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Enhanced Glutathione Peroxidase Activity of Water-Soluble and Polyethylene Glycol-Supported Selenides, Related Spirodioxyselenuranes, and Pincer Selenuranes

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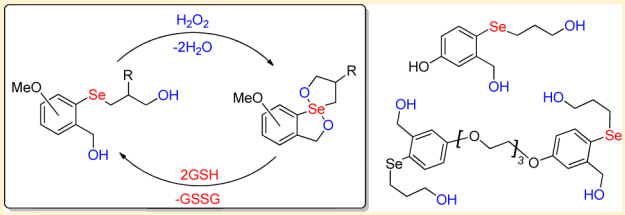
Supporting Information

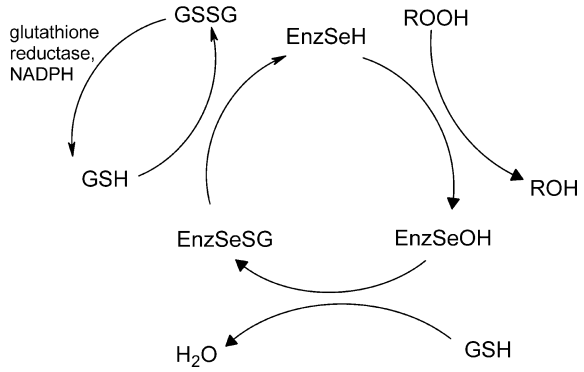
ABSTRACT: Diaryl selenides containing *o*-hydroxymethylene substituents function as peroxide-destroying mimetics of the antioxidant selenoenzyme glutathione peroxidase (GPx), via oxidation to the corresponding spirodioxyselenuranes with hydrogen peroxide and subsequent reduction back to the original selenides with glutathione. Parent selenides with 3-hydroxypropyl or 2,3-dihydroxypropyl groups produced the novel compounds **10** and **11**, respectively, with greatly improved aqueous solubility and catalytic activity. The phenolic derivative **28** displayed similarly ameliorated properties and also modest radical-inhibiting antioxidant activity, as evidenced by an assay based on phenolic hydrogen atom transfer to the stable free radical DPPH. In contrast, several selenides that afford pincer selenuranes (e.g., **20** and **21**) instead of spiroselenuranes upon oxidation showed inferior catalytic activity. Several selenide analogues were attached to polyethylene glycol (PEG) oligomers, as PEG substituents can improve water solubility and bioavailability, while retarding clearance. Again, the PEG derivatives afforded remarkable activity when oxidation generated spirodioxyselenuranes and diminished activity when pincer compounds were produced. Several such compounds proved to be ca. 10- to 100-fold catalytically superior to the diaryl selenides and their spirodioxyselenurane counterparts investigated previously. Finally, an NMR-based assay employing glutathione in D_2O was designed to accommodate the faster reacting water-soluble mimetics and to more closely duplicate in vivo conditions.



INTRODUCTION

The formation of harmful peroxide byproducts and other reactive oxygen species (ROS) is a natural consequence of aerobic metabolism.[1] The one-electron reduction of dioxygen in the mitochondria of cells generates superoxide radical anion, which is converted into hydrogen peroxide by superoxide dismutase (SOD). Ferrous-mediated reduction of hydrogen peroxide then produces highly reactive hydroxyl radicals. Furthermore, oxidation of lipids results in the formation of the corresponding lipid hydroperoxides. Both hydrogen peroxide and lipid hydroperoxides contribute to oxidative stress, which in turn is implicated in a variety of diseases and degenerative conditions.[1,2] Fortunately, homeostasis of ROS is maintained in living organisms by both exogenous and endogenous antioxidants that catalyze the destruction of peroxides or inhibit peroxide-initiated radical chain reactions. The exogenous species include, for example, α-tocopherol, ascorbic acid, anthocyanins, and other plant pigments as well as a wide range of phenolic compounds found in various foods and beverages. The selenoenzyme glutathione peroxidase (GPx)[3] is an endogenous antioxidant that catalyzes the reduction of hydrogen peroxide and lipid peroxides by the tripeptide thiol glutathione. While several isozymes of GPx are known,[4] the most common forms are tetrameric structures,[5] in which the redox properties of each subunit can be attributed to the presence of a selenocysteine residue. The catalytic cycle of this process[6] is shown in Scheme 1, where the selenol group (EnzSeH) of each selenocysteine residue reduces the peroxide and generates the corresponding selenenic acid (EnzSeOH). The latter is then reduced by 2 equiv of glutathione (GSH) via the selenenyl sulfide (EnzSeSG) to restore the original selenocysteine moiety along with the formation of glutathione

Scheme 1



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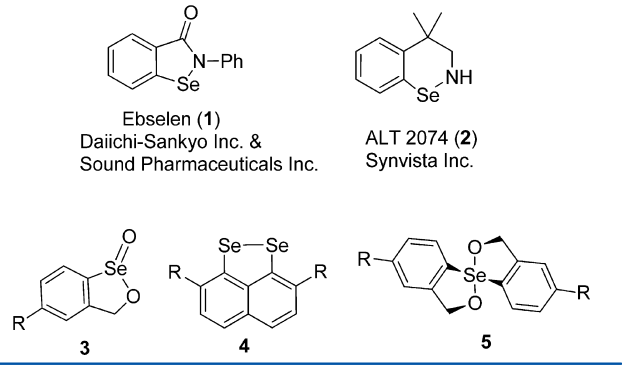
disulfide (GSSG). Finally, the glutathione reductase/NADPH-mediated conversion of the disulfide back to its thiol completes the process.

Certain diseases and degenerative conditions are accompanied by particularly high levels of peroxide formation and accompanying oxidative stress that overwhelm the protective effects of GPx. Thus, ischemic reperfusion of heart attack and stroke patients often results in cardiovascular and neurological injury from the destructive effects of peroxides and other ROS released by neutrophils during the reperfusion process.[7] A variety of small-molecule selenium compounds has been investigated as possible redox catalysts designed to emulate GPx and afford additional protection to such patients.[8] Most notably, ebselen (**1**),[9] a compound that was first reported nearly a century ago,[10] was investigated by Daiichi-Sankyo Inc. in Phase 3 clinical trials for its cardiovascular and neuroprotective effects.[11] More recently, Sound Pharmaceuticals Inc. has completed a Phase 2 clinical trial (NCT01444846) of SPI-1005 (ebselen) for the treatment of noise-induced hearing loss and has begun an investigation of its therapeutic application to bipolar disorder, where in each case oxidative stress has been implicated.[12] Moreover, several investigations have been reported of the antioxidant properties of ALT 2074 (**2**), which was the subject of a trial by Synvista Inc. for the treatment of plaque psoriasis.[13]

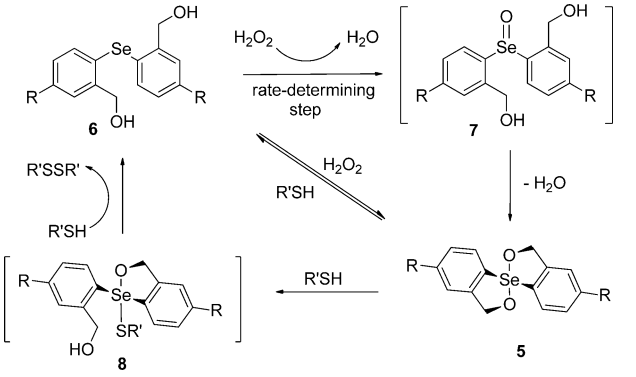
Ebselen in particular has been widely studied for its catalytic redox properties.[9] However, its GPx-like catalytic activity is only moderate, and its very low aqueous solubility makes intravenous administration challenging. On the other hand, despite selenosis concerns associated with many other types of selenium compounds, ebselen has the advantage of proven lack of toxicity from its clinical trials.[14] Relatively low toxicity is typically associated with arylseleno derivatives[15] that are presumably more resistant than aliphatic analogues toward metabolic conversion into more toxic inorganic species such as selenite. Thus, there remains a need for the discovery of novel types of small-molecule arylseleno GPx mimetics with improved catalytic activity, enhanced water-solubility, and ease of synthesis.

Our laboratory has investigated three classes of GPx mimetics to date: cyclic seleninate esters **3**,[16,17] conformationally restricted diselenides **4**,[18] and spirodioxyselenuranes **5**.[16c,d,19] Certain seleninate esters show strong GPx-like catalytic activity, which is however compromised at increasing thiol:peroxide ratios through the formation of selenenyl sulfides that display relatively poor activity, thus creating a competing deactivation pathway. Furthermore, the seleninate esters **3** catalyze the further oxidation of disulfides to thiolsulfinates[20] which could be detrimental in vivo if essential native protein and peptide disulfides are similarly affected. Compounds **3** also catalyze the oxidation of a number of other substrates (e.g., alkenes to epoxides, sulfides to sulfoxides, and enamines to α-hydroxyketones).[21] The diselenides **4** have been less thoroughly investigated as GPx mimetics, but moderate peroxide-destroying catalytic activity was observed.[18] Finally, the spirodioxyselenuranes **5** showed generally high catalytic activity in the reduction of peroxides with thiols, but a much lower proclivity toward the oxidation of the product disulfides or other substrates than in the case of the seleninate esters **3**, and they do not produce the more refractory selenenyl sulfide derivatives.

The spirodioxyselenuranes **5** function as catalysts via the catalytic cycle shown in Scheme 2. We have established that the



Scheme 2



rate-determining step is the oxidation of the selenides **6** to the selenoxides **7**, followed by rapid cyclization and dehydration to afford the spiro compounds **5**. Further reaction with 2 equiv of thiol then regenerates the selenide, presumably via reductive elimination of the corresponding disulfide from the intermediate **8**.[19] As expected, electron-donating substituents enhance the rate of the oxidation step through mesomeric stabilization of the positive charge on the selenium atom, which increases from Se(II) to Se(IV) during the conversion of **6** to **7**.[16d,19c] The cyclic seleninate esters **3** and conformationally restricted diselenides **4** represent the oxidized and reduced states in their respective catalytic cycles and are usually introduced in those forms. In contrast, either oxidation state (spirodioxyselenurane **5** or selenide **6**) can be utilized for the process shown in Scheme 2, as both **5** and **6** are stable and easily handled compounds. However, if it is assumed that there are typically higher concentrations of glutathione and other thiols than of peroxides within living organisms, then it follows that the catalyst would exist primarily in its selenide form in vivo. We now report the preparation and in vitro assay of a series of more water-soluble selenide analogues of **6** containing one aryl and one aliphatic substituent, extra hydroxyl groups on the aliphatic moiety, and/or their polyethylene glycol (PEG) derivatives, along with several other types of selenuranes not previously investigated.

RESULTS AND DISCUSSION

In order to increase the aqueous solubility of selenides **6**, we prepared a series of analogues in which one of the aryl substituents was replaced by the 3-hydroxypropyl group. The other aromatic arylseleno moiety was retained in order to preserve the greater stability and lower toxicity expected of aryl selenides. Since electron-donating groups *para* to selenium improved catalytic activity in previous studies[16d] and had varied effects at other positions,[19c] we prepared the mono-, di-, and

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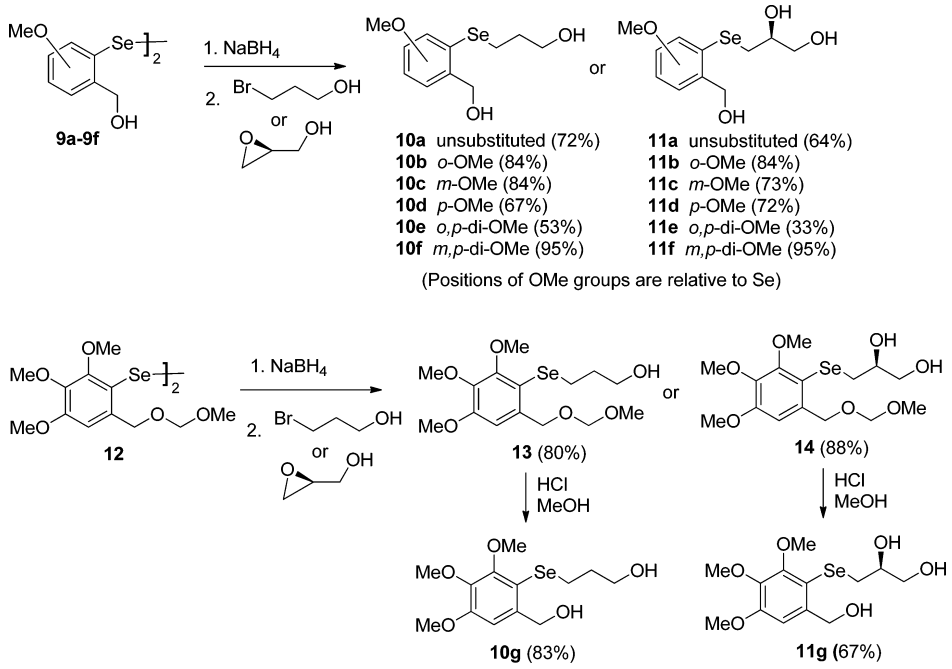
Scheme 3

