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Straightforward synthesis of non-natural L-chalcogen and L-diselenide *N*-Boc-protected-γ-amino acid derivatives†

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The synthesis of new chiral seleno-, telluro-, and thio-*N*-Boc-γ-amino acids is described herein. These new compounds were prepared through a simple and short synthetic route, from the inexpensive and commercially-available amino acid L-glutamic acid. The products, with a highly modular character, were obtained in good to excellent yields, *via* hydrolysis of chalcogen pyroglutamic derivatives with overall retention of the L-glutamic acid stereochemistry. Also, an L-diselenide-*N*-Boc-γ-amino acid was prepared in good yield. This new synthetic route represents an efficient method for preparing new L-chalcogen- and L-diselenide-γ-amino acids with biological potential.

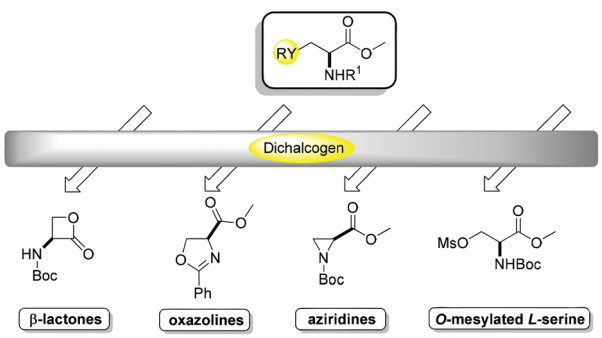
Introduction

Since the discovery of the biological importance of selenium as one of the essential trace elements,[1] organochalcogen compounds have emerged as an exceptional class of structures that exemplify the role of Se in biochemical processes, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements.[2]

In addition, research on amino acids has gained enormous popularity and relevance in recent years, particularly with the emergence of unnatural analogs as components of molecules with therapeutic potential.[3] The most important group of selenium and tellurium compounds with interesting biological properties is derived from the chalcogen cysteine analogues and their derivatives, such as selenocysteine, selenomethionine and the analogous tellurium compounds. Many selenoenzymes have a selenocysteine residue at the active site as a catalyst for various redox reactions.[4] Perhaps the most important of these are glutathione peroxidase (GPx) and thioredoxin reductase (TrxR).[5] It is known that the selenium atom plays a key role in the mode of action of such proteins, which cannot be played by its closest relative, sulfur.[6]

Despite the increasing importance of selenium and tellurium analogues of sulfur amino acids and even though a number of efficient synthetic methods for the synthesis of selenocysteine derivatives have been developed, the introduction of a chalcogen atom into an amino acid remains a significant challenge.[7] In this context, in recent years our group has been working intensively towards the development of protocols to prepare chalcogen α-amino acids, through the ring opening of chiral systems[8] and through the *O*-mesylated L-serine intermediate generated *in situ* and directly substituted with various selenolate anions (Scheme 1).[9]

Although the synthesis of chiral chalcogen amino acids has been successfully accomplished, all procedures reported are restricted to the synthesis of chalcogen α-amino acids. Over the past few years, pyroglutamic acid (also known as



Scheme 1 Retrosynthesis of chalcogen α-amino acid derivatives.

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†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c3ob40879e

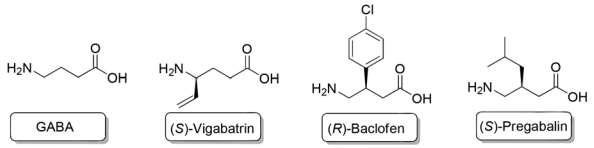


Fig. 1 Examples of important γ-amino acids.

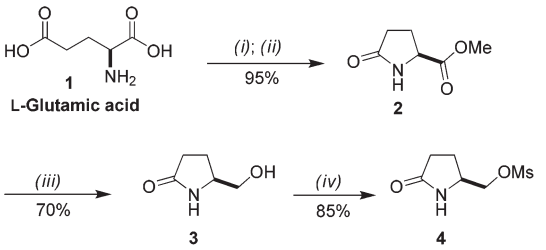
5-oxo-proline)[10] derived from glutamic acid has been the focus of attention as a chiral building block.[11] This has been used as an important starting material for the synthesis of many natural products[12] and for γ-amino acids, easily prepared by hydrolysis under acidic or basic conditions.[13] In this context γ-amino acids have attracted considerable attention as biologically active compounds. γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system of mammals.[14] GABA deficiency is also associated with several important neurological disorders, such as Huntington's and Parkinson's disease, epilepsy, other psychiatric disorders (*e.g.*, anxiety) and pain.[15] Many other γ-amino acids have been the focus of attention due to their biological activity, including 4-amino-5-hexenoic acid (Vigabatrin®), 4-amino-3-(*p*-chlorophenyl)butyric acid (Baclofen) and (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabalin) (Fig. 1).

Stimulated by our recent work on the synthesis of chiral selenium-containing non-natural amino acids[8,9] and peptides,[8e,16] selenium- and tellurium-nucleosides[17] and, more recently, chiral selenium- and telluro-amino acids[18] and organoselenides and diselenides[19] which possess strong glutathione peroxidase-like (GPx-like) activity, we describe herein an efficient and straightforward synthetic route for the preparation of novel chiral chalcogen and diselenide γ-amino acids through the hydrolysis of γ-lactam compounds with a chalcogen atom incorporated into their structures, prepared from L-glutamic acid.

Results and discussion

In keeping with our aim, as the starting point of this study we sought an efficient way to prepare the key chiral mesylate γ-lactam **4** in a short and high yielding sequence. To accomplish this task we used a methodology previously described in the literature,[20] where L-glutamic acid **1** is converted to pyroglutamic acid by heating with H_2O, followed by esterification, in the presence of MeOH and $SOCl_2$ to afford the corresponding pyroglutamic methyl ester **2** in 95% yield. Subsequent reduction with $NaBH_4$ in EtOH led to alcohol **3** in 70% yield.[21] The reaction of the primary hydroxyl group with methanesulfonyl chloride in CH_2Cl_2 using triethylamine as a base delivered the desired mesylate **4** in 85% yield[22] (Scheme 2).

With the required mesylate **4** in hand we turned our attention to the introduction of the organoselenium moiety in the γ-lactam backbone through the nucleophilic substitution of



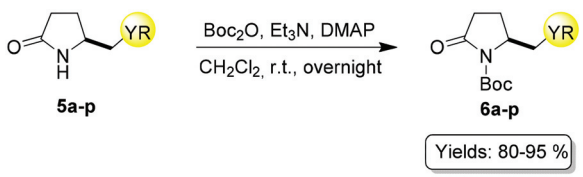
Scheme 2 Synthesis of mesylate γ-lactam **4**. Reagents and conditions: (i) H_2O, reflux, 63 h; (ii) MeOH, $SOCl_2$, room temp., 48 h; (iii) $NaBH_4$, EtOH, room temp., 2 h; (iv) Et_3N, MsCl, CH_2Cl_2, 0 °C, 3 h.

the OMs leaving group (Table 1). Organoselenium anions were generated through the reaction of diphenyl diselenide with $NaBH_4$ in a mixture of THF and ethanol, as previously described.[23] Under these conditions, mesylate **4** was cleanly converted to seleno-γ-lactam and the product was isolated in 80% yield (Table 1, entry 1). Next, we extended our studies to a broader range of selenium nucleophiles, in order to prepare a small library of compounds. The reaction was tolerant to a variety of substituents at the aromatic ring of the organoselenium moiety, allowing the preparation of a series of seleno-γ-lactams. It can be verified that the reaction was not influenced by electronic or steric effects (Table 1, entries 2–4). Aliphatic diselenides were also used as a selenium source, with Bn and Et as R groups, and the compounds were obtained in good yields showing the versatility of the protocol in terms of the selenium moiety (Table 1, entries 7 and 8). It is noteworthy that all reactions proceeded smoothly, with very low by-product formation.

