	54

a) (Benzyloxy)carbonyl; b) (4,5-Dimethoxy-2-nitrobenzyloxy)carbonyl (= (6-Nitroveratryloxy)carbonyl);

c) (9-Fluorenylmethyloxy)carbonyl

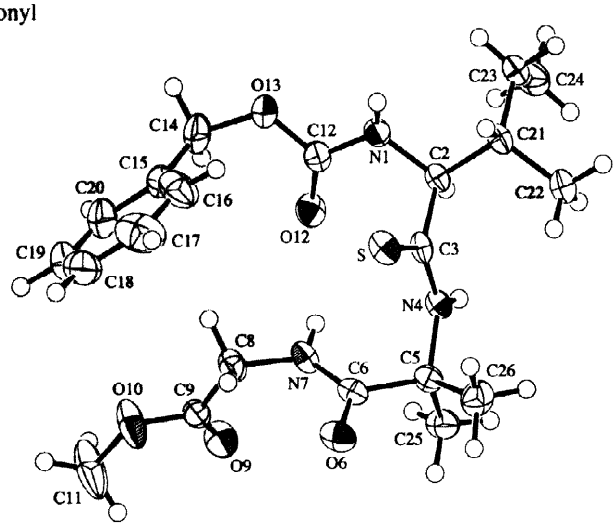


Fig.1. ORTEP Plot[32] with 50% probability ellipsoids of the molecular structure of Z-IleΨ[CSNH]Aib-Gly-OMe (**10a**)

We succeeded in growing single crystals of Z-IleΨ[CSNH]Aib-Gly-OMe (**10a**, Fig.1) and FMOC-IleΨ[CSNH]Aib-Gly-OMe (**10d**, Fig. 2) which were suitable for an X-ray diffraction analysis. In both molecules, N(7)-H interacts intramolecularly with the carbonyl O(12)-atom that is seven atoms along the peptide backbone; graph set: S(10)[31]. This is the normal intramolecular interaction found for peptides containing Aib. This β-turn helps to form a 3_{10}-helix upon extension of the peptide.

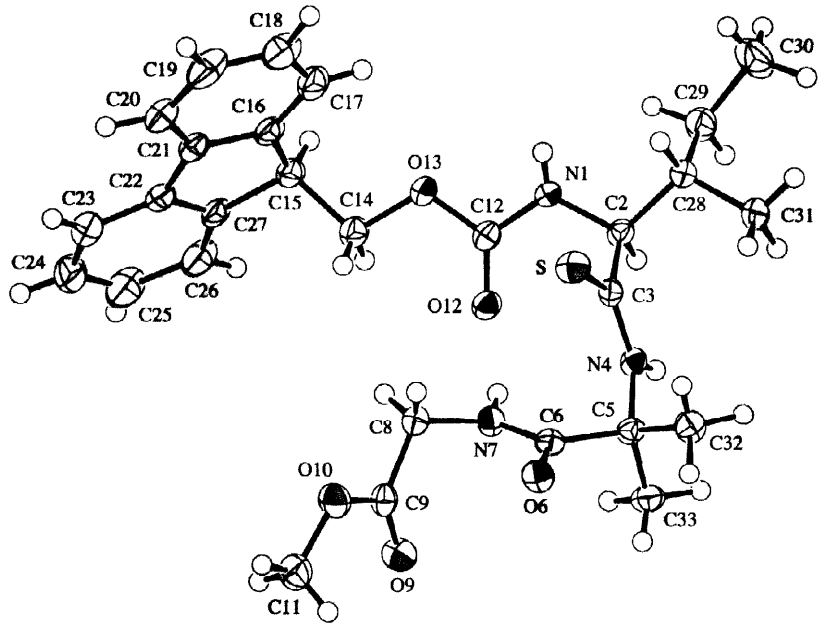
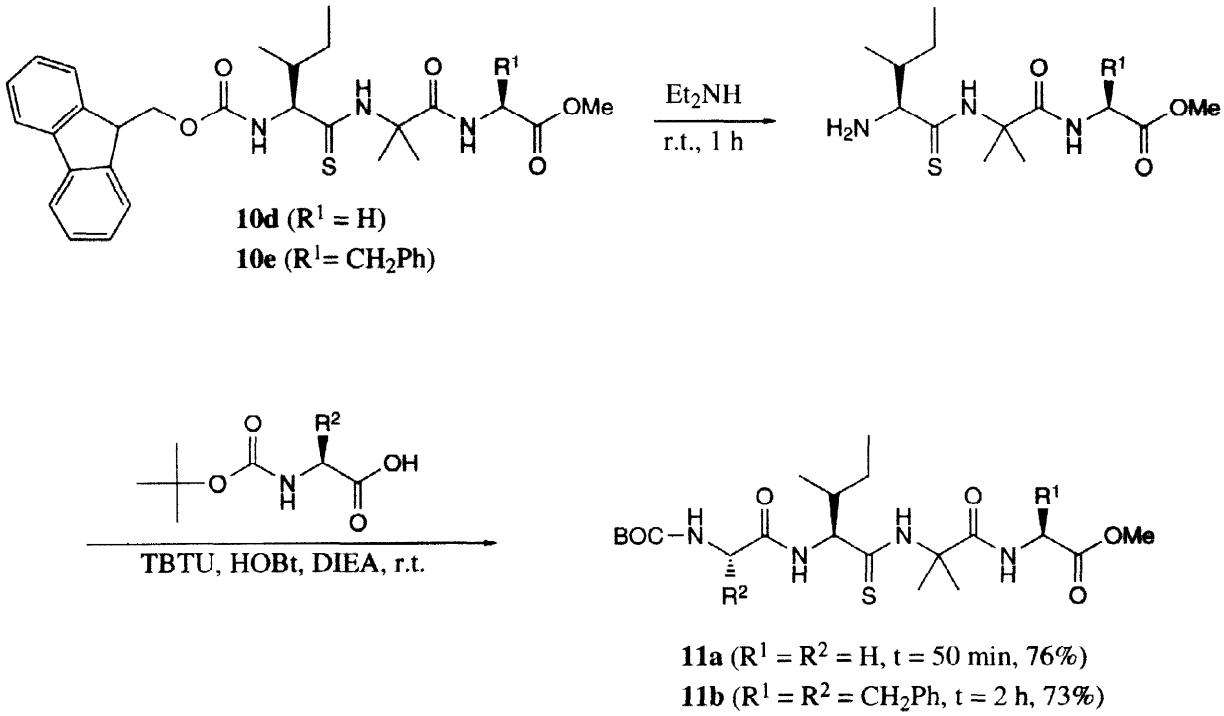


Fig.2. ORTEP Plot with 50% probability ellipsoids of the molecular structure of FMOC-IleΨ[CSNH]Aib-Gly-OMe (**10d**)

The most suitable N-terminal protecting group for the preparation of endothiotripeptides of type **10** is the (benzyloxy)carbonyl group (Z)[33], because of its stability under both the basic and the acidic conditions used during their synthesis. Usually, the Z-protecting group is cleaved by Pd-catalysed hydrogenation. However, in this case we did not succeed, probably because the S-atom in **10** deactivates the Pd-catalyst. Even after treatment for several days with a large excess of catalyst, no reaction could be observed. The alternative cleavage in a strongly acidic medium (HBr/CH_3COOH) was successful, but the product was completely epimerized under these drastic conditions. Some less usual methods for the deprotection of Z-amino groups known from literature (hard acids in combination with soft nucleophiles[34-36], trimethylsilyl iodide[37-40], $Et_3SiH/PdCl_2$[41,42], $AlCl_3$[43], $K_3[Co(CN)_5/H_2$[44]) led to product mixtures. Another N-

protecting group which is stable towards bases and acids is the photolabile (6-nitroveratryloxy)carbonyl (NVOC)-group[45-47]. It can be cleaved photochemically at a wavelength longer than 320 nm. However, the photochemical reaction (λ = 366 nm) of NVOC-IleΨ[CSNH]Aib-Gly-OMe (**10c**) again gave a mixture of products. Probably, the reason for the failure was that at this wavelength the thioamide group also absorbed and then underwent non-selective reactions. Finally, the base-labile (9-fluorenylmethyloxy)carbonyl (FMOC)-potecting group was chosen. It has the disadvantage that for the preparation of the FMOC-endothiodipeptides (e.g. **8d-f**) an exchange of the protecting group is necessary[28].

