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Fluxional Cyclic Seleninate Ester: NMR and Computational Studies, Glutathione Peroxidase-like Behavior, and Unexpected Rearrangement

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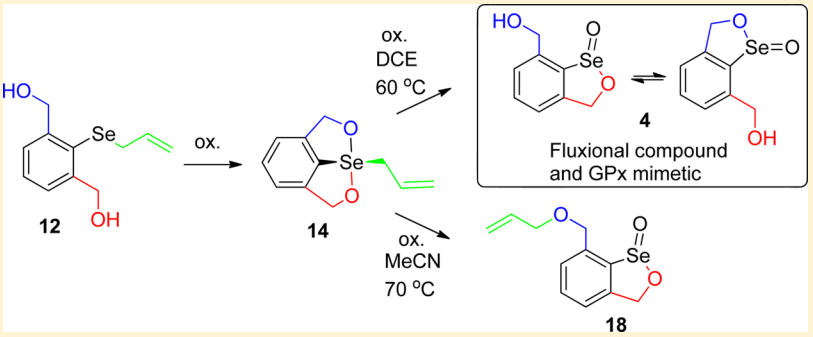
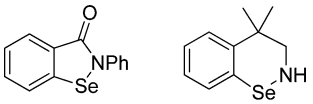
Supporting Information



ABSTRACT: The oxidation of allyl selenide **12** with hydrogen peroxide produced the corresponding allyl selenurane **14**, the cyclic seleninate ester **4**, or the rearranged *O*-allyl seleninate ester **18**, dependng on the conditions. Crossover experiments with selenide **12** and its deuterated crotyl analogue **27** indicated an intramolecular rearrangement that proceeds by an intramolecular pathway where the allyl or crotyl group is translocated via its distal carbon atom to the hydroxymethyl functionality. Variable-temperature NMR experiments with cyclic seleninate ester **4** revealed fluxional behavior at room temperature that was catalyzed by trifluoroacetic acid. Computational studies indicated an activation energy of 12.3 kcal mol^{-1} for hydroxyl interchange at selenium, comparable to the value of 15.5 kcal mol^{-1} derived from the NMR experiments. The glutathione peroxidase-like activity of **4** was measured in an assay where the catalysis of the reduction of hydrogen peroxide with benzyl thiol was monitored by the appearance of dibenzyl disulfide. The catalytic activity of **4** was double that observed with the unsubstituted seleninate ester **2** but was limited by the competing accumulation of the relatively inert selenenyl sulfide **32**, resulting in a deactivation pathway that competes with the primary catalytic cycle.

INTRODUCTION

Glutathione peroxidase (GPx)[1] is a selenoenzyme that plays a key role in protecting higher organisms from oxidative stress caused by the production of reactive oxygen species (ROS) such as peroxides during aerobic metabolism. GPx performs this function by catalyzing the reduction of hydroperoxides and hydrogen peroxide to alcohols or water with glutathione, a tripeptide thiol that is ubiquitous in the cells of higher organisms. Selenium deficiency and excessive formation of ROS have in turn been implicated in inflammation, neurodegenerative, and cardiovascular disease, as well as in cancer and mutagenesis.[2] Paradoxically, selenium compounds can also promote the formation of ROS that, in other circumstances, are beneficial in destroying pathogens and inducing apoptosis of cancer cells.[3] Collateral damage from oxidative stress is of particular concern during ischemic reperfusion of heart attack and stroke patients.[4] Consequently, there has been considerable interest in the discovery of small-molecule selenium compounds that mimic the function of GPx and could serve to augment its protective activity in conditions of exceptionally elevated oxidative stress. The subject has been reviewed,[2a,5] and various types of organoselenium and tellurium species have been investigated for GPx-like activity.[6−19] Two compounds, ebselen[6h,20] and ALT 2074 (formerly BXT 51072),[21] have undergone phase III and phase II clinical trials by Daiichi-Sankyo Inc. and Synvista Inc., respectively, for various conditions related to oxidative stress and inflammation, including reperfusion injury.



Ebselen ALT 2074 (BXT 51072)

Several years ago, we reported the discovery of the simple aliphatic cyclic seleninate ester **1** and observed that it exhibits powerful GPx-like activity.[22] Subsequently, we investigated the aromatic compound **2** and its derivatives[23] because of the

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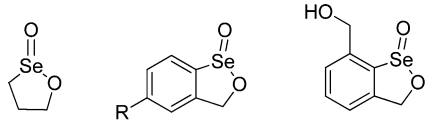
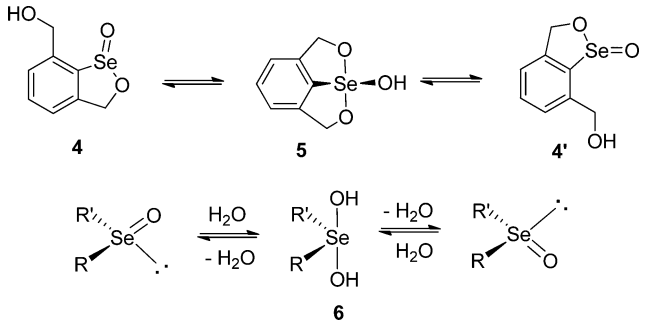
expectation that they would better resist metabolic degradation and prove less toxic than aliphatic derivatives.[5d,24] Unfortunately, aromatic congeners such as **2** typically displayed considerably lower catalytic activity than **1**, although this could be mitigated by the introduction of electron-donating substituents *para* to the selenium atom, as in the methoxy derivative **3**.[23b] Independent investigations of the structural and antioxidant properties of several cyclic seleninate esters were carried out by Singh et al.,[25] while the ability of **2** and its derivatives to catalyze the oxidation of sulfides to sulfoxides, alkenes to epoxides, and enamines to α-hydroxy ketones was reported by our laboratory.[26] The selenium atom of a seleninate ester comprises a stereocenter, and such compounds are therefore chiral. The resolution of cyclic seleninate esters was recently accomplished by Kamigata et al.[27]



The relatively poor water solubility of the aromatic derivatives such as **2** and **3** diminishes their utility as biological antioxidants, as they must be administered by gavage instead of intravenously.[28] To overcome this limitation, we embarked on a study of the novel hydroxymethyl derivative **4**, which was expected to show improved water solubility and thus be more amenable to intravenous administration. We also hypothesized that the latter compound might display fluxional behavior through hydroxyl exchange via the formation of intermediate **5** in a process resembling the racemization of selenoxides via hydrates **6**[29] (Scheme 1). Moreover, it was of interest to

Scheme 1

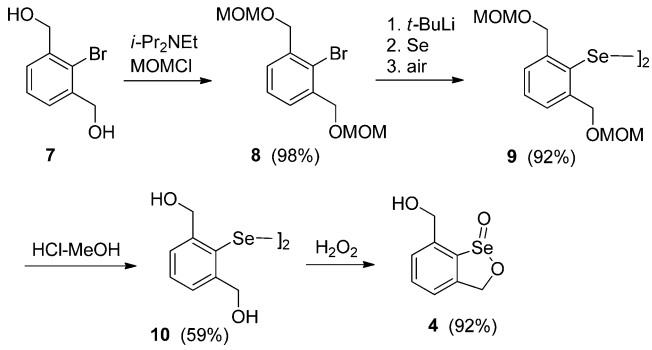


determine what effect this would have on the ability of **4** to catalyze the reduction of peroxides with thiols. We now report the synthesis and catalytic activity of seleninate **4**, along with NMR and computational studies of its fluxional properties. Furthermore, we also describe unexpected rearrangements of allylic substituents from the selenium atom of related selenurane derivatives to the hydroxymethyl moiety that were observed during the course of this work.

RESULTS AND DISCUSSION

The novel cyclic seleninate ester **4** was prepared as shown in Scheme 2. The bromide **7**[30] was protected as the methoxymethyl (MOM) derivative **8** and transmetalated with *t*-butyllithium. Treatment of the resulting anion with elemental selenium, followed by air oxidation, afforded the diselenide **9**,

Scheme 2



which could not be completely purified. Deprotection of crude **9** and oxidation of **10** with hydrogen peroxide then provided the desired product **4** in an overall yield of 49%.

