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ORIGINAL ARTICLE

Novel thiol- and thioether-containing amino acids: cystathionine and homocysteine families

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Abstract Natural L-homocysteine and L,L-cystathionine, along with a series of unnatural analogues, have been prepared from L-aspartic and L-glutamic acid. Manipulation of the protected derivatives provided ω-iodoamino acids, which were used in thioalkylation reactions of sulfur nucleophiles, such as the ester of L-cysteine and potassium thioacetate.

Keywords Cystathionine · Homocysteine · Cysteine thioalkylation · Bis-amino acids · Unnatural amino acids

Abbreviations

All	Allyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Cth	Cystathionine
Hcy	Homocysteine
DCC	*N,N′*-Dicyclohexylcarbodiimide
Fm	9-Fluorenylmethyl
Fmoc	9-Fluorenylmethoxycarbonyl
HOBt	1-Hydroxybenzotriazole
ImH	Imidazole
NMM	*N*-Methylmorpholine
Nva	Norvaline
Pg	Protecting group
SPPS	Solid-phase peptide synthesis
THF	Tetrahydrofurane
TPP	Triphenylphosphine

Introduction

The metabolism of sulfur-containing amino acids has been associated with several aspects of human health and cellular functions. Sulfur-containing amino acids, and small peptides containing them, contribute significantly to the protection and integrity of cellular systems because of their ability to influence the cellular redox state and their capacity to detoxify toxic compounds, free radicals and reactive oxygen species (Finkelstein et al. 1984; Mason 2003; Townsend et al. 2004). Methionine, an amino acid acquired through the diet, is our primary source of sulfur. Sulfur is distributed in various amino acid forms such as cysteine, homocysteine (Hcy), cystathionine (Cth), lanthionine (Lan), and taurine. L,L-Cth (**1**, Fig. 1), also known as carbacystine, is a metabolic intermediate in the pathway to make cysteine from homocysteine. It has been isolated from the urine of humans with alteration in sulfur metabolism (Frimpter 1965), the leaves of *Astragalus pectinari,* (Nigam et al. 1972), and the deproteinized hemolymph of *Bombix mori* (Kondo 1962). It is also a component of ezomycin, the *Streptomyces* derived antifungal that belongs to a family of complex peptidyl nucleoside super-antibiotics (Knapp et al. 2000; Khalaf et al. 2008).

From a chemical perspective, the interest in Hcy and especially in Cth amino acids are due to their extraordinary structural resemblance to cystine. The substitution of a

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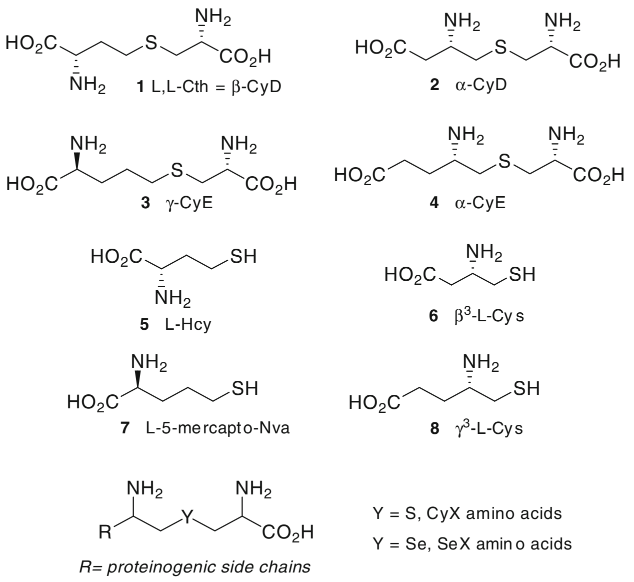


Fig. 1 Cystathionine and homocysteine families and the definition of Cy*X* and Se*X* amino acids

disulfide bond with a reduction-resistant thioether bridge is an attractive means of improving stability while imposing minimal structural perturbation to a natural bioactive peptide. Cth-containing bioactive peptides have been prepared by SPPS methods based on in situ Cth formation via cysteine thioalkylation (Mayer et al. 1995), by the incorporation of pre-formed Cth-containing segments (Jones et al. 1998), or through the direct desulfurization of cystine-containing peptides (Galande et al. 2003).