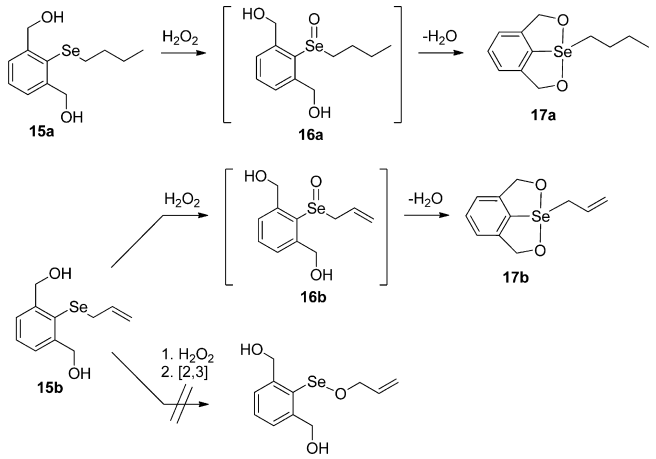


trimethoxyaryl selenide derivatives **10b**–**10g**, along with the unsubstituted parent selenide **10a** for comparison (Scheme 3). The required precursor diselenides **9a**,[16c,17a] **9b**,[16f] **9c**,[16f] **9d**,[16d] **9e**,[16f] and **9f**[16f] were obtained as reported previously, as was the methoxymethyl (MOM)-protected diselenide **12**.[16f] Diselenides **9a**–**9f** and **12** were then reduced with sodium borohydride and treated with 3-bromopropanol to afford **10a**–**10f** as well as **13**. Deprotection of the latter provided selenide **10g**. These compounds all displayed modest aqueous solubility, but typically required the presence of ca. 5% ethanol to attain useful concentrations. In order to improve water solubility further, a parallel series of 2,3-dihydroxypropyl compounds **11a**–**11g** was prepared by employing (*S*)-glycidol in place of 3-bromopropanol (Scheme 3). The presence of the additional free hydroxyl group on the propyl substituent in compounds **11** resulted in improved solubility, as expected. All of the selenides **10** and **11** reported here are novel compounds.

We recently reported[16e] the preparation and further oxidation with hydrogen peroxide of selenides **15a**,**b**, thus affording the corresponding pincer selenuranes **17a**,**b** via initially formed selenoxides **16a**,**b**.[22] The absence of products derived from the [2,3]sigmatropic rearrangement of **16b** was noteworthy, as such rearrangements typically occur rapidly. The preferential formation of **17b** indicates that the dehydrative cyclization of the selenoxide to the pincer compound is exceptionally facile (Scheme 4). In order to improve the water-solubility of these selenides, we prepared the novel 3-hydroxypropyl analogue **20** from the easily obtained diselenide **18**[16e] via the protected selenide **19**. As expected, oxidation with hydrogen peroxide produced the corresponding pincer selenurane **21**. The formation of the alternative spiroselenurane oxidation/cyclization product **22** was ruled out by the NMR spectra of the product, which were consistent with the more symmetrical structure **21** (Scheme 5).

The phenolic derivative **28** was synthesized via the diselenide **26**, as shown in Scheme 6. The selenide **28** is of special interest as it has the potential to fill a dual role as an antioxidant not only by catalyzing the reduction of peroxides with thiols but

Scheme 4



also by serving as a radical inhibitor through hydrogen atom donation from the phenolic moiety to chain-propagating radicals in lipid peroxidation and other radical-mediated processes.[23] By analogy, many phenols, such as α-tocopherol, possess radical-inhibiting properties, while various phenolic selenides and tellurides have been previously investigated in this context by Engman et al.[24]

The poor bioavailability due to high clearance rates, poor water-solubility, or untargeted distributions of certain small-molecule drugs can sometimes be mitigated by attachment to a suitable support. The use of PEG polymers or oligomers has proven particularly effective for this purpose, as PEG derivatives tend to be water-soluble, nontoxic and nonimmunogenic.[25−27] Thus, in order to further refine the properties of the above GPx mimetics, their attachment to PEG supports was investigated. In order to produce compounds with uniform molecular weights, we chose oligomers with only three or four PEG units, instead of higher polymers of PEG. The preparation of these compounds is illustrated in Scheme 7. Thus, diselenide **18** was reduced and alkylated with the monotosylated PEG reagents

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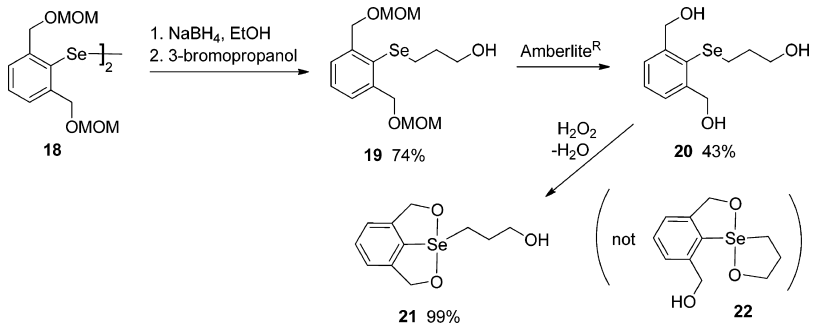
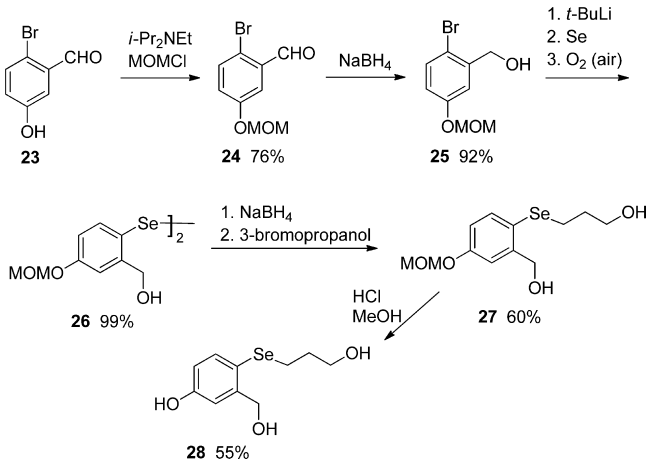
Scheme 5



Scheme 6



39a and **39b** to afford PEGylated selenides **30a** and **30b**, respectively, after deprotection. Similar treatment of **18** with the ditosylated PEG reagents **40a** and **40b** produced the dimeric species **32a** and **32b**. Furthermore, dibenzoylation of the free alcohol functionalities of **27**, followed by deprotection of the phenolic hydroxyl group provided selenide **34**. PEGylation followed by saponification then furnished the PEGylated compound **36**. The conversion of **34** to the dimeric product **37** was achieved similarly by employing the bistosylate **40a** and subsequent saponification provided **38**. An attempt was also made to prepare **38** directly from the unprotected trihydroxy precursor **28** by exploiting the greater acidity of its phenolic moiety relative to the aliphatic alcohols. However, selective formation and alkylation of the phenoxide of **28** by treatment with potassium carbonate and bistosylate **40a** afforded at best only 16% of the desired product, even in the presence of 18-crown-6.

With the desired suite of water-soluble selenides in hand,[28] the next stage was their evaluation as GPx mimetics. In previous work,[16,18−20,29] we had employed an HPLC-based assay that measured the rate of disulfide formation when hydrogen peroxide or *t*-butyl hydroperoxide were reduced with benzyl thiol in the presence of catalytic amounts of the selenium compound. This thiol was chosen because it possesses both an aromatic chromophore for UV detection and a well-separated methylene NMR signal to aid in identifying products and intermediates. Furthermore, the aliphatic benzyl thiol more closely resembles glutathione than do aromatic thiols such as benzenethiol, due to the considerably greater acidity of the latter and the greater ease of oxidation of the resulting thiolate anion compared to its conjugate acid. The assay was performed in dichloromethane-methanol (95:5) because this solvent was capable of dissolving all of our previously investigated catalysts, which were generally highly insoluble in water. In order to compare the catalytic activity of various types of GPx mimetics, we typically measured the time ($t_{1/2}$) required for oxidation of 50% of the thiol. The use of rate constants for this purpose was avoided because of kinetic irregularities resulting from anomalously rapid initial reaction rates when the catalysts were introduced in their oxidized form in all three classes of compounds **3**−**5**. This can be attributed to the rapid reduction of the oxidized catalysts with the thiol accompanied by disulfide formation, compared to the considerably slower and rate-limiting subsequent oxidation of Se(II) to Se(IV). Moreover, in the case of seleninates **3**, the accumulation of less reactive selenenyl sulfide byproducts in the later stages of the catalytic cycle suppressed the reaction rate considerably. However, it should be noted that the thiol (benzyl thiol) and solvent (dichloromethane-methanol) employed in this assay are poorly representative of in vivo conditions.

In order to circumvent these limitations and to take advantage of the aqueous solubility of the present compounds, we devised a ^{1}H NMR-based assay in D_2O for the present work.[30] This employed the reduction of hydrogen peroxide with glutathione (GSH) with accompanying formation of the disulfide (GSSG) in the presence of the selenide catalyst. A typical reaction with catalyst **11d** is shown in Figure 1, where spectrum A was recorded prior to the addition of hydrogen peroxide (t_0), spectrum B represents ca. 50% completion ($t_{1/2}$), and spectrum C was obtained from an authentic sample of GSSG. These spectra reveal that the signal for H-2 (GSH) and H-2′ (GSSG) remains essentially unchanged in this process, while that for H-4 (GSH) gradually disappears and the corresponding peak H-4′ (GSSG) appears further downfield, where it overlaps with the residual water peak (not shown). Furthermore, the signal for H-5′a is well-separated from its diastereotopic counterpart H-5′b (GSSG) as well as from H-5 (GSH). Thus, it is possible to integrate either the disappearance of the H-4 or the appearance of the H-5′a peak against the constant H-2 plus H-2′ signal to determine the extent of completion of the process at any given time.

The assays were carried out in phosphate-buffered D_2O solution at a pD of 2.3 and are corrected for the uncatalyzed background reaction of hydrogen peroxide with glutathione, which is considerably slower under these conditions. However, attempts to perform the assays at physiological pH produced a much faster control reaction[30a,31] that resulted in poor reproducibility of the corrected results with the catalyst present. Overall, advantages of the NMR assay include a medium that more closely resembles biological conditions, despite the low

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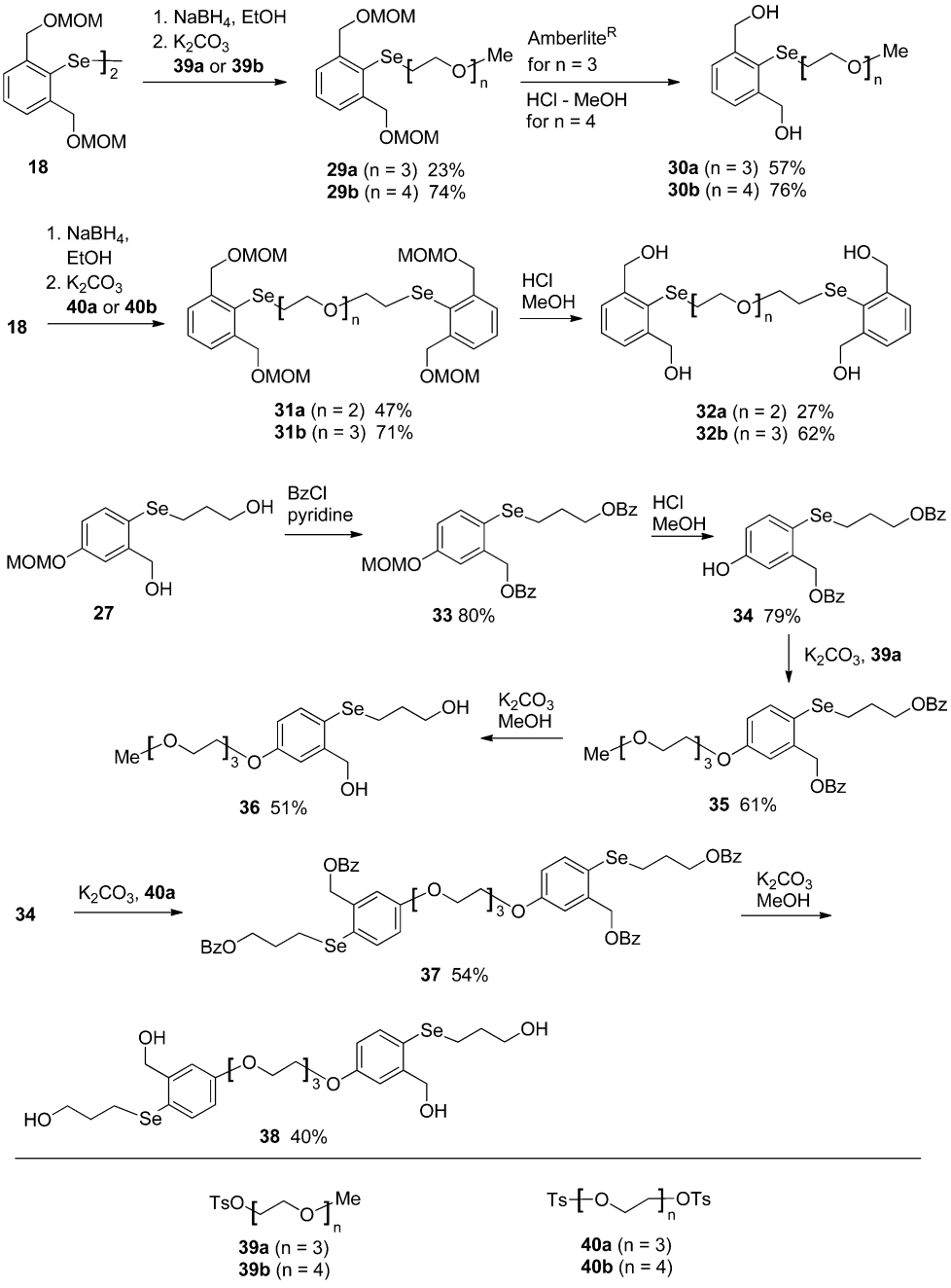
Scheme 7



pD, and faster acquisition of data, which proved useful for the most active catalysts. The results of both the HPLC and NMR assays are provided in Table 1.

