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A Facile One-Pot Synthesis of Selenoureidopeptides Employing LiAlHSeH through Staudinger Aza-Wittig-Type Reaction

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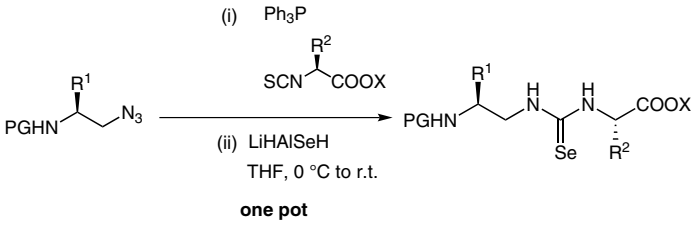

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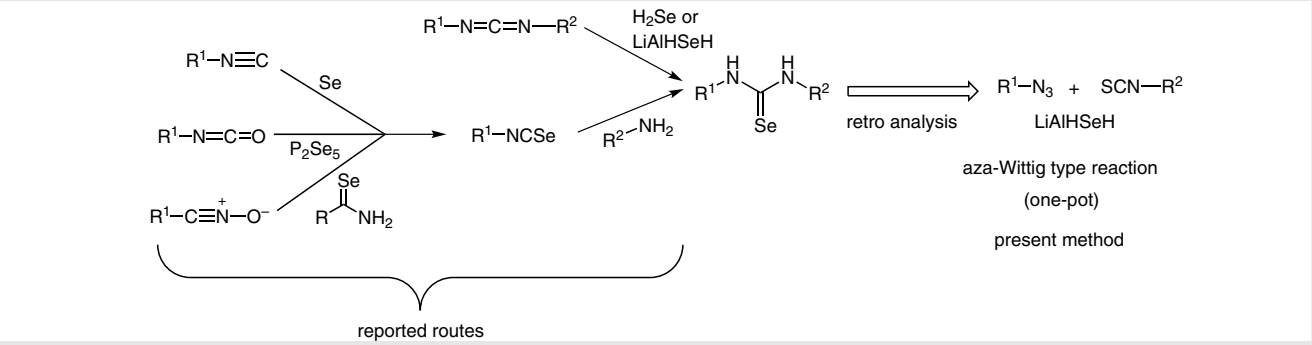
Abstract A one-pot protocol for the synthesis of selenoureidopeptides employing lithium aluminum hydride hydroselenide (LiAlHSeH) as a selenating agent via a Staudinger aza-Wittig-type reaction is reported. The protocol involves the use of N$^{\alpha}$-protected aminoalkyl azides and isothicyanato esters to afford the desired products in good yields. This protocol is a direct approach to the synthesis of selenourea compounds that avoids the synthesis of isoselenocyanates and does not require multistep synthesis.

Key words selenation, Staudinger aza-Wittig-type reaction, LiAlHSeH, selenoureidopeptide mimics

Interest in the use of organoselenium compounds in chemical biology[1] is growing steadily due to (i) an increase in the availability of stable organoselenium compounds and (ii) the beneficial effects associated with them as antioxidants, enzyme inhibitors, cytokine inducers, immunomodulators, and antitumor, antihypertensive, antiviral, antibacterial, antifungal, and anti-infective agents.[2] Woollins' reagent is employed in various selenation protocols.[3] Several strategies and reagents for the efficient incorporation of selenium functionality into molecular architecture are being developed.[4] Their utility in the construction of several classes of heterocycles such as selenazoles[5] and selenohydantoins[6] is well documented.

The synthesis of selenium-containing compounds is of interest in peptide science owing to the discovery of a number of selenoproteins.[7] Selenocysteine (Sec) is regarded as 21st proteinogenic amino acid because its insertion into protein sequences is genetically controlled.[8] Glutathione peroxidase (GPx),[9] possessing selenocysteine in the active site, is an antioxidant enzyme that protects various organisms from oxidative damage.[10] Selenocysteine-mediated chemoselective ligation is useful in the chemical synthesis and semisynthesis of polypeptides and a range of proteins through native chemical ligation.[11] Despite the growing importance of selenopeptides/proteins, the insertion of selenium into a peptide sequence is mainly limited to the above-described studies.