Two recent examples of thioether-containing peptides (Tabor 2011), the analogues of the therapeutic peptide Compstatin obtained by SPPS methods (Knerr et al. 2011) and the α-conotoxin ImI (Dekan et al. 2011), demonstrated that the thioether analogues maintained a similar biological activity, but increased its metabolic stability to reduction, making this new class of analogues a promising alternative for the therapeutic applications.

Although L,L-Cth **1** is a key intermediate for studies on sulfur metabolism and an excellent candidate for peptidomimetic chemistry, few synthetic methods for this compound have been reported. One example involves a procedure starting from methionine (Shiraiwa et al. 2002). Another method, which was first developed for lanthionine synthesis (Zhu et al. 2003), involves the phase-transfer condensation of Fmoc- and *tert*-butyl ester L-cysteine with protected γ-bromo-L-aminobutyrate that is derived from L-homoserine (Knerr et al. 2011). Additionally, some biotechnological procedures employ the bacterial CGL (Kanzaki et al. 1987) or the aminohexyl-Sepharose immobilised enzyme (Yamagata et al. 2003), but these procedures are limited to the preparation of natural L,L-Cth **1**.

Materials and methods

General methods

The melting points were measured with a Kofler apparatus, and they are reported uncorrected. The optical rotations were measured with a Jasco1010 polarimeter ($k = 589$ nm). ^{1}H- and ^{13}C-NMR spectra were recorded with Varian Inova 500 and Bruker DRX-400 spectrometers: chemical shifts are in ppm (δ), and J coupling constants are in Hz. RP-HPLC were carried out with a Shimadzu SCL-10 Avp system with a photodiode array detector, using a binary solvent system consisting of 0.01 % TFA in H_2O and 0.01 % TFA in CH_3CN; an analytical Vydac C18 column was used (4.6 mm diameter with a flow rate of 1 mL/min). Low-resolution mass spectra were recorded on a Thermo Finnigan LXQ linear trap. High-resolution ES mass spectra were obtained with a Micromass Q-TOF UltimaTM API. The microwave reactions were performed on a Mars system from CEM. TLC was carried out on silica gel Merck 60 F254 plates (0.2 mm layer thickness) and developed with ninhydrin (0.25 % in MeOH) or visualised by UV. Column chromatography was performed on a Merck Kieselgel 60 (70–230 mesh). Inorganic, protected α-amino acids and other reagents, including $NaBD_4$ (98 % D) and D_2O (99.9 % D), were purchased from Aldrich at the highest purity grade and used without further purification. Dry solvents were distilled immediately before use. All compounds for which analytical and spectroscopic data are reported were homogeneous by TLC and HPLC, and the solids were crystallised.

Preparation of N,C-protected ω-iodoamino acids

Methyl chloroformate (1.8 mL, 23.3 mmol) was added dropwise to a solution of NMM (2.6 mL, 23.3 mmol) and Boc-amino acids (21.2 mmol) in THF (70 mL) at 0 °C with magnetic stirring. After 15 min, the solution was filtered, and the salt was washed with THF (3 × 20 mL). A suspension of $NaBH_4$ (1.1 g, 26.5 mmol) in H_2O (8 mL) was then added dropwise to the filtrate in an ice bath and under magnetic stirring. The ice bath was removed, and the temperature of the mixture was allowed to increase to room temperature. After 10 min, the solvent was evaporated under reduced pressure. The remaining residue was dissolved in EtOAc (100 mL), and the solution was washed with brine until neutral. The organic layer was separated and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give the crude alcohol (95–98 %). To a solution of triphenylphosphine (2.8 g, 10.6 mmol) and dry imidazole (1.4 g, 21.2 mmol) in anhydrous THF (70 mL), iodine (2.7 g, 10.8 mmol) was added at room temperature under an argon atmosphere and magnetic stirring. After 15 min, the crude alcohol (8.5 mmol), which was dissolved in the same solvent (20 mL), was added; the reaction mixture was allowed to reflux until the consumption of the starting material (~ 1 h, TLC). The mixture was then cooled, diluted with EtOAc (100 mL), and washed with 10 % aq. $Na_2S_2O_4$ (40 mL) and brine (2 × 50 mL). The organic layer was dried, and the solvent was evaporated under reduced pressure to give the crude iodide moiety in mixture with Ph_3PO as a white solid. Rapid flash chromatography purification (20 % of EtOAc in Hexane) yielded (77–90 %) the pure iodides. Using these conditions, iodides **9–15** were prepared. For their characterization, see the electronic supplementary material.

