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FULL PAPER

Selenocystine peptides performance in 5-*endo-dig* reactions

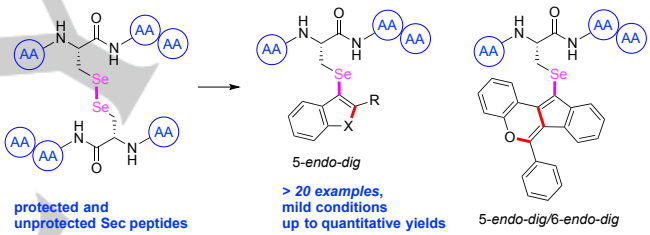
Sindija Lapcinska[a] and Dr. Pavel Arsenyan [a]*

Abstract: Herein we present methods for the generation of selenocysteinyl electrophile by weak Lewis acids or oxidants. The electrophilic selenium species were further utilized in 5-*endo-dig* cyclization reactions with 2-ethynyl phenols, anisoles and anilines yielding substituted benzo[*b*]furans and indoles bearing short selenocysteine-containing peptides. Copper(II) bromide promoted 5-*endo-dig* cyclization can be successfully applied for protected and unprotected peptides in high yields. Elaborated protocol allows the construction of phenylindeno[1,2-*c*]chromene moiety in 5-*endo-dig*/6-*endo-dig* cascade reactions.

Introduction

Benzo[*b*]furan[1] and indole[2] are among the most important heterocycles found in many natural products. Due to the biological activity of natural and synthetic derivatives of these heterocycles they are relevant scaffolds for pharmaceuticals.[3,4] Furthermore, both - benzo[*b*]furan and indole - are considered as "privileged structures" thanks to their ability to act as ligands for various receptors.[5]

The most popular approaches for introduction of selenium atom in benzo[*b*]furan and indole moieties is either direct selenylation[6-10] of these heterocycles or electrophilic cyclization of 2-(1-alkynyl)anisoles/phenols and 2-(1-alkynyl)anilines in the presence of selenium electrophile. [11] The electrophilic species usually employed are arylselanyl chloride[12,13] or arylselanyl iodide generated *in situ* from diselenides using I_2,[14] Fe/I_2,[15] KI/*m*-CPBA system[6] or copper(I) iodide. [16] Copper(I) iodide has also been used as catalyst for the generation of selenium electrophile. [17] Lewis acid ($FeCl_3$) mediated generation of selenium electrophile has been used for preparation of 3-selanyl benzo[*b*]furans[18] and indoles[19] as well. Very recently, Perin *et al.* reported the synthesis of 2,3-dichalcogenyl substituted benzo[*b*]chalcogenophenes employing oxone induced generation of selenium electrophile. [20] Another sulfur-containing oxidant (persulfates) induced generation of selenium electrophile has been used for the direct selenylation of indole[8] and arenofurans. [9] It is noteworthy that previous research has only focused on the use of simple diaryl diselenides except for Cohen *et al.* who reported a sophisticated method[21,22] for the generation of selenocysteine[23,24] (Sec, U) electrophile. This approach is based on the electrophilic character of (5-nitropyridylthio)-Sec peptides and was used in Sec-peptide and small molecule (including some indoles) late stage conjugation. Recently, our group demonstrated novel copper(II) bromide mediated method[25] for the generation of selenocysteinyl electrophile from selenocystine containing peptides. The electrophilic species were used in 5-*endo-dig* cyclization with 2-propargyl *N*-pyridines forming corresponding indolizinium salts whereas *6-endo-dig* cyclization with 2-ethynylbiaryls led to formation of polyaromatic systems containing Sec peptides. In continuation of our research we would like to present the formation of selenocysteine containing benzo[*b*]furans and indoles *via* 5-*endo-dig* cyclization utilizing copper(II) bromide or oxidant induced generation of Sec electrophile. Notably, methods are tolerant to both unprotected and protected selenocystine containing peptides. Moreover, developed protocol allows the formation of phenylindeno[1,2-*c*]chromene moiety in 5-*endo-dig*/6-*endo-dig* cascade reactions.



Results and Discussion

Knowing that copper(II) bromide is a suitable promoter for the Sec electrophile generation, we continued our research in purpose to expand the application scope of this method in 5-*endo-dig* cyclization reactions. Initially we chose 2-(phenylethynyl)anisole (**1a**) and diphenyl diselenide as model substrates employing previously established optimal reaction conditions (Scheme 1). Copper(II) bromide (1.2 equiv.) was added to a solution of Ph_2Se_2 (1.0 equiv.) in CH_2Cl_2 followed by addition of anisole **1a** (1.2 equiv.) after 30 min of stirring. After 24 hours we were delighted to observe the formation of product **2a**, however, the diselenide still remained in the reaction mixture therefore we elevated the reaction temperature to 40 °C, which resulted in full consumption of the diselenide in 16 hours and the product **2a** was obtained in 83% yield. Furthermore, the structure of **2a** was unambiguously confirmed by x-ray analysis (Figure 1, CCDC 1943954). Interestingly, that Kazmierczak *et al.*, who developed method for synthesis of 3-selanyl benzo[*b*]furans via 5-*endo-dig* cyclization of 2-alkynyl phenols using diaryl diselenide and copper(I) iodide,[17] stated that the reaction of diphenyl diselenide and 2-(phenylethynyl)phenol in the presence of $CuBr_2$ in DMSO provides the product **2a** in only 9% yield. They hypothesized that

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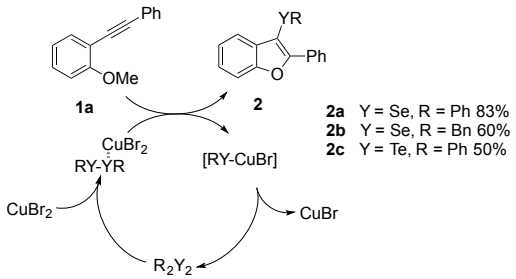
the halogen atom plays a crucial role. Probably, less polar solvent elongates the existence of diphenyl diselenide – copper(II) bromide adduct in the reaction mixture providing an increase of a product yield up to 83%. Analogously, 3-chalcogenyl benzo[*b*]furans **2b** and **2c** were synthesized employing dibenzyl diselenide and diphenyl ditelluride. Previously **2b** and **2c** have been obtained only by Zeni *et al.* using $FeCl_3$ promoted cyclization of 2-phenylethynyl anisole.[18] Inspecting both methods, it could be concluded that in case of **2b** the yields are similar (60% - $CuBr_2$ method, 64% - $FeCl_3$). However, $CuBr_2$ promoted cyclization led to the formation of 2-phenyl-3-(phenyltellanyl)benzo[*b*]furan (**2c**) in 50% yield which is a considerable improvement comparing to $FeCl_3$ promoted phenyltellanyl electrophile generation (36%). Based on previous studies[25] we believe that electrophilic selenium species are formed *via* $CuBr_2$-diselenide adduct **A**.



Scheme 1. 3-Selanyl and 3-tellanyl benzo[*b*]furans formation: feasibility studies. *Reaction conditions*: **1a** (1.2 equiv.), R_2Y_2 (1.0 equiv.), $CuBr_2$ (1.2 equiv.), CH_2Cl_2, 40 °C.

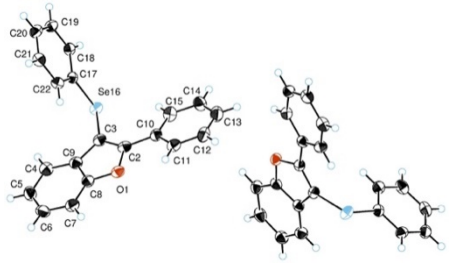
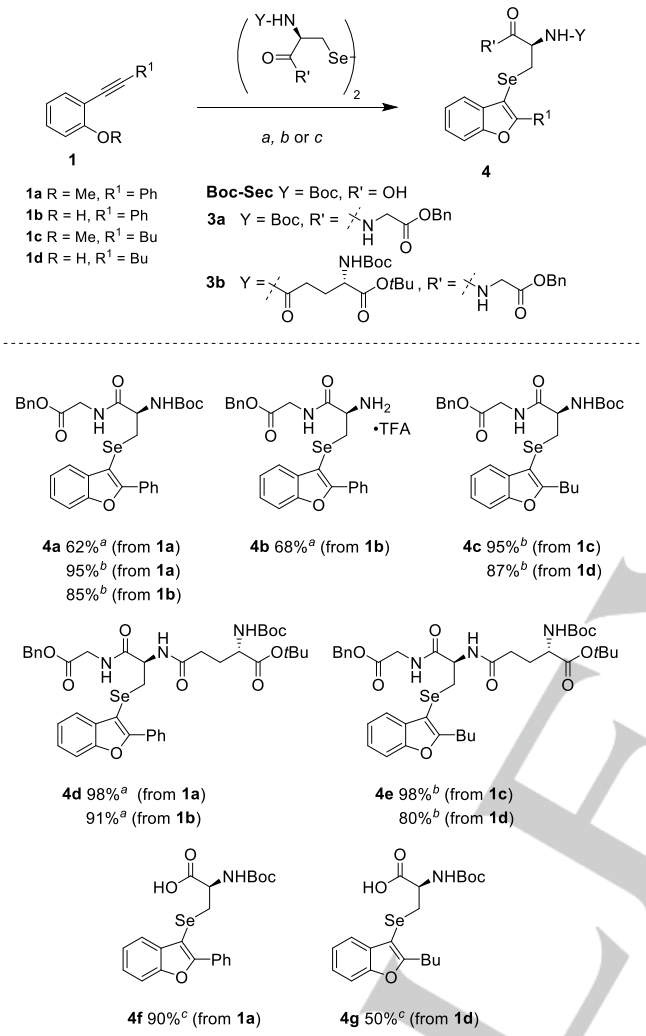