In the next step, the FMOC protecting group was cleaved by treatment of **10d** and **e** with diethylamine and the crude product was directly coupled with the next C-terminal protected amino acid. In that manner the endothiotetrapeptides **11a** and **b** were prepared in 76% and 73% yields, respectively (Scheme 4).



10d (R^1 = H)
10e (R^1 = CH_2Ph)

11a (R^1 = R^2 = H, t = 50 min, 76%)
11b (R^1 = R^2 = CH_2Ph, t = 2 h, 73%)

Scheme 4

We also succeeded in growing single crystals of BOC-Phe-IleΨ[CSNH]Aib-Phe-OMe (**11b**), which were suitable for an X-ray diffraction analysis. There are two independent molecules A and B of **11b** in the asymmetric unit (Fig. 3). They have the same configuration and very similar conformations, with the exception of the ethyl arm of the isoleucine, where the torsion angles about the C(29)-C(31) bond in molecule A differ by about 95° from those about the corresponding C(79)-C(81) bond in molecule B. Both

molecules exhibit an identical set of intramolecular hydrogen bonds. In molecule A, N(7)-H and N(10)-H each interact intramolecularly with the carbonyl O-atoms that are seven atoms along the peptide backbone (O(16) and O(3), resp.); graph set: S(10)[31]. These are the normal intramolecular interactions found for Aib-containing peptides and help to form a 3_{10}-helix upon extension of the molecule. Molecule B exhibits an identical set of intramolecular hydrogen bonds

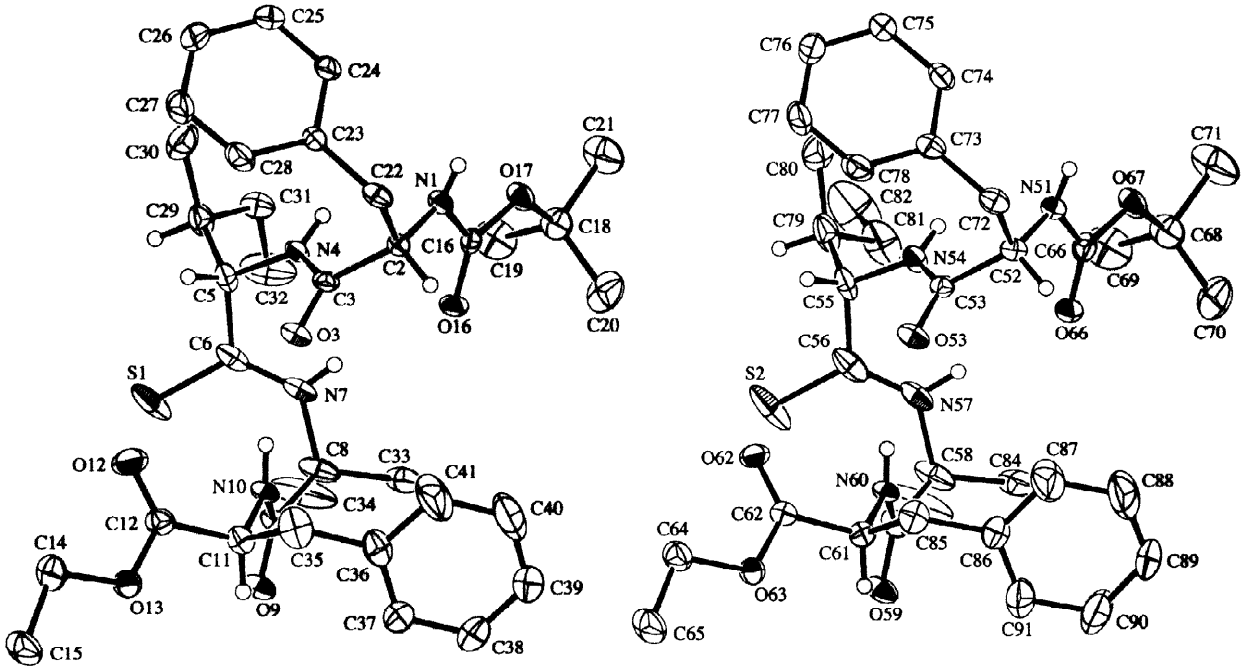


Fig. 3: ORTEP Plot with 30% probability ellipsoids of the two symmetry-independent molecules in the molecular structure of BOC-Phe-IleΨ[CSNH]Aib-Phe-OMe (**11b**).

In conclusion, this paper describes the use of the endothiodipeptides of type **8**, which can be obtained in high yields by a variation of the 'azirine/oxazolone method', for the formation of longer endothiopeptides with the thiocarbonyl group next to the bulky Aib. With this novel methodology, endothiopeptides can be prepared selectively without epimerization and in satisfactory yields. The utility of this methodology has already been illustrated by the synthesis of the decaendothiopeptide BOC-Trp-Ile-Ala-Aib-Ile-ValΨ[CSNH]Aib-Leu-Aib-Pro-OMe[48].

EXPERIMENTAL SECTION

Thin-layer chromatography (TLC): *Merck* 60 F_{254} silica gel-coated glass plates, 0.25 mm. Column chromatography: *Merck* 60 230-400 mesh silica gel. HPLC: *Bischoff* Nucleosil 100-7, 7μm, *Bischoff* Spherisorb ODS2, 5μm, 250 x 4.6 mm, detection at 254 nm. NMR spectra: *Bruker*-ARX-300 and *Bruker*-AMX-600; chemical shifts δ (ppm) refer to residual $CHCl_3$ (7.27 ppm, ^1H) and to $CDCl_3$ (77.0 ppm, ^{13}C). Mass spectra: *Finnigan* MAT SSQ-700 (CI) and *Finnigan* MAT TSQ-700 (ESI). Optical rotations: *Perkin-Elmer* 241 polarimeter (c in g/100 ml $CHCl_3$, 20°C). IR: *Perkin-Elmer* 1600 Series FTIR, data in cm^{-1}. Mp.: *Mettler* FP5/FP52. Solvents were purified by standard procedures.

General pocedure A: To a solution of 1 eq. endothiodipeptideanilide **8** in CH_2Cl_2, 1.1 eq. (±)-camphor-10-sulfonic acid (CSA) were added. After stirring for 1.5 min at r.t., the reaction mixture was quenched with $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated. The residue was chromatographed on silica gel.

General procedure B: A solution of 1 eq. 1,3-thiazol-5(4*H*)-one **9** in CH_3CN was treated with 2 eq. DIEA, 2 eq. HOBt, and 1.1 eq. of a C-terminal protected amino acid hydrochloride. After stirring at r.t., the reaction mixture was transferred into a separatory funnel, diluted with CH_2Cl_2, and extracted three times with 5% $NaHCO_3$ and 5% $KHSO_4$ solution. The combined organic layers were dried ($MgSO_4$) and filtered, the filtrate was concentrated and purified by chromatography on silica gel.

