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Synthesis of Selenoxo Peptides and Oligoselenoxo Peptides Employing LiAlHSeH⊥

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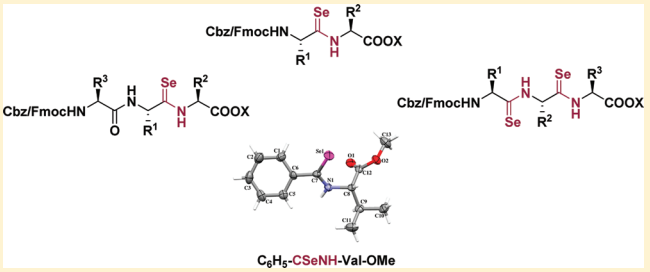
Supporting Information

ABSTRACT: Synthesis of selenoxo peptides by the treatment of N^{α}-protected peptide esters with a combination of PCl_5 and LiAlHSeH is delineated. The method is simple, high-yielding, and free from racemization. Thus obtained selenoxo peptides are used as units for N-terminal chain extension through N^{α}-deprotection/coupling to yield peptide−selenoxo peptide hybrids. Multiple selenation is demonstrated by conversion of two peptide bonds of tripeptides into selenoxo peptide bonds. Amino acid derived arylamides are also converted into aryl selenoamides. C_6H_5-CSeNH-Val-OMe **8f** is obtained as single crystal, and its structure was determined through X-ray diffraction study.



INTRODUCTION

Intrinsic inadequacies of native peptides as therapeutic agents are often ameliorated by modification of the peptide backbone.[1] Thus, an array of peptidomimetics containing non-native linkages as peptide bond surrogates have been designed to suit their use in biology.[2] Such molecules have shown to be useful in biology,[3] medicine,[4] pharmacology,[5] and in organic synthesis (as organocatalysts).[6,7] In the pursuit of mimicking the peptide's three-dimensional structure through the use of peptide bond isosteres, thionation of peptide bonds has received considerable attention (Figure 1).[8] Thioxo peptides,[9] popularly known as thiopeptides, where one or more "CONH" bonds (peptide bonds) are converted to "CSNH" bonds, are shown to possess remarkably different and fruitful chemical, physical, and biological properties than native peptides.[10] They exhibit increased stability against enzymatic degradation.[11]

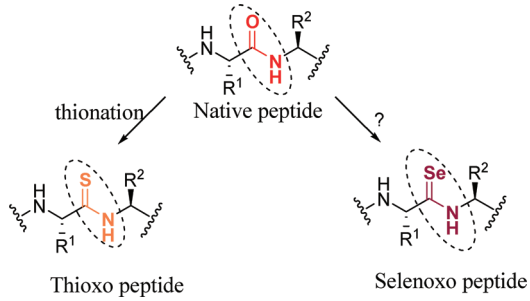


Figure 1. Representation of native peptide, thioxo peptide, and selenoxo peptides.

Furthermore, their conformational and catalytic properites[12,13] and their importance in the total synthesis of natural products[14] have also been demonstrated. Because of the good nucleophilic nature of sulfur, thiopeptides are employed for the synthesis of triazoles,[15] tetrazoles,[16] and thiazoles,[17] reduced amide isosteres,[18] and a wide range of peptidomimetics as well.

Selenium, the next element after sulfur, shares several properties with the latter;[19] hence, replacement of O or S in biologically active molecules with Se has been found to be beneficial.[20] Synthesis of organoselenuium compounds has been an intense topic of research because of the broad spectrum of biological activity of organoselenuium compounds[21] and significantly different properties compared to O and S counterparts. Many of the organoselenuium compounds possess anticancer, antiviral, antibacterial, and antihypertensive activities.[22] Incorporation of Se into proteins has shown to facilitate structure determination through X-ray crystallography.[23] Notably, selenoamides have elicited considerable interest as pharmaceutical agents[24,25] and as synthetically important molecules (e.g., precursors for heterocycles).[26] Among the myriad protocols for the preparation of selenoamides, reaction of nitriles,[27] amides,[28] or imidoyl chlorides[29] with selenating reagents have been largely employed. A wide range of selenium transfer reagents such as Woollins,[30] P_2Se_5,[31] Se/CO,[32] Al_2Se_3,[33] NaSeH,[34] LiAlHSeH,[35] $(Et_4N)_2WSe_4$,[36] $(Me_3Si)_2Se$,[37] $(Me_2Al)_2Se$,[38] and DIBAL-H/Se[39] have also been developed. Among these, Woollins reagent and LiAlHSeH (Ishihara reagent) have been preferred, and the latter is particularly

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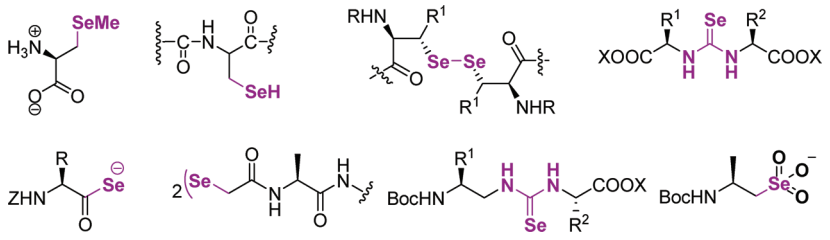


Figure 2. Selected examples of selenium linked peptides and amino acids.

interesting because of high reactivity, good yields, and easy and cost-effective preparation. Reaction of imidoyl chloride with LiAlHSeH has been demonstrated for the preparation of tertiary selenoamides and a few secondary selenoamides. Perhaps aliphatic selenoamides are expected to be less stable than thioamides; thus efforts to obtain such selenoamides are rare.[40]

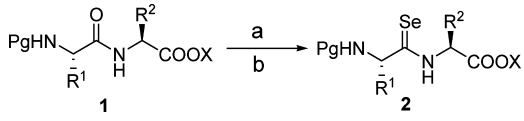
Stimulated by promising applications of organoselenuium compounds, chemists have focused toward the preparation of selenium containing biomolecules. At present, a number of selenium possessing enzymes,[41] proteins,[42] peptides,[43] carbohydrates,[44] nucleotides, and nucleosides[45] have been synthesized, and their biological activities are under scrutiny. Of particular interest is the selenocystine possessing peptides (selenopeptides) and selenium tethered unnatural amino acids/amino acid derivatives, which have been used for the assembly of newer classes of peptidomimetics with potential pharmacological properties (Figure 2).[46] With the advent of methods for the incorporation of selenium, there has been a marked growth in the diversity of selenium containing peptide and peptide mimics.

Interestingly, despite the diversity in the currently available Se containing amino acid/peptide derivatives, there has not been a focused effort in isoelectronic replacement of the oxygen atom of the peptide bond with a selenium atom leading to selenoxo peptides. When this work was underway, Fischer et al. reported three examples of *N*-Boc protected selenoxo dipeptide methyl esters, which were prepared by refluxing a solution of dipeptide methyl ester with Woollin's reagent.[47] The synthetic methodology was not further elaborated, presumably as a consequence of low yield (35−42%) of the reaction. However, biophysical studies revealed that these molecules could display perspective applications as photoswitches.[48] Apart from this, a thorough investigation on the synthesis of selenoxo peptides has not appeared to date. In this communication, we report the preparation of a wide range of *N*-protected selenoxo dipeptide esters,[47c] diselenoxo tripeptide esters and peptide-selenoxo peptide hybrids,[47] and studies on their synthetic methodology. The protocol is simple and involves addition of LiAlHSeH to in situ generated imidoyl chloride from protected dipeptide ester. Furthermore, selenation of amino acid aryl amides are also described.

RESULTS AND DISCUSSION

The selenating reagent LiAlHSeH was prepared according to the method reported by Ishihara,[35] which involves treatment of $LiAlH_4$ with selenium powder in THF. In the initial part of the study, Cbz-Val-Ala-OMe **1a** was treated with PCl_5 for 20 min at rt[49] followed by the addition of freshly prepared solution of LiAlHSeH. After 10 min of the reaction, the expected selenoxo peptide **2a** was obtained in 58% yield along with significant amount of unreacted peptide **1a** (26%, Scheme 1). To improve

Scheme 1. Synthesis of Selenoxo Dipeptidomimetics 2[a]



Pg = Fmoc, Z
X = Me, Et, Bn

[a]Reagents and conditions: (a) PCl_5 (1.0 equiv), DMF (0.3 equiv with respect to the amount of PCl_5), dry C_6H_6 (5 mL), rt, 20 min; (b) LiAlHSeH (1.0 equiv), rt, 5−10 min.

the yield, a systematic study on the usefulness of different chlorinating agents (required for the conversion of the peptide into imidoyl chloride intermediate prior to selenation) and solvents was undertaken. $POCl_3$ and $SOCl_2$ have poor efficiency to generate imidoyl chloride; consequently, their use led to poor yield of selenoxo peptide **2a** (Table 1, entries 1−3), where as triphosgene and oxalyl chloride did not yield the expected product (Table 1, entries 5 and 6). However, further investigations revealed that PCl_5 in presence of a catalytic amount of DMF (Table 1, entry 8) drastically increases the yield to 91%.

Table 1. Optimization of Reaction Conditions for the Synthesis of 2a

entry	chlorinating reagent[a]	solvent	yield (%)
1	$POCl_3$	CH_2Cl_2	42
2	$SOCl_2$	$CHCl_3$	38
3	PCl_5	CH_2Cl_2	41
4	PCl_5	C_6H_6	58
5	triphosgene	C_6H_6	NR[b]
6	oxalyl chloride	C_6H_6	NR[b]
7	$POCl_3$	C_6H_6	31
8	PCl_5 + DMF[c]	C_6H_6	91

[a]1.1 equiv was used. [b]NR: No reaction. [c]0.3 equiv of DMF with respect to the amount of PCl_5.

The selenoxo dipeptide **2a** was obtained upon reaction for 25 min at rt. The product was inferred initially by the TLC analysis [R_f 0.42 (ethyl acetate/hexane 3:7), reddish brown spot on TLC]. A simple workup followed by column purification gave the pure product (IR absorption, strong peak at 1538 cm^{-1} for —C═Se stretching; ^{13}C NMR δ 211 ppm for —C═Se carbon; ^{77}Se NMR δ 523.14 ppm). Prior to finding the scope of the above optimized protocol to be applicable for a series of peptides, we confirmed the generation of imidoyl chloride from dipeptides employing PCl_5/DMF to be free from racemization.[50]

Versatility of the method for selenation of the peptide bond was next examined by conversion of a series of dipeptides into selenoxo peptides. The different substrate used had variations

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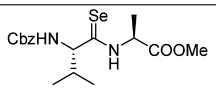
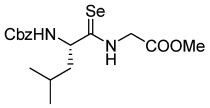
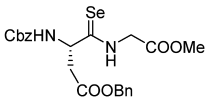
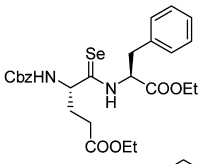
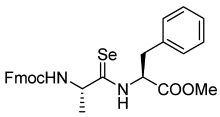
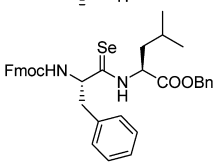
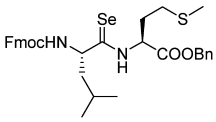
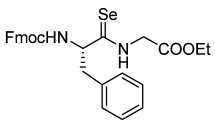
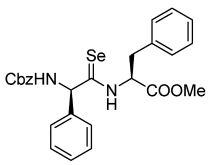
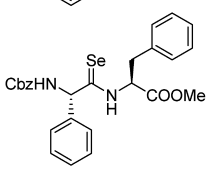
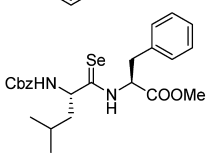
Table 2. List of Selenoxo Dipeptide Esters Synthesized

Entry	Selenoxo dipeptide esters **2**	Yield[a] (%)	$[\alpha]^{D}25$ (*c* 1, $CHCl_3$)	^{77}Se NMR ($CDCl_3$)	HRMS Calcd	$[M+Na]^+$ Obsd
2a		91	-98.4	523.1	423.0799	423.0796
2b		88	-136.1	494.9	401.09	401.0[b]
2c		90	+78.1	511.5	515.0697	515.0665
2d		86	-135.8	525.4	633.1480	633.1429
2e		85	-18.6	495.5	559.1112	559.0922
2f		91	-59.7	519.8	677.1894	677.1827
2g		90	-139.1	522.2	661.1615	661.1603
2h		89	-89.8	523.2	559.1112	559.1110
2i		85	+14.9	527.1	533.0955	533.0924
2j		88	-143.3	534.5	533.0955	533.0824
2k		79	-126.1	544.3	513.1628	513.1236

[a]Yields of isolated products. [b]ESI-MS $[M + Na]^+$.

with respect to N and C protectors and usage of side chain protected bifunctional amino acids. As delineated in Table 2, it was found that all the selenoxo peptides were obtained in good to excellent yields after column purification. The isolated selenoxo peptides were stable for up to 4−5 days when stored at 5 °C.

