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Straightforward synthesis of non-natural chalcogen peptides via ring opening of aziridines

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ABSTRACT

The synthesis of new chiral non-natural seleno-, thio-, and telluro-peptides is described herein. These new compounds were prepared through simple and brief synthetic route, from inexpensive and commercially available amino acids. The products, possessing a highly modular character, were obtained in good to excellent yields (50–96%), via ring opening of aziridines with chalcogenolate anions, generated using indium(I) iodide as a reducing agent.

1. Introduction

The interest in synthesizing small molecules that mimic the structures of bioactive peptides has become an important goal in synthetic organic chemistry.[1] A special emphasis has been given to the replacement of natural amino acids in peptides for non-proteinogenic derivatives in order to obtain drug-like target molecules.[2] Moreover the interest in the biological and medicinal properties of selenium and organoselenium compounds is also increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[3] This increasing interest has attracted considerable attention in the development of new organoselenium compounds. In this context, synthetic methods for the preparation of selenocysteine,[4] selenium based peptides,[5] selenoglycosides,[6] selenonucleosides,[7] seleno-carbohydrates,[8] and other important natural coumpounds[9] are currently an area of intensive research.

Among selenium and tellurium compounds, the chalcogen amino acids have emerged as an exceptional class of structures in recent years, due to their interesting biological properties, such as selenocysteine, selenomethionine and the analogous tellurium compounds, in which the amino acid side chain is isosteric with cysteine or methionine.[10] Many selenoenzymes have a selenocysteine residue at the active site as a catalyst for various redox reactions.[11] Perhaps the most important and studied enzyme is glutathione peroxidase (GPx), which protects the body against the potentially damaging effects of reactive oxygen species formed during aerobic metabolism.[12] Several neurodegenerative diseases, including Alzheimer's, Parkinson's and other physiological and inflammatory processes are associated with oxidative stress.[13] Since the discovery that selenium plays a pivotal role in GPx enzymes, synthetic developments toward design of new chalcogen based catalytic antioxidants have attracted considerable attention.[3a,14] In this context, novel compounds derived from amino acids containing chalcogen atom have arisen as excellent candidates for GPx mimics.[15]

Chalcogen-containing peptides offer attractive and practical potential toward the development of new ligands for asymmetric transformations.[16] Further, they are easily prepared from readily available, modular chiral building blocks.

On the other hand, chiral aziridines are one of the most versatile three-membered ring systems in modern synthetic chemistry.[17] They constitute a useful class of nitrogen-containing compounds and are also key intermediates for the regiocontrolled introduction of a chalcogen atom in the product. In this context different β-seleno amines and selenocysteine derivatives have been prepared via ring opening of aziridines with chalcogen nucleophiles, generated by reducing agents, such as $NaBH_4$, $LiBHEt_3$, Zn, rongalite and KOH/CuO.[18] In recent years our group developed an indium (I) protocol for the preparation of selenocysteine derivatives through the ring opening of aziridine-2-carboxylate. By this method, a series of

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selenoamino acids could be synthesized in good to excellent yields.[19] In this work we discovered that when the selenolate anion was generated using $NaBH_4$/EtOH the reaction failed to prepare selenocysteine derivatives. Notably, indium selenolate promoted faster aziridine ring opening in the absence of a Lewis acid (Fig. 1).

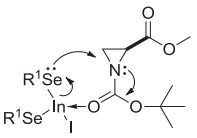
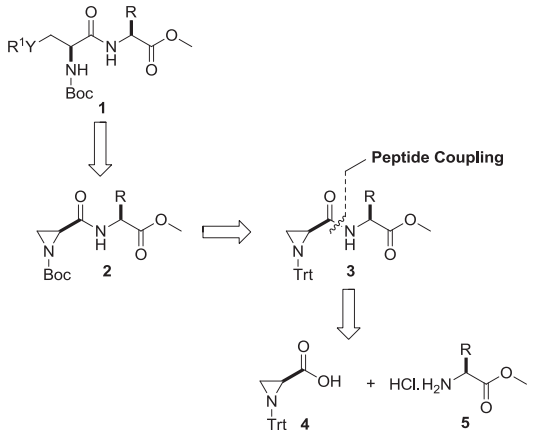


Fig. 1. Proposed mechanism for the aziridine ring opening.

In this context, and as a part of our growing interest in chalcogen compounds,[20] we describe herein an easy, inexpensive and straightforward synthetic route for the preparation of a series of non-natural chalcogen peptides. Our approach to the preparation of these new *N*-Boc chalcogen peptides took advantage of our previous protocol,[19] and consisted of a ring opening reaction of aziridine by indium chalcogenolate anions as depicted in the proposed retrosynthetic analysis (Scheme 1). For the preparation of the key aziridines, we selected some procedures already described in the literature, which explores the preparation of these aziridines starting from common available amino acids.

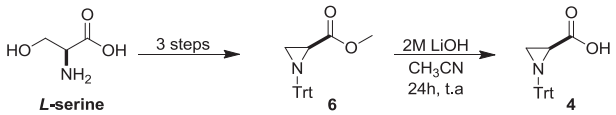


Scheme 1. Retrosynthetic analysis for chalcogen peptides **1**.

2. Results and discussion

According to our objectives and as the starting point for the synthesis of chalcogen peptides **1** we had to devise an efficient method of preparation for chiral *N*-Boc-aziridines **2** in a short and high yielding sequence. To accomplish this task we used methodologies already described in the literature.