The general route available for the synthesis of selenourea molecules is by the reaction of an amine with an isoselenocyanate.[12] Ishihara and co-workers reported the synthesis of selenoureas by the reaction of *N*,*N*′-dialkyl- or *N*,*N*′-diarylcarbodiimides with lithium aluminum hydride hydroselenide (LiAlHSeH).[13] Selenoureas can also be accessed by treating a carbodiimide with hydrogen selenide, which is highly toxic and air-sensitive.[14] Only a few studies of isoselenocyanates have been reported. The reported syntheses of isoselenocyanates include the reaction of isocyanides with selenium,[12c] phenylimidoyl chloride with sodium selenide,[15] isocyanate with phosphorus pentaselenide,[16] and alkyl/aryl isoselenocyanates from N-monosubstituted formamides.[16b,c] The preparation of isoselenocyanates involves the reaction of N-protected aminoalkyl isocyanides with selenium powder and also the synthesis of the isocyanide itself is a multistep protocol. Alternatively, the isoselenocyanate moiety can be inserted in place of an amino group of an α-amino acid through N-formylation followed by reaction with selenium.[17] An apparently convenient protocol would be the treatment of an amine with carbon diselenide, but this procedure is of very limited use due to the use of carbon diselenide which is not commercially available.[18,19] Another report describes the synthesis of isoselenocyanates via the cycloaddition reaction of a nitrile oxide with a primary selenoamide[20] (Scheme 1). Many of the protocols are not general applicable, use unstable reactants, and lack of broad functional group tolerance.

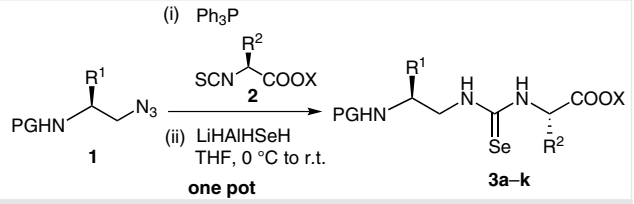


Scheme 1 Methods for the synthesis of selenoureas

Aza-Wittig reactions have undergone tremendous development over the last three decades and they have now become a powerful tool in organic synthesis for the construction of acyclic and cyclic compounds, mainly because the reaction is conducted in neutral solvents in the absence of a catalyst and generally at low temperatures, and it usually proceeds in high yield.[21]

Among various methods available for the construction of the carbodiimide functionality,[22] the intermolecular aza-Wittig-type reaction of iminophosphoranes with heterocumulenes, such as isocyanates/isothiocyanates, is a useful protocol[23] as it can be executed under neutral conditions. Thus we augmented the aza-Wittig condensation of alkyl azides with isothiocyanates to achieve our present objective. The proposed protocol is simple and involves the addition of lithium aluminum hydride hydroselenide to an in situ generated carbodiimide to form selenoureidopeptides.

To address our synthetic objective, we designed an alternative protocol involving Staudinger reaction followed by aza-Wittig condensation employing an N^{β}-urethane-protected aminoalkyl azide[24] and an isothiocyanato ester[25] as precursor components. Thus the in situ generated carbodiimide served as the active intermediate, which further participated in the subsequent step leading to the formation of selenoureidopeptides (Scheme 2).



