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Novel selenium-containing non-natural diamino acids☆

Romualdo Caputo,* Stefania Capone,† Marina Della Greca, Luigi Longobardo and Gabriella Pinto

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Via Cynthia 4, I-80126 Napoli, Italy

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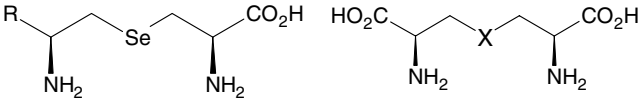
Abstract—The general synthesis of a new class of non-natural diamino acids, 2-amino-3-[(2′-aminoalkyl)seleno]propanoic acids, or Se-(aminoalkyl)selenocysteines, is reported. Under the conditions devised, enantiopure *N*-Boc-protected β-L-iodoamines, which are readily generated from proteinogenic α-amino acids, were treated with the selenolate anion obtained from $NaBH_4$ splitting of the Se–Se bond in commercial L-selenocystine. The Se-alkylation products were enantiomerically pure and the reaction is high yielding (92–98%), without any detectable traces of accompanying by-products.

Selenium is an essential micronutrient for animals and humans: to date, its bio-availability seems to depend upon the naturally occurring selenium-containing amino acids selenocysteine (Sec) and selenomethionine, although other selenoamino acids, such as Se-methylselenocysteine, selenohomocysteine and selenocystathionine, are also involved in selenoamino acid metabolic pathways.[1]

In recent years, organoselenium chemistry has emerged as an exceptional class of structures, due to its pivotal role in the synthesis of a large number of biological compounds and important therapeutic products ranging from antiviral and anticancer agents to naturally occurring food supplements.[2]

Simple organochalcogenide compounds have been reported to display antioxidant activity in vitro and in vivo. It has been suggested that the exploitation of the redox activity of selenium, as in the case of tellurium, could provide antioxidants of considerable potency, which would be suitable tools in free radical biology, as the scavengers of reactive oxidizing agents.[3]

Exciting areas of research using chiral organoselenium compounds also include catalytic asymmetric reactions to provide enantiomerically enriched compounds, representing a new trend in this field of organometallic chemistry. In this context, chiral selenide- and diselenide-containing ligands have been employed as useful catalysts in various asymmetric transformations including enantioselective addition of diethylzinc to aldehydes,[4,5] the 1,4-addition of Grignard reagents to enones,[6] and palladium-catalyzed asymmetric allylic substitution.[7]



1 **2**

a (X = S), **b** (X = Se)

Here we report the synthesis of new enantiopure non-natural diamino acids (**1**) containing selenium. They represent a new family of chalcogenide diamino acids paralleling their sulfurated analogues that we have recently reported.[8] The interest of both classes of such novel non-natural diamino acids depends essentially upon their structural similarities with natural *meso*-lanthionine (**2a**), key-residue of lanthibiotic peptides and *meso*-selenolanthionine (**2b**), respectively. Even more interesting is their inclusion in peptides[8] that performs formal 'bioconjugation' processes,[9,10] mimicking the results of the alkylation, by proteinogenic α-amino acid moieties, at the chalcogen atom of selenocysteines (Sec), or cysteines (Cys) already present in peptide

Keywords: Organoselenium; Selenolanthionine; Selenocystine; β-Iodoamines; Diamino acids.

☆ Chiral aminoalkyl cation equivalents, 2.

* Corresponding author. Tel.: +39 081 674117; fax: +39 081 674 102; e-mail: rocaputo@unina.it

† Present address: Laboratorium für Organische Chemie, ETH Zürich, HCI Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland.

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chains. An illustrative example of the use of *N*(Boc)-β-iodoamines, obtained from aspartic and glutamic acids, to alkylate a pre-existing cysteine in a solid-phase growing peptide was already reported.[11]

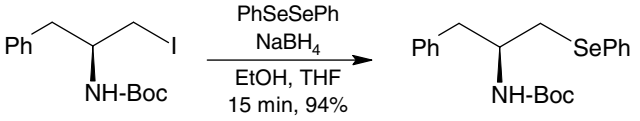
The synthesis of compounds **4a–c** (Scheme 1) was accomplished in a very simple, clean and high yielding synthetic route starting from commercial L-selenocystine and *N*(Boc)-β-L-iodoamines as Se-alkylation species. The procedure reported for the synthesis of their sulfur-containing analogues[8] could not be adapted, due to the high tendency of L-selenocysteine to undergo oxidation. Hence, L-selenocystine was refluxed with $NaBH_4$ in dry EtOH, under argon atmosphere, to produce in situ (*R*)-2-amino-2-carboxyethaneselenolate anion. The formation of the latter could be observed by the disappearance of the initial intense yellow colour of selenocystine ethanolic solution.[12] The corresponding[13,14] *N*(Boc)-β-L-iodoamine **3a–c** (obtained from Phe, Pro and Val, respectively) was then added to the solution to alkylate the anion and after refluxing the reaction mixture for a few more minutes, the Boc monoprotected selenodiamino acids **4a–c** were observed as sole products (TLC, LC–MS). Attempts to use cystine under the same conditions to prepare sulfur analogues of **4a–c** were disappointing, due to the poorest reaction yields.