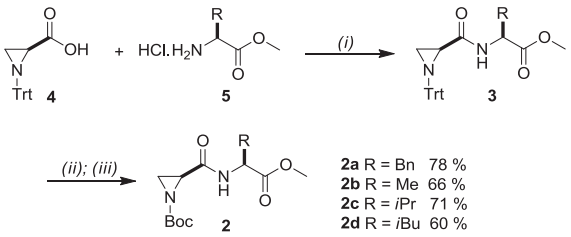
Following the protocol previously reported, the (*S*)-methyl 1-tritylaziridine-2-carboxylate **6** was prepared in high yields starting from L-serine.[21] In the next step the hydrolysis of methyl ester was achieved by reaction with 2 M lithium hydroxide in acetonitrile affording (*S*)-1-tritylaziridine-2-carboxylic acid **4** in 91% yield (Scheme 2).[22]



Scheme 2. Synthesis of (*S*)-1-tritylaziridine-2-carboxylic acid **4** from L-serine.

With the (*S*)-1-tritylaziridine-2-carboxylic acid **4** in hand, we turned your attention toward coupling with L-amino esters **5**. To accomplish this transformation, we chose the mixed anhydride method.[23] Coupling conditions consisted of treatment of the (*S*)-1-tritylaziridine-2-carboxylic acid **4** with *N*-methylmorpholine in chloroform, followed by the addition of ethyl chloroformate to afford the mixed anhydride in situ, which was then treated with L-amino esters **5** and other equivalent of *N*-methylmorpholine to form the amide bond (Scheme 3). A series of compounds was synthesized through variation of the amino ester residues. Compounds of type **3** were submitted to a short purification over silica gel to remove the unreacted starting materials.

In order to facilitate an efficient ring opening of the aziridine, it was necessary to replace the trityl group with an electron withdrawing group, such as *tert*-butoxycarbonyl (Boc). Following the protocol reported in the literature,[24] the protecting group interconversion **3**→**2** was achieved using a one-pot strategy in order to avoid the isolation of the intermediate free aziridines. Hence, removal of trityl group from **3** using trifluoroacetic acid, basification with excess of triethylamine and in situ reprotection with Boc_2O gave the *N*-Boc aziridines **2a**–**d** in good yields (Scheme 3).



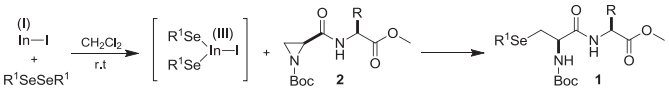
Scheme 3. Synthetic strategies to prepare *N*-Boc aziridines **2a**–**d**. Reagents and conditions: (i) NMM, ethyl chloroformate, NMM, $CHCl_3$, 0 °C, then 24 h rt; (ii) TFA, MeOH, CH_2Cl_2, 0 °C, 30 min (iii) Et_3N, Boc_2O, 0 °C, then 15 h rt.

It is worth noting that we did not observe any epimerization at the original chiral center from **4**. This result was confirmed through the synthesis of a racemic aziridine *rac*-**4**, which was coupling with L-amino ester of alanine, followed by the removal of trityl group and in situ reprotection with Boc_2O to afford a mixture of diastereoisomers **2b**. By the comparison of both spectra of ^1H NMR, we could then confirm the absence of epimerization, since only a single set of signals was observed for an enantiomerically pure *N*-Boc aziridine **2b**, when compared with a mixture of diastereoisomers **2b** (see Supplementary data).

With the *N*-Boc aziridines **2a**–**d** in hand, we promoted the insertion of the organochalcogen moiety through the nucleophilic ring opening with different selenium anions. To accomplish this task the selenium nucleophile was generated by reduction of diphenyl diselenide with sodium borohydride in a mixture of THF and ethanol. However, under these conditions the ring opening of aziridine **2a** failed and the product was not obtained. This result is in agreement with those previously reported in the literature for a similar aziridine.[19] Attempting to solve this problem we decided to use our protocol, which employs indium (I) iodide to promote the cleavage of diorganoyl diselenides.[19] According to that, indium (I) iodide undergoes an oxidative insertion into a suitable substrate, generating the complex bis(organoylseleno)iodoindium (III). This complex is readily prepared by reacting equimolar amounts of InI and R^1SeSeR^1 in dichloromethane (Scheme 4).

As outlined in the sequence below, the preparation of chalcogen peptides proceeds through the regioselective nucleophilic attack of the organoselenolate anion at the less hindered carbon of the aziridine ring.

After optimization of the reaction conditions, several aziridines and diorganoyl dichalcogenides were applied in order to check the

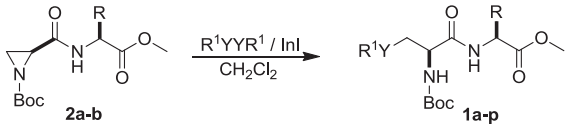


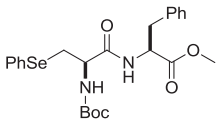
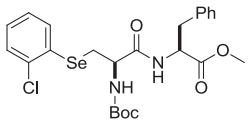
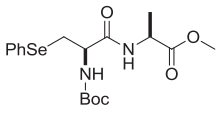
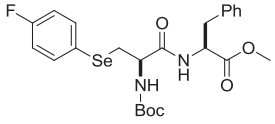
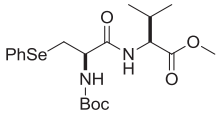
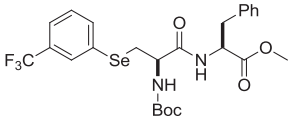
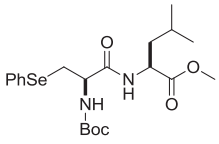
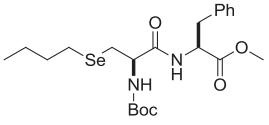
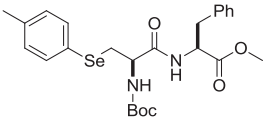
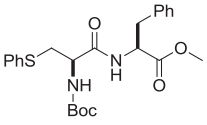
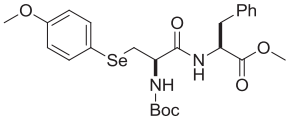
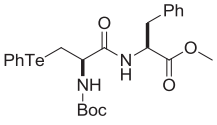
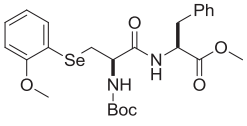
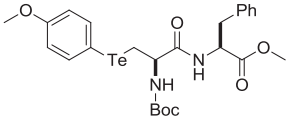
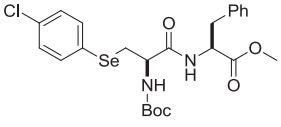
Scheme 4. Indium (I) iodide-mediated *N*-Boc aziridine ring opening with diorganoyl diselenides.