S-Alkylation of potassium thioacetate with protected ω-iodoamino acids

Under an argon atmosphere, potassium thioacetate (228 mg, 2 mmol) was added in one portion to a stirred solution of N,C-protected *ω*-iodoamino acids (1 mmol) in dry acetonitrile (5 mL). Stirring was continued in the dark at room temperature for 1 h. The mixture was evaporated under vacuum, and the residue was suspended in EtOAc (50 mL) and shaken with H_2O (3 × 25 mL). The organic layer was separated and dried, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (Hex–EtOAc 80/20). Using these conditions, the fully protected thiol amino acids **16**, **17**, **20**, **21** and **22** were obtained (91–96 %). For their characterization, see the electronic supplementary material.

S-Alkylation of L-cysteine ethyl ester with protected ω-iodoamino acids

To a stirred solution of N,C-protected *ω*-iodoamino acids (1 mmol) and L-cysteine ethyl ester hydrochloride (185 mg, 1 mmol) in dry DMF (5 mL) under argon, solid Cs_2CO_3 (652 mg, 2 mmol) was added in one portion. Stirring was continued in the dark at room temperature for 3 h. The mixture was suspended in EtOAc (50 mL) and shaken with H_2O (3 × 25 mL). The organic layer was then dried, and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 98/2). Using these conditions, the tri protected thioether containing amino acids **18**, **19**, **23**, **24**, and **25** was obtained (82–88 %).

(S)-benzyl-4-[(R)-2-amino-3-ethoxy-3-oxopropylsulfanyl]-3-[(tert-butoxycarbonyl)amino] butanoate, H-α-Cy*D*(Boc,OBn)-OEt, (**18**), viscous oil, $[\alpha]_D^{25}$ = 12.4 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.28 (t, 3H, $J = 7$ Hz), 1.43 (s, 9H), 1.73 (brs, 2H), 2.69 (dd, 1H, $J = 6$ and 16 Hz), 2.71–2.84 (m, 2H), 2.92 (dd, 1H, $J = 6$ and 16 Hz), 3.62 (dd, 1H, $J = 5$ and 7 Hz), 4.05–4.14 (m, 1H), 4.19 (q, 2H, $J = 7$ Hz), 5.12 (brs, 2H), 5.35 (brd, 1H, $J = 9$ Hz), 7.31–7.38 (m, 5 H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 14.2, 28.4, 36.9, 37.7, 47.4, 54.4, 61.3, 66.6, 79.6, 128.3, 128.4, 128.6, 135.6, 155.1, 171.1, 173.6. HRMS (ESI), calcd for [$C_{21}H_{33}N_2O_6S$, $(M+H)^+$] 441.2054, found 441.2047. For the characterization of compounds **19**, **23**, **20**, **24** and **25,** see the electronic supplementary material.