The presence of electron-donating methoxy groups at various positions of the aromatic rings of **10a**–**10g** had a significant effect on the reaction rates. Thus, in the HPLC assay in Table 1, the *p*-methoxy (i.e., *para* to the Se substituent) derivative **10d** (entry 4; $t_{1/2}$ = 35 min) was more active than the unsubstituted derivative **10a** (entry 1; $t_{1/2}$ = 55 min), as expected because of resonance stabilization by the electron-donating group of the increasing positive charge on the selenium atom during the rate-determining oxidation step. The *ortho* and *meta* isomers **10b** and **10c** (entries 2 and 3, respectively), however, showed only slight rate enhancements relative to **10a** and provided inferior activity compared to **10d**. The *o*,*p*-dimethoxy derivative **10e** (entry 5) produced essentially the same results as **10d**, while the *m*,*p*-analogue **10f** catalyzed a remarkably rapid consumption of the thiol (entry 6, $t_{1/2}$ = 10.0 min). These results indicate that the presence of a single methoxy group in the *para* position is more effective than its *ortho* or *meta*-substituted isomers in promoting the reduction of the peroxide. Furthermore, the ineffectiveness of a second methoxy substituent in the *ortho* position suggests a balance between resonance enhancement and steric suppression of the rate of the process. In contrast, a second methoxy group at the *meta* position provided a strong further promotive effect compared to **10d**. The relatively poor performance of the trimethoxy analogue **10g** (entry 7; $t_{1/2}$ = 102 min) was unexpected, but clearly shows that the

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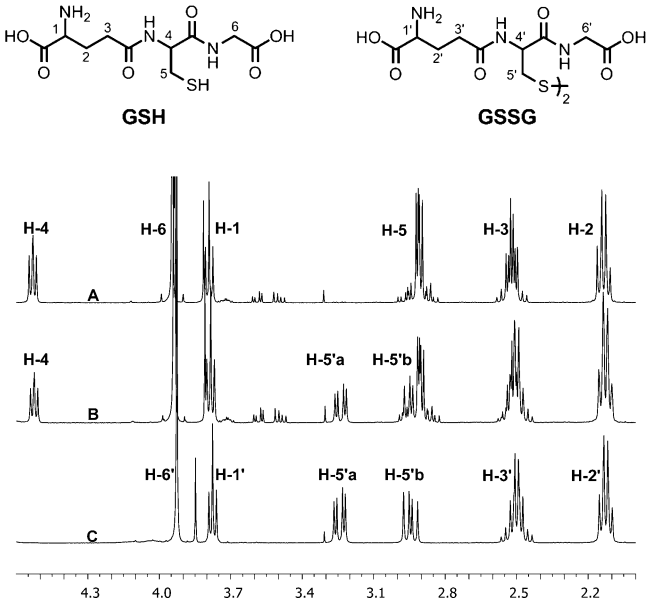

Figure 1. Conversion of GSH to GSSG with H_2O_2 in the presence of 10 mol % of selenide **11d**, as monitored by ^1H NMR (400 MHz) spectroscopy. Spectrum A: at t_0. Spectrum B: at $t_{1/2}$. Spectrum C: authentic GSSG.

Table 1. Assays of Catalytic Activity of GPx Mimetics

entry	compd	HPLC assay[a,b] $t_{1/2}$ (min)	NMR assay[b,c] $t_{1/2}$ (min)
1	**10a**	55	–
2	**10b**	48	–
3	**10c**	44	–
4	**10d**	35	12.7
5	**10e**	37	–
6	**10f**	10.0	4.7
7	**10g**	102	–
8	**11a**	79	61
9	**11b**	103	241
10	**11c**	49	81
11	**11d**	36	22 (31)[d]
12	**11e**	43	58
13	**11f**	70	24
14	**11g**	150	627
15	**15a**	570[e]	–
16	**15b**	1260[e]	–
17	**20**	306	–
18	**28**	–	10.5
19	**30a**	–	1086
20	**30b**	–	1008
21	**32a**	–	921[f]
22	**32b**	–	924
23	**36**	–	12.5
24	**38**	–	6.9

[a]Conducted with 35 mM hydrogen peroxide, 31 mM benzyl thiol, and 3.1 mM (10 mol %) of the catalyst in dichloromethane-methanol (95:5) at 18 °C. [b]Each $t_{1/2}$ value is the average of at least two runs and is corrected for the uncatalyzed background oxidation of thiol with H_2O_2. For more detail, including kinetic plots, see the Experimental Section and Supporting Information. [c]Conducted with the same concentrations as the HPLC assay in D_2O containing a phosphate buffer (pD 2.3) at 22 °C. [d]Value in parentheses was obtained in unbuffered D_2O. [e]Value taken from ref 16e. [f]Value obtained in unbuffered DMSO-d_6 due to poor solubility in D_2O.

introduction of a third methoxy substituent is counterproductive.

The analogous series of selenides **11a**–**11g**, containing an additional free hydroxyl group, provided generally comparable activity in the HPLC assay, but with some differences. Thus, the *p*-methoxy derivative **11d** (entry 11; $t_{1/2}$ = 36 min) was considerably more active than the unsubstituted analogue **11a** (entry 8; $t_{1/2}$ = 79 min), again attributed to mesomeric effects. In contrast, the *o*-methoxy substituent in **11b** (entry 9; $t_{1/2}$ = 103 min) suppressed reactivity considerably, presumably because of dominant steric effects. The *m*-methoxy compound **11c** (entry 10; $t_{1/2}$ = 49 min) showed a modest increase in reaction rate compared to **11a** (entry 8). No further improvement relative to the *para* derivative **11d** was observed when multiple methoxy groups were introduced in **11e**–**11g** (entries 12–14). As in the previous series of selenides **10**, the trimethoxy product **11g** provided the slowest rate of all (entry 14; $t_{1/2}$ = 150 min) of the compounds **11**. It is noteworthy that all of the compounds **10** and **11** exhibited considerably superior catalytic activity to the variously substituted diaryl selenides **6** reported previously ($t_{1/2}$ = 5.5–21 h),[19c] or to ebselen ($t_{1/2}$ = 24 h) under similar conditions.[16d]

The NMR assay was only run on two compounds, **10d** and **10f**, from the 3-hydroxypropyl selenides **10** due to solubility constraints in the D_2O solvent, but revealed further improvement in catalytic activity in the aqueous medium (**10d**, entry 4, $t_{1/2}$ = 12.7 min; **10f**, entry 6, $t_{1/2}$ = 4.7 min) compared to the HPLC assay and barely within the time limitations for monitoring by NMR. The NMR assay again confirmed that the strongest catalytic activity of compounds **11** was obtained with the *p*-methoxy derivative **11d** (entry 11; $t_{1/2}$ = 22 min), although the *m*,*p*-dimethoxy analogue **11f** was comparable (entry 13; $t_{1/2}$ = 24 min). In this assay, *o*-methoxy groups suppressed the catalytic activity of **11b**, **11e**, and **11g** (entries 9, 12, and 14, respectively), relative to the *p*-methoxy selenide **11d**, although the *o*,*p*-dimethoxy compound **11e** was comparable to the unsubstituted selenide **11a**.

The selenide precursors **15a** and **15b** of the corresponding pincer selenuranes **17a** and **17b** were reported previously,[16e] and their corresponding HPLC assay data are included in Table 1 for comparison (entries 15 and 16). These compounds and the related derivative **20** (entry 17) all showed greatly inferior catalytic activity compared to the selenides **10a**–**10g** and **11a**–**11f** in this assay.

The phenolic selenide **28** (entry 18) proved sufficiently water-soluble to be subjected to the NMR assay and produced a remarkably short $t_{1/2}$ of only 10.5 min. Since other phenols have been reported to undergo oxidation to quinones with benzeneseleninic acid and anhydride,[32] we performed several control reactions to investigate its behavior further. When oxidized with hydrogen peroxide in the absence of a thiol, it afforded the corresponding spiroselenurane **41** in high yield in ca. 15 min (Scheme 8). The product was isolated and then treated with 2 equiv of benzyl thiol in the absence of hydrogen peroxide, resulting in the immediate precipitation of the original selenide **28**. These experiments establish that **41** is a plausible intermediate in the catalytic cycle of **28**, which we postulate is analogous to that shown in Scheme 2. They also demonstrate that the thiolysis of **41** is even faster than the oxidation of **28**, by at least an order of magnitude. Although there was no evidence of quinone formation during the oxidation step under these conditions, prolonged exposure to excess hydrogen peroxide, or to MCPBA, produced more

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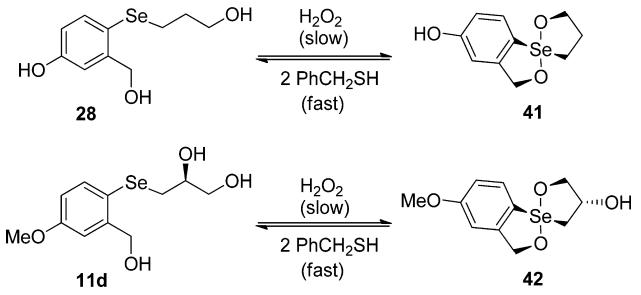
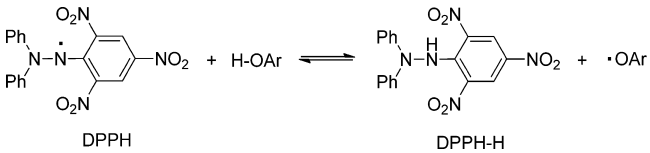
Scheme 8



complex mixtures that could not be separated. Furthermore, control experiments with selenide **11d**, chosen as a representative of the aryl 3-hydroxy and 2,3-dihydroxypropyl selenide series **10** and **11**, similarly revealed a relatively slow oxidation with hydrogen peroxide in the absence of a thiol that required ca. 1 h to go to completion. A much faster reduction of the resulting spirodioxyselenurane **42** with benzyl thiol was observed in the absence of the peroxide, where conversion back to the original selenide **11d** was complete in <2 min (Scheme 8). It therefore appears that the oxidation of Se(II) to Se(IV) is again the rate-determining step in the catalytic cycles of **28** and **11d**, as had been observed previously for GPx mimetics **3**−**5**.