Formation and Rearrangement of Selenurane 14. In previous syntheses of other cyclic seleninate esters by this method, difficulties in the purification of diselenide intermediates (often caused by the formation of small amounts of selenides and polyselenides) were overcome by prior conversion to the more easily purified allyl selenides. The latter could then be transformed directly into cyclic seleninate esters by a series of oxidation and [2,3] sigmatropic rearrangement steps.[22,23] In the present case, diselenide **9** was similarly converted into the allyl selenide **11**, which was deprotected with Amberlite IR-120 (H) resin (Scheme 3). The resulting diol **12** was then treated with 2 equiv of hydrogen peroxide in dichloromethane at room temperature, affording the allyl selenurane **14** in quantitative yield.[31−33] The competing formation of the cyclic seleninate ester **4** was not observed under these conditions. Evidently, the pincer-like cyclization of the initially formed selenoxide **13** by the two hydroxymethyl substituents proceeds even faster than the expected [2,3] sigmatropic rearrangement to the selenenate ester **15**. This is noteworthy, as allyl selenoxides are known to undergo rapid [2,3] shifts,[34] even at room temperature. On the other hand, the use of 1,2-dichloroethane at the elevated temperature of 60 °C produced seleninate ester **4**, albeit in only 54% yield, thus offering no significant advantage over its preparation by direct oxidation of diselenide **10**. Oxidation of authentic **14** under the latter conditions afforded **4** in 50% yield, thus confirming that **14** is a likely intermediate in the formation of **4** from selenide **12**. We suggest that in the presence of 2 equiv of hydrogen peroxide at elevated temperature, the initially formed selenurane is further oxidized to the corresponding *Se*-oxide **16**, which undergoes a [2,3] shift to **17**, prior to hydrolysis to **4** via **5**. Alternatively, nucleophilic attack by water upon the allyl group of the preceding intermediate **16**, with reductive elimination at the selenium center, would also provide a possible route to **4**. In a third experiment, the oxidation of **12** was repeated in the more polar solvent acetonitrile at elevated temperature. To our surprise, the principal product was neither the selenurane **14** nor the seleninate ester **4**, which was formed in only 29% yield. Instead, we isolated a 65% yield of a product that contained an *O*-allyl group but, unlike **14**, had clearly become desymmetrized, as evident from its ^{1}H and ^{13}C NMR spectra. The spectra of this product were consistent with the structure of the rearranged allyl ether **18**. A small amount of **18** (<20%) was also detected in the previous experiment in 1,2-dichloroethane at 60 °C.

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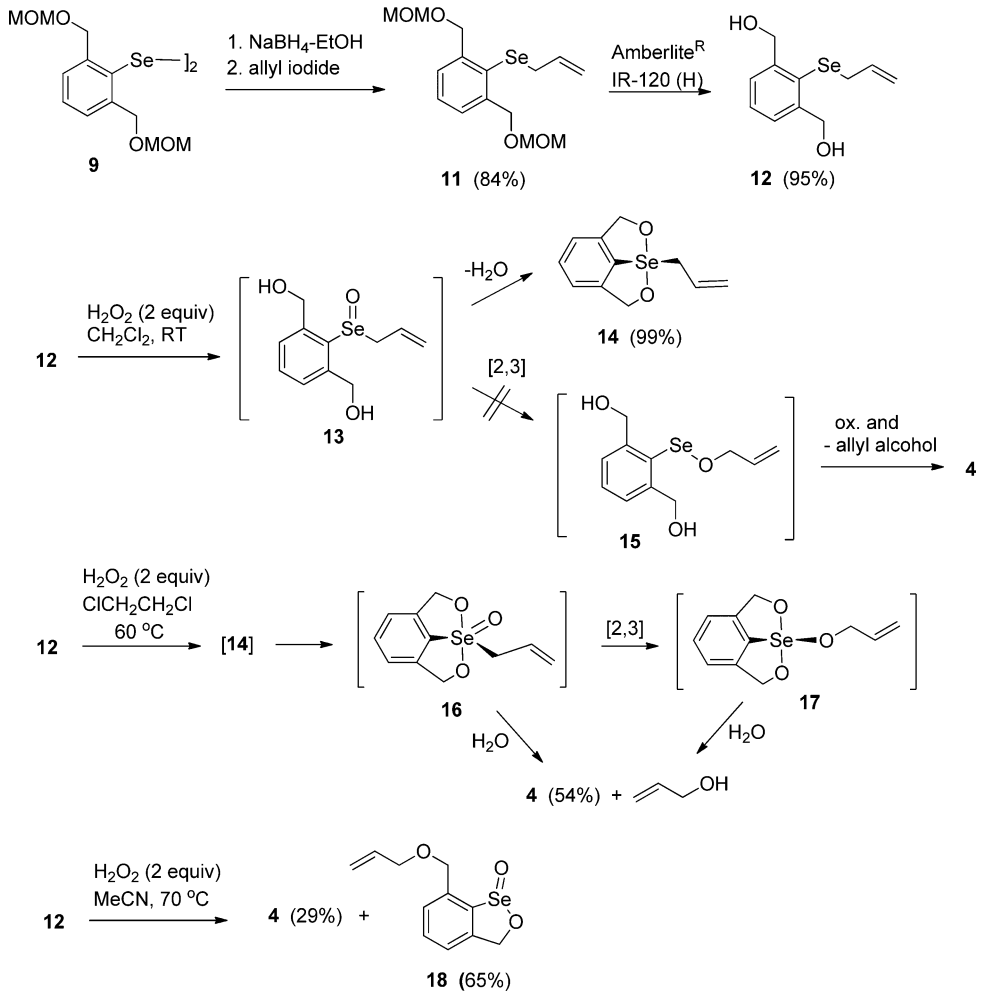
Scheme 3



When the experiment in acetonitrile at 70 °C was repeated with authentic selenurane **14** instead of with selenide **12**, products **4** and **18** were again observed, consistent with the relatively rapid initial formation of **14** from **12**, followed by its rearrangement to **18**.

In order to rationalize the formation of allyl ether **18** from allyl selenide **12** in acetonitrile (and to a lesser extent in 1,2-dichloroethane), we considered four hypothetical pathways, as shown in Scheme 4. In one scenario, the oxidation and [2,3] sigmatropic rearrangement of **12** first produces selenurane **17** via **14** and **16**, as shown previously in Scheme 3. This is followed by Se−O hydrolysis in **17**, with cleavage of the Se bond to the allylic oxygen (path a) or of an oxaselenolane Se−O bond (path b). Intermolecular reaction of the intermediate **5** in path a with allyl alcohol at the benzylic position would then afford the rearranged product **18**.[35] Furthermore, an intramolecular nucleophilic substitution in **19** in path b could also account for the formation of **18** but would require either an S_N2 mechanism via a 7-*endo-tet* transition state or an S_N2' pathway via an entropically disfavored nine-centered transition state. In path c, hydrolysis of the *Se*-oxide **16**, followed by intramolecular S_N2 substitution of the intermediate **20**, albeit via a disfavored 6-*endo-tet* transition state, would also afford product **18**, as would the corresponding 8-centered S_N2' reaction.[36,37] It is also possible that the reactions of **16** or **17** proceed via their ionization to produce **22**−**24** instead of the hydrolyzed species **5**, **19**, and **20**, assisted by the polar solvent and by electron donation to selenium from the adjacent oxaselenolane oxygen atoms. The subsequent allyl transposition could then take place direcly from ion pair **22** or zwitterions **23** and **24**. Finally, we considered the possibility that the further reaction of allyl alcohol with cyclic seleninate ester **4**, both first produced as shown in Scheme 3, affords **18** via attack of the alcohol upon the benzylic methylene group of **4**, followed by recyclization of **21** (path d in Scheme 4). However, when authentic **4** was heated at 70 °C with allyl alcohol in acetonitrile, no detectable amount of **18** was observed and 85% of the unreacted seleninate ester **4** was recovered, thereby unequivocally ruling out path d.

