Synthesis of Water-Soluble Vinyl Selenides and Their High Glutathione Peroxidase (GPx)-Like Antioxidant Activity

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Abstract: A convenient procedure for the synthesis of novel bis-(1-hydroxymethyl-2-halo-3-hydroxy-1-propylene) selenides has been developed. On oxidation these compounds form novel seleno-spiro compounds and their glutathione peroxidase mimetic activity has been studied. They promote the hydrogen peroxide oxidation of phenylmethanethiol to the corresponding disulfide via a catalytic cycle.

Key words: alkynes, selenium, oxidation, spiro compounds, diols

Glutathione peroxidase (GPx) is a selenoenzyme that protects cells by catalyzing the reduction of peroxides with the stoichiometric reductant glutathione.[1] The enzyme catalytic site includes a selenocysteine residue in which the selenium undergoes a redox cycle involving the selenolate anion as the active form, which reduces hydroperoxides. The selenol is first oxidized to a selenenic acid EnzSeOH, which reacts with reduced glutathione GSH to form the selenyl sulfide EnzSeSG. A second glutathione then regenerates the active form of the enzyme by attacking the EnzSeSG to form the oxidized glutathione GSSG. The overall catalytic cycle is depicted in Figure 1.[2]

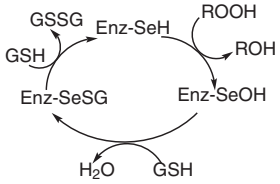
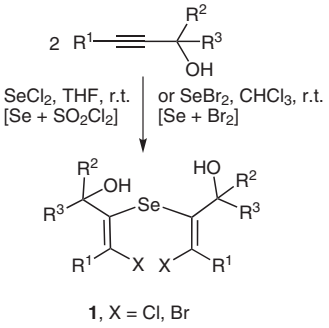


Figure 1 Catalytic cycle for the reduction of peroxides

Ebselen [2-phenyl-1,2-benzoisoselenazol-3(2*H*)-one] has been known as a mimetic of glutathione peroxidase (GPx), able to interact with active oxygen species present in living cells.[3–6] However, its use under nonenzymic conditions as a catalyst for hydrogen peroxide oxidation of thiols to disulfides gave poor results. Recently, Back et al.[7,8] have demonstrated the exceptional glutathione peroxidase-like activity of the simple bis(3-hydroxypropyl) selenide and the unexpected role of its oxidation product, spirodioxaselenanone, as an intermediate in the catalytic redox cycle for GPx.

In view of the known role of organoselenium compounds in biological systems,[9–12] in addition to their unique characteristics in organic synthesis,[13] the design and synthesis of novel organoselenium compounds with potential biological activity constitutes an ongoing challenge. Recently, we have found that in situ prepared selenium dichloride, readily obtained from elemental selenium and sulfuryl chloride,[14] undergoes smooth 1,2-addition to the triple bond of various propargylic alcohols resulting in the formation of symmetrical (*Z*,*Z*)-bis(1-hydroxymethyl-2-chlorovinyl) selenides **1** in high yields and in completely regio- and stereospecific manner (Scheme 1).[15,16] Of special mechanistic interest is the observed *syn*-addition and anti-Markovnikov orientation.



Scheme 1 Regio- and stereospecific synthesis of functionalized divinyl selenides

Inspired by the above findings, we applied our regio- and stereospecific $SeCl_2$ addition protocol in the planned preparation of novel GPx-mimetics of spirodioxaselenurane type.[8] Those divinyl selenides formed by *syn*-addition of $SeCl_2$ to the triple bond, which do not bear a vicinal hydrogen capable of *cis* elimination, gave stable selenoxides **2a**,**b** and selenone **3** in good yield upon oxidation with *tert*-butyl hydroperoxide or with 2 equivalents of MCPBA, respectively (Scheme 2). The divinyl selenoxides **2c**,**d** derived from the unsubstituted or monosubstituted propargyl alcohols are relatively unstable, presumably due to *syn*-elimination. The divinyl selenoxides **2a** and **2b** do not cyclize to spiro compounds (see below) presumably because of ring strain of four-membered rings.

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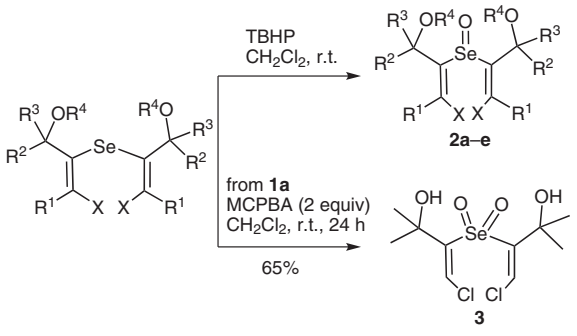
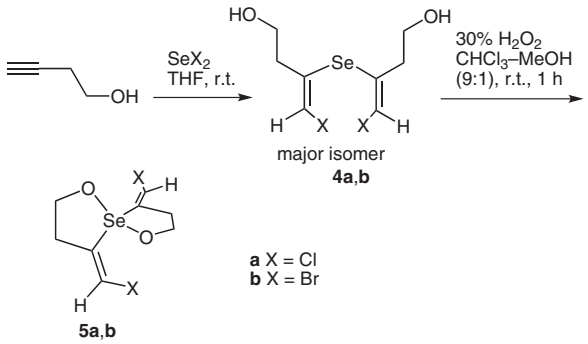