Figure 1. ORTEP molecular structure of **2a**

Satisfied with the results, we turned our attention to preparation of Sec containing benzo[*b*]furans. Gratifyingly, generation of selenium electrophile from bis-dipeptide (Boc)Sec-Gly-OBn **3a** with $CuBr_2$ and reaction with anisole **1a** finalized with the isolation of **4a** in 62% yield (Scheme 2). Similarly, 2-(phenylethynyl)phenol (**1b**) provided product **4b** in 68% yield. Since dipeptide **3a** was convenient for the benzo[*b*]furan formation process, we decided to test more complicated system – *bis*-tripeptide selenoglutathione **3b** – a seleno-analogue of natural glutathione.[26] Under the same reaction conditions benzo[*b*]furan **4d** with selenoglutathione moiety was isolated in almost quantitative yield (98% employing **1a**, 91% - **1b**). Obviously, the complexity of the diselenide does not interfere with the reaction yield. However, treatment of 2-(hex-1-yn-1-yl)phenol (**1d**) with dipeptide **3a** in the presence of $CuBr_2$ led to the formation of a mixture of unidentified compounds probably due to the formation of aryl group stabilized vinyl cation thus preventing 5-*endo-dig* cyclization. The desired 2-butyl-3-selanylbenzo[*b*]furan **4c** formed in low yield forcing us to search for a different method for the generation of Sec electrophile. It is known that selenium electrophile can be generated from diselenides using inorganic and organic oxidants. The choice of reagent depends on the substrate and its functional groups.[27] We tested several of the most popular oxidation agents used for diselenide oxidation to see whether it is possible to employ oxidant for generation of Sec electrophile from Sec containing peptide and use it further in 5-*endo-dig* cyclization for benzo[*b*]furan ring formation. Among the most popular oxidants for selenium electrophile generation are persulfates producing strongly electrophilic alkyl or aryl selanyl sulfate which has been proposed by Tiecco *et al.*[28] and proven by Kumar *et al.* [29] based on ^{77}Se NMR data. [9,28-31] Interestingly, Kumar *et al.* emphasized that TFA is crucial for phenylselanyl electrophile generation in the presence of $K_2S_2O_8$. Probably, it is related with the fact that diphenyl diselenide reaction with persulfate is very slow, furthermore, the solubility of $K_2S_2O_8$ in organic solvents is low as well. Tiecco *et al.* also reported[31] that addition of TfOH to a mixture of Ph_2Se_2 and ammonium persulfate in acetonitrile resulted in completion of reaction in just several minutes. Although most likely that under these conditions the selanylating agent was a mixture of phenylselanyl sulfate and phenylselanyl triflate.[31] Unfortunately, the addition of TFA was prohibited since it would remove protecting groups from peptide. Furthermore, Hajra *et al*. in 2017 reported direct selanylation of arenofuranes using $Na_2S_2O_8$ mediated oxidation of diaryl diselenide[9] without addition of any acid. Utilization of only 1.2 equivalents of oxidant was enough for reaction completion. Treating mixture of dipeptide **3a** and 2-(hexynyl)phenol (**1d**) in MeCN with 5 equiv. of $K_2S_2O_8$ resulted in selective, but slow formation of the product **4c**. Ammonium persulfate provided similar results, yet it was slightly less effective and required more time for full conversion of **3a**. In case of potassium iodate, the reaction was even slower compared to persulfates whereas oxone provided complex mixture of unidentified compounds and only traces of product. Unsatisfactory results were also obtained employing *m*-CPBA, $NaIO_4$, cerium ammonium nitrate and (diacetoxyiodo)benzene. Therefore, $K_2S_2O_8$ is the most suitable oxidant for 2-alkyl-3-selanylbenzo[*b*]furan formation. Next, the necessary quantity of oxidant for the reaction completion was studied (1, 2, 3 and 5 equiv. of $K_2S_2O_8$). According to experimental results, 5 equivalents of oxidant were required for full conversion of starting material in the shortest period (3 days). It should be noted that 5 equivalent excess of oxidant is acceptable for the further studies only because potassium persulfate is a very cheap inorganic reagent. The solvent change from MeCN to CH_2Cl_2 and temperature increase to 40 °C did not give any improvement, so we settled reaction conditions on more environmentally friendly solvent at room temperature. Next, we were focused on the scope and limitations studies. Reaction of **3a** with 2-(hex-1-yn-1-yl)phenol (**1d**) proceeded smoothly to yield 2-butyl-3-selanylbenzo[*b*]furan **4c** in very good yield (87%). The use of 2-(hex-1-yn-1-yl)anisole (**1c**) resulted in even higher yield of **4c** (95%). We also prepared previously obtained compound **4a** to

compare the impact of alkyl and aryl substituents attached to the triple bond. Both substituents were equally suitable for the preparation of 2-substituted benzo[*b*]furans. It is worth mentioning that product **4a** was prepared in significantly higher yield than employing $CuBr_2$ mediated cyclization.



Scheme 2. 3-selanyl benzo[*b*]furan formation: scope and limitation studies. *Reaction conditions*: *a)* 1. $CuBr_2$ (1.5 equiv.), CH_2Cl_2, 40 °C; (2. TFA, CH_2Cl_2, 0 °C); *b)* $K_2S_2O_8$ (5 equiv.), MeCN, rt; *c*) $K_2S_2O_8$ (50 equiv.), MeCN, rt.

Notably, selenoglutathione-benzo[*b*]furan conjugate **4e** was obtained from phenol **1d** in 80% yield whereas the use of anisole **1c** resulted in preparation of **4e** in almost quantitative yield (98%). Unfortunately, neither $CuBr_2$, nor $K_2S_2O_8$ was suitable for the generation of respective sulfenyl electrophile from sulfur analogue of **3b** with consequent formation of glutathione containing benzo[*b*]furan. Treatment of Boc-Sec with **1a** in the presence of $CuBr_2$ or $K_2S_2O_8$ (5 equiv.) led only to traces of the desired product **4f** even after several days. However, increasing the amount of oxidant up to 50 equiv. led to selective formation of **4f** only in 16 hours providing the product in high yield. Product **4g** was obtained analogously, but in lower yield.

Elaborated reaction conditions using 2-ethynyl substituted anilines were tested in purpose to obtain Sec-containing indoles. Previously, Zeni's group reported an elegant $FeCl_3$ promoted cyclization[19] of *o*-alkynyl anilines with diphenyl diselenide, unfortunately, this method led to a very low conversion of peptide **3a**. Similarly to benzo[*b*]furan formation, the treatment of (Boc)Sec-Gly-OBn **3a** with *N*-tosyl-2-(phenylethynyl)aniline **5a** in the presence of $CuBr_2$ in CH_2Cl_2 at room temperature was slow. However, elevation of the temperature to 40 °C led to full consumption of diselenide within 16 hours yielding **6a** in 87% yield (Scheme 3). Under the optimal reaction conditions, substrate scope of alkynyl anilines was examined. Nosyl protected 2-(phenylethynyl)aniline **5c** showed even better result compared to tosyl aniline. Corresponding *N*-nosylindole **6c** was isolated in 91% yield after treatment with TFA. Notably, 2,4-dinitro-benzenesulfonyl protection (**5e**) resulted in loss of reactivity, the reaction mixture showed only traces of product **6e**. Pleasingly, Boc protected 2-(phenylethynyl)aniline **5f** produced indole **6f** in 62% yield after treatment with TFA. However, the developed method does not allow the use of unprotected 2-(phenylethynyl)aniline as a starting material: only a mixture of unidentified compounds was obtained. Additionally, *N,N*-dimethyl- and *N,N*-dibenzyl 2-(phenylethynyl)anilines **5h** and **5i** were tested with the aim to improve the substrate scope. In both cases complex mixture of unidentified compounds was obtained. The same was observed employing *N*-benzyl-2-(phenylethynyl)aniline **5j**. Under the optimal reaction conditions, we prepared selenoglutathione-indole conjugates **6j**, **6l**, **6m**. Again, we observed that the use of selenoglutathione **3b** showed superior yield (75-90%) compared to (Boc)Sec-Gly-OBn **3a** probably due to steric hindrance of the Boc protecting group in **3a**. Treatment of peptide **3a** with 2-(hexynyl)aniline **5b** in the presence of $CuBr_2$ led to formation of a mixture of unidentified compounds showing only traces of product. Thus, an oxidant-promoted selenium electrophile generation was utilized for preparation of 2-alkyl-3-selanylindoles. Tosyl and nosyl anilines were well tolerated under the chosen reaction conditions providing corresponding 3-selanyl indoles in good yields (75 – 98%). However, (2,4-dinitrophenylsulfonyl), Boc and Bn protected anilines were not suitable substrates, as well as dimethyl and dibenzyl anilines. Remarkably, selenocysteinyl indoles **6n-p** were obtained in quantitative yield employing 50 equiv. of $K_2S_2O_8$. Boc-Sec moiety containing benzo[*b*]furans and indoles are without doubt important building blocks that can be easily used for synthesis of more sophisticated structures.

Although both methods for Sec electrophile generation provided products in good yields and the substrate scope was quite broad, obviously the main limitation of this reaction to be used for more sophisticated peptides is the employment of protecting groups. Consequently, we decided to test the reaction between Ts-aniline **5a** and unprotected dipeptide Sec-Gly-OBn **3aa**, although we did not have high expectations. However, the reaction in the presence of $CuBr_2$ led to selective formation of corresponding 3-Sec-indole due to protonation of amino group that prevented the formation of

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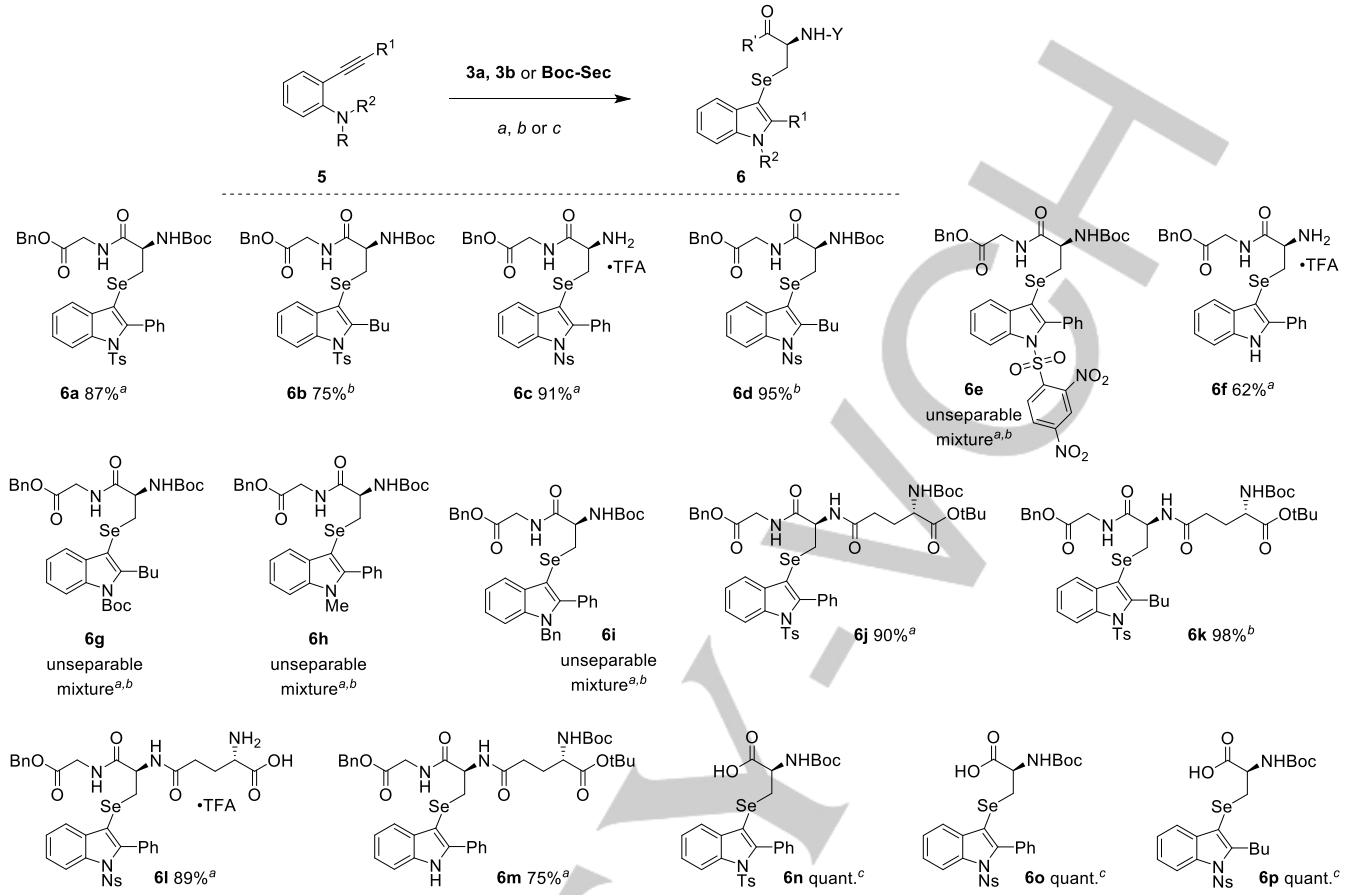

Scheme 3. Scope and limitation studies in synthesis of 3-selanylindoles. *Reaction conditions*: *a*) 1. $CuBr_2$ (1.5 equiv.), CH_2Cl_2, 40 °C; (2. TFA, CH_2Cl_2, 0 °C); *b*) $K_2S_2O_8$ (5 equiv.), MeCN, rt; *c*) $K_2S_2O_8$ (50 equiv.), MeCN, rt. **5a** R^1 = Ph, R^2 = Ts, R = H; **5b** R^1 = Bu, R^2 = Ts, R = H; **5c** R^1 = Ph, R^2 = Ns, R = H; **5d** R^1 = Bu, R^2 = Ns, R = H; **5e** R^1 = Ph, R^2 = (2,4-dinitrophenylsulphonyl), R = H; **5f** R^1 = Ph, R^2 = Boc, R = H; **5g** R^1 = Bu, R^2 = Boc, R = H; **5h** R^1 = Ph, R^2 = R= Me; **5i** R^1 = Ph, R^2 = R = Bn; **5j** R^1 = Ph, R^2 = Bn, R = H.

complex with copper salt. Increase of temperature to 40 °C provided the product **6r** in very good yield (74%) (Scheme 4). The product was also formed employing $K_2S_2O_8$, however, with considerably lower yield and formation of side products.