In a simple but preliminary test to determine whether phenol **28** could also serve as an antioxidant radical inhibitor, we allowed it to react with the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) while monitoring the UV−vis absorption of the latter at 515 nm.[33] A decrease in the absorbance of DPPH then indicates that a test substance has the ability to transfer a hydrogen atom to it, thus producing the corresponding hydrazine (DPPH-H), which is essentially transparent at this wavelength, along with the radical species derived from the hydrogen donor (Scheme 9). The results are

Scheme 9



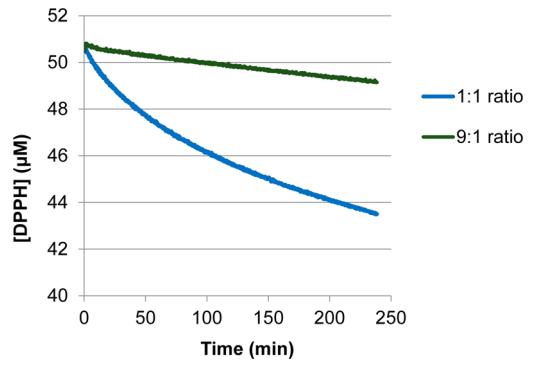


Figure 2. Decrease of [DPPH] with time as measured by the decrease in its absorption at 515 nm. Upper line (green) represents a DPPH:**28** ratio of 9:1; lower curve (blue) corresponds to a DPPH:**28** ratio of 1:1.

shown in Figure 2 at two different molar ratios. While a significant decrease in the absorbance of DPPH was observed at a DPPH:**28** ratio of 1:1, the reaction did not go to completion even after a relatively prolonged period of 4 h. In the presence of only 10 mol % of the phenol, the reaction barely proceeded. This suggests that a hydrogen transfer equilibrium may be gradually established between DPPH and the phenol or that other reactions consume DPPH under these conditions. Thus, on the basis of this assay, **28** does not appear to be especially well-suited for suppressing radical chain reactions such as lipid oxidations.[34]

Finally, we tested the PEGylated compounds in the NMR assay. Selenides **30a** and **30b** (entries 19 and 20 in Table 1) as well as the dimeric species **32a** and **32b** (entries 21 and 22) contain the PEG chains attached to the selenium atom. They were therefore expected to react via pincer selenuranes upon oxidation, analogous to selenuranes **17a** and **17b** (Scheme 4) and **21** (Scheme 5). Compound **32a** proved too insoluble in either D_2O or dichloromethane-methanol to permit analysis via either assay. The NMR assay was therefore run in DMSO-d_6 and produced a relatively long $t_{1/2}$ of 921 min (15.4 h).[35] Its homologue **32b** as well as the selenurane monomers **30a** and **30b** also proved to be poor catalysts, with $t_{1/2}$ values of ca. 17−18 h. Thus, like the non-PEGylated compounds **15a**, **15b**, and **20**, these analogues are relatively poor GPx mimetics. In contrast, the remaining selenides **36** and **38** are derivatives of the phenolic compound **26**, with attachment of the PEG chain at the phenolic hydroxyl group. They were therefore expected to generate the more reactive spirodioxyselenuranes upon oxidation. Both the monomer **36** (entry 23; $t_{1/2}$ = 12.5 min) and the dimer **38** (entry 24; $t_{1/2}$ = 6.9 min) displayed excellent catalytic activity, approaching the limit of monitoring ability, even by the more rapid NMR method. It is interesting to note that the dimeric species **38** exhibited a $t_{1/2}$ roughly half that of the monomer **36**, consistent with the presence of two redox centers in **38** instead of a single one in **36**.[36] In this way, **38** more closely emulates the multivalent selenoenzyme GPx, which it will be recalled possesses four redox-active selenocysteine moieties.

SUMMARY AND CONCLUSIONS

These results show that the water-soluble selenides **10a**−**10g** and **11a**−**11g** are highly active catalysts for the reduction of hydrogen peroxide with thiols, as evidenced by both HPLC and NMR-based assays. In both series **10** and **11**, the single *p*-methoxy substituents in **10d** and **11d** as well as the *m*,*p*-analogue **10f** provided the fastest reaction rates compared to their unsubstituted or otherwise methoxy-substituted analogues. We attribute this to resonance stabilization of increased positive charge on the selenium atom during the rate-determining oxidation step. On the other hand, when introduced *ortho* to the selenium atom, a single methoxy group strongly suppressed reactivity in **11b**, but had little effect in **10b**, presumably due to a balance between mesomeric and steric effects. The incorporation of a *m*-methoxy substituent afforded less predictable results, with a slightly faster rate for **10c** and **11c** compared to **10a** and **11a**, respectively, observed in the HPLC assay in dichloromethane-methanol (95:5), and a slower rate recorded for **11c** compared to **11a** in buffered D_2O. The incorporation of multiple methoxy groups provided no further benefit compared with a single *p*-methoxy substituent, except in the case of the remarkably active *m*,*p*-derivative **10f**. In contrast to selenides that produce spirodioxyselenuranes

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upon oxidation, analogues **15a**, **15b**, **20**, **30a**, **30b**, **32a**, and **32b** that instead afford the corresponding pincer selenuranes proved far less effective as catalysts, regardless of the presence or absence of a PEG support. However, we were pleased to discover that the PEGylated compounds **36** and **38** as well as the phenol **28** and the *m,p*-dimethoxy derivative **10f** revealed excellent catalytic activity, with $t_{1/2}$ values significantly shorter than those of any other organoselenium compound previously investigated in our laboratory and more than 2 orders of magnitude faster than ebselen, which could only be subject to the HPLC protocol. These water-soluble compounds therefore merit further investigation as potentially useful biological antioxidants.

EXPERIMENTAL SECTION

General Experimental. Diselenides **9a**,[16c] **9b**,[16f] **9c**,[16f] **9d**,[16d] **9e**,[16f] **9f**,[16f] **12**,[16f] and **18**[16e] were obtained as reported previously. ^{1}H NMR spectra were recorded at 400 MHz, while ^{13}C and ^{77}Se NMR spectra were obtained at 101 and 76 MHz, respectively. Chemical shifts of ^{77}Se NMR spectra were measured with diphenyl diselenide in $CDCl_3$ at 463.0 ppm[37] as the standard, relative to dimethyl selenide at 0.0 ppm. High-resolution mass spectra were obtained with a time-of-flight (TOF) analyzer and electron impact (EI) ionization or with a quadrupole TOF analyzer and electrospray ionization (ESI).

The HPLC-based assay for catalytic activity was performed by adding the catalyst (0.031 mmol; 10 mol % relative to benzyl thiol) to a mixture of hydrogen peroxide (ca. 30%; 35 mM) and benzyl thiol (31 mM) in 10.0 mL of dichloromethane-methanol (95:5) while maintaining the temperature at 18 °C. The HPLC instrument employed a UV detector at 254 nm and a reversed phase column (Novapak C18; 3.9 × 150 mm). The eluent was acetonitrile-water (isocratic or gradient as required), with a flow rate of 0.9 mL/min. Naphthalene (8.0 mM) was employed as an internal standard. Benzyl thiol was redistilled, and hydrogen peroxide was titrated[38] prior to use. At least two replicates were performed for each compound, and each run was performed in a clean, new vial.

For the NMR assay, a buffer solution was prepared by dissolving NaH_2PO_4 (105 mg, 0.875 mmol) and phosphoric acid (111 μL, 85%, 0.162 mmol) in 25 mL of D_2O to afford a solution with pD = 2.3.[39] A fresh solution of GSH (31 mM) and the catalyst (3.1 mM) in the buffered D_2O was prepared in a clean, new vial for each run. Sufficient aqueous hydrogen peroxide (ca. 30%) was added to produce a final concentration 35.4 mM, thereby initiating the reaction. The solution was pipetted into a clean, dry NMR tube and immediately placed in the spectrometer. Acquisition of data typically commenced within 2−3 min of the addition of hydrogen peroxide, and data collection continued until nearly complete conversion of GSH to GSSG had occurred. The NMR spectrometer parameters were set to a 90° pulse program with a relaxation delay of 3 s and a minimum of 8 scans per spectrum. At least two replicates were performed for each compound.

The DPPH assay of phenolic selenide **28** was conducted in methanol at 22 °C. The DPPH concentration was obtained from a calibration plot of absorbance at 515 nm vs concentration. After the DPPH and the desired amount of **28** were mixed and placed in a cuvette, the reaction mixture was scanned four times per min, and the DPPH concentration thus obtained was plotted vs time as shown in Figure 2.

*Typical Procedure for the Preparation of Selenides **10a**−**10f**. Preparation of 2-(Hydroxymethyl)phenyl 3-Hydroxypropyl Selenide (**10a**).* Diselenide **9a** (515 mg, 1.38 mmol) was dissolved in 35 mL of THF-ethanol (3:1) and cooled to 0 °C. Sodium borohydride (261 mg, 6.90 mmol) was added, and after 5 min 1-bromo-3-propanol (0.271 mL, 417 mg, 3.00 mmol) was added. The mixture was warmed to room temperature, left for an additional 2 h, and quenched with 25 mL of water. The mixture was extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes-ethyl acetate, 2:1) to afford 488 mg (72%) of the product as a colorless solid, mp 42−43 °C (from ethyl acetate); IR (solid) 3376, 3303, 2911, 2838, 1436, 1180, 1051 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.39 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.26 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.21 (td, *J* = 7.4, 1.6 Hz, 1 H), 4.76 (d, *J* = 5.6 Hz, 2 H), 3.70 (q, *J* = 5.3 Hz, 2 H), 2.98 (t, *J* = 7.2 Hz, 2 H), 2.62 (t, *J* = 6.0 Hz, 1 H), 1.95 (t, *J* = 4.4 Hz, 1 H), 1.91 (p, *J* = 6.7 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 142.5, 133.8, 130.0, 128.7, 128.6, 127.7, 65.5, 62.2, 32.7, 24.6; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 230.7; mass spectrum *m*/*z* (EI, relative intensity) 246 (100, M$^+$), 229 (27), 187 (36), 170 (38), 107 (90), 91 (26), 78 (90); HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{10}H_{14}O_2{}^{80}Se$: 246.0159; found: 246.0163. Anal. calcd for $C_{10}H_{14}O_2Se$: C, 48.99; H, 5.76; found: C, 49.02; H, 5.73.

Compounds **10b**−**10f** and **13** were prepared similarly from diselenides **9b**−**10f** and **12**, respectively.

*3-Hydroxypropyl 6-Methoxy-2-(hydroxymethyl)phenyl Selenide (**10b**).* From 200 mg (0.463 mmol) of **9b**. Yield: 213 mg, 84%. Colorless solid; mp 49−50 °C (from ethyl acetate); IR (solid) 3362, 3267, 2933, 1567, 1462, 1262, 1038 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.29 (t, *J* = 8.0 Hz, 1 H), 7.04 (dd, *J* = 7.6, 1.2 Hz, 1 H), 6.84 (dd, *J* = 8.0, 1.2 Hz, 1 H), 4.80 (s, 2 H), 3.88 (s, 3 H), 3.68 (t, *J* = 6.0 Hz, 2 H), 2.94 (t, *J* = 7.0 Hz, 2 H), 2.83 (br s, 1 H), 2.03 (br s, 1 H), 1.81 (tt, *J* = 7.0, 6.0 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.2, 145.9, 129.9, 121.2, 117.3, 110.5, 66.1, 62.3, 56.3, 32.9, 24.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 127.3; mass spectrum *m*/*z* (EI, relative intensity) 276 (92, M$^+$), 217 (28), 200 (40), 137 (92), 108 (100); HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{11}H_{16}O_3{}^{80}Se$: 276.0265; found: 276.0275. Anal. calcd for $C_{11}H_{16}O_3Se$: C, 48.01; H, 5.86; found: C, 47.99; H, 5.99.

*3-Hydroxypropyl 5-Methoxy-2-(hydroxymethyl)phenyl Selenide (**10c**).* From 200 mg (0.463 mmol) of **9c**. Yield: 215 mg, 84%. Colorless solid; mp 58−59 °C (from ethyl acetate); IR (solid) 3352, 3271, 2930, 1594, 1468, 1279, 1221, 1041 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 2.8 Hz, 1 H), 6.75 (dd, *J* = 8.4, 2.4 Hz, 1 H), 4.67 (s, 2 H), 3.78 (s, 3 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 2.83 (br s, 1 H), 2.44 (br s, 1 H), 1.89 (tt, *J* = 7.0, 6.0 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.3, 134.7, 131.5, 130.0, 119.2, 112.5, 64.9, 62.0, 55.5, 32.6, 24.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 228.5; mass spectrum *m*/*z* (EI, relative intensity) 276 (100, M$^+$), 217 (82), 199 (24), 135 (50), 108 (62); HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{11}H_{16}O_3{}^{80}Se$: 276.0265; found: 276.0267. Anal. calcd for $C_{11}H_{16}O_3Se$: C, 48.01; H, 5.86; found: C, 47.95; H, 5.87.

*3-Hydroxypropyl 4-Methoxy-2-(hydroxymethyl)phenyl Selenide (**10d**).* From 310 mg (0.717 mmol) of **9d**. Yield: 265 mg, 67%. Colorless solid; mp 44−45 °C; IR (film) 3329, 2929, 1595, 1476, 1295, 1229, 1057 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 2.8 Hz, 1 H), 6.74 (dd, *J* = 8.6, 3.0 Hz, 1 H), 4.76 (s, 2 H), 3.80 (s, 3 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 2.99 (br s, 1 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 2.24 (br s, 1 H), 1.85 (tt, *J* = 7.2, 6.0 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.9, 145.0, 137.2, 119.0, 114.1, 113.9, 65.5, 62.0, 55.3, 32.6, 25.4; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 212.5; mass spectrum *m*/*z* (EI, relative intensity) 276 (100, M$^+$), 200 (38), 137 (45), 108 (90); HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{11}H_{16}O_3{}^{80}Se$: 276.0265; found: 276.0270. Anal. calcd for $C_{11}H_{16}O_3Se$: C, 48.01; H, 5.86; found: C, 48.24; H, 5.69.