The first step is the reaction of DMF with PCl_5 to give a reactive intermediate **I** (Vilsmeier type reagent), iminium chloride (for ESI-MS of the intermediate, see the Supporting Information S157). In the next step, the peptide reacts with **I** to form imidoyl chloride **III** with the release of DMF (Scheme 2). The **III** then reacts with LiAlHSeH to produce the imidoyl selenol species, which rearranges into the desired selenoxo peptide. The observed byproduct of the reaction is *N*,*N*-dimethylselenoformamide, which was produced in varying amounts depending on the equivalents of DMF used. It was observed to an extent of 8% with 0.3 equiv of DMF (0.1 mL/1.0 g of PCl_5; for LC−MS profile of crude product **2e**, see the

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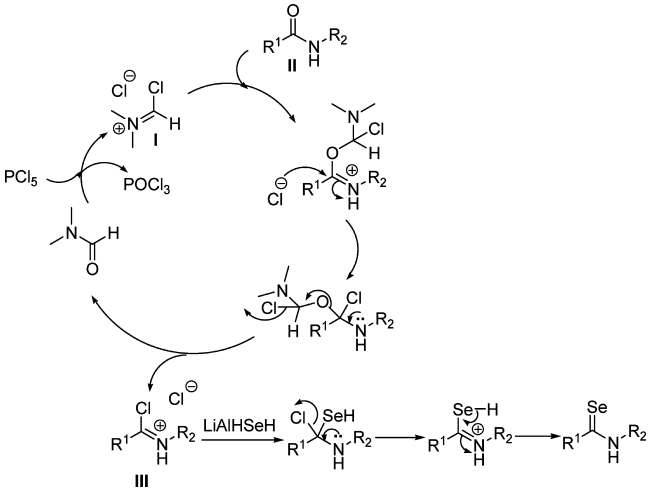
Scheme 2. Postulated Mechanism for the DMF/PCl_5-Mediated Selenation of the Peptide Bond



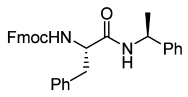
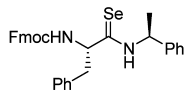
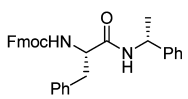
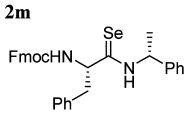
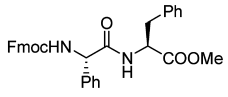
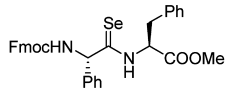
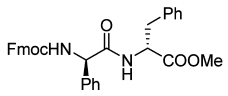
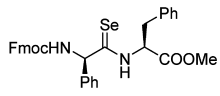
Supporting Information S156). However, when an equal amount of DMF was used (1.0 mL/1.0 g of PCl_5, Vilsmeier reagent), its amount increased to 45% (for LC–MS profile of crude product **2e**, see the Supporting Information S155). Hence, the amount of DMF is crucial in minimizing the formation of *N*,*N*-dimethylselenoformamide. It has been found that 0.3 equiv of DMF (0.1 mL of DMF for 1.0 g of PCl_5) is sufficient for the present synthesis [the formation of Vilsmeier type reagent takes place at this amount of DMF as evident by the ESI-MS spectrum of the reaction mixture before the addition of peptide, $(M + Cl^-)^+$]. The catalytic activity of DMF at lower equivalents has been recorded in earlier reports.[51]

Racemization Studies. To ascertain whether the present protocol is racemization free, ^{1}H NMR and HPLC analyses were carried out on epimeric selenoxo peptides synthesized via the present protocol. Fmoc-Phe-OH was coupled with (*R*)- and (*S*)-phenethylamine separately by standard peptide coupling conditions, and the resulting products were converted to selenoamides **2l** and **2m** via the present route (Table 3). The ^{1}H NMR spectrum of **2l** and **2m** had one methyl group doublets at δ 1.20 ppm (J = 6.0 Hz) and 1.26 ppm (J = 9 Hz), respectively, while the intentionally made mixture of epimers **2l** and **2m** showed two doublets for methyl group at δ 1.295 ppm (J = 3.0 Hz) and 1.32 ppm (J = 6 Hz), corresponding to two doublets (see the Supporting Information for ^{1}H NMR spectrum and HPLC chromatogram of 1:1 mixture of **2l** and **2m**). The HPLC profile also had distinct major peak corresponding to only one epimer. A similar ^{1}H NMR and HPLC profile was shown by epimers **2n** and **2o** (distinct singlets at δ 3.51 for **2n** and 3.54 for **2o** corresponding to respective methyl ester protons, whereas a mixture of **2n** and **2o** showed two singlets at δ 3.50 and 3.52). Because of broad chemical shift range and sensitivity of the ^{77}Se nucleus (over 3000 ppm, abundance: 6.93×10^{-3} with respect to ^{1}H and 2.98 compared to ^{13}C), the ^{77}Se NMR spectroscopy has emerged as a useful technique for determining the optical purity. Consequently, several selenium containing chiral derivatizing agents have been developed to estimate the enantiomeric ratio via ^{77}Se NMR.[52] Accordingly, it would be possible to evaluate the optical purity of the selenoxo peptides using ^{77}Se NMR,[52e] which confirmed that the present protocol yields optically homogeneous selenoxo peptides.

Peptide–Selenoxo Peptide Hybrids: *N*-Terminal Extension of Selenoxo Dipeptides. The chain extension from the *N*-terminus of Fmoc protected selenoxo peptides leading to tri/tetra peptides bearing one selenoxo peptide bond and the peptide bond(s) in the backbone was undertaken. In a typical example, selenoxo dipeptide **2e** was treated with diethylamine in dry DCM (40%), and the free amino selenoxo dipeptide ester **3e** (not isolated) was coupled to Fmoc-Val-OH under standard peptide coupling conditions using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/ 1-hydroxybenzotriazole (HOBt) (Scheme 3). The resulting hybrid peptide **4e** was isolated after column purification in good yield (Table 4). Using the same strategy, tri- and tetrapeptidemimetics **4a–4f** were obtained in good yields.

Diselenoxo Tripeptides: Tripeptides Possessing Two Selenoxo Bonds. The scope of the present protocol was explored for selenation of two peptide bonds of tripeptide esters **5** (preparation of tripeptide esters **5** has been cited in the

Table 3. Racemization Experiment Carried out for Two Pairs of Diastereomers

Entry	Dipeptide **1**	Selenoxo dipeptide **2**	$[\alpha]^D_{25}$ (c 1 $CHCl_3$)	^{77}Se NMR ($CDCl_3$)	HPLC[a]
1		**2l** 	-57.9	539.7	20.0
2		**2m** 	+62.8	535.1	19.5
3		**2n** 	+29.2	533.6	20.1
4		**2o** 	-58.9	534.1	19.6

[a]HPLC particulars: λ = 254 nm, flow 0.50 mL/min; method: gradient 0.1% TFA water-acetonitrile; acetonitrile 30–70% in 30 min.

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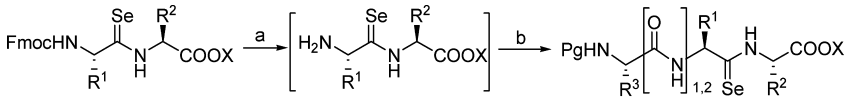
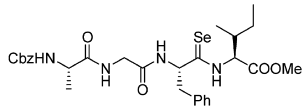
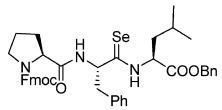
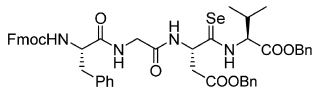
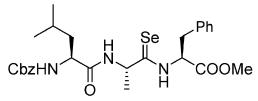
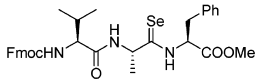
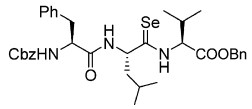
Scheme 3. Synthesis of Peptide−Selenoxo Peptide Hybrids 4[a]



[a]Reagents and conditions: (a) DEA (40%), CH_2Cl_2, rt, 30 min; (b) Pg-Xaa−OH, EDC, HOBt CH_2Cl_2, 0 °C to rt, 1−2 h.

Table 4. List of Selenoxo Peptide−Peptide Hybrids Prepared

Entry	Compound **4**	Yield[a] (%)	HRMS (M+Na)$^+$ Calcd/ Obsd
1	**4a** 	78	641.1854/ 641.1846
2	**4b** 	85	752.2603/ 752.2601
3	**4c** 	79	903.28/ 903.2[b]
4	**4d** 	80	584.1640/ 584.1630
5	**4e** 	76	658.1796/ 658.1702
6	**4f** 	86	688.23/ 688.1[c]

[a]Yields are given after column purification. [b]ESI-MS $[M + H]^+$. [c]ESI-MS $[M + Na]^+$.

Experimental Section). For this, initial experiments were carried out using 2 equiv of each reagent; however, it lead to the isolation of the product **6** in about 38−42% yield. Later, on careful optimization, it was found that 3 equiv of PCl_5, 0.9 equiv of DMF, and 3.2 equiv of LiAlHSeH was necessary to obtain the acceptable yield of products **6** (Scheme 4, Figure 3). However, further increase in the amount of reagents led to difficulty in isolation of the desired product.

Selenation of Amino Acid Arylamides. Amino acid arylamides are widely used in preparation of polymers, dendrimers, peptidomimetics, and pharmaceuticals.[53] The present study also encompassed the conversion of amino acid arylamides to selenoamides. The amino acid aryl amides **7a−e** were prepared by coupling N^{α}-protected amino acids to diversely functionalized aryl amines containing OH, NO_2, NH_2 on the aromatic ring. Another two N^{α}-acyl amino acid

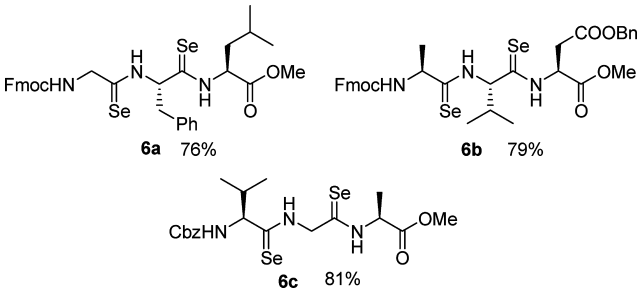


Figure 3. Isolated yields of diselenoxo tripeptide esters synthesized.

esters **7f** and **7g** were also synthesized by coupling amino acid ester with aromatic acids. The above arylamides were then treated with PCl_5 and LiAlHSeH by using the conditions shown in Scheme 1. The products **8** (Table 5) were obtained in moderate to good yields.

The selenoxo peptide esters **2a−2o** have been found to be stable for several days at room temperature under anhydrous conditions. For the isolation of these compounds, a regular workup involving a sequential washing of Na_2CO_3 (5%) and dilute HCl (10%) followed by column chromatography was carried out. Their stability under basic conditions has been demonstrated by synthesizing selenoxo peptide esters **4** through treatment of DEA to Fmoc protected selenoxo peptide esters. The products **4** and **6** have also shown to possess a similar degree of stability toward acid and base treatment. A small degree of decomposition (selenium−oxygen exchange) was observed for when selenoxo peptides were kept in air for 3−4 days. In the case of seleno arylamides of amino acids **7**, no detectable degradation was observed even on long storage for over a month under anhydrous condition. Further, Fischer et al. delineated on the stability of selenoxo peptides.[47a] The selenoxo peptides synthesized by them were stable at pH 4.2, 6.0, and 7.2 for over 3−4 days.