Z-Ile-1,3-thiazol-5(4H)-one (**9a**): The preparation was carried out according to the *general procedure A* with 0.588 g (1.291 mmol) Z-IleΨ[CSNH]Aib-N(Me)Ph (**8a**), 30 ml CH_2Cl_2, and 0.331 g (1.42 mmol) CSA. Chromatography on silica gel (AcOEt/hexane 1:5) led to **9a** (0.447 g, 99%) as a colourless, viscous oil. $[\alpha]_D$ = -16.4 (c = 0.764). IR ($CHCl_3$): 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*. ^1H NMR (300 MHz, $CDCl_3$): 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*, α-HC(Ile^t)); 1.98-1.00 (*m*, β-HC(Ile^t) und γ1-H_2C(Ile^t)); 1.39, 1.38 (2*s*, $(CH_3)_2C$); 0.98-0.87 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 210.6 (*s*, thiazolone-C(5)); 165.6 (*s*, thiazolone-C(2)); 156.2 (*s*, urethane-CO); 136.1, 128.5, 128.2, 128.0 (6 arom. C); 83.2 (*s*, thiazolone-C(4)); 67.1 (*t*, CH_2O); 58.0 (*d*, α-HC(Ile)); 38.0 (*d*, β-HC(Ile)); 26.4 (*t*, γ1-H_2C(Ile)); 24.5, 24.2 (2*q*, $(CH_3)_2C$); 13.4 (2*q*, δ- and γ2-H_3C(Ile)). MS (ESI): 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-IleΨ[CSNH]Aib-Gly-OMe (**10a**): The synthesis was carried out according to the *general procedure B* with 1.50 g (4.30) Z-Ile-1,3-thiazol-5(4*H*)-one (**9a**), 1.13 g (8.74 mmol) DIEA, 0.61 g (4.79 mmol) Gly-OMe·HCl, 1.33 g (8.69 mmol) HOBt, and 20 ml CH_3CN (reaction time: 4 d). Chromatography on silica gel (AcOEt/hexane 1:1) gave **10a** (1.62 g, 89%) as a colourless, thick oil, which solidified under high vacuum. Recrystallization from a mixture of AcOEt and hexane gave single crystals which were suitable for

an X-ray diffraction analysis. Mp. 111.4-112.0°C. $[\alpha]_D$ = +5.1 (c = 0.971). IR ($CHCl_3$): 3420*w*, 3380*w*, 3280*w*, 3020*m*, 3005*m*, 2970*m*, 2930*w*, 2880*w*, 1745*s*, 1710*s*, 1680*s*, 1505*s*, 1455*m*, 1440*m*, 1420*m*, 1385*w*, 1365*m*, 1310*w*, 1280*w*, 1220*s*, 1180*m*, 1130*w*, 1110*w*, 1090*w*, 1040*m*, 1075*w*, 975*w*, 925*w*, 880*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.52 (*s*, CS(Ile^t)); 7.63-7.52 (*m*, 5 arom. H); 6.94 (br *s*, NH); 5.81 (*d*, *J* = 7.9, NH); 5.40-5.35 (*m*, CH_2O); 4.30-4.00 (*m*, α-HC(Ile^t) and α-H_2C(Gly)); 3.96 (*s*, CH_3O); 2.29-1.37 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 2.00, 1.95 (2*s*, 2 β-H_3C(Aib)); 1.18-1.13 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5, $CDCl_3$): 203.7 (*s*, CS(Ile^t)); 173.0, 170.3 (2*s*, 2 CO); 157.0 (*s*, urethane-CO); 136.3, 128.7, 128.4, 127.9 (6 arom. C); 67.7 (*d*, α-HC(Ile^t)); 67.2 (*t*, CH_2O); 60.9 (*s*, α-C(Aib)); 52.3 (*q*, CH_3O); 41.7 (*t*, α-H_2C(Gly)); 39.2 (*q*, β-HC(Ile^t)); 25.8 (*q*, 1 β-H_3C(Aib)); 25.0 (*t*, γ1-H_2C(Ile^t)); 23.2 (*q*, 1 β-H_3C(Aib)); 15.7, 11.1 (2*q*, δ- and γ2-H_3C(Ile^t)). MS (ESI): 460 ([*M*+Na]$^+$). Anal. calc. for $C_{21}H_{31}N_3O_5S$ (437.56): C 57.64, H 7.14, N 9.60, S 7.33; found: C 57.49, H 6.89, N 9.69, S 7.39.

*Z-Phe-1,3-thiazol-5(4*H*)-one* (**9b**): The preparation was carried out according to the *general procedure A* with 0.508 g (1.037 mmol) Z-PheΨ[CSNH]Aib-N(Me)Ph (**8b**), 0.276 g (1.188 mmol) CSA, and 20 ml CH_2Cl_2. Chromatography on silica gel (AcOEt/hexane 1:5) gave **9b** (0.350 g, 88%) as a colourless, thick oil. IR ($CHCl_3$): 3750*w*, 3480*s*, 3400*m*, 3300*m*, 3100*m*, 3070*m*, 3010*s*, 2960*m*, 2900*m*, 2450*w*, 1960*w*, 1820*m*, 1720*s*, 1620*s*, 1610*m*, 1590*m*, 1520*m*, 1490*s*, 1460*s*, 1400*m*, 1380*m*, 1340*s*, 1140*m*, 1040*s*, 980*s*, 940*m*, 910*s*, 840*m*. ^{1}H NMR (300 MHz, $CDCl_3$): 7.35-7.11 (*m*, 10 arom. H); 5.55 (*d*, *J* = 6.4, NH); 5.09 (*s*, CH_2O); 4.83-4.81 (*m*, α-HC(Phe)); 3.16-2.93 (*m*, β-H_2C(Phe)); 1.18, 1.13 (2*s*, $(CH_3)_2C$)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 208.6 (*s*, thiazolone-C(5)); 162.9 (*s*, thiazolone-C(2)); 153.6 (*s*, urethane-CO); 134.4, 133.4, 127.8, 126.7, 126.5, 126.3, 125.4 (12 arom. C); 81.3 (*s*, thiazolone-C(4)); 65.3 (*t*, CH_2O); 53.9 (*d*, α-HC(Phe)); 36.8 (*t*, β-H_2C(Phe)); 22.4 (2*q*, $(CH_3)_2C$)). MS (CI): 385 (7), 384 (23), 383 (100, [*M*+1]$^+$).

Z-PheΨ[CSNH]Aib-Ala-OEt (**10b**): The preparation was carried out according to the *general procedure B* with 0.270 g (0.706 mmol) Z-Phe-1,3-thiazol-5(4*H*)-one (**9b**), 0.211 g (1.632 mmol) DIEA, 0.226 g (1.476 mmol) HOBt, 0.121 g (0.788 mmol) Ala-OEt·HCl, and 5 ml CH_3CN (reaction time: 68 h). Chromatography on silica gel (AcOEt/hexane 1:1.3) led to **10b** (0.248 g, 72%) as a white solid. Mp. 152-153°C. $[\alpha]_D$ = +72.4 (1.00). IR ($CHCl_3$): 3480*m*, 3440*m*, 3120*w*, 3060*m*, 3040*m*, 2970*m*, 1720*s*, 1680*s*, 1630*m*, 1500*s*, 1450*m*, 1420*m*, 1380*m*, 1340*m*, 1140*m*, 1040*m*, 1020*m*, 980*m*, 920*m*. ^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (br *s*, CS(Phe^t)); 7.37-7.21 (*m*, 10 arom. H); 6.50 (*d*, *J* = 6.7, NH); 5.77 (*d*, *J* = 7.4, NH); 5.11-5.02 (*m*, CH_2O); 4.53-4.44 (*m*, α-HC(Phe^t and Ala)); 4.16 (*q*, *J* = 7.1, CH_3CH_2O); 3.16-3.02 (*m*, β-H_2C(Phe^t)); 1.52, 1.43 (2*s*, 2 β-H_3C(Aib)); 1.31 (*d*, *J* = 7.2, β-H_3C(Ala)); 1.25 (*t*, *J* = 7.2, CH_3CH_2O). ^{13}C NMR (75.5 MHz, $CDCl_3$): 202.0 (*s*, CS(Phe^t)); 172.8, 171.7 (2*s*, 2 CO); 156.1 (*s*, urethane-CO); 136.3, 136.1, 129.4, 128.8, 128.6, 128.2, 127.9, 127.2 (12 arom. C); 67.1 (*t*, CH_2O); 64.0 (*d*, α-HC(Phe^t)); 61.3 (*t*, CH_3CH_2O); 60.5 (*s*, α-C(Aib)); 48.4 (*d*, α-HC(Ala)); 41.5 (*t*, β-

$H_2C(Phe^t)$); 25.9, 22.1 (2*q*, 2 β-H_3C(Aib)); 17.9 (*q*, β-H_3C(Ala)); 14.1 (*q*, CH_3CH_2O). MS (ESI): 522 ([*M*+Na]$^+$).