2a $R^1 = R^4 = H$, $R^2 = R^3 = Me$, X = Cl; 88%
2b $R^1 = R^4 = H$, $R^2 = R^3 = Me$, X = Br; 87%
2c $R^1 = Me$, $R^2 = R^3 = R^4 = H$, X = Cl; 85%
2d $R^1 = R^2 = R^3 = R^4 = H$, X = Cl; 82%
2e $R^1 = R^2 = R^3 = H$, $R^4 = Bn$, X = Cl, 93%

Scheme 2 Oxidation of divinyl selenides

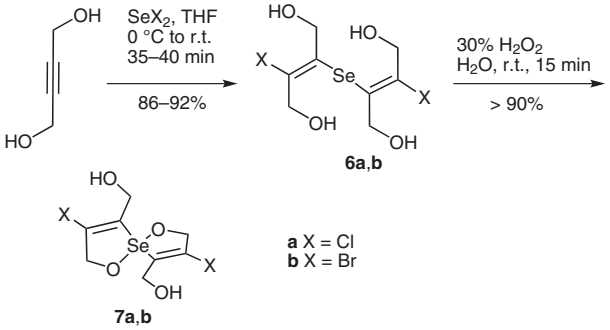
In contrast to the above, were our findings in the reaction of selenium dihalides with homopropargyl alcohol.[16] Although some loss of stereo- and regioselectivity was observed, *Z-anti*-Markovnikov adducts **4** were chromatographically isolated as major products and underwent oxidation with H_2O_2 to the corresponding five-membered spiroselenuranes **5** with exocyclic double bonds (Scheme 3).



a X = Cl
b X = Br

Scheme 3 Reaction of homopropargyl alcohol with $SeCl_2$ and $SeBr_2$

In an alternative approach to the preparation of spirodioxaselenuranes, we have found that but-2-yn-1,4-diol smoothly reacts with selenium dihalides in a completely stereospecific manner and affords the corresponding water-soluble tetrahydroxymethyldivinyl selenides **6a**,**b** in high yields. Noteworthy is the fact that unlike the *syn*-addition of SeX_2 to the triple bond of propargyl alcohols containing a single hydroxymethyl functionality, but-2-yn-1,4-diol gives under the similar conditions exclusively 1,2-*anti*-adducts. The mechanistic explanation of this striking difference is still under investigation. However, in general *anti*-addition of electrophilic selenium reagents to multiple bonds is the expected stereochemical result.[17] Compounds **6** upon oxidation with 30% hydrogen peroxide in aqueous solution produce the spiroselenurane compounds **7** with the endocyclic double bonds in excellent yields (Scheme 4). Spiroselenurane compounds precipitated from the reaction mixture as white needles within 15 minutes, and were recrystallized from water and fully characterized by spectroscopic methods. The structure of the chloro-substituted compound **7a** was confirmed by X-ray crystallography (Figure 2).



a X = Cl
b X = Br

Scheme 4 Formation of dioxydroxymethyl spiroselenuranes

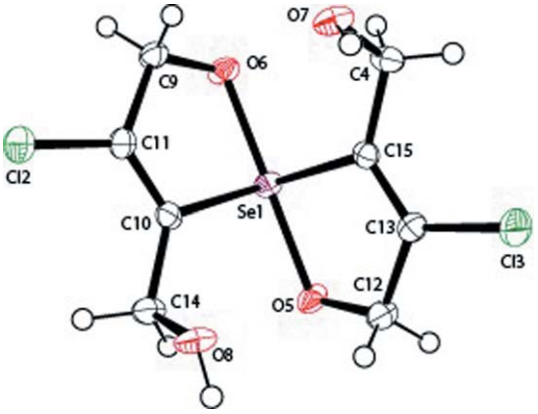
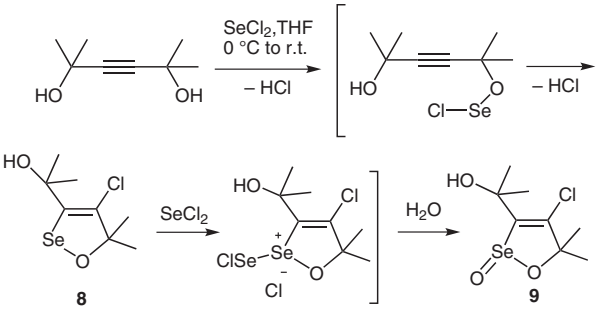


