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Stereoselective synthesis of Boc-protected L-seleno- and tellurolanthionine, L-seleno- and tellurocystine and derivatives

Alex Schneider,[a] Oscar E. D. Rodrigues,[b] Márcio W. Paixão,[c] Helmoz R. Appelt,[b] Antonio L. Braga[c] and Ludger A. Wessjohann[a,*]

[a]*Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany*
[b]*Centro Universitário Franciscano—UNIFRA, 97010-032, Santa Maria, RS, Brazil*
[c]*Departamento de Química, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brazil*

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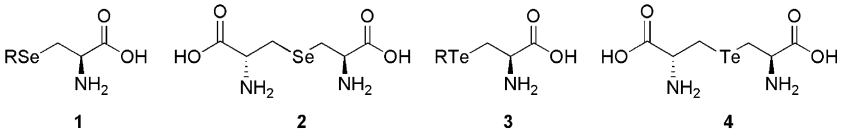
Abstract—Optically active seleno- and telluro amino acids can be synthesized from serine via its β-lactone with selenides and tellurides under overall retention of the serine stereochemistry. Boc-protected L-selenolanthionine, L-tellurolanthionine, L-selenocystine, L-tellurocystine and L-tellurocysteine derivatives can be obtained in good yields.

In biochemistry, organochalcogenides gain increasing interest beyond the obvious importance of the proteinogenic sulfur amino acids cyst(e)ine and methionine, and more recently selenocysteine.[1,2] In recent years, it was shown that various selenium and tellurium compounds can function as antioxidants, chemoprotectors, apoptosis inducers, and effective chemopreventors in a variety of organs, including brain, mammary gland, liver, skin, colon, lung, and prostate.[3–5] In comparison to sulfur compounds, the corresponding selenium analogues were more effective in cancer prevention.[6,7] Tellurium compounds were shown to be much more effective antioxidants and chemoprotectors than their corresponding selenium and sulfur analogues.[5,8]

The most important group of selenium and tellurium compounds with interesting biological properties is derived from the higher chalcogenide cysteine analogues and derivatives (Fig. 1), such as selenocysteine (Sec, U, **1** with R = H), selenocystine, selenolanthionine (**2**), and selenocysteine-*Se*-conjugates [(R)Sec, **1**]; and the analogous tellurium compounds (**3** and **4**). Especially, the latter ones are almost unexplored with respect to both synthesis and biological properties.

Selenocysteine (Sec) usually is considered the 21st natural amino acid. It is encoded in DNA and has a special function in a number of naturally occurring proteins.[2,9] Vermeulen and co-workers[10] reported that tellurocysteine Te-conjugates in particular *Te*-Phenyl-L-tellurocysteine (cf. compound **8**) might be an interesting prodrug for the formation of biologically active tellurols.

Despite the increasing importance of selenium and tellurium analogues of sulfur amino acids, very few methods are available for their production. The synthesis is complicated by facile decomposition, especially by oxidation to form, for example, higher oligochalcogenides (e.g.,



1 2 3 4

Figure 1. Chemical structures of selenocysteine **1** (Sec, U; R = H), Sec-conjugates **1** (R ≠ H), like Se-lanthionine **2**, tellurocysteine **3** (Tec, R = H) and Tec-conjugates **3** (R ≠ H), like Te-lanthionine **4**.

* Corresponding author. Tel.: +49 345 5582 1301; fax: +49 345 5582 1309; e-mail: wessjohann@ipb-halle.de

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R-(Se)$_n$-R) and Se- or Te-cystine. This constitutes problems if the unprotected form is required for further synthesis, for example, of peptides. We wanted to develop short syntheses of optically active *N*-*t*-Boc-protected L-Se- and L-Te-cystine as ready precursors to the reduced forms Sec and Tec, respectively, to Se- and Te-lanthionine, and to Sec- and Tec-conjugates, which can be deprotected on demand.