Further insight into the mechanism of the rearrangement was achieved by means of a crossover experiment. The crotyl selenide **25** (formed as a 5:1 mixture of *E*/*Z* isomers) was first obtained via an analogous route to that employed for the preparation of the allyl derivative **12** and was observed to undergo the same rearrangement as the latter compound upon oxidation and heating in acetonitrile to afford the branched product **26** as a 1:1 mixture of two diastereomers (Scheme 5). The deuterated analogue **27** was then prepared, and a mixture of **27** with an equal amount of the nondeuterated allyl selenide **12** was treated under similar conditions to those used in the preparation of **18** in Scheme 3 and **26** in Scheme 5. Of the four possible products **18**, **26**, **28**, and **29**, only the conserved pair

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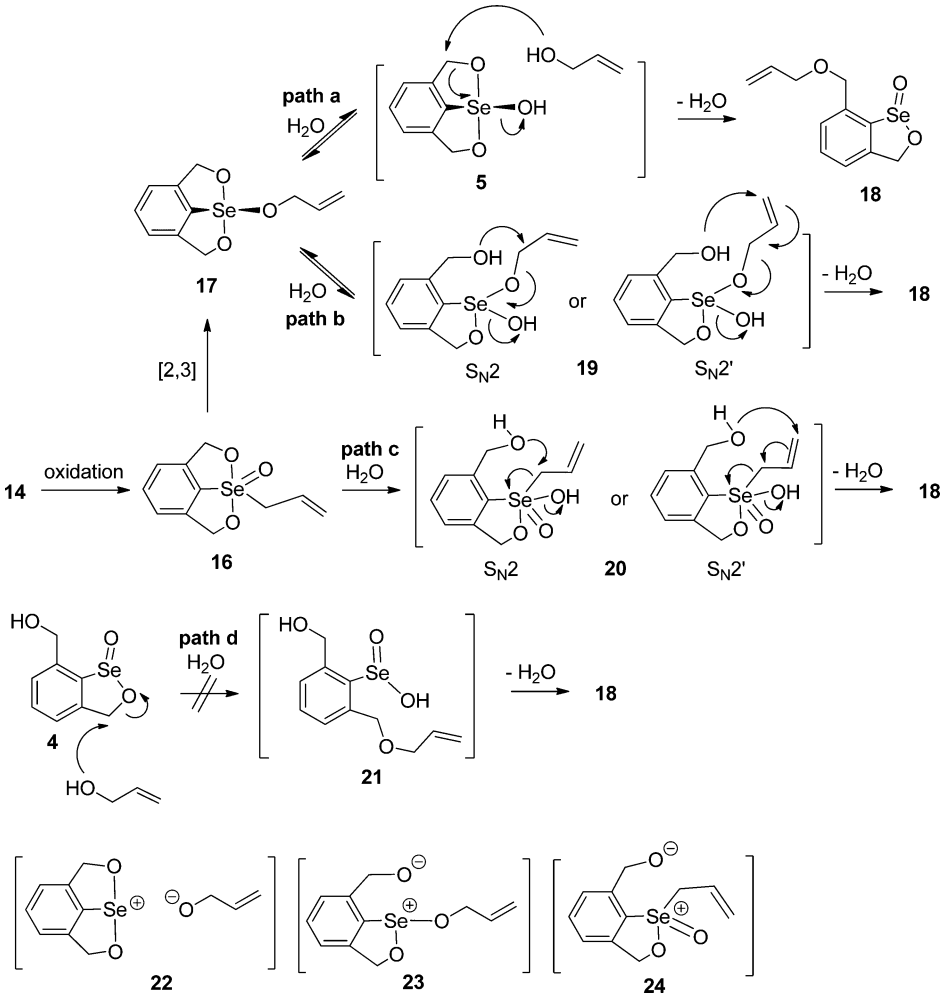
Scheme 4



(**18** and **28**) was produced, as determined by NMR and mass spectroscopy. Thus, the unseparated product mixture produced ^{1}H and ^{13}C NMR spectra that closely resembled the superimposed spectra of authentic **18** and **28** (for the NMR spectra of the crossover products, see the Supporting Information). In addition, the mass spectrum of the mixture revealed the expected parent ions and isotope clusters for the latter products at *m*/*z* 271.9953 and 290.0370 (based on ^{80}Se), respectively, but not the corresponding peaks for the crossover products **26** and **29**. The absence of **26** and **29** therefore rules out the intermolecular process as depicted in paths a and d of Scheme 4 and is consistent with the intramolecular rearrangements via path b or c. Furthermore, the observed formation of the branched 2-(but-3-enyl) product **26**, instead of its linear 1-(but-2-enyl) isomer, from **25** in Scheme 5 provides additional insight if it is assumed that the analogous pathways to b and c in Scheme 4 are also applicable to the crotyl series shown in Scheme 5. In path b, where the allylic transposition step is preceded by a [2,3] sigmatropic rearrangement, an intramolecular S_N2 substitution would be required to obtain the branched product **26**, whereas in path c, where no prior [2,3] shift occurs, the intramolecular S_N2' process would lead to the observed product **26**.

In a second crossover experiment, the allyl selenurane **14** was heated with 1 equiv of hydrogen peroxide and 1 equiv of crotyl alcohol in acetonitrile at 70 °C (Scheme 5) in order to determine whether this would afford the transposed allyl ether **18** or the crotyl derivative **26**. Product **18** was isolated in 63% yield, along with 35% of the seleninate ester **4**, while none of the crotyl product **26** was detected, thus providing further corroboration of the intramolecular nature of the rearrangement.

The crossover experiments and the exclusive formation of the branched product **26** in Scheme 5 therefore enable us to rule out not only the intermolecular processes shown in paths a and d in Scheme 4 but also the S_N2' variation of path b and the S_N2 substitution in path c. While an unequivocal choice between the remaining S_N2 variation of path b and the S_N2' variation of path c cannot be made, path c may be the more compelling mechanism based on its superior leaving group, where the departing selenium atom is in a higher oxidation state.

Fluxional Behavior of Cyclic Seleninate Ester 4. A series of variable-temperature ^{1}H NMR experiments were performed with cyclic seleninate ester **4** in order to investigate its possible fluxional behavior. At room temperature, a sample in $CDCl_3$ displayed significantly broadened peaks for both pairs of methylene protons, as well as for the signals from the two aromatic protons *meta* to the selenium atom (Figure 1). Extreme broadening of all signals except that from the aromatic *para* hydrogen was observed upon heating the sample to 328 K, with coalescence of the *meta* hydrogen signals occurring at ca.

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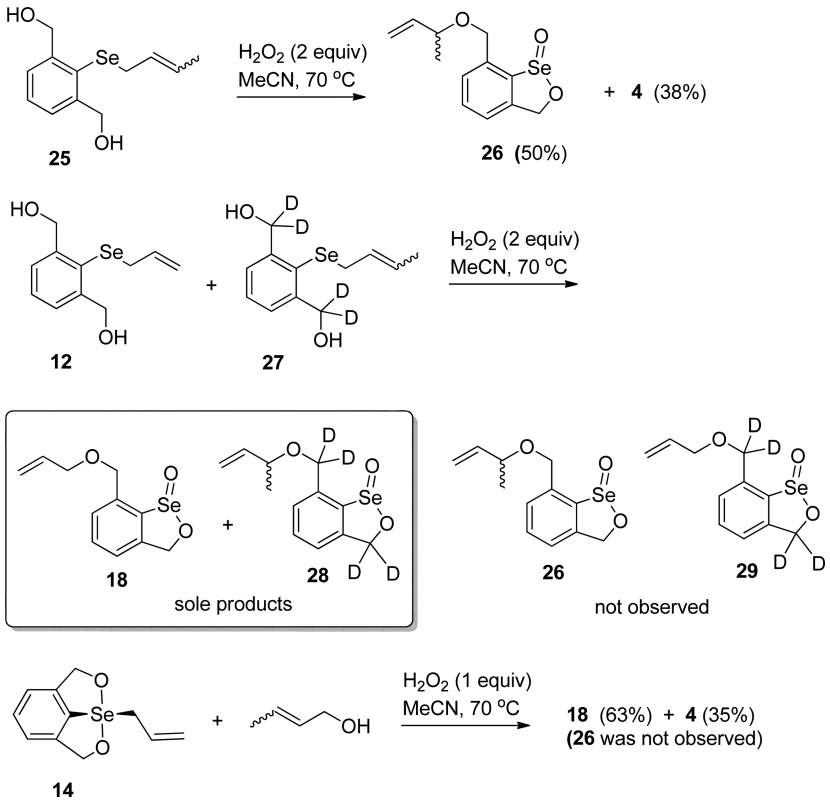
Scheme 5