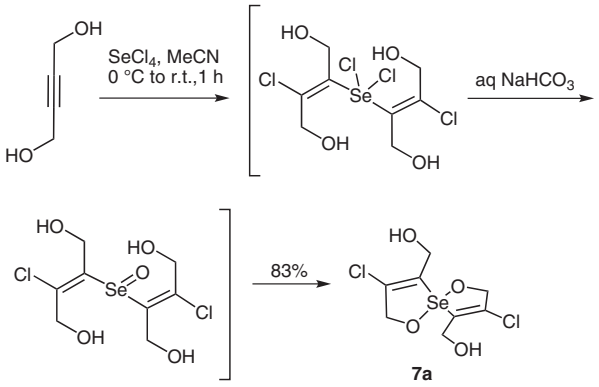
Figure 2 X-ray structure of (3,8-dichloro-9-hydroxymethyl-1,6-dioxa-5-selenaspiro[4.4]nona-3,8 diene-4-yl)methanol (**7a**); ORTEP diagram of spiroselenurane **7a**[18]

The reaction of substituted alkyne diols with selenium dihalogenides was used for the preparation of a series of spirodioxaselenuranes. However, in the case of 2,5-dimethylhex-3-yne-2,5-diol the reaction with $SeCl_2$ proceeded slowly and produced, not a divinyl selenide, but the seleninate ester **9**, presumably via **8** (Scheme 5). Steric hindrance of the four methyl groups precluded addition to the triple bond.[16]



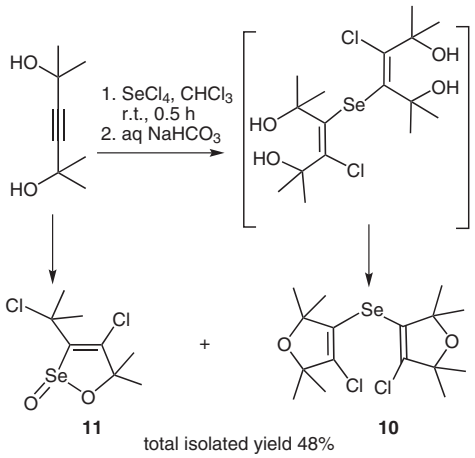
Scheme 5 Formation of cyclic seleninate ester **9**

Recently, we have shown that the addition of commercially available selenium tetrachloride to the triple bond of propargyl alcohols proceeded easily with the same regio- and stereochemistry as selenium dichloride and produces unstable divinylselenium dichloride intermediates.[19] The latter underwent hydrolysis to the corresponding divinyl selenoxides during basic workup.[19] In the case in hand, but-2-yn-1,4-diol reacted stereospecifically with selenium tetrachloride in anhydrous acetonitrile and afforded the expected spiroselenurane compound **7a** in a one-pot manner and in good yield (Scheme 6).

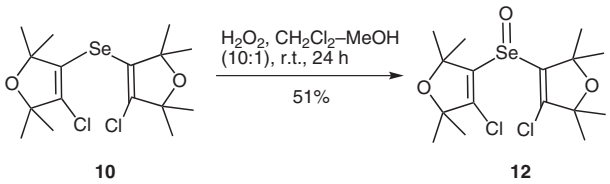


Scheme 6 One-pot preparation of dihydroxymethyl spiroselenuranes

Even the sterically hindered 2,5-dimethylhex-3-yne-2,5-diol reacted easily with $SeCl_4$ and produced, in an almost 1:1 ratio, two products, **10** and **11**, which were separated by column chromatography (Scheme 7). The first product, selenium-bridged dihydrofuran derivative **10**, presumably was formed via *syn*-addition of $SeCl_4$ to the triple bond followed by double intramolecular dehydrative cyclization. The second one **11**, was identified as a chlorinated analogue of the seleninate ester **9**. Dicylic selenide **10** upon oxidation with hydrogen peroxide gave the expected stable selenoxide **12** (Scheme 8). The structure of the latter was unambiguously confirmed by X-ray crystallography (Figure 3).



Scheme 7 Reaction of 2,5-dimethylhex-3-yne-2,5-diol with $SeCl_4$



Scheme 8 Oxidation of dihydrofuran selenide derivative **10**

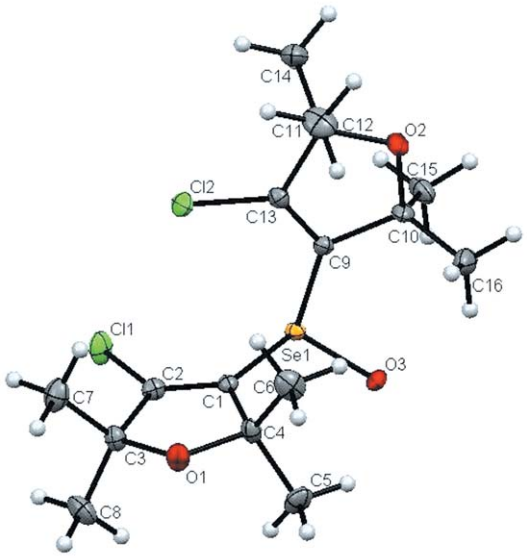
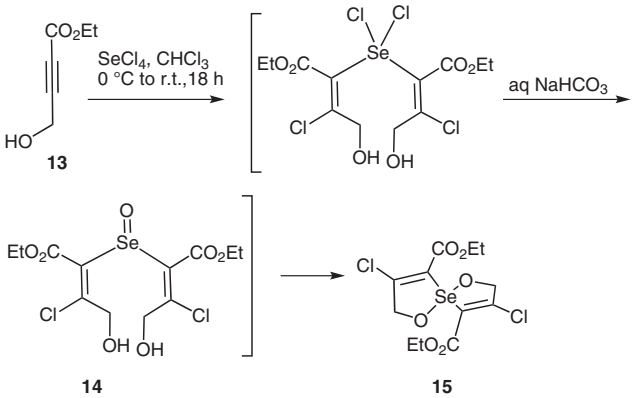