Due to the success achieved in the preparation of a wide range of chiral seleno-γ-lactams, we decided to extend our studies to thio and telluro analogues, in order to prepare a series of chalcogen-γ-lactam derivatives. In fact, the reduction of diorganyl ditelluride or diorganyl disulfide with $NaBH_4$, followed by reaction with **4**, delivered the corresponding telluro-γ-lactams **5i** and **5j** and thio-γ-lactams **5l–5p** in good yields (Table 1, entries 9–15).

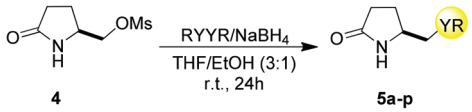
Following the protocol previously reported,[24] the compounds **5a–p** were protected with Boc_2O, in the presence of triethylamine and 4-dimethylaminopyridine in CH_2Cl_2, to afford the L-chalcogen-*N*-Boc-γ-lactams **6a–p** in excellent yields (Scheme 3). This protection is necessary in order to render the "amide" carbonyl more susceptible to nucleophilic attack under mild conditions.[25]

With the L-chalcogen-*N*-Boc-γ-lactams (**6a–p**) in hand, we turned our attention to performing the hydrolysis under basic

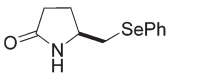
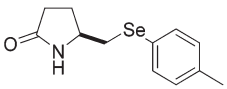
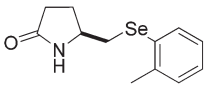
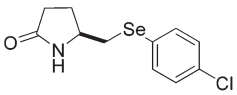
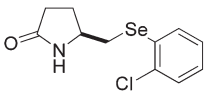
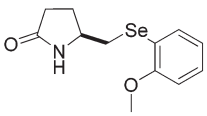
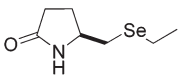
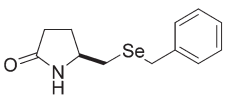
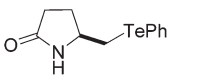
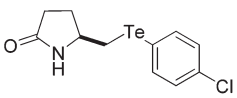
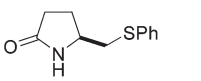
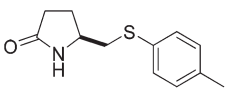
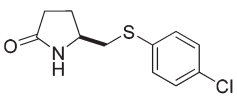
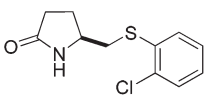
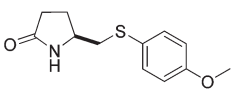


Scheme 3 Synthesis of L-chalcogen-*N*-Boc-γ-lactams **6a–p**.

Table 1 Synthesis of selenium-, telluro- and thio-γ-lactams[a]



4 5a-p

Entry	RYYR	Product		Yield[b] (%)
1	$(PhSe)_2$		**5a**	80
2	$(4\text{-}MePhSe)_2$		**5b**	77
3	$(2\text{-}MePhSe)_2$		**5c**	80
4	$(4\text{-}ClPhSe)_2$		**5d**	75
5	$(2\text{-}ClPhSe)_2$		**5e**	80
6	$(2\text{-}MeOPhSe)_2$		**5f**	78
7	$(EtSe)_2$		**5g**	70
8	$(BnSe)_2$		**5h**	71
9	$(PhTe)_2$		**5i**	75
10	$(4\text{-}ClPhTe)_2$		**5j**	73
11	$(PhS)_2$		**5l**	75
12	$(4\text{-}MePhS)_2$		**5m**	77
13	$(4\text{-}ClPhS)_2$		**5n**	69
14	$(2\text{-}ClPhS)_2$		**5o**	78
15	$(4\text{-}MeOPhS)_2$		**5p**	62

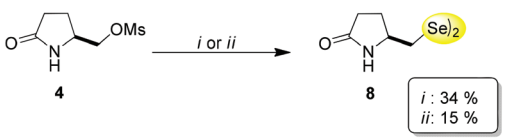
[a] Reactions were performed in the presence of mesylate **4** (2.2 mmol), diorganyl dichalcogenide (1.1 mmol) and THF–EtOH (3 : 1) at room temperature under an argon atmosphere overnight. [b] Isolated yields.

conditions[26] in order to prepare a small library of L-chalcogen-*N*-Boc-γ-amino acids (Table 2).

As summarized in Table 2, a series of L-chalcogen-*N*-Boc-γ-amino acids were obtained in moderate to good yields. It can be observed that steric effects exerted some influence during the hydrolysis. Substituents attached to the *para*-position of seleno-*N*-Boc-γ-lactams furnished better yields (Table 2, entries 2 and 4) than the same substituents in the *ortho* position (entries 3 and 5). On the other hand, electron-donating (Table 2, entries 2, 3 and 6) and electron-withdrawing (entries 4 and 5) groups attached to the aromatic ring did not display any influence on the yield. Additionally, aliphatic groups attached to the selenium-γ-lactams showed good results. For instance, the benzyl group furnished the product **7h** in good yield (Table 2, entry 8), whereas the ethyl group attached to selenium afforded the product **7g** in moderate yield (entry 7). Moreover, the hydrolysis reaction of telluro- and thio-*N*-Boc-γ-lactams provided the corresponding *N*-Boc-γ-amino acids **7i–p** in good to excellent yields (Table 2, entries 9–15).

Encouraged by the success in the synthesis of L-chalcogen-*N*-Boc-γ-amino acids we decided to synthesize an L-diselenide-*N*-Boc-γ-amino acid **12**. To accomplish this task, we took advantage of our previous strategy for the synthesis of chiral β-amino diselenides, which employs the nucleophilic ring opening of *N*-Boc aziridines with lithium diselenide.[27] The treatment of mesylate γ-lactam **4** with lithium diselenide, which is readily accessible through the addition of appropriate amounts of Super Hydride (1 M solution in THF) to powdered gray selenium, afforded the product in unacceptably low yield (34%) with a complex mixture of by-products (Scheme 4). This result prompted us to look for an alternative approach to achieve our aim. It is reported in the literature that the formation of diselenides *via* the cross-coupling of aryl and alkyl iodides with elemental selenium, under basic conditions using copper oxide as a catalyst in DMSO, can be accomplished efficiently in high yield.[28] However, with this approach, the diselenide-γ-lactam **8** was prepared in only 15% yield and the results are summarized in Scheme 4. Although the yield obtained in this reaction was lower compared to that obtained using lithium diselenide, the product was easily isolated after purification.