*4,6-Dimethoxy-2-(hydroxymethyl)phenyl 3-Hydroxypropyl Selenide (**10e**).* From 100 mg (0.203 mmol) of **9e**. Yield: 66 mg, 53%. Colorless solid; mp 66−67 °C; IR (solid) 3352, 3243, 2933, 1581, 1310, 1167, 1029 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.64 (d, *J* = 2.4 Hz, 1 H), 6.41 (d, *J* = 2.8 Hz, 1 H), 4.79 (s, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.69 (t, *J* = 6.2 Hz, 2 H), 2.84 (t, *J* = 7.2 Hz, superimposed on br s, 3 H), 2.02 (br s, 1 H), 1.79 (tt, *J* = 7.2, 6.0 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 161.6, 161.3, 147.0, 107.7, 105.4, 98.2, 66.3, 62.4, 56.3, 55.5, 32.7, 24.6; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 109.3; mass spectrum *m*/*z* (EI, relative intensity) 306 (100, M$^+$), 230 (32), 166 (96), 138 (66); HRMS (EI-TOF) *m*/*z*: [M]$^+$ Calcd for $C_{12}H_{18}O_4{}^{80}Se$: 306.0370; found: 306.0367. Anal. calcd for $C_{12}H_{18}O_4Se$: C, 47.22; H, 5.94; found: C, 47.25; H, 5.76.

*4,5-Dimethoxy-2-(hydroxymethyl)phenyl 3-Hydroxypropyl Selenide (**10f**).* From 210 mg (0.427 mmol) of **9f**. Yield: 247 mg, 95%. Colorless solid; mp 38−39 °C (from ethyl acetate); IR (solid) 3300,

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2924, 1505, 1452, 1252, 1152; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.11 (s, 1 H), 6.97 (s, 1 H), 4.75 (d, J = 5.6 Hz, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.70 (q, J = 5.3 Hz, 2 H), 2.91 (t, J = 7.0 Hz, 2 H), 2.56 (t, J = 6.0 Hz, 1 H), 1.92−1.83 (m 3 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 149.4, 148.5, 136.6, 119.4, 119.0, 112.1, 65.6, 62.2, 56.3, 56.1, 32.8, 25.8; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 228.3; mass spectrum m/z (EI, relative intensity) 306 (22, M^+), 247 (15), 165 (20), 138 (100), 123 (22), 95 (25); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{18}O_4{}^{80}Se$: 306.0370; found: 306.0372. Anal. calcd for $C_{12}H_{18}O_4Se$: C, 47.22; H, 5.94; found: C, 47.46; H, 5.89.

*3-Hydroxypropyl 2,3,4-Trimethoxy-2-[(methoxymethoxy)-methyl]phenyl Selenide (**13**).* From 347 mg (0.542 mmol) of **12**. Yield: 329 mg, 80%. Colorless oil; IR (neat) 3457, 2943, 1576, 1486, 1319, 1262, 1105, 1033, 724 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.87 (s, 1 H), 4.77 (s, 2 H), 4.73 (s, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.71 (t, J = 6.2 Hz, 2 H), 3.43 (s, 3 H), 2.90 (t, J = 7.0 Hz, 2 H), 1.91 (br s, 1 H), 1.81 (tt, J = 7.0, 6.2 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.2, 154.1, 142.0, 137.5, 115.4, 108.3, 96.1, 70.2, 62.2, 61.2, 61.1, 56.1, 55.7, 32.9, 25.2; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 146.1; mass spectrum m/z (EI, relative intensity) 380 (100, M^+), 317 (40), 289 (50), 197 (80), 181 (40), 168 (25); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{15}H_{24}O_6{}^{80}Se$: 380.0738; found: 380.0729.

*3-Hydroxypropyl 2,3,4-Trimethoxy-6-(hydroxymethyl)phenyl Selenide (**10g**).* Selenide **13** (214 mg, 0.564 mmol) was dissolved in 10 mL of methanol along with 6 drops of concentrated HCl. The mixture was heated at 60 °C for 5 h. It was then poured into 10 mL of water, extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (hexanes-ethyl acetate, 1:3) to afford 157 mg (83%) of the deprotected product **10g** as a colorless oil, IR (neat) 3490, 2943, 1590, 1476, 1319, 1157, 1095, 1010 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.83 (s, 1 H), 4.76 (s, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.69 (t, J = 6.0 Hz, 2 H), 2.98 (br s, 1 H), 2.90 (t, J = 7.0 Hz, 2 H), 2.27 (br s, 1 H), 1.81 (quintet, J = 6.6 Hz, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.2, 154.2, 141.8, 140.5, 114.2, 108.1, 66.0, 62.1, 61.3, 61.0, 56.1, 32.8, 25.4; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 138.4; mass spectrum m/z (EI, relative intensity) 336 (100, M^+), 277 (34), 196 (28), 181 (20), 168 (76), 153 (21); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{13}H_{20}O_5{}^{80}Se$: 336.0476; found: 336.0468.

*Typical Procedure for the Preparation of Selenides **11a**−**11f**. Preparation of (S)-2,3-Dihydroxypropyl 2-(Hydroxymethyl)phenyl Selenide (**11a**).* Diselenide **9a** (335 mg, 0.900 mmol) was dissolved in 20 mL of THF-ethanol (3:1) and cooled to 0 °C. Sodium borohydride (239 mg, 6.32 mmol) was added, and after 5 min (*S*)-(−)-glycidol (0.240 mL, 267 mg, 3.62 mmol) was added. The mixture was warmed to room temperature, left for an additional 2 h, and quenched with 20 mL of water. The mixture was extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (elution with ethyl acetate) to afford 302 mg (64%) of the product **11a** as a colorless solid, mp 36−37 °C (from ethyl acetate); $[\alpha]_D^{20}$ +20.5 (c 2.37, MeOH); IR (solid) 3233, 2910, 1719, 1438, 1190, 1057 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.58 (dd, J = 7.6, 0.8 Hz, 1 H), 7.35 (dd, J = 7.4, 1.4 Hz, 1 H), 7.26 (td, J = 7.4, 1.2 Hz, 1 H), 7.20 (td, J = 7.4, 1.5 Hz, 1 H), 4.80 (d, J = 12.4 Hz, 1 H), 4.69 (d, J = 12.0 Hz, 1 H), 4.04 (br s, 1 H), 3.68−3.62 (m, 2 H), 3.56 (d, J = 11.2 Hz, 1 H), 3.43 (dd, J = 11.2, 6.4 Hz, 1 H), 3.22 (br s, 1 H), 2.98 (dd, J = 12.8, 4.4 Hz, 1 H), 2.84 (dd, J = 12.8, 8.4 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 142.8, 135.3, 129.7, 129.3, 128.9, 128.3, 70.7, 65.7, 65.6, 32.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 196.3; mass spectrum (EI) m/z (relative intensity) 262 (42, M^+), 185 (64), 170 (62), 107 (100), 105 (66), 91 (48), 78; HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{14}O_3{}^{80}Se$: 262.0108; found: 262.0108. Anal. calcd for $C_{10}H_{14}O_3Se$: C, 45.89; H, 5.39; found: C, 45.82; H, 5.18.

Compounds **11b**−**11f** and **14** were prepared similarly from diselenides **9b**−**9f** and **12**, respectively.

*(S)-2,3-Dihydroxypropyl 6-Methoxy-2-(hydroxymethyl)phenyl Selenide (**11b**).* From 200 mg (0.463 mmol) of **9b**. Yield: 223 mg, 84%. Colorless solid; mp 64−65 °C; $[\alpha]_D^{20}$ + 38.3 (c 3.53, MeOH); IR (film) 3261, 2923, 1568, 1454, 1253, 1038 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1 H), 7.02 (d, J = 7.2 Hz, 1 H), 6.86 (d, J = 8.0 Hz, 1 H), 4.90 (dd, J = 11.8, 3.4 Hz, 1 H), 4.70 (dd, J = 11.8, 4.2 Hz, 1 H), 4.17 (br s, 1 H), 3.89 (s, 3 H), 3.73 (br s, 1 H), 3.54−3.51 (m, 2 H), 3.43−3.40 (m, 1 H), 3.06 (dd, J = 12.8, 4.8 Hz, 1 H), 2.97 (br s, 1 H), 2.69 (dd, J = 12.8, 9.2 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.2, 145.8, 130.3, 121.9, 116.7, 110.7, 70.5, 66.1, 65.8, 56.3, 31.4; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 105.5; mass spectrum m/z (EI, relative intensity) 292 (55, M^+), 215 (24), 200 (38), 169 (12), 137 (100), 108 (52); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{16}O_4{}^{80}Se$: 292.0214; found: 292.0219. Anal. calcd for $C_{11}H_{16}O_4Se$: C, 45.28; H, 5.53; found: C, 45.29; H, 5.07.

*(S)-2,3-Dihydroxypropyl 5-Methoxy-2-(hydroxymethyl)phenyl Selenide (**11c**).* From 200 mg (0.463 mmol) of **9c**. Yield: 196 mg, 73%. Colorless solid; mp 78−79 °C (ethyl acetate-methanol); $[\alpha]_D^{20}$ + 25.0 (c 5.37, MeOH); IR (film) 3269, 2914, 1589, 1479, 1247, 1018 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.27 (d, J = 8.4 Hz, 1 H), 7.17 (d, J = 2.4 Hz, 1 H), 6.80 (dd, J = 8.4, 2.4 Hz, 1 H), 4.77 (d, J = 12.0 Hz, 1 H), 4.66 (d, J = 12.0 Hz, 1 H), 4.19 (br s, 1 H), 3.80 (s, 3 H), 3.75−3.42 (m, 4 H), 3.27 (br s, 1 H), 3.02 (dd, J = 13.2, 4.0 Hz, 1 H), 2.88 (dd, J = 12.8, 8.4 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 159.5, 135.1, 131.0, 130.6, 120.8, 113.3, 70.7, 65.7, 65.0, 55.4, 32.6; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 194.8; mass spectrum m/z (EI, relative intensity) 292 (74, M^+), 217 (64), 137 (100), 121 (56), 108 (70); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{16}O_4{}^{80}Se$: 292.0214; found: 292.0227. Anal. calcd for $C_{11}H_{16}O_4Se$: C, 45.28; H, 5.53; found: C, 45.30; H, 5.54.

*(S)-2,3-Dihydroxypropyl 4-Methoxy-2-(hydroxymethyl)phenyl Selenide (**11d**).* From 332 mg (0.768 mmol) of **9d**. Yield: 321 mg, 72%. Colorless solid; 51−52 °C (from ethyl acetate); $[\alpha]_D^{20}$ + 25.6 (c 1.25, MeOH); IR (film) 3243, 2914, 1595, 1471, 1286, 1219, 1038; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 1 H), 6.96 (d, J = 2.8 Hz, 1 H), 6.76 (dd, J = 8.4, 2.8 Hz, 1 H), 4.81 (d, J = 11.6 Hz, 1 H), 4.67 (d, J = 12.0 Hz, 1 H), 3.89 (br s, 1 H), 3.79 (s, 3 H), 3.65−3.53 (m, 3 H), 3.47−3.40 (m, 1 H), 3.00 (br s, 1 H), 2.91 (dd, J = 12.6, 4.2 Hz, 1 H), 2.76 (dd, J = 12.8, 8.4 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 160.3, 145.2, 138.3, 119.2, 115.1, 114.6, 70.7, 66.0, 65.8, 55.5, 33.3; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 177.5; mass spectrum m/z (EI, relative intensity) 292 (100, M^+), 200 (42), 137 (58), 108 (84); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{16}O_4{}^{80}Se$: 292.0214; found: 292.0209. Anal. calcd for $C_{11}H_{16}O_4Se$: C, 45.28; H, 5.53; found: C, 45.59; H, 5.38.

*(S)-2,3-Dihydroxypropyl 4,6-Dimethoxy-2-(hydroxymethyl)-phenyl Selenide (**11e**).* From 200 mg (0.406 mmol) of **9e**. Yield: 85 mg, 33%. Colorless solid; mp 77−78 °C; $[\alpha]_D^{20}$ + 36.0 (c 0.96, MeOH); IR (film) 3402, 3312, 2903, 1586, 1428, 1329, 1203, 1171, 1068 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.61 (d, J = 2.8 Hz, 1 H), 6.40 (d, J = 2.4 Hz, 1 H), 4.86 (d, J = 12.4 Hz, 1 H), 4.65 (d, J = 12.4 Hz, 1 H), 4.22 (br s, 1 H), 3.91 (br s, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.55−3.45 (m, 2 H), 3.39 (dd, J = 10.6, 6.2 Hz, 1 H), 3.18 (br s, 1 H), 2.95 (dd, J = 12.6, 3.4 Hz, 1 H), 2.61 (dd, J = 12.6, 9.0 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 161.8, 161.4, 147.0, 107.3, 106.3, 98.4, 70.6, 66.3, 65.9, 56.4, 55.6, 31.7; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 74.9; mass spectrum m/z (EI, relative intensity) 322 (64, M^+), 230 (32), 166 (100), 138 (56); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{18}O_5{}^{80}Se$: 322.0319; found: 322.0321. Anal. calcd for $C_{12}H_{18}O_5Se$: C, 44.79; H, 5.64; found: C, 44.98; H, 5.64.