Selenoamide C_6H_5-CSeNH-Val-OMe **8f** was obtained as single crystal, and its structure was solved through X-ray diffraction (CCDC number 802869). An ORTEP drawing of **8f** is shown in Figure 4, along with the selected bond lengths, bond angles, and torsion angles. An anti-configuration with respect to C−N single bond in **8f** is established by the torsion angle C6−C7−N1−C8 of 177.8(5)°. The benzene ring (C1−C6) in the molecule deviates from the plane formed by the Se1, C7, C6, and N1 atoms; the dihedral angle between the least-squares planes being 36.9(2)°. Similar deviation of the aromatic

Scheme 4. Synthesis of Diselenoxo Tripeptides 6

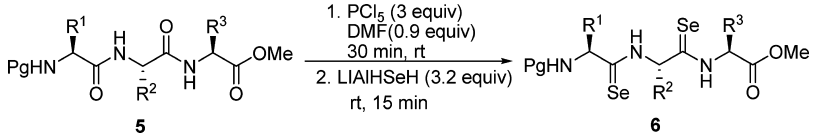


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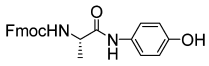
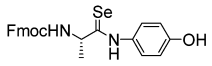
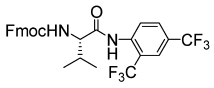
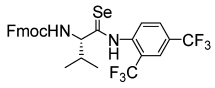
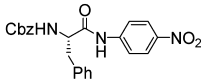
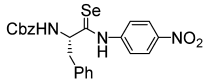
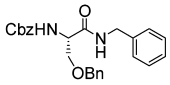
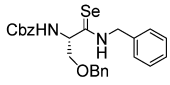
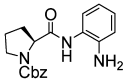
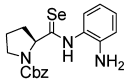
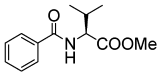
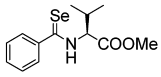
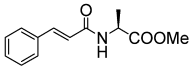
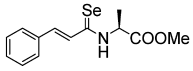
Table 5. Synthesis of Amino Acid Derived Aryl Selenoamides

Entry	Reactant **7**	Product **8**	Yield[a] (%)	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)	^{77}Se NMR
1	**7a** 	**8a** 	86	-18.6	604.6
2	**7b** 	**8b** 	74	-34.1	596.7
3	**7c** 	**8c** 	69	-11.8	632.2
4	**7d** 	**8d** 	82	-38.4	582.9
5	**7e** 	**8e** 	71	-45.2	606.2
6	**7f** 	**8f** 	79	+ 55.1	613.1
7	**7g** 	**8g** 	89	-22.1	575.8

[a]Yields of the purified product.

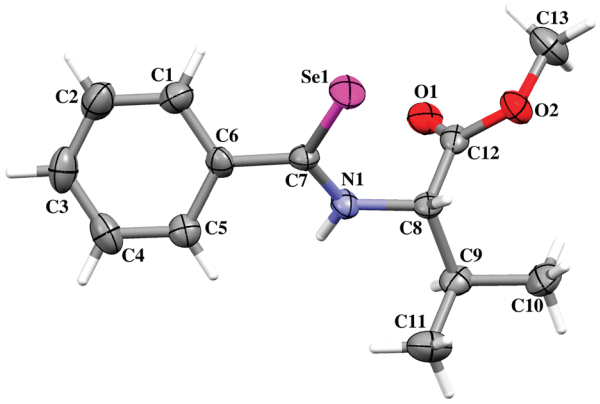


Figure 4. An ORTEP view of compound **8f** with atom numbering scheme. Thermal ellipsoids are drawn at the 30% probability level. Selected bond lengths (Å): Se1−C7 1.813 (5); N1−C7 1.324(6); N1−C8 1.461(5). Selected bond angles (deg): N1−C7−Se1 122.2(3); C6−C7−Se1 121.2 (4). Selected torsion angles (deg): C5−C6−C7−Se1 −143.5 (5); C8−N1−C7−Se1 −2.8 (7); C1−C6−C7−Se1 −36.5 (8); C6−C7−N1−C8 177.8(5).

ring attached to the carbon atom of the selenoamide group has been reported in the literature.[54] The C7−Se1 bond length [1.813(5) Å] in **8f** is comparable with that observed in related structures[55] but shorter than a typical C−Se single bond (1.94 Å),[56] which implies that the carbon−selenium bond in the compound shows a partial double-bond character.

The crystal packing in **8f** exhibits N−H···O hydrogen bonds forming cyclic rings which are further linked through $\pi-\pi$ interactions. In the graph-set notation, the cyclic rings can be denoted by $R_m^n(X)$, where *m* and *n* are the number of donor and acceptor atoms forming the ring and *X* is the total number of atoms in the pattern.[57] In **8f**, the N1-atom in the molecule at (*x*, *y*, *z*) is hydrogen bonded to O1-atom in the molecule at (−*x*, −*y*, 2−*z*) [N1···O1 2.976(5) Å, H1···O1 2.14 Å, N1−H1···O1 163°], thus generating an $R_2^2(10)$ ring centered at (0, 0, 1) (Figure 5). The $\pi-\pi$ interaction between phenyl rings (C1−C6) at (*x*, *y*, *z*) and (1−*x*, 1−*y*, 2−*z*) with an interplanar spacing of 3.348(3)Å, the ring-centroid separation of 3.662(4)Å, and ring offset of 1.49 Å connects the $R_2^2(10)$

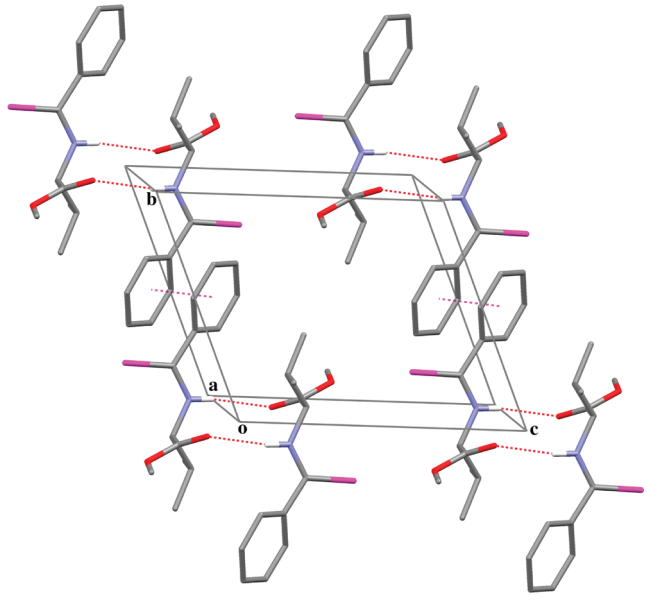


Figure 5. Packing diagram of compound **8f** as viewed as crystallographic *a*-axis. The dashed lines indicate intermolecular N−H···O hydrogen bonds, and $\pi\cdots\pi$ interactions.

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rings, thus forming parallel chains propagating along the [010] direction (Figure 5).

CONCLUSION

Selenoxo peptides and oligoselenoxo peptides can be prepared in good yields employing the selenating reagent LiAlSeH. The method offers a high-yielding, racemization-free, and cost-effective way to access the title compounds. The versatility of the method is demonstrated by its application to peptides containing differential N^{α}- and carboxyl protection and those with protected bifunctional amino acid residues. The selenoxo peptides are isolable, possess good degree of stability, and further, selenoxo peptide−peptide hybrids can be prepared by peptide coupling to N^{α}-free amino selenoxo peptides. One example of a selenated N^{α} acyl amino acid ester (**8f**) has been crystallized, and its structure was solved by X-ray crystallography. The different types of selenoxo peptides described present new classes of compounds for a variety of studies.

EXPERIMENTAL SECTION

General Information. Melting points were recorded on a Kofler hot block and are uncorrected. ^{1}H, ^{13}C, and ^{77}Se NMR were recorded in $CDCl_3$ solution with TMS as internal standard. Mass spectra were recorded on high resolution mass spectra (HRMS) Q-T of micro mass spectrometer. HPLC analyses were carried out at λ = 254 nm, flow 0.50 mL/min, Column: XDB-C18, pore size 5 μm, diameter × length = 4.6 × 150 mm; method: gradient 0.1% TFA water/acetonitrile; acetonitrile 30−70% in 30 min. X-ray diffraction data for compound **8f** were collected at 293(2) K on an X-ray diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å). The crystal structures were solved by direct methods using SIR2004.[58] Column chromatography was performed with silica gel (100−200) at normal atmospheric pressure. Solvents and other reagents were purchased and used as supplied. All reactions using anhydrous conditions were performed using flame-dried apparatus under an atmosphere of argon. Spectral data is only provided here for all selenium containing compounds.

1. Preparation of LiAlHSeH. To a solution of selenium powder (0.80 g, 10.0 mmol) in dry THF (100 mL) was added lithium aluminum hydride (LAH, 0.38 g, 10.0 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min. The reagent lithium hydrogen selenide (LiAlHSeH) was formed in situ, and the formed gray solution was directly used in our present studies.

Note: Reagent to be prepared prior to use.

2. General Procedure for the Synthesis of Dipeptides 1a−o.[59] A solution of N^{α}-protected amino acid (17.8 mmol), EDC (17.8 mmol), and HOBt (18.7 mmol) in CH_2Cl_2 was cooled to 0 °C. To this solution was added DIPEA (35.2 mmol), then activated amino acid ester (17.8 mmol). The solution was allowed to warm to room temperature and stirred overnight. The solution was then diluted with 20 mL of CH_2Cl_2 and was washed with 5% Na_2CO_3 (2 × 10 mL), 10% citric acid (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL), and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure, and the products were purified by column chromatography. Melting points and optical rotations are compared with the literature data.

Characterization data for **1a−o**. [1] Cbz-Val-Ala-OMe (**1a**): Yield 95%, $[\alpha]_D^{25}$ −50.45 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 162−163/162.5−163 °C;[59a] [2] Cbz-Leu-Gly-OMe (**1b**): Yield 98%, $[\alpha]_D^{25}$ −29.6 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 95−97/94−96 °C;[59b] [3] Cbz-Asp(β-OBn)-Gly-OMe (**1c**): Yield 94%, $[\alpha]_D^{25}$ +11.2 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 129−131/128.5−131 °C;[59c] [4] Cbz-Glu(γ-OBn)-Phe-OEt (**1d**): Yield 98%, $[\alpha]_D^{25}$ +24.8 (*c*, 1.0 $CHCl_3$), white solid, mp 161−163 °C; [5] Fmoc-Ala-Phe-OMe (**1e**): Yield 95%, $[\alpha]_D^{25}$ +22.9 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 158−160/159−160 °C;[59d] [6] Fmoc-Phe-Leu-OBn (**1f**): Yield 91%, $[\alpha]_D^{25}$ −61.3 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 155−157/155−158 °C;[59e] [7] Fmoc-Leu-Met-OBn (**1g**): Yield 88%, $[\alpha]_D^{25}$ +11.6 (*c*, 1.0 $CHCl_3$), white solid, mp 131−133 °C; [8] Fmoc-Phe-Gly-OEt (**1h**): Yield 97%, $[\alpha]_D^{25}$ +22.9 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 158−160/159−160 °C;[59d] [9] Cbz-(D)Phg-Phe-OMe (**1i**): Yield 85%, $[\alpha]_D^{25}$ −6.41 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 155−156/158−160 °C;[59f] [10] Cbz-Phg-Phe-OMe (**1j**): Yield 88%, $[\alpha]_D^{25}$ +81.4 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 154−155/153−155 °C;[59f] [11] Cbz-Leu-Phe-OMe (**1k**): Yield 94%, $[\alpha]_D^{25}$ −22.68 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 83−84/80−81 °C;[59g] [12] Fmoc-Phe-(*R*) Phenyethylamine (**1l**): Yield 89%, $[\alpha]_D^{25}$ +13.9 (*c*, 1.0 $CHCl_3$),[59h] white solid, mp 105−107 °C; [13] Fmoc-Phe-(*S*) Phenyethylamine (**1m**): Yield 92% $[\alpha]_D^{25}$ −12.1 (*c*, 1.0 $CHCl_3$), white solid, mp 103−105 °C; [14] Fmoc-Phg-Phe-OMe (**1n**): Yield 94%, $[\alpha]_D^{25}$ +23.12 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 192−194/194−194.5 °C;[59f] [15] Fmoc-(D) Phg-Phe-OMe (**1o**): Yield 90%, $[\alpha]_D^{25}$ −27.87 (*c*, 1.0 $CHCl_3$), white solid, mp (Obsd/lit) 192−194/192−194 °C.[59f]

3. General Procedure for the Preparation of Dipeptide Acids Used.[60] To a solution of N^{α}-protected amino acid (1 mmol) in dry DCM (5 mL) cooled to 0 °C, EDC (1 mmol), HOBt (1.2 mmol), and *O*,*N*-bis-TMS-amino acid (1.5 mmol) were added.[59a] After completion of the reaction (usually 6−7 h, TLC analysis), the reaction mixture was diluted with H_2O and washed twice with ether. The aqueous layer was acidified by using 10% HCl and extracted with EtOAc (20 mL). The organic layer was then washed with water (2 × 10 mL) followed by brine (1 × 10 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the resulting crude products were recrystallized (Et_2O/*n*-hexane).

