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A novel methodology for the synthesis of condensed selenium heterocycles based on the annulation and annulation–methoxylation reactions of selenium dihalides†

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A novel methodology to accelerate annulation reactions leading to condensed selenium heterocycles was developed. The reactions of selenium dihalides with methyleugenol, allyl thymyl ether, allyl 1-naphthyl and 1-naphthyl propargyl ethers were carried out in the presence of alcohols, which considerably accelerated the annulation reactions. In solvent systems CH_2Cl_2/MeOH or $CHCl_3$/MeOH, the reactions proceeded as annulation–methoxylation affording condensed methoxylated heterocycles. In the presence of isopropanol, the reactions were not accompanied by alkoxylation giving condensed halogen-containing products. The annulation reaction of selenium dihalides with 1-naphthyl propargyl ether included stereoselective *anti*-addition to the triple bond. The efficient selective synthesis of the first representatives of novel families of condensed selenium heterocycles with promising biological activity was developed.

Introduction

Organoselenium compounds have been attracting growing attention due to their importance in organic synthesis, bioorganic chemistry and enzymology.[1–3] Different kinds of organoselenium compounds especially selenium-containing heterocycles possess various types of biological activities including antibacterial, antitumor, anti-HIV, anti-inflammatory, and glutathione peroxidase-like activity.[2–4] A selenium heterocyclic compound with immunomodulatory, anti-inflammatory and glutathione peroxidase-like activity, ebselen, is currently used for prophylaxis and treatment of cardiovascular diseases, especially for prevention of ischemic stroke and overcoming acute stroke.[4] Besides, ebselen has been recommended for treatment of various disorders and diseases including arthritis and cancer (in combination with other medicines).[4]

Development of efficient synthetic approaches to novel selenium heterocycles and studies of their properties remain an important task for organic chemists. Electrophilic selenium reagents are widely used in modern organic synthesis.[1,5] Previously we successfully applied selenium dihalides in the synthesis of organoselenium compounds.[6] These reagents can be easily generated from elemental selenium and sulfuryl chloride or bromine.[6,7] In spite of slow disproportionation[7] of $SeCl_2$ and $SeBr_2$ in solutions, these freshly prepared reagents can be immediately involved in reactions *in situ* affording organoselenium products with high selectivity.[6] Efficient regio- and stereoselective approaches to functionalized and heterocyclic compounds have been developed based on selenium dihalides.[6,8–12] These reagents participated in cyclization reactions with divinyl sulfide,[8] divinyl selenide[9] and divinyl sulfone[10] affording novel organoselenium heterocyclic compounds. The transannular addition of selenium dihalides to *cis*,*cis*-cycloocta-1,5-diene gave 2,6-dihalo-9-selenabicyclo[3.3.1]nonanes in high yield.[11,12] The latter compounds formed with $SeCl_2$ and $SeBr_2$ the 2 : 1 complexes, which are the first representatives of coordination compounds with the Se···Se···Se bond.[12]

Selenium dihalides are able to undergo annulation reactions with benzene derivatives containing unsaturated moieties leading to condensed heterocyclic compounds. Previously we developed the first examples of annulation of 3-chloromethyl- and 3-chloromethylene-2,3-dihydro-1,4-oxaselenine to the benzene ring by reactions of selenium dichloride with allyl phenyl and propargyl phenyl ethers (Scheme 1).[13] Equimolar ratios of the reagents were used in these one-pot annulation reactions which proceeded in chloroform in two stages. The addition of $SeCl_2$ to allyl or propargyl moieties with the formation of intermediates **A** or **B** (the first stage) was carried out with cooling (−60 °C). The second stage included refluxing the reaction mixture in chloroform in order to effect the aromatic electrophilic substitution.

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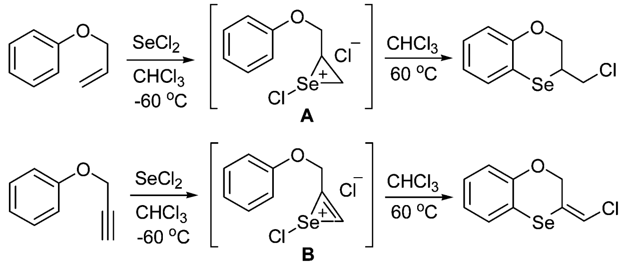
† Electronic supplementary information (ESI) available: Crystallographic data for compounds **2** and **4b**. CCDC 1893458 (**2**) and 1893457 (**4b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9nj04707g



Scheme 1 One-pot, two-stage annulation reactions of selenium dihalides with allylphenyl and propargylphenyl ethers in chloroform.

This approach allowed regio- and stereoselective preparation of condensed products in high yields. Application of selenium dibromide under similar conditions did not lead to annulation products apparently due to the lower electrophilicity of $SeBr_2$ compared to that of selenium dichloride.

Chemistry of natural products is very important in medicine for providing knowledge to derive active components as lead compounds for drug discovery. It is known that the majority of new drugs have been developed from natural products and synthesis of novel compounds based on natural products is very promising for searching biologically active substances. Annulation reactions of selenium dihalides with natural compounds can represent a valuable approach to novel selenium-containing condensed scaffolds for drug discovery.