versatility of the protocol, and the results are summarized in Table 1. In general, all reactions proceeded smoothly and the target compounds **1a**–**p** were obtained in good to excellent yields, ranging from 50 to 96 %. Changing the amino acid residue did not produce a pronounced effect on the yield of the products (Table 1, Entries 2–4).

We found that electronic effects had no significant influence on the reactivity of the process, as the products were obtained without meaningful change on the reaction yield (Table 1 Entries 1 and 5–7 vs 8–11). We observed that steric effects exerted some influence during the reaction and the substituents attached to the *para* position of diselenide furnished better yields (Table 1, Entries 6 and 8) than those with the same substituents in the *ortho* position (Entries 7 and 9). Moreover, the introduction of aliphatic group (Bu, entry 12, 79% yield) was also achieved in very good yield. Due to the success obtained with the preparation of the seleno-peptides, we decided to extend our studies to sulfur and tellurium analogs. In this way, the reduction of diphenyl disulfide with InI, under the same conditions used for the diselenides, followed by the ring opening of *N*-Boc aziridine **2a**, afforded the corresponding thio-peptide **1n** in good yield (Table 1, Entry 13). For the preparation of the telluro-peptides it was necessary to alter the procedure somewhat, since it was observed that the organotellurolate anion underwent decomposition under the reaction conditions. In this

Table 1
Synthesis of *N*-Boc chalcogen peptides **1a**–**p**

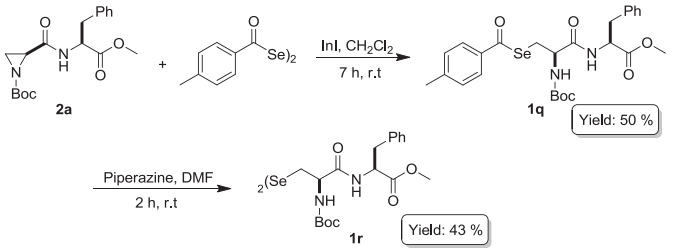


Entry	R	Product		Yield (%)[a]	Entry	R	Product		Yield (%)[a]
1	Bn		**1a**	77	9	Bn		**1i**	86
2	Me		**1b**	86	10	Bn		**1j**	71
3	^{i}Pr		**1c**	86	11	Bn		**1l**	82
4	^{i}Bu		**1d**	83	12	Bn		**1m**	79
5	Bn		**1e**	77	13	Bn		**1n**	86
6	Bn		**1f**	85	14	Bn		**1o**	80
7	Bn		**1g**	80	15	Bn		**1p**	50
8	Bn		**1h**	96					

[a] Yields of isolated materials.

case diphenyl ditelluride or di-(*p*-methoxyphenyl) ditelluride were added to a solution of *N*-Boc aziridine **2a** followed by InI and allowed to react for 2 h, affording the telluro-peptides in good and moderate yields (Table 1, Entries 14 and 15).

One of the major advantages of this 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 the diselenide **1r** (Scheme 5). To accomplish this task, we took advantage of our previous strategy for the synthesis of telluro-peptides, which employs a nucleophilic ring opening of *N*-Boc aziridine **2a**. In this way the treatment of *N*-Boc aziridine **2a** with di-(4-methylbenzoyl) diselenide and InI afforded after 7 h the key intermediate **1q** in 50% yield. The selenoester group was then removed from selenopeptide **1q** through the reaction with piperazine in dry *N*,*N*-dimethylformamide, furnishing diselenide **1r** after air oxidation in 43% yield.[25]



Scheme 5. Synthesis of diselenide **1r**.

3. Conclusion

In summary, we have described herein a novel synthetic entry into selenium-, thio- and teluro-peptides systems. These compounds were prepared in a concise and flexible route in good to excellent yields, which permitted the synthesis of a wide range of compounds with a highly modular character. Additionally, the method was easily adapted for the synthesis of diselenide species. We also believe that this modular approach may have significant importance for biological screenings. Further research efforts are currently underway in our laboratories to investigate the influence of amino acid sequence and the chalcogen identity toward biological activity of this class of compounds.

4. Experimental

4.1. General information

Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained, on a Varian INOVA, 300 MHz spectrometer and on a Bruker AVANCE III 400 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 (δ), multiplicity (br=broad, s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet), and coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 75 MHz and 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 measured at the Universidade de São Paulo with a LC-MS Bruker Daltronics MicroTOF in ESI mode. Optical rotations were carried out on a Perkin Elmer Polarimeter 341. Column chromatography was performed using Merck Silica Gel (70–230 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. The yields of the products included in all tables refer to isolated yields. The following solvents were dried and purified by distillation from the reagents indicated: THF from sodium with benzophenone indicator, EtOH from magnesium/iodine, CH_2Cl_2 from phosphorus pentoxide and DMF from magnesium sulfate. All other solvents were ACS or HPLC grade unless otherwise noted. The chalcogenides were conveniently prepared from classical procedures.[25,26] (*S*)-1-tritylaziridine-2-carboxylic acid **4** was prepared according the procedures described in literature.[21,22] All others reagents and solvents were purchased from commercial suppliers. Air- and moisture-sensitive reactions were conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe techniques.