[1] Fmoc-Phe-Gly-OH (**9a**): Yield 91%, $[\alpha]_D^{25}$ +89.8 (*c* 1, EtOH), white solid, mp (Obsd/lit) 175−178/175−180 °C;[60a] [2] Cbz-Ala-Gly-OH (**9b**): Yield 94%, $[\alpha]_D^{25}$ −19.3 (*c* 1, EtOH), white solid, mp (Obsd/lit) 127−129/127−128 °C;[60b] [3] Fmoc-Gly-Phe-OH (**9c**): Yield 91%, $[\alpha]_D^{25}$ −17.6 (*c* 1, EtOH), white solid, mp 170−173 °C; [4] Fmoc-Ala-Val-OH (**9d**): Yield 94%, $[\alpha]_D^{25}$ +77.8 (*c* 1, EtOH), white solid, mp (Obsd/lit) 146−148/145−150 °C;[60a] [5] Cbz-Val-Gly-OH (**9e**): Yield 92%, $[\alpha]_D^{25}$ −22.4 (*c* 1, EtOH), white solid, mp (Obsd/lit) 121−123/120−125 °C.[60c]

4. General Procedure for the Synthesis of Tripeptide Esters 5 Used in Scheme 3. To a solution of N^{α}-protected dipeptide acid (17.8 mmol) in THF (20 mL) cooled to 0 °C, EDC (18.2 mmol), HOBt (20.0 mmol), and DIPEA (35.2 mmol) were added. After it was stirred for 10 min, a neutralized solution of amino acid ester (20.0 mmol) was added. The solution was allowed to warm to room temperature and stirred overnight. The mixture was diluted with 20 mL of CH_2Cl_2 and was washed with 5% Na_2CO_3 (2 × 10 mL), 10% citric acid (2 × 10 mL), water (2 × 10 mL), and brine (1 × 10 mL) and dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure, and the products were purified by column chromatography. [1] Fmoc-Gly-Phe-Leu-OMe (**5a**): Yield 78%, $[\alpha]_D^{25}$ +158.6 (*c* 1, DMF), white solid, mp 183−185 °C; [2] Fmoc-Ala-Val-Asp(β-OBn)-OMe (**5b**): Yield 81%, $[\alpha]_D^{25}$ 236.4 (*c* 1, DMF), white solid, mp 201−204 °C; [3] Cbz-Val-Gly-Ala-OMe (**5c**): Yield 91%, $[\alpha]_D^{25}$ +131.4 (*c* 1, DMF), white solid, mp 133−135 °C.[61]

5. General Procedure for the Synthesis of Aryl Amides 7a−g.[62] *Note*: Because of weak nucleophilicity of several organic amines, we observed fewer yields of aryl amides when EDC/HOBt was employed as coupling agents. Hence, we used CDI as coupling agents for the synthesis of 7.

Procedure. To a solution of protected amino acid (10.0 mmol) in THF (10 mL) was added CDI (1.95 g, 10 mmol). After the effervescence subsided, the solution was stirred for 1 h, and aromatic amines (10.5 mmol) were added. After stirring overnight, the solvent was removed, and the residue was taken up in EtOAc (50 mL) and washed with $NaHCO_3$ (2 × 10 mL), 1 M HCl (2 × 10 mL), and H_2O. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. After recrystallization, the crude products were afforded analytically pure aryl amides.

Characterization data for **7a−7g**. [**7a**]: Yield 89%, $[\alpha]_D^{25}$ +16.1 (*c* 1, $CHCl_3$), white solid, mp 121−123 °C; [**7b**]: Yield 78%, $[\alpha]_D^{25}$ +32.4 (*c* 1, $CHCl_3$), white solid, mp 117−119 °C; [**7c**]: Yield 91%, $[\alpha]_D^{25}$

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+56.4 (*c* 1, $CHCl_3$), white solid, mp (Obsd/lit) 158−160/157−160 °C;[62a] [**7d**]: Yield 90%, $[\alpha]_D^{25}$ −118.4 (*c* 1, $CHCl_3$), white solid, mp 97−99 °C; [**7e**]: Yield 85%, $[\alpha]_D^{25}$ +25.6 (*c* 1, $CHCl_3$), white solid, mp 103−105 °C; [**7f**]: Yield 74%, $[\alpha]_D^{25}$ +46.3 (*c* 1, $CHCl_3$), white solid, mp (Obsd/lit) 85−87/86−89 °C;[62b] [**7g**]: Yield 92%, $[\alpha]_D^{25}$ +54.8 (*c* 1, $CHCl_3$), white solid, mp 102−104 °C.[62c]

6. Test for Racemization at Imidoyl Chloride Stage: A Typical Experimental Procedure for the Preparation of Cbz-Val-Ala-OMe 1a via Imidoyl Chloride Method. To a solution of enantiopure Cbz-Val-Ala-OMe **1a** (337 mg, 1.0 mmol), PCl_5 (205 mg, 1.0 mmol) and DMF (0.02−0.03 mL) were added at room temperature. After 30 min of stirring, TLC analysis showed the complete consumption of **1a** (yellow color solution). To this solution, 10 equiv of H_2O (0.18 mL) and 5 mL of dioxane were added, and the assembly was allowed to reflux at 50 °C for 1 h. The reaction mixture was then cooled to rt, and an excess of H_2O was added to it. The crude solid product was slowly settled and was filtered off. The optical rotation and HPLC profile of the crude product was identical to the parent peptide **1a**, which was prepared from EDC/HOBT method. HPLC R_t 11.472 (30−70% ACN, 30 min).

7. General Procedure for the Synthesis of *N*-Fmoc/*Z*-Selenoxo Dipeptide Esters 2a−o. To a stirred suspension of protected dipeptide ester (1.0 mmol) in dry benzene (5 mL) was added crystalline PCl_5 (0.205 mg, 1.0 mmol) and DMF (0.025−0.03 mL) at room temperature. A clear yellow solution was formed after 10 min. The stirring was continued for another 10−20 min. A freshly prepared THF solution of LiAlHSeH (115.2 mg, 1.0 mmol) was added. The reaction mixture was protected from light and stirred at same temperature for another 10 min. After the reaction was complete (TLC analysis), solvent was evaporated under vacuum and diluted with EtOAc (10 mL). Organic phase was washed with 1 N $NaHCO_3$ (3 × 10 mL), 1 N citric acid (2 × 10 mL), H_2O (2 × 10 mL), and saturated NaCl (10 mL) solution and dried over Na_2SO_4. The solvent was filtered and evaporated under reduced pressure. The crude reaction mixture was purified under column chromatography using hexane/ethyl acetate (9:1) as the eluent to afford the desired product.

*7.1. (S)-Methyl 2-((S)-2-(Benzyloxycarbonyl)-3-methylbutaneselenoamido)propanoate (**2a**).* $[\alpha]_D^{25}$ −98.4 (*c* 1.2, $CHCl_3$); R_f 0.42 (*n*-hexane/EtOAc, 7:3) Yellow solid, mp 101−103 °C; HRMS (ESI) Calcd for $C_{17}H_{24}N_2O_4Se$ *m*/*z* 423.0799 $(M + Na)^+$, found 423.0796; HPLC R_t 17.845 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3089, 1739, 1734, 1540, 1107 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 523.142; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J* = 3.2 Hz, 6H), 1.39 (d, *J* = 5.6 Hz, 3H), 2.11 (m, 1H), 3.71 (s, 3H), 3.91 (m, 1H), 4.44−4.62 (m, 1H), 5.12 (s, 2H), 5.36 (s, br, 1H), 6.32 (s, br, 1H), 7.25−7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 18.7, 34.8, 53.1, 53.3, 53.9, 67.6, 128.3, 128.4, 128.7, 129.0, 136.5, 156.6, 172.0, 211.7. Anal. Calcd for $C_{17}H_{24}N_2O_4Se$: C, 51.13; H, 6.06; N, 7.01; O, 16.03; Se, 19.77. Found: C, 51.01; H, 5.98; N, 6.97; O, 15.99; Se, 19.57.

*7.2. (S)-Methyl 2-(2-(Benzyloxycarbonyl)-4-methylpentaneselenoamido)acetate (**2b**).* $[\alpha]_D^{25}$ −136.1 (*c* 1.0, $CHCl_3$); R_f 0.32 (*n*-hexane/EtOAc, 7:3); Yellow gum; ESI-MS Calcd for $C_{17}H_{24}N_2O_4Se$ *m*/*z* 401.09 $(M + H)^+$, found 401.09; HPLC R_t 18.377 (30−70%, ACN, 30 min) IR (Neat) υ_{max} 3490, 1730, 1728, 1498, 1110 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 494.981; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, *J* = 4.8 Hz, 6H,), 1.11−1.24 (m, 2H), 1.53−1.72 (m, 1H), 3.06−3.39 (m, 3H), 3.69 (s, 3H), 5.01 (s, 2H), 5.61 (s, br, 1H), 7.15−7.32 (m, 5H), 9.46 (s, br, 1H); ^{13}C NMR ($CDCl_3$) 21.9, 22.6, 42.4, 45.2, 49.7, 52.5, 66.8, 127.7, 127.9, 128.0, 128.4, 135.9, 156.1, 168.7, 213.1. Anal. Calcd for $C_{17}H_{24}N_2O_4Se$: C, 51.13; H, 6.06; N, 7.01; O, 16.03; Se, 19.77. Found: C, 51.11; H, 6.02; N, 7.04; O, 15.96; Se, 19.53.

*7.3. (S)-Benzyl 3-(Benzyloxycarbonyl)-4-(2-methoxy-2-oxoethylamino)-4-selenoxobutanoate (**2c**).* $[\alpha]_D^{25}$ +78.1 (*c*, 1.0 $CHCl_3$); R_f 0.21 (*n*-hexane/EtOAc, 7:3); Yellow solid; mp 87−89 °C; HRMS (ESI) Calcd for $C_{22}H_{24}N_2O_6Se$ *m*/*z* 515.0697 $(M + Na)^+$, found 515.0665; HPLC R_t 15.845 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3292, 1751, 1741, 1651, 1200 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 511.561; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (d, *J* = 7.8 Hz, 1H), 3.06 (d, *J* = 9.1 Hz, 1H), 3.71 (s, 2H), 3.94 (s, 3H), 4.36 (m, 1H), 5.12 (s, 4H), 5.98 (s, br, 1H), 7.19−7.53 (m, 10H), 9.19 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.1, 41.2, 50.9, 52.2, 66.8, 67.3, 128.1, 128.2, 128.3, 128.5, 135.2, 135.9, 156.0, 169.7, 170.5, 211.1. Anal. Calcd for $C_{22}H_{24}N_2O_6Se$: C, 53.77; H, 4.92; N, 5.70; O, 19.54; Se, 16.07. Found: C, 53.17, H, 4.79, N, 5.28, O, 19.00, Se, 15.71.