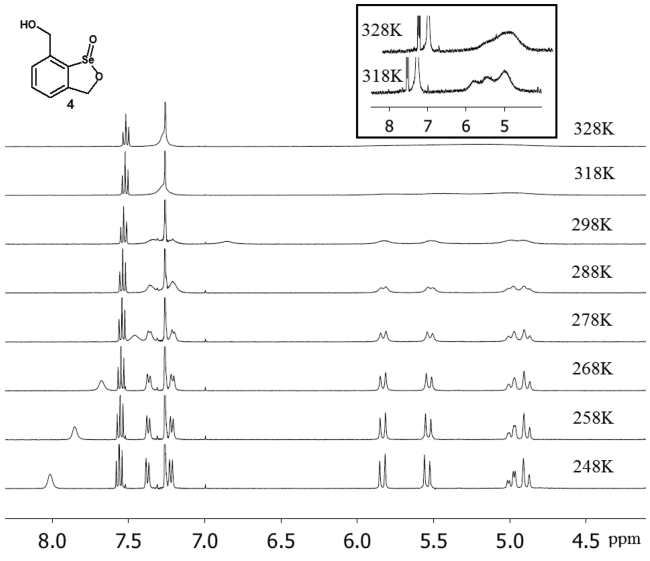


Figure 1. Variable-temperature ^{1}H NMR spectra of **4** in $CDCl_3$. Inset shows the region between 5 and 8 ppm at temperatures near coalescence.

318 K, corresponding to an activation energy $\Delta G^{\ddagger}$ = 15.5 kcal mol^{-1}.[38a] On the other hand, cooling to 248 K resolved the methylene signals into a well-defined AB quartet and a multiplet and revealed three distinct sets of aromatic signals. Furthermore, the downfield resonance of the hydroxyl proton at 8.05 ppm is consistent with a strongly hydrogen-bonded structure. Similar observations were made in CD_3CN solution in the temperature range of 238−318 K (Supporting Information). Finally, when the heating and cooling cycles were complete in either solvent and the samples were returned to room temperature, the original spectra were restored, indicating that the process is reversible. However, when a sample was heated in increments to 418 K in DMF-d_7, extreme broadening of the signals was again evident,[38b] but the original spectrum was not regenerated upon recooling to room temperature, suggesting that irreversible polymerization or decomposition of the sample had occurred at this higher temperature. These results indicate a very facile fluxional exchange process that is rapid on the NMR time scale, even at room temperature.[38c] As expected, the addition of 5% TFA to the $CDCl_3$ solution (Figure 2) catalyzed the exchange process significantly, presumably by protonation of the selenoxide-like oxygen atom of **4**, thus facilitating the formation of the intermediate **5** (see Scheme 1) or its trifluoroacetoxy derivative.

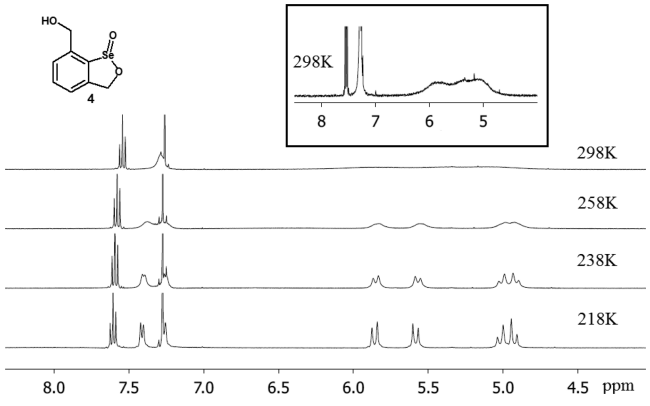


Figure 2. Variable-temperature ^{1}H NMR spectra of **4** in $CDCl_3$ containing 5% TFA. Inset shows the region between 5 and 8 ppm near coalescence.

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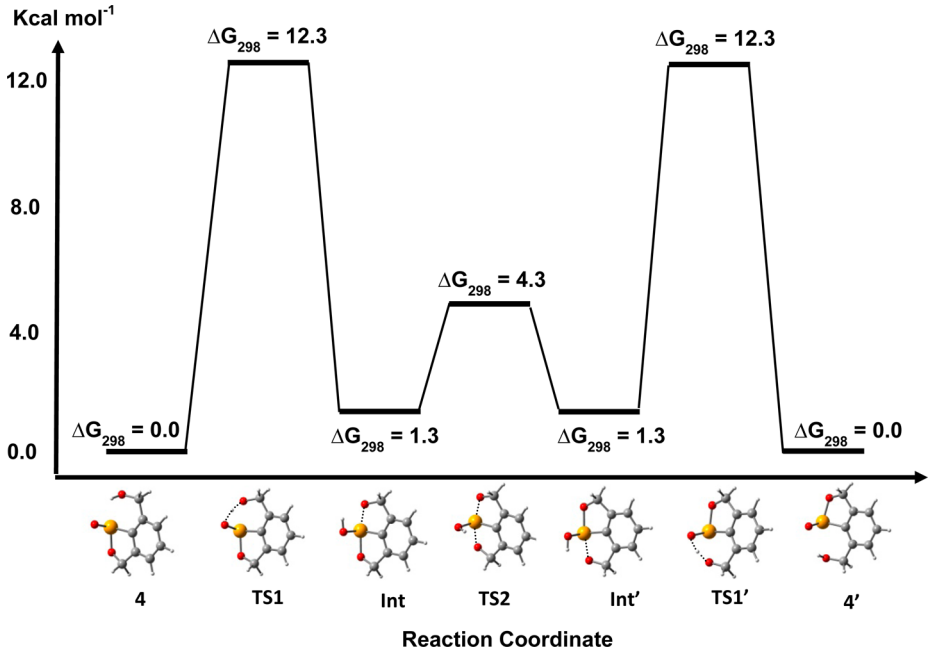


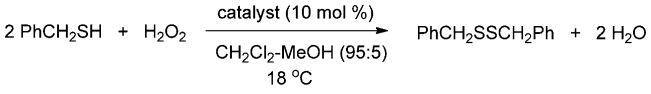
Figure 3. Potential energy surface for fluxional interconversion of **4** to **4′**.

This is evident from a comparison of the spectra in the presence or absence of 5% TFA at 258 K, where **4** in $CDCl_3$ alone displays clearly resolved methylene and aromatic signals, while these signals are almost completely coalesced in the presence of the acid.

Computational Results. Computational experiments on the proposed fluxional process in cyclic seleninate ester **4** via the selenurane intermediate **5** (see Scheme 1) were performed as described in the Experimental Section. The potential energy surface is shown in Figure 3, and additional computational details are contained in the Supporting Information. The results indicate a Gibbs free energy of activation ($\Delta G^{\ddagger}$) of 12.3 kcal mol^{-1}, leading to a transition state (TS1) where proton transfer from the hydroxymethyl group to the selenoxide oxygen atom is in progress and leads to an intermediate (Int) resembling a slightly distorted selenurane **5**, with unequal Se−OCH_2 bond lengths of 1.988 and 1.911 Å. The process then continues via rotation about the Se−OH bond to produce a symmetrical transition state (TS2) closely resembling **5**, with essentially equal Se−OCH_2 bond lengths (1.953 and 1.952 Å) and a smaller activation energy ($\Delta G^{\ddagger}$ = 3.0 kcal mol^{-1}). Finally, oxygen exchange at selenium is completed via an intermediate (Int′) and transition state (TS1′) analogous to Int and TS1. These computational results are roughly in accord with the experimental $\Delta G^{\ddagger}$ of 15.5 kcal mol^{-1} and are consistent with a facile fluxional hydroxyl exchange process at the selenium center of seleninate **4**. However, attempts to isolate or detect the intermediate by low- or room-temperature ^1H or ^{77}Se NMR spectroscopy were unsuccessful.