Diamino acids **4a–c** were not isolated as such,[15] but were converted into N,N-protected compounds, ready for peptide coupling, bearing either a second Boc group (**5a–c**) or orthogonal Boc/Fmoc (**6a–c**) protection (Scheme 1).

We propose for any of these new chalcogen-containing diamino acids an acronym to avoid cumbersome systematic names in the current laboratory practice and in order to readily recognize their presence in peptide sequences as well. The proposed acronym is composed of 'Se' (from 'Sec') [as well as 'Cy' (from 'Cys') for the terms containing the sulfur atom] and the italicized 'one-letter code' denoting the α-amino acid whose side chain (R in formula **3** and others therefrom) is present in it. Accordingly, the selenodiamino acids reported in this Letter are shown in Table 1 with their acronyms and the whole family should be referred to as 'Se*X*' family [as well as 'Cy*X*' family for the sulfur-containing terms].

The stereochemical integrity of the final products was assessed by RP-HPLC, ^1H and ^{13}C NMR.

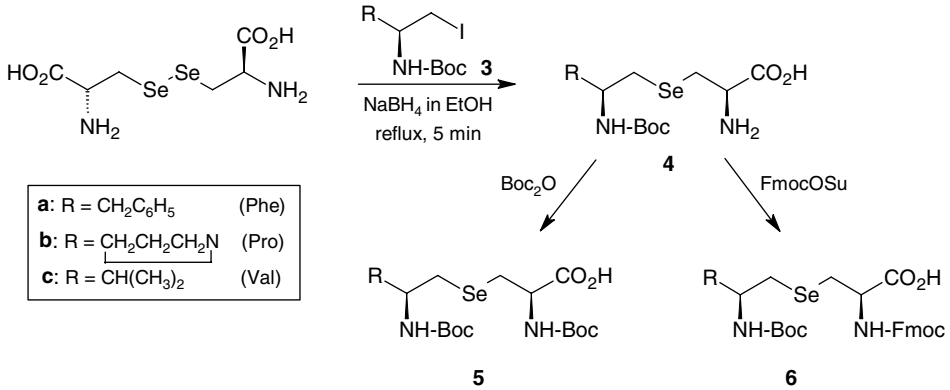
Selenium nucleophiles have been reported[16] to react with aziridines that act as chiral aminoalkyl cation equivalents. In our experience, chiral β-iodoamines appear to be strongly competitive with aziridines: as an illustrative example, we obtained almost quantitative formation of (*S*)-*tert*-butyl 1-phenyl-3-(phenylselenyl)propan-2-ylcarbamate (**7**), in only a few minutes using the protected β-iodoamine **3a**, from *N*(Boc)-L-phenylalanine, and benzeneselenolate anion generated in situ from diphenyl diselenide and $NaBH_4$ in refluxing EtOH. The same product had been reported[17] to be formed in 24 h, 72% yield, using the same benzeneselenolate anion and *N*(Boc)-aziridine from *N*(Boc)-L-phenylalanine.



3a **7**

In conclusion, these new, non-natural selenylated diamino acids can be obtained enantiopure, in good yields and if required, in orthogonally protected forms ready for insertion into peptide sequences. The synthesis is very simple and the starting materials are generally inexpensive and easily accessible as well. All the mentioned observations highlight the synthetic value of the enantiomerically pure *N*(Boc)-β-iodoamines as aminoalkyl cation equivalents.

It is also worth noting that the lysine-like configuration of our diamino acids, associated with a proteinogenic side chain, prompts their exploitation as branching diamino acids to build up chalcogen-containing peptide-bond based new dendrimeric structures. Work is already in progress in our lab to produce enzyme-mimicking dendrimeric scaffolds including proteinogenic α-amino



Scheme 1. Synthesis of N,N-protected Se*X* diamino acids from L-selenocystine and β-L-iodoamines.