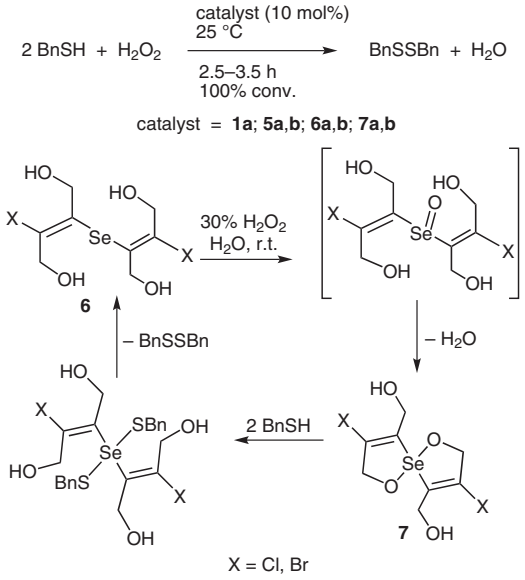
Figure 3 X-ray structure of [bis(4-chloro-2,2,5,5-tetramethyl-2,5-dihydrofuran-3-yl]seleninyl **12**; ORTEP diagram of selenoxide **12**[18]

An interesting result was obtained using ethyl 4-hydroxybut-2-ynoate (**13**) as a hydroxyalkyne substrate. Whereas selenium dichloride does not react with this alcohol, selenium tetrachloride undergoes smooth 1,2-addition to the deactivated triple bond of this propargyl alcohol. However, the regiochemistry differ from the one observed in a 'normal' $SeCl_2$ addition (see, Scheme 1) and produces, after hydrolysis of the intermediate, the divinyl selenium oxide **14** with the geometry that permits its subsequent cyclization to the spiro derivative **15** (Scheme 9).



Scheme 9 Reaction of ethyl 4-hydroxybut-2-ynoate (**13**) with $SeCl_4$

The novel selenium-containing spiro compounds **5a**,**b** and **7a**,**b** were found to exhibit higher glutathione peroxidase mimetic activity than the widely studied compound ebselen (in nonenzymic conditions). To examine the glutathione peroxidase-like (GPx) catalytic activity of the spiroselenurane compounds, 30% H_2O_2 and benzylthiol (BnSH) were chosen as the oxidant and stoichiometric reductant, respectively. The oxidation of BnSH to the disulfide BnSSBn was monitored by ^{1}H NMR spectroscopy. When 10 mol% of the catalyst **6a** or **7a** was used in the presence of excess 30% H_2O_2, 75% of BnSH was converted into BnSSBn after 1.5 hours. (3*Z*)-4-Chloro-3-{[(*Z*)-2-chloro-1-(1-hydroxy-1-methylethyl)vinyl]selanyl}-2-methylbut-3-en-2-ol (**1a**) exhibits a similar GPx-like catalytic activity. In the control experiment in the absence of the catalyst under the same reaction condition after 24 hours, only 4% of BnSSBn was observed in the reaction mixture according to ^{1}H NMR spectrum. The suggested catalytic cycle of compounds **6** and **7** is shown on Scheme 10.



Scheme 10 GPx-like activity of divinyl selenium systems

Thus, an easy and efficient synthesis of the water-soluble divinyl selenides has been achieved. These divinyl selenides perform as glutathione peroxidase mimetics with high efficacy. Spiroselenurane **7a** also showed some antifungal activity in preliminary experiments.

The THF solution of $SeCl_2$ was prepared by the known procedure[14] and used immediately. All solvents and reagents were obtained from Aldrich or Fluka and used without further purification with the following exception: THF was distilled from sodium benzophenone dianion just before use and $CHCl_3$ was distilled from P_2O_5. All reactions were carried out under dry argon atmosphere using oven-dried glassware. Reagents and solvents were handled by using standard syringe-septum cap techniques. Column chromatography was performed with Merck silica gel 60 (230–400 mesh), and TLC was run on precoated Merck silica gel plates 60 F_{254} (2.00 mm). Preparative TLC was carried out in glass sheets precoated with Merck silica gel 60 F_{254} (0.25 mm). All new compounds have satisfactory analytical and spectroscopic data.