4.2. General procedure for the synthesis of *N*-Boc aziridines (2)

Under a nitrogen atmosphere, *N*-methylmorpholine (0.303 g, 3.0 mmol) was added to a solution of (*S*)-1-tritylaziridine-2-carboxylic acid **4** (0.987 g, 3.0 mmol) in $CHCl_3$ (20 mL) at 0 °C. After stirring for 15 min at this temperature, ethyl chloroformate (0.324 g, 3.0 mmol) was added dropwise and stirring was prolonged for additional 30 min at 0 °C. After this time the appropriate amino ester (3.0 mmol) was added, followed by 1 equiv of *N*-methylmorpholine and the resulting solution was stirred at 0 °C for additional 1 h and then at room temperature for 24 h. After this time the solution was diluted with 30 mL of $CHCl_3$, washed with saturated $NaHCO_3$ (2×20 mL), 10% aqueous citric acid (2×20 mL), and brine (20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting products were purified through a short column and were used in the next step. Trifluoroacetic acid (0.48 mL, 6.25 mmol) was added dropwise over 1 min to a stirred solution of the appropriate *N*-Trt aziridine **3** (2.5 mmol) in dichloromethane (20 mL) and methanol (0.1 ml, 2.5 mmol) at 0 °C under an atmosphere of nitrogen. The solution was stirred at 0 °C for 30 min and then triethylamine (2.17 mL, 15.62 mmol) was added dropwise over 2 min. The mixture was stirred at 0 °C for an additional 10 min, and then di-*tert*-butyl dicarbonate (0.60 g, 2.75 mmol) in dichloromethane (5 mL) was added over 5 min. The solution was warmed to room temperature, stirred for 15 h and then washed with 10% aqueous citric acid solution (3×10 ml) and water (2×10 mL). The combined organic extracts were dried with Na_2SO_4 and the solvent concentrated under vacuum to afford the crude products, which were purified by chromatography on silica gel using 7:3 hexane:ethyl acetate.

4.2.1. (S)-tert-Butyl 2-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl) carbamoyl)aziridine-1-carboxy-late ***2a***. Colorless oil. Yield: 78%; $[\alpha]_D^{20}$=+15.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.19 (m, 3H), 7.08–7.06 (m, 2H), 6.72 (d, J=7.8 Hz, 1H), 4.83 (q, J^1=14.1 Hz, J^2=6.6 Hz, 1H), 3.72 (s, 3H), 3.17 (dd, J^1=13.9 Hz, J^2=5.6 Hz, 1H), 3.01 (dd, J^1=13.9 Hz, J^2=6.6 Hz, 1H), 2.94–2.91 (m, 1H), 2.36 (d, J=6.3 Hz, 1H), 2.02 (d, J=3.4 Hz, 1H), 1.44 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.29, 167.14, 159.94, 135.59, 129.05, 128.36, 126.98, 82.19, 52.58, 52.19, 37.62, 36.65, 31.69, 27.66 ppm HRMS (ESI) calcd for $C_{18}H_{24}N_2O_5$ [M+Na$^+$]: 371.1583 *m*/*z*; observed: 371.1572 *m*/*z*.

4.2.2. (S)-tert-Butyl 2-(((S)-1-methoxy-1-oxopropan-2-yl)carbamoyl) aziridine-1-carboxylate ***2b***. Colorless oil. Yield: 66%; $[\alpha]_D^{20}$=−59.0 (*c*=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.00 (d, J=7.0 Hz, 1H), 4.53–4.43 (m, 1H), 3.68 (s, 3H), 2.97–2.94 (m, 1H), 2.37 (d, J=6.4 Hz, 1H), 2.27 (d, J=2.9 Hz, 1H), 1.38 (s, 9H), 1.32 (d, J=7.6 Hz, 3H) ppm ^{13}C

NMR (75 MHz, $CDCl_3$): δ=172.60, 166.94, 159.88, 81.97, 52.19, 47.59, 36.38, 31.47, 27.55, 17.83 ppm HRMS (ESI) calcd for $C_{12}H_{20}N_2O_5$ [M+Na^+]: 295.1269 *m*/*z*; observed: 295.1259 *m*/*z*.

4.2.3. (S)-tert-Butyl 2-(((S)-1-methoxy-3-methyl-1-oxobutan-2-yl) carbamoyl)aziridine-1-carboxylate ***2c***. Colorless oil. Yield: 71%; $[\alpha]_D^{20}$=−24.0 (*c*=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.93 (d, *J*=8.8 Hz, 1H), 4.47–4.42 (m, 1H), 3.67 (s, 3H), 3.01–2.98 (m, 1H), 2.38 (d, *J*=6.4 Hz, 1H), 2.26 (d, *J*=3.5 Hz, 1H), 2.13–2.02 (m, 1H), 1.38 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.59, 167.27, 159.79, 81.86, 56.53, 51.82, 36.48, 31.52, 30.90, 27.47, 18.58, 17.46 ppm HRMS (ESI) calcd for $C_{14}H_{24}N_2O_5$ [M+Na^+]: 323.1583 *m*/*z*; observed: 323.1575 *m*/*z*.

4.2.4. (S)-tert-Butyl 2-(((S)-1-methoxy-4-methyl-1-oxopentan-2-yl) carbamoyl)aziridine-1-carboxylate ***2d***. Colorless oil. Yield: 60%; $[\alpha]_D^{20}$=−36.0 (*c*=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.88 (d, *J*=8.8 Hz, 1H), 4.57–4.49 (m, 1H), 3.66 (s, 3H), 2.99–2.96 (m, 1H), 2.37 (d, *J*=5.8 Hz, 1H), 2.25 (d, *J*=2.3 Hz, 1H), 1.59–1.45 (m, 3H), 1.38 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.60, 167.15, 159.82, 81.91, 51.99, 50.12, 41.02, 36.41, 31.46, 27.49, 24.45, 22.46, 21.51 ppm HRMS (ESI) calcd for $C_{15}H_{26}N_2O_5$ [M+Na^+]: 337.1739 *m*/*z*; observed: 337.1736 *m*/*z*.

