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PAPER

2-Phenoxyethanol derived diselenide and related compounds; synthesis of a seven-membered seleninate ester†

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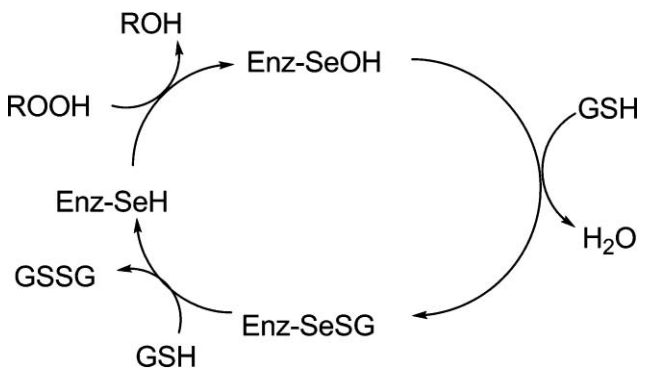
Syntheses of several diorganodiselenides and, in particular, a seven-membered cyclic seleninate ester derived from 2-phenoxyethanol are described. The seleninate ester was obtained from allyl (2-(2-hydroxyethoxy)phenyl) selenide through a series of oxidation and [2,3] sigmatropic rearrangement steps. The ester exhibits good GPx-like activity in the coupled reductase assay.

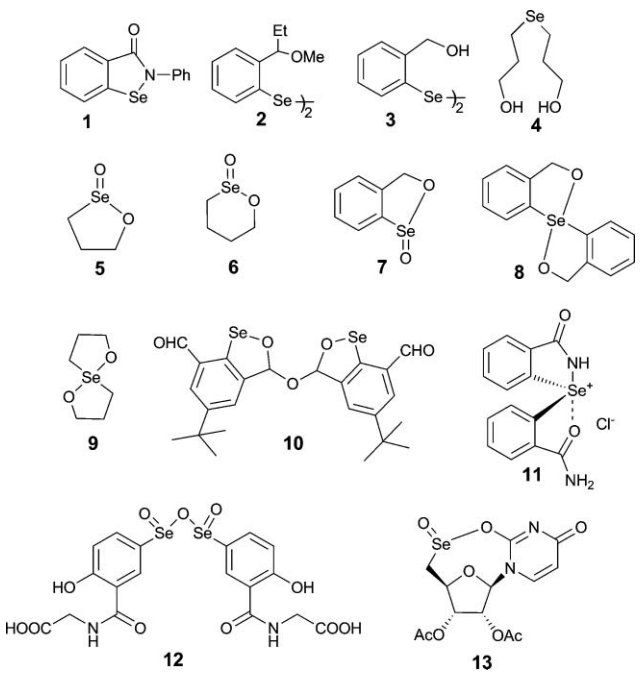
Introduction

The growing interest in the biochemistry of selenium has been mainly driven by the discovery of selenocysteine in a number of enzymes which include glutathione peroxidase,[1] iodothyronine deiodinase,[2] and thioredoxin reductase.[3] Glutathione peroxidase (GPx) is a well known mammalian selenoenzyme that functions as an antioxidant and is responsible for the destruction of harmful peroxides in various living organisms. This selenoprotein, bearing selenol (Enz-SeH) at the active site, catalyzes the reduction of harmful peroxides in the presence of cofactor glutathione (GSH) and thereby protects the lipid membranes as well as biologically important molecules against oxidative stress (Scheme 1). After the discovery of ebselen (**1**) as a GPx mimic,[4] several organoselenium derivatives[5] including ebselen derivatives[6] have been reported in literature for their antioxidant activity.



Scheme 1 Catalytic cycle of GPx.

Mugesh and Bhabak have shown that the *N*-phenyl group present in ebselen is important for its antioxidant activity.[7] Recently, several other classes of organoselenium compounds which exhibit GPx-like antioxidant activity have been reported in the literature. These include diselenides **2**,[8a] **3**,[8c] and selenide **4**,[8b] cyclic seleninate esters **5**,[9a] **6**,[9b] **7**,[9c,9d] spirodioxyselenuranes **8**,[8c,9c] **9**[9c,9d] selenenate ester **10**,[10] azaselenonium chloride **11**,[11] seleninic acid anhydride **12**,[12] having either Se···O intramolecular interaction or Se–O linkage.



Weak intramolecular interaction (Se···N/O) plays an important role in stabilizing organoselenium compounds[13] and modulating the GPx-like activity of enzyme mimetics.[14] Our group has been involved in the synthesis of organochalcogens having hydroxyl or ether groups in the vicinity of Se which can be involved in Se···O intramolecular interaction.[8c,10,15] The importance of systems containing hydroxyl group or multiple ether

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† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, ^{77}Se NMR spectra, ES-MS, HRMS and all computational data. CCDC reference numbers 739448 and 739449. For ESI and crystallographic data in CIF or other electronic format see 10.1039/c0ob00038h