NVOC-Ile-1,3-thiazol-5(4H)-one (**9c**): The synthesis was carried out according to the *general procedure A* with 0.626 g (1.117 mmol) NVOC-IleΨ[CSNH]Aib-N(Me)Ph (**8c**), 35 ml CH_2Cl_2, and 0.286 g (1.231 mmol) CSA. Chromatography on silica gel (AcOEt/hexane 1:2) gave **9c** (0.494 g, 97%) as a white solid. $[\alpha]_D$ = -33.8 (0.783). IR ($CHCl_3$): 3680*w*, 3430*w*, 3020*m*, 2970*m*, 2930*m*, 2880*w*, 1730*s*, 1620*m*, 1585*m*, 1525*s*, 1505*s*, 1465*m*, 1440*m*, 1425*w*, 1380*m*, 1360*m*, 1335*s*, 1280*s*, 1175*m*, 1130*w*, 1095*w*, 1070*s*, 1035*w*, 990*w*, 920*w*, 875*w*, 845*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 7.71 (*s*, arom. HC(3)); 7.01 (*s*, arom. HC(6)); 5.62-5.59 (br *d*, NH); 5.54 (*s*, CH_2O); 4.68-4.64 (*m*, α-HC(Ile^t)); 3.98, 3.96 (2*s*, 2 CH_3O of NVOC); 1.96-1.14 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.41, 1.39 (2*s*, $(CH_3)_2C$)); 1.03 (*d*, *J* = 6.8, γ2-H_3C(Ile^t)); 0.94 (*t*, *J* = 7.3, δ-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 208.5 (*s*, thiazolone-C(5)); 163.3 (*s*, thiazolone-C(2)); 153.7 (*s*, urethane-CO); 151.7 (*s*, arom. C(5)); 146.4 (*s*, arom. C(4)); 138.1 (*s*, arom. C(2)); 126.0 (*s*, arom. C(1)); 108.4, 106.4 (2*d*, arom. C(3), C(6)); 81.2 (*s*, thiazolone-C(4)); 62.1 (*t*, CH_2O); 57.8 (*d*, α-HC(Ile)); 54.6 (*q*, 2 CH_3O); 36.3 (*d*, β-HC(Ile)); 22.7, 22.4 (2*q*, $(CH_3)_2C$); 13.8, 9.7 (2*q*, δ- and γ2-H_3C(Ile)). MS (CI): 454 ([*M*+1]$^+$). Anal. calc. for $C_{20}H_{27}N_3O_7S$ (453.52): C 52.97, H 6.00, N 9.26, S 7.07; found: C 52.32, H 6.17, N 9.05, S 6.71.

NVOC-IleΨ[CSNH]Aib-Gly-OMe (**10c**): The preparation was carried out according to the *general procedure B* with 0.439 g (0.968 mmol) NVOC-Ile-1,3-thiazol-5(4*H*)-one (**9c**), 0.271 g (2.097 mmol) DIEA, 0.298 g (1.948 mmol) HOBt, 0.140 g (1.115 mmol) Gly-OMe·HCl, and 5 ml CH_3CN (reaction time: 4 d). Chromatography on silica gel (AcOEt/hexane 1.5:1) led to **10c** (0.426 g, 81%) as a colourless, viscous oil which solidified under high vacuum. $[\alpha]_D$ = -31.1 (c = 1.10). IR ($CHCl_3$): 3680*w*, 3420*w*, 3380*w*, 3280*w*, 3020*m*, 3000*m*, 2970*m*, 2930*w*, 1750*m*, 1725*s*, 1715*s*, 1695*m*, 1680*m*, 1635*w*, 1620*w*, 1585*m*, 1525*s*, 1505*s*, 1465*m*, 1455*m*, 1440*m*, 1420*m*, 1385*m*, 1365*m*, 1330*m*, 1280*s*, 1180*m*, 1130*w*, 1070*s*, 1040*w*, 1030*w*, 1010*w*, 990*w*, 930*w*, 875*w*, 850*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.50 (*s*, NH); 7.71 (*s*, arom. HC(3)); 7.00 (*s*, arom. HC(6)); 6.69 (br *t*, N*H*); 5.80 (*d*, *J* = 8.3, NH); 5.64-5.40 (*m*, CH_2O); 4.05-3.94 (*m*, α-HC(Ile^t)); 3.99, 3.95 (2*s*, 2 CH_3O of NVOC); 3.68 (*s*, CH_3O); 1.95-1.14 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.77, 1.66 (2*s*, 2 β-H_3C(Aib)); 0.94-0.89 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 202.1 (*s*, CS(Ile^t)); 170.9, 168.2 (2*s*, 2 CO); 154.5 (*s*, urethane-CO); 152.1 (*s*, arom. C(5)); 146.2 (*s*, arom. C(4)); 137.4 (*s*, arom. C(2)); 126.6 (*s*, arom. C(1)); 107.2, 106.3 (2*d*, arom. C(3), C(6)); 65.1 (*d*, α-HC(Ile^t)); 62.0 (*t*, CH_2O); 59.0 (*s*, α-C(Aib)); 54.8, 54.6 (2*q*, 2 CH_3O of NVOC); 50.3 (*q*, CH_3O); 39.4 (*t*, α-H_2C(Gly)); 37.3 (*d*, β-HC(Ile^t)); 24.2 (*q*, 1 β-H_3C(Aib)); 23.2 (*t*, γ1-H_2C(Ile^t)); 20.6 (*q*, 1 β-H_3C(Aib)); 13.5, 9.0 (2*q*, δ- and γ2-H_3C(Ile^t)). MS (ESI): 564 ([*M*+Na]$^+$).