4.3. General procedure for the synthesis of selenium- and sulfur-peptides (1)

To a 25 mL round-bottomed flask, under a nitrogen atmosphere, InI (0.121 g, 0.5 mmol) was added to a solution of the appropriate diorganyl diselenide (0.5 mmol) in dry CH_2Cl_2 (5 mL). The mixture was allowed to stir until all InI was dissolved (1 h). Following this, the appropriate protected *N*-Boc aziridine (0.5 mmol) was added and the reaction was stirred at room temperature for 2 h. The mixture was quenched with H_2O, extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. The solvent was then removed under vacuum yielding the crude products, which were purified by column chromatography on silica gel (8:2 hexane:ethyl acetate).

4.3.1. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenylselanyl)propanamido)-3-phenyl-propanoate ***1a***. Pale yellow solid. Yield: 77%; $[\alpha]_D^{20}$=−16.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.50–7.48 (m, 2H), 7.27–7.18 (m, 6H), 7.10–7.08 (m, 2H), 6.78 (d, *J*=7.5 Hz, 1H), 5.29 (d, *J*=8.0 Hz, 1H), 4.75 (q, J^1=13.7 Hz, J^2=5.8 Hz, 1H), 4.33 (br s, 1H), 3.66 (s, 1H), 3.20–3.15 (m, 2H), 3.11 (dd, J^1=13.9 Hz, J^2=5.8 Hz, 1H), 3.03 (dd, J^1=13.9 Hz, J^2=6.1 Hz, 1H), 1.39 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.23, 170.01, 154.96, 135.57, 132.83, 129.10, 129.03, 128.33, 127.18, 126.89, 80.11, 54.23, 53.19, 52.05, 37.66, 29.59, 28.03 ppm HRMS (ESI) calcd for $C_{24}H_{30}N_2O_5Se$ [M+Na^+]: 529.1218 *m*/*z*; observed: 529.1212 *m*/*z*.

4.3.2. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenylselanyl)propanamido)propanoate ***1b***. Pale yellow solid. Yield: 86%; $[\alpha]_D^{20}$=−16.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.46–7.44 (m, 2H), 7.18–7.15 (m, 3H), 6,91 (br s, 1H), 5.40 (d, *J*=8.0 Hz, 1H), 4.42–4.35 (m, 1H), 4.32 (br s, 1H), 3.22–3.16 (m, 2H), 1.34 (s, 9H), 1.27 (d, *J*=7.3 Hz, 3H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.64, 169.99, 155.10, 132.68, 128.91, 127.02, 79.92, 53.95, 52.17, 47.87, 29.70, 27.97, 17.84 ppm HRMS (ESI) calcd for $C_{18}H_{26}N_2O_5Se$ [M+Na^+]: 453.0905 *m*/*z*; observed: 453.0901 *m*/*z*.

4.3.3. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenylselanyl)propanamido)-3-methylbutanoate ***1c***. Pale yellow solid. Yield: 86%; $[\alpha]_D^{20}$=−33.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47–7.46 (m, 2H), 7.20–7.18 (m, 3H), 6.79 (br s, 1H), 5.30 (d, *J*=7.8 Hz, 1H), 4.42–4.39 (m, 1H), 4.29 (br s, 1H), 3.65 (s, 3H), 3.23–3.15 (m, 2H) 2.11–2.01 (m, 1H), 1.35 (s, 9H), 0.83 (t, *J*=8.3 Hz, 6H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.78, 170.44, 155.34, 133.03, 129.20, 127.37, 80.37, 57.16, 54.37, 52.07, 31.23, 29.38, 28.16, 18.84, 17.64 ppm HRMS (ESI) calcd for $C_{20}H_{30}N_2O_5Se$ [M+Na^+]: 481.1218 *m*/*z*; observed: 481.1218 *m*/*z*.

4.3.4. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenylselanyl)propanamido)-3-methylbutanoate ***1d***. Pale yellow solid. Yield: 83%; $[\alpha]_D^{20}$=−55.0 (*c*=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.84–7.46 (m, 2H), 7.20–7.18 (m, 3H), 6.62 (br s, 1H), 5.22 (br s, 1H), 4.52–4.25 (m, 1H), 4.27 (br s, 1H), 3.64 (s, 3H), 3.22–3.10 (m, 2H), 1.58–1.40 (m, 3H), 1.34 (s, 9H), 0.84 (d, *J*=5.2 Hz, 6H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.83, 170.23, 155.30, 133.03, 129.21, 127.39, 80.41, 54.23, 52.24, 50.77, 41.42, 29.52, 28.14, 24.67, 22.72, 21.83 ppm HRMS (ESI) calcd for $C_{21}H_{32}N_2O_5Se$ [M+Na^+]: 495.1374 *m*/*z*; observed: 495.1378 *m*/*z*.