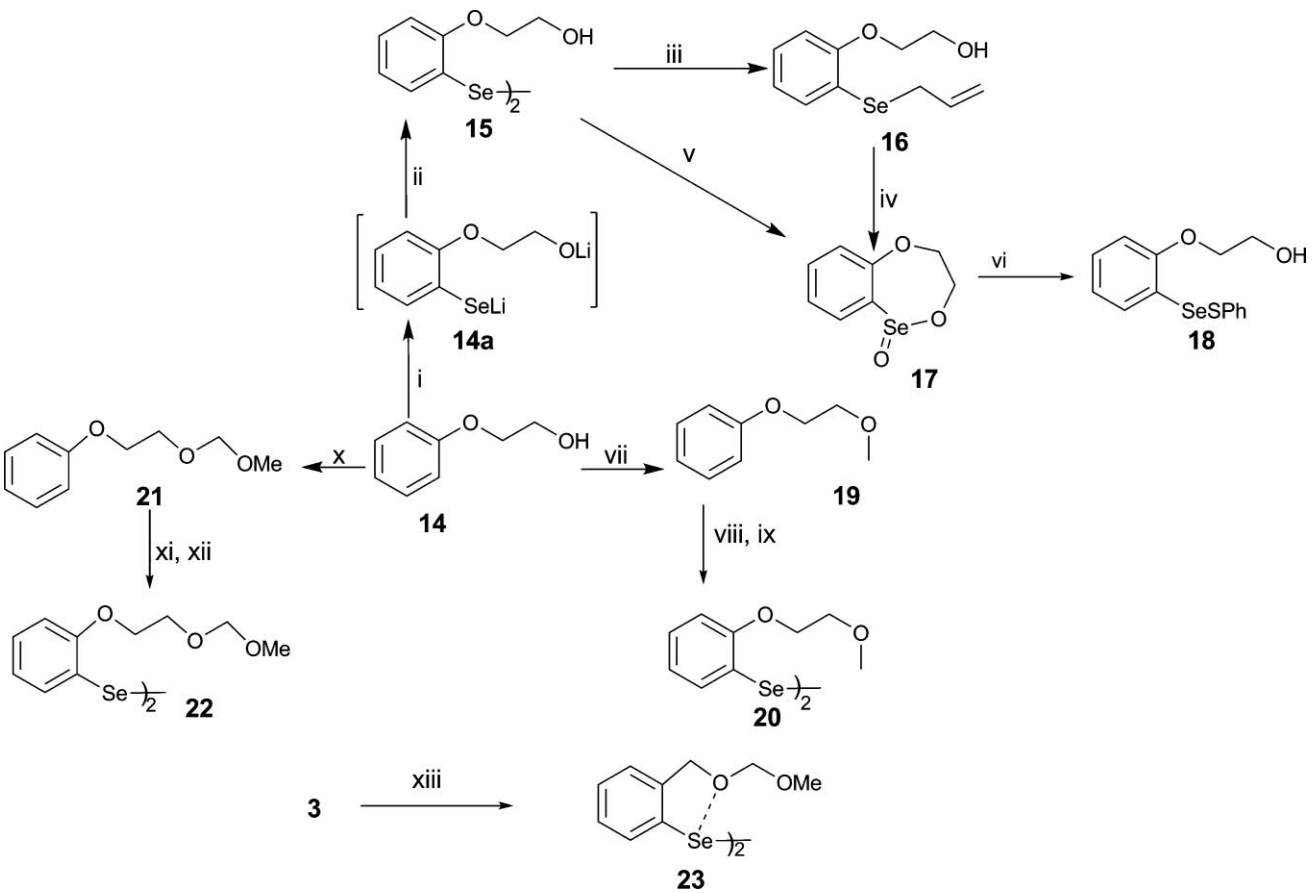
groups stems from the need for higher water solubility of the suitable antioxidants in the bio-system. We earlier demonstrated that diselenide **3**, having five-membered Se···O intramolecular interaction and its five-membered seleninate ester **7** showed excellent GPx-like activity in the coupled reductase assay. However, the corresponding monoselenide of **3** and its spirodioxyselenurane **8** showed relatively poor catalytic activity.[8c] Back and coworkers also reported similar observations for **7** as well as **8**[9c] and very good GPx-like activity of di(3-hydroxypropyl) selenide **4**.[8b] In continuation of our work on the synthesis of organochalcogens containing oxygen as donor atom, we now report the synthesis and GPx-like activity of a novel seven-membered seleninate ester **17**. Although seleninate esters where selenium(IV) is incorporated in a five-membered ring (**5**), six-membered ring (**6**), and eight-membered ring (**13**)[16] are known, to our knowledge, a seleninate ester in which selenium(IV) is part of a seven-membered ring has not been reported in the literature.

Results and discussion

Syntheses

Diorganodiselenide **15** was synthesized from 2-phenoxyethanol **14** by the *ortho*-lithiation route.[17] The reaction of 2-phenoxyethanol with 2 equivalents of *n*-BuLi at −78 °C followed by the addition of selenium and subsequent air oxidation gave a yellow solid, which was recrystallized from dichloromethane to give yellow needles of **15** (Scheme 2). It is worth mentioning that air oxidation of the intermediate selenolate ion **14a** to its diselenide **15** always led to significant extrusion of elemental red selenium during the work-up. The difficulty faced in isolation of the diselenide was overcome by a faster work-up at 0 °C. Attempts to prepare seleninate ester **17** by the direct oxidation of diselenide **15** with *tert*-butyl hydroperoxide yielded the product in poor yield. To improve the yield, **17** was synthesised by the oxidation of allyl selenide **16** which could be easily derived from **15**. The synthesis of allyl derivative **16** was accomplished by the reduction of diselenide **15** with sodium borohydride followed by addition of allyl bromide.