FMOC-Ile-1,3-thiazol-5(4H)-one (**9d**): The preparation was carried out according to the *general procedure A* with 0.615 g (1.133 mmol) FMOC-IleΨ[CSNH]Aib-N(Me)Ph (**8d**), 0.290 g (1.248 mmol) CSA, and 20 ml CH_2Cl_2. Chromatography on silica gel (AcOEt/hexane 1:6) gave **9d** (0.490 g, 99%) as a

colourless, thick oil. $[\alpha]_D$ = -21.9° (c = 1.00). IR ($CHCl_3$): 3675*w*, 3070*w*, 3030*w*, 2970*m*, 2930*m*, 2880*w*, 1720*s*, 1620*m*, 1505*s*, 1480*w*, 1465*m*, 1450*m*, 1405*m*, 1380*w*, 1360*w*, 1330*w*, 1250*m*, 1105*w*, 1065*w*, 1040*w*, 990*w*, 920*w*, 870*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 7.77 (*m*, 8 arom. H); 5.42 (br *d*, NH); 4.64-4.62 (*m*, α-HC(Ile)); 4.60-4.38 (*m*, $CHCH_2O$); 4.23 (*t*, *J* = 6.8, $CHCH_2O$); 1.98-1.02 (*m*, β-HC(Ile) and γ1-H_2C(Ile)); 1.41, 1.39 (2*s*, $(CH_3)_2C$); 1.01 (*d*, *J* = 6.6, γ2-H_3C(Ile)); 0.92 (*t*, *J* = 7.3, δ-H_3C(Ile)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 210.7 (*s*, thiazolone-C(5)); 165.4 (*s*, thiazolone-C(2)); 156.1 (*s*, urethane-CO); 143.8, 143.7, 141.4, 127.7, 127.1, 125.1, 125.0, 120.0 (12 arom. C); 83.0 (*s*, thiazolone-C(4)); 66.9 (*t*, $CHCH_2O$); 59.6 (*d*, α-HC(Ile)); 47.3 (*d*, $CHCH_2O$); 38.0 (*d*, β-HC(Ile)); 24.6, 24.3 (2*q*, $(CH_3)_2C$); 15.7, 11.6 (2*q*, δ- and γ2-H_3C(Ile)). MS (ESI): 459 ([*M*+Na]$^+$). Anal. calc. for $C_{25}H_{28}N_2O_3S$ (436.57): C 68.78, H 6.46, N 6.42, S 7.34; found: C 68.22, H 6.45, N 6.33, S 7.34.

FMOC-IleΨ[CSNH]Aib-Gly-OMe (**10d**): The synthesis was carried out according to the *general procedure B* with 0.719 g (1.647 mmol) FMOC-Ile-1,3-thiazol-5(4*H*)-one (**9d**), 0.233 g (1.803 mmol) DIEA, 0.505 g (3.301 mmol) HOBt, 0.228 g (1.816 mmol) Gly-OMe·HCl, and 8 ml CH_3CN (reaction time: 5d). Chromatography on silica gel (AcOEt/hexane 1:1) gave **10d** (0.793 g, 92%) as a colourless, thick oil which solidified under high vacuum. Recrystallization from a mixture of hexane and EtOH gave single crystals which were suitable for an X-ray diffraction analysis. Mp. 82.9-84.1°C. $[\alpha]_D$ = -15.7 (c = 1.08). IR ($CHCl_3$): 3680*w*, 3420*w*, 3375*m*, 3280*w*, 3060*w*, 3020*m*, 3000*m*, 2970*m*, 2930*m*, 2880*w*, 1745*s*, 1715*s*, 1695*s*, 1680*s*, 1515*s*, 1505*s*, 1465*m*, 1450*s*, 1440*m*, 1420*m*, 1390*m*, 1365*m*, 1310*m*, 1185*m*, 1130w, 1105*w*, 1040*m*, 985*w*, 930*w*, 880*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.48 (*s*, NH); 7.76-7.26 (*m*, 8 arom. H); 6.71 (br *s*, NH); 5.71 (*d*, *J* = 8.4, NH); 4.36-3.94 (*m*, $CHCH_2O$, α-HC(Ile^t) and α-H_2C(Gly)); 3.57 (*s*, CH_3O); 1.96-1.16 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.75, 1.67 (2*s*, 2 β-H_3C(Aib)); 0.92-0.88 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 203.9 (*s*, CS(Ile^t)); 172.9, 170.2 (2*s*, 2 CO); 156.9 (*s*, urethane-CO); 143.7, 143.6, 141.3, 141.2, 127.8, 127.2, 127.1, 125.12, 125.09, 120.0 (12 arom. C); 67.3 (t, $CHCH_2O$); 67.1 (*d*, α-HC(Ile^t)); 60.8 (*s*, α-C(Aib)); 52.1 (*q*, CH_3O); 47.0 (*d*, $CHCH_2O$); 41.5 (*t*, α-H_2C(Gly)); 39.2 (*d*, β-HC(Ile^t)); 25.9 (*q*, 1 β-H_3C(Aib)); 25.0 (*t*, γ1-H_2C(Ile^t)); 22.8 (*q*, 1 β-H_3C(Aib)); 15.5, 11.0 (2*q*, δ- and γ2-H_3C(Ile^t)). MS (ESI): 548 ([*M*+Na]$^+$]). Anal. calc. for $C_{28}H_{35}N_3O_5S$ (525.67): C 63.97, H 6.71, N 7.99; found: C 63.63, H 6.91, N 7.62.

BOC-Gly-IleΨ[CSNH]Aib-Gly-OMe (**11a**): To a solution of 0.199 g (0.378 mmol) FMOC-IleΨ[CSNH]Aib-Gly-OMe (**10d**) in 5 ml CH_3CN, 0.5 ml Et_2NH were added. After stirring for 1 h at r.t., during which the colour turned to intense yellow, the solution was concentrated in a rotary evaporator and the yellow residue was dried under high vacuum. The crude H_2N-IleΨ[CSNH]Aib-Gly-OMe, dissolved in 2 ml CH_3CN, was added to a solution of 73.7 mg (0.421 mmol) BOC-Gly, 60.1 mg (0.465 mmol) DIEA, 0.149 g (0.464 mmol) TBTU, and 70.9 mg (0.463 mmol) HOBt in 2 ml CH_3CN. The reaction mixture was stirred at r.t. for 50 min and then transferred into a separatory funnel, diluted with Et_2O, and extracted three times with 5% $NaHCO_3$ and 5% $KHSO_4$-solution. The combined organic phases were dried over

$MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (AcOEt/hexane 3:1) to give **11a** (0.129 g, 76%) as a colourless, viscous oil which solidified under high vacuum. $[\alpha]_D$ = -10.0 (c = 1.00). IR ($CHCl_3$): 3670*w*, 3420*w*, 3370*w*, 3280*w*, 3020*m*, 3000*m*, 2970*m*, 2930*w*, 1745*m*, 1715*s*, 1705*s*, 1675*s*, 1515*s*, 1505*s*, 1455*m*, 1440*m*, 1420*m*, 1390*m*, 1385*m*, 1370*s*, 1325*w*, 1275*m*, 1240*s*, 1170*s*, 1110*w*, 1080*w*, 1050*w*, 1025*w*, 985*w*, 930*w*, 860*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.73 (*s*, NH); 6.98 (*d*, *J* = 8.0, NH); 6.68-6.63 (*m*, NH); 5.46-5.42 (*m*, NH); 4.44-4.38 (*m*, α-HC(Ile^t)); 4.10-3.72 (*m*, 2 α-H_2C(Gly)); 3.73 (*s*, CH_3O); 2.05-0.99 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.76, 1.67 (2*s*, 2 β-H_3C(Aib)); 1.46 (*s*, $(CH_3)_3C$); 0.93-0.87 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 203.1 (*s*, CS(Ile^t)); 173.1, 170.6, 165.7 (3*s*, 3 CO); 156.2 (*s*, urethane-CO); 80.4 (*s*, $(CH_3)_3C$); 65.0 (*d*, α-HC(Ile^t)); 60.9 (*s*, α-C(Aib)); 52.2 (*q*, CH_3O); 44.7, 41.6 (2*t*, 2 α-H_2C(Gly)); 38.6 (*d*, β-HC(Ile^t)); 28.3 (2*q*, $(CH_3)_3C$)); 26.1, 23.0 (2*q*, 2 β-H_3C(Aib)); 24.8 (*t*, γ1-H_2C(Ile^t)); 15.4, 11.1 (2*q*, δ- and γ2-H_3C(Ile^t)). MS (ESI): 483 ([*M*+Na)$^+$].

