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Efficient Synthesis of Modular Amino Acid Derivatives Containing Selenium with Pronounced GPx-Like Activity

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New chiral selenide- and diselenide amino acid derivatives have been synthesized. By a simple and efficient two-step route, these new compounds were obtained from inexpensive and commercially available L-amino acids. The products, with a highly modular character, were obtained in good to excellent yields. Selected examples were also efficiently used as GPx mimics, catalyzing the reduction of H_2O_2 to water at the expense of PhSH.

Introduction

The interest in organochalcogen compounds has been growing since the 1970s, when many reports described the identification of various selenoproteins, which are involved in a wide number of mammals' biochemistry mechanisms.[1] Synthetic developments and the design of new organoselenium compounds have been attracting considerable attention,[2] especially because these compounds have the capacity to mimic natural compounds with important biological proprieties (e.g., antioxidant, antitumor, anti-inflammatory, and anti-infective activity).[3] One of the most impacting studies determined that selenium plays a pivotal role in glutathione peroxidase enzymes (GPx), which protect organisms from oxidative stress, inherent from oxygen metabolism.[4] More important, selenium is considered an essential trace element,[5] and it is appointed as an important agent in cancer prevention, immunology, aging, male reproduction, neurodegenerative diseases, including Alzheimer's and Parkinson's disease, and other physiological processes.[6]

Selenium-based methods have developed rapidly over the past years and have become a useful tool in the hands of organic chemists.[7] Organoselenium compounds have found such wide utility because of their effects on an extraordinary number of different reactions, including carbon–carbon bond formation, under relatively mild reaction conditions.[8] Moreover, chiral selenide- and diselenide-containing ligands offer attractive and practical options in the development of asymmetric transformations.[9]

As part of our growing interest in amino acid derivatives containing chalcogens, as chiral building blocks in organic synthesis[10] or for biological screenings,[11] and in connection with the increasing importance of the synthesis of small libraries of compounds with programmed variations of substituents, we describe herein an easy, inexpensive, and two-step synthetic route for the preparation of a series of chiral amino acid derivatives containing selenium. Our approach allows a modular construction, affording the products in a short synthetic route in good to excellent yields, avoiding the use of protecting group chemistry. Some of these new compounds were also efficiently used as GPx mimics, catalyzing the reduction of H_2O_2 to water at the expense of PhSH.

Results and Discussion

According to our aim, initially we promoted the synthesis of key chiral bromo amides **2a**–**h**. The treatment of bromo carboxylic acids with *N*-methylmorpholine (NMM) and ethyl chloroformate produced the mixed anhydride in situ,[12] which was then treated with L-amino esters and another equivalent of NMM to form the amide bond in good yields under very mild conditions (Scheme 1). A series of compounds was synthesized through variation of the amino acid residues and the chain length between the bromide atom and the amino ester moiety.

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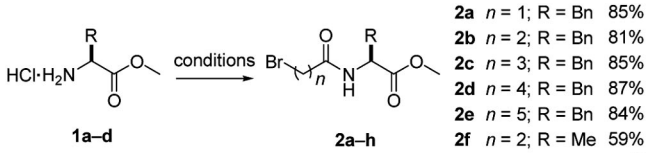


Scheme 1. Conditions: bromo carboxylic acid (1 mmol), NMM (1 mmol), ethyl chloroformate (1 mmol), L-amino ester (1 mmol), NMM (1 mmol), $CHCl_3$ (5 mL).

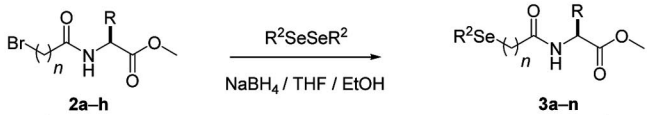
With the bromo amides in hands we promoted the insertion of the organochalcogen moiety, through the nucleophilic attack of selenium anions generated by reaction of diselenides with $NaBH_4$ in a mixture of THF and ethanol (Table 1).