The conversion of allyl (2-(2-hydroxyethoxy)phenyl) selenide **16** to ester **17** with *tert*-butyl hydroperoxide involves a series of oxidation and [2,3] sigmatropic rearrangement steps as proposed by Back and coworkers for similar allyl selenides.[9a] The ester was purified by column chromatography followed by recrystallization. Repeated attempts to crystallize **17** did not yield good quality crystals. Interestingly, **17** always gets associated with one molecule of water which was evident from its FT-IR spectrum that showed a sharp peak for the OH group at 3376 cm^{-1}. Elemental analysis of **17** was consistent with one molecule of water of crystallization. Selenenyl sulfide **18** was generated *in situ* by the



Scheme 2 *Reagents and conditions*: (i) (a) *n*-BuLi, TMEDA, Pentane/−78 to 25 °C, 24 h, (b) Se/THF, 8 h; (ii) [O_2], 17%; (iii) (a) $NaBH_4$, C_2H_5OH, 1 h (b) C_3H_5Br, 6 h, 60%; (iv) TBHP, CH_2Cl_2, 6 h, 41%; (v) TBHP, CH_2Cl_2, 5 h, 20%; (vi) PhSH, 5 min, CH_2Cl_2, (vii) NaH/THF, CH_3I, 61%; (viii) *n*-BuLi, Pentane/−78 to 25 °C, 24 h; (ix) Se/THF, 8 h and then [O_2], 28%; (x) CH_3OCH_2Cl, Et_3N/0 to 25 °C, 24 h, HCl, 54%; (xi) *n*-BuLi, Pentane/−78 to 25 °C, 24 h; (xii) Se/THF, 8 h and then [O_2], 45%; (xiii) CH_3OCH_2Cl, Et_3N/0 to 25 °C, 8 h, HCl, 42%.

reaction of compound **17** with an excess of PhSH. Its formation involves (i) the nucleophilic substitution at selenium by thiol, (ii) addition of thiol across Se═O bond, followed by reductive elimination of disulfide to give selenenic acid. Selenenic acid upon reaction with thiol affords selenenyl sulfide.[9b] Attempted isolation of **18** led to its disproportionation to the corresponding diselenide and disulfide. However, the selenenyl sulfide was stable enough for characterization in solution by ES-MS and ^{77}Se NMR spectroscopy.

The diselenides **20** and **22** with multiple ether groups were synthesized by *ortho*-lithiation of **19** and **21** respectively, followed by selenium insertion and then oxidative workup. Diselenide **23** with a plausible Se···O interaction in a five-membered ring was obtained as a viscous yellow oil by the reaction of bis((2-hydroxymethyl)phenyl) diselenide **3** with chloro(methoxy)methane in triethylamine.

The ^{77}Se NMR signal for diselenide **15** was observed at 323 ppm which is 105 ppm upfield as compared to diselenide **3** which exhibits a strong Se···O interaction.[8c] The large difference in the chemical shift may be due to weak Se···O interaction in **15**. It is well established that weak intramolecular (Se···O/N) interaction leads to a significant downfield shift in the ^{77}Se NMR chemical shift.[5d] The ^{77}Se NMR signal of seleninate ester **17** was observed at 1204 ppm which is close to the ^{77}Se chemical shift (1215 ppm) reported for the six-membered seleninate ester **6**.[9b] However, this value of 1204 ppm for **17** in ^{77}Se-NMR shows an upfield shift of 150 ppm when compared with the five-membered seleninate ester **7**, for which the peak appears at 1353 ppm. Selenenyl sulfide **18** showed an expected chemical shift at 473 ppm due to higher positive charge on selenium as compared to diselenide **15** (See Table S1 in ESI†).

X-ray crystallographic study

Molecular structure of 15. The ORTEP diagram of **15** is shown in Fig. 1. The important bond distances and bond angles along with the calculated values (*vide infra*) are given in Table 1. Compound **15** crystallizes in $I4_1/a$ space group with a

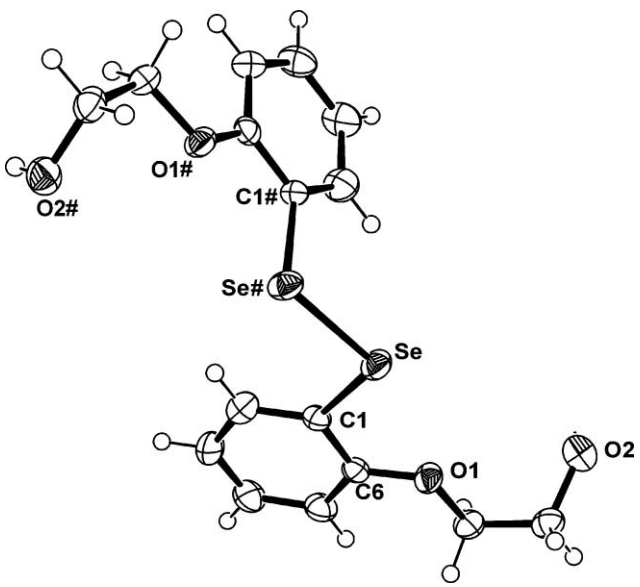


Fig. 1 Molecular structure of **15** at 50% ellipsoidal probability.