Next, the substrate scope was determined, and we found out that only Ts-aniline **5a** and anisole **1a** were suitable substrates for 5-*endo*-*dig* cyclization. In both cases, the use of unprotected dipeptide **3aa** resulted in excellent yields, furthermore, they exceeded the ones obtained employing protected dipeptide **3a**. This observation encouraged us to test more complex Sec peptides. Unprotected selenoglutathione Glu-Sec-Gly-OBn **3ba** provided benzo[*b*]furan **4i** and indole **6s** in excellent yields (85% and quantitative yield, correspondingly). Tetrapeptide dimer Tyr-Sec-Gly-Phe-NH_2 **3ca** that mimics the active site of glutathione peroxidase[32] (GPx-4) gave corresponding benzo[*b*]furan **4j** in quantitative yield. Tripeptide Sec-Lys-Phe-NH_2 **3da** provided benzo[*b*]furan **4k** in lower yield due to complications in purification process.

Next, we were interested to see whether it is possible to generate selenium electrophile and perform cascade reaction due to the attractive nature of such transformation. This route allows the formation of multiple bonds in a single step providing polycyclic structures. The main advantages of cascade reaction are atom economy, short reaction time and less waste supporting the basic principles of green chemistry. We chose to utilize anisole-containing aryldiyne **7** for the construction of indeno[1,2-*c*]chromene skeleton. Chromene moiety is often found in biologically active natural products, furthermore, compounds containing indeno[1,2-*c*]chromene core show high potential for use in dye-sensitized photovoltaic cells.[34] Notably, only few methods exist for the construction of indeno[1,2-*c*]chromene moiety. Previously, TfOH mediated cascade reaction of anisole **7** has been performed for the synthesis of 6-phenylindeno[1,2-*c*]chromene, [34] while halogen-mediated cascade reaction has been reported by Chen *et al.* for the synthesis of halogenated 6-phenylindeno[1,2-*c*]chromenes. [35]

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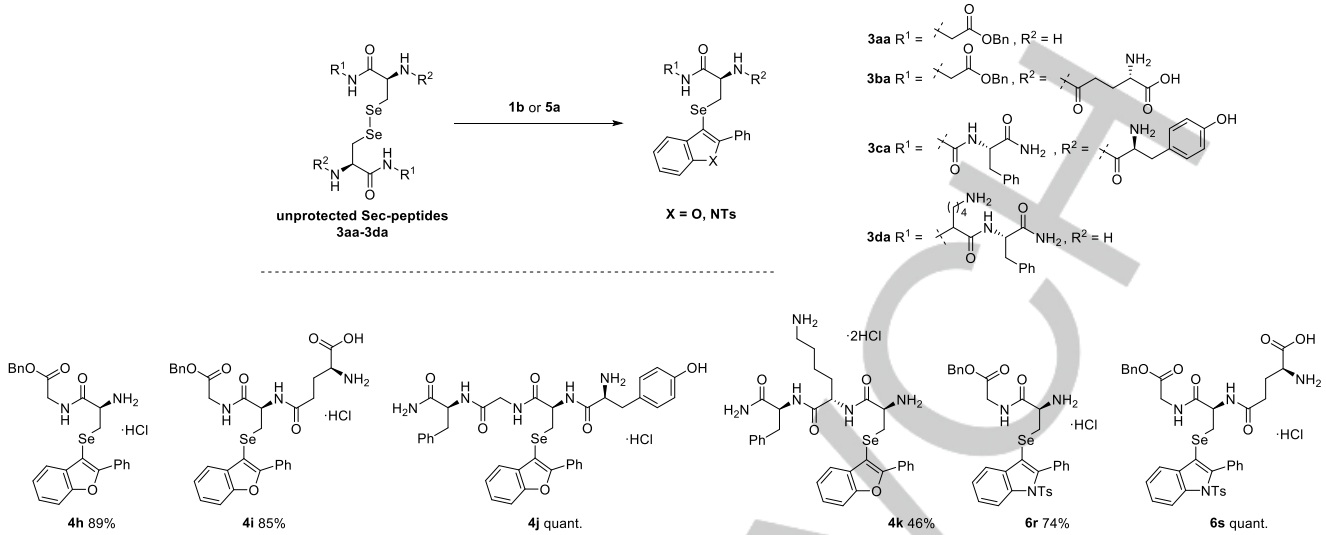
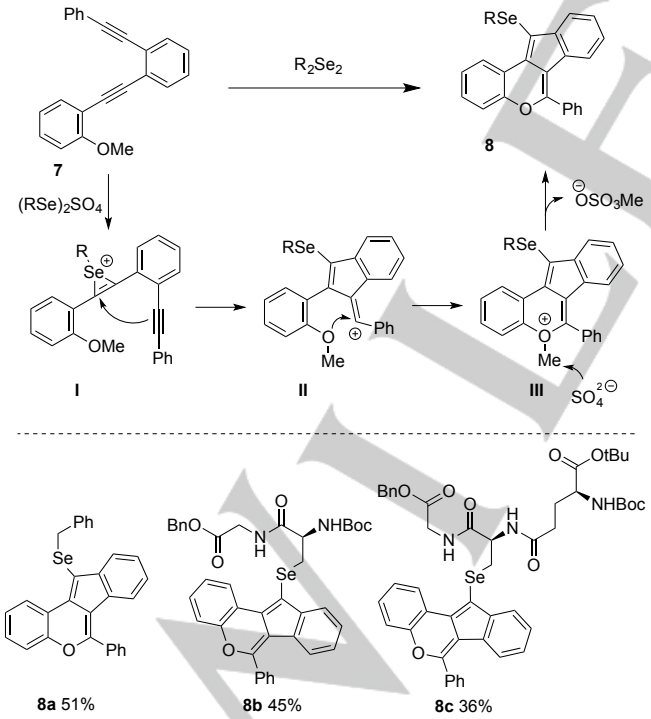


Scheme 4. Preparation of benzo[*b*]furans and indoles employing unprotected Sec peptides. *Reaction conditions*: $CuBr_2$ (2.5 equiv.), CH_2Cl_2/MeCN, 40 °C.

Initially, we tested the reaction of Ph_2Se_2 with **7** in the presence of $CuBr_2$. However, only 11-bromo-6-phenylindeno[1,2-*c*]chromene was detected in the reaction mixture. Potassium persulfate induced electrophile generation lead only to the traces of the desired product even employing 50 equiv. of oxidant. Next, we decided to test Bn_2Se_2. Fortunately, the reaction of Bn_2Se_2 with anisole **7** in the presence of $K_2S_2O_8$ provided 11-(benzylselanyl)-6-phenylindeno[1,2-*c*]chromene (**8a**) (Scheme 5).



Scheme 5. Plausible mechanism for cascade 5-*endo*/6-*endo*-*dig* cyclization. *Reaction conditions*: $K_2S_2O_8$ (5 equiv.), MeCN, rt.

The structure of **8a** was unambiguously confirmed by x-ray analysis (Figure 2, CCDC 1949753).Similarly, the use of peptides **3a** and **3b** led to the formation of Sec containing 6-phenylindeno[1,2-*c*]chromenes as the major product. However, complicated purification of products **8b** and **8c** was responsible f or the low yield of products. Unfortunately, Boc-Sec was not suitable substrate for this reaction. The plausible mechanism for this transformation includes following steps: selanyl electrophile coordinates to the more electron rich double bond forming selenirenium cation **I**. Next, the other triple bond attacks the selenirenium cation with the closure of indene cycle (intermediate **II**). Methoxy group then attacks the carbocation giving cyclization intermediate **III** that after demethylation provides the product **8**. Chen *et al.* [35] performed DFT studies to confirm the cyclization path for *o*-methoxy aryldiynes and stated that the pathway for *o*-amino, thio and carboxy substituents would be different due to the nucleophilic attack of heteroatom to the coordinated triple bond.

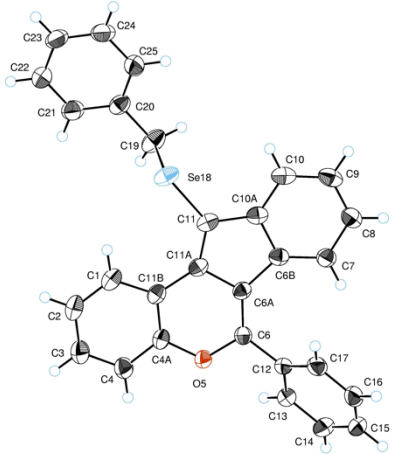


Figure 2. ORTEP molecular structure of **8a**

Conclusions

Preparation of 2-aryl- as well as 2-alkyl-3-selanylbenzo[*b*]furans and indoles by ring closure *via* 5-*endo*-*dig* cyclization employing $CuBr_2$ and $K_2S_2O_8$ mediated generation of Sec electrophile was presented. Copper(II) bromide is effective promoter for the generation of Sec electrophile from protected and unprotected peptides for the formation of 2-aryl-3-Sec-benzo[*b*]furans and indoles up to quantitative yields. However, utilization of $CuBr_2$ is not suitable for preparation of 2-alkyl-3-Sec-benzo[*b*]furans and indoles. Out of all tested oxidants, potassium persulfate is the top choice for the Sec electrophile generation to provide both 2-alkyl- and 2-aryl-3-Sec benzo[*b*]furans and indoles as well. Although the reaction is rather slow and more than equimolar amount of oxidant is required, the yields are excellent and superior to the ones obtained by $CuBr_2$ promoted reaction. Oxidant induced Sec electrophile generation tolerated anilines with Ts and Ns protecting groups whereas $CuBr_2$ promoted cyclization tolerated also Boc aniline. Moreover, based on optimized conditions construction of indeno[1,2-*c*]chromene skeleton is possible. As a result, the use of selenocystine containing peptides results in the formation of Sec containing 6-phenylindeno[1,2-*c*]chromenes. To sum up, the elaborated methods are efficient for the synthesis of 3-Sec-benzo[*b*]furans, indoles and indeno[1,2-*c*]chromenes employing mild conditions, tolerating broad substrate scope and providing products in good to excellent yields.

Experimental Section

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using MERCK Silica gel 60 F254 plates and visualized by UV (254 nm) fluorescence. ZEOCHEM silica gel (ZEOprep 60/35-70 microns – SI23501) was used for column chromatography. ^{1}H, ^{13}C and ^{77}Se NMR[36] spectra were recorded on a Bruker Avance Neo spectrometer at 400, 101 and 76 MHz correspondingly at 298 K in CD_3OD or $CDCl_3$. Dimethyl selenide was used as a standard. Infrared (IR) spectra were recorded with a Prestige-21 FTIR spectrometer (Shimadzu, Kyoto, Japan). HRMS were recorded on Waters Synapt GII Q-ToF UPLC/MS system. Single crystals of **2a** and **8a** were investigated on a Rigaku XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at 140.0(1) K during data collection. Using Olex2,[36] the structure was solved with the olex2.solve[37] structure solution program using Charge Flipping and refined with the ShelXL[38] refinement package using Least Squares minimization.