4.3.5. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(p-tolylselanyl)propanamido)-3-phenyl-propanoate ***1e***. Pale yellow solid. Yield: 77%; $[\alpha]_D^{20}$=−13.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (d, *J*=7.8 Hz, 2H), 7.29–7.21 (m, 3H), 7.10–7.05 (m, 4H), 6.68 (d, *J*=7.0 Hz, 1H), 5.14 (br s, 1H), 4.75 (q, J^1=13.4 Hz, J^2=6.1 Hz, 1H), 4.27 (br s, 1H), 3.69 (s, 3H), 3.18–3.02 (m, 4H), 2.30 (s, 3H), 1.40 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.38, 170.11, 155.14, 137.57, 135.71, 133.56, 130.06, 129.28, 128.51, 127.09, 125.26, 80.35, 54.48, 53.33, 52.22, 37.87, 29.98, 29.63, 28.17, 21.02 ppm HRMS (ESI) calcd for $C_{25}H_{32}N_2O_5Se$ [M+Na^+]: 543.1374 *m*/*z*; observed: 543.1376 *m*/*z*.

4.3.6. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((4-methoxyphenyl)selanyl)propanamido)-3-phenylpropanoate ***1f***. Yellow solid. Yield: 85%; $[\alpha]_D^{20}$=−29.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (d, *J*=8.7 Hz, 2H), 7.28–7.20 (m, 3H), 7.10 (d, *J*=6.4 Hz, 2H), 6.79 (d, *J*=8.7 Hz, 2H), 6.70 (d, *J*=7.3 Hz, 1H), 5.17 (m, 1H), 4.76 (q, J^1=13.7 Hz, J^2=6.1 Hz, 1H), 4.25 (br s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 3.15–3.02 (m, 4H), 1.40 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.36, 170.11, 159.62, 155.13, 135.85, 135.68, 129.24, 128.47, 127.05, 118.87, 114.96, 80.30, 55.17, 54.41, 53.27, 52.18, 37.84, 30.58, 28.16 ppm HRMS (ESI) calcd for $C_{25}H_{32}N_2O_6Se$ [M+Na^+]: 559.1323 *m*/*z*; observed: 559.1320 *m*/*z*.

4.3.7. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((2-methoxyphenyl)selanyl)propanamido)-3-phenylpropanoate ***1g***. Pale yellow solid. Yield: 80%; $[\alpha]_D^{20}$=−14.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52–7.50 (m, 1H), 7.29–7.20 (m, 4H), 7.12 (d, *J*=6,4 Hz, 2H), 6.90–6.84 (m, 3H), 5.64 (br s, 1H), 4.78 (q, J^1=13.1 Hz, J^2=5.8 Hz, 1H), 4.34 (br s, 1H), 3.87 (s, 1H), 3.68 (s, 1H), 3.33 (br s, 1H), 3.16–3.00 (m, 3H), 1.39 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.34, 170.34, 158.39, 155.41, 135.73, 134.63, 129.30, 128.45, 126.98, 121.48, 118.22, 110.70, 80.20, 55.74, 54.16, 53.34, 52.17, 37.28, 28.29, 28.17 ppm HRMS (ESI) calcd for $C_{25}H_{32}N_2O_6Se$ [M+Na^+]: 559.1323 *m*/*z*; observed: 559.1322 *m*/*z*.

4.3.8. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((4-chlorophenyl)selanyl)propanamido)-3-phenylpropanoate ***1h***. Pale yellow solid. Yield: 96%; $[\alpha]_D^{20}$=−17.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44 (d, *J*=8.1 Hz, 2H), 7.29–7.20 (m, 5H), 7.08 (d, *J*=6.7 Hz, 2H), 5.18 (br s, 1H), 4.75 (q, J^1=13.4 Hz, J^2=6.1 Hz, 1H), 4.31 (br s, 1H), 3.70 (s, 3H), 3.24–3.03 (m, 4H), 1.41 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.32, 169.82, 155.05, 135.55, 134.41, 133.69, 129.33, 129.22, 128.52, 127.36, 127.12, 80.44, 54.24, 53.26, 52.29, 37.77, 30.07, 28.16 ppm HRMS (ESI) calcd for $C_{24}H_{29}ClN_2O_5Se$ [M+Na^+]: 563.0828 *m*/*z*; observed: 563.0826 *m*/*z*.

4.3.9. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((2-chlorophenyl)selanyl)propanamido)-3-phenylpropanoate ***1i***. White solid. Yield: 86%; $[\alpha]_D^{20}$=−27.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.42 (m, 1H), 7.30–7.26 (m, 1H), 7.23–7.16 (m, 4H), 7.12–7.09 (m, 2H), 7.03–7.00 (m, 2H), 6.66–6.64 (m, 1H), 5.17 (br s,

1H), 4.70 (q, J^1=13.5 Hz, J^2=6.0 Hz, 1H), 4.32 (br s, 1H), 3.63 (s, 3H), 3.29–3.26 (m, 1H), 3.16–3.11 (m, 1H), 3.06 (dd, J^1=13.8 Hz, J^2=5.8 Hz, 1H), 2.99 (dd, J^1=13.8 Hz, J^2=6.0 Hz, 1H), 1.33 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.26, 169.92, 155.11, 135.79, 135.59, 132.33, 130.01, 129.60, 129.24, 128.53, 128.08, 127.40, 127.11, 80.49, 54.02, 53.39, 52.26, 37.80, 28.49, 28.16 ppm HRMS (ESI) calcd for $C_{24}H_{29}ClN_2O_5Se$ [M+Na^+]: 563.0828 *m*/*z*; observed: 563.0827 *m*/*z*.

4.3.10. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((4-fluorophenyl)selanyl)propanamido)-3-phenylpropanoate ***1j***. Yellow solid. Yield: 71%; $[\alpha]_D^{20}$=−20.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.51–7.47 (m, 2H), 7.28–7.20 (m, 3H), 7.09 (d, *J*=6.7 Hz, 2H), 6.94 (t, *J*=8.7 Hz, 2H), 6.72 (d, *J*=7.6, 1H), 5.26 (d, *J*=7.8 Hz, 1H), 4.76 (q, J^1=13.4 Hz, J^2=6.1 Hz, 1H), 4.30 (br s, 1H), 3.68 (s, 3H), 3.15–3.06 (m, 4H), 1.41 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.32, 169.93, 163.70, 161.23, 155.04, 135.69, 135.61, 135.56, 129.17, 128.44, 127.02, 123.53, 116.40, 116.18, 80.27, 54.21, 53.21, 52.18, 37.74, 30.48, 28.11 ppm HRMS (ESI) calcd for $C_{24}H_{29}FN_2O_5Se$ [M+Na^+]: 547.1123 *m*/*z*; observed: 547.1122 *m*/*z*.

