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ORIGINAL ARTICLE

Novel sulfur and selenium containing bis-α-amino acids from 4-hydroxyproline

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Abstract The synthesis of new substituted prolines carrying at C-4 a second α-amino acid residue is reported. The amino acid, L-cysteine or L-selenocysteine, is linked to the proline ring through the sulfur or the selenium atom, respectively. The products were prepared with different stereochemistry at C-4, in few and clean high-yielding steps, with suitable protections for solid phase applications. The introduction of both sulfur and selenium atoms at C-4 of the proline ring seems to enhance significantly the cis geometry at the prolyl amide bond.

Keywords 4-Substituted proline · Cysteine thioalkylation · Selenocystine · Bis-α-amino acids · Unnatural amino acids

Introduction

Proline and its (*R*)-4-hydroxyl derivative (Hyp) are unique among the protein amino acids, characterized by limited rotation of the ϕ dihedral angle as their side chain is fused to the peptide backbone. Consequently, there is a reduction in the energy difference between *cis* and *trans* prolyl amide isomers that makes them nearly isoenergetic (Fischer 2000). The result is the higher *cis*-amide content relative to the other α-amino acids, whereas the cis conformation appears with a frequency of 5–6% in protein structures (Pal and Chakrabarti 1999). The *cis*/*trans* equilibrium of the prolyl amide bond has been reported to be the rate-determining step in the folding pathways of many peptides and proteins (Lu et al. 2007; Halab and Lubell 2002): in particular, various substituted proline derivatives exhibit strong and disparate conformational biases that are dependent on the stereochemistry and the electronics of the substitution (Thomas et al. 2005). Such effects on peptide conformations have aroused a great interest towards design and synthesis of substituted proline analogues, although the conformational restrictions induced by the substitution have not received broad attention in the context of peptide secondary structures.

Therefore, we considered worthy of note the preparation we have devised of an undoubtedly new class of substituted prolines carrying at C-4 a second α-amino acid residue, namely L-cysteine or L-selenocysteine, linked to the proline ring through the sulfur or the selenium atom, respectively.

In fact, pursuing our current interest for the synthesis of new non-natural amino acids containing chalcogen atoms (Bolognese et al. 2006; Caputo et al. 2007), we have performed a simple and fully stereoselective synthesis of the new bis-α-amino acids **1** and **2** that can be obtained (vide infra) protected with the common groups used in peptide synthesis and, hence, ready for being incorporated in growing peptide chains.

A retrosynthetic analysis showing the preparation of the backbones of both **1** and **2**, starting from *trans*-L-4-hydroxyproline (Hyp) is reported in Scheme 1.

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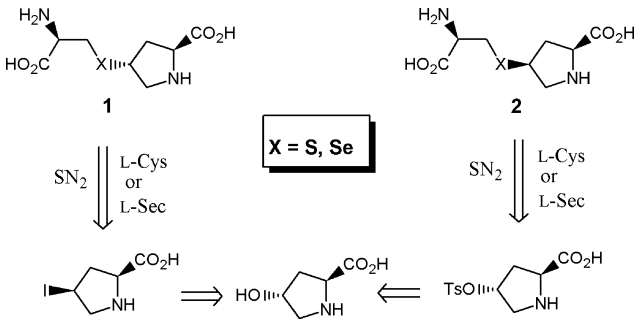