The starting diselenide **9e** contained a substantial amount of the corresponding diaryl selenide, which could not be separated until this step, in which 57 mg were recovered.

*(S)-2,3-Dihydroxypropyl 4,5-Dimethoxy-2-(hydroxymethyl)-phenyl Selenide (**11f**).* From 185 mg (0.375 mmol) of **9f**. Yield: 228 mg, 95%. Colorless solid; mp 74−75 °C (from ethyl acetate); $[\alpha]_D^{20}$ + 25.4 (c 3.51, MeOH); IR (film) 3406, 3243, 2931, 1499, 1260, 1018; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.13 (s, 1 H), 6.92 (s, 1 H), 4.80 (d, J = 12.0 Hz, 1 H), 4.68 (d, J = 11.6 Hz, 1 H), 4.02 (br s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.70−3.61 (m, 2 H), 3.57 (dd, J = 11.2, 3.2 Hz, 1 H), 3.44 (dd, J = 11.4, 6.6 Hz, 1 H), 3.11 (br s, 1 H), 2.94 (dd, J = 12.8, 4.0 Hz, 1 H), 2.79 (dd, J = 12.8, 8.4 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 149.7, 148.9, 136.8, 119.7, 119.5, 112.7, 70.9, 65.9, 65.8, 56.3, 56.1, 33.5; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 195.2; mass

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spectrum m/z (EI, relative intensity) 322 (100, M^+), 246 (36), 167 (62), 151 (24), 138 (78); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{18}O_5{}^{80}Se$: 322.0319; found: 322.0311. Anal. calcd for $C_{12}H_{18}O_5Se$: C, 44.79; H, 5.64; found: C, 45.13; H, 5.69.

*(S)-2,3-Dihydroxypropyl 4,5,6,-Trimethoxy-2-[(methoxymethoxy)methyl]phenyl Selenide (**14**).* From 347 mg (0.542 mmol) of **12**. Yield: 376 mg, 88%. Colorless oil; IR (neat) 3433, 2933, 1576, 1476, 1333 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.85 (s, 1 H), 4.83 (d, J = 11.6 Hz, 1 H), 4.72 (s, 2 H), 4.72 (d, J = 11.6 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.60 (dd, J = 10.6, 3.4 Hz, 1 H), 3.57−3.51 (m, 1 H), 3.47 (dd, J = 10.6, 6.2 Hz, 1 H) 3.43 (s, 3 H), 3.01 (dd, J = 12.4, 3.2 Hz, 1 H), 2.68 (dd, J = 12.4, 8.8 Hz, 1 H), 2.35 (br s, 2 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.2, 154.5, 142.1, 137.7, 114.3, 109.2, 96.0, 70.4, 70.2, 65.9, 61.5, 61.1, 56.2, 55.8, 33.1; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 103.2; mass spectrum m/z (EI, relative intensity) 396 (95, M^+), 289 (35), 275 (100), 181 (70), 167 (32); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{15}H_{24}O_7{}^{80}Se$: 396.0687; found: 396.0685.

*Preparation of (S)-2,3-Dihydroxypropyl 4,5,6-Trimethoxy-2-(hydroxymethyl)phenyl Selenide (**11g**).* Selenide **14** (163 mg, 0.412 mmol) was dissolved in 8 mL of methanol, along with 6 drops of concentrated HCl. The mixture was heated at 60 °C for 5 h. It was poured into 10 mL of water, extracted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (elution with ethyl acetate-methanol gradient) to afford 97 mg (67%) of the deprotected product **11g** as a colorless solid, mp 54−55 °C (from ethyl acetate-methanol); $[\alpha]_D^{20}$ + 31.8 (c 2.10, MeOH); IR (film) 3276, 2930, 1589, 1463, 1383, 1315, 1108, 1005 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 6.82 (s, 1 H), 4.86 (d, J = 12.4 Hz, 1 H), 4.67 (d, J = 12.0 Hz, 1 H), 4.11 (br s, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.60−3.50 (m, 3 H), 3.47−3.40 (m, 1 H), 3.02 (dd, J = 12.4, 3.2 Hz, 1 H), 2.83 (br s, 1 H), 2.67 (dd, J = 12.6, 9.0 Hz, 1 H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.3, 154.6, 142.0, 140.6, 113.6, 108.9, 70.6, 66.2, 65.9, 61.5, 61.1, 56.2, 32.6; ^{77}Se NMR (76 MHz; $CDCl_3$) δ 103.5; mass spectrum m/z (EI, relative intensity) 352 (100, M^+), 277 (12), 260 (24), 196 (62), 168 (91), 153 (28); HRMS (EI-TOF) m/z: $[M]^+$ Calcd $C_{13}H_{20}O_6{}^{80}Se$: 352.0425; found: 352.0440. Anal. calcd for $C_{13}H_{20}O_6Se$: C, 44.45; H, 5.74; found: C, 44.49; H, 5.86.

*Preparation of 2,6-Bis[(methoxymethoxy)methyl]phenyl 3-Hydroxypropyl Selenide (**19**).* Diselenide **18** (352 mg, 0.578 mmol) was suspended in 20 mL of dry THF under nitrogen, and the solution was cooled to 0 °C. Sodium borohydride (109 mg, 2.89 mmol) was added, followed by 2.5 mL of absolute ethanol. After 10 min the solution became light yellow in color, and 3-bromopropanol (0.10 mL, 1.1 mmol) was added. The mixture was warmed to room temperature and stirred for 3 h, resulting in a white, opaque solution. The reaction was quenched with 1 M HCl and diluted with ethyl acetate. The ethyl acetate was dried, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed (elution with hexanes-ethyl acetate, 1:1) to give 310 mg (74%) of **19** as a clear oil; IR (film) 3452, 1467, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.7 Hz, 2 H), 7.38 (dd, J = 8.2, 6.8 Hz, 1 H), 4.91 (s, 4 H), 4.75 (s, 4 H), 3.69 (q, J = 5.8 Hz, 2 H), 3.43 (s, 6 H), 2.82 (t, J = 7.2 Hz, 2 H), 1.90−1.80 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$), δ 142.3, 129.5, 129.1, 128.4, 95.1, 70.3, 62.1, 55.7, 33.1, 25.1; ^{77}Se NMR (76 MHz, $CDCl_3$), δ 135.2; mass spectrum (EI-TOF) m/z (relative intensity) 364 (70, $[M]^+$), 287 (95), 198 (100); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{15}H_{24}O_5{}^{80}Se$: 364.0789; found: 364.0775.

*Preparation of 2,6-Di(hydroxymethyl)phenyl 3-Hydroxypropyl Selenide (**20**).* Selenide **19** (310 mg, 0.853 mmol) was dissolved in 50 mL of methanol. Amberlite IR-120(H) acidic resin was added, and the mixture was heated at 55 °C for 20 h. The resin was filtered, and the filtrate was concentrated in vacuo. The resulting yellow oil was chromatographed (elution with ethyl acetate-hexanes 1:2 to ethyl acetate-hexanes 2:1, followed by ethyl acetate-methanol 9:1) to give 101 mg (43%) of **20** as a white solid: mp 80−81 °C; IR (film) 3381, 1448, 1062 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 7.50−7.47 (m, 2 H), 7.39 (dd, J = 8.4, 6.6 Hz, 1 H), 4.92 (s, 4 H), 3.58 (t, J = 6.2 Hz, 2 H), 2.78 (t, J = 7.3 Hz, 2 H), 1.82−1.73 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 146.9, 130.0, 128.5, 127.8, 66.0, 62.4, 34.3, 26.4; ^{77}Se NMR (76 MHz, CD_3OD) δ 123.7; mass spectrum (EI-TOF) m/z (relative intensity) 276 (20, $[M]^+$), 198 (100); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{16}O_3{}^{80}Se$: 276.0265; found: 276.0256.

*Oxidation of Selenide **20** with Hydrogen Peroxide.* Selenide **20** (101 mg, 0.366 mmol) was dissolved in 5 mL of dichloromethane and 0.25 mL of methanol. Hydrogen peroxide (0.090 mL, 29%, 0.73 mmol) was added, and the solution was stirred at room temperature for 6 h. The solution was concentrated in vacuo and immediately chromatographed (elution with ethyl acetate-methanol 7:3) to give 100 mg (>99%) of selenurane **21** as a white solid. This compound decomposed over a period of 24 h under ambient conditions. ^1H NMR (400 MHz, CD_3OD), δ 7.67 (t, J = 7.4 Hz, 1 H), 7.40 (d, J = 7.4 Hz, 2 H), 5.08 (d, J = 14.2 Hz, 2 H), 4.97 (d, J = 14.2 Hz, 2 H), 3.58 (t, J = 6.1 Hz, 2 H), 3.29 (t, J = 7.7 Hz, 2 H), 1.82−1.73 (m, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 144.7, 134.4, 123.7, 123.6, 66.6, 61.6, 55.8, 28.9; ^{77}Se NMR (76 MHz, CD_3OD) δ 822.5; mass spectrum (EI-TOF) m/z (relative intensity) 274 (20, $[M]^+$), 216 (100); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{14}O_3{}^{80}Se$: 274.0108; found: 274.0111.

*Preparation of 2-Bromo-5-(methoxymethoxy)benzaldehyde (**24**).*[40] Phenol **23** (10.0 g, 49.7 mmol) was dissolved in 165 mL of dichloromethane under a nitrogen atmosphere, and the solution was cooled to 0 °C. Diisopropylethylamine (13.0 mL, 74.6 mmol) was added, followed by methoxymethyl chloride (4.5 mL, 59 mmol). The solution was stirred at room temperature for 24 h and quenched by addition of water. The solution was extracted with diethyl ether. The ether extracts were combined, washed with brine, dried, and concentrated to afford a brown oil. The crude product was chromatographed (elution with hexanes-ethyl acetate, 2:1) to afford 9.2 g (76%) of **24** as a clear, colorless oil; IR (film) 3088, 2963, 2898, 1699, 1468, 1259, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1 H), 7.57 (d, J = 3.1 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 1 H), 7.15 (dd, J = 8.7, 3.1 Hz, 1 H), 5.19 (s, 2 H), 3.47 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 157.0, 134.8, 134.3, 124.2, 119.0, 116.6, 94.6, 56.4; mass spectrum, (EI-GC TIC) m/z (relative intensity) 244 (90, M^+), 63 (100); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_9H_9{}^{79}BrO_3$: 243.9735; found: 243.9731.

*Preparation of (2-Bromo-5-(methoxymethoxy)phenyl)methanol (**25**).*[41] Aldehyde **24** (6.02 g, 24.6 mmol) was dissolved in 100 mL of THF-ethanol (4:1) under a nitrogen atmosphere, and the solution was cooled to 0 °C. Sodium borohydride (1.85 g, 48.9 mmol) was slowly added to the solution. The solution was warmed to room temperature and stirred for 1.5 h, following which a 5% sodium bicarbonate solution was added, and the solution was extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried, and concentrated in vacuo. The crude product was chromatographed (elution with ethyl acetate-hexanes, 1:2) to yield 5.56 g (92%) of **25** as a white solid, mp 54−56 °C; IR (film) 3454, 2958, 2903, 1467, 1157, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 1 H), 7.19 (d, J = 3.0 Hz, 1 H), 6.86 (dd, J = 8.7, 3.0 Hz, 1 H), 5.17 (s, 2 H), 4.71 (d, J = 6.3 Hz, 2 H), 3.47 (s, 3 H), 2.00 (t, J = 6.4 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 140.8, 133.2, 116.9, 116.7, 113.9, 94.4, 65.0, 56.0; mass spectrum, (EI, TIC) m/z (relative intensity) 246 (100, M^+), 216 (30), 63 (20); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_9H_{11}{}^{79}BrO_3$: 245.9892; found: 245.9900.

*Preparation of Di[(2-hydroxymethyl)-4-(methoxymethoxy)-phenyl] Diselenide (**26**).* Bromide **25** (1.00 g, 4.05 mmol) was dissolved in 50 mL of dry THF under a nitrogen atmosphere, and the solution was cooled to −78 °C. *t*-Butyllithium (5.3 mL, 1.6 M, 8.5 mmol) was slowly added, and the solution was stirred at −78 °C for 30 min and warmed to 0 °C for 30 min. Selenium (352 mg, 4.46 mmol) was added, and the solution was stirred at 0 °C for 1.5 h. The solution became homogeneous and yellow in color. Saturated ammonium chloride solution was added, and air was bubbled through the solution. The mixture was filtered, and the filtrate was diluted with ethyl acetate, washed with brine, dried, and concentrated under reduced pressure. The crude product was chromatographed (elution with hexanes-ethyl acetate, 2:1 and then ethyl acetate-hexanes, 2:1) to afford 987 mg (99%) of diselenide **26** as a dark orange oil. IR (film) 3407, 2995, 2921, 1463, 1231, 1148, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

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7.48 (d, J = 8.5 Hz, 2 H), 7.14 (d, J = 2.8 Hz, 2 H), 6.85 (dd, J = 8.4, 2.8 Hz, 2 H), 5.19 (s, 4 H), 4.63 (s, 4 H), 3.48 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 145.5, 138.7, 121.9, 116.3, 116.2, 94.4, 65.5, 56.3; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 445.7; mass spectrum, HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}NaO_6{}^{80}Se_2$: 516.9639; found: 516.9642.