Boc-L-selenocystine,[39] peptides **3a**,**b**,**c**,[25] 2-(1-alkynyl)anisoles **1a**,[40] **b**,[41] 2-(1-alkynyl)phenols **1c**,**d**,[42] 2-(1-alkynyl)anilines **5a-c**,[43] **f**,[44] **g**,[45] **h**,**i**,[46] **j**,[47] and **7**[34] were prepared according to literature procedures.

***N*-(2-(hex-1-yn-1-yl)phenyl)-4-nitrobenzenesulfonamide (5d)**

To a solution of 2-(hex-1-yn-1-yl)aniline (0.3 g, 1.73 mmol, 1 equiv.) in CH_2Cl_2 (7 ml) pyridine (0.28 ml, 3.46 mmol, 2 equiv.) and *p*-nitrobenzenesulfonyl chloride (0.48 g, 2.08 mmol, 1.2 equiv.) were added at 0 °C. The reaction mixture was stirred for 16 h at room temperature, then it was poured into ice water and extracted with CH_2Cl_2, washed with 2M HCl and brine, dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash chromatography (PE/EtOAc 10:1 – 3:1) to give the title compound **5d** (0.43 g, 69%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 2H), 7.60 (d, *J* = 7.9, 1H), 7.30 – 7.21 (m, 3H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.60 – 1.51 (m, 2H), 1.49 – 1.37 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 144.8, 136.4, 132.4, 129.2, 128.6, 125.6, 124.2, 120.9, 116.1, 98.4, 75.2, 30.7, 22.2, 19.3, 13.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{18}H_{19}N_2O_4S]^+$ 359.1066; found 359.1071.

2,4-Dinitro-*N*-(2-(phenylethynyl)phenyl)benzenesulfonamide (5e)

To a solution of 2-(phenylethynyl)aniline (0.3 g, 1.55 mmol, 1 equiv.) in CH_2Cl_2 (7 ml) pyridine (0.25 ml, 3.10 mmol, 2 equiv.) and 2,4-dinitrobenzenesulfonyl chloride (0.51 g, 1.86 mmol, 1.2 equiv.) were added at 0 °C. The reaction mixture was stirred for 16 h at room temperature, then it was poured into ice water and extracted with CH_2Cl_2, washed with 2M HCl and brine, dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash chromatography (PE/EtOAc 10:1 – 3:1) to give the title compound **5e** (0.34 g, 52%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.18 (d, *J* = 2.2 Hz, 1H), 8.05 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.38 – 7.24 (m, 6H), 7.18 – 7.12 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 148.1, 138.9, 135.8, 133.0, 132.5, 131.5, 130.0, 129.6, 128.8, 127.0, 126.8, 124.2, 121.6, 121.0 117.2, 96.1, 83.6, 77.5, 77.2, 76.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{20}H_{14}N_3O_6S]^+$ 424.0603; found 424.0592.

Preparation of Sec-peptide 3d

Benzyl *tert*-butyl ((*S*)-6-(((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-6-oxohexane-1,5-diyl)dicarbamate (9)

To a solution of (*S*)-2-amino-3-phenylpropanamide hydrochloride (0.79 g, 3.94 mmol, 1.5 equiv.) in DMF (5 ml) at 0 °C was added NMM (0.58 ml, 5.26 mmol, 2 equiv.) and the mixture was stirred for 5 minutes. Then to the reaction mixture was added a solution of N^6-((benzyloxy)carbonyl)-N^2-(*tert*-butoxycarbonyl)-L-lysine (1 g, 2.63 mmol, 1 equiv.) in DMF (5 ml), HOBt (0.402 g, 2.63 mmol, 1 equiv.) and EDC×HCl (1 g, 5.26 mmol, 2 equiv.). The reaction mixture was stirred at 0 °C for 10 minutes and at rt for 2 hours. After evaporation, the residue was purified by reverse phase chromatography (C-18, MeCN/H_2O+AcOH 10-85%) to give the title compound **9** (1.2 g, 87%) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 – 7.15 (m, 10H), 5.07 (s, 2H), 4.63 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.84 (dd, *J* = 8.1, 5.8 Hz, 1H), 3.20 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.06 (t, *J* = 6.9 Hz, 2H), 2.95 (dd, *J* = 13.8, 9.0 Hz, 1H), 1.58 – 1.47 (m, 2H), 1.46-1.34 (m, 11H), 1.30 – 1.12 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.9, 175.0, 158.9, 158.2, 138.5, 138.4, 130.4, 129.5, 128.9, 128.8, 127.8, 80.9, 67.3, 56.8, 55.2, 41.3, 38.4, 32.7, 32.4, 30.5, 28.7, 23.8, 23.7, 14.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{28}H_{39}N_4O_6]^+$ 527.2870; found 527.2868.

***Tert*-butyl (2-(trimethylsilyl)ethyl) ((*S*)-6-(((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-6-oxohexane-1,5-diyl)dicarbamate (10)**

To a solution of **9** (0.54 g, 1.02 mmol) in MeOH with few drops of AcOH was added Pd/C (0.11 g, 0.09 mmol) and H_2 was bubbled through the mixture for 1 hour. The product was filtered, evaporated and dissolved in a mixture of THF (2 ml) and saturated $NaHCO_3$ (2 ml) and Teoc-OSu (0.396 g, 1.53 mmol, 1.5 equiv.) was added. The resulting reaction mixture was stirred for 2 hours, followed by evaporation. Residue was extracted with EtOAc, and washed with brine yielding the title compound (0.4 g, 74%) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 – 7.12 (m, 5H), 4.64 (dd,

J = 8.8, 5.4 Hz, 1H), 4.18 – 4.07 (m, 2H), 3.86 (dd, *J* = 8.2, 5.7 Hz, 1H), 3.20 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.03 (t, *J* = 7.0 Hz, 2H), 2.96 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.59 – 1.47 (m, 2H), 1.46 – 1.35 (m, 11H), 1.30 – 1.13 (m, 2H), 1.03 – 0.93 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.9, 175.0, 159.3, 158.2, 138.5, 130.4, 129.5, 127.8, 80.9, 63.7, 56.8, 55.2, 41.2, 38.4, 32.5, 30.6, 28.7, 23.9, 18.7, -1.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{26}H_{45}N_4O_6Si]^+$ 537.3108; found 537.3109.

(12*S*,15*S*)-16-amino-15-benzyl-2,2-dimethyl-6,13,16-trioxo-5-oxa-7,14-diaza-2-silahexadecan-12-aminium 4-methylbenzenesulfonate (11)

To a solution of **10** (0.4 g, 0.75 mmol, 1 equiv.) in Et_2O (7 ml) *p*TsOH (0.156 g, 0.82 mmol, 1.1 equiv.) was added and the mixture was stirred until full dissolution and then it was evaporated and held at 40 °C for 4 hours. The residue was purified by reverse phase chromatography (C-18, MeCN/H_2O 10-85%) to give the title compound (220 mg, 51%) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.16 (m, 7H), 4.64 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.12 (t, *J* = 8.4 Hz, 2H), 3.82 (t, *J* = 6.3 Hz, 1H), 3.14 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.97 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.37 (s, 3H), 1.90-1.76 (m, 2H), 1.54 – 1.44 (m, 2H), 1.44 – 1.31 (m, 2H), 1.02 – 0.93 (m, 2H), 0.05 (s, 8H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.5, 170.1, 159.4, 143.5, 141.7, 138.3, 130.3, 129.8, 129.5, 127.9, 127.0, 63.8, 56.1, 54.2, 41.1, 38.8, 32.3, 30.5, 22.9, 21.3, 18.7, -1.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{21}H_{37}N_4O_4Si]^+$ 437.2584; found 437.2586.

Di-*tert*-butyl (2-(trimethylsilyl)ethyl) ((12*S*,15*R*,20*R*,23*S*)-23-(((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)carbamoyl)-12-(((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)carbamoyl)-2,2-dimethyl-6,14,21-trioxo-5-oxa-17,18-diselena-7,13,22-triaza-2-silaheptacosane-15,20,27-triyl)tricarbamate (3d)

To a solution of **10** (200 mg, 0.33 mmol, 3 equiv.) in DMF (5 ml) NMM (0.05 ml, 0.45 mmol, 4 equiv.) was added and the mixture was stirred for 5 minutes at 0 °C. Then HOBt (34 mg, 0.22 mmol, 2 equiv.) was added followed by the addition of solution of Boc-L-selenocystine (60 mg, 0.11 mmol, 1 equiv.) in DMF (3 ml) and EDC×HCl (87 mg, 0.45 mmol, 4 equiv.). The reaction mixture was stirred for 10 minutes at 0 °C and additionally for 1 hour at rt, then it was evaporated and the residue was purified by reverse phase chromatography (C-18, MeCN/H_2O 10-85%) to give the title compound (110 mg, 71%) as light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 – 7.14 (m, 5H), 4.67 (t, *J* = 7.1 Hz, 1H), 4.48-4.43 (m, 2H), 4.11 (t, *J* = 8.3 Hz, 2H), 3.30-3.24 (m, 1H), 3.13 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.04 (t, *J* = 6.9 Hz, 2H), 2.96 (dd, *J* = 13.7, 8.3 Hz, 1H), 1.77 – 1.51 (m, 2H), 1.50-1.37 (m, 11H), 1.39 – 1.22 (m, 2H), 1.03 – 0.92 (m, 2H), 0.04 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.8, 173.8, 173.3, 159.2, 157.6, 138.3, 130.4, 129.5, 127.8, 80.9, 63.7, 56.2, 55.7, 54.9, 41.4, 39.1, 33.5, 33.0, 30.5, 28.8, 23.9, 18.7, -1.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{58}H_{97}N_{10}O_{14}Se_2Si_2]^+$ 1373.5055; found 1373.5100.

General procedure for $CuBr_2$ promoted cyclization of diorganyl dichalcogenide and 2-(phenylethynyl)anisole (1a)

$CuBr_2$ (1.2 equiv.) was added to a solution of diorganyl dichalcogenide (1 equiv.) in CH_2Cl_2 and the mixture was stirred for 30 min at rt. Then a solution of **1a** (1.2 equiv.) in CH_2Cl_2 was added. Reaction mixture was stirred for 16 h at 40 °C, and then it was evaporated and purified by flash chromatography (petroleum ether/ethyl acetate 10:0-4:1) to give **2a**-**c**.

2-phenyl-3-(phenylselanyl)benzofuran (2a)[18]

Colorless crystals (104 mg, 83%). Prepared from Ph_2Se_2 (112 mg, 0.36 mmol), $CuBr_2$ (97 mg, 0.43 mmol), and **1a** (90 mg, 0.43 mmol). Crystallized from petroleum ether – ethyl acetate. Melting point: 86-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.16 (m, 2H), 7.56-7.10 (m, 12H).

3-(benzylselanyl)-2-phenylbenzofuran (2b)[18]

Yellow oil (64 mg, 60%). Prepared from Bn_2Se_2 (123 mg, 0.36 mmol), $CuBr_2$ (97 mg, 0.43 mmol), and **1a** (90 mg, 0.43 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 2H), 7.60 – 7.56 (m, 1H), 7.52 (m, 1H), 7.44 – 7.24 (m, 5H), 7.16 – 7.02 (m, 5H), 3.98 (s, 2H).

2-phenyl-3-(phenyltellanyl)benzofuran (2c)[18]

Yellow oil (72 mg, 50%). Prepared from Ph_2Te_2 (148 mg, 0.36 mmol), $CuBr_2$ (97 mg, 0.43 mmol), and **1a** (90 mg, 0.43 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.10 (m, 2H), 7.57 – 7.52 (m, 2H), 7.50-7.42 (m, 5H), 7.38-7.30 (m, 2H), 7.18 – 7.07 (m, 3H).