Table 1 Comparison of experimentally obtained structural parameters (Å and deg) with those computed at B3LYP/6-31G(d) level for **15**

	Expt	Calcd		Expt	calcd
Se–C1	1.930(3)	1.940	C1–Se–Se#	103.03(9)	101.25
Se–Se#	2.3099(6)	2.326	O1–Se–Se#	157.42	155.54
Se–O1	2.843	2.856			
Se–O2	4.648	4.644			

Table 2 Comparison of experimentally obtained structural parameters (Å and deg) with those computed at B3LYP/6 – 31G(d) level for **22**

	Expt	Calcd		Expt	Calcd
Se1–C1	1.929(7)	1.931	C1–Se1–Se2	102.6(2)	100.62
Se2–C11	1.930(7)	1.931	C11–Se2–Se1	101.9(2)	100.60
Se1–Se2	2.3060(11)	2.372	O1–Se1–Se2	157.62	156.50
Se1–O1	2.817	2.849	O4–Se2–Se1	153.15	156.52
Se2–O4	2.838	2.847			

bent geometry around the selenium atom. The C1–Se–Se#–C1# dihedral angle is –94.01°, indicating a "transoid" conformation for the diselenide. In **15** the Se···O1 distance is 2.843 Å, which is less than sum of the van der Waals radii (3.42 Å).[18] However, Se···O2 distance is 4.648 Å which excludes the possibility of any weak seven-membered intramolecular Se···O interaction. The computed intramolecular Se···O distances for **15** obtained from geometry optimization are in good agreement with the experimental values.

The hydroxyl group in diselenide **15** is involved in intermolecular O–H···O hydrogen bonding with the H···O distance and O–H···O angle being 1.926 Å and 162.7° respectively. This hydrogen bonding is responsible for the formation of cavities encompassing four molecules of diselenide that extends to give a three dimensional network (See Fig S38 in ESI†).

Molecular structure of 22. The molecular structure of **22** is shown in Fig. 2. The important bond distances and bond angles along with the calculated values (*vide infra*) are given in Table 2.

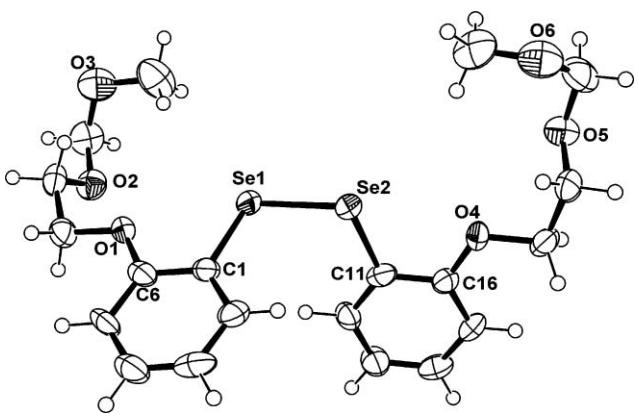


Fig. 2 Molecular structure of **22** at 50% ellipsoidal probability.

The C1–Se1–Se2–C11 dihedral angle is –78.36°, indicating "cisoid" conformation for the diselenide. In **22**, the Se1···O1 and Se2···O4 distances are 2.817 Å and 2.838 Å. However, Se1···O2 and Se1···O3 distances are 4.575 and 5.401 Å respectively, which are higher than their sum of van der Waals radii.

In the absence of crystal structure of **17** due to difficulty in crystallisation, geometry optimization of **17** was performed in order to gain an idea about the structural features of the seleninate ester. The optimized geometry of the ester revealed that the geometry around selenium is pyramidal, with the Se–O3 bond distance being 1.649 Å (Fig. 3). This is close to the 1.630 Å reported for the five-membered ester (**7**).[8c] The computed ^{77}Se NMR chemical shift for **17** is 1203 ppm and is in excellent agreement with the experimental value of 1204 ppm (See Table S1 in ESI†).

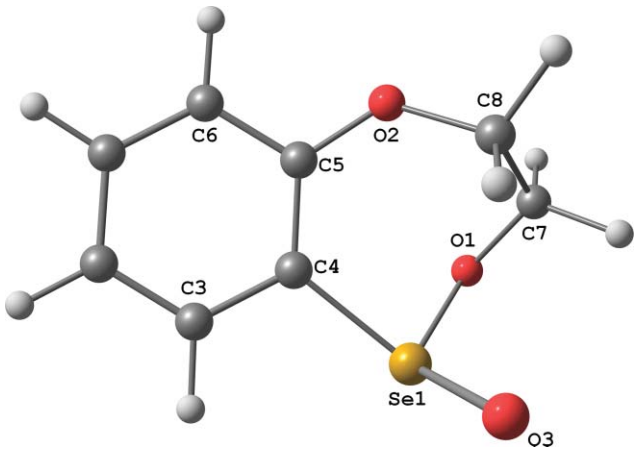


Fig. 3 Optimized geometry of **17**.

Intramolecular Se···O interaction in the synthesised diselenides

Se···O interaction in the synthesized diselenides has been quantified using density functional theory in Gaussian03.[19] The second order perturbation energies (at B3LYP/6-311+g** level) obtained from NBO analyses[20] for Se···O (phenoxy/hydroxy/alkoxy) interaction in all the compounds (except **3** and **23**) were found to be of the order of 2 kcal mol^{-1}. Diselenides **3** and **23** have orbital interaction energy values of 4.56 and 3.88 kcal mol^{-1} respectively (See Table S1 in ESI†). AIM analysis[21] showed the absence of bond critical points in all the compounds with plausible four-membered Se···O rings.‡ The analysis substantiated our earlier observation on the absence of a weak intramolecular interaction in four-membered Te···O system.[8c] However, there exists a distinct bond critical point (bcp) for **3** and **23** involving a five-membered Se···O ring with electron density (ρ) value of 0.018 a.u. for **3** and 0.021a.u for **23** (See Figure S46 in ESI†).