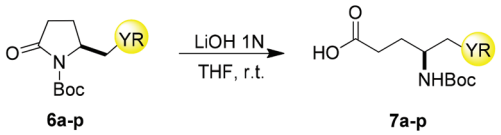
In an alternative approach, we decided to change the leaving group in the side-chain of γ-lactam **4** to a tosyl group *via* treatment of the aminoalcohol **3** with *p*-toluenesulfonyl chloride in the presence of triethylamine and using 4-dimethylaminopyridine as a catalyst, providing the corresponding



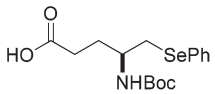
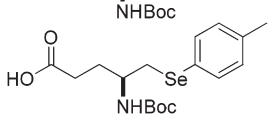
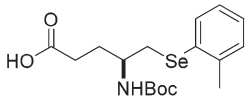
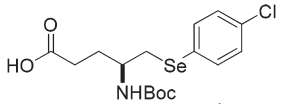
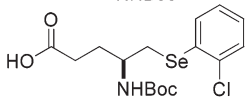
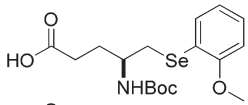
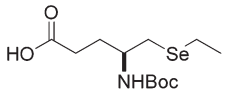
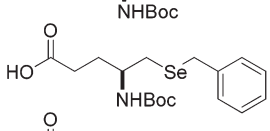
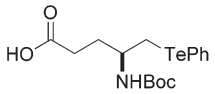
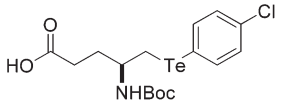
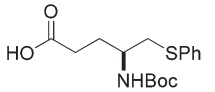
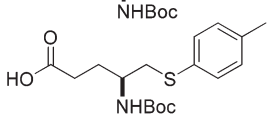
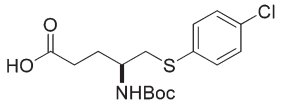
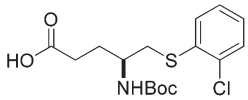
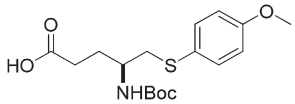
4 8

Scheme 4 Synthesis of L-diselenide-γ-lactam **8**. Reagents and conditions: (i) Se^0, $LiEt_3BH$, THF, reflux, 30 min, this solution was then added dropwise to mesylate γ-lactam **4** under −78 °C, room temp., 12 h, (ii) Se^0, 20 mol% CuO, KOH, DMSO, 90 °C, 24 h.

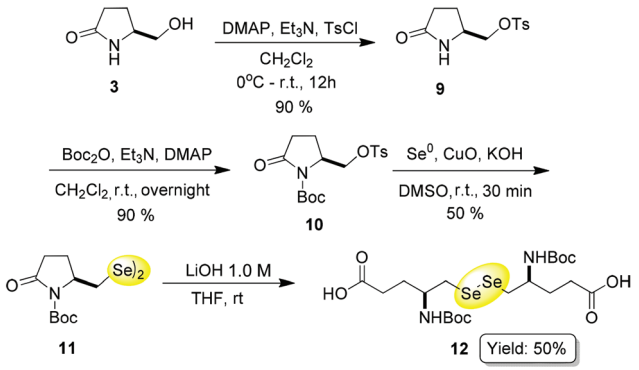
Table 2 Synthesis of L-chalcogen-*N*-Boc-γ-amino acids **7a–p**[a]



6a-p **7a-p**

Entry	Product		Yield[b] (%)
1		**7a**	70
2		**7b**	80
3		**7c**	70
4		**7d**	75
5		**7e**	50
6		**7f**	80
7		**7g**	55
8		**7h**	78
9		**7i**	72
10		**7j**	80
11		**7l**	60
12		**7m**	98
13		**7n**	84
14		**7o**	84
15		**7p**	93

[a] Reactions were performed in the presence of L-chalcogen-*N*-Boc-γ-lactams (1.0 mmol), THF (3.0 mL) and a 1.0 M solution of LiOH at room temperature. [b] Isolated yields.



Scheme 5 Synthesis of L-diselenide-*N*-Boc-γ-amino acid **12**.

tosylate **9** in 90% yield, as depicted in Scheme 5.[29] Subsequent protection with di-*tert*-butyl dicarbonate afforded the tosylate *N*-Boc-γ-lactam **10** in good yield.[30] Treatment of tosylate *N*-Boc-γ-lactam with elemental selenium under basic conditions, using 20 mol% of copper oxide as a catalyst, in DMSO, furnished the diselenide **11** in moderate 50% yield. Finally, treatment of L-diselenide-*N*-Boc-γ-lactam with LiOH 1 N and THF at room temperature afforded L-diselenide-*N*-Boc-γ-amino acid **12** in 50% yield.

Conclusions

In summary, we have described herein the preparation of a new class of chiral selenium-, telluro-, and thio-*N*-Boc-γ-amino acid derivatives from L-glutamic acid. These compounds were prepared *via* a concise and flexible route, in good to excellent yields, which permitted the preparation of a wide range of compounds with a highly modular character. Additionally, the method was easily adapted to the synthesis of L-diselenide-*N*-Boc-γ-amino acid.

We also emphasize that this modular approach may have significant importance in the design of new L-chalcogen and L-diselenide *N*-Boc-γ-amino acid compounds for biological screening.

Experimental section

General

Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a Bruker DPX-400 MHz or DPX-200 MHz spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million, referenced to the solvent peak of TMS. Data are reported as follows: chemical shift (d), multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet), and coupling constant (*J*) in hertz and integrated intensity. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained at 50 MHz or 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. High-resolution mass spectra (ESI) were

obtained at the Institute of Plant Biochemistry, Halle-Saale, Germany, using a Bruker BioApex 70 eV spectrometer. Optical rotations were carried out on a Perkin Elmer Polarimeter 341. Column chromatography was performed using Merck Silica Gel (230–400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. Anhydrous solvents were obtained as follows: THF was distilled from sodium and benzophenone. Dichloromethane and triethylamine were distilled from CaH_2. All other solvents were used as purchased. CuO nanoparticles (the mean particle size, 33 nm, surface area, 29 $m^2\ g^{-1}$ and purity of 99.99%) were purchased from Sigma Aldrich. The pyroglutamic methyl ester[20] **2**, the corresponding amino alcohol[21] **3**, mesylate γ-lactam[22] **4**, tosylate γ-lactam[29] **9** and tosylate *N*-Boc-γ-lactam[30] **10** have been previously prepared and characterized.

General procedure for the synthesis of L-chalcogen-γ-lactams derivatives 5a–p

Under an argon atmosphere, $NaBH_4$ (0.09 g, 2.5 mmol) was added to a solution of diorganyl dichalcogenide (0.34 g, 1.1 mmol) in THF (3.3 mL) at room temperature. Ethanol (1.1 mL) was added dropwise and the mixture was stirred for 10 minutes. After this time a solution of mesylate γ-lactam **4** in THF (3.0 mL) was added, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with 10 mL of a NH_4Cl solution, and the aqueous layer was extracted with CH_2Cl_2 (3.0 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude products were purified in a silica gel column for chromatographic purification, using hexane–ethyl acetate (10 : 90) as the eluent.

(*S*)-5-(Phenylselanylmethyl)pyrrolidin-2-one (5a). Yellow oil. Yield: 80%; $[\alpha]_D^{20}$ = +73 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 2 H), 7.28–7.27 (m, 3 H), 6.79 (br, 1 H), 3.83–3.76 (m, 1 H), 3.01 (dd, 1 H, J^1 = 12.8 Hz, J^2 = 6 Hz), 2.91 (dd, 1 H, J^1 = 12.8 Hz, J^2 = 7.6 Hz), 2.44–2.26 (m, 3 H), 1.85–1.76 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.75, 133.33, 129.21, 128.62, 127.50, 53.93, 34.10, 30.18, 27.14 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{13}NOSe$ $[M + Na]^+$ 278.0060; found 278.0059.

(*S*)-5-(*p*-Tolylselanylmethyl)pyrrolidin-2-one (5b). Yellow oil. Yield: 77%; $[\alpha]_D^{20}$ = +61 (*c* = 1.04; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, 2 H, *J* = 8.4 Hz), 7.08 (d, 2 H, *J* = 8.4 Hz), 6.80 (br, 1H), 3.80–3.74 (m, 1 H), 2.95 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 6 Hz), 2.87 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 7.2 Hz), 2.42–2.21 (m, 6 H), 1.83–1.74 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.74, 137.60, 133.76, 129.97, 124.70, 53.94, 34.30, 30.16, 27.09, 20.95 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NOSe$ $[M + Na]^+$ 292.0217; found 292.0213.