Scheme 2 One-pot synthesis of selenoureidopeptides

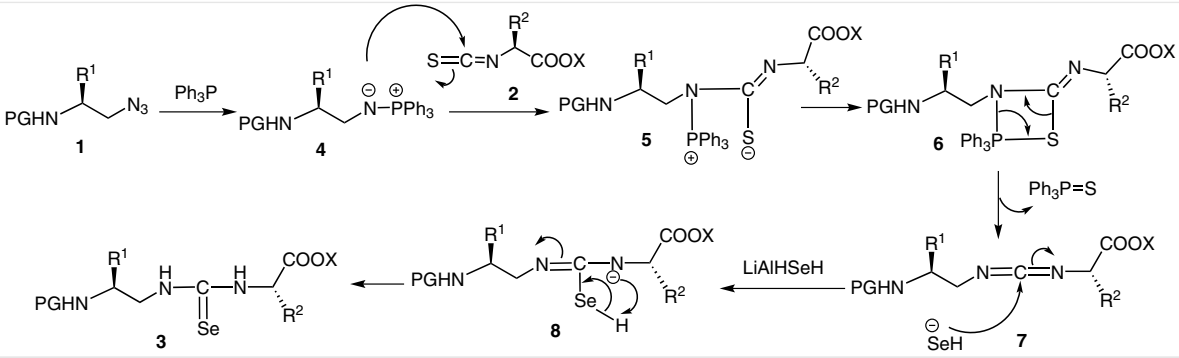
A Cbz-Phe-OH derived aminoalkyl azide was chosen as a model substrate; it reacted with triphenylphosphine in anhydrous tetrahydrofuran at 0 °C to room temperature and the disappearance of the starting azide was observed by TLC analysis. This was then followed by the addition of the isothiocyanato ester of an amino acid, alanine. The reaction mixture was stirred for about three hours and the disappearance of the isothiocyanato ester and the formation of a complex (formed by the reaction of isothiocyanate, Ph_3P, and azide) was observed followed by the appearance of a new spot in the TLC analysis. During the course of the reaction, IR analysis of the reaction mixture revealed the presence of a strong absorption band in the region 2118 cm^{-1} corresponding to the N=C=N stretch of the carbodiimide and thus clearly indicates the formation of a carbodiimide. This was then treated with a suitable selenating agent. In this step, various selenating agents viz, phosphorus pentaselenide, Woolins' reagent, lithium aluminum hydride hydroselenide, and phosphorus pentachloride/selenium were screened (Table 1). Among them, lithium aluminum hydride hydroselenide afforded the corresponding selenourea **3a** in good (86%) yield within 10 minutes. The selenating reagent lithium aluminum hydride hydroselenide, required for the selenation of the in situ generated carbodiimide, was prepared according to the method reported by Ishihara et al.,[4a] which involves the treatment of lithium aluminum hydride with selenium powder in anhydrous tetrahydrofuran at room temperature.

Table 1 Screening of Selenating Agents[a]

Entry	Selenating agent	Yield[b] (%) of **3a**
1	P_2Se_5	36
2	Woolins' reagent	48
3	LiAlHSeH	86
4	PCl_5/Se	32

[a] Reaction condition: Cbz-Phe-CH_2N_3 (1.0 mmol), Ph_3P (1.2 mmol), THF, 0 °C, 10–15 min, then addition of isothiocyanatoalaninate (1.3 mmol) followed by selenating agent (1.2 mmol) at 0 °C–r.t., 3 h.
[b] Isolated yield.

The first step of the reaction involves the formation of a carbodiimide (*vide infra*). The general mechanism of the carbodiimide synthesis by aza-Wittig condensation proceeds through the reaction of an alkyl azide **1** with isothiocyanate **2** to form phosphinimine intermediate **5** that un-



Scheme 3 Possible mechanism for the formation of selenoureidopeptides

dergoes the desired transformation through intermediate **6** to form carbodiimide **7** with loss of triphenylphosphine sulfide. In the next step, the in situ generated carbodiimide **7** reacts with lithium aluminum hydride hydroselenide to produce the carbodiimidoyl selenol species **8**, which then rearranges further to form the desired selenoureidopeptides **3** (Scheme 3).

With the reaction conditions established, a variety of amino acids **1** were employed and the corresponding selenoureidopeptides **3a**–**k** were obtained in good yields (Table 2). Urethane protecting groups, such as Cbz, Fmoc, and Boc, also worked well in affording the desired products in good yields. All the products were purified by column chromatography and characterized by mass spectrometry, ^{1}H, ^{13}C, and ^{77}Se NMR analyses.

The optical purity of the N-protected guanidinopeptide mimic was evaluated by an ^{1}H NMR study of the model compound prepared via the present protocol. The diastereomeric selenoureidopeptide mimics **3j** and **3k** were synthesized by coupling Fmoc-Phg-ψ[CH_2N_3] with L- and D-Ala-OMe, respectively, in presence of lithium aluminum hydride hydroselenide in separate experiments. ^{1}H NMR of **3j** and **3k** showed a single distinct methyl group doublet at **3j**: δ = 1.17, 1.18 and **3k**: δ = 1.24, 1.25. Furthermore, the mixture prepared by coupling Fmoc-Phg-ψ[CH_2N_3] with racemic L,D-Ala-OMe showed methyl groups as two doublets with at δ = 1.15, 1.16 and 1.23, 1.24 indicating the presence of two isomers and confirming that the protocol is free from epimerization.