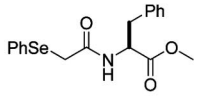
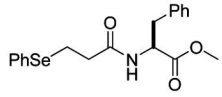
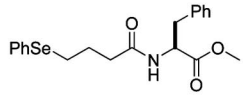
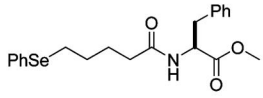
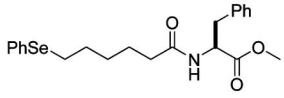
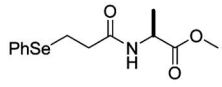
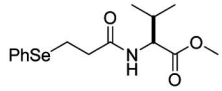
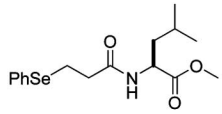
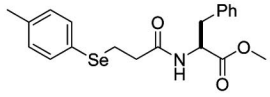
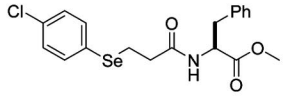
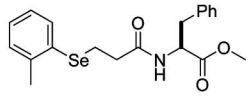
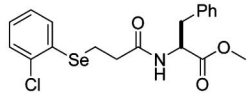
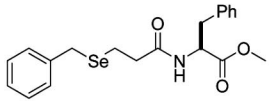
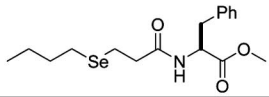
The target compounds were obtained in good to excellent yields; compound **3a** was achieved in 92% yield (Table 1, Entry 1). When the chain length between the bromide atom and the amino ester moiety was increased, the yield of compound **3e** was still high, but a slight decrease in comparison to that of **3a**–**d** was observed (Table 1, Entry 5). The change of the amino acid residue did not produce a pronounced effect on the yield of the products (Table 1, Entries 6–8). At this point, we turned our attention to check if steric and electronic diversity in the aryl moiety attached to selenium would promote some changes in the yield of the given products (Table 1, Entries 9–12). We found that electronic effects did not display an important role in the formation of the products. Compounds **3i** with methyl and **3j** with chlorine attached in the *para* position of the benzyl ring showed almost the same results (Table 1, Entries 9 and 10). In contrast, when we employed these same substituents, but in the *ortho* position, the yields were drastically lower (Table 1, Entries 11 and 12). We also used dibenzyl and dibutyl diselenides as selenium sources, producing compounds **3m** and **3n** in good yields (Table 1, Entries 13 and 14).

One of the major advantages of this developed strategy is its modular construction, where modifications in the structure of the products can be easily introduced. In this way, and as a further extension of the present methodology, we attempted the synthesis of diselenides **4a**–**h** (Table 2). Bromo amides **2a**–**h** were added to a THF solution of Li_2Se_2, affording diselenides **4a**–**h** in good yields. The yields of the diselenide series from L-phenylalanine derivatives were not affected by the increase in the carbon chain length. Diselenides **4a**–**e** were produced with yields from 55 to 76% (Table 2, Entries 1–5). Diselenides with other amino acid residues were also prepared, affording the desired products in good yields (Table 2, Entries 6–8).

Recently we developed a series of telluro amino acid derivatives with remarkable GPx-like activity.[13] Although the telluro analogues showed high catalytic activity (T_{50} about 2 min), the selenide ones were not able to promote the reduction of H_2O_2 at an appreciable rate. Encouraged by the well-known ability of diselenides to act as GPx mimics,[14] we selected diselenides **4a**–**c** to evaluate their GPx like ac-

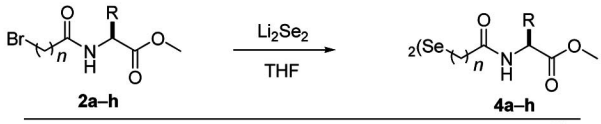
Table 1. Synthesis of selenides **3a**–**n**.

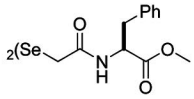
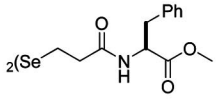
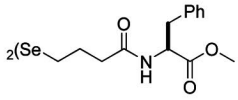
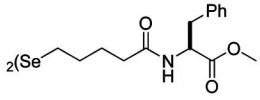
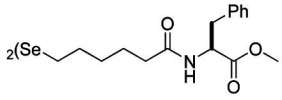
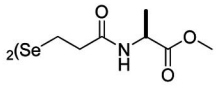
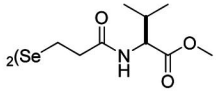
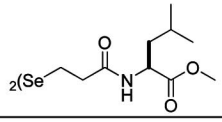


Entry	R	Product		Yield[a] [%]
1	Bn		**3a**	92
2	Bn		**3b**	89
3	Bn		**3c**	81
4	Bn		**3d**	78
5	Bn		**3e**	75
6	Me		**3f**	75
7	*i*Pr		**3g**	88
8	*i*Bu		**3h**	69
9	Bn		**3i**	84
10	Bn		**3j**	82
11	Bn		**3k**	54
12	Bn		**3l**	59
13	Bn		**3m**	63
14	Bn		**3n**	65

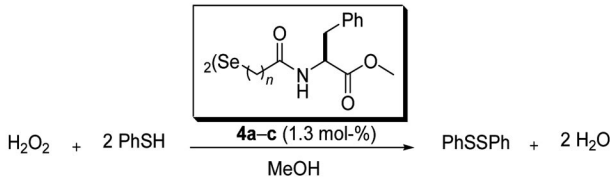
[a] Isolated yields.