*7.4. (S)-Benzyl 4-(Benzyloxycarbonyl)-5-((S)-1-ethoxy-1-oxo-3-phenylpropan-2-ylamino)-5-selenoxopentanoate (**2d**).* $[\alpha]_D^{25}$ −135.8 (*c*, 1.0 $CHCl_3$); R_f 0.19 (*n*-hexane/EtOAc, 7:3); Yellow solid; mp 121−123 °C; HRMS (ESI) Calcd for $C_{31}H_{34}N_2O_6Se$ *m*/*z* 633. 1480 $(M + Na)^+$, found 633.1429; HPLC R_t 14.337 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3490, 1740, 1732, 1601, 1190 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 525.412; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3H, *J* = 5.6 Hz), 1.82−1.94 (m, 2H), 2.13 (t, 2H, J = 4.5 Hz), 2.94−3.18 (m, 2H), 3.49 (m, 1H), 3.77 (m, 1H), 4.09−4.15 (m, 2H), 5.11 (s, 4H), 5.61 (s, br, 1H), 7.03−7.51 (m, 15H), 9.18 (s, br, 1H); ^{13}C NMR (CDC_3) 13.9, 28.0, 30.2, 37.7, 42.3, 61.2, 61.4, 67.1, 67.5, 127.0, 127.9, 128.1, 128.2, 128.4, 129.2, 135.6, 136.1, 138.5, 155.2, 170.6, 171.0, 211.6. Anal. Calcd for $C_{31}H_{34}N_2O_6Se$: C, 61.08; H, 5.62; N, 4.60; O, 15.75; Se, 12.95. Found: C, 60.74; H, 5.19; N, 4.49; O, 15.74; Se, 12.89.

*7.5. (S)-Methyl 2-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-propaneselenoamido)-3-phenylpropanoate (**2e**).* $[\alpha]_D^{25}$ −18.6 (*c*, 1.5 $CHCl_3$); R_f 0.40 (*n*-hexane/EtOAc, 7:3); Pale Yellow solid, mp 108−110 °C; HRMS (ESI) Calcd for $C_{28}H_{28}N_2O_4Se$ *m*/*z* 559.1112 $(M + Na)^+$, found 559.0922; HPLC R_t 22.967 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3219, 1743, 1740, 1520, 1290 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 495.589; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, *J* = 5.2 Hz, 3H), 2.92 (d, *J* = 4.8 Hz, 1H), 3.11 (d, *J* = 8.1 Hz, 1H), 3.62 (s, 3H), 4.02−4.29 (m, 2H), 4.51 (t, *J* = 6.5 Hz, 1H), 4.71 (d, *J* = 4.9 Hz, 2H), 5.66 (br, 1H), 6.95−7.74 (m, 13H), 8.92 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 34.8, 40.0, 47.5, 50.1, 56.8, 69.5, 124.4, 125.6, 127.6, 128.2, 128.5, 129.0, 129.5, 139.7, 141.7, 143.1, 156.6, 172.0, 211.7. Anal. Calcd for $C_{28}H_{28}N_2O_4Se$: C, 62.80; H, 5.27; N, 5.23; O, 11.95; Se, 14.75. Found: C, 62.74; H, 5.20; N, 5.18; O, 11.88; Se, 14.70.

*7.6. (S)-Benzyl 2-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-3-phenylpropaneselenoamido)-4-methylpentanoate (**2f**).* $[\alpha]_D^{25}$ −59.7 (*c*, 1.0 $CHCl_3$); R_f 0.38 (*n*-hexane/EtOAc, 7:3); Pale Yellow solid, mp 113−115 °C; HRMS (ESI) Calcd for $C_{37}H_{38}N_2O_4Se$ *m*/*z* 677.1894 $(M + Na)^+$, found 677.1827; HPLC R_t 18.377 (30−70%, ACN, 30 min); IR (KBr)υ_{max} 3228, 1748, 1739, 1549, 1200 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 519.895; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, *J* = 5.4 Hz, 6H), 1.42 (t, *J* = 7.1 Hz, 2H), 1.49−1.63 (m, 1H), 2.51 (d, *J* = 3.9 Hz, 1H), 2.59 (d, *J* = 6.5 Hz, 1H), 3.29 (t, *J* = 11.1 Hz, 1H), 3.895 (m, 1H), 4.36 (t, *J* = 4.9 Hz, 1H), 4.74 (d, *J* = 3.9 Hz, 2H), 5.22 (s, 2H), 6.01 (s, br, 1H), 6.92−7.75 (m, 18H), 9.31 (s, br, 1H); ^{13}C NMR (CDC_3) δ 22.8., 23.0, 34.3, 40.4, 47.4, 48.0, 60.03, 65.3, 67.7, 125.7, 126.4, 127.6, 128.2, 128.6, 128.9, 129.2, 129.8, 136.6, 139.7, 141.7, 143.1, 156.2, 171.1, 212.7. Anal. Calcd for $C_{37}H_{38}N_2O_4Se$: C, 67.98; H, 5.86; N, 4.29; O, 9.79; Se, 12.08. Found: C, 67.85; H, 5.79; N, 4.26; O, 9.80; Se, 12.07.

*7.7. (S)-Benzyl 2-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-4-methylpentaneselenoamido)-4-(methylthio)butanoate (**2g**).* $[\alpha]_D^{25}$ −139.1 (*c*, 1.5 $CHCl_3$); R_f 0.25 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{33}H_{38}N_2O_4SSe$ *m*/*z* 661.1615 $(M + Na)^+$, found 661.1603; HPLC R_t 16.367 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3219, 1745, 1735, 1528, 1178 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 522.282; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 4.5 Hz, 6H), 1.44 (m, 2H), 1.71−1.88 (m, 1H), 2.01 (s, 3H), 2.17−2.31 (m, 2H), 2.41 (t, *J* = 3.6 Hz, 2H), 3.21 (t, *J* = 6.1 Hz, 1H), 3.29 (t, *J* = 2.9 Hz, 1H), 4.43 (t, *J* = 7.1 Hz, 1H), 4.68 (d, *J* = 5.8 Hz, 2H), 5.31 (s, 2H), 5.62 (s, br, 1H), 7.05−7.782 (m, 13H), 9.71 (s, br, 1H); ^{13}C NMR (75 MHz, CDC_3) δ 14.6, 23.2, 23.5, 30.2, 32.1, 41.4, 43.2, 47.5, 55.6, 67.8, 68.2, 125.9, 126.4, 127.6, 127.9, 128.2, 128.5, 129.0, 129.5, 140.7, 141.5, 144.1, 156.6, 171.21, 213.9. Anal. Calcd for $C_{33}H_{38}N_2O_4SSe$: C, 62.15; H, 6.01; N, 4.39; O, 10.04; S, 5.03; Se, 12.38. Found: C, 62.02; H, 5.87; N, 4.11; O, 9.59; S, 5.10; Se, 12.05.

*7.8. (S)-Ethyl 2-(2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-3-phenylpropaneselenoamido)acetate (**2h**).* $[\alpha]_D^{25}$ −89.8 (*c*, 1.0

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$CHCl_3$); R_f 0.21 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{28}H_{28}N_2O_4Se$ *m*/*z* 559.1112 (M + Na)$^+$, found 559.1110; HPLC R_t 14.565 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3289, 1751, 1500, 1173 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 543.760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* = 4.7 Hz, 3H), 2.63 (d, *J* = 3.2 Hz, 1H), 2.74 (d, *J* = 5.7 Hz, 1H), 3.49 (s, 2H), 3.85 (m, 1H), 3.15 (m, 2H), 4.32 (t, *J* = 5.9 Hz, 1H), 4.65 (d, *J* = 3.1 Hz, 2H), 5.48 (s, br, 1H), 6.82 (s, br, 1H), 7.15−7.79 (m, 13H); ^{13}C NMR (75 MHz, CDC_3) δ 14.1, 38.4, 47.6, 50.0, 60.2, 67.5, 125.4, 127.0, 127.6, 128.2, 129.1, 129.6, 130.5, 130.9, 137.9, 141.8, 144.1, 156.0, 170.1, 213.8. Anal. Calcd for $C_{28}H_{28}N_2O_4Se$: C, 62.80; H, 5.27; N, 5.23; O, 11.95; Se, 14.75. Found: C, 62.55; H, 5.11; N, 5.04; O, 11.18; Se, 14.64.

*7.9. (S)-Methyl 2-((R)-2-(Benzyloxycarbonyl)-2-phenylethaneselenoamido)-3-phenylpropanoate (**2i**).* $[\alpha]_D^{25}$ +14.9 (*c*, 1.0 $CHCl_3$); R_f 0.47 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_4Se$ *m*/*z* 533.0955 (M + Na)$^+$, found 533.0924; HPLC R_t 15.812 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3450, 1741, 1738, 1154 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 527.117; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (d, *J* = 3.7 Hz, 1H), 3.08 (d, *J* = 2.9 Hz, 1H), 3.5 (s, 1H), 3.67 (m, 1H), 4.80 (s, 1H), 5.12 (s, 2H), 5.58 (br, 1H), 6.96−7.55 (m, 15H), 8.72 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.5, 48.6, 50.9, 62.3, 66.1, 125.0, 126.3, 127.0, 127.5, 127.6, 128.4, 140.6, 141.4, 143.6, 155.6, 171.2, 208.8. Anal. Calcd for $C_{26}H_{26}N_2O_4Se$: C, 61.30; H, 5.14; N, 5.50; O, 12.56; Se, 15.50. Found: C, 61.22; H, 5.11; N, 5.29; O, 12.21; Se, 14.77.

*7.10. (S)-Methyl 2-((S)-2-(Benzyloxycarbonyl)-2-phenylethaneselenoamido)-3-phenylpropanoate (**2j**).* $[\alpha]_D^{25}$ −143.3 (*c*, 1.0 $CHCl_3$); R_f 0.48 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{26}H_{26}N_2O_4Se$ *m*/*z* 533.0955 (M + Na)$^+$, found 533.0824; HPLC R_t 15.699 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3089, 1750, 1742, 1537, 1150 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 534.540; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (d, 1H, *J* = 4.6 Hz), 3.11 (d, 1H, *J* = 7.2 Hz), 3.61 (s, 3H), 3.82 (m, 1H), 4.93 (s, 1H), 5.19 (s, 2H), 5.51 (br, 1H), 7.02−7.51 (m, 15 H), 8.88 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.5, 49.9, 53.2, 61.9, 66.4, 126.8, 127.6, 127.8, 128.6, 129.0, 129.3, 129.5, 138.6, 140.0, 140.8, 155.8, 170.8, 208.8. Anal. Calcd for $C_{26}H_{26}N_2O_4Se$: C, 61.30; H, 5.14; N, 5.50; O, 12.56; Se, 15.50. Found: C, 61.25; H, 5.07; N, 5.45; O, 12.47; Se, 15.28.

*7.11. (S)-Methyl 2-((S)-2-(Benzyloxycarbonyl)-4-methylpentaneselenoamido)-3-phenylpropanoate (**2k**).* $[\alpha]_D^{25}$ −126.1 (*c*, 1.0 $CHCl_3$); R_f 0.51 (*n*-hexane/EtOAc, 7:3); Pale Yellow solid, mp 82−84 °C; HRMS (ESI) Calcd for $C_{24}H_{30}N_2O_4Se$ *m*/*z* 513.1268 (M + Na)$^+$, found 513.1236; HPLC R_t 15.992 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3488, 1747, 1739, 1530, 1114 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 513.261; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, *J* = 3.8 Hz, 6H), 1.15−1.22 (m, 2H), 1.71−1.83 (m, 2H), 2.91 (d, *J* = 4.2 Hz, 1H), 3.08 (d, *J* = 5.8 Hz, 1H), 3.22 (m, 1H), 3.48 (s, 3H), 3.61 (m, 1H), 5.04 (s, 2H), 6.21 (s, br, 1H), 7.01−7.29 (m, 10H), 9.30 (s, br, 1H); ^{13}C NMR (75 MHz, CDC_3) δ 23.2, 23.5, 36.9, 41.2, 42.7, 51.1, 58.4, 67.1, 125.5, 127.5, 128.2, 128.5, 129.0, 129.2, 138.4, 140.6, 156.4, 170.0, 209.7. Anal. Calcd for $C_{24}H_{30}N_2O_4Se$: C, 58.89; H, 6.18; N, 5.72; O, 13.07; Se, 16.13. Found: C, 58.71; H, 6.10; N, 5.61; O, 13.00; Se, 16.11.