‡ It is important to note that the short contacts observed for Se–O interaction in plausible four-membered ring are a characteristic feature for 1,2-disubsituted phenyl systems. We carried out geometry optimization of a series of 1,2-disubstituted phenyl systems and found that the distance between the two atoms present in the *ortho* position is less than the sum of their van der Waals radii in all the cases. Therefore, the short distance between any atom X (X = C, N, O, F, P, S, Cl, Se, Br) and O in 1,2-position in the phenyl ring may be due to the geometrical position. Therefore, the short distance between Se and O in crystal structures of **15** and **22** does not necessarily imply Se–O intramolecular interaction. See Table S19 in ESI for comparision.†

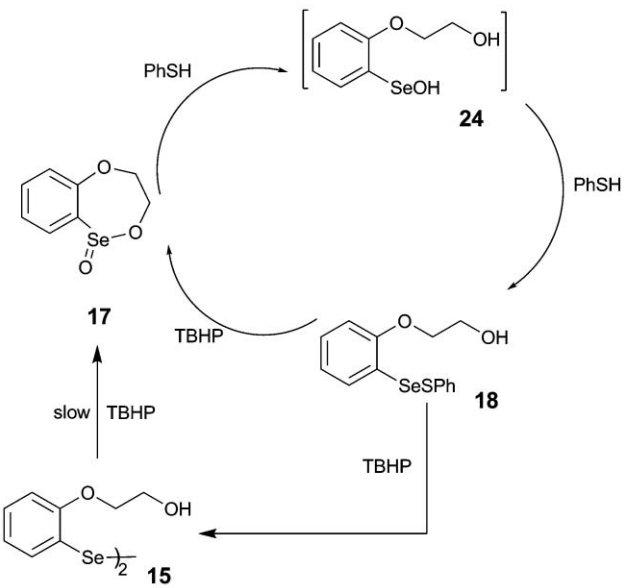
Table 3 Initial reduction rate (V_o) of glutathione peroxidase-like activity of selenium compounds by coupled-reductase assay at 27 °C

Entry	catalyst	Vo (μM min^{-1})
1	None	4.3 ± 0.4
2	**1**	106.4 ± 3.8
3	**3**	180.1 ± 8.3
4	**7**	451.5 ± 5.6
5	**15**	206.6 ± 3.6
6	**17**	421.5 ± 6.0
7	**20**	113.6 ± 3.4
8	**22**	123.3 ± 2.8
9	**23**	134.6 ± 3.3

GPx-like activity of the seleninate ester 17 and its catalytic cycle

The GPx-like antioxidant activities of the organoselenium compounds were determined by the coupled reductase assay (Table 3). It was found that the antioxidant activity of the ester **17** is at a par with the five membered seleninate ester (**7**) but much higher than diselenide **15** and other ether-containing diselenides. Interestingly, both **15** and **3** have similar GPx-like activity in the coupled-reductase assay. In comparison to the well known GPx mimic ebselen, slightly higher values of initial rates were observed for the diselenides **20** and **23**. To rule out the possibility that the reaction rate becomes considerably slower after the initial stages of the catalytic cycle or becomes zero, the assay was followed spectrophotometrically for a longer time (10000 s) for seleninate ester **17** at 10 μM concentration. It was observed that the amount of H_2O_2 taken (200 μM) was almost completely consumed in 3000 s. (See Fig S53 and Fig S54 in ESI.†).

The antioxidant activity of five-membered seleninate esters **5** and **7** is well studied and their catalytic mechanism involves the formation of selenenic acid and thioseleninate as intermediates.[8b,9b] To understand the detailed mechanism for the GPx-like activity of the seleninate ester **17**, we used ^{77}Se NMR spectroscopy to identify the possible intermediates. The reactions were followed by observing ^{77}Se NMR signals for 0–10 min after the addition of reactants. The signals, generally, appeared within a minute and did not change positions with the passage of time. The reaction of **17** with one equivalent of PhSH immediately afforded the selenenyl sulfide **18** whose ^{77}Se NMR signal appeared at 473 ppm along with the signal of **17**. This indicates that the initial reaction of **17** with thiol is very fast. When one more equivalent of PhSH was added to this reaction mixture, the signal due to the seleninate ester **17** disappeared completely and the signal for **18** got intensified. The signal due to selenenic acid **24** was not be observed in the ^{77}Se-NMR spectrum which may be due to the fast conversion of **17** to **18**. When this reaction mixture was treated with two equivalents of *tert*-butyl hydroperoxide, the peak due to seleninate ester **17** reappeared. On further addition of an excess of *tert*-butyl hydroperoxide (4 equivalents), the peaks due to seleninate ester **17**, selenenyl sulfide **18** along with diselenide **15** were observed. The formation of diselenide **15** indicated the disproportionation of selenenyl sulfide **18** in the presence of excess of *tert*-butyl hydroperoxide. This may also be an alternate pathway in the regeneration of **17** from **18** (Scheme 3). However, independent reaction of **15** with TBHP suggests that the direct formation of the seleninate ester from the diselenide is a rather slow process (*vide supra*). The slow reaction of diselenide **15** with *tert*-butyl



Scheme 3 GPx catalytic cycle of seleninate ester **17**.

hydroperoxide to form the seleninate ester **17** is responsible for the lower antioxidant activity of the diselenide **15** as compared to that of the seleninate ester **17**.