(*S*)-5-(*o*-Tolylselanylmethyl)pyrrolidin-2-one (5c). Pale yellow solid. mp 42–44 °C; yield: 80%; $[\alpha]_D^{20}$ = +73 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 1 H), 7.32 (br, 1 H), 7.20–7.04 (m, 3 H), 3.85–3.73 (m, 1 H), 2.93 (d, 2 H, *J* = 6.4 Hz), 2.44–2.23 (m, 6 H), 1.89–1.71 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.82, 139.57, 132.34, 129.89, 129.65, 127.14, 126.35, 53.78, 32.72, 30.01, 26.89, 22.23 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NOSe$ $[M + Na]^+$ 292.0217; found 292.0209.

(*S*)-5-((4-Chlorophenylselanyl)methyl)pyrrolidin-2-one (5d). Pale yellow solid. mp 80–81 °C; yield: 75%; $[\alpha]_D^{20}$ = +76 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 2 H, *J* = 8.4 Hz), 7.24 (d, 2 H, *J* = 8.4 Hz), 6.54 (br, 1 H), 3.83–3.77 (m, 1 H), 3.01 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 5.6 Hz), 2.89 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 7.2 Hz), 2.44–2.22 (m, 3 H), 1.84–1.75 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.99, 134.58, 133.60, 129.25, 126.91, 53.87, 34.39, 30.15, 26.90 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{12}ClNOSe$ $[M + Na]^+$ 311.9670; found 311.9667.

(*S*)-5-((2-Chlorophenylselanyl)methyl)pyrrolidin-2-one (5e). Yellow oil. Yield: 80%; $[\alpha]_D^{20}$ = +29 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (br, 1 H), 7.36–7.29 (m, 2 H), 7.17–7.15 (m, 2 H), 3.87–3.81 (m, 1 H), 3.02 (d, 2 H, *J* = 6.4 Hz), 2.43–2.24 (m, 3 H), 1.86–1.78 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.89, 135.62, 132.01, 130.04, 129.39, 127.85, 127.10, 54.50, 32.47, 29.97, 28.85 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{12}ClNOSe$ $[M + Na]^+$ 311.9670; found 311.9660.

(*S*)-5-((2-Methoxyphenylselanyl)methyl)pyrrolidin-2-one (5f). White solid. mp 112–113 °C; yield: 70%; $[\alpha]_D^{20}$ = +83 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 1 H), 7.30–7.26 (m, 1 H), 6.92–6.86 (m, 2 H), 6.33 (br, 1 H), 3.92 (s, 3 H), 3.80–3.74 (m, 1 H), 3.06 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 5.2 Hz), 2.81 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 8.4 Hz), 2.45–2.25 (m, 3 H), 1.87–1.77 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.51, 158.36, 133.40, 128.94, 121.41, 117.27, 110.71, 55.78, 53.94, 31.86, 30.20, 27.31 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NO_2Se$ $[M + Na]^+$ 308.0268; found 308.0163.

(*S*)-5-(Ethylselanylmethyl)pyrrolidin-2-one (5g). Pale yellow oil. Yield: 70%; $[\alpha]_D^{20}$ = +14 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (br, 1 H), 3.89–3.82 (m, 1 H), 2.74 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 6 Hz), 2.64–2.59 (m, 3 H), 2.43–2.29 (m, 3 H), 1.86–1.77 (m, 1 H), 1.40 (t, 3 H, *J* = 7.6 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.02, 54.37, 30.28, 29.61, 27.19, 17.94, 15.73 ppm. HRMS-ESI: *m*/*z* calcd for $C_7H_{13}NOSe$ 230.0060; found 230.0054.

(*S*)-5-(Benzylselanylmethyl)pyrrolidin-2-one (5h). Pale yellow solid. mp 68–69 °C; yield: 71%; $[\alpha]_D^{20}$ = +50 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 6.17 (br, 1H), 3.81 (s, 2 H), 3.75–3.63 (m, 1 H), 2.63 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 5.4 Hz), 2.51 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 7.6 Hz), 2.39–2.20 (m, 3 H), 1.76–1.62 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.02, 138.61, 128.65, 128.37, 126.71, 54.05, 30.13, 29.82, 27.43, 26.95 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NOSe$ $[M + Na]^+$ 292.0217; found 292.0212.

(*S*)-5-(Phenyltellanylmethyl)pyrrolidin-2-one (5i). Dark yellow oil. Yield: 75%; $[\alpha]_D^{20}$ = +39 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.73 (m, 2 H), 7.36–7.17 (m, 3 H), 6.64 (br, 1 H), 3.92–3.79 (m, 1 H), 3.06 (dd, 1 H, J^1 = 12 Hz, J^2 = 6 Hz), 2.90 (dd, 1 H, J^1 = 12 Hz, J^2 = 6.8 Hz), 2.43–2.22 (m, 3 H), 1.84–1.66 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.34, 139.03, 129.44, 128.21, 110.41, 55.04, 30.50, 28.85, 15.86 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{13}NOTe$ $[M + Na]^+$ 327.9957; found 327.9960.

(*S*)-5-((4-Chlorophenyltellanyl)methyl)pyrrolidin-2-one (5j). Pale yellow solid. mp 74–75 °C; yield: 73%; $[\alpha]_D^{20}$ = +23 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, 2 H, *J* = 8.4 Hz), 7.19 (d, 2 H, *J* = 8.4 Hz), 6.68 (br, 1 H), 3.88–3.82 (m, 1 H), 3.05 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 6.4 Hz), 2.90 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 6.8 Hz), 2.46–2.27 (m, 3 H), 1.80–1.70 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.70, 140.41, 134.85, 129.69, 107.81, 54.86, 30.56, 28.64, 16.51 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{12}ClNOTe$ $[M + Na]^+$ 361.9567; found 361.9555.

(*S*)-5-(Phenylthiomethyl)pyrrolidin-2-one (5l). Colorless oil. Yield: 75%; $[\alpha]_D^{20}$ = +90 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H), 7.29–7.18 (m, 3 H), 7.15 (br, 1 H), 3.80–3.74 (m, 1 H), 3.00–2.97 (m, 2 H), 2.40–2.20 (m, 3 H), 1.87–1.78 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.89, 134.69, 130.02, 128.88, 126.55, 53.29, 40.11, 29.81, 26.09 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{13}NOS$ $[M + Na]^+$ 230.0616; found 230.0609.

(*S*)-5-(*p*-Tolylthiomethyl)pyrrolidin-2-one (5m). White solid. mp 86–87 °C; yield: 77%; $[\alpha]_D^{20}$ = +92 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, 2 H, *J* = 8.4 Hz), 7.09 (d, 2 H, *J* = 8.4 Hz), 6.47 (br, 1 H), 3.77–3.71 (m, 1 H), 2.98 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 5.6 Hz), 2.88 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 7.4 Hz), 2.40–2.20 (m, 6 H), 1.86–1.76 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.50, 137.19, 131.23, 131.06, 129.88, 53.52, 41.36, 29.86, 26.49, 20.86 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NOS$ $[M + Na]^+$ 244.0772; found 244.0764.

(*S*)-5-((4-Chlorophenylthio)methyl)pyrrolidin-2-one (5n). White solid. mp 51–53 °C; yield: 69%. $[\alpha]_D^{20}$ = +80 (*c* = 1.0; CH_2Cl_2). NMR ^{1}H (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 4 H), 5.80 (br, 1 H), 3.79–3.78 (m, 1 H), 3.06 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 5 Hz), 2.87 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 8.2 Hz), 2.42–2.26 (m, 3 H), 1.88–1.69 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.67, 133.56, 133.04, 131.78, 129.22, 53.41, 41.00, 29.86, 26.41 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{12}ClNOS$ $[M + Na]^+$ 264.0226; found 264.0221.