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FTIR instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker DPX-300, DMX-600 or Avance-III-700 spectrometers in either $CDCl_3$ or other deuterated solvents, using TMS as internal standard. Chemical shifts are reported in δ units, and coupling constants in Hz. COSY and NOSY experiments have been carried out in order to assign ^{1}H and ^{13}C spectra and confirmed the structures of new compounds. Mass spectra were obtained on Auto flex Tof/Tof Bruker MALDI (matrix assisted laser desorption ionization) instrument with graphite matrix. High-resolution mass spectra were obtained on a VG-Fison Autospec instrument. Elemental analyses were performed on Thermo CHNS Analyzer FlashEA instrument.

Divinyl selenides **1a–d** were prepared according to our reported procedure.[15,16] Ethyl 4-hydroxybut-2-ynoate (**13**) was prepared by the known procedure.[20]

Oxidation of Divinyl Selenides with TBHP; General Procedure

An excess of TBHP (0.90 mL, 5 mmol, ~5.5 M solution in nonane) was added to divinyl selenide **1a–d** (1 mmol) dissolved in CH_2Cl_2 (10 mL) and the solution was stirred at r.t. for 18 h. After completion of the reaction (TLC, eluent: hexanes–EtOAc, 4:1), the solvent was evaporated to dryness under reduced pressure. All selenoxides **2a–d** were purified by removing the excess of TBHP overnight under vacuum. In the case of stable compounds, further purification can be done by column chromatography, if required, using EtOAc–MeOH (4:1) as eluent.

(3*Z*)-4-Chloro-3-{[(*Z*)-2-chloro-1(1-hydroxy-1-methylethyl)vinyl]seleninyl}-2-methylbut-3-en-2-ol (2a)

Yield: 0.294 g (88%); white solid; mp 126 °C.

IR (KBr): 3355, 2936, 2560, 1604, 1466, 1426, 1370, 1305, 1173, 1149, 981, 901, 821, 786 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 6 H), 1.73 (s, 6 H), 5.67 (br s, 2 H), 6.73 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8 (CH_3), 28.4 (CH_3), 73.6 [$^2J_{C,Se}$ = 12.2 Hz, $(CH_3)_2C$], 122.4 (=CCl), 157.1 ($^1J_{C,Se}$ = 123.6 Hz, =CSe).

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_{17}Cl_2O_3{}^{80}Se$: 334.9720; found: 334.9720.

Anal. Calcd for $C_{10}H_{16}Cl_2O_3Se$: C, 35.95; H, 4.83; O, 14.37. Found: C, 35.56; H, 4.76; O, 14.35.

(3*Z*)-4-Bromo-3-{[(*Z*)-2-bromo-1(1-hydroxy-1-methylethyl)vinyl]seleninyl}-2-methylbut-3-en-2-ol (2b)

Yield: 0.368 g (87%); white solid; mp 112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 6 H), 1.75 (s, 6 H), 6.31 (br s, 2 H), 6.74 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7 (CH_3), 28.4 (CH_3), 74.3 (C), 110.3 (C=), 158.8 (C=).

(2*Z*)-3-Chloro-2-{[(1*Z*)-2-chloro-1-(hydroxymethyl)prop-1-enyl]seleninyl}but-2-en-1-ol (2c)

Eluent EtOAc–MeOH (4:1); yield: 0.260 g (85%); white solid; mp 81–83 °C.

IR (KBr): 3102, 1623, 1434, 1373, 1131, 1007, 806 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 6 H), 4.68 (br s, 2 H), ABq: 4.58 (d, *J* = 15.4 Hz, 2 H), 4.70 (d, *J* = 15.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.03 (CH_3), 58.06 (CH_2), 137.02 (C=), 140.43 (C=).

(2*Z*)-3-Chloro-2-{[(*Z*)-2-chloro-1-(hydroxymethyl)vinyl]seleninyl}prop-2-en-1-ol) (2d)

Yield: 0.228 g (82%); viscous liquid.

^{1}H NMR (300 MHz, acetone-d_6): δ = 4.22 (s, 2 H), ABq: 4.53 (dd, *J* = 14.3, 1.5 Hz, 2 H), 4.73 (dd, *J* = 14.3, 1.5 Hz, 2 H), 7.02 (t, 1.5 Hz, 2 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 57.4 (CH_2), 123.6 (CH=), 146.4 ($^1J_{CSe}$ = 136.2 Hz, C=).

({[(2*Z*,2′*Z*)-Seleninylbis(3-chloroprop-2-ene-2,1-diyl)]bis(oxy)}bis(methylene))dibenzene (2e)
Eluent: EtOAc–hexane (1:1); yield: 0.504 g (93%); viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = superposition of two ABq: ABq 4.28 (d, *J* = 13.1 Hz, 2 H), 4.45 (d, *J* = 13.1 Hz, 2 H) and ABq 4.40 (d, *J* = 11.6 Hz, 2 H), 4.47 (d, *J* = 11.6 Hz, 2 H), 6.85 (s, 2 H), 7.29 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.80 ($^2J_{C,Se}$ = 6.8 Hz, *C*H_2CSe), 72.98 (*C*H_2Ph), 125.81 ($^2J_{C,Se}$ = 21 Hz, CH=), 127.67 (CH), 128.28 (CH), 136.67 (C-*ipso*), 142.17 ($^1J_{C,Se}$ = 125.4 Hz, C=).