General procedure for preparation of 3-selanyl benzo[*b*]furans 4a-e and indoles 6a-m.

Method A. To a solution of Sec-peptide **3** (1 equiv.) in CH_2Cl_2 $CuBr_2$ (1.5 equiv.) was added and the mixture was stirred for 30 min at rt. Then a solution of 2-(1-alkynyl)anisole/phenol/aniline (2 equiv.) in CH_2Cl_2 was added. Reaction mixture was stirred for 16 h at 40 °C, and then it was evaporated and purified by reverse phase chromatography (C-18, MeCN/H_2O 10-85%) to give the product.

Method B. To a solution of peptide **3a** or **3b** (1 equiv.) and 2-(1-alkynyl)aniline/phenol/anisole (2 equiv.) in MeCN $K_2S_2O_8$ (5 equiv.) was added and the mixture was stirred for 3 days at rt. After evaporation the mixture was purified by reverse phase chromatography (C-18, MeCN/H_2O 10-85%) to give the product.

Boc and tBu cleavage. To a solution of protected peptide in CH_2Cl_2 TFA at 0 °C was added. Reaction mixture was stirred until disappearance of starting material (1-3 hours). After evaporation the mixture was purified by reverse phase chromatography (C-18, MeCN/H_2O 10-80%).

Benzyl (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-((2-phenylbenzofuran-3-yl)selanyl)propanoyl)glycinate (4a)

White solid. Prepared by method A in 62% yield from **3a** (100 mg, 0.12 mmol), $CuBr_2$ (40 mg, 0.18 mmol), alkyne **1a** (50 mg, 0.24 mmol), CH_2Cl_2 (5 ml). Prepared by method B from **3a** (100 mg, 0.12 mmol), $K_2S_2O_8$ (165 mg, 0.61 mmol), alkyne **1a** 50 mg, 0.24 mmol) or alkyne **1b** (47 mg, 0.24 mmol, MeCN (4 ml) in 95% (70 mg) or 85% (63 mg) yield, correspondingly. NMR spectra presented in SI are from product obtained by method B using alkyne **1a**. $[\alpha]_D^{20}$ -9.0 (c 0.96, $CHCl_3$). IR ν_{max} (film): 3064, 2978, 2933, 1751, 1686, 1517, 1253, 1178. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.10 (m, 2H), 7.61 – 7.52 (m, 1H), 7.45 – 7.32 (m, 3H), 7.32 – 7.13 (m, 8H), 6.64 (s, 1H), 5.14 (d, *J* = 8.2 Hz, 1H), 5.04 (s, 2H), 4.25 (s, 1H), 3.77 (qt, *J* = 18.3, 2.7 Hz, 2H), 3.12 (m, 1H), 2.99 (dd, *J* = 12.6, 5.7 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 169.3, 156.1, 155.4, 153.9, 135.2, 132.0, 130.2, 129.3, 128.7, 128.6, 128.4, 127.8, 125.3, 123.5, 120.8, 111.3, 100.0, 80.5, 67.2, 54.3, 41.4, 29.7, 28.2. ^{77}Se (76 MHz, $CDCl_3$) δ 68.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{31}H_{33}N_2O_6Se]^+$ 609.1504; found 609.1501.

(*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenylbenzofuran-3-yl)selanyl)propan-2-aminium trifluoroacetate (4b)

Yellow solid (50 mg, 68%). Prepared by method A from **3a** (100 mg, 0.12 mmol), $CuBr_2$ (40 mg, 0.18 mmol), alkyne **1b** (71 mg, 0.24 mmol), CH_2Cl_2 (5 ml). Product was isolated after Boc deprotection. $[\alpha]_D^{20}$ +5.2 (c 1.2, MeOH). IR ν_{max} (film): 3064, 3031, 2934, 1748, 1674, 1668, 1662, 1512, 1192, 1189. ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 – 8.22 (m, 2H), 7.75 – 7.68 (m, 1H), 7.60 – 7.48 (m, 2H), 7.46 – 7.37 (m, 1H), 7.37 – 7.28 (m, 7H), 5.12 (s, 2H), 3.76 (s, 2H), 3.41 (dd, *J* = 7.3, 5.2 Hz, 1H), 3.12 (dd, *J* = 12.3, 5.2 Hz, 1H), 2.98 (dd, *J* = 12.3, 7.3 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.8, 170.9, 157.5, 155.3, 137.1, 133.4, 131.6, 130.3, 129.6, 129.5, 129.4, 128.8, 126.5, 124.6, 122.0, 112.1, 101.0, 67.9, 55.9, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 41.9, 34.3. ^{77}Se NMR (76 MHz, CD_3OD) δ 59.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{26}H_{25}N_2O_4Se]^+$ 509.0980; found 509.0989.

Benzyl (*R*)-(2-amino-3-((2-butylbenzofuran-3-yl)selanyl)propanoyl)glycinate (4c)

White solid. Prepared by method B from **3a** (100 mg, 0.12 mmol), $K_2S_2O_8$ (165 mg, 0.61 mmol), alkyne **1c** (45 mg, 0.24 mmol) or alkyne **1d** (42 mg, 0.24 mmol, MeCN (4 ml) in 95% (67 mg) and 87% (62 mg) yield, correspondingly. $[\alpha]_D^{20}$ -23.0 (c 1.1, $CHCl_3$). IR ν_{max} (film): 3322, 2958, 2930, 1752, 1685, 1523, 1452, 1367, 1251, 1171. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 – 7.53 (m, 1H), 7.46 – 7.40 (m, 1H), 7.37 – 7.18 (m, 7H), 5.13 (s, 2H), 4.14 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.89 (d, *J* = 5.7 Hz, 2H), 3.11 (dd, *J* = 12.8, 4.5 Hz, 1H), 2.99 (td, *J* = 7.4, 5.4 Hz, 2H), 2.90 – 2.77 (m, 1H), 1.72 (q, *J* = 7.6 Hz, 2H), 1.43 (s, 8H), 1.40 – 1.26 (m, 4H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 170.8, 164.3, 157.5, 155.8, 137.1, 132.2, 129.5, 129.3, 125.2, 124.2, 121.1, 111.8, 100.8, 80.9, 67.9, 56.1, 42.1, 31.6, 30.3, 28.7, 27.9, 23.3, 14.2. ^{77}Se (76 MHz, CD_3OD) δ 58.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{29}H_{37}N_2O_6Se]^+$ 589.1817; found 589.1813.

***Tert*-butyl N^5-((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenylbenzofuran-3-yl)selanyl)propan-2-yl)-N^2-(*tert*-butoxycarbonyl)-L-glutaminate (4d)**

Yellow solid. Prepared by method A from **3b** (100 mg, 0.083 mmol), $CuBr_2$ (28 mg, 0.12 mmol), alkyne **1c** (35 mg, 0.167 mmol) or alkyne **1d** (49 mg, 0.167 mmol), CH_2Cl_2 (5 ml) in 98% (65 mg) or 91% (60 mg) yield, correspondingly. IR ν_{max} (film): 3295, 3069, 2978, 2933, 1734, 1653, 1646, 1517, 1455, 1368, 1253, 1154. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 – 8.22 (m, 2H), 7.71 – 7.65 (m, 1H), 7.57 – 7.24 (m, 12H), 5.10 (s, 2H), 4.43 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.92 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.81 (d, *J* = 2.4 Hz, 2H), 3.25 (dd, *J* = 12.6, 5.1 Hz, 1H), 2.97 (dd, *J* = 12.6, 9.1 Hz, 1H), 2.24 – 2.11 (m, 1H), 2.08 – 1.87 (m, 2H), 1.81 – 1.67 (m, 1H), 1.54 – 1.37 (m, 18H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.6, 173.3, 173.0, 170.7, 158.1, 157.5, 155.3, 137.1, 133.4, 131.6, 130.3, 129.6, 129.5, 129.3, 128.9, 126.4, 124.6, 122.0, 112.1, 100.8, 82.8, 80.5, 67.9, 55.4, 54.8, 49.4, 42.1, 32.8, 29.8, 28.8, 28.3. ^{77}Se NMR (76 MHz, CD_3OD) δ 82.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{40}H_{49}N_3O_9Se]^+$ 794.2556; found 794.2559.

***Tert*-butyl N^5-((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-3-((2-butylbenzofuran-3-yl)selanyl)-1-oxopropan-2-yl)-N^2-(*tert*-butoxycarbonyl)-L-glutaminate (4e)**

Yellow oil. Prepared by method A from **3b** (100 mg, 0.083 mmol), $CuBr_2$ (28 mg, 0.12 mmol), alkyne **1c** (32 mg, 0.17 mmol) or alkyne **1d** (29 mg, 0.17 mmol), CH_2Cl_2 (5 ml) in 98% (63 mg) or 80% (51 mg) yield, correspondingly. IR ν_{max} (film): 3295, 2977, 2932, 1718, 1646, 1529, 1452, 1367, 1250, 1155. ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 – 7.51 (m, 1H), 7.44 – 7.40 (m, 1H), 7.36 – 7.21 (m, 7H), 5.12 (s, 2H), 4.42 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.98 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.87 (d, *J* = 1.2 Hz, 2H), 3.13 (dd, *J* = 12.7, 4.8 Hz, 1H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.86 (dd, *J* = 12.7, 9.5 Hz, 1H), 2.35-2.20 (m, 2H), 2.10-2.00 (m, 1H), 1.88 – 1.78 (m, 1H), 1.71 (p, *J* = 7.5 Hz, 2H), 1.51 – 1.34 (m, 22H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.8, 173.3, 170.8, 164.3, 155.8, 137.1, 132.2, 129.6, 129.34, 129.31, 128.3, 128.0, 125.3, 124.2, 121.2, 111.8, 82.8, 80.6, 67.9, 65.2, 55.4, 55.0, 42.1, 41.8, 33.1, 31.6, 28.8, 28.5, 28.3, 27.9, 23.4, 14.2. ^{77}Se (76 MHz, CD_3OD) δ 62.9. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{38}H_{51}N_3O_9SeNa]^+$ 796.2688; found 796.2698.

Benzyl (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-((2-phenyl-1-tosyl-1*H*-indol-3-yl)selanyl)propanoyl)glycinate (6a)

Yellow solid (40 mg, 87%). Prepared by method A from **3a** (50 mg, 0.06 mmol), $CuBr_2$ (20.2 mg, 0.09 mmol), alkyne **5a** (41.9 mg, 0.12 mmol), CH_2Cl_2 (5 ml). $[\alpha]_D^{20}$ -13.1 (c 1.1, MeOH). IR ν_{max} (film): 2982, 2931, 1669, 1448, 1369, 1177, 1091. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.24 (m, 13H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.10 (s, 2H), 4.05 – 3.95 (m, 1H), 3.76 (s, 2H), 2.83 (dd, *J* = 12.5, 5.1 Hz, 1H), 2.69 (dd, *J* = 12.5, 8.2 Hz, 1H), 2.27 (s, 3H), 1.42-22 (m, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.4, 170.6, 157.1, 146.8, 145.3, 138.4, 137.1, 136.4, 133.6, 133.2, 132.6, 130.7, 130.1, 129.5, 129.32, 129.29, 128.3, 127.9, 126.6, 125.6, 122.2, 117.0, 111.1, 80.9, 67.9, 55.9, 42.0, 30.0, 28.7, 21.5. ^{77}Se NMR (76 MHz, CD_3OD) δ 86.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{38}H_{40}N_3O_7SSe]^+$ 762.1752; found 762.1741.