Scheme 1 Retrosynthetic analysis for bis-α-amino acids **1** and **2** from Hyp

Materials and methods

General

Inorganics, organic reagents, and solvents were commercial pure compounds (Fluka, Aldrich) and used without further purification. Melting points were measured with a Kofler apparatus and are uncorrected. TLC analyses were performed using silica gel plates (E. Merck silica gel 60 F-254) visualized by UV light, iodine, and ninhydrin spray. Column chromatography was carried out on silica gel (E. Merck, 70-230 mesh). RP-HPLC was carried out with Agilent 1100 system, photodiode-array detector, using a binary solvent system [0.01% TFA in H_2O and 0.01% TFA in MeCN] on analytical C_{18} column (Gemini 100 × 4.6 mm), flow rate 0.5 ml/min). ^1H and ^{13}C NMR spectra were recorded on Varian Inova 500 and Varian Gemini 300 spectrometers: chemical shifts are in ppm (δ) and J coupling constants in Hz; split signals denote the presence of two rotamers of the carbamate bond, *trans* (major) and *cis* (minor). Low-resolution MS spectra were recorded on Thermo-Finnigan LXQ linear trap. Optical rotations were measured with Jasco 1,010 polarimeter ($\lambda = 589$ nm). All compounds for which analytical and spectroscopic data are quoted were homogeneous by TLC and HPLC, and solids were crystallized.

(2S,4R)-2-benzyl 1-tert-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (**3**) The title compound **3** was already known (Qiu and Qing 2002) and was prepared from commercial Hyp by modification of the reported procedure, using benzyl bromide in DMF and K_2CO_3 as the base for the esterification of the carboxyl group: colorless oil (92%). $[\alpha]_D^{20} = -59.4$ ($c = 1.10$, $CHCl_3$). [Lit., $[\alpha]_D^{20} = -58.0$ ($c = 1.24$, $CHCl_3$]. ^1H NMR (300 MHz, CD_3OD) spectrum was consistent with that reported: split signals δ 1.31 and 1.44 (2s, 9H); ($K_{trans/cis} = 2.03$).

(2S,4S)-2-benzyl 1-tert-butyl 4-iodopyrrolidine-1,2-dicarboxylate (**4**) Pure **4** was prepared according to a reported general procedure (Bolognese et al. 2006; Caputo et al. 1995b): colorless oil (80%) solidifying upon standing at 4°C, m.p. = 71–72°C (Et_2O-hexane); $[\alpha]_D^{25} = -27.1$ ($c = 0.75$, MeOH). ^1H NMR (500 MHz, CD_3OD) ($K_{trans/cis} = 1.51$): δ 1.30 and 1.45 (2s, 9H); 2.29 (m, 1H); 2.92 (m, 1H); 3.59 (m, 1H); 4.03 (m, 1H); 4.28 (m, 1H); 4.35 (m, 1H); 5.12 and 5.19 (d, $J = 12.7$, 1H); 5.21 and 5.25 (d, $J = 12.7$, 1H); 7.28–7.43 (m, 5H). ^{13}C NMR (125 MHz, CD_3OD): δ 13.7 and 14.6; 28.9 and 29.1; 43.6 and 44.5; 58.9 and 59.3; 60.7 and 61.0; 68.6 and 68.7; 82.3 and 82.6; 129.8, 130.0; 130.3; 137.6; 155.3 and 155.6; 173.4 and 173.6.

(2S,4R)-2-benzyl 1-tert-butyl 4-(tosyloxy) pyrrolidine-1,2-dicarboxylate (**5**) The compound **5** was prepared according to a reported procedure (Kondo et al. 2007): colorless solid (82%), m.p. = 79–81°C (Et_2O-hexane); $[\alpha]_D^{25} = -35.9$ ($c = 1.30$, EtOH). ^1H NMR (300 MHz, CD_3OD) spectrum was consistent with that reported: split signals δ 1.29 and 1.40 (2s, 9H); ($K_{trans/cis} = 1.64$). ^{13}C NMR (125 MHz, CD_3OD): δ 22.1; 28.9 and 29.0; 37.4 and 38.3; 53.6 and 53.9; 59.2 and 59.4; 68.6 and 68.7; 80.8 and 81.6; 82.7 and 82.8; 129.4; 129.7; 129.8; 130.1; 130.2; 131.8; 137.5; 147.4; 156.0 and 156.3; 173.7 and 173.9.