(*S*)-5-((2-Chlorophenylthio)methyl)pyrrolidin-2-one (5o). Pale yellow oil. Yield: 78%. $[\alpha]_D^{20}$ = +70 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.34 (m, 2 H), 7.17–7.15 (m, 2 H), 6.97 (br, 1 H), 3.87–3.81 (m, 1 H), 3.07–2.96 (m, 2 H), 2.43–2.24 (m, 3 H), 1.86–1.78 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.62, 134.93, 133.99, 130.66, 129.73, 127.54, 127.07, 53.13, 39.35, 29.67, 26.22 ppm. HRMS-ESI: *m*/*z* calcd for $C_{11}H_{12}ClNOS$ $[M + Na]^+$ 264.0226; found 264.0219.

(*S*)-5-((4-Methoxyphenylthio)methyl)pyrrolidin-2-one (5p). Colorless oil. Yield: 62%. $[\alpha]_D^{20}$ = +98 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, 2 H, *J* = 8.8 Hz), 7.13 (br, 1 H), 6.81 (d, 2 H, *J* = 8.8 Hz), 3.74 (s, 3 H), 3.71–3.67 (m, 1 H), 2.87 (d, 1 H, *J* = 6.4 Hz), 2.37–2.15 (m, 3 H), 1.82–1.73 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.44, 158.91, 133.23, 124.87, 114.39, 54.82, 53.17, 41.70, 29.51, 25.80 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{15}NO_2S$ $[M + H]^+$ 238.0902; found 238.0896.

General procedure for the synthesis of L-chalcogen-*N*-Boc-γ-lactams 6a–p

To a 0.50 M solution of L-chalcogen-γ-lactam **5** (1.0 mmol) in CH_2Cl_2, Et_3N (0.14 mL, 1.0 mmol), Boc_2O (0.27 mL, 2.0 mmol), and DMAP (0.12 g, 1.0 mmol) were added. The solution was stirred at room temperature under an argon atmosphere overnight. The solvent was removed and the residue was purified by chromatography on silica gel. Elution with hexane–ethyl acetate (50 : 50) afforded the desired products.

(*S*)-*tert*-Butyl 2-oxo-5-(phenylselanylmethyl)pyrrolidine-1-carboxylate (6a). Pale yellow oil. Yield: 95%; $[\alpha]_D^{20}$ = −42 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2 H), 7.26–7.24 (m, 3 H), 4.35–4.30 (m, 1 H), 3.33 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 2.8 Hz), 2.97 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 9 Hz), 2.67–2.58 (m, 1 H), 2.43–2.36 (m, 1 H), 2.18–2.08 (m, 1 H), 2.01–1.95 (m, 1 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.64, 149.16, 132.93, 128.89, 128.66, 127.13, 82.56, 57.24, 31.24, 30.78, 27.54, 22.11 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{21}NO_3Se$ $[M + Na]^+$ 378.0584; found 378.0573.

(*S*)-*tert*-Butyl 2-oxo-5-(*p*-tolylselanylmethyl)pyrrolidine-1-carboxylate (6b). Yellow oil. Yield: 80%; $[\alpha]_D^{20}$ = −22 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.40 (m, 2 H), 7.08–7.05 (m, 2 H), 4.34–4.29 (m, 1 H), 3.29 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 2.8 Hz), 2.95 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 9.4 Hz), 2.64–2.57 (m, 1 H), 2.42–2.34 (m, 1 H), 2.30 (s, 3 H), 2.15–2.07 (m, 1 H), 2.01–1.93 (m, 1 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.57, 149.40, 137.33, 133.49, 129.81, 125.12, 82.64, 57.50, 31.76, 30.95, 27.70, 22.34, 20.74 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_3Se$ $[M + Na]^+$ 392.0843; found 392.0734.

(*S*)-*tert*-Butyl 2-oxo-5-(*o*-tolylselanylmethyl)pyrrolidine-1-carboxylate (6c). Pale yellow oil. Yield: 90%; $[\alpha]_D^{20}$ = −63 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.53 (m, 1 H), 7.19–6.07 (m, 3 H), 4.34–4.29 (m, 1 H), 3.31 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 2.8 Hz), 2.91 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 9.6 Hz), 2.66–2.57 (m, 1 H), 2.43 (s, 3 H), 2.38–2.22 (m, 1 H), 2.18–1.99 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.69, 149.28, 139.41, 132.51, 129.84, 129.67, 127.16, 126.36, 82.71, 57.20, 30.78, 29.99, 27.60, 22.25, 22.19 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_3Se$ $[M + Na]^+$ 392.0741; found 392.0738.

(*S*)-*tert*-Butyl 2-((4-chlorophenylselanyl)methyl)-5-oxopyrrolidine-1-carboxylate (6d). Pale yellow oil. Yield: 95%; $[\alpha]_D^{20}$ = −32 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, 2 H, *J* = 8.4 Hz), 7.23 (d, 2 H, *J* = 8.4 Hz), 4.36–4.31 (m, 1 H), 3.33 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 2.6 Hz), 3.01 (dd, 1 H, J^1 = 12.6 Hz, J^2 = 8.6 Hz), 2.68–2.58 (m, 1 H), 2.45–2.37 (m, 1 H), 2.21–2.13 (m, 1 H), 1.98–1.91 (m, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.24, 149.64, 134.44, 133.68, 129.25, 127.25, 82.93, 57.30, 32.02, 31.06, 27.81, 22.59 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{20}ClNO_3Se$ $[M + Na]^+$ 412.0195; found 412.0186.

(*S*)-*tert*-Butyl 2-((2-chlorophenylselanyl)methyl)-5-oxopyrrolidine-1-carboxylate (6e). Pale yellow oil. Yield: 95%; $[\alpha_D]$ = −38 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 1 H), 7.33–7.30 (m, 1 H), 7.20–7.17 (m, 2 H), 4.40–4.35 (m, 1 H), 3.44 (dd, 1 H, J^1 = 12.3 Hz, J^2 = 2.6 Hz), 2.99 (dd, 1 H, J^1 = 12.3 Hz, J^2 = 9.6 Hz), 2.69–2.59 (m, 1 H), 2.47–2.39 (m, 1 H), 2.22–2.13 (m, 1 H), 2.07–2.00 (m, 1 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.72, 149.77, 135.75, 132.38,

130.23, 129.68, 128.12, 127.40, 83.29, 57.17, 31.08, 29.80, 27.93, 22.68 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{20}ClNO_3Se$ $[M + Na]^+$ 412.0195; found 412.0190.

(*S*)-*tert*-Butyl 2-((2-methoxyphenylselanyl)methyl)-5-oxopyrrolidine-1-carboxylate (6f). Yellow oil. Yield: 85%; $[\alpha]_D^{20} = -64$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.54–7.50 (m, 1 H), 7.29–7.21 (m, 1 H), 6.95–6.83 (m, 2 H), 4.41–4.30 (m, 1 H), 3.88 (s, 3 H), 3.37 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 2.9 Hz), 2.90 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 10 Hz), 2.70–2.56 (m, 1 H), 2.49–2.34 (m, 1 H), 2.18–2.00 (m, 2 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.99, 157.96, 149.71, 132.44, 128.48, 121.47, 118.06, 110.60, 83.04, 57.57, 55.80, 31.14, 28.55, 27.91, 22.58 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_3Se$ $[M + Na]^+$ 408.0690; found 408.0681.