*7.12. (9H-Fluoren-9-yl)methyl (S)-3-Phenyl-1-((S)-1-phenylethylamino)-1-selenoxopropan-2-ylcarbamate (**2l**).* $[\alpha]_D^{25}$ −57.9 (*c*, 1.0 $CHCl_3$); R_f 0.56 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{32}H_{30}N_2O_2Se$ *m*/*z* 577.1370 (M + Na)$^+$, found 577.1326; HPLC R_t 20.063 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3229, 1745, 1498, 1200 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 539.766; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.0 Hz, 3H), 2.53 (d, *J* = 2.9 Hz, 1H), 2.71 (d, *J* = 7.1 Hz, 1H), 3.88 (m, 1H), 3.98 (m, 1H), 4.45 (t, *J* = 5.9 Hz, 1H), 4.69 (d, *J* = 8.2 Hz, 2H), 5.67 (s, br, 1H),7.11−7.95 (m, 18H), 8.94 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 38.2, 44.5, 46.0, 54.2, 67.1, 119.9, 125.0, 127.1, 127.2, 127.6, 128.5, 128.6, 129.1, 138.3, 140.1, 142.0, 142.3, 155.4, 208.2. Anal. Calcd for $C_{32}H_{30}N_2O_2Se$: C, 69.43; H, 5.46; N, 5.06; O, 5.78; Se, 14.26. Found: C, 69.37; H, 5.35; N, 4.47; O, 5.01; Se, 13.65.

*7.13. (9H-Fluoren-9-yl)methyl (S)-3-Phenyl-1-((R)-1-phenylethylamino)-1-selenoxopropan-2-ylcarbamate (**2m**).* $[\alpha]_D^{25}$ +62.8 (*c*, 1.0 $CHCl_3$); R_f 0.55 (*n*-hexane/EtOAc, 7:3); gum; HRMS (ESI) Calcd for $C_{32}H_{30}N_2O_2Se$ *m*/*z* 577.1370 (M + Na)$^+$, found 577.1322; HPLC R_t 19.589 (30−70%, ACN, 30 min); IR (Neat) υ_{max} 3425, 1749, 1503, 1215 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 535.136; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J* = 9.0 Hz, 3H), 2.62 (d, *J* = 4.4 Hz, 1H), 2.78 (d, *J* = 7.1 Hz, 1H), 3.94 (m, 1H), 4.19 (m, 1H), 4.33 (t, *J* = 5.8 Hz, 1H), 4.68 (d, *J* = 7.9 Hz, 2H), 5.71 (s, br, 1H), 7.04−7.91 (m, 18H), 8.92 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 38.5, 44.4, 46.8, 54.9, 66.8, 120.9, 125.5, 127.3, 128.1, 128.3, 128.5, 129.0, 129.5, 138.7, 140.0, 142.5, 155.0, 209.7. Anal. Calcd for $C_{32}H_{30}N_2O_2Se$: C, 69.43; H, 5.46; N, 5.06; O, 5.78; Se, 14.26. Found: C, 69.41; H, 5.28; N, 4.91; O, 5.55; Se, 13.70.

*7.14. (S)-Methyl 2-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-2-phenylethaneselenoamido)-3-phenylpropanoate (**2n**).* $[\alpha]_D^{25}$ +29.2 (*c*, 1.0 $CHCl_3$); R_f 0.38 (*n*-hexane/EtOAc, 7:3); Yellow Solid, mp 115−116 °C; ESI-MS Calcd for $C_{33}H_{30}N_2O_4Se$ *m*/*z* 599.1 (M + H)$^+$, found 599.2; HPLC R_t 20.115 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3417, 1745, 1737, 1498, 1120 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 533.629; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (d, *J* = 4.8 Hz, 1H), 3.10 (d, *J* = 2.9 Hz, 1H), 3.51 (s, 3H), 3.78 (m, 1H), 4.42 (t, *J* = 7.1 Hz, 1H), 4.64 (d, *J* = 3.9 Hz, 2H), 4.88 (s, 1H), 5.53 (s, br, 1H), 7.03−7.79 (m, 18H), 8.98 (s, br, 1H); ^{13}C NMR (75 MHz, CDC_3) δ 36.6, 47.1, 49.8, 50.0, 58.8, 67.3, 125.9, 126.5, 126.9, 127.1, 128.1, 128.2, 128.3, 128.5, 135.1, 141.3, 142.1, 142.7, 156.2, 171.2, 207.2. Anal. Calcd for $C_{33}H_{30}N_2O_4Se$: C, 66.33; H, 5.06; N, 4.69; O, 10.71; Se, 13.21. Found C, 66.12; H, 5.00; N, 4.42; O, 10.55; Se, 13.09.

*7.15. (S)-Methyl 2-((R)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-2-phenylethaneselenoamido)-3-phenylpropanoate (**2o**).* $[\alpha]_D^{25}$ −58.9 (*c*, 1.0 $CHCl_3$); R_f 0.38 (*n*-hexane/EtOAc, 7:3); Yellow Solid, mp 112−114 °C; HRMS (ESI) Calcd for $C_{33}H_{30}N_2O_4Se$ *m*/*z* 621.1268 (M + Na)$^+$, found 621.0536; HPLC R_t 19.602 (30−70%, ACN, 30 min); IR (KBr) υ_{max} 3177, 1751, 1748, 1520, 1235 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 534.126; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (d, *J* = 4.2 Hz, 1H), 3.11 (d, *J* = 4.6 Hz, 1H), 3.63 (s, 3H), 3.81 (m, 1H), 4.23 (t, *J* = 8.2 Hz, 1H), 4.69 (d, *J* = 5.8 Hz, 2H), 4.89 (s, 1H), 5.62 (s, br, 1H), 6.98−7.78 (m, 18H), 8.95 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.2, 47.1, 49.5, 50.7, 58.2, 68.5, 125.4, 126.6, 127.6, 127.7, 128.2, 128.3, 128.4, 129.0, 129.1, 138.9, 141.8, 142.2, 144.1, 155.7, 170.8, 208.9. Anal. Calcd for $C_{33}H_{30}N_2O_4Se$: C, 66.33; H, 5.06; N, 4.69; O, 10.71; Se, 13.21. Found: C, 63.11; H, 4.88; N, 4.39; O, 10.23; Se, 12.96.

8. General Procedure for the Preparation of Selenoxo Peptides 4a−f. Step 1. To a solution of Fmoc protected selenoxo dipeptide ester **2** (1.0 mmol) in CH_2Cl_2 (10.0 mL), 18 mL of 40% DEA in CH_2Cl_2 was added, and the solution was stirred for 20 min at rt. After complete deprotection of the Fmoc group (observed by TLC analysis), the solvent and excess DEA were removed completely under reduced pressure with repeated coevaporation with CH_2Cl_2. The resulting amino free selenoxo dipeptide ester was dissolved in anhydrous THF (5.0 mL) and maintained at 0 °C. **Step 2.** Activation of Fmoc/Z-amino/dipeptide acids (1.1 mmol) was carried out separately by dissolving with dry THF (5 mL) and cooled to 0 °C. EDC (1.0 mmol) and HOBt (1.2 mmol) were added to the above solution and stirred for 10 min. While maintaining the temperature at 0 °C, the above amino free selenoxo peptide ester (1.1 mmol) was added, and the resulting mixture was stirred for 1−2 h, during which the coupling was complete. The solvent was evaporated under a vacuum and diluted with EtOAc (10 mL). Organic phase was washed with 1 N $NaHCO_3$ (3 × 10 mL), 1 N citric acid (2 × 10 mL), H_2O (2 × 10 mL), and brine (10 mL) solution and dried over Na_2SO_4. The solvent was filtered and evaporated under reduced pressure. The crude reaction mixture was purified under column chromatography using hexane/ethyl acetate (8:2) as the eluent.

*8.1. (2R,3R)-Methyl 2-((S)-2-(2-((S)-2-(Benzyloxycarbonyl)-propanamido)acetamido)-3-phenylpropaneselenoamido)-3-methylpentanoate (**4a**).* $[\alpha]_D^{25}$ +127.6 (*c*, 1.5 $CHCl_3$); R_f 0.38 (*n*-hexane/EtOAc, 6:4); yellow solid, mp 133−135 °C; HRMS (ESI) Calcd for $C_{29}H_{38}N_4O_6Se$ *m*/*z* 641.1854 (M + Na)$^+$, found 641.1846; IR (Neat) υ_{max} 3418, 1749, 1740, 1651, 1647, 1539, 1390, 1208, 1178 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 539.215; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, *J* = 3.9 Hz, 3H), 0.94 (d, *J* = 5.7 Hz, 3H), 1.14 (m, 2H), 1.38

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(d, J = 3.3 Hz, 3H), 2.25−2.41 (m, 1H), 2.64−2.91 (m, 2H), 3.15 (d, J = 6.8 Hz, 1H), 3.56 (s, 3H), 3.82 (m, 1H), 3.99 (s, 2H), 4.37 (m, 1H), 5.23 (s, 2H), 5.81 (s, br, 1H),7.45−7.67 (m, 10H), 8.12 (s, br, 1H), 8.34−8.6 (2s, br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.9, 17.0, 27.5, 34.0, 39.1, 42.8, 46.6, 51.5, 52.1, 59.1, 66.9, 122.0, 124.2, 125.6, 127.6, 128.1, 128.3, 128.7, 139.5, 141.9, 156.0, 170.9, 171.5, 171.8, 212. Anal. Calcd for $C_{29}H_{38}N_4O_6Se$: C, 56.40; H, 6.20; N, 9.07; O, 15.54; Se, 12.79. Found: C, 56.01; H, 5.67; N, 8.13; O, 15.11; Se, 12.81.

*8.2. (S)-(9H-Fluoren-9-yl)methyl 2-(((S)-1-((S)-1-(Benzyloxy)-4-methyl-1-oxopentan-2-ylamino)-3-phenyl-1-selenoxopropan-2-yl)-carbamoyl)pyrrolidine-1-carboxylate (**4b**).* $[\alpha]_D^{25}$ +154.5 (c, 1.5 $CHCl_3$); R_f 0.21 (n-hexane/EtOAc, 6:4); gum; HRMS (ESI) Calcd for $C_{42}H_{45}N_3O_5Se$ m/z 752.2603 $(M + H)^+$, found 752.2601; IR (Neat) υ_{max} 3456, 1765, 1752, 1669, 1535, 1219, 1105 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 510.732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 4.1 Hz, 6H), 1.31−1.45 (m, 2H), 1.49−1.61 (m, 2H), 1.62−1.81 (m, 3H), 2.62 (d, J = 5.2 Hz, 1H), 2.77 (d, J = 5.3 Hz, 1H), 3.15−3.29 (m, 2H), 3.33 (t, J = 3.3 Hz, 1H), 3.75−3.83 (m, 1H), 4.21 (m, 1H), 4.39 (t, J = 5.4 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 5.29 (s, 2H), 5.79 (s, br, 1H), 6.45 (s, br, 2H), 7.11−7.82 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 23.7, 24.5, 29.3, 38.7, 40.5, 46.9, 47.3, 54.9, 60.1, 66.6, 67.5, 68.1, 120.0, 124.8, 127.1, 127.6, 127.7, 128.6, 128.7, 129.2, 130.8, 141.3, 143.7, 143.8, 155.8, 170.1, 170.8, 213.8. Anal. Calcd for $C_{42}H_{45}N_3O_5Se$: C, 67.19; H, 6.04; N, 5.60; O, 10.66; Se, 10.52. Found C, 67.02; H, 5.71; N, 5.15; O, 10.34; Se, 10.43.