Results and discussion

Eugenol, thymol and some of their derivatives are aromatic natural compounds found in essential oils. We studied the annulation reactions of selenium dihalides with methyleugenol and allyl thymyl ether as well as with allyl 1-naphthyl and 1-naphthyl propargyl ethers. These compounds contain unsaturated moieties along with organyloxy and alkyl groups which activate the benzene ring with respect to aromatic electrophilic substitution.

We found that the application of the previously developed methodology (Scheme 1)[13] to the reactions of selenium dihalides with methyleugenol did not allow realizing the annulation reactions and obtaining condensed selenium-containing heterocycles.

Instead, the reaction generally led to double bond halogenation products **1a,b** (Scheme 2), the formation of which was likely the result of decomposition of an intermediate mono-adduct (an analogue of the intermediate **A**, Scheme 1) accompanied by selenium precipitation on the second stage of the reaction upon heating.

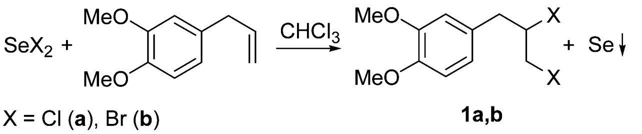
However, we found that addition of alcohols, especially methanol, to chloroform or methylene chloride reaction media considerably accelerated the annulation reactions of selenium dihalides.[14] The annulation reactions of selenium dihalides with methyleugenol were successfully realized by carrying them out in the system chloroform/methanol. Along with annulation, the reactions were accompanied by methoxylation. Thus, the reaction of selenium dichloride with methyleugenol in an equimolar ratio in the system chloroform/methanol afforded 5,6-dimethoxy-2-methoxymethyl-2,3-dihydrobenzoselenophene **2** in 45% yield and 3,6,7-trimethoxyselenochromane **3** in 53% yield (98% total yield). The structure of compounds **2** was studied by single crystal X-ray diffraction (Fig. 1) (see also the ESI†). Noteworthily, the aromatic substitution reaction in the presence of alcohols smoothly proceeded at room temperature that allowed avoiding heating the reaction mixture and decomposition.

We found that in the presence of isopropanol the annulation reactions of selenium dihalides were also accelerated but not accompanied by alkoxylation giving condensed halogen-containing compounds.

The reaction of selenium dichloride with methyleugenol in the system chloroform/isopropanol led to 2-chloromethyl derivatives of dihydrobenzoselenophene **4a** and selenochromane **5a** (Scheme 3), which were isolated by column chromatography on silica gel (41% and 44% yields of pure compounds **4a** and **5a**, respectively). These conditions provide an alternative opportunity to carry out the annulation reactions without alkoxylation and to obtain condensed halogen-containing products, which can be used in further functionalization by nucleophilic substitution of the halogen atom.

The reaction of selenium dibromide with methyleugenol under the same conditions occurred in a similar manner with the formation of dihydrobenzoselenophene derivative **4b** (45% yield) and selenochromane **5b** (40% yield) (Scheme 3). The structure of compound **4b** was proved by single crystal X-ray diffraction analysis (Fig. 2).

A derivative of thymol, allyl thymyl ether (2-allyloxy-1-isopropyl-4-methylbenzene), was involved in the annulation reactions with selenium dihalides. The annulation–methoxylation reaction was carried out in the system methylene chloride/methanol affording 8-isopropyl-3-(methoxymethyl)-5-methyl-2,3-dihydro-1,4-benzoxaselenine **6** (Scheme 4). Selenium dibromide was more efficient than $SeCl_2$ in this reaction which completed in 2 h giving product



Scheme 2 The reactions of selenium dihalides with methyleugenol in $CHCl_3$.

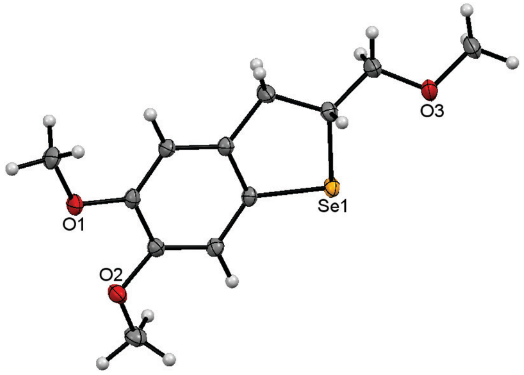
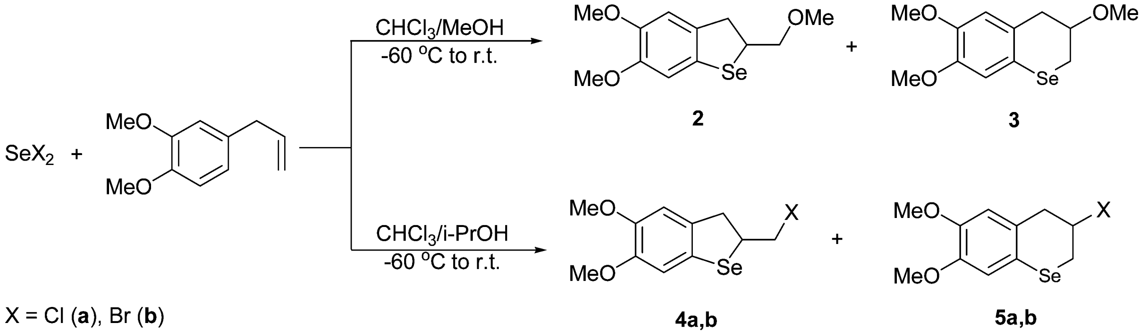


Fig. 1 ORTEP molecular structure of compound **2**.