(2S,4R)-2-benzyl 1-tert-butyl 4-((R)-2-amino-3-ethoxy-3-oxopropylsulfanyl)pyrrolidine-1,2-dicarboxylate (**6**) To a stirred solution of **4** (0.4 g, 1 mmol) and L-cysteine ethyl ester hydrochloride (0.2 g, 1 mmol) in dry DMF (5 ml), under nitrogen, solid Cs_2CO_3 (0.6 g, 2 mmol) was added in one portion. Stirring was continued in the dark at room temperature for 3 h. Most of the solvent was then carefully (<45°C) evaporated in vacuo and the residue was suspended in EtOAc (75 ml) and shaken with H_2O (3 × 20 ml). The organic layer was then dried (Na_2SO_4) and the solvent evaporated in vacuo. Column chromatography (0–5% MeOH in CH_2Cl_2) of the residue gave pure **6**, as colorless oil (85%), $[\alpha]_D^{25} = -33.1$ ($c = 0.34$, $CHCl_3$). ^1H NMR (500 MHz, CD_3OD) ($K_{trans/cis} = 1.65$): δ 1.27 (t, $J = 6.8$, 3H); 1.31 and 1.45 (2s, 9H); 2.16–2.30 (m, 2H); 2.90 (m, 2H); 3.31 (m, 1H); 3.45 (m, 1H); 3.63 (m, 1H); 3.83 (m, 1H); 4.17 (q, $J = 6.8$, 2H); 4.37 and 4.42 (2dd, $J = 4.9$ and 8.8, $J = 3.9$ and 8.8, 1H); 5.12 and 5.15 (d, $J = 12.7$, 1H); 5.20 and 5.22 (d, $J = 12.7$, 1H); 7.29–7.42 (m, 5H). ^{13}C NMR (125 MHz, CD_3OD): δ 15.0; 28.9 and 29.2; 37.3; 38.7; 42.5 and 43.0; 54.2 and 54.6; 55.6; 60.3 and 60.5; 62.9; 68.5; 82.2 and 82.3; 129.7; 129.8; 130.1; 130.2; 137.6; 155.8 and 156.2; 174.1 and 174.3; 175.3. ES-MS (EI): 353.2 (30); 453.0 (100), 475.2 (10); 904.5 (55). Calculated for $C_{22}H_{32}N_2O_6S$: C, 58.39%; H, 7.13%; N, 6.19%; S, 7.09%; found: C, 58.45%; H, 7.29%; N, 6.12%; S, 7.11%.

(2S,4S)-2-benzyl 1-tert-butyl 4-((R)-2-amino-3-ethoxy-3-oxopropylsulfanyl)pyrrolidine-1,2-dicarboxylate (**7**) The title compound **7** was prepared from L-cysteine ethyl ester hydrochloride (0.2 g, 1 mmol) and tosylate **5** (0.5 g, 1 mmol) under the conditions reported for the preparation of **6**, but the temperature that was kept at 50°C for 3 h: colorless oil (88%), $[\alpha]_D^{25} = -37.2$ ($c = 0.85$, $CHCl_3$). ^{1}H NMR (300 MHz, CD_3OD) ($K_{trans/cis} = 1.52$): δ 1.28 (t, $J = 7.5$, 3H); 1.31 and 1.44 (2s, 9H); 1.90 (m, 1H); 2.69 (m, 1H); 2.88 (m, 2H); 3.18 (m, 1H); 3.41 (m, 1H); 3.62 (m, 1H); 3.91 (m, 1H); 4.20 (q, $J = 7.5$, 2H); 4.35 (dd, $J = 7.5$ and 7.5, 1H); 5.09 and 5.16 (d, $J = 12.3$, 1H); 5.19 and 5.23 (d, $J = 12.3$, 1H); 7.37 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD): δ 15.0; 28.9 and 29.2; 37.5; 39.1; 42.5 and 43.4; 54.5 and 54.8; 55.8; 60.4 and 60.7; 62.8; 68.6; 82.3 and 82.4; 129.8; 130.1; 130.2; 137.6; 155.7 and 156.1; 174.0 and 174.2; 175.2. ES-MS (EI): 453.13 ($M + H^+$). Calculated for $C_{22}H_{32}N_2O_6S$: C, 58.39%; H, 7.13%; N, 6.19%; S, 7.09%; found:C, 58,18%; H, 7.20%; N, 6.15%; S, 7.01%.