(*S*)-*tert*-Butyl 2-(ethylselanylmethyl)-5-oxopyrrolidine-1-carboxylate (6g). Yellow oil. Yield: 80%; $[\alpha]_D^{20} = -57$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.35–4.30 (m, 1 H), 2.96 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 3 Hz), 2.74 (dd, 1 H, J^1 = 12.5 Hz, J^2 = 9.2 Hz), 2.68–2.63 (m, 3 H), 2.46–2.38 (m, 1 H), 2.21–2.15 (m, 1 H), 2.00–1.92 (m, 1 H), 1.54 (s, 9 H), 1.42 (t, 3 H, *J* = 7.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.45, 149.77, 82.77, 57.75, 31.07, 27.90, 27.10, 22.62, 17.95, 15.71 ppm. HRMS-ESI: *m*/*z* calcd for $C_{12}H_{21}NO_3Se$ $[M + Na]^+$ 330.0584; found 330.0577.

(*S*)-*tert*-Butyl 2-(benzylselanylmethyl)-5-oxopyrrolidine-1-carboxylate (6h). Pale yellow oil. Yield: 90%; $[\alpha]_D^{20} = -44$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 5 H), 4.33–4.28 (m, 1 H), 3.86–3.78 (m, 2 H), 2.94 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 2.8 Hz), 2.69 (dd, 1 H, J^1 = 12.4 Hz, J^2 = 9.2 Hz), 2.57–2.50 (m, 1 H), 2.39–2.32 (m, 1 H), 2.14–2.01 (m, 1 H), 1.85–1.79 (m, 1 H), 1.51 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.37, 149.91, 138.85, 128.78, 128.45, 126.83, 82.94, 57.63, 31.17, 27.99, 27.88, 27.81, 22.76 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_3Se$ $[M + Na]^+$ 392.0741; found 392.0732.

(*S*)-*tert*-Butyl 2-oxo-5-(phenyltellanylmethyl)pyrrolidine-1-carboxylate (6i). Pale yellow oil. Yield: 90%; $[\alpha]_D^{20} = -45$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.76 (m, 2 H), 7.30–7.17 (m, 3 H), 4.42–4.36 (m, 1 H), 3.37 (dd, 1 H, J^1 = 14 Hz, J^2 = 3.2 Hz), 3.03 (dd, 1 H, J^1 = 14 Hz, J^2 = 9.6 Hz), 2.63–2.53 (m, 1 H), 2.42–2.35 (m, 1 H), 2.21–2.11 (m, 1 H), 1.88–1.81 (m, 1 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.54, 149.77, 138.98, 129.34, 128.09, 110.63, 82.94, 59.92, 31.22, 27.97, 24.08, 13.58 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{21}NO_3Te$ $[M + Na]^+$ 428.0481; found 428.0475.

(S)-*tert*-Butyl 2-((4-chlorophenyltellanyl)methyl)-5-oxopyrrolidine-1-carboxylate (6j). Yellow oil. Yield: 88%; $[\alpha]_D^{20} = -47$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, 2 H, *J* = 8.4 Hz), 7.18 (d, 2 H, *J* = 8.4 Hz), 4.44–4.33 (m, 1 H), 3.33 (dd, 1 H, J^1 = 12.1 Hz, J^2 = 2.6 Hz), 3.00 (dd, 1 H, J^1 = 12.1 Hz, J^2 = 9.6 Hz), 2.73–2.34 (m, 2 H), 2.28–2.08 (m, 1 H), 1.91–1.77 (m, 1 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.69, 149.48, 140.30, 134.66, 129.49, 107.88, 82.94, 58.57, 31.10, 27.73, 23.80, 14.04 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{20}ClNO_3Te$ $[M + Na]^+$ 462.0092; found 462.0092.

(*S*)-*tert*-Butyl 2-oxo-5-(phenylthiomethyl)pyrrolidine-1-carboxylate (6l). Colorless oil. Yield: 90%; $[\alpha]_D^{20} = -35$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.17 (m, 5 H), 4.33–4.28 (m, 1 H), 3.41 (dd, 1 H, J^1 = 13.5 Hz, J^2 = 3.2 Hz), 2.98 (dd, 1 H, J^1 = 13.5 Hz, J^2 = 9 Hz), 2.67–2.57 (m, 1 H), 2.44–2.36 (m, 1 H), 2.15–2.01 (m, 2 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.43, 149.73, 135.26, 130.11, 129.00, 126.64, 82.97, 57.06, 37.52, 31.05, 27.93, 21.77. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{21}NO_3S$ $[M + Na]^+$ 330.1140; found 330.1131.

(*S*)-*tert*-Butyl 2-oxo-5-(*p*-tolylthiomethyl)pyrrolidine-1-carboxylate (6m). White solid. mp 51–53 °C; yield: 91%. $[\alpha]_D^{20} = -43$ (*c* = 1.0; CH_2Cl_2). NMR ^1H (400 MHz, $CDCl_3$): δ = 7.32 (d, 2 H, *J* = 8 Hz), 7.09 (d, 2 H, *J* = 8 Hz), 4.31–4.25 (m, 1 H), 3.33 (dd, 1 H, J^1 = 13.5 Hz, J^2 = 2.8 Hz), 2.94 (dd, 1 H, J^1 = 13.5 Hz, J^2 = 9 Hz), 2.67–2.57 (m, 1 H), 2.44–2.36 (m, 1 H), 2.30 (s, 3 H), 2.15–2.02 (m, 2 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.45, 149.80, 137.03, 131.58, 130.95, 129.91, 83.07, 57.30, 38.20, 31.21, 28.01, 21.84, 20.92 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_3S$ $[M + Na]^+$ 344.1296; found 344.1302.

(*S*)-*tert*-Butyl 2-((4-chlorophenylthio)methyl)-5-oxopyrrolidine-1-carboxylate (6n). Colorless oil. Yield: 94%. $[\alpha]_D^{20} = -30$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, 2 H, *J* = 8.8 Hz), 7.25 (d, 2 H, *J* = 8.8 Hz), 4.33–4.27 (m, 1 H), 3.38 (dd, 1 H, J^1 = 13.8 Hz, J^2 = 2.4 Hz), 2.98 (dd, 1 H, J^1 = 13.8 Hz, J^2 = 8.8 Hz), 2.68–2.57 (m, 1 H), 2.46–2.38 (m, 1 H), 2.19–1.99 (m, 2 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.28, 149.96, 133.89, 132.94, 131.42, 129.27, 83.25, 56.98, 37.82, 31.19, 28.02, 21.89 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{20}ClNO_3S$ $[M + Na]^+$ 364.0750; found 364.0738.

(*S*)-*tert*-Butyl 2-((2-chlorophenylthio)methyl)-5-oxopyrrolidine-1-carboxylate (6o). Yellow oil. Yield: 84%. $[\alpha]_D^{20} = -44$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, J^1 = 7.9 Hz, J^2 = 1.6 Hz), 7.37 (dd, 1 H, J^1 = 7.9 Hz, J^2 = 1.4 Hz), 7.25–7.20 (m, 1 H), 7.17–7.13 (m, 1 H), 4.35–4.29 (m, 1 H), 3.44 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 2.4 Hz), 2.98 (dd, 1 H, J^1 = 13.6 Hz, J^2 = 9.6 Hz), 2.70–2.60 (m, 1 H), 2.47–2.39 (m, 1 H), 2.20–2.07 (m, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.40, 149.84, 134.84, 134.32, 130.60, 129.94, 127.61, 127.30, 83.21, 56.75, 36.32, 31.03, 27.96, 21.96 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{20}ClNO_3S$ $[M + Na]^+$ 364.0750; found 364.0745.