HRMS (DCI + CH_4): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}Cl_2O_3{}^{80}Se$: 459.0033; found: 459.0071.

Oxidation of Divinyl Selenide 1a with MCPBA; Preparation of Compounds 2a and 3
4-Chloro-3-[2-chloro-1-(1-hydroxy-1-methylethyl)vinylselanyl]-2-methylbut-3-en-2-ol (**1a**; 318 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL) and a CH_2Cl_2 solution (15 mL) of MCPBA (77%, 491 mg, 2.2 mmol) was added slowly. The reaction mixture was then stirred for 24 h at r.t. TLC (eluent: EtOAc–MeOH, 4:1) indicated the formation of two products. The mixture was then quenched with sat. aq Na_2SO_3 (10 mL) under ice cold conditions. The product was extracted with CH_2Cl_2 (30 mL), and the CH_2Cl_2 layer was washed with sat. aq $NaHCO_3$ (5 mL), H_2O (10 mL), and brine (10 mL). Drying ($MgSO_4$) and evaporation of the solvent under reduced pressure produced the crude mixture of corresponding selenoxide **2a** and selenone **3**. The products were separated by column chromatography using EtOAc–MeOH (80:20) as an eluent. The selenone, which is less polar than selenoxide eluted first, followed by selenoxide. Overall isolated yield (0.333 g, 97%); product distribution selenone/selenoxide = 65:35.

For the physical and spectral data of **2a**, see above.

(3*Z*)-4-Chloro-3-{[(*Z*)-2-chloro-1(1-hydroxy-1-methylethyl)vinyl]selenonyl}-2-methylbut-3-en-2-ol (3)
Yield: 0.22 g (63%); white solid; mp 160–162 °C.

IR (KBr): 3342, 3052, 2495, 1603, 1459, 1369, 1309, 1170, 1134, 979, 901, 867, 838 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 12 H), 3.42 (br s, 2 H), 7.44 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.8 (CH_3), 74.1 (C), 130.3 (C=), 157.3 (C=).

HRMS: *m*/*z* [M + H] calcd for $C_{10}H_{17}Cl_2O_4{}^{78}Se$: 350.9669; found: 350.9647.

Anal. Calcd for $C_{10}H_{16}Cl_2O_4Se$: C, 34.31; H, 4.61. Found: C, 34.42; H, 4.63.

Oxidation of Divinyl Selenides with H_2O_2; Preparation of 5a, 5b, and 12
The corresponding divinyl selenide **4a**, **4b**, or **10** (0.545 mmol) was dissolved in a mixture of $CHCl_3$ and MeOH (9:1, 10 mL), respectively, and 30% aq H_2O_2 (0.05 mL, 1.635 mmol) was added. The mixture was stirred for 1 h at r.t., the solvent was evaporated, and the product was isolated by silica gel column chromatography.

(4*Z*,9*Z*)-4,9-Bis(chloromethylene)-1,6-dioxa-5λ^4-selenospiro[4,4]nonane (5a)
Eluent: EtOAc–MeOH (8:1); yield: 0.06 g (40%); white solid; mp 78–80 °C.

IR (neat): 3396 (br), 2955, 2116, 1614, 1420, 1260, 1062, 778, 417 cm^{-1}.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.79 (m, 4 H), 4.02 (dt, *J* = 9.6, 6.1 Hz, 2 H), 4.17 (dt, *J* = 9.6, 6.1 Hz, 2 H), 7.17 (t, *J* = 2.5 Hz, 2 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 31.6 (CH_2), 64.3 (CH_2), 125.6 ($^2J_{C,Se}$ = 25 Hz, C_q–Cl), 138.5 ($^1J_{C,Se}$ = 101.5 Hz, C_q–Se).

MS (DCI/CH_4): *m*/*z* (%) = 288.9 (78), 252.9 (26), 236.9 (14), 206.9 (17), 183.9 (79), 168.9 (14), 123.0 (15), 83.9 (100).

HRMS: *m*/*z* [M$^+$] calcd for $C_8H_{10}Cl_2O_2Se$: 287.9223; found: 288.0302.

(4*Z*,9*Z*)-4,9-Bis(bromomethylene)-1,6-dioxa-5λ^4-selenospiro[4,4]nonane (5b)
Eluent: EtOAc–MeOH (8:1); yield: 0.18 g (89%); white solid; mp 65–67 °C.

^{1}H NMR (700 MHz, $CDCl_3$): δ = 2.77 (m, 4 H), 4.02 (ddd, *J* = 9.6, 7.5, 6.0 Hz, 2 H) 4.18 (dddd, *J* = 9.6, 7.5, 6.0, 0.14 Hz, 2 H), 7.40 (t, *J* = 2.5 Hz, 2 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 33.6 (CH_2), 64.2 (CH_2O), 114.1 ($^2J_{C,Se}$ = 22.6 Hz, CH), 140.0 ($^1J_{C,Se}$ = 103.0 Hz, C_q).

MS (CI/CH_4): *m*/*z* (%) = 378.8 (88), 296.9 (13), 227.8 (100), 118.9 (8).