Scheme 3 The reactions of selenium dihalides with methyleugenol.

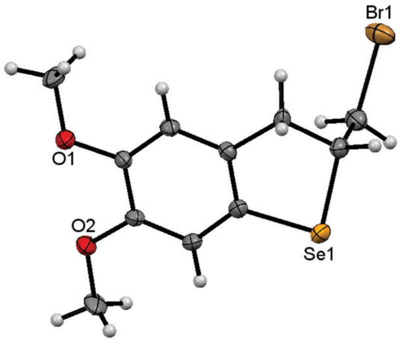
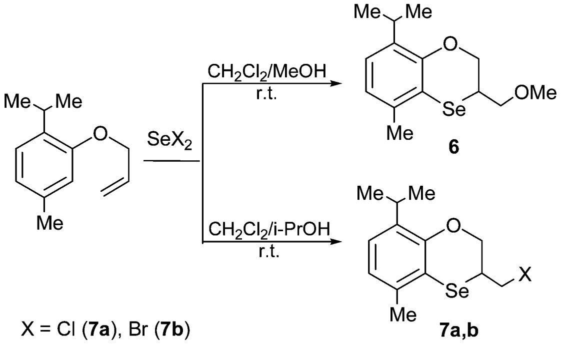
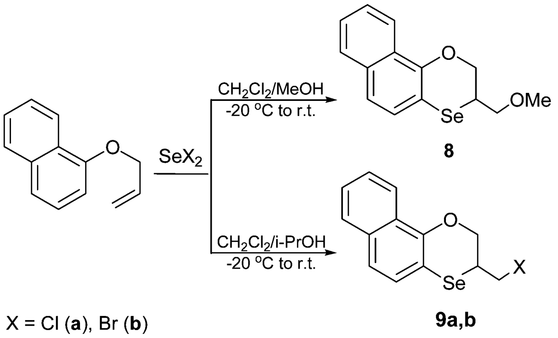


Fig. 2 ORTEP molecular structure of compound **4b**.



Scheme 4 Synthesis of compounds **6** and **7a**,**b** by the reaction of selenium halides with allyl thymyl ether.



Scheme 5 Synthesis of compounds **8** and **9a**,**b** by the reaction of selenium halides with allyl 1-naphthyl ether.

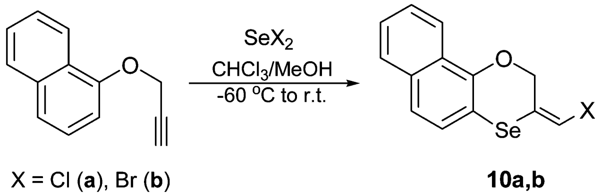
6 in 90% yield. In the case of selenium dichloride, the yield of compound **6** was lower (83%).

However, unlike the reaction of selenium dihalides with methyleugenol, which required mixing the reagents at −60 °C, the reaction with allyl thymyl ether proceeded selectively at room temperature and cooling was not necessary in this case.

The annulation reaction of selenium dihalides with allyl thymyl ether was found to occur efficiently at room temperature in the system methylene chloride/isopropanol affording chloro- and bromo-containing benzoxaselenines **7a,b** in 86% and 90% yields, respectively (Scheme 4).

The annulation–methoxylation reaction of selenium dibromide with allyl 1-naphthyl ether was carried out in the system methylene chloride/methanol leading to 3-(methoxymethyl)-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenine **8** in 90% yield (Scheme 5). It was found that the annulation reaction of selenium dihalides with allyl 1-naphthyl ether proceeded efficiently in the system chloroform/isopropanol giving 3-(chloromethyl)- and 3-(bromomethyl)-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenines **9a,b** in 85–86% yields. Mixing the reagents at −20 °C was found to be favorable for selective formation of products **8** and **9a,b**.

Finally, 1-naphthyl propargyl ether as an example of a compound with the propargyloxy function was involved in the annulation reaction. It was established that favorable conditions for the stereoselective reaction of selenium dihalides with 1-naphthyl propargyl ether included the use of methanol and mixing the reagents at −60 °C followed by the reaction proceeding at room temperature. The reaction was realized in the system chloroform/methanol affording 3-[(*E*)-chloromethylidene]- and 3-[(*E*)-bromomethylidene]-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenines **10a,b** in 80% and 76% yields, respectively (Scheme 6). The addition of



Scheme 6 Synthesis of compounds **10a**,**b** by the reaction of selenium halides with 1-naphthyl propargyl ether.

selenium dihalides to the triple bond of 1-naphthyl propargyl ether occurred as an *anti* process leading to products with (*E*)-stereochemistry of the 2-halomethylidene moieties. The addition of methanol accelerated the annulation reaction but methoxylation did not occur since nucleophilic substitution of the halogen atom at the double bond required more severe conditions.