(2S,4S)-2-methyl 1-tert-butyl 4-iodopyrrolidine-1,2-dicarboxylate (**8**) The title compound was already reported (Schumacher et al. 1998) and was prepared by the same procedure described above for the iodide **4**, starting from commercial Boc-L-Hyp-OMe: colorless oil (80%) solidifying upon standing at 4°C, m.p. = 63–65°C (Et_2O-petrol ether); $[\alpha]_D^{25} = -22.1$ ($c = 0.92$, $CHCl_3$). [Lit., m.p. = 64° C, $[\alpha]_D^{20} = -20.9$ ($c = 1.24$, $CHCl_3$)].

(2S,4R)-2-methyl 1-tert-butyl 4-(tosyloxy) pyrrolidine-1,2-dicarboxylate (**9**) The title compound was prepared according to a reported procedure (Lowe and Vilaivan 1997), starting from commercial Boc-L-Hyp-OMe: colorless solid (84%), m.p. = 76–78°C (Et_2O-petrol ether); $[\alpha]_D^{25} = -36.5$ ($c = 0.85$, $CHCl_3$). [Lit., m.p. = 78–79°C, $[\alpha]_D^{25} = -37.4$ ($c = 0.70$, $CHCl_3$)].

(R)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-((3R,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-3-ylselanyl) propanoic acid (**12**) L-Selenocystine (0.3 g, 1 mmol) was suspended in anhydrous EtOH (10 ml) under nitrogen atmosphere. Solid $NaBH_4$ (0.2 g, 5 mmol) was added in one portion and the yellow mixture refluxed for 5 min, until clear and colorless. Iodide **8** (0.7 g, 2 mmol) dissolved in anhydrous EtOH (4 ml) was then added in one portion and the reaction mixture was slowly cooled to room temperature (1 h). After evaporation of the solvents in vacuo, the residue was dissolved in THF (10 ml), cooled at 0°C, and treated with Fmoc-Cl (0.3 g, 1 mmol) under standard conditions. Column chromatography of the residue afforded the pure acid **12** (81%), m.p. 124–126°C (CH_2Cl_2-hexane); $[\alpha]_D^{25} = 67.2$ ($c = 0.23$, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD) ($K_{trans/cis} = 1.47$): δ 1.39 and 1.43 (2s, 9H); 2.34 (m, 2H); 2.98 (m, 1H); 3.16 (m, 1H); 3.40 (m, 1H); 3.61 (m, 1H); 3.71 and 3.72 (2s, 3H); 3.86 (m, 1H); 4.26 (t, $J = 6.8$, 1H); 4.36 (m, 2H); 4.41 (m, 2H); 7.31 (t, $J = 7.8$, 2H); 7.39 (t, $J = 7.8$, 2H); 7.69 (d, $J = 7.8$, 2H); 7.79 (d, $J = 7.8$, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 26.2; 29.0 and 29.1; 35.0 and 35.6; 39.0 and 39.6; 48.9; 53.3; 54.9 and 55.2; 56.6; 60.4 and 60.7; 68.6; 82.4; 121.4; 126.8; 128.7; 129.3; 143.1; 145.8; 155.8; 158.9; 174.3 and 174.9; 175.2. ES-MS (EI): 517.19 (56); 519.21 (100); 641.17(10); 657.17 (6); 1256.56 (10); 1272.09 (9); Calculated for $C_{29}H_{34}N_2O_8Se$: C, 56.40%; H, 5.55%; N, 4.54%; Se, 12.79%; found: C, 56.24%; H, 5.34%; N, 4.44%.