In conclusion, herein we have described a one-pot protocol for the synthesis of selenoureidopeptides employing lithium aluminum hydride hydroselenide as the selenating agent via a Staudinger aza-Wittig-type reaction. The protocol involves the use of N^{α}-protected aminoalkyl azides and isothiocyanato esters. The present protocol affords the desired products in good yields and can be extended to simple as well as bifunctional amino acids. This protocol is a direct approach to the synthesis of selenourea compounds and avoids the synthesis of isoselenocyanates, and thus the synthesis of N^{α}-protected aminoalkyl isocyanides, which precludes multistep synthesis.

Table 2 Selenoureidopeptides Synthesized[a]

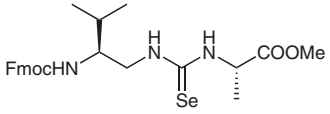
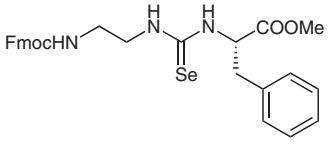
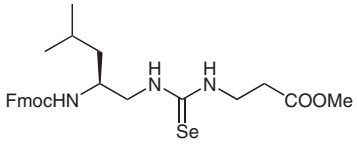
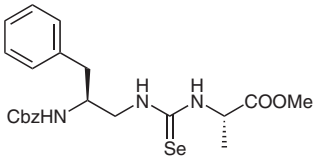
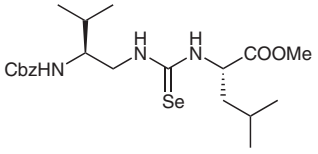
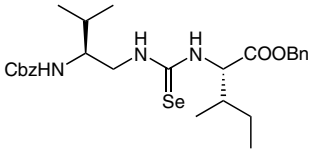
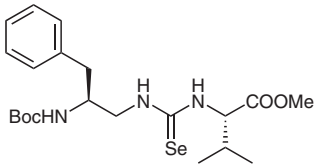
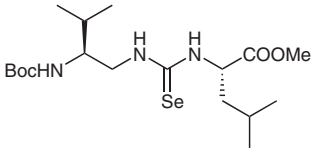
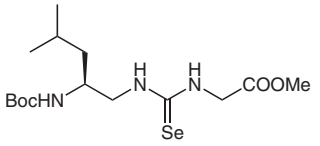
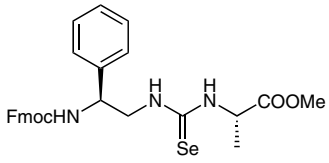
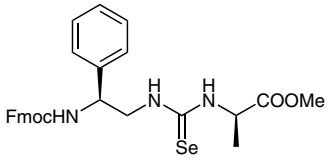
Entry	Product		Yield[b] (%)
1	**3a**		86
2	**3b**		84
3	**3c**		83
4	**3d**		89
5	**3e**		81
6	**3f**		78

Table 2 (continued)

Entry	Product		Yield[b] (%)
7	**3g**		82
8	**3h**		78
9	**3i**		80
10	**3j**		80
11	**3k**		82

[a] Reaction conditions: N$^{\alpha}$-protected aminoalkyl azide **1** (1.0 mmol), Ph_3P (1.2 mmol), THF, 0 °C, 10–15 min, then addition of isothiocyanato ester **2** (1.3 mmol) followed by LiAlHSeH (1.2 mmol), anhydrous THF, 0 °C–r.t., 3 h.
[b] Isolated yield.

All amino acids were used as obtained from Sigma-Aldrich Company, USA. Unless otherwise mentioned, all amino acids used were of L-configuration. All the solvents were dried and purified using recommended literature procedures whenever necessary. High-resolution mass spectra were recorded on a Micromass Q-TOF mass spectrometer using electrospray ionization mode. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz and 100 MHz spectrometer, respectively, at the Indian Institute of Science, Bangalore. IR spectra were recorded on a Shimadzu model FT-IR spectrophotometer at Bangalore University, Bangalore. Melting points were determined in an open capillary and are uncorrected. TLC experiments were carried out on Merck aluminum TLC sheets (silica gel 60 F_{254}) and chromatograms were visualized by exposing in an iodine chamber or with a UV lamp, or by spraying with $KMnO_4$ followed by heating. Column chromatography was performed on neutralized silica gel (100–200 mesh) using mixtures of ethyl acetate and hexane as eluents.