Conclusions

In conclusion, we have synthesized a series of diorganodiselenides with alkoxy group *ortho* to selenium. Diselenide **15** gave access to novel seven-membered seleninate ester **17**, which showed good GPx-like antioxidant activity. X-ray structures exclude the possibility of plausible seven-membered or nine-membered Se···O interaction in the synthesised compounds.

Experimental

General methods

Compounds **3**[8c] and **19**[22] were prepared by reported methods. All reactions were carried out under nitrogen or argon atmosphere using standard vacuum-line techniques. Solvents were purified by standard procedures and were freshly distilled prior to use. Melting points were recorded in capillary tubes. ^{1}H (399.88 MHz), ^{13}C (100.56 MHz) and ^{77}Se (57.26 MHz) NMR spectra were recorded on a Varian 400 MHz and 300 MHz spectrometers at room temperature. Chemical shifts cited were referenced to TMS (^{1}H, ^{13}C) as internal and Me_2Se (^{77}Se) as external standard. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer with KBr pellets or liquid film. Elemental analyses were performed on a Thermo Quest FLASH 1112 series (CHNS) elemental analyzer. The Electro-spray mass spectra (ES-MS) were performed in a Q-Tof micro (YA-105) mass spectrometer. Column chromatography was performed with silica gel (60–120 mesh).

Synthesis of bis[2-(2-hydroxyethoxy)phenyl] diselenide (15). To a solution of 2-phenoxyethanol (3.0 g, 21.7 mmol) in pentane (50 mL), taken in a three-necked (250 mL) flask fitted with rubber septum and a nitrogen inlet, was added dropwise *n*-BuLi (30 mL, 48 mmol) at –78 °C over a period of 10 min. The reaction mixture was allowed to warm up to the room temperature and stirred for 24 h. Pentane was removed from the reaction mixture with a syringe and 30 mL of dry tetrahydrofuran was added to the lithiated product. To this, selenium (1.7 g, 21.5 mmol) powder was added at 0 °C under a brisk flow of nitrogen and the solution was stirred for 8 h at room temperature. The reaction mixture was poured into the beaker containing 100 mL of 5% sodium bicarbonate solution at 0 °C. The organic layer and the ether extracts from the aqueous layer were combined and dried over sodium sulfate. Solvent was evaporated *in vacuo* to afford 1.2 g of the crude product which was recrystallized from tetrahydrofuran–hexane (0.81 g, 17% yield) m.p. 163–165 °C; IR (KBr) 3267, 2925, 1458, 1439, 1234, 749 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (dd, J = 7.6, 1.5 Hz, 2H), 7.22 (m, 2H), 7.00 (dd, J = 8.2, 0.9 Hz, 2H), 6.90 (td, J = 7.6, 0.9 Hz, 2H), 4.95 (t, J = 5.2 Hz, 2H), 4.11 (t, J = 4.9 Hz, 4H), 3.77 (q, J = 5.2 Hz, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 155.9, 129.4, 128.6, 122.1, 117.7, 112.2, 70.7, 59.6; ^{77}Se NMR (300 MHz, DMSO-d_6) δ 323; ES-MS, m/z (relative intensity) 456.9 (28, $[M + Na]^+$); exact mass calcd for $C_{16}H_{18}O_4Se_2Na$ ($M + Na^+$) 456.9433, found 456.9456.

Allyl (2-(2-hydroxyethoxy)phenyl) selenide (16). Sodium borohydride (0.13 g, 3.44 mmol) was added portionwise to an ice-cold suspension of diselenide **15** (0.3 g, 0.69 mmol) in 25 mL of absolute ethanol. After completion of addition, the ice bath was removed and the mixture was stirred at room temperature for 1 h. Allyl bromide (0.3 mL, 3.47 mmol) was added to the colorless reaction mixture and stirring was continued for additional 6 h. The reaction mixture was poured into the 100 mL ether, washed with a saturated solution of NH_4Cl, NaCl and with water. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. The residue was chromatographed (elution with 10% ethyl acetate–petroleum ether) to afford a colorless liquid (0.21 g, 60% yield). IR (neat) 3412, 2930, 1578, 1474, 1242, 1059, 1035, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.6, 1.5 Hz, 1H), 7.19–7.24 (m, 1H), 6.93 (td, J = 7.6, 1.2 Hz, 1H), 6.87 (dd, J = 8.3, 1.2 Hz, 1H), 5.90–5.98 (m, 1H), 4.97–5.12 (m, 2H), 4.15–4.17 (m, 2H), 3.94 (q, J = 4.0 Hz, 2H), 3.55 (dt, J = 7.6, 1.3 Hz, 2H), 2.51 (t, J = 6.1 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.2, 134.3, 132.2, 128.3, 122.3, 120.6, 117.4, 113.0, 71.1, 61.4, 28.4; ^{77}Se NMR (300 MHz, $CDCl_3$) δ 255; ES-MS, m/z (relative intensity) 258.9 (100, M^+); exact mass calcd for $C_{11}H_{15}O_2Se$ (MH^+) 259.0237, found 259.0226.