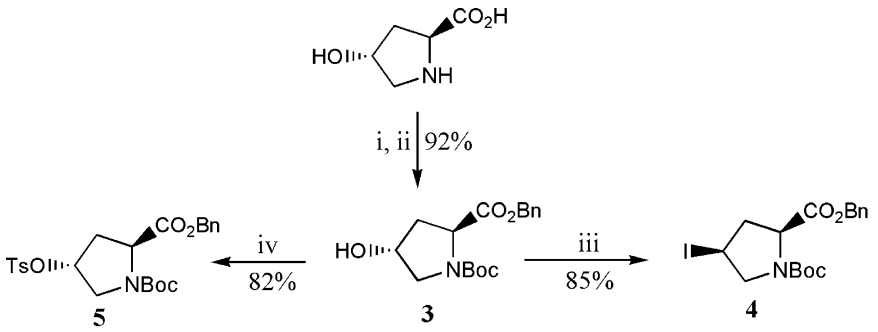
(R)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-((3S,5S)-1-(tert-butoxycarbonyl)-5-(methoxycarbonyl)pyrrolidin-3-ylselanyl)propanoic acid (**13**) The title compound **13** was prepared from L-selenocystine (0.3 g, 1 mmol) and tosylate **9** (0.8 g, 2 mmol) under the conditions reported for the preparation of **12**: colorless solid (77%), m.p. = 134–136°C (CH_2Cl_2-hexane); $[\alpha]_D^{25} = 18.0$ ($c = 0.47$, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD) ($K_{trans/cis} = 1.26$): δ 1.39 and 1.43 (2s, 9H); 2.31 (m, 2H); 3.00 (m, 1H); 3.18 (m, 1H); 3.38 (m, 1H); 3.57 (m, 1H); 3.69 and 3.70 (s, 3H); 3.84 (m, 1H); 4.20–4.32 (m, 4H); 4.43 (m, 1H); 7.23 (t, $J = 7.5$, 2H); 7.38 (t, $J = 7.5$, 2H); 7.67 (m, 2H); 7.78 (d, $J = 8.0$, 2H). ^{13}C NMR (125 MHz, CD_3OD): δ 28.0; 29.1 and 29.2; 34.8 and 35.3; 39.1 and 39.7; 53.3; 55.0 and 55.4; 57.9; 60.5 and 60.7; 68.6; 79.9 and 82.3; 121.4; 126.9; 128.7; 129.3; 143.1; 145.8; 156.0 and 156.5; 158.7; 174.9 and 175.3; 178.2. ES-MS (EI): 517.20 (20); 519.22 (100); 641.19 (13); 657.17 (6); 1254.23 (20); 1272.99 (8). Calculated for: $C_{29}H_{34}N_2O_8Se$: C, 56.40%; H, 5.55%; N, 4.54%; Se, 12.79%; found: C, 56.14%; H, 5.29%; N, 4.46%.

Results and discussion

The *S*-alkylation reaction of the *trans*-4-hydroxy-L-proline ring at C-4 by the cysteinyl residue is a S_N2 process involving the existing hydroxyl group that, therefore, needs to be converted into a good leaving group. The stereochemical outcome of the replacement can be controlled at this stage: as a matter of fact, the hydroxyl group can be either transformed into its tosyl ester, thus maintaining the *trans* configuration, or replaced by an iodine atom, using triphenylphosphine-iodine complex (Caputo et al. 1995a). This way leads to *cis*-4-iodo-L-proline.