Hydrolysis and peptide coupling of protected CyD amino acids

(S)-2-amino 4-[(R)-2-amino-2-carboxyethylsulfanyl] butanoic acid dihydrochloride, H-*β*-CyD-OH 2HCl (**26**), L,L-Cth: H-*β*-CyD(Boc,OtBu)-OEt **23** (100 mg) was mixed in a microreactor with 10 mL of 3 M aq. HCl and placed in the microwave apparatus. The temperature was fixed to 120 °C, and the mixture was stirred magnetically for 15 min. After this time, a direct LC–MS aliquot control showed the presence of only molecular species with a mass of MH^+ 223.08. The mixture was then cooled to room temperature, diluted with 10 mL of H_2O, and frozen and lyophilised twice to give the product as a foam (70 mg, 97 %), $[\alpha]_D^{25}$ = 22.8 (c 0.7, 1 M HCl), in agreement with the literature value ($[\alpha]_D^{25}$ = 23.4) (Shiraiwa et al. 2002); ^{1}H-NMR (500 MHz, D_2O) δ: 2.05 (m, 1H); 2.17 (m, 1H); 2.60–2.70 (m, 2H); 3.01 (dd, 1H, $J = 6$ and 15 Hz); 3.10 (dd, 1H, $J = 5$ and 15 Hz); 4.04 (dd, 1H, $J = 5$ and 7 Hz); 4.09 (dd, 1H, $J = 5$ and 7 Hz). ^{13}C-NMR, (125 MHz, D_2O) δ: 24.3, 26.7, 28.3, 48.9 (minor), 49.0 (major), 49.6 (minor), 49.7 (major). HRMS (ESI), calcd for [$C_7H_{15}N_2O_4S$, $(M+H)^+$] 223.0747, found 223.0749, 246.0646 [$(M+Na)^+$].

(S)-allyl 4-[(R)-2-(S)-2-{[(9H-fluoren-9-yl)methoxycarbonyl]amino}propanamido-3-ethoxy-3-oxopropylsulfanyl]-2-[(tert-butoxycarbonyl) amino] butanoate, Fmoc-Ala-*β*-CyD(Boc,OAll)-OEt, (**27**): H-*β*-CyD(Boc,OAll)-OEt **22**, (177 mg, 0.45 mmol), Fmoc-L-Ala-OH (140 mg, 0.45 mmol), and dry HOBt (61 mg, 0.45 mmol) were dissolved in dry THF (5 mL). The solution was cooled to 0 °C, and DCC (93 mg, 0.45 mmol) was added in one portion. After stirring for 1 h at 0 °C and 2 h at room temperature, the white precipitate was filtered, and the filtrate was diluted with 50 ml of EtOAc and washed with H_2O (3 × 25 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated under vacuum. The residue, which was purified by flash chromatography using $CHCl_3$, furnished 292 mg (95 %) of pure dipeptide **27** as a white solid: m.p. (CH_2Cl_2/Hex) 61–62 °C; $[\alpha]_D^{25}$ = +18.7 (c 0.9, $CHCl_3$); ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.25 (t, 3H, $J = 7$ Hz); 1.36 (d, 3H, $J = 7$ Hz); 1.40 (s, 9H); 1.60 (m, 1H); 1.65–1.75 (m, 2H); 1.80–1.88 (m, 2H); 1.93 (m, 1H); 2.02

(m, 1H); 2.56 (m, 1H); 2.68 (m, 1H); 2.90 (dd, 1H, $J = 7$ and 14 Hz); 3.00 (dd, 1H, $J = 6$ and 16 Hz); 3.45 (m, 1H); 4.20 (dd, 2H, $J = 7$ and 16 Hz); 4.36 (m, 1H); 4.50–4.70 (m, 2H); 5.18 (d, 1H, $J = 10$ Hz); 5.30 (d, 1H, $J = 16$ Hz); 5.90 (m, 1H); 7.31 (t, 2H, $J = 8$ Hz); 7.39 (t. 2H, $J = 8$ Hz); 7.68 (t, 2H, $J = 8$ Hz); 7.78 (t, 2H, $J = 8$ Hz). ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 14.1; 18.3; 28.3; 29.7; 32.6; 33.9; 34.1; 47.1; 50.4; 52.3; 52.6; 61.9; 66.0; 67.2; 80.1; 119.9; 125.1; 127.1; 127.7; 131.4; 141.2; 143.8; 155.5; 156.1; 170.2; 171.8; 172.2. HPLC method: gradient start from 50 % $CH_3CN–H_2O$ 10 min to 100 % CH_3CN over 15 min and 15 min at 100 % CH_3CN, with monitoring at λ 280 nm. A single peak was collected at 17.55 min. HRMS (ESI), calcd for [$C_{35}H_{46}N_3O_9S$, $(M+H)^+$] 684.1529, found 684.1525.