*8.3. (S)-3-(2-((S)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanamido)acetamido)-4-((S)-1-(benzyloxy)-3-methyl-1-oxobutan-2-ylamino)-4-selenoxo benzoate (**4c**).* $[\alpha]_D^{25}$ +78.1 (c, 1.5 $CHCl_3$); R_f 0.25 ($CHCl_3$:MeOH, 9:1); Yellow Solid, mp 144−145 °C; ESI-MS Calcd for $C_{49}H_{50}N_4O_8Se$ m/z 903.2 $(M + H)^+$, found 903.2; IR (Neat) υ_{max} 3365, 1755, 1749, 1623, 1534, 1251, 1125 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 521.463; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 5.8 Hz, 6H), 2.36 (m, 1H), 2.52 (m, 2H), 2.92 (d, J = 3.5 Hz, 1H), 3.04 (d, J = 4.9 Hz, 1H), 3.29 (d, J = 6.3 Hz, 1H), 3.95 (s, 2H), 4.12 (m, 1H), 4.38 (t, J = 5.9 Hz, 1H), 4.59 (d, J = 10.2 Hz, 2H), 4.74 (m, 1H), 5.32 (s, 4H), 6.01 (s, br, 1H), 7.01−7.75 (m, 23H), 8.29 (s, br, 1H), 8.52 (s, br, 1H), 9.49 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.9, 30.9, 35.9, 37.8, 38.0, 43.1, 47.0, 53.3, 59.9, 66.9, 67.1, 125.0, 127.0, 127.1, 127.7, 128.2, 128.3, 128.4, 128.5, 128.7, 129.1, 135.3, 136.3, 141.2, 143.6, 156.2, 170.1, 171.3, 171.5, 171.8, 211.1. Anal. Calcd for $C_{49}H_{50}N_4O_8Se$: C, 65.25; H, 5.59; N, 6.21; O, 14.19; Se, 8.75. Found: C, 64.01; H, 5.18; N, 5.93; O, 14.01; Se, 8.88.

*8.4. (S)-Methyl 2-((S)-2-((S)-2-(Benzyloxycarbonyl)-4-methylpentanamido)propaneselenoamido)-3-phenylpropanoate (**4d**).* $[\alpha]_D^{25}$ +87.6 (c, 1.0 $CHCl_3$); R_f 0.31 (n-hexane/EtOAc, 6:4); gum; HRMS (ESI) Calcd for $C_{27}H_{35}N_3O_5Se$ m/z 584.1640 $(M + Na)^+$, found 584.1613; IR (Neat) υ_{max} 3451, 1749, 1738, 1665, 1590, 1210, 1150 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 523.321; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 5.2 Hz, 6H),1.13 (d, J = 4.8 Hz, 3H) 1.41−1.69 (m, 3H), 2.82 (d, J = 3.6 Hz, 1H), 2.78 (d, J = 7.1 Hz, 1H), 3.59 (s, 3H), 3.69−3.81 (m, 2H), 4.43 (t, J = 3.9 Hz, 1H), 5.24 (s, 2H), 6.18 (s, br, 1H), 7.23−7.62 (m, 10H), 8.38 (s, br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4, 22.6, 24.8, 38.8, 40.0, 41.1, 51.3, 52.9, 58.2, 66.7, 127.1, 127.5, 128.1, 128.4, 128.8, 129.2, 139.2, 140.8, 156.4, 170.7, 171.1, 209.1. Anal. Calcd for $C_{27}H_{35}N_3O_5Se$: C, 57.85; H, 6.29; N, 7.50; O, 14.27; Se, 14.09. Found: C, 57.05; H, 6.10; N, 6.19; O, 13.97; Se, 13.79.

*8.5. (R)-Methyl 2-((S)-2-((S)-2-(((9H-Fluoren-9-yl)methoxy)-carbonyl)-3-methylbutanamido)propaneselenoamido)-3-phenyl-propanoate (**4e**).* $[\alpha]_D^{25}$ +79.5 (c, 1.0 $CHCl_3$); R_f 0.41 (n-hexane/EtOAc, 6:4); yellow solid, mp 128−129 °C; HRMS (ESI) Calcd for $C_{33}H_{37}N_3O_5Se$ m/z 658.1796 $(M + Na)^+$, found 658.1702; IR (KBr) υ_{max} 3452, 1748, 1740, 1650, 1549, 1390, 1196 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 521.153; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 4.7 Hz, 6H), 1.09 (d, J = 7.2 Hz, 3H), 2.49 (m, 1H), 3.12 (d, J = 2.5 Hz, 1H), 3.27 (d, J = 4.4 Hz, 1H), 3.49 (s, 3H), 3.71−3.83 (m, 2H), 4.28 (d, J = 6.6 Hz, 1H), 4.42 (t, J = 11.1 Hz, 1H), 4.70 (d, J = 3.9 Hz, 2H) 5.81 (s, br, 1H), 7.12−7.78 (m, 13H), 8.49 (s, br, 1H),9.45 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 18.3, 31.2, 37.7, 41.1, 47.1, 52.3, 58.8, 60.3, 67.0, 119.9, 125.0, 127.0, 127.1, 127.6, 128.5, 128.6, 129.2, 135.5, 141.3, 143.7, 156.3, 171.4, 171.5, 212.4. Anal. Calcd for $C_{33}H_{37}N_3O_5Se$: C, 62.45; H, 5.88; N, 6.62; O, 12.61; Se, 12.44. Found: C, 61.67; H, 5.23; N, 6.41; O, 12.19; Se, 12.39.

*8.6. (S)-Benzyl 2-((S)-2-((S)-2-(Benzyloxycarbonyl)-3-phenylpropanamido)-4-methylpentaneselenoamido)-3-methylbutanoate (**4f**).* $[\alpha]_D^{25}$ +187.6 (c, 1.0 $CHCl_3$); R_f 0.44 (n-hexane/EtOAc, 6:4); yellow solid, mp 107−109 °C; ESI-MS Calcd for $C_{35}H_{43}N_3O_5Se$ m/z 688.1 $(M + Na)^+$, found 688.2; IR (Neat) υ_{max} 3249, 1755, 1748, 1642, 1525, 1228, 1159 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 531.549; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 5.8 Hz, 6H), 0.94 (d, J = 4.9 Hz, 6H), 1.27−1.43 (m, 2H), 1.62−1.85 (m, 1H), 2.51−2.62 (m, 1H), 2.74 (d, J = 7.2 Hz, 1H), 2.83 (d, J = 5.5 Hz, 1H), 3.25 (d, J = 6.3 Hz, 1H), 3.41 (t, J = 9.1 Hz, 1H), 4.39−4.61 (m,1H), 5.19 (s, 4H), 5.41 (s, br, 1H), 6.89−7.55 (m, 15H), 8.19 (s, br, 1H), 8.71 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 21.0, 22.8, 30.9, 37.7, 41.2, 42.8, 53.1, 62.7, 64.1, 67.0, 127.1, 128.1, 128.3, 128.6, 128.9, 129.2, 139.9, 140.0, 155.7, 170.1, 170.7, 213.0. Anal. Calcd for $C_{35}H_{43}N_3O_5Se$: C, 63.24; H, 6.52; N, 6.32; O, 12.04; Se, 11.88. Found: C, 62.94; H, 6.11; N, 5.89; O, 11.74; Se, 11.69.

9. General Procedure for the Synthesis of Diselenoxo Tripeptides 6. To a stirred suspension of protected tripeptide ester (1.0 mmol) in dry benzene (10 mL) was added crystalline PCl_5 (615 mg, 3.0 mmol) and DMF (0.062 mL). A clear solution was formed after 30 min at rt. A THF solution of LiAlHSeH (386.7 mg, 3.2 mmol) was added. The flask was protected from light and was stirred at the same temperature for another 30 min. After the reaction was complete (TLC analysis), solvent was evaporated under vacuum and diluted with EtOAc (10 mL). Organic phase was washed with 1 N $NaHCO_3$ (3 × 10 mL), 1 N citric acid (2 × 10 mL), H_2O (2 × 10 mL), and brine (10 mL) solution followed by drying over Na_2SO_4. The solvent was filtered and evaporated under reduced pressure. The crude reaction mixture was purified under column chromatography using hexane/ethyl acetate (8:2) as the eluent.

*9.1. (S)-Methyl 2-((S)-2-(2-(((9H-Fluoren-9-yl)methoxy)carbonyl)-ethaneselenoamido)-3-phenylpropaneselenoamido)-4-methylpentanoate (**6a**).* $[\alpha]_D^{25}$ +9.8 (c, 1.5 $CHCl_3$); R_f 0.34 ($CHCl_3$/MeOH, 9:1); Pale Yellow solid, mp 143−144 °C; HRMS (ESI) Calcd for $C_{33}H_{37}N_3O_4Se_2$ m/z 722.1012 $(M + Na)^+$, found 722.1002; IR (KBr) υ_{max} 3157, 1747, 1738, 1551, 1548, 1287, 1159 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 534.106, 534.545; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 5.4 Hz, 6H), 1.45−1.71 (m, 3H), 2.52−2.63 (m, 2H), 2.79 (m, 1H), 2.97 (s, 2H), 3.31 (t, J = 4.2 Hz, 1H), 3.69 (s, 3H), 4.32 (t, J = 2.9 Hz, 1H), 4.49 (d, J = 7.2 Hz, 2H), 5.69 (s, br, 1H), 6.2 (s, br, 1H), 7.09−7.81 (m, 13H), 8.82 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.5, 38.4, 41.1, 44.2, 46.9, 50.8, 52.0, 54.3, 67.2, 119.8, 125.0, 126.8, 126.9, 127.6, 128.3, 129.2, 136.2, 141.1, 143.7, 156.6, 170.7, 209.7, 210.0. Anal. Calcd for $C_{33}H_{37}N_3O_4Se_2$: C, 56.82; H, 5.35; N, 6.02; O, 9.17; Se, 22.64. Found: C, 56.19; H, 5.04; N, 5.91; O, 9.00; Se, 22.17.

*9.2. (S)-4-Benzyl 1-Methyl 2-((S)-2-((S)-2-(((9H-Fluoren-9-yl)-methoxy)carbonyl)propaneselenoamido)-3-methylbutaneselenoamido)succinate (**6b**).* $[\alpha]_D^{25}$ +208.5 (c, 1.5 $CHCl_3$); R_f 0.41 ($CHCl_3$:MeOH, 7:3); yellow solid, mp 155−157 °C ; HRMS (ESI) Calcd for $C_{35}H_{39}N_3O_6Se_2$ m/z 780.1067 $(M + Na)^+$, found 780.1054; IR (KBr) υ_{max} 3257, 1758, 1750, 1741, 1590, 1584, 1200, 1190 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 561.932, 563.311; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 3.7 Hz, 6H), 1.17 (d, J = 6.4 Hz, 3H), 2.12 (m, 1H), 2.41 (d, J = 4.8 Hz, 1H), 2.82 (d, J = 7.1 Hz, 1H), 2.89 (d, J = 11.2 Hz, 1H), 3.52 (s, 3H), 3.63 (m, 1H), 3.85 (m, 1H), 4.51 (t, J = 6.6 Hz, 1H), 4.81 (d, J = 5.6 Hz, 2H), 5.38 (s, 2H), 6.12 (s, br, 1H), 6.93 (s, br, 1H), 7.12−7.75 (m, 13H), 8.91 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 18.9, 30.9, 37.1, 42.7, 46.9, 49.4, 55.4, 57.9, 66.6, 66.9, 119.7, 124.9, 126.8, 127.5, 128.0, 128.3, 135.4, 141.0, 143.6, 143.7, 156.6, 170.1, 171.6, 211.1, 211.9. Anal. Calcd for $C_{35}H_{39}N_3O_6Se_2$(%): C, 55.63; H, 5.20; N, 5.56; O, 12.70; Se, 20.90. Found: C, 55.28; H, 5.07; N, 5.19; O, 12.48; Se, 20.77.