*Preparation of of 2-(Hydroxymethyl)-4-(methoxymethoxy)-phenyl 3-Hydroxypropyl Selenide (**27**).* Diselenide **26** (177 mg, 0.359 mmol) was dissolved in 34 mL of THF-ethanol (4:1) under a nitrogen atmosphere, and the solution was cooled to 0 °C. Sodium borohydride (65 mg, 1.7 mmol) was added, and after 10 min, 3-bromo-1-propanol (0.07 mL, 0.8 mmol) was added. The solution was warmed to room temperature and stirred for 2 h. Water was added, and the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried, and concentrated under vacuum. The crude product was chromatographed (elution with hexanes-ethyl acetate, 1:1) to afford 130 mg (60%) of selenide **27** as a clear, colorless oil. IR (film) 3371, 2940, 1468, 1157, 1000 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 1 H), 7.13 (d, J = 2.8 Hz, 1 H), 6.90 (dd, J = 8.5, 2.8 Hz, 1 H), 5.17 (s, 2 H), 4.77 (s, 2 H), 3.78−3.64 (m, 2 H), 3.47 (s, 3 H), 2.91 (t, J = 7.2 Hz, 2 H), 2.39 (br s, 1 H), 1.90 (tt, J = 7.3, 6.1 Hz, 2 H), 1.54 (br s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 144.9, 137.0, 120.8, 116.5, 116.2, 94.4, 65.6, 62.2, 56.2, 32.7, 25.4; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 216.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{18}NaO_4{}^{80}Se$: 329.0263; found: 329.0253.

*Preparation of 2-(Hydroxymethyl)-4-hydroxyphenyl 3-Hydroxypropyl Selenide (**28**).* Selenide **27** (211 mg, 0.691 mmol) was dissolved in 7 mL of methanol. Concentrated hydrochloric acid (5 drops) was added, and the solution was heated at 55 °C for 3 h. The solution was diluted with ethyl acetate and washed with water and brine. The ethyl acetate was dried and concentrated in vacuo, and the product was recrystallized from ethyl acetate to provide 100 mg (55%) of selenide **28** as a white solid, mp 74−76 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 8.3 Hz, 1 H), 6.98 (d, J = 2.8 Hz, 1 H), 6.64 (dd, J = 8.3, 2.8 Hz, 1 H), 4.72 (s, 2 H), 3.60 (t, J = 6.3 Hz, 2 H), 2.81 (t, J = 7.3 Hz, 2 H), 1.80 (tt, J = 7.4, 6.3 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 157.5, 145.3, 136.8, 116.9, 114.40, 114.36, 63.9, 60.9, 32.6, 24.1; ^{77}Se NMR (76 MHz, CD_3OD) δ 209.3; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{14}NaO_3{}^{80}Se$: 285.0000; found: 285.0006. Anal. calcd for $C_{10}H_{14}O_3Se$: C, 45.99; H, 5.40; found: C, 46.22; H, 5.42.

*Oxidation of Selenide **28**.* Selenide **28** (50 mg, 0.19 mmol) was dissolved in 2 mL of dichloromethane, and hydrogen peroxide (27 μL, 26%, 0.21 mmol) was added. After 10 min the reaction was complete, and the solution was concentrated in vacuo. The crude product was chromatographed over silica-gel (ethyl acetate-methanol, 9:1) to afford 47 mg (95%) of the corresponding spirodioxyselenurane **41** as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, J = 8.7 Hz, 1 H), 6.85 (dd, J = 8.7, 2.5 Hz, 1 H), 6.77 (d, J = 2.5 Hz, 1 H), 5.26 (d, J = 14.3 Hz, 1 H), 5.02 (d, J = 14.4 Hz, 1 H), 4.22 (ddd, J = 9.5, 5.8, 3.9 Hz, 1 H), 3.79 (td, J = 9.2, 4.4 Hz, 1 H), 3.62 (ddd, J = 11.9, 7.7, 4.3 Hz, 1 H), 3.25 (ddd, J = 11.8, 9.7, 6.9 Hz, 1 H), 2.12−1.87 (m, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 162.2, 147.7, 129.7, 121.5, 116.8, 111.9, 70.6, 68.3, 50.0, 29.1; ^{77}Se NMR (76 MHz, CD_3OD) δ 797.9; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}O_3{}^{80}Se$: 261.0024; found: 261.0017.

*Reduction of Spiroselenurane **41**.* Selenurane **41** (200 mg, 0.772 mmol) was dissolved in 10 mL of dichloromethane, and benzyl thiol (0.18 mL, 1.5 mmol) was added. The original selenide **28** precipitated immediately. The mother liquor was concentrated in vacuo and chromatographed over silica-gel (elution with ethyl acetate, then ethyl acetate-methanol, 9:1) to afford 190 mg (95%) of selenide **28.**

*Oxidation of Selenide **11d**.* Selenide **11d** (10 mg) was dissolved in 2 mL of dichloromethane, and hydrogen peroxide (4 μL; 30%) was added. The mixture was monitored by TLC, and after 75 min the starting material was completely consumed. The solvent was evaporated, and the solid white residue was flash chromatographed (dichloroethane-methanol 90:10) to afford 8 mg (ca. 80%) of the spiroselenurane **42** as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 1 H), 6.95 (dd, J = 8.8, 2.5 Hz, 1 H), 6.84 (d, J = 2.5 Hz, 1 H), 5.35 (d, J = 14.5 Hz, 1 H), 5.18 (d, J = 14.5 Hz, 1 H), 4.45 (d, J = 3.6 Hz, 1 H), 4.39 (dt, J = 10.8, 1.4 Hz, 1 H), 3.87 (s, 3 H), 3.67 (dd, J = 10.8, 1.9 Hz, 1 H), 3.62 (d, J = 13.0 Hz, 1 H), 3.33 (dd, J = 12.8, 3.9 Hz, 1 H); ^{13}C NMR (101 MHz, CD_3OD) δ 162.5, 146.6, 128.8, 122.1, 114.7, 109.1, 72.5, 70.6, 70.4, 56.9, 55.7.

*Reduction of Spiroselenurane **42**.* Spiroselenurane **42** (4 mg,) was dissolved in dichloromethane, and benzyl thiol (3.5 μL) was added. The starting material was completely consumed within 2 min (TLC). The solvent was evaporated, and the product was flash chromatographed (ethyl acetate-methanol, 9:1) to afford 3 mg (ca. 75%) of selenide **11d**.

*Preparation of 2,6-Di[(methoxymethoxy)methyl]phenyl 2-[2-(2-Methoxyethoxy)ethoxy]ethyl Selenide (**29a**).* The diselenide **18** (150 mg, 0.247 mmol) was suspended in 6 mL of dry THF under nitrogen, and the mixture was cooled in an ice bath. Sodium borohydride (47.0 mg, 1.24 mmol) was added, followed by 2.0 mL of absolute ethanol. After 10 min, the solution became light yellow in color. Triethylene glycol monomethyl ether monotosylate **39a** (161 mg, 0.506 mmol) was added, and the mixture was warmed to room temperature and stirred for 3 h, resulting in a white, opaque solution. Hydrochloric acid (1 M) was added until the solution turned clear and colorless. The mixture was extracted with ethyl acetate, dried, concentrated under vacuum, and flash chromatographed over silica gel (elution with hexanes-ethyl acetate, 2:1) to afford 52 mg (23%) of selenide **29a** as a pale yellow oil; IR (film) 2921, 1458, 1400, 1149, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.8 Hz, 2 H), 7.36 (dd, J = 8.3, 6.8 Hz, 1 H), 4.88 (s, 4 H), 4.74 (s, 4 H), 3.62−3.55 (m, 6 H), 3.54−3.48 (m, 4 H), 3.42 (s, 6 H), 3.35 (s, 3 H), 2.87 (t, J = 6.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 129.0, 128.7, 128.0, 96.1, 71.9, 70.6, 70.5, 70.2, 70.0, 59.0, 55.5, 28.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 131.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{32}NaO_7{}^{80}Se$: 475.1205; found: 475.1204.

*Preparation of 2,6-Di(hydroxymethyl)phenyl 2-{2-[2-(Methoxyethoxy)ethoxy]ethoxy}ethyl Selenide (**30a**).* Selenide **29a** (52 mg, 0.12 mmol) was dissolved in 2 mL of methanol, and Amberlite acidic resin was added. The mixture was stirred at 55 °C for 48 h. The resin was filtered, the filtrate was concentrated, and the resulting oil was flash chromatographed over silica gel (elution with ethyl acetate-methanol, 9:1) to afford 24 mg (57%) of selenide **30a** as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (crude d, J = 8.2 Hz, 2 H), 7.35 (dd, J = 8.7, 6.2 Hz, 1 H), 4.89 (s, 4 H), 3.62−3.50 (m, 10 H), 3.37 (s, 3 H), 3.10 (broad s, 2 H), 2.96 (t, J = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 129.7, 128.2, 127.5, 72.0, 70.64, 70.57, 70.2, 69.9, 66.1, 59.1, 28.9; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 122.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{24}NaO_5{}^{80}Se$: 387.0681; found: 387.0683.

*Preparation of the Homologues **29b** and **30b**.* Diselenide **18** (418 mg, 0.687 mmol) and tosylate **39b** (268 mg, 0.739 mmol; limiting reagent) afforded 272 mg (74%) of **29b** as a pale yellow oil by the same procedure as employed for the preparation of **29a**; IR (film) 2881, 1459, 1149, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 2 H), 7.31 (dd, J = 8.2, 6.9 Hz, 1 H), 4.83 (s, 4 H), 4.69 (s, 4 H), 3.58−3.45 (m, 14 H), 3.36 (s, 6 H), 3.30 (s, 3 H), 2.82 (t, J = 7.0 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 128.9, 128.6, 127.9, 95.9, 71.8, 70.47, 70.45, 70.38, 70.37, 70.1, 69.9, 58.9, 55.3, 28.1; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 131.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{36}NaO_8{}^{80}Se$: 519.1468; found: 519.1462.

The deprotection of **29b** (255 mg, 0.515 mmol) was carried out in HCl-methanol, as in the deprotection of **27**, to afford 159 mg (76%) of **30b** as a pale yellow oil; IR (film) 3383, 2875, 1453, 1101, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (crude d, J = 8.6 Hz, 2 H), 7.31 (dd, J = 8.6, 6.2 Hz, 1 H), 4.83 (s, 4 H), 3.62−3.45 (m, 14 H), 3.38 (br s, 2 H), 3.33 (s, 3 H), 2.89 (t, J = 6.0 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 129.5, 127.9, 127.2, 71.9, 70.6, 70.52, 70.48, 70.45, 70.0, 69.9, 65.8, 59.0, 28.6; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 122.4; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{28}NaO_6{}^{80}Se$: 431.0943; found: 431.0938.

*Preparation of Bis(selenide) (**31a**).* Sodium borohydride (123 mg, 3.25 mmol) was added to a solution of diselenide **18** (428 mg, 0.703

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mmol) in dry THF (11 mL) under nitrogen at 0 °C, forming a yellow mixture. Absolute ethanol (7 mL) was added, followed by the dropwise addition of a solution of triethylene glycol di(*p*-toluenesulfonate) (**40a**) (294 mg, 0.641 mmol; limiting reagent) in dry THF (8 mL). The reaction stirred for 30 min at 0 °C, then refluxed for 3.5 h. The resulting cloudy yellow mixture was quenched with HCl (1 M, 9 mL) until it became transparent and pink, followed by extraction with ethyl acetate. The combined organic extracts were washed with 1 M NaOH and brine. The solution was dried and concentrated in vacuo to afford a yellow oil. The crude product was flash chromatographed over silica gel (hexanes:ethyl acetate, 1:1) and rechromatographed with (chloroform:ethyl acetate, 3:1, containing 1% methanol) to afford **31a** as a yellow oil (220 mg, 47%); IR (film) 2930, 2882, 1457, 1148, 1102, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 4 H), 7.38 (dd, J = 8.3, 6.8 Hz, 2 H), 4.89 (s, 8 H), 4.76 (s, 8 H), 3.57 (t, J = 7.0 Hz, 4 H), 3.48 (s, 4 H), 3.43 (s, 12 H), 2.86 (t, J = 7.0 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 129.0, 128.7, 128.0, 96.1, 70.7, 70.2, 70.0, 55.5, 28.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 131.4; mass spectrum, HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{46}NaO_{10}{}^{80}Se_2$: 749.1314; found: 749.1312.