Seleninate ester (17). To a solution of allyl selenide **16** (0.15 g, 0.58 mmol) in 20 mL dichloromethane was added *tert*-butyl hydroperoxide (0.43 mL of a 70% aqueous solution, 3.36 mmol) and this was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed (elution with 10% methanol–ethyl acetate) to yield **17** as a white powder. It was then recrystallized from 1 : 1 dichloromethane–petroleum ether mixture. (0.06 g, 41% yield). m.p 83–85 °C. IR (KBr) 3376, 2925, 1584, 1471, 1453, 1279, 1072, 1048, 789, 685 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, J = 7.7 Hz, 1H), 7.50–7.56 (m, 1H), 7.16–7.23 (m, 2H), 4.13 (t, J = 4.6 Hz, 2H), 3.70 (t, J = 4.9 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 156.9, 136.6, 133.4, 124.9, 121.0, 113.3, 70.8, 59.3; ^{77}Se NMR (300 MHz, DMSO-d_6) δ 1204; ES-MS, m/z (relative intensity) 232.9 (100, M^+), exact mass calcd for $C_8H_8O_3Se$ (M^+) 232.9717, found 232.9727.

Selenenyl sulfide (18). Thiophenol (0.04 mL) was added to a solution of seleninate ester **17** (0.021 g, 0.08 mmol) in 2 mL dichloromethane and stirred for 5 min. The colorless solution changed immediately to light yellow color. Solvent was removed *in vacuo* to get a light yellow residue which could not be purified and was characterised as such. IR, (neat), 3422, 2926, 2876, 1572, 1056, 748.cm^{-1}; ^{77}Se NMR (300 MHz, $CDCl_3$) δ 473; ES-MS, *m/z* (relative intensity); 326.9 (60, M^+), 348.9 (20, $[M + Na]^+$)

Bis(2-(2-methoxyethoxy)phenyl) diselenide (20). To a solution of (2-methoxyethoxy)benzene **19** (0.98 g, 6.44 mmol) in pentane (25 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (4.1 mL, 6.6 mmol) at −78 °C. The reaction mixture was allowed to warm up slowly to the room temperature and stirred for additional 24 h. The white lithiated product obtained was allowed to settle down and the supernatant solvent was removed from this mixture by cannula. The reaction mixture was cooled to 0 °C and tetrahydrofuran (20 mL) was added, followed by addition of Se powder (0.51 g, 6.44 mmol) under a brisk flow of nitrogen gas. The stirring was continued for additional 8 h. After this, oxygen was bubbled through the solution for 10 min, and the resulting mixture was poured into a beaker containing cold aqueous $NaHCO_3$ solution. The oily product was extracted with ethyl acetate and then washed with water. The organic phase was separated, dried over Na_2SO_4, and filtered. The compound was purified by chromatography (elution with 5% ethyl acetate–petroleum ether) to give **20** as a viscous yellow liquid (0.41 g, 28% yield). IR (neat) 2927, 1575, 1469, 1237, 1125, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.9, 1.5 Hz, 2H), 7.18 (td, J = 7.6, 1.5 Hz, 2H), 6.82–6.89 (m, 4H), 4.22 (t, J = 4.8 Hz, 4H), 3.81 (t, J = 4.5 Hz, 4H), 3.50 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.2, 130.6, 128.1, 122.5, 119.4, 111.8, 71.1, 68.9, 59.7; ^{77}Se NMR (300 MHz, $CDCl_3$) δ 327; ES-MS, *m/z* (relative intensity) 461.8 (100, M^+); exact mass calcd for $C_{18}H_{22}O_4Se_2$ (M^+) 461.9849, found 461.9837.

(2-(Methoxymethoxy)ethoxy)benzene (21). To a solution of 2-phenoxyethanol (3.00 g, 21.7 mmol) in triethylamine (20 ml) at 0 °C, was added dropwise chloro(methoxy)methane (10 mL, 132 mmol) for a period of 45 min. The reaction mixture was allowed to warm up slowly to the room temperature and stirred for 24 h. The reaction was quenched with 5% aqueous ammonia solution, stirred for 15 min and carefully acidified with 1 M HCl. It was then extracted with diethyl ether, the solvent was removed *in vacuo* and the residue purified by column chromatography (elution with 10% ethyl acetate–petroleum ether) to afford **21** as a colorless liquid (2.12 g, 54% yield). IR (neat), 2934, 1601, 1498, 1248, 1042, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.27 (t, J = 8.0 Hz, 2H), 6.92–6.97 (m, 3H), 4.72 (s, 2H), 4.14 (t, J = 4.9 Hz, 2H), 3.90 (t, J = 4.6 Hz, 2H), 3.40 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.8, 129.5, 120.9, 114.7, 96.6, 67.2, 66.1, 55.3; ES-MS, *m/z* (relative intensity), 205.0 (100, $[M + Na]^+$), 183.1 (42, $[M + 1]^+$),151.1 (22, $[M - OCH_3]^+$); exact mass calcd for $C_{10}H_{14}O_3$ ($M + Na^+$) 205.0841, found 205.0835.