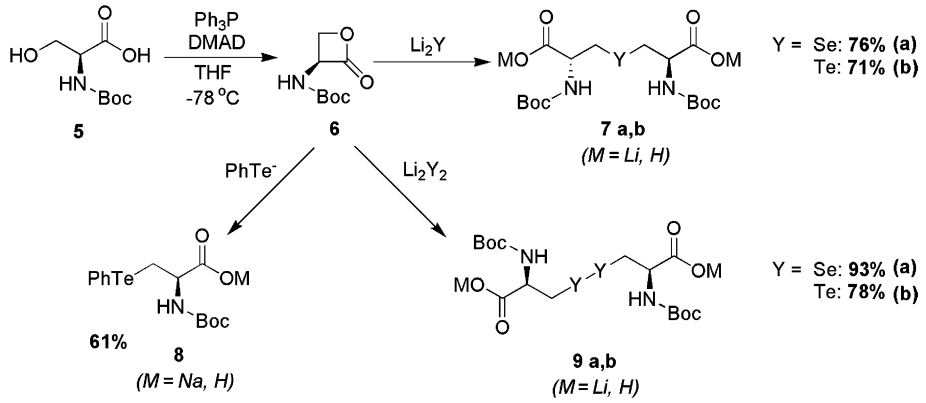
Previously reported syntheses of L-Se-cystine and -lanthionine describe an overall yield of 55% and 41%, respectively.[11] Apart from the moderate yields, the use of an excess of hydrogen selenide for the preparation of one of the starting materials (sodium hydrogen selenide) is highly impractical for labeling purposes and with respect to safety. Another synthesis of selenocysteine and tellurocysteine is based on suitably protected aziridine carboxylates,[12] or β-haloalanines.[13] For example, for the latter approach Boc-protected serine methyl ester was converted into iodoalanine methyl ester via its tosylate and reacted with lithium diselenide or lithium ditelluride to afford the protected selenocystine or tellurocystine derivatives, respectively. The overall yields of deprotected L-selenocystine and L-tellurocystine from Boc-protected serine methyl ester were 47% and 14%. Unfortunately, the yields of this multistep synthesis do not transfer to scale-up procedures. Van der Donk and co-workers[14] reported an alternative synthetic route to selenocystine and Fmoc-*Se*-phenylselenocysteine with three orthogonal protecting groups for the amino, carboxylate, and selenol function. The four-step sequence provided doubly protected Sec in 61% yield and *N*-protected (Ph)Sec in 37% overall yield on a 15 g scale.

As part of our study program of higher organochalcogenides,[15] we decided to improve the synthetic route to selenocysteine Se-conjugates and tellurocysteine Te-conjugates with respect to the number of steps and scale-up. Our synthetic strategy is based on a previously reported similar method for the generation of the unnatural amino acid (Se-phenyl)selenocysteine [(Ph)Sec] by ring opening of Boc-L-serine β-lactone **6**.[16] Vederas and co-workers reported an efficient synthesis of β-lactones under Mitsunobu conditions.[17] Both procedures produce *N*-(*t*-Boc)-β-lactone in high yield—84% from *N*-(*t*-Boc)-D-serine and 72% from *N*-(*t*-Boc)-L-serine **5**—and can be ring opened by nucleophiles to form β-substituted α-amino acids.

In order to demonstrate the wider scope of this ring opening reaction, we investigated the possibility of transforming a serine β-lactone[18] with several selenium and tellurium anions to the corresponding seleno- and tellurocysteine derivatives (Scheme 1). L-Selenolanthionine **7a** and L-tellurolanthionine **7b** are readily prepared using dilithium chalcogenides (Li_2Se and Li_2Te) available from the reaction of elemental selenium or tellurium with lithium triethyl-borohydride (super hydride).[19] Furthermore, using dilithium dichalcogenides (Li_2Se_2 and Li_2Te_2), L-selenocystine **9a** and L-tellurocystine **9b** are obtained in good yields (Scheme 1). For the preparation of tellurocysteine conjugates, for example, **8**, the monoaryl- and monoalkyl telluride anions, produced by the reduction of the corresponding ditellurides with sodium borohydride, can be employed as nucleophiles. However, non-aromatic (R)-Tec-compounds are very sensitive, especially Te-cystine and Tec itself.

Thus, the most difficult task in the whole procedure is the purification. Selenium compounds tend to contain elemental selenium or mono-, di-, or oligoselenide impurities. The non-aromatic Te compounds are air, light, base, and electrophile sensitive and decompose on prolonged exposure to silica. They can be cleaned to some extent on RP-18 or similar material. Eventually, direct crystallization of the alkaline metal salts of the telluro- and selenocysteine derivatives **7** and **9** proved best with respect to purity, at the same time giving acceptable yields. Ph-Tec-compound **8** also can be crystallized, but shows co-crystallization of diphenylditelluride. Free acids **7**–**9** (R = H) can be obtained by acidification with hydrochloric acid and rapid extraction.[20]

In summary, we have developed an efficient and versatile synthesis of optically active seleno- and telluro-derivatives of cysteine, cystine, and lanthionine from serine, using simple reactions with good yields.



Scheme 1. Yields are for crystallized compounds (M = Li or Na). Acidification to pH ≈ 2 with HCl provides free acids (R = H, limited stability).