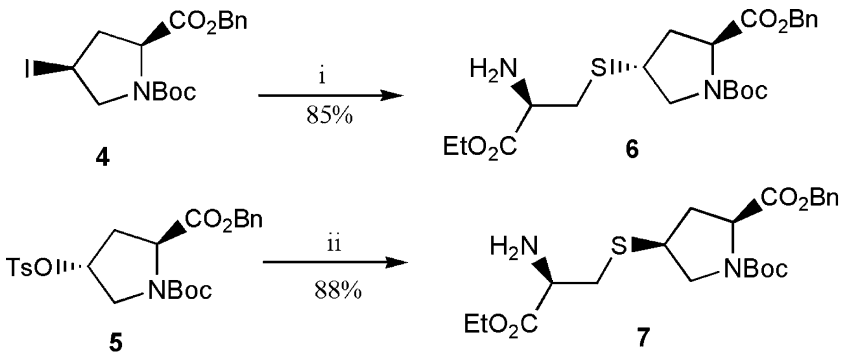
Under these circumstances, the subsequent attack by the proper cysteinyl nucleophile may afford either *trans*-4-*S*-cysteinyl-L-proline (from iodide) or *cis*-4-*S*-cysteinyl-L-proline (from tosylate).

Scheme 2 Conversion of Hyp into *cis*-4-iodo and *trans*-4-tosyloxy derivatives



i: Boc_2O, NaOH, H_2O-AcCN; ii: BnBr, DMF, K_2CO_3 ; iii: TPP-I_2, ImH, CH_2Cl_2, reflux, 1h; iv: TsCl, Py, 12h

Scheme 3 *S*-alkylation of L-cysteine with cis 4-iodo or *trans* 4-tosyloxy proline derivatives



i:HCl·L-Cys-OEt, DMF, Cs_2CO_3, rt, 3h; ii:HCl·L-Cys-OEt, DMF, Cs_2CO_3, 50°C, 3h

In the same way, two diastereomeric *trans*- and *cis*-4-*Se*-selenocysteinyl-L-prolines are obtained from the attack of a suitable selenocysteinyl nucleophile.

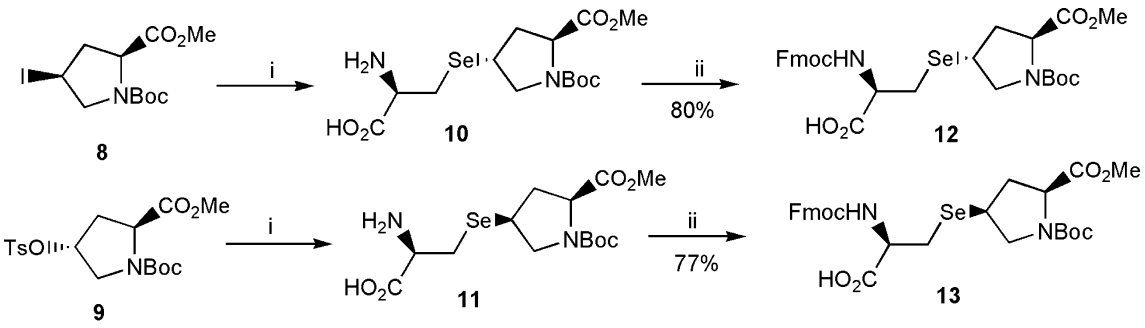
The reactions described so far are reported in detail in Schemes 2–4: commercial 4-hydroxy-L-proline (Hyp) was first converted, under standard conditions, into its corresponding *N*-Boc benzyl ester **3**. This was divided in two aliquots: one was treated with triphenylphosphine-iodine complex and imidazole, in anhydrous dichloromethane (Caputo et al. 1995b), to get the *cis*-4-iodo derivative **4**, whereas the other aliquot was treated under usual conditions with tosyl chloride in pyridine to afford the *trans*-4-tosyloxy derivative **5** (Scheme 2).

The *S*-alkylation reaction of cis iodide **4** was performed in anhydrous DMF, at room temperature, with L-cysteine ethyl ester hydrochloride (1 eq) and Cs_2CO_3 (2 eq) as the base. The substitution product, **6** (2*S*,4*R*,2′*R*), was obtained within three hours in 85% yield.