(*S*)-*tert*-Butyl 2-((4-methoxyphenylthio)methyl)-5-oxopyrrolidine-1-carboxylate (6p). Pale yellow solid. mp 94–95 °C; yield: 85%. $[\alpha]_D^{20} = -43$ (*c* = 1.0; CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, 2 H, *J* = 8 Hz), 6.84 (d, 2 H, *J* = 8 Hz); 4.28–4.22 (m, 1 H), 3.78 (s, 3 H), 3.27 (dd, 1 H, J^1 = 13.5 Hz, J^2 = 3.2 Hz), 2.90 (dd, 2 H, J^1 = 13.5 Hz, J^2 = 9 Hz), 2.68–2.59 (m, 1 H), 2.45–2.38 (m, 1 H), 2.14–2.03 (m, 2 H), 1.42 (s, 9 H) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = 173.84, 159.56, 149.74, 133.78, 125.57, 114.94, 83.00, 57.40, 55.37, 39.44, 31.25, 28.00, 21.82 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{23}NO_4S$ $[M + Na]^+$ 360.1245; found 360.1257.

General procedure for the synthesis of L-chalcogen-*N*-Boc-γ-amino acids 7a–p

To a 0.2 M solution of L-chalcogen-*N*-Boc-γ-lactam (1.0 mmol) in THF, 3.0 mL (3.0 mmol) of a 1.0 N solution of LiOH was

added. This mixture was stirred at room temperature and the product formation was monitored by TLC. After removal of THF under vacuum, the basic aqueous residue was acidified by addition of 1.0 M HCl and extracted with diethyl ether. The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed under vacuum. The crude products were purified in a silica gel column for chromatographic purification, using hexane–ethyl acetate (20 : 80) as the eluent.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(phenylselanyl)pentanoic acid (7a). Pale yellow solid. mp 82–83 °C; yield: 70%; $[\alpha]_D^{20}$ = +6.0 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 2 H), 7.25–7.22 (m, 3 H), 3.88–3.78 (m, 1 H), 3.18–3.00 (m, 2 H), 2.38 (t, 2 H, J = 7.2 Hz), 1.99–1.90 (m, 1 H), 1.81–1.73 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.11, 155.40, 132.80, 129.94, 129.08, 127.03, 79.56, 50.09, 34.12, 30.75, 29.55, 28.21 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{23}NO_4Se$ $[M + Na]^+$ 396.0792; found 396.0683.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(*p*-tolylselanyl)pentanoic acid (7b). White solid. mp 72–73 °C; yield: 80%; $[\alpha]_D^{20}$ = +23 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, 2 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 3.83–3.77 (m, 1 H), 3.01–2.97 (m, 2 H), 2.35 (t, 2 H, J = 7.2 Hz), 2.28 (s, 3 H), 2.01–1.89 (m, 1 H), 1.80–1.73 (m, 1 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.05, 155.41, 137.81, 134.00, 130.09, 124.63, 79.46, 50.12, 34.17, 30.81, 29.67, 28.22, 20.99 ppm. HRMS-ESI: m/z calcd for $C_{17}H_{25}NO_4Se$ $[M + Na]^+$ 410.0846; found 410.0846.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(*o*-tolylselanyl)pentanoic acid (7c). Colorless oil. Yield: 70%; $[\alpha]_D^{20}$ = +12 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.46 (m, 1 H), 7.17–7.05 (m, 3 H), 3.94–3.78 (m, 1 H), 3.01–2.99 (m, 2 H), 2.42 (s, 3 H), 2.36 (t, 2 H, J = 7.2 Hz), 2.02–1.97 (m, 1 H), 1.81–1.73 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.47, 155.37, 139.24, 132.71, 130.87, 129.90, 127.47, 126.84, 79.45, 54.44, 32.83, 30.73, 29.63, 28.14, 22.28 ppm. HRMS-ESI: m/z calcd for $C_{17}H_{25}NO_4Se$ $[M + Na]^+$ 410.0949; found 410.0839.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(4-chlorophenylselanyl)-pentanoic acid (7d). Pale yellow solid. mp 104–105 °C; yield: 75%; $[\alpha]_D^{20}$ = +15 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 2 H, J = 8.4 Hz), 7.23 (d, 2 H, J = 8.4 Hz), 3.87–3.78 (m, 1 H), 3.08–3.00 (m, 2 H), 2.39 (t, 2 H, J = 7.2 Hz), 2.02–1.92 (m, 1 H), 1.81–1.71 (m, 1 H), 1.41 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.79, 155.30, 134.30, 133.39, 129.24, 128.14, 79.63, 50.44, 34.32, 30.70, 29.59, 28.23 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{22}ClNO_4Se$ $[M + Na]^+$ 430.0300; found 430.0297.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(2-chlorophenylselanyl)-pentanoic acid (7e). Orange oil. Yield: 50%; $[\alpha]_D^{20}$ = +8.0 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.13 (m, 4 H), 3.96–3.78 (m, 1 H), 3.18–2.97 (m, 2 H), 2.40 (t, J = 7.2 Hz, 2 H), 2.06–1.94 (m, 1 H), 1.88–1.74 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.78, 155.43, 135.70, 132.12, 130.63, 129.57, 127.74, 127.28, 79.67, 50.04, 32.59, 30.77, 29.70, 28.25 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{22}ClNO_4Se$ $[M + Na]^+$ 430.0300; found 430.0292.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(2-methoxyphenylselanyl)-pentanoic acid (7f). White solid. mp 102–103 °C; yield: 80%; $[\alpha]_D^{20}$ = +8.0 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 1 H), 7.27–7.19 (m, 1 H), 6.89–6.81 (m, 2 H), 3.87 (s, 3 H), 3.83–3.78 (m, 1 H), 3.10–3.00 (m, 2 H), 2.36 (t, 2 H, J = 7.2 Hz), 2.03–1.90 (m, 1 H), 1.84–1.77 (m, 1 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.91, 157.95, 155.36, 133.46, 128.89, 121.42, 118.87, 110.63, 79.41, 55.71, 50.04, 31.61, 30.84, 29.74, 28.19 ppm. HRMS-ESI: m/z calcd for $C_{17}H_{25}NO_5Se$ $[M + Na]^+$ 426.0796; found 426.0792.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(ethylselanyl)pentanoic acid (7g). White solid. mp 67–68 °C; yield: 55%; $[\alpha]_D^{20}$ = +16 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82–3.74 (m, 1 H), 2.78–2.66 (m, 2 H), 2.63–2.57 (m, 2 H), 2.42 (t, 2 H, J = 7.2 Hz), 2.02–1.93 (m, 1 H), 1.80–1.72 (m, 1 H), 1.44 (s, 9 H), 1.39 (t, 3 H, J = 7.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.92, 155.49, 79.46, 51.96, 30.82, 29.51, 28.21, 26.89, 18.04, 15.66 ppm. HRMS-ESI: m/z calcd for $C_{12}H_{23}NO_4Se$ $[M + Na]^+$ 348.0690; found 348.0684.