FMOC-IleΨ[CSNH]Aib-Phe-OEt (**10e**): The preparation was carried out according to the *general procedure B* with 0.190 g (0.435 mmol) FMOC-Ile-1,3-thiazol-5(4*H*)-one (**9d**), 0.124 g (0.959 mmol) DIEA, 0.133 g (0.869 mmol) HOBt, 0.110 g (0.479 mmol) Phe-OEt·HCl, and 3 ml CH_3CN (reaction time: 14 d). Chromatography on silica gel (AcOEt/hexane 1:2) gave **10e** (0.152, 55%) as a colourless, thick oil which solidified under high vacuum. $[\alpha]_D$ = +9.9 (c = 1.02). IR ($CHCl_3$): 3680*w*, 3420*w*, 3370*w*, 3280*w*, 3070*m*, 3000*m*, 2970*m*, 2930*m*, 1730*s*, 1725*s*, 1680*s*, 1675*s*, 1645*w*, 1605*w*, 1515*s*, 1505*s*, 1480*m*, 1465*m*, 1450*m*, 1420*m*, 1385*s*, 1375*m*, 1350*w*, 1300*w*, 1130*w*, 1105*w*, 1075*w*, 1030*m*, 980*w*, 925*w*, 880*w*, 850*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.34 (*s*, NH); 7.76-7.06 (*m*, 13 arom. H); 6.42 (br *d*, *J* = 6.6, NH); 5.62 (*d*, *J* = 8.5, NH); 4.82-4.76 (*m*, α-HC(Phe)); 4.42-4.34 (*m*, $CHCH_2O$); 4.21 (*t*, *J* = 7.1, $CHCH_2O$); 4.12-4.00 (*m*, CH_3CH_2O and α-HC(Ile^t)); 3.13-3.01 (*m*, β-H_2C(Phe)); 1.99-0.90 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.71, 1.66 (2*s*, 2 β-H_3C(Aib)); 1.15 (*t*, *J* = 7.1, CH_3CH_2O); 0.92-0.88 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 203.9 (*s*, CS(Ile^t)); 172.3, 171.4 (2*s*, 2 CO); 156.4 (*s*, urethane-CO); 143.8, 143.7, 141.3, 135.9, 129.3, 128.4, 127.7, 127.1, 127.0, 125.1, 120.0 (18 arom. C); 67.1 (*t*, $CHCH_2O$); 67.0 (*d*, α-HC(Ile^t)); 61.4 (*t*, CH_3CH_2O); 60.7 (*s*, α-C(Aib)); 53.7 (*d*, α-HC(Phe)); 47.1 (*d*, $CHCH_2O$); 39.4 (*d*, β-HC(Ile^t)); 38.0 (*t*, β-H_2C(Phe)); 24.8 (*t*, γ1-H_2C(Ile^t)); 24.3, 23.2 (2*q*, 2 β-H_3C(Aib)); 15.6, 14.0, 11.1 (3*q*, δ-, γ2-H_3C(Ile^t) and CH_3CH_2O). MS (ESI): 652 ([*M*+Na]$^+$). Anal. calc. for $C_{36}H_{43}N_3O_5S$ (629.81): C 68.11, H 6.83, N 6.62; found: C 67.32, H 6.78, N 6.28.

BOC-PheΨ[CSNH]Ile-Aib-Phe-OMe (**11b**): To a solution of 0.113 g (0.178 mmol) FMOC-IleΨ[CSNH]Aib-Phe-OEt (**10e**) in 2 ml CH_3CN, 0.2 ml Et_2NH were added. After stirring for 1 h at r.t., during which the colour turned to intense yellow, the solution was concentrated in a rotary evaporator and the yellow residue was dried under high vacuum. The crude H_2N-PheΨ[CSNH]Aib-Phe-OMe, dissolved in 0.5 ml CH_3CN, was added to a solution of 34.2 mg (0.195 mmol) BOC-Phe, 30.0 mg (0.232 mmol)

DIEA, 69.2 mg (0.216 mmol) TBTU, 34.1 mg (0.223 mmol) HOBt in 0.5 ml CH_3CN. The reaction mixture was stirred at r.t. for 2 h and then transferred into a separatory funnel, diluted with Et_2O, and extracted three times with 5% $NaHCO_3$ and 5% $KHSO_4$ solution. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (AcOEt/hexane 1:1) to give **11b** (0.085 g, 73%) as a colourless solid. Recrystallization from a mixture of hexane and CH_2Cl_2 led to single crystals suitable for an X-ray diffraction analysis. Mp. = 141.4-142.1°C. $[\alpha]_D$ = -14.5 (c = 1.04). IR ($CHCl_3$): 3675*w*, 3430*m*, 3290*w*, 3005*m*, 2970*m*, 2930*m*, 2875*m*, 1705*s*, 1675*s*, 1605*w*, 1500*s*, 1455*m*, 1395*m*, 1370*m*, 1350*m*, 1170*s*, 1080*w*, 1050*w*, 1030*w*, 920*w*, 860*w*. ^1H NMR (300 MHz, $CDCl_3$): 8.53 (*s*, NH); 7.32-7.16 (*m*, 10 arom. H); 6.79 (br *d*, NH); 6.57 (*d*, NH); 5.06 (*d*, NH); 4.80 (*q*, α-HC(Ile^t)); 4.38-4.30 (*m*, 2α-HC(Phe)); 4.14 (*q*, *J* = 7.1, CH_3CH_2O); 3.15-2.96 (*m*, 2β-CH_2(Phe)); 2.14-0.92 (*m*, β-HC(Ile^t) and γ1-H_2C(Ile^t)); 1.67, 1.60 (2*s*, 2 β-H_3C(Aib)); 1.40 (*s*, $(CH_3)_3C$); 1.20 (*t*, *J* = 7.1, CH_3CH_2O); 0.88-0.83 (*m*, δ- and γ2-H_3C(Ile^t)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 201.5 (*s*, CS(Ile^t)); 172.4, 171.7, 171.5 (3*s*, 3 CO); 155.6 (*s*, urethane-CO); 136.3, 129.4, 129.3, 128.8, 128.4, 127.1, 126.9 (12 arom. C); 80.6 (*s*, $(CH_3)_3C$); 66.0 (*d*, α-HC(Ile^t)); 61.4 (*t*, CH_3CH_2O); 60.8 (*s*, α-C(Aib)); 56.2, 53.8 (2*d*, 2α-HC(Phe)); 38.8 (*d*, β-HC(Ile^t)); 38.0, 37.4 (2*t*, 2β-H_2C(Phe)); 28.2 (*q*, $(CH_3)_3C$); 24.9 (*q*, 1 β-H_3C(Aib)); 24.4 (*t*, γ1-H_2C(Ile^t)); 23.5 (*q*, 1 β-H_3C(Aib)); 15.7 (*q*, CH_3CH_2O); 14.1 (*q*, δ- and γ2-H_3C(Ile^t)); 11.2 (γ2-H_3C(Ile^t)). MS (ESI): 677 ([*M*+Na]$^+$). Anal. calc. for $C_{35}H_{50}N_4O_6S$ (654.86): C 64.19, H 7.70, N 8.56; found: C 64.36, H 7.73, N 8.27.