Glutathione Peroxidase Activity of Cyclic Seleninate Ester 4 and Its Derivatives. Several years ago, we developed an assay for measuring the catalytic activity of various small-molecule selenium compounds in the reduction of peroxides with benzyl thiol (Scheme 6).[39] The reaction can be easily followed by monitoring the production of dibenzyl disulfide by HPLC or ^1H NMR spectroscopy. The time required for the reaction to reach 50% completion ($t_{1/2}$) provides a convenient parameter for comparing various catalysts, some of which are

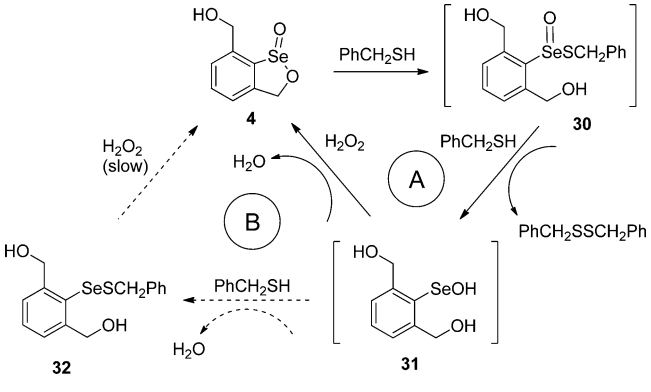
Scheme 6



catalyst	$t_{1/2}$ (h)
none (control)	>300
2	50 (ref. 23b)
4	25
32	80
12	21
37	9.5

shown in Scheme 6. We had previously postulated that the catalytic activity of cyclic seleninates such as **1**−**3** can be represented by cycle A in Scheme 7 (illustrated for **4** herein), where rapid thiolysis of the cyclic seleninate to thiolseleninate **30**[40] is followed by reaction with a second mole of thiol and finally by rate-limiting oxidation and cyclization of the resulting intermediate **31** to regenerate **4**. However, we also observed a competing deactivation pathway (cycle B), in which formation of the relatively inert selenenyl sulfide **32** occurs instead of the

Scheme 7



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oxidation and cyclization of **31** back to the cyclic seleninate.[22,23a,41] Furthermore, the competition between cycles A and B is highly dependent on the conditions, especially the ratio of thiol to peroxide. In the presence of excess thiol, the deactivation pathway B is followed almost exclusively, thereby limiting the utility of these compounds as GPx mimetics.

The kinetic plot for the formation of dibenzyl disulfide from the corresponding thiol and hydrogen peroxide in the presence of seleninate **4** as measured by HPLC is shown in Figure 4 and

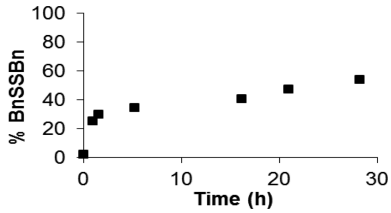


Figure 4. Kinetic plot for the reduction of hydrogen peroxide with benzyl thiol in dichloromethane–methanol (95:5) in the presence of 10 mol % of seleninate ester **4**.

indicates that $t_{1/2}$ for this process under the standard conditions in dichloromethane–methanol (95:5) is 25 h (see Scheme 6). This represents a 2-fold improvement compared to **2**, with the value of $t_{1/2}$ = 50 h,[23b] but is inferior to several related spirodioxyselenuranes that were previously investigated under these conditions.[23,32] The salutary effect of the hydroxymethyl group of **4** compared to the unsubstituted seleninate **2** can be attributed to the electron-donating properties of the substituent, which are known to accelerate such processes,[23b] and possibly to the ability of the *ortho*-hydroxymethyl group to facilitate the oxidation of the intermediate **31** through more extensive hydrogen bonding with the hydrogen peroxide. It is not known whether oxidation with hydrogen peroxide precedes or follows cyclization in the conversion of selenenic acid **31** to cyclic seleninate ester **4** in Scheme 7 or whether the fluxional behavior of **4** contributes to its improved catalytic ability compared to that of seleninate **2**.

It is also noteworthy that the plot in Figure 4 shows a very rapid initial reaction rate until ca. 20% of the thiol has been consumed, followed by slower, more linear progress of the reaction. This is consistent with the very rapid consumption of the 10 mol % of the catalyst present in the initial stages of the process, with concomitant conversion of 20% of the thiol to disulfide, followed by a much slower overall rate as the rate-determining reoxidation of **31** to **4** takes place to eventually establish a steady-state concentration of the seleninate ester.[42]

When the reaction was repeated in acetonitrile (Figure 5), a very rapid initial rate was again observed, but disulfide formation stopped completely once ca. 40% conversion of

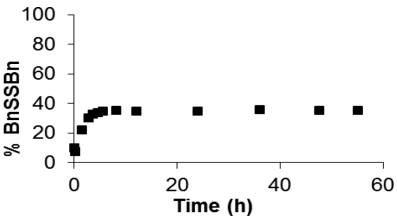


Figure 5. Kinetic plot for the reduction of hydrogen peroxide with benzyl thiol in acetonitrile in the presence of 10 mol % of seleninate ester **4**.

the thiol was reached and HPLC analysis revealed that a new product had accumulated at the expense of the disulfide. This product proved to be the selenenyl sulfide **32**, as determined by comparison with an authentic sample prepared by the reaction of seleninate ester **4** with excess benzyl thiol in the absence of the peroxide. The selenenyl sulfide was then independently subjected to the usual assay. As expected, the reaction proved extremely slow and gave a $t_{1/2}$ of 80 h (Figure 6 and Scheme 6),

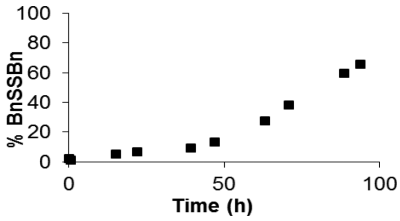
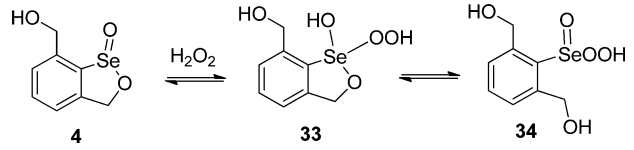


Figure 6. Kinetic plot for the reduction of hydrogen peroxide with benzyl thiol in dichloromethane–methanol (95:5) in the presence of 10 mol % of selenenyl sulfide **32**.

thus confirming that the selenenyl sulfide is a poor catalyst and that its formation results in the deactivation pathway (cycle B in Scheme 7). A relatively long induction period of ca. 40 h in Figure 6 is apparent from an exceptionally slow rate of thiol to disulfide conversion, followed by a more rapid process. This suggests that the relatively inert selenenyl sulfide produced in the early stages of the process is eventually converted into a catalytically more active species in dichloromethane–methanol solvent but presumably not in acetonitrile, where disulfide production ceases completely after the initial period of its rapid formation (Figure 5) as the selenenyl sulfide accumulates. Indeed, when authentic selenenyl sulfide **32** was treated with hydrogen peroxide in dichloromethane–methanol at room temperature in the absence of the thiol, the gradual appearance of the seleninate ester **4** was noted by TLC analysis, and the latter product was isolated in 18% yield after 48 h. This confirms that regeneration of **4** from selenenyl sulfide **32** is possible but is a slow and inefficient process. It is likely that this oxidation proceeds via the thiolseleninate **30**.