Benzyl (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-((2-butyl-1-tosyl-1*H*-indol-3-yl)selanyl)propanoyl)glycinate (6b)

Yellow oil (67 mg, 75%). Prepared by method B from **3a** (100 mg, 0.12 mmol), $K_2S_2O_8$ (165 mg, 0.61 mmol), alkyne **5b** (80 mg, 0.24 mmol), MeCN (5 ml). $[\alpha]_D^{20}$ -10°.2 (c 1.12, $CHCl_3$). IR ν_{max} (film): 2959, 2931, 1750, 1686, 1455, 1368, 1173. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 – 8.03 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.35 – 7.19 (m, 9H), 5.11 (s, 2H), 4.00 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.86 (s, 2H), 3.36 – 3.32 (m, 2H), 3.08 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.76 (dd, *J* = 12.6, 9.9 Hz, 1H), 2.24 (s, 3H), 1.75-1.55 (m, 2H), 1.51 – 1.28 (m, 12H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.9, 170.7, 157.5, 148.0, 146.6, 138.1 137.0, 136.7, 133.4, 131.1, 129.5, 129.31, 129.26, 127.4, 125.7, 125.2, 121.5, 116.1, 108.8, 80.9, 67.9, 55.7, 42.1, 34.8, 30.3, 29.3, 28.8, 23.7, 21.5, 14.3. ^{77}Se (76 MHz, CD_3OD) δ 68.6. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{36}H_{43}N_3O_7SeSNa]^+$ 764.1885; found 764.1893.

(*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-3-((1-((4-nitrophenyl)sulfonyl)-2-phenyl-1*H*-indol-3-yl)selanyl)-1-oxopropan-2-aminium 2,2,2-trifluoroacetate (6c)

Yellow oil (87 mg, 78%). Prepared by method A from **3a** (80 mg, 0.1 mmol), $CuBr_2$ (32.3 mg, 0.16 mmol), alkyne **5c** (73 mg, 0.19 mmol), CH_2Cl_2 (5 ml). Product was isolated after Boc deprotection. $[\alpha]_D^{20}$ -4.2 (c 1.2, MeOH). IR ν_{max} (film): 3109, 3028, 1748, 1683, 1532, 1349, 1184, 1088. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (d, *J* = 8.2 Hz, 1H), 8.22 (d, *J* = 8.9 Hz, 2H), 7.73 – 7.63 (m, 3H), 7.54 – 7.37 (m, 7H), 7.32 (s, 5H), 5.12 (s, 2H), 3.70 (d, *J* = 2.6 Hz, 2H), 3.20 – 3.02 (m, 1H), 2.88 (dd, *J* = 12.2, 4.5 Hz, 1H), 2.73 – 2.57 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.8, 152.3, 145.3, 143.8, 138.3, 137.1, 133.8, 133.2, 132.3, 130.4, 129.6, 129.39, 129.36, 128.6, 127.2, 126.3, 125.4, 122.5, 117.0, 112.3, 67.9, 41.9. ^{77}Se NMR (76 MHz, $CDCl_3$) δ 332.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{32}H_{29}N_4O_7SSe]^+$ 693.0922; found 693.0934.

Benzyl (*R*)-(2-((*tert*-butoxycarbonyl)amino)-3-((2-butyl-1-((4-nitrophenyl)sulfonyl)-1*H*-indol-3-yl)selanyl)propanoyl)glycinate (6d)

Yellow oil (90 mg, 95%). Prepared by method B from **3a** (100 mg, 0.12 mmol), $K_2S_2O_8$ (165 mg, 0.61 mmol), alkyne **5d** (80 mg, 0.24 mmol),

MeCN (5 ml). $[\alpha]_D^{20}$ +5.1 (c 1.06, $CHCl_3$). IR ν_{max} (film): 2960, 2931, 1749, 1684, 1539, 1179. ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.96 – 7.91 (m, 2H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.34-7.22 (m, 8H), 5.11 (s, 2H), 3.85 (s, 2H), 3.75 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.38-3.32 (m, 2H), 3.06 (dd, *J* = 12.8, 4.2 Hz, 1H), 2.68 (dd, *J* = 12.8, 10.4 Hz, 1H), 1.82-1.70 (m, 1H), 1.67-1.58 (m, 1H), 1.51 – 1.33 (m, 12H), 1.33 – 1.25 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 170.7, 157.6, 152.2, 148.2, 143.9, 138.1, 137.0, 133.5, 129.5, 129.27, 129.26, 129.0, 126.3, 126.0, 125.8, 121.9, 116.3, 110.3, 80.9, 67.9, 55.5, 42.1, 34.7, 29.9, 29.5, 28.8, 23.6, 14.3. ^{77}Se (76 MHz, CD_3OD) δ 74.9. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{35}H_{40}N_4O_9SeSNa]^+$ 795.1579; found 795.1579.

(*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenyl-1*H*-indol-3-yl)selanyl)propan-2-aminium 2,2,2-trifluoroacetate (6f)

Yellow oil (45 mg, 62%). Prepared by method A from **3a** (100 mg, 0.12 mmol), $CuBr_2$ (40.4 mg, 0.18 mmol), alkyne **5f** (71 mg, 0.24 mmol), CH_2Cl_2 (5 ml). Product was isolated after Boc deprotection. $[\alpha]_D^{20}$ +6.3 (c 1, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 – 8.23 (m, 2H), 7.75 – 7.65 (m, 1H), 7.59 – 7.27 (m, 11H), 5.12 (s, 2H), 3.76 (s, 2H), 3.45-3.36 (m, 1H), 3.12 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.98 (dd, *J* = 12.3, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.9, 157.4, 155.3, 137.1, 133.4, 131.6, 130.3, 129.6, 129.5, 129.3, 128.8, 126.4, 124.6, 122.0, 112.1, 101.0, 67.9, 42.0. ^{77}Se NMR (76 MHz, CD_3OD) δ 59.5. ESI-MS m/z: 508.20 $[M+H]^+$. Elemental analysis calculated for $C_{26}H_{25}N_3O_3Se \times TFA \times 1.3H_2O$: C, 52.30; H, 4.48; N, 6.53; found: C, 52.39; H, 4.57; N, 6.38.

***Tert*-butyl N^5-((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenyl-1-tosyl-1*H*-indol-3-yl)selanyl)propan-2-yl)-N^2-(*tert*-butoxycarbonyl)-L-glutaminate (6j)**

Yellow oil (76 mg, 90%). Prepared by method A from **3b** (100 mg, 0.082 mmol), $CuBr_2$ (27.8 mg, 0.13 mmol), alkyne **5a** (87 mg, 0.24 mmol), CH_2Cl_2 (5 ml). IR ν_{max} (film): 3306, 2 978, 2933, 1739, 1654, 1517, 1368, 1178, 1090. ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 7.7, 1H), 7.50 – 7.27 (m, 16H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.11 (s, 2H), 4.23-4.11 (m, 1H), 3.98-3.90 (m, 1H), 3.76 (d, *J* = 3.8 Hz, 2H), 2.91 (dd, *J* = 12.5, 5.4 Hz, 1H), 2.65 (dd, *J* = 12.5, 8.8 Hz, 1H), 2.29 (s, 3H), 2.20 – 2.09 (m, 1H), 2.09 – 1.98 (m, 1H), 1.98 – 1.91 (m, 1H), 1.80 – 1.70 (m, 1H), 1.46 (m, 18H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.5, 173.3, 172.9, 170.7, 158.1, 146.8, 145.6, 138.5, 137.1, 136.3, 133.6, 133.3, 132.6, 130.7, 130.1, 129.6, 129.34, 129.31, 128.3, 127.9, 126.7, 125.7, 122.2, 117.0, 110.9, 82.8, 80.5, 67.9, 55.4, 54.6, 49.4, 42.0, 32.8, 29.2, 28.8, 28.3, 21.5. ^{77}Se (76 MHz, CD_3OD) δ 89.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{47}H_{55}N_4O_{10}SSe]^+$ 947.2804; found 947.2789.

***Tert*-butyl N^5-((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-3-((2-butyl-1-tosyl-1*H*-indol-3-yl)selanyl)-1-oxopropan-2-yl)-N^2-(*tert*-butoxycarbonyl)-L-glutaminate (6k)**

Yellow oil (37 mg, 98%). Prepared by method B from **3b** (50 mg, 0.04 mmol), $K_2S_2O_8$ (56 mg, 0.21 mmol), alkyne **5b** (27 mg, 0.08 mmol), MeCN (4 ml). IR ν_{max} (film): 2971, 2931, 1662, 1457, 1369, 1172. ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 – 8.05 (m, 1H), 7.67 – 7.61 (m, 2H), 7.59 – 7.53 (m, 1H), 7.37 – 7.23 (m, 10H), 5.12 (s, 2H), 4.37 – 4.28 (m, 1H), 4.04 – 3.98 (m, 1H), 3.87 (s, 2H), 3.10 (dd, *J* = 12.6, 4.8 Hz, 1H), 2.80 (dd, *J* = 12.6, 9.7 Hz, 1H), 2.34-2.23 (m, 5H), 2.13-2.02 (m, 1H), 1.96 – 1.84 (m, 1H), 1.75-1.57 (m, 2H), 1.51 – 1.37 (m, 20H), 1.32-1.25 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.8, 173.3, 173.1, 170.7, 158.1, 147.9, 146.7, 138.1, 137.1, 136.8, 133.4, 131.1, 129.6, 129.34, 129.29, 127.5, 125.8, 125.3, 121.5, 116.2, 108.9, 82.8, 80.6, 67.9, 55.4, 54.5, 42.1, 34.7, 33.1, 29.4, 28.8, 28.3, 23.7, 21.5, 14.3. ^{77}Se (76 MHz, CD_3OD) δ 71.4. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{45}H_{58}N_4O_{10}SeSNa]^+$ 949.2937; found 949.2926.

(*S*)-4-(((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-3-((1-((4-nitrophenyl)sulfonyl)-2-phenyl-1H-indol-3-yl)selanyl)-1-oxopropan-2-yl)amino)-1-carboxy-4-oxobutan-1-aminium trifluoroacetate (6l)

Yellow solid (30 mg, 89%). Prepared by method A from **3b** (50 mg, 0.042 mmol), $CuBr_2$ (14.0 mg, 0.06 mmol), alkyne **5c** (39.4 mg, 0.10 mmol), CH_2Cl_2 (5 ml). Product was isolated after Boc deprotection. IR ν_{max} (film): 3062, 3028, 2932, 1744, 1653, 1532, 1349, 1184. ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (d, *J* = 8.1 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 2H), 7.67 (dd, *J* = 8.0, 3.7 Hz, 3H), 7.59 – 7.25 (m, 12H), 5.14 (s, 2H), 4.06 (d, *J* = 9.3 Hz, 1H), 3.79 (s, 2H), 3.55 (s, 1H), 3.03 (dd, *J* = 12.6, 4.4 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.35 (s, 2H). Due to low solubility of **6l** only ^{1}H NMR spectra was acquired. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{37}H_{36}N_5O_{10}SSe]^+$ 822.1348; found 822.1346.

***Tert*-butyl N^5-((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenyl-1*H*-indol-3-yl)selanyl)propan-2-yl)-N^2-(*tert*-butoxycarbonyl)-l-glutaminate (6m)**

Yellow oil (49 mg, 75%). Prepared by method A from **1c** (100 mg, 0.083 mmol), $CuBr_2$ (28.4 mg, 0.124 mmol), alkyne **5f** (49 mg, 0.167 mmol), CH_2Cl_2 (5 ml). IR ν_{max} (film): 3295, 2977, 2934, 1743, 1645, 1534, 1455, 1367, 1253, 1175, 1172, 1154. ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 – 8.21 (m, 2H), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.45 – 7.39 (m, 1H), 7.39 – 7.26 (m, 7H), 5.10 (s, 2H), 4.43 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.93 (d, *J* = 4.7 Hz, 1H), 3.80 (d, *J* = 2.5 Hz, 2H), 3.24 (dd, *J* = 12.6, 5.1 Hz, 1H), 2.97 (dd, *J* = 12.6, 9.1 Hz, 1H), 2.24 – 2.13 (m, 1H), 2.08 – 1.89 (m, 2H), 1.80 – 1.67 (m, 1H), 1.45 (d, *J* = 8.0 Hz, 18H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.6, 173.3, 173.0, 170.7, 158.1, 157.5, 155.3, 137.1, 133.4, 131.6, 130.3, 129.6, 129.5, 129.33, 129.30, 128.9, 126.4, 124.6, 122.0, 112.1, 100.8, 82.8, 80.5, 67.9, 55.4, 54.8, 42.4, 32.8, 29.8, 28.8, 28.3. ^{77}Se NMR (76 MHz, CD_3OD) δ 82.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{40}H_{49}N_4O_8Se]^+$ 793.2716; found 794.2537.