Noteworthily, the obtained products are the first representatives of novel families of compounds with promising biological activity. For example, compounds **8**, **9a**,**b** and **10a**,**b** are the first representatives of the hitherto unknown 2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenine scaffold. Derivatives of the analogous sulfur-containing scaffold, 2,3-dihydronaphtho[1,2-*b*][1,4]oxathiine, exhibit anticancer activity.[15]

Benzoselenophene derivatives containing 5,6-diorganyloxy substituents and 3,6,7-triorganyloxy selenochromane derivatives were also hitherto unknown. The known derivatives of dihydroselenophene and selenochromane exhibited antitumor and antivirus activities along with high antioxidant properties and were proposed for treatment of cancer in combination with other medicines as well as for treatment of disorders caused by oxidative tissue damage.[16]

Selenochromane is the structural part of α-selenotocopherol[17] and selenoflavanones.[18] The introduction of the selenium atom into organic molecules may bring in new properties. For example, it has been found that selenoflavanones showed improved neuroprotective properties compared to flavanones, suggestive of the ability to pass through the blood–brain barrier.[18]

The electron-donating methoxy and methyl groups are present in many natural antioxidants.[19] The presence of the methoxy group in the benzene ring of aryl selenides increased their antioxidant properties.[20,21] It has been found that the introduction of the methoxy group into the benzene ring especially at the *para*-position with respect to the selenium atom considerably enhanced the glutathione peroxidase-like activity of aryl selenides.[21]

The structural characterization of the synthesized compounds was made using single crystal X-ray diffraction analysis and ^{1}H, ^{13}C and ^{77}Se NMR spectroscopy including two-dimensional homonuclear (2D COZY) and heteronuclear (2D HMBC, 2D HSQC) methods. (*E*)-Configuration of compounds **10a**,**b** was assigned based on 2D NOESY NMR experiments (see the ESI†).

Conclusions

A novel methodology for the synthesis of condensed selenium heterocycles was developed based on the reactions of selenium dihalides with methyleugenol, allyl thymyl ether, allyl 1-naphthyl and 1-naphthyl propargyl ethers. It was found that the annulation reactions were considerably accelerated by addition of alcohols to the reaction mixture. In the systems chloroform/methanol or methylene chloride/methanol the reactions proceeded as annulation–methoxylation leading to condensed methoxylated products. The reaction proceeding in the system chloroform/isopropanol allowed obtaining condensed halogen-containing products. High selectivity, mild reaction conditions and very simple work-up procedures are important features of this methodology. Efficient synthesis of the hitherto unknown condensed heterocycles **2–10a**,**b** with promising biological activity was developed based on these reactions. This methodology may be useful for acceleration of aromatic substitution reactions of other electrophilic reagents (*e.g.*, organylselenenyl halides).

The compounds **4a**,**b**, **7a**,**b** and **9a**,**b** are open for further functionalization by nucleophilic substitution reactions. The halogen atoms situated at the β-position with respect to the selenium atom are considerably activated with respect to nucleophilic substitution by the anchimeric assistance effect of selenium.[11]

Experimental

X-ray diffraction experiments were carried out with a Bruker D8 Venture Photon 100 CMOS diffractometer with an Mo-K$_\alpha$ radiation source (λ = 0.71073 Å). X-Ray crystallographic data for compounds **2** (CCDC 1893458) and **4b** (CCDC 1893457) are shown in the ESI.† ^{1}H (400.1 MHz), ^{13}C (100.6 MHz) and ^{77}Se (76.3 MHz) NMR spectra were recorded on a Bruker DPX-400 spectrometer in 5–10% solution in $CDCl_3$, referenced to TMS (^{1}H and ^{13}C NMR, internal) and Me_2Se (^{77}Se NMR, external).

5,6-Dimethoxy-2-methoxymethyl-2,3-dihydro-1-benzoselenophene (2) and 3,6,7-trimethoxyselenochromane (3)