We also considered the possibility that the hydroperoxyselenurane **33** or peroxyseleninic acid **34** is generated from the reaction of **4** with hydrogen peroxide instead of the reaction of **4** with benzyl thiol in the first step of the catalytic cycle (Scheme 8). We had previously postulated analogous

Scheme 8



intermediates in the oxidation of sulfides to sulfoxides, alkenes to epoxides, and enamines to α-hydroxy ketones with hydrogen peroxide, catalyzed by the related cyclic seleninate ester **2**.[26] Braga, Detty, and their co-workers proposed similar hydroperoxyselenurane species in the reaction of selenoxides with hydrogen peroxide in the presence of thiols,[43] while related peroxyseleninic acids have been recognized as intermediates in a variety of oxidation reactions promoted by benzeneseleninic acid derivatives in the presence of hydrogen peroxide.[44] While

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we cannot unequivocally rule out the participation of **33** or **34**, especially at high hydrogen peroxide/benzyl thiol ratios, such intermediates seem less likely under the conditions of the present assay. Benzyl thiol is a stronger reducing agent than sulfides, alkenes, or enamines and reacts very rapidly with seleninate esters such as **2** or **4**, even in the absence of hydrogen peroxide. Moreover, oxidations of sulfides and alkenes catalyzed by **2** were performed in the presence of TFA, a Bronsted acid that protonates the selenoxide-like bond of **2** and facilitates the attack of hydrogen peroxide at the resulting cationic selenium center. It is also noteworthy that oxidations carried out with peroxyseleninic acids are often facilitated by electron-withdrawing nitro or fluoro substituents.[44] In contrast, the reduction of peroxides with thiols is accelerated by the presence of electron-donating groups *para* to the selenium atom of cyclic seleninate ester catalysts. A Hammett plot with a negative reaction constant ρ supports the hypothesis that the rate-determining step involves an increase of positive charge at selenium, as occurs in the step where Se(II) is converted into Se(IV).[23b] We also note that *t*-butyl hydroperoxide, which cannot form peroxyseleninic acid intermediates, has been used effectively in place of hydrogen peroxide in our assay for GPx-like activity with other cyclic seleninate esters.[22,23a] In the present case, *t*-butyl hydroperoxide provided a similar result with **4** (see Figure 7 and

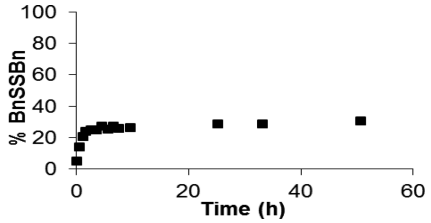


Figure 7. Kinetic plot for the reduction of *t*-butyl hydroperoxide with benzyl thiol in dichloromethane–methanol (95:5) in the presence of 10 mol % of cyclic seleninate ester **4**.

compare with Figures 4 and 5). Finally, a catalytic cycle in which the catalyst shuttles between seleninate **4** and peroxide species **33** or **34** would not account for the formation of selenenyl sulfide **32** in the presence of equivalent or excess amounts of hydrogen peroxide.

Since the allyl selenide **12** serves as the precursor of seleninate **4** when oxidized by hydrogen peroxide, the selenide itself was also tested in the standard assay (Figure 8). It displayed a $t_{1/2}$ of 21 h (Scheme 6), comparable to that of **4**, but without the initial rapid reaction rate displayed by the latter. This is consistent with its Se(II) starting oxidation state, where

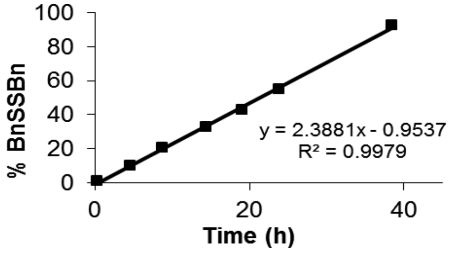
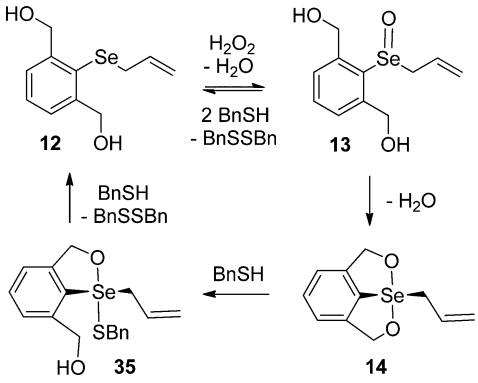


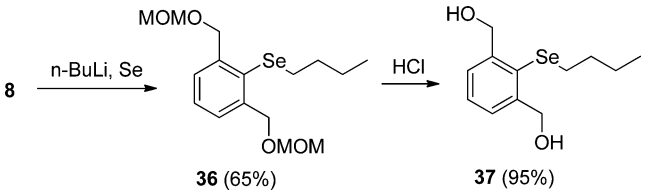
Figure 8. Kinetic plot for the reduction of hydrogen peroxide with benzyl thiol in dichloromethane–methanol (95:5) in the presence of 10 mol % of allyl selenide **12**.

the relatively slow oxidation to Se(IV) must occur right from the beginning of the reaction. It is also possible that the allyl selenide does not generate **4** in situ in the actual assay, where both benzyl thiol and hydrogen peroxide are present. Under these conditions, the initially formed selenoxide **13** (or selenurane **14**) might react faster with the thiol than with hydrogen peroxide, thereby bypassing **4** altogether in the catalytic cycle (Scheme 9). Surprisingly, the *n*-butyl selenide **37**

Scheme 9



Scheme 10



(prepared via Scheme 10), which cannot undergo a [2,3] sigmatropic rearrangement, showed even better catalytic activity ($t_{1/2}$ = 9.5 h) compared to the allyl derivative (Figure 9 and Scheme 6), demonstrating that a [2,3] shift is not an essential step in generating an active catalyst from the corresponding selenide.

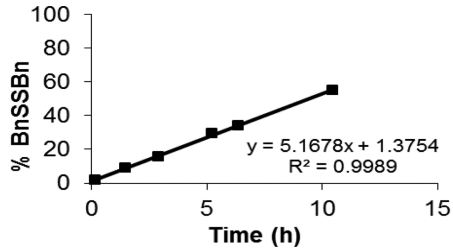


Figure 9. Kinetic plot for the reduction of hydrogen peroxide with benzyl thiol in dichloromethane–methanol (95:5) in the presence of 10 mol % of *n*-butyl selenide **37**.

SUMMARY AND CONCLUSIONS

In conclusion, the cyclic seleninate **4** was easily synthesized by oxidation of the diselenide **10** or the allyl selenide **12** with hydrogen peroxide, with the isolable selenurane **14** serving as an intermediate in the latter process. The formation of **14** indicates that the pincer-like cyclization of the putative

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selenoxide **13** is even more rapid than the typically fast [2,3] sigmatropic rearrangement of allylic selenoxides. Unexpectedly, the Se→O rearrangement leading to product **18** predominated at the expense of seleninate **4** when the reaction was performed at the elevated temperature of 70 °C in acetonitrile. The analogous crotyl derivative **26** was obtained similarly from the crotyl selenide **25** and was reattached proximally to the crotyl methyl group, consistent with a [2,3] sigmatropic rearrangement or an intramolecular S_N2'reaction during the overall process. Moreover, the absence of crossover products between the nondeuterated allyl selenide **12** and the deuterium-labeled crotyl derivative **27**, as well as the exclusive formation of **18** instead of **26** from the similar reaction of **14** in the presence of crotyl alcohol, indicates that the rearrangement is intramolecular. These observations are consistent with the [2,3] rearrangement and S_N2 variation of path b or the S_N2' variation of path c in Scheme 4.

The fluxional behavior of cyclic seleninate **4** was established by variable-temperature ^{1}H NMR experiments, which demonstrated that hydroxyl exchange occurs rapidly on the NMR time scale at room temperature but can be frozen out at temperatures below ca. 248 K in $CDCl_3$. Both the coalescence temperature and a computational simulation of the process indicated a low activation energy ($\Delta G^{\ddagger}$) of 15.5 and 12.3 kcal mol^{-1}, respectively, for hydroxyl interchange.

Finally, the GPx-like properties of the hydroxymethyl-substituted cyclic seleninate ester **4** were measured in a standard assay previously developed for this purpose. This compound produced catalytic activity approximately double that of the unsubstituted analogue **2**, as indicated by their relative $t_{1/2}$ values in this assay, but poorer activity compared to structurally related spirodioxyselenuranes that had been investigated previously. The formation of the relatively inert selenenyl sulfide **32** comprises a deactivation pathway (path B in Scheme 7) that impedes the catalytic destruction of hydrogen peroxide, particularly in the more polar acetonitrile solvent.