(*S*)-5-(Benzylselanyl)-4-(*tert*-butoxycarbonylamino)pentanoic acid (7h). Pale yellow oil. Yield: 78%; $[\alpha]_D^{20}$ = +3 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 4 H), 7.20–7.16 (m, 1 H), 3.79 (s, 2 H), 3.79 (s, 2 H), 3.79–3.70 (m, 1 H), 2.64–2.61 (m, 2 H), 2.36 (t, 2 H, J = 7.6 Hz), 1.94–1.86 (m, 1 H), 1.74–1.65 (m, 1 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.06, 155.53, 138.91, 128.84, 128.47, 126.76, 79.60, 49.83, 30.82, 29.79, 29.72, 28.29, 27.74 ppm. HRMS-ESI: m/z calcd for $C_{17}H_{25}NO_4Se$ $[M + Na]^+$ 410.0846; found 410.0844.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(phenyltellanyl)pentanoic acid (7i). White solid. mp 86–88 °C; yield: 72%; $[\alpha]_D^{20}$ = +66 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.73 (m, 2 H), 7.27–7.14 (m, 3 H), 3.83–3.75 (m, 1 H), 3.07–3.06 (m, 2 H), 2.36 (t, 2 H, J = 7.2 Hz), 1.96–1.88 (m, 1 H), 1.80–1.70 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.82, 155.32, 138.52, 129.19, 127.73, 111.37, 79.52, 50.53, 31.19, 30.81, 28.22, 16.93 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{23}NO_4Te$ $[M + Na]^+$ 446.0587; found 446.0587.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(4-chlorophenyltellanyl)-pentanoic acid (7j). Dark yellow oil. Yield: 80%; $[\alpha]_D^{20}$ = +11 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, 2 H, J = 8.4 Hz), 7.14 (d, 2 H, J = 8.4 Hz), 3.83–3.72 (m, 1 H), 3.10–3.04 (m, 2 H), 2.36 (t, 2 H, J = 7.6 Hz), 1.96–1.84 (m, 1 H), 1.77–1.68 (m, 1 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.25, 155.42, 140.11, 134.51, 129.53, 108.88, 79.75, 50.80, 31.27, 30.78, 28.30, 17.29 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{22}ClNO_4Te$ $[M + Na]^+$ 480.0197; found 480.0201.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(phenylthio)pentanoic acid (7l). White solid. mp 73–74 °C; yield: 60%; $[\alpha]_D^{20}$ = +15 (c = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2 H), 7.28–7.24 (m, 2 H), 7.20–7.16 (m, 1 H), 3.88–3.73 (m, 1 H), 3.11–3.00 (m, 2 H), 2.39 (t, 2 H, J = 7.2 Hz), 2.06–1.96 (m, 1 H), 1.83–1.73 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.65, 155.67, 136.07, 129.93, 129.03, 126.45, 79.61, 50.10, 39.71, 30.75, 29.04, 28.32 ppm. HRMS-ESI: m/z calcd for $C_{16}H_{23}NO_4S$ $[M + Na]^+$ 348.1245; found 348.1238.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(*p*-tolylthio)pentanoic acid (7m). White solid. mp 89–91 °C; yield: 98%. $[\alpha]_D^{20}$ = +18 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, 2 H, *J* = 8.4 Hz), 7.08 (d, 2 H, *J* = 8.4 Hz), 3.83–3.74 (m, 1 H), 3.06–2.94 (m, 2 H), 2.38 (t, 2 H, *J* = 7.2 Hz), 2.30 (s, 3 H), 2.03–1.95 (m, 1 H), 1.82–1.73 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.38, 155.92, 136.71, 132.32, 130.79, 129.84, 79.96, 50.48, 40.45, 30.71, 29.12, 28.34, 20.91 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{25}NO_4S$ $[M + Na]^+$ 362.1402; found 362.1397.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(4-chlorophenylthio)pentanoic acid (7n). White solid. mp 106–107 °C; yield: 84%. $[\alpha]_D^{20}$ = +20 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 4 H), 3.88–3.69 (m, 1 H), 3.12–2.91 (m, 2 H), 2.45–2.36 (m, 2 H), 2.07–1.93 (m, 1 H), 1.81–1.71 (m, 1 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.81, 155.47, 134.48, 132.45, 131.12, 129.14, 79.82, 49.87, 39.77, 30.70, 28.85, 28.27 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{22}ClNO_4S$ $[M + Na]^+$ 382.0856; found 382.0865.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(2-chlorophenylthio)pentanoic acid (7o). White solid. mp 73–75 °C; yield: 84%. $[\alpha]_D^{20}$ = +12 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 2 H), 7.22–7.09 (m, 2 H), 3.90–3.76 (m, 1 H), 3.16–2.97 (m, 2 H), 2.41 (t, 2 H, *J* = 7.2 Hz), 2.06–2.02 (m, 1 H), 1.86–1.78 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.59, 155.76, 135.17, 134.52, 130.07, 129.83, 127.22, 127.17, 80.09, 49.88, 38.51, 30.73, 28.99, 28.28 ppm. HRMS-ESI: *m*/*z* calcd for $C_{16}H_{22}ClNO_4S$ $[M + Na]^+$ 382.0958; found 382.0862.

(*S*)-4-(*tert*-Butoxycarbonylamino)-5-(4-methoxyphenylthio)-pentanoic acid (7p). Colorless oil. Yield: 93%. $[\alpha]_D^{20}$ = +116. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, 2 H, *J* = 8.4 Hz), 6.82 (d, 2 H, *J* = 8.4 Hz), 3.77 (s, 3 H), 3.74–3.66 (m, 1 H), 3.05–2.93 (m, 2 H), 2.37 (t, 2 H, *J* = 7.2 Hz), 2.05–1.90 (m, 1 H), 1.82–1.68 (m, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.51, 159.14, 155.68, 133.40, 126.19, 114.74, 79.99, 55.23, 50.40, 41.41, 30.65, 28.94, 28.23 ppm. HRMS-ESI: *m*/*z* calcd for $C_{17}H_{25}NO_5S$ $[M + H]^+$ 356.1532; found 356.1543.

(5*S*,5′*S*)-*tert*-Butyl 5,5′-diselanediylbis(methylene)bis(2-oxopyrrolidine-1-carboxylate) (11). To a 0.5 M solution of tosylate γ-lactam **9** (0.269 g, 1.0 mmol) in CH_2Cl_2, Et_3N (0.14 mL, 1.0 mmol), Boc_2O (0.27 mL, 2.0 mmol) and DMAP (0.12 g, 1.0 mmol) were added. The solution was stirred for 8 h at room temperature under an argon atmosphere. The solvent was removed and the residue was purified by chromatography on silica gel using hexane–ethyl acetate (50 : 50) as the eluent to afford tosylate *N*-Boc-γ-lactam **10** in 90% yield. To a stirred solution of Se^0 (0.158 g, 2.0 mmol) and tosylate *N*-Boc-γ-lactam **10** (0.369 g, 1.0 mmol) in dry DMSO (2.0 mL), CuO nanoparticles (0.016 g, 20 mol%) and KOH (0.11 g, 2.0 mmol) were added under an argon atmosphere at room temperature. The reaction was monitored by TLC. After the reaction was complete, the resulting mixture was purified by flash chromatography, first eluting with hexane and then with a hexane–ethyl acetate (50 : 50) mixture to give the product in 50% yield; yellow oil. $[\alpha]_D^{20}$ = −32 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46–4.40 (m, 1 H), 3.44 (dd, 1 H, J^1 = 12.2 Hz, J^2 = 3 Hz), 3.06 (dd, 1 H, J^1 = 12.2 Hz, J^2 = 9.4 Hz), 2.67–2.58 (m, 1 H), 2.49–2.42 (m, 1 H), 2.22–2.14 (m, 1 H), 2.07–2.00 (m, 1 H), 1.54 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.49, 149.74, 83.24, 58.18, 32.92, 31.13, 28.06, 22.39 ppm. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{32}N_2O_6Se_2$ $[M + Na]^+$ 579.0489; found 579.0486.

(4*S*,4′*S*)-5,5′-Diselanediylbis(4-(*tert*-butoxycarbonylamino)-pentanoic acid) (12). Prepared according to the procedure described for chalcogen-*N*-Boc-γ-amino acids **7a–p**. Dark yellow oil. Yield: 50%; $[\alpha]_D^{20}$ = +17 (*c* = 1.0; CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94–3.76 (m, 1 H), 3.33–3.11 (m, 2 H), 2.47–2.43 (m, 2 H), 2.04–1.97 (m, 1 H), 1.83–1.73 (m, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.12, 156.20, 80.09, 51.03, 34.21, 30.73, 29.64, 28.43 ppm. HRMS-ESI: *m*/*z* calcd for $C_{20}H_{36}N_2O_8Se_2$ $[M + Na]^+$ 615.0700; found 615.0700.

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