Selenium dichloride (2.5 mmol) was prepared from elemental selenium (0.197 g, 2.5 mmol) and sulfuryl chloride (0.338 g, 2.5 mmol) in chloroform. The obtained solution of selenium dichloride (2.5 mmol) in chloroform (10 mL) and a solution of methyleugenol (0.44 g, 2.5 mmol) in chloroform (10 mL) were added separately and simultaneously over 15 min to a cooled (−60 °C) flask containing a stirred mixture of chloroform (45 mL) and methanol (25 mL). The mixture was stirred for 30 min at −60 °C and the cooling bath was removed. The mixture was allowed to warm and stirred for 4 h at room temperature. The solvents were removed on a rotary evaporator. The residue was washed with cold (−20 °C) diethyl ether (4 × 2 mL) on the Schott filter. After removing the solvent from the filtrate the obtained residue was subjected to column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 4) giving compound **2** as a colorless solid (0.07 g, 10% yield, mp 106–108 °C) and compound **3** as a colorless oil, yield: 0.38 g (53%). A solid from the Schott filter was dried in vacuum and identified as compound **2**, colorless solid, yield: 0.25 g (35%). The total yield of compound **2** was 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10–3.20 (m, 2H, CH_2), 3.24 (s, 3H, $CH_2OC\underline{H}_3$), 3.36–3.45 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3,98 (m, 1H, CH), 6.56 (s, 1H, CH_{Ar}), and 6.62 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.42 ($C_{Ar}\underline{C}H_2$), 44.95 (SeCH, $J_{C–Se}$ = 48.64), 55.93 (CH_3O), 55.96 (CH_3O), 58.55 (CH_3O), 75.83 ($\underline{C}H_2OMe$), 108.87 (HC_{Ar}), 109.36 (HC_{Ar}), 125.84 (SeC_{Ar}, $J_{C–Se}$ = 92.88), 133.10 ($H_2C\underline{C}_{Ar}$), 147.08 ($MeO\underline{C}_{Ar}$), and 148.55 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 387.4. Found: C 49.91; H 5.74; Se 27.21. Calc. for $C_{12}H_{16}O_3Se$: C 50.18; H 5.61; Se, 27.49. X-ray crystallographic data for **2** is shown in the ESI.† Compound **3**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.62–2.69 (m 1H, CH_2), 2.83–2.88 (m, 2H, CH_2), 2.99–3.03 (m, 1H, CH_2), 3.39 (s, 3H, OCH_3), 3.70–3.73 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.48 (s, 1H, CH_{Ar}), and 6.61 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.43 ($SeCH_2$, $J_{C\text{–}Se}$ = 57.05), 37.06 ($C_{Ar}\underline{C}H_2$), 56.02 (CH_3O), 56.02 (CH_3O), 56.28 (CH_3O), 75.27 (CHO), 111.51 (HC_{Ar}), 114.18 (HC_{Ar}), 117.21 (SeC_{Ar}, $J_{C\text{–}Se}$ = 98.98), 127.23 ($H_2C\underline{C}_{Ar}$), 147.11 ($MeO\underline{C}_{Ar}$), and 148.04 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 195.2. Found: C 49.91; H 5.74; Se 27.21. Calc. for $C_{12}H_{16}O_3Se$: C 50.18; H 5.61; Se, 27.49.

2-Chloromethyl-5,6-dimethoxy-2,3-dihydro-1-benzoselenophene (4a) and 2-chloro-6,7-dimethoxyselenochromane (5a)

The reaction was carried out in a similar manner to the synthesis of compounds **2** and **3** but by using isopropanol (20 mL) instead of methanol. The mixture was stirred for 1 h at −60 °C and for 4 h at room temperature. The solvents were removed on a rotary evaporator. The residue was washed with cold (−20 °C) diethyl ether (4 × 2 mL) on the Schott filter. After removing the solvent from the filtrate the obtained residue was subjected to column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 4) giving compound **4a** as a colorless solid (0.04 g, 5% yield, m.p. 99–101 °C) and compound **5a** as a colorless oil, yield: 0.32 g (44%). A solid from the Schott filter was dried in vacuum and identified as compound **4a**, yield: 0.26 g (36%). The total yield of compound **4a** was 41%. ^1H NMR (400 MHz, $CDCl_3$) δ 3.30–3.37 (m, 1H, $C\underline{H}_2$), 3.42–3.48 (m, 1H, CH_2), 3.54–3.61 (m, 1H, CH_2), 3.71–3.78 (m, 1H, CH_2), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.98–4.06 (m, 1H, CH), 6.68 (s, 1H, CH_{Ar}), and 6.70 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.88 ($C_{Ar}\underline{C}H_2$), 45.75 (SeCH), 47.32 (CH_2Cl), 55.64 (CH_3O), 55.73 (CH_3O), 109.62 (HC_{Ar}), 110.52 (HC_{Ar}), 126.13 ($H_2C\underline{C}_{Ar}$), 131.56 (SeC_{Ar}), 147.96 ($MeO\underline{C}_{Ar}$), and 149.38 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 420.1. Found: C 45.59; H 4.32; Cl 12.42; Se 26.79. Calc. for $C_{11}H_{13}ClO_2Se$: C 45.30; H 4.49; Cl 12.16; Se, 27.08. Compound **5a**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.97–3.05 (m, 1H, CH_2), 3.13–3.21 (m, 2H, CH_2), 3.25–3.32 (m, 1H, CH_2), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.39–4.47 (m, 1H, CHCl), 6.45 (s, 1H, CH_{Ar}), and 6.56 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.59 ($C_{Ar}\underline{C}H_2$), 41.10 ($SeCH_2$), 55.39 (CHCl), 55.43 (CH_3O), 55.55 (CH_3O), 111.68 (HC_{Ar}), 114.38 (HC_{Ar}), 115.69 ($H_2C\underline{C}_{Ar}$), 126.4 (SeC_{Ar}), 147.47 ($MeO\underline{C}_{Ar}$), and 148.82 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 237.9. Found: C 45.03; H 4.62; Cl 11.97; Se 27.29. Calc. for $C_{11}H_{13}ClO_2Se$: C 45.3; H 4.49; Cl 12.16; Se, 27.08.