EXPERIMENTAL SECTION

Spectoscopic Experiments. ^{1}H NMR spectra were recorded at 300 or 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 obtained with diphenyl diselenide in $CDCl_3$ (463.0 ppm)[45] as the standard, relative to dimethyl selenide (0.0 ppm). Variable-temperature proton NMR experiments were carried out at 400 MHz on a spectrometer equipped with a compressed gas heat exchanger for higher temperatures and a liquid nitrogen evaporator for low temperatures. Temperature calibration of the controller was carried out using the temperature-dependent chemical shifts of methanol (low temperature) and ethylene glycol (high temperature).[46] High-resolution mass spectra were obtained using a time-of-flight (TOF) analyzer with electron impact (EI) ionization or a quadrupole TOF analyzer with electrospray ionization (ESI).

Computations. All calculations were performed using the Gaussian 09 package.[47] Geometry optimizations were performed with the B3PW91 hybrid DFT functional, composed of Becke's three-parameter exchange functional[48a] and the correlation functional proposed by Perdew and Wang.[48b] The 6-311+G(d,p) Pople basis set[49] was employed as it was shown to be reliable for the prediction of organoselenium geometries and energetics by Boyd et al.[50] Transition states were located with Schlegel's synchronous transit-guided quasi-Newton (STNQ) method[51a,b] and were linked to the reactants and products by intrinsic reaction coordinate calculations.[51c,d] Frequency calculations were performed on all optimized structures at the same level of theory to confirm whether the structure was a local minimum or first-order saddle point.

HPLC Assay for Catalytic Activity. Catalytic activity was measured by adding the catalyst (10 mol %) to a mixture of 29% hydrogen peroxide[52] (0.035 M) and redistilled benzyl thiol (0.031 M) in dichloromethane−methanol (95:5) while maintaining the temperature at 18 °C. The reactions were monitored by HPLC analysis, using a UV detector at 254 nm and a reversed-phase column (Novapak C18; 3.9 × 150 mm), with naphthalene (0.0080 M) as an internal standard. Acetonitrile−water was employed as the solvent (isocratic: 80:20 over 5 min with a flow rate of 0.9 mL/min). Each $t_{1/2}$ value in Scheme 6 is the average of at least two runs.

The assay in Figure 7 was performed under the same conditions with the same molar ratios of reactants and catalysts, except that 56% *t*-butyl hydroperoxide was employed instead of hydrogen peroxide.

2-Bromo-1,3-bis[(methoxymethoxy)methyl]benzene (8). (2-Bromo-1,3-phenylene)dimethanol (7)[30] (824 mg, 3.80 mmol) was suspended in 50 mL of dry dichloromethane under nitrogen and cooled in an ice-bath. Diisopropylethylamine (1.3 mL, 7.5 mmol) was added, followed by the slow addition of chloromethyl methyl ether (0.58 mL, 7.6 mmol). The solution was warmed to room temperature and stirred for 16 h, resulting in a clear, colorless solution. The reaction was quenched with water and extracted with diethyl ether. The combined organic phases were dried and concentrated in vacuo to afford a yellow oil, which was chromatographed over silica gel (30% ethyl acetate−hexanes) to give 1.134 g (98%) of product **8** as a clear oil: IR (film) 1213, 1151, 1115, 1052 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 7.5 Hz, 2 H), 7.34 (dd, J = 8.4, 6.6 Hz, 1 H), 4.77 (s, 4 H), 4.70 (s, 4 H), 3.43 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 128.3, 127.3, 123.3, 96.3, 69.1, 55.6; mass spectrum (EI-TOF), m/z (relative intensity) 306 (95, M$^+$, ^{81}Br), 304 (100, M$^+$, ^{79}Br); HRMS (EI-TOF) m/z [M]$^+$ $C_{12}H_{17}{}^{81}BrO_4$ 306.0290; found 306.0283; [M]$^+$ calcd for $C_{12}H_{17}{}^{79}BrO_4$ 304.0310; found 304.0300.

2-({2,6-Bis[(methoxymethoxy)methyl]phenyl}diselanyl)-1,3-bis[(methoxymethoxy)methyl]benzene (9). 2-Bromo-1,3-bis-[(methoxymethoxy)methyl]benzene (**8**) (1.841 g, 6.033 mmol) was dissolved in 40 mL of dry, degassed THF under nitrogen. The clear, colorless solution was then cooled to −78 °C, and *tert*-butyllithium (7.0 mL, 1.7 M, 12 mmol) was added dropwise. The yellow solution was warmed to 0 °C over 1.5 h, and elemental selenium (478 mg, 6.05 mmol) was added. After 15 min, the solution became dark orange and was warmed to room temperature. The reaction mixture was quenched with saturated NH_4Cl solution, filtered, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried and concentrated in vacuo to afford a red oil, which was chromatographed over silica gel (ethyl acetate−hexanes 15:85 to 70:30) to give 1.701 g (92%) of the crude diselenide **9** as a red gel, which was employed in the next step without further purification.

(2-{[2,6-Bis(hydroxymethyl)phenyl]diselanyl}-3-(hydroxymethyl)phenyl)methanol (10). Diselenide **9** (660 mg, 1.08 mmol) was dissolved in 11 mL of methanol, and six drops of concentrated HCl were added. The solution was heated at 60 °C for 16 h and then cooled to room temperature, resulting in the formation of an orange precipitate. The precipitate was collected to give 274 mg (59%) of the desired product **10**: mp 189−191 °C; IR (KBr) 3262, 1071 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (br s, 6 H), 5.10 (t, J = 5.5 Hz, 4 H), 4.37 (d, J = 5.4 Hz, 8 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.9, 129.5, 126.6, 125.4, 63.2; ^{77}Se NMR (76 MHz, DMSO-d_6) δ 339.4; mass spectrum (ESI-TOF), m/z (relative intensity) 457 (100, [M + Na]$^+$); HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{18}NaO_4{}^{80}Se_2$ 456.9431; found 456.9436.

1,3-Bis[(methoxymethoxy)methyl]-2-(prop-2-en-1-ylselanyl)benzene (11). Diselenide **9** (527 mg, 0.866 mmol) was dissolved in 25 mL of dry, degassed THF under nitrogen. The solution was placed in an ice bath, and sodium borohydride (164 mg, 4.33 mmol) was added, resulting in a brown solution. Absolute ethanol (3 mL) was added, and after 5 min, the solution became clear and colorless. Allyl iodide (0.16 mL, 1.7 mmol) was added, and the solution was warmed to room temperature and stirred for 3 h. The reaction was quenched with 1 M HCl, diluted with water, and

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extracted with ethyl acetate. The ethyl acetate layer was dried, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed over silica gel (15% ethyl acetate−hexanes) to furnish 492 mg (84%) of the product **11** as a light yellow oil: IR (film) 1148, 1100, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 7.8 Hz, 2 H), 7.38 (dd J = 8.5, 6.6 Hz, 1 H), 5.87 (ddt, J = 17.6, 10.0, 7.8 Hz, 1 H), 4.88 (s, 4 H), 4.83−4.74 (m, 6 H), 3.44 (s, 6 H), 3.34 (dt, J = 7.7, 0.7 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 134.3, 129.2, 129.0, 128.1, 116.7, 96.3, 70.4, 55.6, 32.1; ^{77}Se NMR ($CDCl_3$) δ 194.2; mass spectrum (EI-TOF), m/z (relative intensity) 346 (100, M^+), 199 (64), 183 (65); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{15}H_{22}O_4{}^{80}Se$ 346.0683; found 346.0671.

[3-(Hydroxymethyl)-2-(prop-2-en-1-ylselanyl)phenyl]-methanol (12). Selenide **11** (523 mg, 1.51 mmol) was dissolved in 25 mL of methanol. Amberlite IR-120(H) acidic resin was added, and the mixture was heated at 55 °C for 24 h. The resin was filtered, and the filtrate was concentrated in vacuo. The resulting yellow oil was chromatographed over silica gel (ethyl acetate−hexanes 70:30) to give 370 mg (95%) of product **12** as a white solid: mp 56.5−58.5 °C; IR (film) 3338, 1619, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.30 (m, 3 H), 5.85 (ddt, J = 17.5, 9.9, 7.8 Hz, 1 H), 4.84 (s, 4 H), 4.87−4.75 (m, 2 H), 3.34 (d, J = 7.7 Hz, 2 H), 2.64 (s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 134.0, 129.6, 127.9, 127.4, 117.1, 66.0, 31.9; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 185.1; mass spectrum (EI-TOF), m/z (relative intensity) 258 (15, M^+), 199 (100), 170 (90); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{11}H_{14}O_2{}^{80}Se$ 258.0158; found 258.0167. Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 51.37; H, 5.49. Found: C, 51.35; H, 5.58.