4.3.11. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((3-(trifluoromethyl)phenyl)selanyl)pro-panamido)-3-phenylpropanoate ***1l***. Yellow oil. Yield: 82%; $[\alpha]_D^{20}$=−9.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.75 (s, 1H), 7.67 (d, *J*=7.8 Hz, 1H), 7.47 (d, *J*=7.6 Hz, 1H), 7.35 (t, *J*=7.8 Hz, 1H), 7.27–7.19 (m, 3H), 7.09 (d, *J*=6.7 Hz, 2H), 6.85 (d, *J*=7,3 Hz, 1H), 5.39 (d, *J*=7,8 Hz, 1H), 4.78 (q, J^1=13.7 Hz, J^2=6.1 Hz, 1H), 4.41 (br s, 1H), 3.67 (s, 3H), 3.25–3.28 (m, 2H), 3.12 (dd, J^1=13.7 Hz, J^2=5.8 Hz, 1H), 3.05 (dd, J^1=13.7 Hz, J^2=6.1 Hz, 1H), 1.40 (s, 9H) ppm ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.26, 169.87, 155.03,135.66, 135.50, 131.21 (q, $^2J_{CF}$=32.2 Hz), 129.32, 129.09, 126.96, 123.80, 123.48 (q, $^1J_{CF}$=272.9 Hz), 80.24, 54.05, 53.22, 52.12, 37.61, 29.87, 27.99 ppm HRMS (ESI) calcd for $C_{25}H_{29}F_3N_2O_5Se$ [M+Na^+]: 597.1091 *m*/*z*; observed: 597.1088 *m*/*z*.

4.3.12. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(butylselanyl)propanamido)-3-phenylpropanoate ***1m***. Pale yellow solid. Yield: 79%; $[\alpha]_D^{20}$=−3.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.13 (m, 3H), 7.06–7.03 (m, 2H), 6.83 (d, *J*=7.3 Hz, 1H), 5.34 (d, *J*=7.0 Hz, 1H), 4.76 (q, J^1=13.8 Hz, J^2=6.0 Hz, 1H), 4.23 (br s, 1H), 3.61 (s, 3H), 3.06 (dd, J^1=13.8 Hz, J^2=5.8 Hz, 1H), 3.01 (dd, J^1=13.8 Hz, J^2=6.0 Hz, 1H), 2.87–2.82 (m, 1H), 2.72 (dd, J^1=12.8 Hz, J^2=6.2 Hz, 1H), 2.50 (t, *J*=7.3 Hz, 2H), 1.57–1.49 (m, 2H), 1.36 (s, 9H), 1.32–1.25 (m, 2H), 0.82 (t, *J*=7.3 Hz, 3H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.28, 170.29, 155.04, 135.55, 129.11, 128.36, 126.93, 80.08, 54.08, 53.22, 52.11, 37.69, 32.33, 28.09, 25.57, 24.70, 22.69, 13.39 ppm HRMS (ESI) calcd for $C_{22}H_{34}N_2O_5Se$ [M+Na^+]: 509.1531 *m*/*z*; observed: 509.1534 *m*/*z*.

4.3.13. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenylthio)propanamido)-3-phenylpropanoate ***1n***. White solid. Yield: 86%; $[\alpha]_D^{20}$=−14.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30 (d, *J*=7.3 Hz, 2H), 7.22–7.11 (m, 6H), 7.01 (d, *J*=7.8 Hz, 2H), 6.70 (d, *J*=7.3 Hz, 1H), 5.18 (d, *J*=7.0 Hz, 1H), 4.69 (q, J^1=12.8 Hz, J^2=5.7 Hz, 1H), 4.17 (br s, 1H), 3.61 (s, 3H), 3.18 (br s, 1H), 3.04 (dd, J^1=13.8 Hz, J^2=5.7 Hz, 1H), 2.97 (dd, J^1=13.8 Hz, J^2=5.7 Hz, 1H), 1.34 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.28, 169.84, 155.09, 135.56, 134.50, 130.04, 129.18, 129.03, 128.45, 127.02, 126.74, 80.36, 53.83, 53.28, 52.25, 37.72, 35.99, 28.11 ppm HRMS (ESI) calcd for $C_{24}H_{30}N_2O_5S$ [M+Na^+]: 481.1773 *m*/*z*; observed: 481.1768 *m*/*z*.

4.4. General procedure for the synthesis of telluro-peptides (1)

To a 25 mL round-bottomed flask, under a nitrogen atmosphere, diorganyl ditelluride (0.5 mmol) was added to a solution of the *N*-Boc aziridine **2a** (0.174 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL), followed by InI (0.121 g, 0.5 mmol). The mixture was allowed to stir at room temperature for 2 h. The mixture was quenched with H_2O, extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were dried over Na_2SO_4 and filtered. The solvent was then removed under vacuum yielding the crude products, which were purified by column chromatography on silica gel (8:2 hexane:ethyl acetate).