FMOC-Val-1,3-thiazol-5(4H)-one (**9f**): The synthesis was carried out according to the *general procedure A* with 0.174 g (0.328 mmol) FMOC-ValΨ[CSNH]Aib-N(Me)Ph (**8f**), 84.0 mg (0.361 mmol) CSA, and 5 ml CH_2Cl_2. Chromatography on silica gel (AcOEt/hexane 1:6) gave **9f** (0.137, 99%) as a colourless, viscous oil. $[\alpha]_D$ = -28.3 (c = 1.04). IR ($CHCl_3$): 3675*w*, 3435*m*, 3070*w*, 3030*w*, 2970*m*, 2935*m*, 2875*w*, 1720*s*, 1620*m*, 1505*s*, 1465*m*, 1450*s*, 1390*w*, 1380*w*, 1350*m*, 1305*m*, 1265*m*, 1110*m*, 1065*m*, 1030*m*, 990*m*, 920*m*, 865*w*, 690*w*. ^1H NMR (300 MHz, $CDCl_3$): 7.77-7.25 (*m*, 8 arom. H); 5.42 (br *d*, *J* = 8.3, NH); 4.63-4.22 (*m*, $CHCH_2O$ and α-HC(Val)); 2.21-2.17 (*m*, β-HC(Val)); 1.41, 1.39 (2*s*, 2 β-H_3C(Aib)); 1.04, 0.92 (2*d*, *J* = 6.5 bzw. 6.7, 2 γ-H_3C(Val)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 210.5 (*s*, thiazolone-C(5)); 165.3 (*s*, thiazolone-C(2)); 156.1 (*s*, urethane-CO); 143.8, 143.6, 141.3, 127.7, 127.0, 125.0, 124.9, 119.9 (12 arom. C); 83.0 (*s*, α-C(Aib)); 66.9 (*t*, $CHCH_2O$); 59.9 (*d*, α-HC(Val)); 47.2 (*d*, $CHCH_2O$); 31.3 (*d*, β-HC(Val)); 24.5, 24.2 (2*q*, $(CH_3)_2C$); 19.3, 16.6 (2*q*, 2 γ-H_3C(Val)). MS (CI): 425 (7), 424 (24), 423 (100, [*M*+1]$^+$), 320 (9), 227 (7), 201 (54), 179 (27), 178 (10).

FMOC-ValΨ[CSNH]Aib-Leu-OMe (**10f**): The preparation was carried out according to the *general procedure B* with 0.235 g (0.555 mmol) FMOC-Val-1,3-thiazol-5(4*H*)-one (**9f**), 0.144 g (1.11 mmol) DIEA, 0.170 g (1.11 mmol) HOBt, 0.110 g (0.606 mmol) Leu-OMe·HCl, and 5 ml CH_3CN (reaction time: 7 d). Chromatography on silica gel (AcOEt/hexane 1:2) led to **10f** (0.203 g, 65%) as a colourless, thick oil which solidified under high vacuum. $[\alpha]_D$ = +4.6 (c = 1.03). IR ($CHCl_3$): 3670*w*, 3430*w*, 3375*m*,

3280*w*, 3005*m*, 2965*m*, 2875*w*, 1740*s*, 1710*s*, 1675*s*, 1505*s*, 1470*m*, 1450*s*, 1420*m*, 1390*m*, 1365*m*, 1310*m*, 1260*m*, 1125*m*, 1100*w*, 1030*m*, 980*w*, 860*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.35 (*s*, NH); 7.76-7.26 (*m*, 8 arom. H); 6.48 (br *d*, NH); 5.67 (*d*, *J* = 8.4, NH); 4.60-3.95 (*m*, C*H*C*H*$_2$O and α-HC(Leu and Val^t)); 3.68 (*s*, CH_3O); 2.20-1.45 (*m*, β-HC(Val^t), β-H_2C(Leu) and γ-HC(Leu)); 1.76, 1.69 (2*s*, 2 β-H_3C(Aib)); 0.99-0.82 (*m*, 2 γ-H_3C(Val^t), 2δ-H_3C(Leu)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 203.1 (*s*, CS(Val^t)); 173.3, 172.4 (2*s*, 2 CO); 156.6 (*s*, urethane-CO); 143.7, 141.3, 127.8, 127.1, 125.1, 120.0 (12 arom. C); 68.3 (*d*, α-HC(Val^t)); 67.3 (*t*, CH*C*H$_2$O); 60.8 (*s*, α-C(Aib)); 52.2 (*q*, CH_3O); 51.1 (*d*, α-HC(Leu)); 47.1 (*d*, *C*HCH$_2$O); 41.2 (*t*, β-H_2C(Leu)); 33.3 (*d*, β-HC(Val^t)); 25.7, 24.8, 22.8, 22.6, 21.8, 19.5, 18.5 (7*q*, 2 β-H_3C(Aib), 2 δ-H_3C(Leu), 2 γ-H_3C(Val^t) and γ-HC(Leu)). MS (ESI): 590 ([*M*+Na]$^+$). Anal. calc. for $C_{31}H_{41}N_3O_5S$ (567.74): C 65.58, H 7.28, N 7.40; found: C 65.70, H 7.39, N 7.12.

*FMOC-Ala-1,3-thiazol-5(4*H*)-one* (**9g**): The preparation was carried out according to the *general procedure A* with 0.193 g (0.385 mmol) FMOC-AlaΨ[CSNH]Aib-N(Me)Ph (**8g**), 98.5 mg (0.425 mmol) CSA, and 5 ml CH_2Cl_2. Chromatography on silica gel (AcOEt/hexane 1:4) gave 0.150 g (99%) **9g** as a colourless, thick oil. $[\alpha]_D$ = -13.9 (c = 1.14). IR ($CHCl_3$): 3565*w*, 3435*m*, 3070*w*, 3030*m*, 2990*w*, 2935*w*, 2450*w*, 1725*s*, 1625*s*, 1505*s*, 1450*s*, 1405*w*, 1380*m*, 1360*w*, 1335*m*, 1250*m*, 1105*m*, 1080*m*, 1015*s*, 990*m*, 920*s*, 845*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 7.76-7.44 (*m*, 8 arom. H); 5.52 (br *d*, *J* = 6.0, NH); 4.76-4.66 (*m*, α-HC(Ala)); 4.52-4.36 (*m*, CHC*H*$_2$O); 4.22 (*t*, *J* = 6.8, C*H*CH$_2$O); 1.48 (*d*, *J* = 6.6, β-H_3C(Ala)); 1.41, 1.39 (2*s*, $(CH_3)_2$C). ^{13}C NMR (75.5 MHz, $CDCl_3$): 210.5 (*s*, thiazolone-C(5)); 166.7 (*s*, thiazolone-C(2)); 155.4 (*s*, urethane-CO); 143.7, 143.6, 141.3, 127.7, 127.0, 125.0, 124.9, 119.9 (12 arom. C); 83.2 (*s*, thiazolone-C(4)); 66.9 (*t*, CH*C*H$_2$O); 51.0, 47.1 (2*d*, *C*HCH$_2$O and α-HC(Ala)); 24.4, 24.3 (2*q*, (*C*H$_3$)$_2$C); 19.4 (*q*, β-H_3C(Ala)). MS (CI): 395 (100, [*M*+1]$^+$), 179 (10), 173 (13). Anal. calc. for $C_{22}H_{22}N_2O_3S$ (394.48): C 66.98, H 5.62, N 7.40; found: C 66.81, H 5.59, N 7.05.