*9.3. (S)-Methyl 2-(2-((S)-2-(Benzyloxycarbonyl)-3-methylbutaneselenoamido)ethaneselenoamido)propanoate (**6c**).* $[\alpha]_D^{25}$ +69.7 (c, 1.5 $CHCl_3$); R_f 0.38 ($CHCl_3$/MeOH, 9:1); gum; HRMS (ESI) Calcd for $C_{19}H_{27}N_3O_4Se_2$ m/z 544.0230 $(M + Na)^+$, found 544.0217; IR (Neat) υ_{max} 33316, 1747, 1729, 1575, 1548, 1254,

1147 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 555.614, 555.935; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 4.8 Hz, 6H), 1.12 (d, J = 7.1 Hz, 3H), 2.19−2.37 (m, 1H), 2.42 (s, 2H), 3.31−3.49 (m, 5H), 5.45 (s, 2H), 6.18 (s, br, 1H), 6.47 (s, br, 1H), 7.24 (s, 5H), 8.55 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 19.1, 30.8, 48.1, 52.3, 52.9, 53.0, 67.0, 127.9, 128.1, 128.4, 136.1, 156.6, 168.4, 209.1, 210.2. Anal. Calcd for $C_{19}H_{27}N_3O_4Se_2$: C, 43.94; H, 5.24; N, 8.09; O, 12.32; Se, 30.41. Found: C, 42.57; H, 4.96; N, 7.79; O, 12.19; Se, 30.34.

10. General Procedure for the Synthesis of 8. To a solution of arylamide 7 (1.0 mmol) in dry benzene (5 mL), PCl_5 (0.250 mg, 1.0 mmol) and DMF (0.02−0.03 mL) were added at room temperature. After the solution was stirred for 20 min, freshly prepared LiAlHSeH (0.115 mg, 1.0 mmol) was added. The flask was protected from light and stirred until completion of the reaction (TLC analysis). The solvent was evaporated under a vacuum, and the crude product was extracted with EtOAc (10 mL), and the organic layer was washed with 1 N HCl (7 mL), 1 N $NaHCO_3$ (7 mL), and brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product under column chromatography using hexane/ethyl acetate (8:2) affords **8** as pure solids.

*10.1. (S)-(9H-Fluoren-9-yl)methyl 1-(4-Hydroxyphenylamino)-1-selenoxopropan-2-ylcarbamate (**8a**).* $[\alpha]_D^{25}$ +28.1 (*c*, 1.0 $CHCl_3$); R_f 0.41 (*n*-hexane/EtOAc, 8:2); Yellow solid, mp 78−79 °C; HRMS (ESI) Calcd for $C_{24}H_{22}N_2O_3Se$ m/z 467.0874 $(M + H)^+$, found 467.0826; IR (KBr) υ_{max} 3219, 3014, 1748, 1440, 1211 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 604.611; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, J = 5.5 Hz, 3H), 3.39 (m, 1H), 4.33 (t, J = 7.1 Hz, 1H), 4.71 (d, J = 4.4 Hz, 2H), 4.92 (s, br, 1H), 5.20 (s, br, 1H), 6.01 (d, J = 3.2 Hz, 2H), 6.21 (d, J = 4.4 Hz, 2H), 7.12−7.75 (m, 8H), 8.52 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 44.1, 46.1, 65.1, 114.3, 114.9, 126.4, 127.8, 128.4, 128.7, 137.5, 140.8, 143.1, 146.9, 155.3, 211.3. Anal. Calcd for $C_{24}H_{22}N_2O_3Se$: C, 61.94; H, 4.76; N, 6.02; O, 10.31; Se, 16.97. Found: C, 61.88; H, 4.43; N, 5.78; O, 10.21; Se, 16.87.

*10.2. (S)-(9H-Fluoren-9-yl)methyl 1-(2,4-Bis(trifluoromethyl)-phenylamino)-3-methyl-1-selenoxobutan-2-ylcarbamate (**8b**).* $[\alpha]_D^{25}$ +9.4 (*c*, 1.0 $CHCl_3$); R_f 0.29 (*n*-hexane/EtOAc, 8:2); Yellow solid, mp 101−103 °C; HRMS (ESI) Calcd for $C_{28}H_{24}F_6N_2O_2Se$ m/z 615.0985 $(M + H)^+$, found 615.0945; IR (Neat) υ_{max} 3119, 3058, 1742, 1490, 1120 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 596.731; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 5.6 Hz, 6H), 2.42 (m, 1H), 3.42 (d, J = 3.9 Hz, 1H), 4.22 (t, J = 7.1 Hz, 1H), 4.46 (s, br, 1H), 4.82 (d, J = 11.2 Hz, 2H), 6.21 (d, J = 14.2 Hz, 1H), 7.27−7.83 (m, 10H), 8.31 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 32.6, 47.1, 54.0, 68.5, 113.0, 113.8, 123.9, 124.1, 125.8, 127.7, 128.2, 128.3, 128.4, 129.0, 141.8, 142.1, 143.8, 155.7. 209.9. Anal. Calcd for $C_{28}H_{24}F_6N_2O_2Se$: C, 54.82; H, 3.94; F, 18.58; N, 4.57; O, 5.22; Se, 12.87. Found: C, 54.55; H, 3.14; F, 18.33; N, 4.51; O, 5.12; Se, 12.78.

*10.3. (S)-Benzyl 1-(4-Nitrophenylamino)-3-phenyl-1-selenoxopropan-2-ylcarbamate (**8c**).* $[\alpha]_D^{25}$ −19.8 (*c*, 1.0 $CHCl_3$); R_f 0.41 (*n*-hexane/EtOAc, 8:2); Pale brown solid, mp 81−83 °C; HRMS (ESI) Calcd for $C_{23}H_{21}N_3O_4Se$ m/z 484.0776 $(M + H)^+$, found 484.0734; IR (Neat) υ_{max} 3177, 3029, 1739, 1550, 1145, 745 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 632.217; ^1H NMR (300 MHz, $CDCl_3$) δ 2.49 (d, J = 4.5 Hz, 1H), 2.75 (d, J = 7.1 Hz, 1H), 3.61 (s, br, 1H), 3.93−4.09 (m, 1H), 5.24 (s, 2H), 6.50 (d, J = 11.6 Hz, 2H), 7.01−7.31 (m, 10H), 7.78 (d, J = 9.6 Hz, 2H), 8.73 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.2, 47.1, 63.9, 115.1, 119.9, 124.9, 127.0, 127.7, 128.7, 129.1, 138.3, 139.6, 140.6, 149.5, 155.7, 211.3. Anal. Calcd for $C_{23}H_{21}N_3O_4Se$: C, 57.27; H, 4.39; Ns, 8.71; O, 13.27; Se, 16.37. Found: C, 57.11; H, 4.23; N, 8.88; O, 13.32; Se, 16.28.

*10.4. (S)-Benzyl 1-(Benzylamino)-3-(benzyloxy)-1-selenoxopropan-2-ylcarbamate (**8d**).* $[\alpha]_D^{25}$ −1.8 (*c*, 1.5 $CHCl_3$); R_f 0.54 (*n*-hexane/EtOAc, 8:2); Pale yellow solid, mp 94−96 °C; HRMS (ESI) Calcd for $C_{25}H_{26}N_2O_3Se$ m/z 483.1187 $(M + H)^+$, found 483.1173; IR (Neat) υ_{max} 3224, 1742, 1738, 1597, 1256 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 582.946; ^1H NMR (300 MHz, $CDCl_3$) δ 3.39−3.51 (m, 2H), 3.55−3.71 (m, 1H), 3.91 (s, 2H), 4.43 (s, 2H), 4.85 (s, br, 1H), 5.31 (s, 2H), 7.12−7.51 (m, 15H), 7.722−7.89 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.8, 50.0, 62.1, 70.0, 74.5, 126.7, 127.3, 128.7, 128.8, 128.9, 129.1, 129.2, 129.3, 129.5, 138.6, 139.7, 140.5, 155.8, 212.2. Anal. Calcd for $C_{25}H_{26}N_2O_3Se$ C, 62.37; H, 5.44; N, 5.82; O, 9.97; Se, 16.40. Found: C, 62.04; H, 5.32; N, 5.88; O, 9.29; Se, 16.38.

*10.5. (S)-Benzyl 2-((2-Aminophenyl)carbamoselenoyl)pyrrolidine-1-carboxylate (**8e**).* $[\alpha]_D^{25}$ −25.3 (*c*, 1.0 $CHCl_3$); R_f 0.58 (*n*-hexane/EtOAc, 5:5); Yellow solid, mp 114−115 °C; HRMS (ESI) Calcd for $C_{19}H_{21}N_3O_2Se$ m/z 404.0877 $(M + H)^+$, found 404.0857; IR (Neat) υ_{max} 3148, 3029, 1755, 1600, 1258 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 606.239; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59−1.83 (m, 4H), 3.21−3.59 (m, 3H), 4.37 (s, br, 2H), 5.19 (s, 2H), 5.72 (s, br, 1H), 6.17 (d, J = 4.7 Hz, 2H), 6.51 (d, J = 5.2 Hz, 2H), 7.31 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 28.6, 47.5, 50.0, 67.0, 117.6, 119.1, 128.6, 129.2, 129.6, 132.4, 137.0, 142.6, 157.5, 211.6. Anal. Calcd for $C_{19}H_{21}N_3O_2Se$ C, 56.72; H, 5.26; N, 10.44; O, 7.95; Se, 19.62. Found: C, 56.31; H, 5.11; N, 10.34; O, 7.58; Se, 19.10.

*10.6. (S)-Methyl 3-Methyl-2-phenylselenoamidobutanoate (**8f**).* $[\alpha]_D^{25}$ −43.4 (*c*, 1.0 $CHCl_3$); R_f 0.61 (*n*-hexane/EtOAc, 8:2); Yellow solid, mp 87−89 °C; HRMS (ESI) Calcd for $C_{13}H_{17}NO_2Se$ m/z 300.0503 $(M + H)^+$, found 300.0494; IR (KBr) υ_{max} 2049, 1742, 1594, 1390 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 613.109; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 5.8 Hz, 6H), 2.51 (m, 1H),3.32 (d, J = 2.9 Hz, 1H), 3.58 (s, 3H), 4.97 (br, s, 1H), 7.31 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 31.4, 50.0, 59.1, 125.4, 127.5, 128.2, 128.9, 144.2, 156.5, 171.2, 209.2. Anal. Calcd for $C_{13}H_{17}NO_2Se$ C, 52.35; H, 5.75; N, 4.70; O, 10.73; Se, 26.48. found C, 52.24; H, 5.67; N, 4.58; O, 10.67; Se, 26.35.

*10.7. (S,E)-Methyl 2-(3-Phenylprop-2-eneselenoamido)-propanoate (**8g**).* $[\alpha]_D^{25}$ −49.5 (*c*, 1.0 $CHCl_3$); R_f 0.61 (*n*-hexane/EtOAc, 8:2); Yellow solid, mp 119−121 °C; HRMS (ESI) Calcd for $C_{13}H_{15}NO_2Se$ m/z 298.0346 $(M + H)^+$, found 298.0337; IR (Neat) υ_{max} 3119, 2501, 1739, 1588, 1129 cm^{-1}; ^{77}Se NMR (75 MHz, $CDCl_3$) δ 522.282; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 5.6 Hz, 3H), 3.41 (m, 1H), 3.55 (s, 3H), 5.13 (s, J = 4.3 Hz, 1H), 6.51 (s, J = 8.6 Hz, 1H), 7.11−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 50.0, 53.4, 109.6, 125.4, 125.5, 127.6, 128.3, 132.7, 135.0, 168.0, 203.9. Anal. Calcd for $C_{13}H_{15}NO_2Se$ C, 52.71; H, 5.10; N, 4.73; O, 10.80; Se, 26.66. Found: C, 52.57; H, 4.89; N, 4.48; O, 10.71; Se, 26.57.

■ ASSOCIATED CONTENT

Supporting Information

HPLC chromatogram of crude **1a** prepared from procedure **6**; copies of ^1H NMR, ^{13}C NMR, ^{77}Se NMR, and HRMS/ESI-MS of all Se-containing products; HPLC chromatograms of **2a−o**; ^1H and ^{77}Se NMR spectra, HPLC chromatogram of 1:1 mixture of **2l**, **2m** and **2n**, **2o**; CIF file of compound **8f**; LC−MS of the crude product **2e** prepared from 1:1 and 0.1:1 ratio of DMF and PCl_5; ESI-MS of the intermediate generated from 0.1:1 ratio of DMF and PCl_5. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

[⊥]Dedicated to the memory of Prof. K. M. Shivanandiah.

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