Such experimental conditions, indeed, were not satisfactory for the *S*-alkylation of *trans* tosylate **5**, likely due to the combination of both the lower leaving tendency of tosylate anion in comparison with iodide ion and the more difficult attack by the nucleophile from the same side of the carboxybenzyl group. In fact, a gentle heating of the reaction mixture at nearly 50°C for three hours enabled the formation of **7** (2*S*,4*S*,2′*R*) in 88% yield (Scheme 3).

It is noteworthy that the synthetic route we have chosen leads to both the bis-α-amino acids **6** and **7** as tri-protected forms, i.e. still having a free α-amino group. Consequently, they can be further converted into orthogonally protected derivatives (*N*-Boc, *N*-Fmoc), via ethyl ester hydrolysis and N^{α}-Fmoc protection (Bolognese et al. 2006), ready for use in solid phase peptide synthesis. Obviously, they can also be directly exploited for couplings with *N*-protected α-amino acids in solution peptide synthesis. For example the bis-α-amino acid **6** was condensed, under mixed anhydride conditions, with Boc-Val-OH and Fmoc-Phe-OH, while **7** was condensed with Boc-Pro-OH, to give the corresponding peptides in good yields.

Due to the high tendency of L-selenocysteine to undergo oxidation, the procedure reported above could not be applied as such to the synthesis of the selenium containing analogues of bis-α-amino acids **6** and **7** and had to be partially modified in order to form in situ the Se-cysteinyl anion nucleophile. Actually, commercial L-selenocystine was refluxed with $NaBH_4$ in dry EtOH, under nitrogen atmosphere (Caputo et al. 2007), to get (R)-2-amino-2-carboxyethaneselenolate anion, whose formation could be



i: L-(Sec)$_2$, EtOH, $NaBH_4$, reflux, 10'; then **8** or **9**, EtOH, reflux to r.t, 1h; ii) THF, Fmoc-Cl, DIPEA, 0° to r.t, 1h

Scheme 4 Se-alkylation of L-selenocysteine with *cis* 4-iodo or *trans* 4-tosyloxy proline derivatives

Table 1 $K_{trans/cis}$ of variously C-4 substituted prolines (^{1}H NMR, 500 MHz, CD_3OD)

Compound [subst.]	**3** [OH]	**5** [OTs]	**6** [S(Cys)]	**12** [Se(Sec)]	**4** [I]	**7** [S(Cys)]	**13** [Se(Sec)]
4(*S*)	–	–	–	–	1.51	1.52	1.26
4(*R*)	2.03	1.64	1.65	1.47	–	–	–

monitored by the disappearance of the initial intense yellow colour of the selenocystine ethanolic solution (Block et al. 2001).

At this stage, the addition of either the cis iodide **8** or the trans tosylate **9** (Scheme 4), prepared as described above from *N*-Boc-L-hydroxyproline methyl ester, followed by slow cooling of the reaction mixture to room temperature completed the coupling step and afforded the partially protected bis-α-amino acids **10** (2*S*,4*R*,2′*R*) and **11** (2*S*,4*S*,2′*R*) respectively. They were not isolated as such, but were directly converted by standard procedures into their orthogonally protected derivatives **12** in 80% yield and **13** in 77% yield, suitably protected for solid phase applications.

The use of methyl rather than benzyl ester to protect the starting hydroxyproline carboxyl group during the synthesis of the selenium containing bis-α-amino acids **12** and **13** was dictated by the simple consideration that, according to the above procedure, the selenocysteinyl residue is introduced with the free carboxyl group and, therefore, the use of benzylated proline derivatives becomes unnecessary.

The NMR spectra of the compounds described by this paper deserve some comments as to the evidences of an equilibrium between trans and cis conformations of the *N*-prolyl carbamate bond. The equilibrium constants ($K_{trans/cis}$) were evaluated for the single compounds by integrating and averaging as many distinct proton signals as possible for both the major and minor isomers in the ^{1}H NMR spectra. Their trend (Table 1) seems to reinforce the suggestion (Hodges and Raines 2005) that poorly electronegative atoms at C-4 of the proline ring lead to a reduction of the trans/cis ratio between the amide bond rotamers, although the 4(*S*) or 4(*R*) stereochemistry, as well as the hindrance, of the C-4 substituents apparently should also be considered.