2-Bromomethyl-5,6-dimethoxy-2,3-dihydro-1-benzoselenophene (4b) and 2-bromo-6,7-dimethoxyselenochromane (5b)

The reaction was carried out in a similar manner to the synthesis of compounds **4a** and **5a** but by using selenium dibromide (2.5 mmol) and isopropanol (10 mL). After removing the solvent from the filtrate the obtained residue was subjected to column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 4) giving compound **4b** as a colorless solid (0.07 g, 8% yield, mp 101–102 °C) and compound **5b** as a colorless oil, yield: 0.34 g (40%). A solid from the Schott filter was dried in vacuum and identified as compound **4b**, yield: 0.31 g (37%). The total yield of compound **4b** was 45%. ^1H NMR (400 MHz, $CDCl_3$) δ 3.42–3.47 (m, 1H, CH_2), 3.56–3.63 (m, 2H, CH_2), 3.79–3.83 (m, 1H, CH_2), 3.87 (s, 3H, $OC\underline{H}_3$), 3.87 (s, 3H, $OC\underline{H}_3$), 4.19–4.22 (m, 1H, CH), 6.78 (s, 1H, CH_{Ar}), and 6.81 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.75 ($C_{Ar}\underline{C}H_2$), 42.42 (SeCH), 45.82 (CH_2Br), 56.17 (CH_3O), 56.25 (CH_3O), 110.31 (HC_{Ar}), 111.20 (HC_{Ar}), 125.61 ($H_2C\underline{C}_{Ar}$), 131.77 (SeC_{Ar}), 148.63 ($MeO\underline{C}_{Ar}$), and 150.03 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 443.6. Found: C 39.58; H 4.07; Br 24.04; Se 23.71. Calc. for $C_{11}H_{13}BrO_2Se$: C 39.31; H 3.90; Br 23.78; Se, 23.49. Selenochromane **5b**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.94–3.02 (m, 1H, CH_2), 3.09–3.17 (m, 2H, CH_2), 3.23–3.29 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.43–4.52 (m, 1H, CHBr), 6.45 (s, 1H, CH_{Ar}), and 6.56 (s, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.53 ($C_{Ar}\underline{C}H_2$), 41.05 ($SeCH_2$), 52.46 (CHCl), 55.36 (CH_3O), 55.47 (CH_3O), 111.63 (HC_{Ar}), 114.43 (HC_{Ar}), 115.75 ($H_2C\underline{C}_{Ar}$), 126.31 (SeC_{Ar}), 147.45 ($MeO\underline{C}_{Ar}$), and 148.73 ($MeO\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 258.9. Found: C 39.60; H 3.74; Br 24.07; Se 23.19. Calc. for $C_{11}H_{13}BrO_2Se$: C 39.31; H 3.90; Br 23.78; Se, 23.49.

8-Isopropyl-3-(methoxymethyl)-5-methyl-2,3-dihydro-1,4-benzoxaselenine (6)

A freshly prepared solution of selenium dibromide (2.5 mmol) in methylene chloride (30 mL) was added dropwise over 5 min to a solution of allyl thymyl ether (0.475 g, 2.5 mmol) in a mixture of methylene chloride (15 mL) and methanol (15 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed on a rotary evaporator. The product was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil. Yield: 0.67 g (90%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.20–1.21 (m, 6H, $CHC\underline{H}_3$), 2.22 (s, 3H, CH_3), 3.27–3.34 (m, 1H, CH), 3.44 (3H, OCH_3) 3.61–3.64 (m, 1H, CH_2), 3.72–3.77 (m, 1H, CH_2), 3.83–3.88 (m, 1H, CH_2), 4.21–4.24 (m, 1H, CH_2), 4.35–4.39 (m, 1H, CH), 6.78 (d, 1H, J = 7.68 Hz, CH_{Ar}), and 6.92 (d, 1H, J = 7.68 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.61 (CH_3), 22.68 ($CH\underline{C}H_3$), 22.79 ($CH\underline{C}H_3$), 26.89 ($\underline{C}HCH_3$), 34.67 (SeCH), 59.01 (OCH_3), 66.49 (CH_2O), 73.57 (CH_2O), 114.69 (C_{Ar}), 122.2 (C_{Ar}), 123.21 ($\underline{C}_{Ar}$), 134.22 (C_{Ar}), 135.96 ($\underline{C}_{Ar}$), and 151.95 ($O\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 208.9. Found: C 56.59; H 6.91; Se 26.67. Calc. for $C_{14}H_{20}O_2Se$: C 56.19; H 6.74; Se, 26.38.

3-Chloromethyl-8-isopropyl-5-methyl-2,3-dihydro-1,4-benzoxaselenine (7a)

A freshly prepared solution of selenium dichloride (0.375 g, 2.5 mmol) in methylene chloride (30 mL) was added dropwise over 5 min to a solution of allyl thymyl ether (0.475 g, 2.5 mmol) in a mixture of methylene chloride (20 mL) and isopropanol (10 mL). The reaction mixture was stirred at room temperature for 4 h. The solvent was removed on a rotary evaporator. The product **7a** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.65 g (86%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–1.25 (m, 6H, $CHC\underline{H}_3$), 2.23 (s, 3H, CH_3), 3.31–3.38 (m, 1H, CH), 3.66–3.72 (m, 1H, CH), 3.86–3.90 (m, 1H, CH_2), 4.03–4.09 (m, 1H, CH_2), 4.12–4.15 (m, 1H, CH_2), 4.68–4.72 (m, 1H, CH_2), 6.82 (d, 1H, J = 7.5 Hz, CH_{Ar}), and 6.97 (d, 1H, J = 7.5 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.15 (CH_3), 22.25 ($CH\underline{C}H_3$), 22.51 ($CH\underline{C}H_3$), 26.53 ($\underline{C}HCH_3$), 35.42 (SeCH), 44.34 (CH_2Cl), 65.27 (CH_2O), 113.63 (C_{Ar}), 122.24 (C_{Ar}), 123.15 ($\underline{C}_{Ar}$), 133.66 (C_{Ar}), 135.96 ($\underline{C}_{Ar}$), and 151.52 ($O\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 241.8. Found: C 51.67; H 5.84; Cl 11.48; Se 25.72. Calc. for $C_{13}H_{17}ClOSe$: C 51.41; H 5.64; Cl 11.67; Se, 26.00.