Table 2. Synthesis of diselenides **4a**–**h**.



Entry	R	Product		Yield[a] [%]
1	Bn		**4a**	69
2	Bn		**4b**	73
3	Bn		**4c**	59
4	Bn		**4d**	55
5	Bn		**4e**	76
6	Me		**4f**	50
7	*i*Pr		**4g**	63
8	*i*Bu		**4h**	52

[a] Isolated yields.



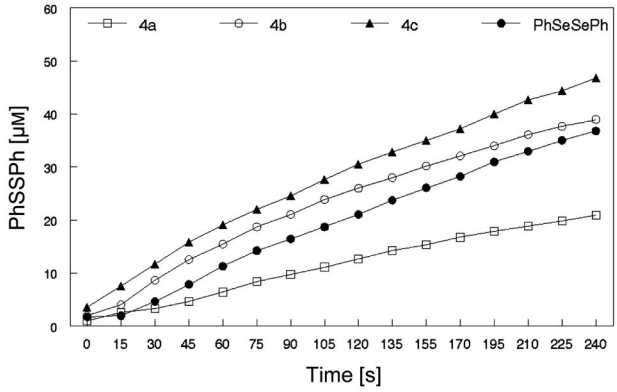


Figure 1. GPx-like behavior of catalysts **4a**–**c**.

Table 3. T_{50} values of catalysts **4a**–**b** and PhSeSePh.

Catalyst[a,b]	T_{50} [min][c]
4a	93.03 (±5.77)[d]
4b	51.38 (±2.45)[d]
4c	45.15 (±3.17)[d]
PhSeSePh	51.80 (±2.83)[d]

[a] Under these conditions, addition of H_2O_2 in the absence of catalyst did not produce any significant oxidation of PhSH. [b] MeOH (1 mL), catalyst (0.025 mM), PhSH (1.9 mM), H_2O_2 (8.8 mM). [c] T_{50} is the time required, in minutes, to reduce the thiol concentration to 50% after the addition of H_2O_2. [d] The experimental error is given in parentheses.

tivity as a preview study. We also used PhSeSePh under the same conditions to compare the results. The catalytic behavior of these compounds, as GPx model enzymes, was tested according to the Tomoda method, using benzenethiol as a glutathione alternative.[15] The reduction of H_2O_2 was monitored through the UV absorption increase at 305 nm, resulting from diphenyl disulfide formation. Linear increases in absorbance were observed by mixing MeOH, PhSeSePh or catalysts **4a**–**c** (1.3 mol-%), PhSH, and H_2O_2 (Figure 1).

Taking advantage of the modular characteristic of our catalysts, we evaluated the influence of the chain length between the diselenide moiety and the amino acid residue in the reduction of hydrogen peroxide. Compounds **4c** and **4b** derived from L-phenylalanine with longer chain length showed better results than PhSeSePh (T_{50} = 45.15 min and 51.38 min, respectively; Table 3). Compound **4a**, with a shorter chain length, was the least effective catalyst in this screening (T_{50} = 93.03 min).

Conclusions

In summary, we have described the synthesis of a new class of chiral selenide- and diselenide amino acid derivatives. These compounds were prepared by a concise and flexible synthetic route in good to excellent yields, which permitted the preparation of a wide range of compounds with a highly modular character. Indeed, we have tested some of these diselenides as GPx mimics, catalyzing the reduction of H_2O_2 to water at the expense of thiophenol by using just 1.3 mol-% of catalyst. Diselenide **4c** considerably accelerated the reaction exhibiting a T_{50} value of 45.15 min, whereas only a marginal accelerating effect was observed for the already known GPx mimic PhSeSePh, which showed a T_{50} of value 51.80 min. Biological screenings of these new selenium amino acid derivatives are currently under investigation in our laboratory.

Supporting Information (see footnote on the first page of this article): General experimental procedures and ^1H and ^{13}C NMR spectra of selected compounds.

Acknowledgments

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