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18. Preparation of *N*-(*tert*-butoxycarbonyl)-L-serine β-lactone (**6**): To triphenylphosphine (6.40 g, 24.4 mmol), dried in vacuo for 72 h over P_2O_5, at −78 °C in anhydrous THF (100 mL) under argon, dimethylazodicarboxylate (3.57 g, 24.4 mmol) is added dropwise over 10 min. A solution of *N*-(*tert*-butoxycarbonyl)-L-serine (5.0 g, 24.4 mmol) in THF (100 mL) is added dropwise over 30 min. The mixture is stirred at −78 °C for 20 min before it is slowly warmed to room temperature within 2.5 h. The solvent is removed in vacuo, and the residual pale yellow syrup is purified by flash column chromatography on silica (hexane/ethyl acetate, 4:1) to give *N*-(*tert*-butoxycarbonyl)-L-serine β-lactone (2.02 g, 44%), a white solid after recrystallization from (CH_3OH/hexane): $[\alpha]_D$ −24.7 (22 °C, *c* 0.5, CH_3CN); ^1H NMR ($CDCl_3$, 399.9 MHz, ppm) δ 1.46 (s, $3\times CH_3$), 4.38–4.50 (m, CH_AH_B), 5.11 (br m, CH), 5.25 (br m, NH); HRMS (ESI, MNa^+) calcd for $C_8H_{13}NO_4Na^+$ 210.0737, found 210.0738.
19. General procedure for *t*-Boc-protected L-seleno- and tellurocystine **9a**,**9b** (a), L-seleno- and tellurolanthionine **7a**,**7b** (b), and phenyltellurocysteine **8** (c) salts. (a, b): To a suspension of elemental selenium or tellurium (a—1.1 mmol, b—0.55 mmol) in freshly distilled THF (3 mL), under argon Super-hydride (1.1 mmol) is added. (c): Diphenyl ditelluride (0.55 mmol) is dissolved in 3 mL ethanol. To this $NaBH_4$ (1.38 mmol) is added. (a–c): The resulting solution is heated to reflux and stirred for 15 min under argon. At room temperature, 6 mL of dry and degassed THF solution of *N*-(*t*-Boc)-L-serine β-lactone (1 mmol) is added dropwise over 10 min and stirred overnight to ensure that the reaction is complete. The solution can be filtered through a pad of reverse phase silica gel (RP-18) in order to remove rests of elemental selenium or tellurium. The product is crystallized from chloroform/hexane. **7a**: ^1H NMR (CD_3OD, 399.9 MHz, ppm) δ 1.45 (s, $3\times CH_3$), 2.93 (dd, $J=8.1$, 12.7 Hz, CH_AH_B), 3.07 (dd, $J=4.3$, 12.7 Hz, CH_ACH_B), 4.35 (br m, CH); ^{13}C NMR (CD_3OD, 100.6 MHz, ppm) δ 27.0, 28.7, 55.6, 80.7, 157.8, 174.4; HRMS (ESI, $M-Li^-$) *m/z* calcd 455.0938, found 455.0940; **7b**: HRMS (ESI, $M-Li^-$) *m/z* calcd 505.0835, found 505.0844; **8**: ^1H NMR ($CDCl_3$, 399.9 MHz, ppm) δ 1.42 (s, $3\times CH_3$), 3.26 (dd, $J=5.8$, 12.6 Hz, CH_AH_B), 3.34 (dd, $J=5.1$, 12.6 Hz, CH_ACH_B), 4.71 (br m, CH), 5.27 (d, $J=7.3$, NH), 7.25 (br m, 3H, m, p-Ar-H), 7.79 (br m, 2H, o-Ar-H); HRMS (ESI, $M-Na^-$) *m/z* calcd 394.0304, found 394.0311; **9a**: ^1H NMR (CD_3OD, 399.9 MHz, ppm) δ 1.45 (s, $3\times CH_3$), 3.20 (dd, $J=9.1$, 12.6 Hz, CH_AH_B), 3.44 (dd, $J=4.8$, 12.6 Hz, CH_ACH_B), 4.40 (br m, CH); HRMS (ESI, $M-Li^-$) *m/z* calcd 535.0103, found 535.0110; **9b**: HRMS (ESI, $M-Li^-$) *m/z* calcd 632.9880, found 632.9881.
20. Isolation of *N*-Boc-amino acids **7b** and **9b** (M = H): To 2 mL stirred THF solution of the reaction mixture or crystallized material, 2 mL degassed water and hydrochloric acid was added dropwise to reach pH 1–2, followed by 2 mL $CHCl_3$. The immediately separated organic layer was washed under argon with 2 mL HCl-acidified degassed water, dried over $MgSO_4$, concentrated in vacuo, and immediately measured. All processes were performed rapidly and strictly under argon. **7b**: ^1H NMR (pyridine-d_5, 499.8 MHz, ppm) δ 1.51 (s, $3\times CH_3$), 3.54 (dd, $J=7.9$, 12.0 Hz, CH_AH_B), 3.72 (dd, $J=5.6$, 12.0 Hz, CH_ACH_B), 5.21 (br m, CH), 8.22 (d, $J=8.2$, NH); **9b**: ^1H NMR (pyridine-d_5, 499.8 MHz, ppm) δ 1.53 (s, $3\times CH_3$), 3.98 (dd, $J=8.5$, 11.4 Hz, CH_AH_B), 4.27 (dd, $J=6.1$, 11.4 Hz, CH_ACH_B), 5.12 (br m, CH), 8.31 (d, $J=7.6$, NH).