3-Bromomethyl-8-isopropyl-5-methyl-2,3-dihydro-1,4-benzoxaselenine (7b)

The reaction was carried out in a similar manner to the synthesis of compound **7a** but by using selenium dibromide (2.5 mmol). The product **7b** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.78 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.91 (m, 6H, $CHC\underline{H}_3$), 1.86 (s, 3H, CH_3), 2.97–3.04 (m, 1H, CH), 3.34–3.43 (m, 2H, CH_2), 3.57–3.62 (m, 1H, CH), 3.77–3.80 (m, 1H, CH_2), 4.39–4.42 (m, 1H, CH_2), 6.38 d (1H, J = 7.7 Hz, CH_{Ar}), and 6.53 d (1H, J = 7.7 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.21 (CH_3), 22.32 ($CH\underline{C}H_3$), 22.60 ($CH\underline{C}H_3$), 26.63 ($\underline{C}HCH_3$), 32.86 (SeCH), 35.04 (CH_2Br), 66.18 (CH_2O), 113.84 (C_{Ar}), 122.34 (C_{Ar}), 123.24 ($\underline{C}_{Ar}$), 133.66 (C_{Ar}), 136.03 ($\underline{C}_{Ar}$), and 151.61 ($O\underline{C}_{Ar}$). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 264.4. Found: C 45.12; H 5.04; Br 23.21; Se 22.46. Calc. for $C_{13}H_{17}BrOSe$: C 44.85; H 4.92; Br 22.95; Se, 22.68.

3-(Methoxymethyl)-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenine (8)

A freshly prepared and cooled to −20 °C solution of selenium dibromide (2.5 mmol) in methylene chloride (30 mL) was added dropwise over 5 min to a cooled to −20 °C solution of allyl 1-naphthyl ether (0.46 g, 2.5 mmol) in a mixture of methylene chloride (15 mL) and methanol (15 mL). The mixture was stirred for 30 min at −20 °C and the cooling bath was removed. The mixture was allowed to warm and stirred for 7 h at room temperature. The solvents were removed on a rotary evaporator. The product **8** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.66 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H, OCH_3), 4.33–4.37 (m, 1H, CH), 4.49–4.53 (m, 1H, CH_2), 4.56–4.60 (m, 1H, CH_2), 5.12–5.16 (m, 1H, CH_2) 5.30–5.34 (m, 1H, CH_2), 7.88–7.90 (m, 1H, CH_{Ar}), 8.04–8.06 (m, 1H, CH_{Ar}), 8.09–8.17 (m, 2H, CH_{Ar}), 8.41–8.43 (m, 1H, CH_{Ar}), and 8.83 (m, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.38 (SeCH), 58.71 (OCH_3), 66.70 (OCH_2), 72.87 (OCH_2) 106.49 (SeC_{Ar}), 120.47 (CH_{Ar}), 121.43 (CH_{Ar}), 125.20 (CH_{Ar}), 125.49 (CH_{Ar}), 126.22 (C_{Ar}), 126.71 (CH_{Ar}), 127.20 (HC_{Ar}), 132.22 (C_{Ar}), and 148.59 (OC_{Ar}). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 242.6. Found: C 57.51; H 4.64; Se 27.21. Calc. for $C_{14}H_{14}O_2Se$: C 57.35; H 4.81; Se, 26.93.

3-(Chloromethyl)-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenine (9a)

A freshly prepared and cooled to −20 °C solution of selenium dichloride (2.5 mmol) in methylene chloride (30 mL) was added dropwise over 5 min to a cooled to −20 °C solution of allyl 1-naphthyl ether (0.46 g, 2.5 mmol) in a mixture of methylene chloride (20 mL) and isopropanol (10 mL). The mixture was stirred for 30 min at −20 °C and the cooling bath was removed. The mixture was allowed to warm and stirred for 7 h at room temperature. The solvent was removed on a rotary evaporator. The product **9a** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.64 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59–3.62 (m, 1H, CH), 3.79–3.83 (m, 1H, CH_2), 3.97–4.03 (m, 1H, CH_2), 4.25–4.29 (m, 1H, CH_2) 4.87–4.90 (m, 1H, CH_2), 7.02–7.04 (m, 1H, CH_{Ar}), 7.25–7.28 (m, 1H, CH_{Ar}), 7.31–7.39 (m, 2H, CH_{Ar}), 7.60–7.62 (m, 1H, CH_{Ar}), and 8.07–8.09 (m, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.92 (SeCH), 44.41 (CH_2Cl), 66.04 (OCH_2) 105.99 (SeC_{Ar}), 121.38 (CH_{Ar}), 122.47 (CH_{Ar}), 125.94 (CH_{Ar}), 126.11 (CH_{Ar}), 126.56 (CH_{Ar}), 127.06 (C_{Ar}), 127.70 (HC_{Ar}), 132.97 (C_{Ar}), and 149.86 (OC_{Ar}). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 275.9. Found: C 52.68; H 3.64; Cl 11.72; Se 26.28. Calc. for $C_{13}H_{11}ClOSe$: C 52.46; H 3.73; Cl 11.91; Se, 26.53.