HRMS: *m*/*z* [M$^+$] calcd for $C_8H_{10}Br_2O_2Se$: 375.8213; found: 375.8251.

Bis(4-chloro-2,2,5,5-tetramethyl-2,5-dihydrofuran-3-yl)selenenyl (12)
Eluent: EtOAc–hexane (1:3); yield: 0.115 g (51%); colorless plates; mp 96–97 °C ($CHCl_3$–hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.40 (s, 6 H), 1.44 (s, 6 H), 1.62 (s, 12 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 27.3 (CH_3), 27.4 (CH_3), 29.0 (CH_3), 30.4 (CH_3), 86.1 (Me_2C), 88.9 (Me_2C), 134.3 ($^1J_{C,Se}$ = 150.6 Hz, =CSe), 143.02 ($^2J_{C,Se}$ = 16.5 Hz, =CCl).

MS (DCI): *m*/*z* (%) = 415.0 (100, [M + H]$^+$), 399.0 (26), 381 (9.37), 159.1 (13.3), 85.0 (48.7).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}O_3{}^{35}Cl^{37}Cl^{78}Se$: 415.0324; found: 415.0317.

Anal. Calcd for $C_{16}H_{24}O_3Cl_2Se$: C, 46.39; H, 5.84. Found: C, 46.67; H, 5.89.

Divinyltetrahydroxy Selenides 6a,b
The THF solution of $SeCl_2$ (1 mmol) prepared by the known procedure[14] was added dropwise to a solution of but-2-yn-1,4-diol (172 mg, 2 mmol) in anhydrous THF (2 mL) at 0 °C. The reaction mixture was then stirred at r.t. for 45 min. After completion of the reaction (TLC, eluent: EtOAc), the mixture was extracted with EtOAc (20 mL) and the EtOAc layer was washed with brine (2 × 5 mL) and dried ($MgSO_4$). After evaporation of the solvent, a crude product containing some black gummy materials and selenide compounds was obtained. This crude product was dissolved in a minimum amount of H_2O and filtered. The filtrate contained the pure selenide **6a**, which was isolated as a light yellowish solid after lyophilization. The corresponding bromo derivative **6b** was prepared by the same procedure using $SeBr_2$[21] instead of $SeCl_2$.

2-Chloro-3-(2-chloro-3-hydroxy-1-hydroxymethylpropenylselanyl)but-2-ene-1-4-diol (6a)
Yield: 0.296 g (92%); yellowish solid; mp 87–89 °C.

IR (KBr): 3300 (br), 2923, 2873, 1597, 1481, 1439, 1356, 1124, 1073, 1004, 934 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 4.42 (s, 4 H), 4.63 (s, 4 H).

^{13}C NMR (75MHz, D_2O): δ = 62.6 (CH_2), 64.8 (CH_2), 128.8 (C=), 137.5 (C=).

HRMS: *m*/*z* [M + H] calcd for $C_8H_{13}Cl_2O_4{}^{80}Se$: 322.9356; found: 322.9306.

Anal. Calcd for $C_8H_{12}Cl_2O_4Se$: C, 29.84: H, 3.76; O, 19.87. Found: C, 30.08; H, 3.60; O, 18.6.

2-Bromo-3-(2-bromo-3-hydroxy-1-hydroxymethylpropenylselanyl)but-2-ene-1-4-diol (6b)
Yield: 0.37 g (90%); colorless solid; mp 103–105 °C.

IR (KBr): 3301 (br), 2923, 2873, 1597, 1481, 1439, 1356, 1124, 1073, 1004, 934 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 4.22 (s, 4 H), 4.40 (s, 4 H).

^{13}C NMR (75MHz, DMSO-d_6): δ = 66.1 (CH_2), 67.2 (CH_2), 128.9 (C=), 132.6 (C=).

HRMS: *m*/*z* [M + H] calcd for $C_8H_{13}Br_2O_4{}^{80}Se$: 322.9356; found: 322.9306.

Anal. Calcd for $C_8H_{12}Br_2O_4Se$: C, 29.84; H, 3.76. Found: C, 30.08; H, 3.60.

Spiroselenuranes 7a,b
The corresponding divinyl selenide **6a** or **6b** (0.545 mmol) was dissolved in H_2O (10 mL) and 30% aq H_2O_2 (0.05 mL, 1.635 mmol) was added. The mixture was stirred for 15 min at r.t. whereupon a colorless solid precipitated. The solid was collected by filtration, washed with distilled H_2O (5 mL), and dried under vacuum overnight to obtain the pure product **7a** or **7b**, respectively.

(3,8-Dichloro-9-hydroxymethyl-1,6-dioxa-5λ⁴-selenaspiro[4.4]nona-3,8-dien-4-yl)methanol (7a)
Yield: 0.16 g (93%); colorless needles; mp 151 °C (H_2O).