Table 1. New N,N-protected Se*X* diamino acids

N(Boc)-β-L-Iodoamine	Se*X* diamino acid		Yield[a] (%)	Mp (°C)	$[\alpha]_D^{25}$ ($CHCl_3$)
3a	Boc–Se*F*(Boc)–OH	(**5a**)	98	132–133	45.1
3a	Fmoc–Se*F*(Boc)–OH	(**6a**)	95	138–139	40.2
3b	Boc–Se*P*(Boc)–OH	(**5b**)	92	Foam	23.8
3b	Fmoc–Se*P*(Boc)–OH	(**6b**)	94	97–98	31.3
3c	Boc–Se*V*(Boc)–OH	(**5c**)	97	Foam	35.7
3c	Fmoc–Se*V*(Boc)–OH	(**6c**)	95	88–89	38.5

[a] Yield of diprotected selenodiamino acid, referred to the starting β-iodoamine.

acids, such as Ser, His and Asp, that are commonly involved in the enzymatic active sites.[18]

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15. Commercial L-selenocystine (0.3 g, 1 mmol) was suspended in anhydrous EtOH (10 mL) under argon atmosphere. Solid $NaBH_4$ (0.2 g, 5 mmol) was added in one portion and the mixture refluxed for 5 min, until clear and colourless. *tert*-Butyl (*S*)-1-iodo-3-methylbutan-2-ylcarbamate **3c** (0.6 g, 2 mmol) dissolved in anhydrous THF (4 mL) was then added. After 10 min under reflux, the reaction mixture was cooled to room temperature and split in two portions. The first one, after evaporation of the solvents under vacuum, was redissolved in THF (10 mL) and treated with FmocOSu (0.3 g, 1 mmol) under standard conditions to afford eventually (*R*)-2-{[(9*H*-fluoren-9-yl)-methoxy]carbonylamino}-3-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutylselenyl]propanoic acid, Fmoc–Se*V*(Boc)–OH (**6c**), (96%). An analytical sample: mp 88–89 °C (from CH_2Cl_2–hexane), $[\alpha]_D^{25}$ +38.5 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, CD_3OD, *J* in Hz): $\delta = 0.87$ (d, 3H, $J = 6.8$), 0.90 (d, 3H, $J = 6.8$), 1.44, (s, 9H), 1.77 (dq, 1H, $J = 6.8$), 2.67 (dd, 1H, $J = 9.3$ and 12.2), 2.82 (dd, 1H, $J = 4.4$ and 12.2), 2.97 (dd, 1H, $J = 7.8$ and 12.7), 3.03 (dd, 1H, $J = 4.9$ and 12.7), 3.50 (m, 1H), 4.25 (t, 1H, $J = 6.8$), 4.34 (m, 2H), 4.44 (m, 1H), 7.31 (t, 2H, $J = 7.8$), 7.39 (t, 2H, $J = 7.8$), 7.69 (d, 2H, $J = 7.8$), 7.79 (d, 2H, $J = 7.8$); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 18.8$, 20.5, 27.0, 29.3, 29.9, 33.9, 48.7, 56.3, 58.0, 68.7, 80.4, 121.4, 126.8, 128.6, 129.3, 142.9, 145.6, 158.8, 174.6. HR-MS (EI): calcd for $C_{28}H_{36}N_2O_6Se$ [M+H$^+$] 576.5626, found 576.5630.
    The second portion, after evaporation of the solvents under vacuum, was also redissolved in THF (10 mL) and treated with Boc_2O (0.2 g, 1 mmol) under standard conditions to afford (*R*)-2-(*tert*-butoxycarbonylamino)-3-[(*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutylselenyl]propanoic acid, Boc–Se*V*(Boc)–OH (**5c**) (97%). An analytical sample: foam, $[\alpha]_D^{25}$ +35.7 (*c* 1.6, $CHCl_3$). ^1H NMR (500 MHz, CD_3OD, *J* in Hz): $\delta = 0.89$ (d, 3H, $J = 6.8$), 0.92 (d, 3H, $J = 6.8$), 1.45 (s, 18H), 1.78 (dq, 1H, $J = 6.8$), 2.65 (dd, 1H, $J = 12.7$ and 8.9), 2.83 (dd, 1H, $J = 12.7$ and 3.9), 2.93 (dd, 1H, $J = 12.7$ and 6.8), 3.0 (dd, 1H, $J = 12.7$ and 4.9), 3.50 (m, 1H), 4.37 (br t, 1H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 18.7$, 20.5, 27.1, 29.3, 29.7, 34.0, 58.5, 80.3, 81.2, 158.2, 158.9, 174.5. HR-MS (EI): calcd for $C_{18}H_{34}N_2O_6Se$ [M+H$^+$] 454.4397, found 454.4402.
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17. Mp 81–82 °C (from Et_2O–hexane), $[\alpha]_D^{25}$ 15.5 (*c* 1.0, CH_2Cl_2); lit.[16] ^1H NMR spectrum consistent with the structure; mp 80.7–81.3 °C, $[\alpha]_D^{25}$ 14.
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