4.4.1. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-(phenyltellanyl)propanamido)-3-phenylpropanoate ***1o***. Orange oil. Yield: 80%; $[\alpha]_D^{20}$=−18.0 (*c*=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65–7.62 (m, 2H), 7.21–7.01 (m, 8H), 6.72 (d, *J*=7.0 Hz, 1H), 5.21 (d, *J*=8.2 Hz, 1H), 4.67 (q, J^1=14.0 Hz, J^2=6.4 Hz, 1H), 4.39 (br s, 1H), 3.60 (s, 3H), 3.16–2.93 (m, 4H), 1.32 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.25, 170.62, 155.10, 138.35, 135.52, 129.14, 128.39, 127.71, 126.97, 112.16, 80.19, 54.51, 53.19, 52.17, 37.64, 28.07, 10.82 ppm HRMS (ESI) calcd for $C_{24}H_{30}N_2O_5Te$ [M+Na^+]: 579.1115 *m*/*z*; observed: 579.1109 *m*/*z*.

4.4.2. (S)-Methyl 2-((R)-2-((tert-butoxycarbonyl) amino)-3-((4-methoxyphenyl)tellanyl)propanamido)-3-phenylpropanoate ***1p***. Orange oil. Yield: 50%; $[\alpha]_D^{20}$=−16.0 (*c*=1, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61 (d, *J*=8.5 Hz, 1H), 7.23–7.14 (m, 4H), 7.03 (d, *J*=8.3 Hz, 2H), 6.67 (d, *J*=8.8 Hz, 2H), 6.62 (br s, 1H), 5.11 (br s, 1H), 4.68 (q, J^1=13.6 Hz, J^2=6.0 Hz, 1H), 4.32 (br s, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 3.09–2.90 (m, 4H), 1.33 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.37, 170.70, 159.88, 155.19, 141.10, 135.64, 129.24, 128.51, 127.08, 115.28, 100.97, 80.36, 55.09, 54.73, 53.29, 52.27, 37.81, 28.19, 11.06 ppm HRMS (ESI) calcd for $C_{25}H_{32}N_2O_6Te$ [M+Na^+]: 609.1220 *m*/*z*; observed: 609.1217 *m*/*z*.

4.5. Procedure for the synthesis (*S*)-methyl 2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((4-methylbenzoyl)selanyl)propanamido)-3-phenylpropanoate 1q

To a 25 mL round-bottomed flask, under a nitrogen atmosphere, di-(4-methylbenzoyl) diselenide (0.198 g, 0.5 mmol) was added to a solution of the *N*-Boc aziridine **2a** (0.174 g, 0.5 mmol) in dry CH_2Cl_2 (5 mL), followed by InI (0.121 g, 0.5 mmol). The mixture was allowed to stir at room temperature for 7 h. The mixture was quenched with H_2O, extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions were collected, dried over Na_2SO_4, and filtered. The solvent was then removed under vacuum yielding the crude products, which were purified by column chromatography on silica gel (8:2 hexane:ethyl acetate). The chalcogen peptide **1q** was used in the next step. Pale yellow solid; Yield: 50%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.72 (d, *J*=8.2 Hz, 2H), 7.20–7.14 (m, 5H), 7.06 (d, *J*=7.6 Hz, 2H), 6.80 (br s, 1H), 5.22–5.20 (m, 1H), 4.76 (q, J^1=12.3 Hz, J^2=5.2 Hz, 1H), 4.36 (br s, 1H), 3.60 (s, 3H), 3.41–3.21 (m, 2H), 3.13 (dd, J^1=14.0 Hz, J^2=5.8 Hz, 1H), 3.01 (dd, J^1=14.0 Hz, J^2=6.4 Hz, 1H), 2.33 (s, 3H), 1.32 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=194.59, 171.37, 170.33, 164.94, 145.10, 135.84, 135.66, 129.48, 129.27, 128.53, 127.45, 127.07, 80.36, 55.12, 53.39, 52.27, 37.93, 28.16, 26.61, 21.73 ppm HRMS (ESI) calcd for $C_{26}H_{32}N_2O_6Se$ [M+Na^+]: 571.1323 *m*/*z*; observed: 571.1302 *m*/*z*.

4.6. Procedure for the synthesis (2*S*,2′*S*)-dimethyl 2,2′-(((2*R*,2′*R*)-3,3′-diselanediylbis(2-((*tert* butoxycarbonyl)amino)propanoyl)) bis(azanediyl))bis(3-phenylpropanoate) 1r

To a solution of **1q** (100 mg, 0.18 mmol in DMF 2.0 mL) in a 25 mL round-bottomed under a nitrogen atmosphere, piperazine (20 mg, 0.24 mmol) was added and the mixture was stirred at room temperature for 2 h (TLC monitoring; 7:3 hexane:ethyl acetate). The reaction mixture was extracted with EtOAc (2×15 mL), the combined organic layer was washed with 2 M HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum yielding the crude product, which was purified by column

chromatography on silica gel (7:3 hexane:ethyl acetate). Yellow solid. Yield: 43%; $[\alpha]_D^{20}=-7.0$ (c=1, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.62 (d, J=7.6 Hz, 1H), 7.19–7.08 (m, 5H), 5.41 (d, J=9.4 Hz, 1H), 4.77 (q, J^1=14.3 Hz, J^2=8.2 Hz, 1H), 4.62 (br s, 1H), 3.59 (s, 3H), 3.21–3.11 (m, 3H), 2.97 (dd, J^1=14.0 Hz, J^2=8.2 Hz, 1H), 1.36 (s, 9H) ppm ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.53, 170.38, 155.42, 136.20, 129.05, 128.48, 126.93, 80.08, 54.79, 53.91, 52.22, 37.70, 36.02, 28.30 ppm HRMS (ESI) calcd for $C_{36}H_{50}N_4O_{10}Se_2$ [M+Na$^+$]: 881.1755 m/z; observed: 881.1759 m/z.

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Supplementary data

Electronic Supplementary data (ESI) available: experimental procedures, details ^{1}H and ^{13}C NMR spectra and high resolution MS. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.08.082.

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