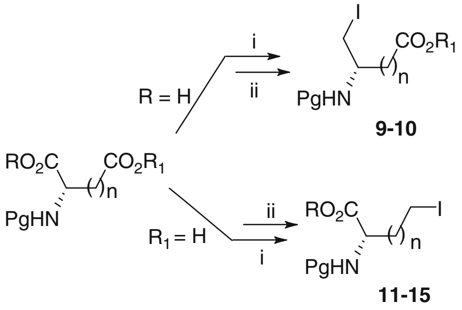
Results and discussion

In an extension of our efforts to create new classes of amino acids containing sulfur and selenium atoms, we report the preparation of new members belonging to the Cy*X* series. The Cy*X* and Se*X* series (Fig. 1), where the *X* denotes the one-letter symbol of a proteinogenic residue attached to the sulfur or selenium atoms of cysteine or selenocysteine through its reduced carboxylic group, are efficiently obtained by the thioalkylation of a cysteine ethyl ester and/or a free selenocysteine with *N*-(Boc)-β-iodoamines (Bolognese et al. 2006; Caputo et al. 2007). These series include (Fig. 1) the compounds α-Cy*D* **2** and β-Cy*D* **1** (L,L-cystathionine, (2*S*, 2′*R*)-Cth), which were acquired from Asp and Cys, and the couple α-Cy*E* **4** and γ-Cy*E* **3**, which were acquired from Glu and Cys, respectively.

The synthesis of Cth and its analogues starts from L-aspartic and L-glutamic acids that bear various orthogonal protecting groups, such as *N*-Boc, *N*-Fmoc and allyl, fluorenyl, benzyl, and *t*-butyl esters. The free carboxylic acid functionality of these derivatives is first converted to a mixed anhydride using MeOCOCl in the presence of NMM as the base. The reductions to the alcohols were obtained with $NaBH_4$ in H_2O (Kokotos 1990).

Treatment of the resultant N,C-protect L-hydroxyl amino acids with the TPP-I_2 complex in the presence of imidazole (Rajagopal et al. 1994; Caputo et al. 1995a, b; Koseki et al. 2011) produced the N,C-protected L-ω-iodoamino acids in high yields (Scheme 1; Table 1). Using $NaBD_4$ in H_2O in the reduction step (Caputo and Longobardo 2007), the related deuterated halides were obtained.

Boc-L-Asp(OBn)-OH furnished γ-iodo-β-amino acid **9** (Scheme 1), while from Boc-L-Asp(OH)-OAll, Boc-L-Asp(OH)-OFm and Boc-L-Asp(OH)-OtBu, the corresponding γ-iodo α-amino acids **11**, **12** and **13** were obtained. Boc-L-Glu(OBn)-OH furnished δ-iodo γ-amino acid **10** and the deuterated analogue **10-d₂**, while Boc-L-Glu(OH)-OBn and Fmoc-L-Glu(OH)-OAll generated the protected δ-iodo α-amino acids **14** and **15**, respectively.



i: NMM, MeOCOCl, THF, 0°C, 15 min, then $NaBH_4$ (or $NaBD_4$), H_2O
ii: TPP-I_2, ImH, THF, reflux, 1 h