IR (KBr): 3392 (br), 2914, 1641, 1422, 1284, 1227, 1094, 1022, 952 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 4.28 (dd, *J* = 12.6, 4.2 Hz, 2 H), 4.44 (dd, *J* = 12.6, 6.3 Hz, 2 H), 4.66 (d, *J* = 16.2 Hz, 2 H), 5.02 (d, *J* = 16.2 Hz, 2 H), 5.12 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75MHz, DMSO-d_6): δ = 56.6 (2 C), 75.7 (2 C), 134.7 (2 C), 142.8 (2 C).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{11}Cl_2O_4{}^{80}Se$: 320.9199; found: 320.9200.

Anal. Calcd for $C_8H_{10}Cl_2O_4Se$: C, 30.02; H, 3.15; O, 20.00. Found: C, 30.32; H, 3.07; O, 20.14.

(3,8-Dibromo-9-hydroxymethyl-1,6-dioxa-5λ⁴-selenaspiro[4.4]nona-3,8-dien-4-yl)methanol (7b)
Yield: 0.20 g (91%); colorless solid; mp 138–140 °C (H_2O).

IR (KBr): 3392 (br), 3224, 2914, 1641, 1422, 1284, 1227, 1094, 1022, 952, 758 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.39 (br s, 2 H), 4.29 (dd, *J* = 12.7, 0.9 Hz, 2 H), 4.46 (d, *J* = 18.0 Hz, 2 H), 4.68 (d, *J* = 16.5 Hz, 2 H), 5.01 (dd, *J* = 16.2, 1.5 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 58.3 (2 C), 77.9 (2 C), 133.8 (2 C), 136.2 (2 C).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{11}Br_2O_4{}^{80}Se$: 408.8189; found: 408.8165.

Anal. Calcd for $C_8H_{10}Br_2O_4Se$: C, 23.50; H, 2.46. Found: C, 23.48; H, 2.32.

Reaction of 2,5-Dimethylhex-3-yne-2,5-diol with $SeCl_4$
The propargyl diol (0.284 g, 2 mmol) was added to a soln of $SeCl_4$ (0.22 g, 1 mmol) in anhyd $CHCl_3$ (12 mL) at 0 °C under argon, and the mixture was stirred at 0 °C for 30 min until full disappearance of insoluble $SeCl_4$. EtOAc (70 mL) was added to the reaction mixture, and the mixture was washed with 10% aq $NaHCO_3$ (15 mL). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give the crude mixture of compounds **10** and **11**. The products were separated by column chromatography using EtOAc–hexane (1:4) as eluent.

Bis(4-chloro-2,2,5,5-tetramethyl-2,5-dihydrofuran-3-yl)selane (10)
Yield: 75 mg (19%); yellow oil; R_f = 0.7 (EtOAc–hexane, 1:4).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 12 H), 1.42 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7 (CH_3), 28.9 (CH_3), 86.3 (*C*Me_2), 88.7 ($^2J_{C,Se}$ 37 Hz, *C*Me_2), 124.9 ($^1J_{C,Se}$ = 132 Hz, = CSe), 141.8 (=CCl).

4-Chloro-3-(2-chloropropan-2-yl)-5,5-dimethyl-5*H*-1,2-oxaselenole 2-oxide (11)
Yield: 53 mg (18%); white crystals; mp 101–102 °C; R_f = 0.42 (EtOAc–hexane, 1:4).

^1H NMR (700 MHz, $CDCl_3$): δ = 1.54 (s, 3 H), 1.72 (s, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (175 MHz, $CDCl_3$): δ = 28.3 (CH_3), 30.5 (CH_3), 32.0 (CH_3), 33.3 (CH_3), 68.5 (Me_2*C*Cl), 99.1 (C-5), 144.0 (C-4), 149.7 ($^1J_{C,Se}$ = 129.4 Hz, C-3).

MS (DCI): *m*/*z* (%) = 290.9 (7.15, $[M + H]^+$), 255.0 (26.3), 223.0 (18.9), 107.2 (13.2), 85.1 (100).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{13}O_2{}^{35}Cl_2{}^{80}Se$: 290.9458; found: 290.9467.

Spiroselenurane 15
Prepared from ethyl 4-hydroxybut-2-ynoate (**13**; 170 mg, 1.35 mmol) and $SeCl_4$ (150 mg, 0.675 mmol) following the above procedure for the preparation of **10** and **11**, with the exception that the mixture was stirred at r.t. for 18 h.

Yield: 8.2 mg (30%); yellow oil; R_f = 0.78 (hexane–EtOAc, 2:1).

^1H NMR ($CDCl_3$, 700 MHz): δ = 1.37 (t, *J* = 7 Hz, 6 H), 4.37 (ABq of q, *J* = 7, 11.2 Hz, 4 H), 5.33 (d, *J* = 17.5 Hz, 2 H), 5.68 (d, *J* = 17.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0 (CH_3), 62.9 (CH_3*C*H_2), 82.9 ($^2J_{C,Se}$ = 12.4 Hz, CH_2O), 138.4 ($^1J_{C,Se}$ = 135.5 Hz, =CSe), 154.1 (=CCl), 159.1 (C=O).

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(18) Crystallographic data for compounds **7a** and **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 956314 and CCDC 956315, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.
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