N-Protected aminoalkyl azides **1**[24] and isothiocyanato esters **2**[25d,e] are known compounds.

Lithium Aluminum Hydride Hydroselenide (LiAlHSeH)

To a solution of Se powder (0.08 g, 1.0 mmol) in anhydrous THF (10 mL) was added $LiAlH_4$ (0.038 g, 1.0 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 20–30 min. The reagent LiAlHSeH was formed in situ, and the gray solution was used directly.

Note: The reagent should be prepared prior to use.

Isothiocyanato Esters 2;[25d,e] General Procedure

To a solution of amino acid ester salt (10 mmol) in CH_2Cl_2 was added CS_2 (11 mmol) followed by Et_3N (40 mmol) at 0 °C; the mixture was stirred at this temperature for 30 min and then at r.t. for 30 min. The mixture was cooled to 0 °C and TsCl (13 mmol) was added. Stirring was continued for 3 h or until completion of the reaction (TLC analysis). Excess CH_2Cl_2 (2 × 5 mL) was added and the organic layer was washed with 10% citric acid solution (2 × 15 mL), water (2 × 10 mL), and brine (2 × 10 mL). It was then dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was subjected to column chromatography (10% EtOAc–hexane) to afford the pure product.

Selenoureidopeptides 3a–k; General Procedure

To a solution of N-protected aminoalkyl azide **1** (1.0 mmol) in anhyd THF (8 mL) at 0 °C was added Ph_3P (1.2 mmol) and the mixture was stirred for 10–15 min. Isothiocyanato ester (1.3 mmol) was added to the mixture and it was stirred for ca. 2 h; freshly prepared LiAlHSeH (1.2 mmol) in anhyd THF (4 mL) was added portionwise to the mixture and it was then stirred until completion of the reaction (TLC monitoring). The organic layer was then evaporated in vacuo to afford the crude product which was purified by column chromatography (EtOAc–*n*-hexane, 30:70).

Fmoc-Val-ψ[CH_2NHC(Se)NH]-Ala-OMe (3a)

White solid; yield: 444.18 mg (86%); mp 171–173 °C.

IR (neat): 1512, 1693, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (dd, *J* = 7.1 Hz, 6 H), 1.40 (d, *J* = 7.2 Hz, 3 H), 2.05–2.20 (m, 1 H), 3.12 (m, 2 H), 3.73 (s, 3 H), 4.00–4.10 (m, 1 H), 4.21 (t, *J* = 7.0 Hz, 1 H), 4.25–4.50 (m, 2 H), 4.50–4.65 (m, 1 H), 5.43 (br s, 1 H), 5.56 (d, *J* = 8.8 Hz, 1 H), 6.56 (br s, 1 H), 7.30 (m, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.59 (d, *J* = 7.1 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.80, 21.6, 29.8, 44.2, 46.8, 52.4, 59.6, 63.2, 65.8, 126.7, 127.2, 127.9, 128.4, 141.1, 142.8, 154.1, 170.4, 183.5.

^{77}Se NMR ($CDCl_3$): δ = 288.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}N_3O_4Se$: 540.0785; found: 540.0781.

Fmoc-Gly-ψ[CH_2NHC(Se)NH]-Phe-OMe (3b)

White solid; yield: 463.42 mg (84%); mp 182–184 °C.

IR (neat): 1515, 1691, 1742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12–3.24 (m, 4 H), 3.67 (s, 3 H), 3.77–3.82 (m, 1 H), 4.12–4.28 (m, 3 H), 4.66 (d, *J* = 5.6 Hz, 2 H), 5.17 (br s, 1 H), 6.45 (br s, 2 H), 7.15–7.41 (m, 9 H), 7.53 (d, *J* = 7.2 Hz, 2 H), 7.68 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6, 39.8, 41.2, 47.6, 56.9, 60.7, 67.3, 120.4, 125.1, 125.6, 127.5, 128.1, 129.4, 129.8, 134.9, 141.7, 144.3, 156.1, 173.8, 183.1.

^{77}Se NMR ($CDCl_3$): δ = 290.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{29}N_3O_4Se$: 574.1221; found: 574.1224.

Fmoc-Leu-ψ[CH_2NHC(Se)NH]-β-Ala-OMe (3c)

White solid; yield: 440.33 mg (83%); mp 173–174 °C.