Scheme 1 Preparation of N,C-protected ω-iodoamino acids

Cysteine esters have traditionally been *S*-alkylated by alkyl halides, using NaOEt in refluxing EtOH (Perrey et al. 2001) or with the reagent system Cs_2CO_3/TBAI in DMF (Salvatore et al. 2005); however, products were generally obtained in modest yields. The best results were recently obtained using free amino acid in the presence of 1,1,3,3-tetramethylguanidine (Włostowski et al. 2010). The *S*-alkylation of C-protected cysteine with a ω-iodoamino acid proceeds very efficiently in DMF and using commercial L-cysteine ethyl ester hydrochloride and Cs_2CO_3 as the base. The substitution products were obtained within 3 h in high yields (Table 2), except for the iodides **12** and **15**. Iodides **9** and **10** gave protected α-Cy*D* **18** and α-Cy*E* **19,** respectively, while iodide **11** and **13** provided the two protected Cth, (β-Cy*D*) **23** and **24**, respectively. Finally, the iodide **14** yielded the protected γ-Cy*E* **25**. These *S*-alkylations were all chemoselective using two eq. of Cs_2CO_3. Neither alkylation of the cysteine amino group nor traces of elimination and/or cyclization products were detected by TLC or ^{1}H-NMR analysis of the crude alkylation products. These bis-amino acids were obtained with three orthogonal protections and one free amino group. However, these amino esters are not suitable for long-term storage, and there conversion into hydrochloride salt is preferred.

In the reaction of iodides **12** and **15**, extensive deprotection of the Fm and Fmoc protecting groups was observed. This *S*-alkylation procedure has been recently used to fix a Cys and/or a Sec residue at position 4 of a protected proline (Caputo et al. 2010). *S*-Alkylations with two eq. of CH_3COSK in dry CH_3CN at room temperature released the expected substitution products in high yields (Scheme 2; Table 2). Iodide **9** yielded the protected β^3-Cys **16**, while iodide **10** and **10-d₂** generated γ^3-Cys **17** and **17-d₂**, respectively. The halides **12** and **13** provided protected L-Hcy **20** and **21,** respectively, while iodide **14** afforded the protected L-5-mercaptonorvaline **22**.

Table 1 N,C-Protected *ω*-Iodoamino Acids (Scheme 1)

Iodide	*n*	R	R$_1$	Pg	Yield (%)^a
9	1	H	Bn	Boc	80
10	2	H	Bn	Boc	77
10-d$_2$	2	H	Bn	Boc	84
11	1	Allyl	H	Boc	79
12	1	Fm	H	Boc	76
13	1	t-Bu	H	Boc	81
14	2	Bn	H	Boc	83
15	2	Allyl	H	Fmoc	90

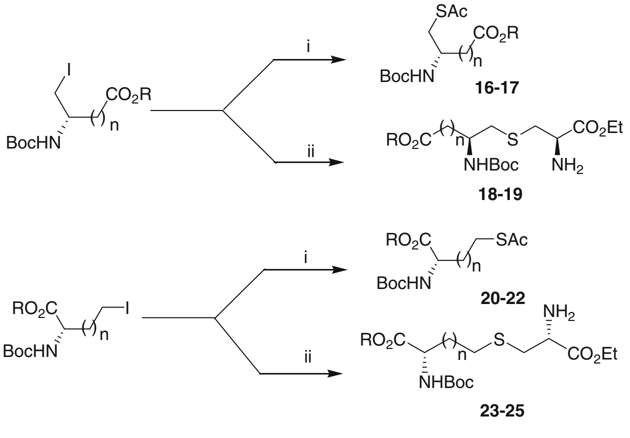
[a] Isolated yield

Table 2 Protected Cystathionine and Homocysteine Families

Amino acids	*n*	Three-letter symbols	R	Yield (%)^a
16	1	Boc-β^3-Cys(Ac)-OBn	Bn	95
17	2	Boc-γ^3-Cys(Ac)-OBn	Bn	93
17-d$_2$	2	Boc-γ^3-Cys(Ac)-OBn-d$_2$	Bn	96
18	1	H-α-Cy*D*(Boc,OBn)-OEt	Bn	85
19	2	H-α-Cy*E*(Boc,OBn)-OEt	Bn	88
20	1	Boc-Hcy(Ac)-OFm	Fm	92
21	1	Boc-Hcy(Ac)-OtBu	t-Bu	94
22	2	Boc-Nva(5-SAc)-OBn	Bn	91
23	1	H-*β*-Cy*D*(Boc,OAll)-OEt	Allyl	82
24	1	H-*β*-Cy*D*(Boc,OtBu)-OEt	t-Bu	87
25	2	H-*γ*-Cy*E*(Boc,OBn)-OEt	Bn	84