3-(Bromomethyl)-2,3-dihydronaphtho[1,2-*b*][1,4]oxaselenine (9b)

The reaction was carried out in a similar manner to the synthesis of compound **9a** but using selenium dibromide (2.5 mmol). The product **9b** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.73 g (85%). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.57–3.71 m (2H), 3.82–3.88 m (1H), 4.24–4.27 m (1H), 4.85–4.87 m (1H), 6.96–6.98 m (1H, CH_{Ar}), 7.20–7.22 m (1H, CH_{Ar}), 7.26–7.32 m (2H, CH_{Ar}), 7.54–7.56 m (1H, CH_{Ar}), and 8.02–8.04 m (1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.37 (SeCH), 35.01 (CH_2Br), 66.53 (OCH_2) 105.71 (SeC_{Ar}), 120.92 (CH_{Ar}), 122.01 (CH_{Ar}), 125.51 (CH_{Ar}), 126.06 (CH_{Ar}), 126.45 (CH_{Ar}), 126.97 (C_{Ar}), 127.24 (HC_{Ar}), 130.92 (C_{Ar}), and 148.67 (OC_{Ar}). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 297.4. Found: C 45.41; H 3.43; Br 23.07; Se 23.28. Calc. for $C_{13}H_{11}BrOSe$: C 45.64; H 3.24; Br 23.36; Se, 23.08.

3-[(*E*)-Chloromethylidene]-2,3-dihydronaphtho[1,2-*b*][1,4]-oxaselenines (10a)

A freshly prepared solution of selenium dichloride (2.5 mmol) in chloroform (10 mL) and a solution of 1-naphthyl propargyl ether (0.456 g, 2.5 mmol) in chloroform (10 mL) were added separately and simultaneously over 15 min to a cooled (−60 °C) flask containing a stirred mixture of chloroform (45 mL) and methanol (25 mL). The mixture was stirred for 1 h at −60 °C and the cooling bath was removed. The mixture was allowed to warm and stirred for 7 h at room temperature. The solvents were removed on a rotary evaporator. The product **10a** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.59 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (m, 2H, CH_2), 6.24 (m, 1H, CH_{vinyl}), 7.08–7.10 (m, 1H, CH_{Ar}), 7.32–7.39 (m, 3H, CH_{Ar}), 7.62–7.64 (m, 1H, CH_{Ar}), and 8.05–8.07 (m, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.92 (CH_2), 108.99 (SeC_{Ar}), 111.60 (CHCl), 121.53 (CH_{Ar}), 123.01 (CH_{Ar}), 125.64 (CH_{Ar}), 126.20 (CH_{Ar}), 126.31 (CH_{Ar}), 127.26 (C_{Ar}), 127.45 (SeC_{Vinyl}), 127.78 (CH_{Ar}), 133.31 (C_{Ar}), and 149.85 (OC_{Ar}). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 339.5.

Found: C 53.04; H 3.24; Cl 12.21; 26.47. Calc. for $C_{13}H_9ClOSe$: C 52.82; H 3.07; Cl 11.99; Se, 26.71.

3-[(*E*)-Bromomethylidene]-2,3-dihydronaphtho[1,2-*b*][1,4]-oxaselenines (10b)

The reaction was carried out in a similar manner to the synthesis of compound **10a** but using selenium dibromide (2.5 mmol). The product **10b** was isolated by column chromatography (silica gel, eluent: hexane → chloroform/hexane 1 : 9) as a light yellow oil, yield: 0.65 g (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58–4.62 (m, 2H, CH_2), 5.98–6.02 (m, 1H, CH_{vinyl}), 6.78–6.82 (m, 1H, CH_{Ar}), 7.02–7.16 (m, 3H, CH_{Ar}), 7.33–7.37 (m, 1H, CH_{Ar}), and 7.79–7.83 (m, 1H, CH_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.23 (CH_2), 108.32 (CHBr), 109.54 (SeC_{Ar}), 121.53 (CH_{Ar}), 123.25 (CH_{Ar}), 125.53 (CH_{Ar}), 126.12 (CH_{Ar}), 126.39 (CH_{Ar}), 126.96 (C_{Ar}), 127.42 (SeC_{Vinyl}), 127.96 (CH_{Ar}), 133.84 (C_{Ar}), and 150.81 (OC_{Ar}). ^{77}Se NMR (76.3 MHz, $CDCl_3$) δ 361.2. Found: C 46.21; H 2.84; Br 23.71; Se 22.93. Calc. for $C_{13}H_9BrOSe$: C 45.91; H 2.67; Br 23.50; Se, 23.22.

Conflicts of interest

There are no conflicts to declare.

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