*Preparation of Bis(selenide) (**32a**).* The MOM-protected bis-selenide **31a** (151 mg, 0.208 mmol) was dissolved in methanol (11 mL), and Amberlite acidic resin (250 mg) was added. The slightly yellow solution was stirred for 24 h at 55 °C. Additional acidic resin (500 mg) was added, but the reaction failed to go to completion. Three drops of concentrated HCl were added, and the mixture was stirred for 48 h at 55 °C. The acidic resin was filtered and rinsed with methanol, and the filtrate was concentrated in vacuo to afford a yellow oil. The crude product was flash chromatographed over silica gel (elution with ethyl acetate) to afford **32a** as an off-white solid (31 mg, 27%); mp 108−109 °C; IR (film) 3338, 2919, 1684, 1384, 1115, 1052 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.45−7.40 (m, 4 H), 7.37 (dd, J = 8.9, 5.8 Hz, 2 H), 5.18 (t, J = 5.5 Hz, 4 H), 4.72 (d, J = 5.6 Hz, 8 H), 3.46 (t, J = 6.7 Hz, 4 H), 3.38 (s, 4 H), 2.79 (t, J = 6.7 Hz, 4 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.1, 128.5, 125.7, 125.5, 69.8, 69.2, 63.8, 27.6; ^{77}Se NMR (76 MHz, DMSO-d_6) δ 115.5; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{30}O_6{}^{80}Se_2$: 551.0446; found: 551.0435.

*Preparation of the Homologues **31b** and **32b**.* Diselenide **18** (397 mg, 0.652 mmol) and ditosylate **40b** (208 mg, 0.414 mmol; limiting reagent) afforded 226 mg (71%) of **31b** as a pale yellow oil by the same procedure as employed for the preparation of **31a**; IR (film) 2932, 2882, 1461, 1149, 1111, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6 Hz, 4 H), 7.37 (dd, J = 8.3, 6.8 Hz, 2 H), 4.88 (s, 8 H), 4.75 (s, 8 H), 3.64−3.47 (m, 12 H), 3.42 (s, 12 H), 2.87 (t, J = 7.0 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 129.0, 128.8, 128.0, 96.1, 70.61, 70.55, 70.2, 70.1, 55.5, 28.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 131.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{50}NaO_{11}{}^{80}Se_2$: 793.1576; found: 793.1570.

The deprotection of **31b** (200 mg, 0.260 mmol) was performed by the same procedure as in the preparation of **32a**, except that Amberlite was omitted. Product **32b** (95 mg, 62%) was produced as a yellow oil; IR (film) 3371, 2865, 1453, 1420, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.40 (m, 4 H), 7.36 (dd, J = 8.6, 6.2 Hz, 2 H), 4.88 (s, 8 H), 3.61 (t, J = 6.0 Hz, 4 H), 3.53−3.49 (m, 8 H), 3.27 (br s, 4 H), 2.96 (t, J = 5.9 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 129.6, 128.1, 127.4, 70.4, 69.94, 69.87, 66.0, 28.8; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 123.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{35}O_7{}^{80}Se_2$: 595.0708; found: 595.0693.

*Preparation of 2-[3-(Benzoyloxy)propylselanyl]-5-(methoxymethoxy)benzyl Benzoate (**33**).* Selenide **27** (217 mg, 0.711 mmol) was dissolved in 7 mL of dichloromethane under a nitrogen atmosphere. Pyridine (0.13 mL, 1.6 mmol) was added, followed by benzoyl chloride (0.18 mL, 1.6 mmol), and the solution was stirred for 16 h. The reaction was quenched by the addition of water and extracted with diethyl ether. The ether was washed with 5% sodium bicarbonate solution, 5% HCl, and brine. The solution was dried, concentrated under vacuum, and chromatographed (elution with hexanes-ethyl acetate, 6:1) to give 290 mg (80%) of **33** as a clear, colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12−8.05 (m, 2 H), 8.03−7.98 (m, 2 H), 7.62−7.50 (m, 3 H), 7.47−7.38 (m, 4 H), 7.21 (d, J = 2.9 Hz, 1 H), 6.96 (dd, J = 8.5, 2.7 Hz, 1 H), 5.52 (s, 2 H), 5.16 (s, 2 H), 4.38 (t, J = 6.2 Hz, 2 H), 3.47 (s, 3 H), 2.97 (t, J = 7.3 Hz, 2 H), 2.11 (quintet, J = 6.6 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.3, 157.5, 140.3, 136.9, 133.2, 133.1, 130.3, 130.2, 129.9, 129.7, 128.6, 128.5, 122.0, 117.7, 116.7, 94.6, 67.2, 64.3, 56.3, 29.6, 25.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 227.8; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{26}H_{30}NO_6{}^{80}Se$: 532.1233; found: 532.1236.

*Preparation of 2-[3-(Benzoyloxy)propylselanyl]-5-hydroxybenzyl Benzoate (**34**).* Compound **33** (290 mg, 0.565 mmol) was dissolved in 5 mL of methanol. Concentrated hydrochloric acid (2 drops) was added, and the solution was heated at 55 °C for 3 h. Water was added, and the solution was extracted with dichloromethane, washed with brine, dried, and concentrated in vacuo. The resulting oil was chromatographed (elution with hexanes-ethyl acetate, 2:1) to give 210 mg (79%) of **34** as a clear, colorless oil; IR (film) 3403, 2931, 1713, 1454, 1264, 1106 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08−8.03 (m, 2 H), 8.01−7.97 (m, 2 H), 7.58−7.50 (m, 3 H), 7.45−7.37 (m, 4 H), 7.03 (d, J = 2.9 Hz, 1 H), 6.76 (dd, J = 8.4, 2.9 Hz, 1 H), 5.91 (br s, 1 H), 5.52 (s, 2 H), 4.37 (t, J = 6.2 Hz, 2 H), 2.93 (t, J = 7.3 Hz, 2 H), 2.09 (quintet, J = 6.7 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.6, 156.3, 140.6, 137.6, 133.3, 133.2, 130.2, 130.0, 129.9, 129.7, 128.6, 128.5, 120.1, 116.5, 116.3, 67.2, 64.4, 29.5, 25.3; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 225.3; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{24}H_{26}NO_5{}^{80}Se$: 488.0971; found: 488.0973.

*Preparation of 2-[3-(Benzoyloxy)propylselanyl]-5-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}benzyl Benzoate (**35**).* Selenide **34** (100 mg, 0.213 mmol) was dissolved in 5 mL of DMF, and potassium carbonate (65 mg, 0.47 mmol) was added, followed by triethylene glycol monomethyl ether monotosylate (**39a**) (75 mg, 0.24 mmol). The solution was heated at 110 °C for 16 h and then cooled to room temperature. It was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, and brine. The organic extract was dried and concentrated under vacuum, and the crude product was chromatographed (elution with ethyl acetate−hexanes 2:1) to give 80 mg (61%) of selenide **35** as a clear, colorless oil. IR (film) 2921, 2870, 1722, 1449, 1273, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08−804 (m, 2 H), 8.03−7.97 (m, 2 H), 7.59−7.52 (m, 3 H), 7.46−7.38 (m, 4 H), 7.08 (d, J = 2.8 Hz, 1 H), 6.81 (dd, J = 8.5, 2.9 Hz, 1 H), 5.53 (s, 2 H), 4.37 (t, J = 6.2 Hz, 2 H), 4.11 (dd, J = 5.7, 4.1 Hz, 2 H), 3.84 (dd, J = 5.7, 4.0 Hz, 2 H), 3.75−3.70 (m, 2 H), 3.70−3.62 (m, 4 H), 3.56−3.52 (m, 2 H), 3.36 (s, 3 H), 2.95 (t, J = 7.3 Hz, 2 H) 2.13−2.05 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 166.2, 159.1, 140.3, 137.2, 133.1, 133.0, 130.2, 130.1, 129.8, 129.6, 128.5, 128.4, 120.6, 116.0, 115.1, 72.0, 70.9, 70.7, 70.6, 69.7, 67.6, 67.2, 64.2, 59.1, 29.4, 25.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 226.4; HRMS (ESI-TOF) m/z: $[M + NH_4]^+$ Calcd for $C_{31}H_{40}NO_8{}^{80}Se$: 634.19137; found: 634.19023.

*Preparation of 2-[3-(Hydroxyl)propylselanyl]-5-{2-[2-(2-methoxyethoxy) ethoxy]ethoxy}benzyl Alcohol (**36**).* Selenide **35** (38 mg, 0.062 mmol) was dissolved in 5 mL of methanol. Potassium carbonate (26 mg, 0.19 mmol) was added, and the mixture was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate, washed with water and brine, dried, and concentrated under reduced pressure. The product was flash chromatographed over silica gel (elution with ethyl acetate-methanol, 9:1) to furnish 13 mg (51%) of selenide **36** as a clear, colorless oil; ^1H NMR (400 MHz, CD_3OD) δ 7.49 (d, J = 8.5 Hz, 1 H), 7.04 (d, J = 2.9 Hz, 1 H), 6.76 (dd, J = 8.5, 2.9 Hz, 1 H), 4.76 (s, 2 H), 4.13 (t, J = 4.9 Hz, 2 H), 3.84 (t, J = 4.8 Hz, 2 H), 3.75−3.62 (m, 8 H), 3.55−3.51 (m, 2 H), 3.37 (s, 3 H), 2.87 (t, J = 7.2 Hz, 2 H), 2.75 ((br s, 1 H), 1.92 (br s, 1 H), 1.86 (quintet, J = 6.6 Hz, 2 H); ^{13}C NMR (101 MHz, CD_3OD) δ 159.1, 145.0, 137.0, 119.1, 115.0, 114.7, 71.9, 70.8, 70.6, 70.5, 69.7, 67.5, 65.4, 62.0, 59.0, 32.6, 25.3; ^{77}Se NMR (76 MHz, CD_3OD) δ 212.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{28}NaO_6{}^{80}Se$: 431.0943; found: 431.0944.

*Preparation of Bis(selenide) (**37**).* Selenide **34** (165 mg, 0.352 mmol) was dissolved in 10 mL of dry DMF under nitrogen, and potassium carbonate (107 mg, 0.773 mmol) was added, followed by the triethylene glycol ditosylate (**40a**) (81 mg, 0.18 mmol). The

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solution was heated at 110 °C for 20 h, cooled, and diluted with ethyl acetate. The solution was washed with saturated sodium bicarbonate, water, and brine and dried. The solution was concentrated under vacuum, and the resulting oil was flash chromatographed over silica gel (elution with hexanes-ethyl acetate, 2:1) to provide 100 mg (54%) of product **37** as a clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.02 (m, 4 H), 7.99−7.95 (m, 4 H), 7.56−7.49 (m, 6 H), 7.42−7.36 (m, 8 H), 7.06 (d, J = 2.8 Hz, 2 H), 6.78 (dd, J = 8.5, 2.9 Hz, 2 H), 5.50 (s, 4 H), 4.35 (t, J = 6.2 Hz, 4 H), 4.08 (t, J = 4.9 Hz, 4 H), 3.82 (t, J = 4.8 Hz, 4 H), 3.70 (s, 4 H), 2.93 (t, J = 7.3 Hz, 4 H), 2.07 (quintet, J = 6.8 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 166.4, 159.2, 140.4, 137.3, 133.3, 133.1, 130.4, 130.2, 129.9, 129.7, 128.6, 128.5, 120.8, 116.2, 115.2, 71.1, 69.9, 67.7, 67.3, 64.3, 29.6, 25.3; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 226.4; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{54}H_{54}NaO_{12}{}^{80}Se_2$: 1077.1838; found: 1077.1807.

*Preparation of Bis(selenide) (**38**).* Selenide **37** (80 mg, 0.076 mmol) was suspended in 5 mL of methanol. Potassium carbonate (412 mg, 2.98 mmol) was added, and the mixture was stirred for 3 h. A solution of 5% sodium bicarbonate was added, and the mixture was extracted with ethyl acetate. The ethyl acetate was washed with 5% sodium bicarbonate solution and brine, dried, and concentrated in vacuo. The crude product was flash chromatographed (elution with ethyl acetate-methanol, 9:1) to afford 19 mg (40%) of product **38** as a clear, colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (d, J = 8.5 Hz, 2 H), 7.12 (d, J = 2.9 Hz, 2 H), 6.79 (dd, J = 8.4, 2.9 Hz, 2 H), 4.75 (s, 4 H), 4.13 (crude t, J = 4.6 Hz, 4 H), 3.86 (crude t, J = 4.6 Hz, 4 H), 3.73 (s, 4 H), 3.61 (t, J = 6.3 Hz, 4 H), 2.85 (t, J = 7.3 Hz, 4 H), 1.82 (quintet J = 6.8 Hz, 4 H); ^{13}C NMR (101 MHz, CD_3OD) δ 159.0, 145.1, 136.2, 118.9, 113.73, 113.66, 70.4, 69.5, 67.3, 63.9, 60.9, 32.7, 24.1; ^{77}Se NMR (76 MHz, CD_3OD) δ 212.9; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{26}H_{39}O_8{}^{80}Se_2$: 639.0970; found: 639.0976.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01593.

^{1}H, ^{13}C and ^{77}Se NMR spectra of final products; kinetic plots for assays of antioxidant activity (PDF)

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Notes

The authors declare no competing financial interest.

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