IR (neat): 1518, 1696, 1742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 1.37 (m, 2 H), 1.66 (m, 1 H), 2.58 (m, 2 H), 3.58 (s, 3 H), 3.65–3.80 (m, 4 H), 4.02 (m, 1 H), 4.19 (t, *J* = 6.8 Hz, 1 H), 4.35 (m, 2 H), 5.21 (br, 1 H), 6.96 (br, 2 H), 7.22–7.76 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 23.5, 25.29, 34.0, 42.3, 47.6, 52.3, 54.0, 64.3, 67.3, 120.4, 125.6, 127.6, 128.2, 141.7, 144.1, 157.7, 173.4, 183.8.

^{77}Se NMR ($CDCl_3$): δ = 288.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{33}N_3O_4Se$: 554.1534; found: 554.1535.

Cbz-Phe-ψ[CH_2NHC(Se)NH]-Ala-OMe (3d)

White solid; yield: 424.02 mg (89%); mp 166–167 °C.

IR (neat): 1510, 1690, 1746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 7.1 Hz, 3 H), 3.08 (m, 4 H), 3.72 (s, 3 H), 4.30–4.45 (m, 1 H), 4.45–4.60 (m, 1 H), 5.00 (s, 2 H), 5.45 (br s, 1 H), 6.81 (br, 2 H), 7.15–7.35 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 33.6, 38.6, 47.3, 53.3, 60.7, 66.6, 126.6, 127.6, 127.9, 128.3, 128.5, 129.0, 136.14, 136.9, 156.7, 172.5, 182.6.

^{77}Se NMR ($CDCl_3$): δ = 290.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{27}N_3O_4Se$: 500.1064; found: 500.1060.

Cbz-Val-ψ[CH_2NHC(Se)NH]-Leu-OMe (3e)

White solid; yield: 381.07 mg (81%); mp 169–170 °C.

IR (neat): 1517, 1689, 1745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 5.9 Hz, 6 H), 0.93 (dd, *J* = 6.8, 12.6 Hz, 6 H), 1.45–1.75 (m, 3 H), 2.00–2.20 (m, 1 H), 3.71 (s, 3 H), 3.89 (m, 1 H), 4.55–4.65 (m, 1 H), 5.02 (s, 2 H), 5.51 (br s, 1 H), 6.70 (br s, 2 H), 7.05–7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 34.0, 40.2, 47.5, 47.9, 51.1, 52.3, 67.4, 120.4, 125.5, 127.5, 128.2, 141.7, 144.1, 157.4, 173.4, 183.2.

^{77}Se NMR ($CDCl_3$): δ = 286.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}N_3O_4Se$: 494.1534; found: 494.1532.

Cbz-Val-ψ[CH_2NHC(Se)NH]-Ile-OBn (3f)

White solid; yield: 426.31 mg (78%); mp 173–174 °C.

IR (neat): 1511, 1689, 1739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61–1.11 (m, 12 H), 1.16–1.35 (m, 2 H), 1.64–1.92 (m, 2 H), 3.36–3.53 (m, 1 H), 3.71–4.00 (m, 2 H), 4.10–4.22 (m, 1 H), 5.22 (s, 4 H), 5.51 (br s, 1 H), 6.89 (br s, 1 H), 7.18–7.38 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1, 15.6, 18.1, 26.3, 33.8, 38.5, 48.6, 54.3, 55.6, 67.3, 68.8, 127.2, 127.7, 128.2, 128.6, 128.8, 135.1, 136.3, 157.4, 171.2, 179.8.

^{77}Se NMR ($CDCl_3$): δ = 290.5.

MS (ES): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{37}N_3O_4Se$: 570.18; found: 570.20.

Boc-Phe-ψ[CH_2NHC(Se)NH]-Val-OMe (3g)

White solid; yield: 385.77 mg (82%); mp 165–166 °C.

IR (neat): 1520, 1697, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.4 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.45 (s, 9 H), 2.00–2.20 (m, 1 H), 3.05–3.20 (m, 4 H), 3.71 (s, 3 H), 3.85–4.00 (m, 1 H), 4.80–4.95 (m, 1 H), 5.04 (d, *J* = 7.7 Hz, 1 H), 6.37 (br s, 2 H), 7.05–7.15 (m, 2 H), 7.25–7.35 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 19.2, 21.4, 29.6, 30.22, 43.66, 48.24, 53.44, 65.23, 82.35, 127.2, 127.7, 128.2, 128.6, 128.8, 135.1, 138.3, 158.0, 172.9, 184.2.