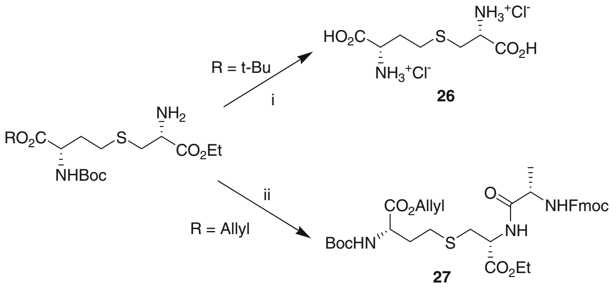
[a] Isolated yields

As previously reported for the Cy*L*, Cy*F*, and Cy*P* amino acids, these sulfur-containing residues may be further converted into related, orthogonally protected acid derivatives, which are ready for use in SPPS, by hydrolysis of the ethyl ester and *N*α-Fmoc protection (Bolognese et al. 2006).



i:) AcSK, CH$_3$CN, r.t, 1 h; ii:) HCl·L-Cys-OEt, Cs$_2$CO$_3$, DMF, r.t., 3 h

Scheme 2 Thioalkylation with N,C-protected *ω*-iodoamino acids



i): aq HCl 3 M, MW, 120°C, 15 min; ii): Fmoc-L-Ala-OH, DCC, HOBt, THF, 3 h

Scheme 3 Hydrolysis and peptide coupling of protected *β*-CyD

Cy*X* residues can be used in direct coupling with *N*-protected α-amino acids in solution synthesis or hydrolysed to the free amino acids. To this end, *β*-CyD **24** was fully deprotected in a single step with aq. 3 M HCl in a microwave oven at 120 °C for 15 min (Scheme 3).

Free L,L-Cth dihydrochloride salt **26** was obtained in high yields after freeze-drying the crude reaction products two times. *β*-CyD **23** was used in a standard peptide coupling with Fmoc-L-Ala-OH to give the expected dipeptide **27** in high yield.

Conclusions

Protected cystathionine and homocysteine amino acid analogues, including deuterium-labelled analogues, were easily obtained from commercially available reagents. These residues can be incorporated into growing peptide chains and used as redox stable isosteres of natural disulfide bonds. Preparing small, cyclic unnatural peptides may be useful in the search for bioactive and metabolically stable peptidomimetics.

Conflict of interest The authors have declared no conflict of interest.

References

Bolognese A, Fierro O, Guarino D, Longobardo L, Caputo R (2006) One-pot synthesis of orthogonally protected enantiopure S-(aminoalkyl)-cysteine derivatives. Eur J Org Chem 1:169–173

Caputo R, Longobardo L (2007) Enantiopure β^3-amino acids-2,2–d$_2$ via homologation of proteinogenic α-amino acids. Amino Acids 32:401–404

Caputo R, Cassano E, Longobardo L, Palumbo G (1995a) Chiral *N*-protected *β*-iodoamines from α-amino acids: a general synthesis. Tetrahedron Lett 36:167–168

Caputo R, Cassano E, Longobardo L, Palumbo G (1995b) Synthesis of enantiopure N-and C-protected *homo*-*β*-amino acids by direct homologation of α-amino acids. Tetrahedron 51:12337–12350

Caputo R, Capone S, DellaGreca M, Longobardo L, Pinto G (2007) Novel selenium-containing non-natural diamino acids. Tetrahedron Lett 48:1425–1427

Caputo R, DellaGreca M, de Paola I, Mastroianni D, Longobardo L (2010) Novel sulfur and selenium containing bis-α-amino acids from 4-hydroxyproline. Amino Acids 38:305–310

Dekan Z, Vetter I, Daly NL, Craik DJ, Lewis RJ, Alewood PF (2011) α-Conotoxin ImI incorporating stable cystathionine bridges maintains full potency and identical three-dimensional structure. J Am Chem Soc 133:15866–15869

Finkelstein JD, Martin JJ (1984) Methionine metabolism in mammals. J Biol Chem 259:9508–9513