1,2-Bis(2-(2-(methoxymethoxy)ethoxy)phenyl) diselenide (22). To a solution of compound **21** (0.83 g, 4.56 mmol) in pentane (25 mL) was added dropwise 1.6 M hexane solution of *n*-BuLi (3 mL, 4.8 mmol) at −78 °C. The reaction mixture was warmed up slowly to the room temperature and stirred for an additional 24 h. A white lithiated product precipitated which was allowed to settle down. The supernatant solvent was removed from the mixture by cannula and freshly dried tetrahydrofuran (20 mL) was added. The reaction mixture was cooled to 0 °C and Se powder (0.36 g, 4.6 mmol) was added under a brisk flow of nitrogen. It was further stirred for 8 h. Oxygen was bubbled through the solution for 10 min, and the resulting mixture was poured into a beaker containing cold aqueous $NaHCO_3$ solution. The oily product was extracted with diethyl ether and then washed with water. The organic phase was separated, dried over Na_2SO_4, and filtered. The compound was purified by chromatography (elution with 20% ethyl acetate–petroleum ether) to yield **22** as a viscous yellow liquid (0.53 g, 45% yield). Recrystallization from dichloromethane–hexane mixture yielded yellow crystals: mp 50–51 °C; IR (KBr) 2926, 2879, 1572, 1026, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.0, 1.5 Hz, 2H), 7.16–7.20 (m, 2H), 6.87 (td, J = 7.3, 1.2 Hz, 2H), 6.82 (dd, J = 7.9, 0.9 Hz, 2H), 4.78 (s, 4H), 4.25 (t, J = 4.5 Hz, 4H), 3.95 (t, J = 4.9 Hz, 4H), 3.43 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 156.1, 130.5, 128.1, 122.4, 119.2, 111.5, 96.9, 68.5, 66.0, 55.5; ^{77}Se NMR (300 MHz, $CDCl_3$) δ 328; ES-MS, (*m/z*, relative intensity), 544.9 (100, $[M + Na]^+$); exact mass calcd for $C_{20}H_{26}O_6Se_2Na$ ($M + Na^+$) 544.9945, found 544.9946.

Bis((methoxymethoxy)benzylether) diselenide (23). Bis((2-hydroxymethyl)phenyl) diselenide **3** (1.00 g, 2.68 mmol) was dissolved in 20 mL of triethyl amine, cooled to 0 °C and an excess of chloro(methoxy)methane (5 mL) was slowly added. The mixture was allowed to warm up slowly to the room temperature and stirred for 8 h. The reaction was quenched with 5% aqueous ammonia solution, stirred for 15 min and carefully acidified with 2 N HCl. After extraction with diethyl ether, the solvent was removed *in vacuo* and the remaining yellow oil purified by chromatography (elution with 10% ethyl acetate–petroleum ether) to afford a yellow oil (0.52 g, 42% yield). IR (neat) 2926, 2879, 1572, 1026, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.3, 1.2 Hz, 2H), 7.34 (dd, J = 7.3, 1.5 Hz, 2H) 7.18–7.24 (m, 4H), 4.70 (s, 4H), 4.68 (s, 4H), 3.42 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.3, 133.4, 131.7, 129.1, 128.9, 127.9, 96.0, 69.6, 55.9; ^{77}Se NMR (300 MHz, $CDCl_3$) δ 426; ES-MS, *m/z* (relative intensity), 338.9 (45, $[M - (C_2H_5O_2)_2]^+$, 400.9 (12, $[M - C_2H_5O_2]^+$).

X-ray crystallography

The diffraction measurements for compounds **15** and **22** were performed at room temperature (Mo-Kα radiation, λ = 0.7107 Å) on Oxford Diffraction Gemini and STOE IPDS Diffractometer respectively. The structure solutions were achieved by using direct methods as implemented in SHELXS-97.[23a] The structures were refined by full least-squares methods using SHELXL-97.[23b]

Computational details

All geometries were optimized using analytical gradient techniques implemented in the Gaussian03 suite of quantum chemical program.[19] Geometries were fully optimized at the B3LYP level of theory with use of the 6-31G(d) basis sets. All stationary points were characterized as minima by evaluating Hessian indices on respective potential energy surfaces. The NMR calculations were performed at the B3LYP/6-311+G(d,p) level on B3LYP/6-31G(d) level optimized geometries by the GIAO method. Orbital

interactions were analyzed by the natural bond orbital (NBO) method at the B3LYP/6-311+G(d,p) level, and charges were calculated by natural population analysis (NPA). The nature of weak intramolecular Se···O interactions was further analyzed by inspecting properties of the bond critical points between selenium and heteroatoms within Bader's Atoms in Molecule (AIM) framework, using the AIM2000 package[24] at the B3LYP/6-311+G(d,p) level.

Coupled Reductase Assay

The GPx-like activity of **15**, **17**, **20**, **22** and **23** were measured spectrophotometrically according to the literature method[5a] using ebselen **1** as the standard. The catalytic reaction was carried out at 27 °C in 1 mL of the solution containing 100 mM potassium phosphate buffer, pH 7.5, 1 mM EDTA, 2 mM GSH, 0.4 mM of NADPH, 1.6 unit of glutathione reductase, 80 μM of catalyst and 1.6 mM of H_2O_2. The activity was followed by the decrease of NADPH absorption at 340 nm (eqn 1–3). Each initial rate for all the compounds was measured at least four times and calculated from the first 5–10% of the reaction by using 6.22×10^3 $M^{-1}cm^{-1}$ as the molar extinction coefficient for NADPH.

$$2GSH + H_2O_2 \xrightarrow[\text{Peroxidase}]{\text{GSH}} GSSG + 2H_2O \quad (1)$$

$$GSSG + NADPH + H^+ \xrightarrow[\text{reductase}]{\text{GSH}} 2GSH + NADP^+ \quad (2)$$

$$\overline{NADPH + H_2O_2 + H^+ \longrightarrow NADP^+ + 2H_2O} \quad (3)$$

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