^{77}Se NMR ($CDCl_3$): δ = 290.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{33}N_3O_4Se$: 494.0785; found: 494.0781.

Boc-Val-ψ[CH_2NHCSeNH]-Leu-OMe (3h)

White solid; yield: 340.43 mg (78%); mp 169–170 °C.

IR (neat): 1515, 1694, 1744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–1.00 (m, 12 H), 1.36 (s, 9 H), 1.62–1.66 (m, 2 H), 1.81–1.85 (m, 1 H), 2.25–2.29 (m, 1 H), 3.27–3.31 (m, 1 H), 3.46–3.51 (m, 1 H), 3.64–4.05 (m, 4 H), 4.30–4.34 (m, 1 H), 4.71–4.74 (m, 1 H), 5.18 (br s, 1 H), 6.28 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 22.9, 25.6, 26.2, 26.6, 28.2, 31.2, 42.3, 47.5, 49.5, 52.3, 55.8, 80.1, 155.4, 170.6, 185.2.

^{77}Se NMR ($CDCl_3$): δ = 239.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{35}N_3O_4Se$: 460.1690; found: 460.1685.

Boc-Leu-ψ[CH_2NHCSeNH]-Gly-OMe (3i)

Gummy; yield: 315.49 mg (80%).

IR (neat): 1509, 1687, 1741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 5.7 Hz, 6 H), 1.37 (s, 9 H), 1.50–1.55 (m, 2 H), 1.76–1.79 (m, 1 H), 2.64–2.88 (m, 2 H), 3.50–3.53 (m, 2 H), 3.63 (s, 3 H), 3.93 (m, 1 H), 5.60 (br s, 1 H), 6.68 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 23.6, 28.1, 43.8, 44.8, 50.1, 53.8, 58.7, 78.8, 155.9, 174.6, 184.1.

^{77}Se NMR ($CDCl_3$): δ = 239.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd $C_{15}H_{29}N_3O_4Se$: 418.1221; found: 418.1214.

Fmoc-Phg-ψ[CH_2-NHC(Se)NH]-(*S*)-Ala-OMe (3j)

White solid; yield: 446.40 mg (80%); mp 171–173 °C.

IR (neat): 1518, 1693, 1743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.18 (d, *J* = 4.0 Hz, 3 H), 3.21–3.57 (m, 2 H), 3.72 (s, 3 H), 4.13–4.20 (m, 3 H), 4.32 (d, *J* = 8.0 Hz, 2 H), 5.24 (br s, 1 H), 6.10 (br s, 1 H), 7.28–7.48 (m, 8 H), 7.56 (d, *J* = 4.0 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 43.9, 46.3, 53.9, 58.2, 67.1, 120.0, 125.0, 127.0, 127.7, 128.3, 128.4, 128.6, 135.5, 141.3, 143.7, 155.1, 171.1, 182.6.

^{77}Se NMR ($CDCl_3$): δ = 270.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd $C_{28}H_{29}N_3O_4Se$: 574.1221; found: 574.1220.

Fmoc-Phg-ψ[CH_2-NHC(Se)NH]-(*R*)-Ala-OMe (3k)

White solid; yield: 451.41 mg (82%); mp 171–173 °C.

IR (neat): 1514, 1688, 1745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.25 (d, *J* = 4.0 Hz, 3 H), 3.20–3.51 (m, 2 H), 3.74 (s, 3 H), 4.10–4.19 (m, 3 H), 4.32 (d, *J* = 8.0 Hz, 2 H), 5.23 (br s, 1 H), 6.07 (br s, 1 H), 7.25–7.49 (m, 8 H), 7.54 (d, *J* = 4.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 43.8, 46.2, 53.7, 58.4, 67.1, 120.1, 125.2, 127.3, 127.7, 128.4, 128.5, 128.6, 135.4, 141.2, 143.6, 155.2, 171.4, 182.3.

^{77}Se NMR ($CDCl_3$): δ = 271.1.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{28}H_{29}N_3O_4Se$: 574.1221; found: 574.1222.

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