Frimpter GW (1965) Cystathioninuria: nature of the defect. Science 149:1095–1096

Galande AK, Trent JO, Spatola AF (2003) Understanding base-assisted desulfurization using a variety of disulfide-bridged peptides. Biopolymers (Peptide Sci) 71:534–551

Jones DS, Gamino CA, Randow ME, Victoria EJ, Yu L, Coutts SM (1998) Synthesis of a cyclic-thioether peptide which binds anti-cardiolipin antibodies. Tetrahedron Lett 39:6107–6110

Kanzaki H, Kobayashi M, Nagasawa T, Yamada H (1987) Production of L-cystathionine using bacterial cystathionine γ-synthase. Appl Microbiol Biotechnol 25:322–326

Khalaf JK, VanderVelde DG, Datta A (2008) Synthetic studies on ezomycins: stereoselective route to a thymine octosyl nucleoside derivative. J Org Chem 73:5977–5984

Knapp S, Gore VK (2000) Synthesis of the ezomycin nucleoside disaccharide. Org Lett 2:1391–1393

Knerr PJ, Tzekou A, Ricklin D, Qu H, Chen H, van der Donk WA, Lambris JD (2011) Synthesis and activity of thioether-containing analogues of the complement inhibitor Compstatin. ACS Chem Biol 6:753–760

Kokotos G (1990) A convenient one-pot conversion of *N*-protected amino acids and peptides into alcohols. Synthesis 299–301

Kondo Y (1962) The cystathionine pathway in the silkworm larva, *Bombyx mori*. J Biochem 51:188–192

Koseki Y, Yamada H, Usuki T (2011) Efficient synthesis of benzyl 2-(*S*)-[(*tert*-butoxycarbonyl) amino]-ω-iodoalkanoates. Tetrahedron Asymmetry 22:580–586

Mason JB (2003) Biomarkers of nutrient exposure and status in one-carbon (methyl) metabolism. J Nutr 133:941S–9417S

Mayer JP, Heil JR, Zhang J, Munson MC (1995) An alternative solid-phase approach to C_1-oxytocin. Tetrahedron Lett 36:7387–7390

Nigam SN, McConnell WB (1972) Isolation and identification of L-cystathionine and L-selenocystathionine from the foliage of Astragalus pectinatus. Phytochemistry 11:377–380

Perrey DA, Uckun FM (2001) An improved method for cysteine alkylation. Tetrahedron Lett 42:1859–1861

Rajagopal D, Eckhardt M, Furlong M, Knoess HP, Berger S, Knochel P (1994) Preparation and reactivity of chiral related configurationally stable zinc organometallics. Tetrahedron 50:2415–2432

Salvatore RN, Smith RA, Nischwitza AK, Terrence GT (2005) A mild and highly convenient chemoselective alkylation of thiols using Cs_2CO_3–TBAI. Tetrahedron Lett 46:8931–8935

Shiraiwa T, Nakagawa K, Kanemoto N, Kinda T, Yamamoto H (2002) Synthesis of optically active homocysteine from methionine and its use in preparing four stereoisomers of cystathionine. Chem Pharm Bull 50:1081–1085

Tabor AB (2011) The challenge of the lantibiotics: synthetic approaches to thioether-bridged peptides. Org Biomol Chem 9:7606–7628

Townsend DM, Tew KD, Tapiero H (2004) Sulfur containing amino acids and human disease. Biomed Pharmacother 58:47–55

Włostowski M, Czarnocka S, Maciejewski P (2010) Efficient S-alkylation of cysteine in the presence of 1,1,3,3-tetramethylguanidine. Tetrahedron Lett 51:5977–5979

Yamagata S, Akamatsu T, Iwama T (2004) Immobilization of Saccharomyces cerevisiae cystathionine γ-lyase and application of the product to cystathionine synthesis. Appl Environ Microbiol 70:3766–3768

Zhu X, Schmidt RR (2003) Efficient synthesis of differently protected lanthionines via β-bromoalanine derivatives. Eur J Org Chem 4069–4072