General procedure for preparation of Boc-Sec containing benzo[*b*]furans 4f,g and indoles 6n-p.

To a solution of Boc-Sec (100 mg, 0.187 mmol, 1 equiv.) and 2-(1-alkynyl)aniline/phenol/anisole (0.28 mmol, 1.5 equiv.) in MeCN (10 ml) $K_2S_2O_8$ (2.53 g, 9.36 mmol, 50 equiv.) was added and the mixture was stirred for 16 hours at rt. After filtration and evaporation, the mixture was purified by reverse phase chromatography (C-18, MeCN/H_2O 10-85%) to give the product.

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((2-phenylbenzofuran-3-yl)selanyl)propanoic acid (4f).

White solid (76 mg, 88%). Prepared from alkyne **1a** (58 mg). $[\alpha]_D^{20}$ +24.2 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 – 8.25 (m, 2H), 7.70 – 7.65 (m, 1H), 7.54 – 7.44 (m, 3H), 7.43 – 7.37 (m, 1H), 7.37 – 7.28 (m, 2H), 4.25 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.34 – 3.26 (m, 1H, overlaps with CD_3OD signal), 3.08 (dd, *J* = 12.5, 8.0 Hz, 1H), 1.37-1.17 (m, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.0, 157.3, 157.2, 155.3, 133.4, 131.6, 130.2, 129.5, 128.7, 126.3, 124.5, 121.9, 112.1, 100.8, 80.6, 55.3, 30.1, 28.6. ^{77}Se (76 MHz, CD_3OD) δ 83.9. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $[C_{22}H_{22}NO_5Se]^-$ 460.0663; found 460.0677.

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((2-butylbenzofuran-3-yl)selanyl)propanoic acid (4g).

Light yellow oil (40 mg, 50%). Prepared from alkyne **1d** (46 mg, 0.24 mmol). $[\alpha]_D^{20}$ +14.1 (c 1.1, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 7.59 – 7.53 (m, 1H), 7.45 – 7.39 (m, 1H), 7.29 – 7.22 (m, 2H), 4.19 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.21 (dd, *J* = 12.6, 4.4 Hz, 1H), 3.03 – 2.88 (m, 3H), 1.73 (p, *J* = 7.4 Hz, 2H), 1.49 – 1.25 (m, 11H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.1, 164.2, 157.5, 155.8, 132.1, 125.2, 124.2, 121.1, 111.8, 100.7, 80.6, 55.3, 31.6, 29.6, 28.6, 27.9, 23.3, 22.1, 14.2. ^{77}Se (76 MHz, CD_3OD) δ 59.0. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $[C_{20}H_{26}NO_5Se]^-$ 440.0976; found 440.0982.

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((2-phenyl-1-tosyl-1*H*-indol-3-yl)selanyl)propanoic acid (6n).

Light yellow solid (115 mg, quant.). Prepared from alkyne **5a** (97 mg). $[\alpha]_D^{20}$ +12.7 (c 0.93, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.26 (m, 9H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.09-4.01 (m, 1H), 2.95 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.76 (dd, *J* = 12.6, 7.6 Hz, 1H), 2.29 (s, 3H), 1.39-1.20 (m, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.7, 157.1, 146.7, 145.3, 138.6, 136.3, 133.6, 133.1, 132.6, 130.6, 130.0, 128.3, 127.8, 126.6, 125.7, 122.1, 117.1, 111.2, 80.7, 55.1, 29.4, 28.6, 21.5. ^{77}Se (76 MHz, CD_3OD) δ 91.3. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{29}H_{30}N_2O_6SSeNa]^+$ 637.0887; found 637.0909.

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((1-((4-nitrophenyl)sulfonyl)-2-phenyl-1*H*-indol-3-yl)selanyl)propanoic acid (6o).

Yellow solid (120 mg, quant.). Prepared from alkyne **5c** (106 mg). $[\alpha]_D^{20}$ +12.6 (c 0.9, $CHCl_3$). ^1H NMR (400 MHz, CD_3CN) δ 8.25 (dt, *J* = 8.4, 0.9 Hz, 1H), 8.21 – 8.10 (m, 2H), 7.73 – 7.60 (m, 3H), 7.60 – 7.39 (m, 7H), 5.25 (d, *J* = 7.9 Hz, 1H), 4.09 – 3.96 (m, 1H), 2.99 (dd, *J* = 12.8, 4.6 Hz, 1H), 2.83 (dd, *J* = 12.8, 7.3 Hz, 1H), 1.39-1.15 (m, 9H). ^{13}C NMR (101 MHz, CD_3CN) δ 172.1, 155.9, 152.0, 144.7, 143.2, 137.8, 133.2, 132.8, 132.0, 130.3, 129.1, 128.5, 127.2, 126.2, 125.5, 122.2, 116.9, 112.1, 80.3, 54.5, 29.1, 28.4. ^{77}Se (76 MHz, CD_3CN) δ 91.3. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $[C_{28}H_{26}N_3O_8SSe]^-$ 644.0606; found 644.0645.

(*R*)-2-((*tert*-butoxycarbonyl)amino)-3-((2-butyl-1-((4-nitrophenyl)sulfonyl)-1*H*-indol-3-yl)selanyl)propanoic acid (6p).

Yellow oil (117 mg, quant.). Prepared from alkyne **5d** (100 mg). $[\alpha]_D^{20}$ 28.8 (c 0.97, $CHCl_3$). ^1H NMR (400 MHz, CD_3OD) δ 8.31 – 8.25 (m, 2H), 8.12 – 8.05 (m, 1H), 8.01 – 7.93 (m, 2H), 7.60-7.55 (m, 1H), 7.36 – 7.25 (m, 2H), 3.78 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.36 (t, *J* = 7.9 Hz, 2H), 3.09 (dd, *J* = 12.7, 4.1 Hz, 1H), 2.75 (dd, *J* = 12.7, 10.0 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.69 – 1.58 (m, 1H), 1.50-1.36 (m, 10H), 1.27-1.20 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.4, 157.6, 152.2, 148.4, 144.0, 138.1, 133.6, 129.0, 126.4, 126.0, 125.8, 121.8, 116.4, 110.2, 80.5, 54.4, 34.7, 29.4, 29.3, 28.8, 23.6, 14.2. ^{77}Se (76 MHz, CD_3OD) δ 78.5. HRMS (ESI/Q-TOF) m/z: $[M-H]^-$ calcd for $[C_{26}H_{30}N_3O_8SSe]^-$ 624.0919; found 624.0943.

General procedure for preparation of 3-selanyl benzo[*b*]furans 4h-k and indoles 6r,s

To a solution of Sec-peptide **3a-d** in CH_2Cl_2 TFA was added at 0 °C. Reaction mixture was stirred until disappearance of starting material. After evaporation the peptides **3aa-3da** were used further without additional purification. To a solution of unprotected Sec-peptide (1 equiv.) in CH_2Cl_2/MeCN (and MeOH in the case of peptides **3ca** and **3da**) $CuBr_2$ (2.5 equiv.) was added and the mixture was stirred for 30 min at rt followed by addition of a solution of **1a** or **5a** (1.5 equiv.) in CH_2Cl_2. Reaction mixture was stirred for 16 h at 40 °C, and then it was evaporated and purified by reverse phase chromatography (C-18, MeCN/H_2O+HCl 10-85%) to give the desired product.

Benzyl (*R*)-(2-amino-3-((2-phenylbenzofuran-3-yl)selanyl)propanoyl)glycinate (4h)

White solid (53 mg, 89%). Prepared from **3a** (90 mg, 0.11 mmol), $CuBr_2$ (61 mg, 0.27 mmol), alkyne **1a** (34 mg, 0.16 mmol), CH_2Cl_2 (4 ml), MeCN (1 ml). ^1H NMR (400 MHz, CD_3OD) δ 8.26 – 8.19 (m, 2H), 7.77 – 7.69 (m, 1H), 7.60 – 7.26 (m, 11H), 5.11 (s, 2H), 4.04 (t, *J* = 6.2 Hz, 1H), 3.73 (d, *J* = 17.8 Hz, 1H), 3.51 (d, *J* = 17.8 Hz, 1H), 3.28-3.21 (m, 2H).

(*S*)-4-(((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenylbenzofuran-3-yl)selanyl)propan-2-yl)amino)-1-carboxy-4-oxobutan-1-aminium chloride (4i)

White solid (47 mg, 85%). Prepared from **3b** (100 mg, 0.083 mmol), $CuBr_2$ (47 mg, 0.21 mmol), alkyne **1a** (26 mg, 0.12 mmol), CH_2Cl_2 (4 ml), MeCN (1 ml). IR ν_{max} (film): 3280, 3064, 2936, 1743, 1653, 1539, 1200. ^1H NMR (400 MHz, CD_3OD) δ 8.28-8.22 (m, 2H), 7.69-7.64 (m, 1H), 7.56 – 7.27 (m, 11H), 5.10 (s, 2H), 4.39 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.93 (t, *J* = 6.4 Hz, 1H), 3.80 (s, 2H), 3.25 (dd, *J* = 12.7, 5.1 Hz, 1H), 2.96 (dd, *J* = 12.7, 9.3 Hz, 1H), 2.46-2.34 (m, 1H), 2.31-2.19 (m, 1H), 2.12-1.94 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.1, 173.0, 171.4, 170.8, 157.6, 155.3, 137.0, 133.4, 131.6, 130.4, 129.6, 129.59, 129.55, 129.4, 129.32, 129.31, 128.9, 126.5, 124.6, 122.0, 112.2, 100.6, 67.9, 55.0, 53.5, 42.0, 32.3, 29.5, 26.9. ^{77}Se (76 MHz, CD_3OD) δ 83.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{31}H_{32}N_3O_7Se]^+$ 638.1405; found 638.1409.

(*S*)-1-(((*R*)-1-((2-(((S)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)amino)-1-oxo-3-((2-phenylbenzofuran-3-yl)selanyl)propan-2-yl)amino)-3-(4-hydroxyphenyl)-1-oxopropan-2-aminium chloride (4j)

White solid (50 mg, 100%). Prepared from (Boc)Tyr-Sec-Gly-Phe-NH_2 (83 mg, 0.066 mmol), $CuBr_2$ (44 mg, 0.19 mmol), alkyne **1a** (20 mg, 0.098 mmol), CH_2Cl_2 (2 ml), MeCN (1 ml), MeOH (2 ml). IR ν_{max} (film): 3269, 3032, 1652, 1506, 1214. ^1H NMR (400 MHz, CD_3OD) δ 8.25 – 8.19 (m, 2H), 7.73 – 7.67 (m, 1H), 7.58 – 7.53 (m, 1H), 7.51-7.45 (m, 2H), 7.43 – 7.29 (m, 3H), 7.27-7.21 (m, 4H), 7.19-7.13 (m, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 4.59 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.39 (t, *J* = 7.2 Hz, 1H), 3.89 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.79 (d, *J* = 16.9 Hz, 1H), 3.38 (d, *J* = 16.9 Hz, 1H), 3.29 – 3.24 (m, 1H), 3.18 – 3.02 (m, 3H), 2.91 (dd, *J* = 13.9, 9.1 Hz, 1H), 2.82 (dd, *J* = 14.4, 8.7 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 176.1, 171.7, 170.7, 169.9, 158.3, 157.4, 155.4, 138.4, 133.3, 131.6, 131.5, 130.4, 130.3, 129.6, 129.5, 128.9, 127.8, 126.5, 125.8, 124.6, 122.0, 116.9, 112.2, 101.1, 55.84, 55.78, 55.6, 43.4, 39.0, 37.6, 29.1. ^{77}Se (76 MHz, CD_3OD) δ 83.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{37}H_{38}N_5O_6Se]^+$ 728.1987; found 728.1984.