In conclusion, this simple synthetic procedure may offer an extraordinary opportunity to have access to new non-natural peptides, in which two distinct peptide chains can be grown from both proline and (seleno)cysteine residues. In fact, the bis-α-amino acids **6**, **7**, **12**, and **13** can be regarded as prompt candidates to build up macromolecules containing substituted proline residues with dendrimeric architecture (Zhang and Schulter 2007). Furthermore, these new proline derivatives are currently under investigation in our lab as organocatalysts in enantioselective aldol and Michael additions, in view of the well recognized catalytic propensity of proline derivatives towards several organic reactions (List 2006; Pellisier 2007).

References

Block E, Birringer M, Jiang W, Nakaodo T, Thompson H, Toscano P, Uzar H, Zhang X, Zhu Z (2001) *Allium* chemistry: synthesis, natural occurrence, biological activity, and chemistry of *Se*-Alk(en)ylselenocysteines and their γ-glutamyl derivatives and oxidation products. J Agric Food Chem 49:458–470

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, pp 169–173

Caputo R, Cassano E, Longobardo L, Palumbo G (1995a) Chiral *N*-protected β-iodoamines from α-aminoacids: 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

Fischer G (2000) Chemical aspects of peptide bond isomerization. Chem Soc Rev 29:119–127

Halab L, Lubell W (2002) Effect of sequence on peptide geometry in 5-tert-butylprolyl type VI β-turn mimics. J Am Chem Soc 124:2474–2484

Hodges JA, Raines RT (2005) Stereoelectronic and steric effects in the collagen triple helix: toward a code for strand association. J Am Chem Soc 127:15923–15932

Kondo T, Nekado T, Sugimoto I, Ochi K, Takai S, Kinoshita A, Tajima Y, Yamamoto S, Kawabata K, Nakai H, Toda M (2007) Design and synthesis of new potent dipeptidyl peptidase IV inhibitors with enhanced ex vivo duration. Bioorg Med Chem 15:2631–2650

List B (2006) The Ying and Yang of asymmetric aminocatalysis. Chem Commun, pp 819–824

Lowe G, Vilaivan T (1997) Amino acids bearing nucleobases for the synthesis of novel peptide nucleic acids. J Chem Soc Perkin Trans 1:539–546

Lu KP, Finn G, Lee TH, Nicholson LK (2007) Prolyl *cis-trans* isomerization as a molecular timer. Nat Chem Biol 3:619–629

Pal D, Chakrabarti P (1999) *Cis* peptide bonds in proteins: residues involved, their conformations, interactions and locations. J Mol Biol 294:271–288

Pellisier H (2007) Asymmetric organocatalysis. Tetrahedron 63:9267–9331

Qiu X, Qing F (2002) Practical synthesis of boc-protected *cis*-4-trifluoromethyl and *cis*-4-difluoromethyl-L-prolines. J Org Chem 67:7162–7164

Schumacher K, Jiang J, Joulliè M (1998) Synthetic Studies toward Astins A, B and C efficient: syntheses of *cis*-3, 4-dihydroxyprolines and (-)-(3S, 4R)-dichloroproline esters. Tetrahedron Asymmetr 9:47–53

Thomas KM, Naduthambi D, Tririya G, Zondlo NJ (2005) Proline editing: a divergent strategy for the synthesis of conformationally diverse peptides. Org Lett 7:2397–2400

Zhang A, Schulter AD (2007) Multigram solution-phase synthesis of three diastereomeric tripeptidic second generation dendron based on (2S,4S)-, (2S,4R)-, and (2R,4S)-4-aminoprolines. Chem Asian J 2:1540–1548