*FMOC-AlaΨ[CSNH]Aib-Ile-OMe (**10g**):* The synthesis was carried out according to the *general procedure B* with 0.236 g (0.599 mmol) FMOC-Ala-1,3-thiazol-5(4*H*)-one (**9g**), 0.157 g (1.215 mmol) DIEA, 0.182 g (1.190 mmol) HOBt, 0.121 g (0.666 mmol) Ile-OMe·HCl, and 5 ml CH_3CN (reaction time: 7 d). Chromatography on silica gel (AcOEt/hexane 1:1) led to **10g** (0.173 g, 54%) as a colourless, viscous oil which solidified under high vacuum. $[\alpha]_D$ = +3.7 (c = 1.02). IR ($CHCl_3$): 3675*w*, 3430*w*, 3375*w*, 3275*w*, 3010*m*, 2970*m*, 2880*w*, 1730*s*, 1675*s*, 1505*s*, 1450*s*, 1420*m*, 1375*m*, 1325*m*, 1250*s*, 1105*w*, 1055*m*, 1000*w*, 840*w*. ^{1}H NMR (300 MHz, $CDCl_3$): 8.44 (*s*, NH); 7.77-7.26 (*m*, 8 arom. H); 6.46 (*d*, *J* = 7.9, NH); 5.66 (*d*, *J* = 7.5, NH); 4.56-4.18 (*m*, C*HC*H$_2$O and α-HC(Ala^t und Ile)); 3.70 (*s*, CH_3O); 1.97-1.08 (*m*, β-HC(Ile) and γ1-H_2C(Ile)); 1.74-1.71 (2*s*, 2 β-H_3C(Aib)); 1.47 (*d*, *J* = 6.8, β-H_3C(Ala^t)); 0.93-0.84 (*m*, δ- and γ2-H_3C(Ile)). ^{13}C NMR (75.5 MHz, $CDCl_3$): 204.0 (*s*, CS(Ala^t)); 172.4, 172.4 (2*s*, 2 CO); 156.0 (*s*, urethane-CO); 143.7, 143.6, 141.3, 127.8, 127.1, 125.1, 120.0 (12 arom. C); 67.4 (*t*, CH*C*H$_2$O); 60.6 (*s*, α-C(Aib)); 57.6, 56.8, 47.0 (3*d*, *C*HCH$_2$O and α-HC(Ala^t and

Ile)); 52.0 (*q*, CH_3O); 37.8 (*d*, β-HC(Ile)); 25.4 (*t*, γ1-H_2C(Ile)); 24.8, 23.6, 21.9 (3*q*, 2 β-H_3C(Aib) and β-H_3C(Ala^t)); 15.5, 11.5 (2*q*, δ- and γ2-H_3C(Ile)). MS (CI): 557 (9, $[M+NH_4]^+$), 540 (16, $[M+1]^+$), 506 (23), 397 (8), 395 (100), 518 (29), 179 (13), 178 (6), 173 (23), 146 (27). Anal. calc. for $C_{29}H_{37}N_3O_5S$ (539.68): C 64.54, H 6.91, N 7.79; found: C 64.60, H 6.34, N 7.58.

Crystal structure determination of **10a**, **10d** and **11b** (see Fig. 1-3)[49]. The intensities were collected on a Rigaku AFC5R diffractometer using graphite-monochromated MoK_α radiation and a 12 kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. The structures were solved by direct methods using SHELXS86[50] which usually revealed the positions of all non-H atoms. For **11b** there are two symmetry-independent molecules in the asymmetric unit and SHELXS86 revealed only part of one molecule. The positions of the remaining non-H atoms were obtained using DIRDIF92[51]. For each structure the non-H atoms were refined anisotropically. All of the H-atoms of **10a** and **10d** and the amide H-atoms of **11b** were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All of the remaining H-atoms of **11b** were fixed in geometrically calculated positions [*d*(C-H) = 0.95 Å] and they were assigned fixed isotropic displacement parameters with a value equal to 1.2 U_{eq} of the parent C-atom. Refinement of each structure was carried out on *F* using full-matrix least-squares procedures, which minimised the function $\Sigma w(|F_o|-|F_c|)^2$. A correction for secondary extinction was applied for **10a** and **10d**, but not for **11b**. Refinements[52] of the absolute structure parameters[53,54] yielded values of -0.02(6), 0.00(7), and 0.07(9) for **10a**, **10d**, and **11d**, respectively, which confirm that the refined coordinates represent the true enantiomorphs. Neutral atom scattering factors for non-H atoms were taken from[55], and the scattering factors for H-atoms from[56]. Anomalous dispersion effects were included in F_{calc}[57], the values for *f'* and *f''* were those of ref.[58]. All calculations were performed using the TEXSAN crystallographic software package[59].

Crystal data for **10a**: A crystal of dimension 0.10 x 0.40 x 0.50 mm was grown from hexane/EtOAc. $C_{21}H_{31}N_3O_5S$, M_r = 437.55, monoclinic, space group $P2_1$, a = 9.605(2), b = 11.424(3), c = 11.246(2) Å, β = 104.21(2)°, V = 1196.3(4) Å^3, Z = 2, D_c 1.215 g cm^{-3}, μ(MoK_α) = 0.169 mm^{-1}; T = 173(1) K, λ = 0.71069 Å. Cell dimension from 25 reflections in the range 2Θ = 38-40°, $\omega/2\Theta$ scans, $2\Theta_{(max)}$ = 55°, 6118 reflections measured, including Friedel opposites of all unique reflections, 5505 symmetry-independent reflections, 4868 reflections with $I > 2\sigma(I)$ used in the refinement of 395 parameters. Final R = 0.0336, wR = 0.0311 ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$), GoF = 1.509, secondary extinction coefficient = 1.0(1) x 10^{-6}, Δ_{max}/σ = 0.0006, $\Delta\rho$(max; min) = 0.17; -0.18 e Å^{-3}.

Crystal data for **10d**: A crystal of dimension 0.32 x 0.36 x 0.48 mm was grown from hexane/ethanol. $C_{28}H_{35}N_3O_5S{\cdot}C_2H_6O$, M_r = 571.73, orthorhombic, space group $P2_12_12_1$, a = 14.800(2), b = 19.885(2), c = 10.837(4) Å, V = 3189(1) Å^3, Z = 4, D_c 1.191 g cm^{-3}, μ(MoK_α) = 0.145 mm^{-1}; T = 173(1) K, λ = 0.71069 Å. Cell dimension from 25 reflections in the range 2Θ = 36-40°, $\omega/2\Theta$ scans, $2\Theta_{(max)}$ = 55°, 9000

reflections measured, including Friedel opposites of all unique reflections, 7297 symmetry-independent reflections, 5940 reflections with $I > 2\sigma(I)$ used in the refinement of 526 parameters. Final $R = 0.0377$, $wR = 0.0331$ ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$), GoF = 1.414, secondary extinction coefficient = 3.8(4) x 10^{-7}, $\Delta_{max}/\sigma = 0.002$, $\Delta\rho$(max; min) = 0.21; -0.19 e Å^{-3}.

Crystal data for **11b**: A crystal of dimension 0.25 x 0.38 x 0.48 mm was grown from hexane/CH_2Cl_2. $C_{35}H_{50}N_4O_6S$, $M_r = 654.86$, monoclinic, space group $P2_1$, $a = 18.351(5)$, $b = 10.437(1)$, $c = 19.137(1)$ Å, $\beta = 93.00(1)°$, $V = 3660(1)$ Å^3, $Z = 4$ (2 formula units per asymmetric unit), D_c 1.188 g cm^{-3}, $\mu(MoK_\alpha) = 0.135$ mm^{-1}; $T = 173(1)$ K, $\lambda = 0.71069$ Å. Cell dimension from 25 reflections in the range $2\Theta = 36$-$40°$, $\omega/2\Theta$ scans, $2\Theta_{(max)} = 50°$, 11324 reflections measured, including Friedel opposites of all unique reflections with $2\Theta < 40°$, 10345 symmetry-independent reflections, 7410 reflections with $I > 2\sigma(I)$ used in the refinement of 860 parameters. Final $R = 0.0517$, $wR = 0.0443$ ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$), GoF = 1.916, $\Delta_{max}/\sigma = 0.002$, $\Delta\rho$(max; min) = 0.35; -0.34 e Å^{-3}. Some terminal groups have large atomic displacement parameters which are indicative of potential slight unmodelled disorder.

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59. TEXSAN: Single Crystal Structure Analysis Software, Version 5.0; Molecular Structure Corporation, The Woodlands: Texas, 1989.