(*S*)-6-(((*S*)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-5-((*R*)-2-ammonio-3-((2-phenylbenzofuran-3-yl)selanyl)propanamido)-6-oxohexan-1-aminium dichloride (4k)

White solid (25 mg, 46%). Prepared from **3d** (100 mg, 0.076 mmol), $CuBr_2$ (42 mg, 0.19 mmol), alkyne **1a** (24 mg, 0.11 mmol), CH_2Cl_2 (2 ml), MeCN (1 ml), MeOH (2 ml). IR ν_{max} (film): 3441, 1646, 1521, 1180, 1142. ^1H NMR (400 MHz, CD_3OD) δ 8.29 – 8.20 (m, 2H), 7.81 – 7.72 (m, 1H), 7.61 – 7.50 (m, 3H), 7.49 – 7.43 (m, 1H), 7.42-7.34 (m, 2H), 7.24 – 7.19 (m, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 7.08 – 7.01 (m, 1H), 4.60 (dd, *J* = 8.7, 5.8 Hz, 1H), 4.31 (t, *J* = 6.9 Hz, 1H), 4.02 (dd, *J* = 7.8, 5.5 Hz, 1H), 3.24 – 3.05 (m, 3H), 3.00 – 2.84 (m, 3H), 1.80-1.69 (m, 1H), 1.67-1.58 (m, 3H), 1.44-1.30 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 175.8, 172.7, 168.2, 158.1, 155.4, 138.2,

133.0, 131.3, 130.7, 130.3, 129.8, 129.4, 129.0, 127.7, 126.7, 124.9, 121.9, 112.3, 100.2, 55.7, 54.7, 54.2, 40.4, 39.0, 32.5, 29.1, 28.0, 23.3. ^{77}Se (76 MHz, CD_3OD) δ 67.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{32}H_{38}N_5O_4Se]^+$ 636.2089; found 636.2079.

(*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenyl-1-tosyl-1*H*-indol-3-yl)selanyl)propan-2-aminium chloride (6r)

White solid (56 mg, 74%). Prepared from **3a** (90 mg, 0.11 mmol), $CuBr_2$ (61 mg, 0.27 mmol), alkyne **1a** (57 mg, 0.16 mmol), CH_2Cl_2 (4 ml), MeCN (1 ml).). $[\alpha]_D^{20}$ +23.5 (c 1, $CHCl_3$). IR ν_{max} (film): 1738, 1669, 1369, 1175. ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (d, *J* = 8.3 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.52 – 7.31 (m, 15H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.13 (d, *J* = 2.9 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 1H), 3.67 (d, *J* = 17.8 Hz, 1H), 3.48 (d, *J* = 17.8 Hz, 1H), 2.90 (dd, *J* = 6.4, 1.5 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.3, 168.4, 147.0, 145.8, 138.3, 137.0, 136.3, 133.3, 133.1, 132.3, 130.8, 130.4, 129.6, 129.45, 129.42, 128.6, 127.9, 126.9, 125.8, 122.1, 116.9, 109.8, 68.1, 54.0, 41.9, 28.1, 21.5. ^{77}Se (76 MHz, CD_3OD) δ 74.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{33}H_{32}N_3O_5SSe]^+$ 662.1228; found 662.1223.

(*S*)-4-(((*R*)-1-((2-(benzyloxy)-2-oxoethyl)amino)-1-oxo-3-((2-phenyl-1-tosyl-1*H*-indol-3-yl)selanyl)propan-2-yl)amino)-1-carboxy-4-oxobutan-1-aminium chloride (6s)

White solid (69 mg, 100%). Prepared from **3b** (100 mg, 0.083 mmol), $CuBr_2$ (47 mg, 0.28 mmol), alkyne **1a** (26 mg, 0.12 mmol), CH_2Cl_2 (4 ml), MeCN (1 ml). IR ν_{max} (film): 3376, 3050, 1652, 1517, 1176. ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.63 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.49 – 7.27 (m, 14H), 7.20 – 7.14 (m, 2H), 5.11 (s, 2H), 4.10 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 1H), 3.75 (s, 2H), 2.92 (dd, *J* = 12.7, 5.3 Hz, 1H), 2.63 (dd, *J* = 12.7, 9.1 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.30 (s, 3H), 2.29 – 2.21 (m, 1H), 2.08 (p, *J* = 7.5, 6.9 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.0, 172.9, 171.5, 170.7, 146.9, 145.7, 138.5, 137.1, 136.3, 133.5, 133.31, 132.6, 130.7, 130.1, 129.6, 129.4, 129.3, 128.3, 127.9, 126.7, 125.7, 122.1, 117.1, 110.6, 67.9, 54.8, 42.0, 32.2, 28.9, 26.9, 21.5.^{77}Se (76 MHz, CD_3OD) δ 90.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{31}H_{32}N_3O_7Se]^+$ 638.1405; found 638.1409.

General procedure for preparation of 11-selanyl-6-phenylindeno[1,2-*c*]chromenes

To a solution of diorganyl diselenide (1 equiv.) and alkyne (1 equiv.) in MeCN $K_2S_2O_8$ (5 equiv.) was added and the mixture was stirred for 3 days at rt. After volatiles evaporation residue was purified by flash chromatography on silica gel (PE/EtOAc 10:1-6:1) (**8a**) or reverse phase chromatography (C-18, MeCN/H_2O 10-85%) (**8b,c**) to give the product.

11-(benzylselanyl)-6-phenylindeno[1,2-*c*]chromene (8a)

Orange crystals (57 mg, 51%). Prepared from dibenzyl diselenide (83 mg, 0.24 mmol), $K_2S_2O_8$ (326 mg, 1.21 mmol), alkyne **7** (75 mg, 0.24 mmol), MeCN (5 ml). Crystallized from *i*PrOH. Melting point: 84-85 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 9.48 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.90 – 7.83 (m, 3H), 7.67 – 7.60 (m, 3H), 7.53 – 7.41 (m, 4H), 7.37 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1H), 7.19 – 7.05 (m, 6H), 4.05 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 152.9, 150.4, 145.5, 139.1, 133.7, 131.6, 130.9, 129.8, 129.0, 128.9, 128.5, 128.4, 127.1, 126.8, 125.8, 124.6, 123.2, 121.4, 120.6, 120.5, 118.0, 117.7, 110.6, 32.4.^{77}Se NMR (76 MHz, CD_3OD) δ 191.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{29}H_{21}OSe]^+$ 465.0758; found 465.0729.

(*R*)-benzyl 2-(2-((*tert*-butoxycarbonyl)amino)-3-((6-phenylindeno[1,2-*c*]chromen-11-yl)selanyl)propanamido)acetate (8b)

Orange oil (77 mg, 45%). Prepared from **3a** (200 mg, 0.24 mmol), $K_2S_2O_8$ (326 mg, 1.21 mmol), alkyne **7** (75 mg, 0.24 mmol), MeCN (7 ml). IR ν_{max} (film): 3341, 2926, 1748, 1684, 1653, 1456, 1214, 755. $[\alpha]_D^{20}$ -7.26 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ 9.56 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.85 – 7.74 (m, 3H), 7.72 – 7.62 (m, 3H), 7.56 – 7.43 (m, 3H), 7.39 (ddd, *J* = 7.9, 7.2, 1.1 Hz, 1H), 7.33 – 7.26 (m, 6H), 7.05 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H), 5.10 (s, 2H), 4.27 – 4.17 (m, 1H), 3.81 (s, 2H), 3.23 (dd, *J* = 12.7, 4.7 Hz, 1H), 3.14 – 3.05 (m, 1H), 1.29 (s, 10H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.8, 170.7, 154.2, 151.8, 146.3, 137.1, 134.8, 132.3, 132.0, 131.0, 130.6, 130.0, 129.9, 129.5, 129.3, 128.2, 126.8, 126.0, 124.2, 122.4, 121.43, 121.38, 118.9, 118.8, 116.8, 80.8, 67.9, 56.5, 42.1, 28.6. ^{77}Se NMR (76 MHz, CD_3OD) δ 91.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $[C_{39}H_{37}N_2O_6Se]^+$ 709.1817; found 709.1807.

(6*S*,11*R*)-benzyl 6-(*tert*-butoxycarbonyl)-2,2-dimethyl-4,9,12-trioxo-11-(((6-phenylindeno[1,2-*c*]chromen-11-yl)selanyl)methyl)-3-oxa-5,10,13-triazapentadecan-15-oate (8c)

Orange oil (52 mg, 36%). Prepared from **3b** (194 mg, 0.16 mmol), $K_2S_2O_8$ (219 mg, 0.81 mmol), alkyne **7** (50 mg, 0.16 mmol), MeCN (7 ml). IR ν_{max} (film): 3307, 2978, 1701, 1636, 1455, 1152. ^{1}H NMR (400 MHz, CD_3OD) δ 9.51 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.80 (m, 3H), 7.76 – 7.62 (m, 3H), 7.62 – 7.23 (m, 11H), 7.05 (m, 1H), 5.09 (s, 2H), 4.45 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.89 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.78 (d, *J* = 2.4 Hz, 2H), 3.28 (m, 1H), 3.05 (dd, *J* = 12.7, 9.2 Hz, 1H), 2.18-2.05 (m, 1H), 2.05 – 1.82 (m, 2H), 1.76-1.64 (m, =1H), 1.43 and 1.42 (2 s, 18H).^{13}C NMR (101 MHz, CD_3OD) δ 174.5, 173.2, 170.7, 158.0, 154.3, 151.7, 146.3, 137.1, 134.8, 132.4, 132.0, 131.0, 130.7, 130.0, 129.9, 129.5, 129.31, 129.29, 128.2, 126.8, 125.9, 124.3, 122.4, 121.5, 121.3, 118.9, 110.0, 82.7, 80.5, 67.9, 55.4, 55.3, 42.1, 32.9, 30.8, 29.9, 28.8, 28.3, 28.2. ^{77}Se NMR (76 MHz, CD_3OD) δ 96.2. HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ calcd for $[C_{48}H_{51}N_3O_9SeNa]^+$ 916.2688; found 916.2653.

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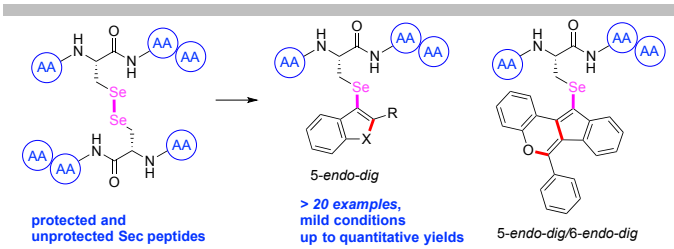

Herein we present copper(II) bromide and oxidant promoted 5-*endo-dig* and 5-*endo-dig*/6-*endo-dig* cascade reactions yielding substituted benzo[*b*]furans, indoles and indeno[1,2-*c*]chromenes bearing Sec-peptides in position 3. It can be successfully applied for protected and unprotected peptides in up to quantitative yields.

Selenocysteine electrophile*

*S. Lapcinska and P. Arsenyan,**

Page No. – Page No.

Selenocystine peptides performance in 5-*endo-dig* reactions