7-(Hydroxymethyl)-3*H*-2,1λ^4-benzoxaselenol-1-one (4). Diselenide **10** (103 mg, 0.238 mmol) was suspended in 5 mL of dichloromethane−methanol (1:1). Hydrogen peroxide (0.050 mL, 29%, 0.48 mmol) was added, and the mixture was stirred at room temperature for 24 h. A second 0.050 mL portion of the peroxide was added, and stirring was continued for another 24 h. The mixture was concentrated in vacuo and chromatographed immediately over silica gel (10% methanol−ethyl acetate) to afford 101 mg (92%) of cyclic seleninate ester **4** as a white solid: mp 161−162 °C; IR (film) 3167, 1049, 980, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 254 K) δ 8.05 (dd, J = 5.4, 2.2 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.21 (d, J = 7.6 Hz, 1 H), 5.83 (d, J = 14.0 Hz, 1 H), 5.53 (d, J = 14.0 Hz, 1 H), 4.97 (dd, J = 15.0, 5.1 Hz, 1 H), 4.88 (d, J = 15.1 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$, 258 K) δ 144.6, 142.2, 141.4, 132.9, 125.0, 121.4, 75.9, 61.5; ^{77}Se (76 MHz, $CDCl_3$, 258 K) δ 1327.7; mass spectrum (ESI-TOF), m/z (relative intensity) 255 (100, $[M + Na]^+$), 233 (20, $[M + H]^+$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_9O_3{}^{80}Se$ 232.97116; found 232.97118. Anal. Calcd for $C_8H_8O_3Se$: C, 41.58; H, 3.49. Found: C, 41.27; H, 3.47.

4-(Prop-2-en-1-yl)-3,5-dioxa-4λ^4-selenatricyclo[5.3.1.0^{4,11}]-undeca-1(11),7,9-triene (14). Selenide **12** (50 mg, 0.19 mmol) was dissolved in 15 mL of dichloromethane, and hydrogen peroxide (0.040 mL, 29%, 0.38 mmol) was added. The clear, colorless solution was stirred at room temperature for 4 h. The solution was concentrated in vacuo and immediately chromatographed over silica gel (10% methanol−ethyl acetate) to provide 49 mg (99%) of selenurane **14** as a yellow oil: IR (film) 1624, 1029, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, J = 7.4 Hz, 1 H), 7.26 (d, J = 7.5 Hz, 2 H), 5.57−5.48 (m, 1 H), 5.08−4.95 (m, 6 H), 3.83 (dd, J = 8.0, 1.1 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 132.9, 128.2, 123.1, 122.7, 122.0, 66.4, 60.5; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 848.9; mass spectrum (ESI-TOF), m/z (relative intensity) 257 (100, $[M + H]^+$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{13}O_2{}^{80}Se$ 257.0076; found 257.0075.

7-[(Prop-2-en-1-yloxy)methyl]-3*H*-2,1λ^4-benzoxaselenol-1-one (18). Allyl selenide **12** (100 mg, 0.389 mmol) was dissolved in 19 mL of acetonitrile. Hydrogen peroxide (0.090 mL, 29%, 0.85 mmol) was added, and the solution was heated at 70 °C for 20 h and then concentrated in vacuo. It was immediately chromatographed over silica gel (10% methanol−ethyl acetate) to afford 68 mg (65%) of cyclic seleninate **18** as a clear oil: IR (film) 1686, 1071, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, J = 7.6 Hz, 1 H), 7.32 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1 H), 6.02 (ddt, J = 17.3, 10.4, 6.0, Hz, 1 H), 5.80 (d, J = 14.1 Hz, 1 H), 5.47 (d, J = 14.1 Hz, 1 H), 5.37 (dd, J = 17.2, 1.5 Hz, 1 H), 5.29 (dd, J = 10.4, 1.0 Hz, 1 H), 4.79 (d, J = 13.6 Hz, 1 H), 4.73 (d, J = 13.5 Hz, 1 H), 4.33 (dd, J = 12.3, 5.7 Hz, 1 H), 4.19 (dd, J = 12.6, 6.5 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 144.0, 138.1, 133.3, 131.9, 124.9, 121.5, 119.5, 76.3, 72.9, 69.1; ^{77}Se NMR (76 MHz, CD_3OD) δ 1312.1; for COSY, HSQC, and HMBC spectra, see the Supporting Information; mass spectrum (EI-TOF), m/z (relative intensity) 272 (15, M^+), 212 (80), 199 (92), 169 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{11}H_{12}O_3{}^{80}Se$ 271.9952; found 271.9949. A small amount (29%) of **4** was also isolated with the same properties as the sample prepared from the oxidation of diselenide **10**.

1-(But-2-enyl) 2,6-bis[(methoxymethoxy)methyl]phenyl selenide (MOM-25). Diselenide **9** (176 mg, 0.289 mmol) was suspended in 8 mL of THF under nitrogen. The mixture was cooled in an ice bath, and sodium borohydride (54 mg, 1.4 mmol) was added. The solution became brown in color. Absolute ethanol (2 mL) was added, and after 10 min, the solution became clear and colorless. Crotyl chloride (0.060 mL, 0.62 mmol) was added, and the solution was warmed to room temperature and stirred for 2 h, resulting in a white, opaque mixture. The reaction was quenched with 1 M HCl, and the solution became clear and colorless. It was extracted with ethyl acetate, and the combined organic layers were dried, concentrated in vacuo, and the resulting yellow oil was chromatographed over silica gel (15% ethyl acetate−hexanes) to provide 185 mg (89%) of the MOM-protected derivative of selenide **25** as a light yellow oil: IR (film) 1149, 1101, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (*E*-isomer) δ 7.47 (d, J = 7.6 Hz, 2 H), 7.36 (dd, J = 8.4, 6.9 Hz, 1 H), 5.57−5.44 (m, 1 H), 5.16 (dqt, J = 15.1, 6.5, 1.1 Hz, 1 H), 4.87 (s, 4 H), 4.75 (s, 4 H), 3.43 (s, 6 H), 3.28 (d, J = 7.8 Hz, 2 H), 1.54 (ddt, J = 6.5, 1.8, 1.0 Hz, 3 H); (minor *Z*-isomer) δ 4.91 (s), 4.58 (s), 3.33 (s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 129.1, 129.0, 128.1, 127.8, 127.0, 96.2, 70.4, 55.5, 31.5, 17.6; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 182.9; mass spectrum (EI-TOF), m/z (relative intensity) 360 (100, M^+), 273 (95); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{16}H_{24}O_4{}^{80}Se$ 360.0840; found 360.0822.

[2-(But-2-en-1-ylselanyl)-3-(hydroxymethyl)phenyl]-methanol (25). The MOM-protected derivative obtained in the preceding procedure (185 mg, 0.515 mmol) was dissolved in 20 mL of methanol, and Amberlite IR-120(H) acidic resin (ca. 150 mg) was added to the solution, and the heterogeneous mixture was heated at 55 °C for 24 h. The resin was filtered and washed with methanol, and the filtrate was concentrated in vacuo. The resulting pale yellow oil was chromatographed over silica gel (elution with 30% ethyl acetate−hexanes) to give 100 mg (72%) of selenide **25** as a pale yellow oil: IR (film) 3335, 1179, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (*E*-isomer) δ 7.39−7.29 (m, 3 H), 5.53−5.40 (m 1 H), 5.20 (dq, J = 15.1, 6.5 Hz, 1 H), 4.80 (s, 4 H), 3.28 (d, J = 7.8 Hz, 2 H), 2.87 (br s, 2 H), 1.55 (d, J = 6.1 Hz, 3 H); (minor *Z*-isomer) δ 4.85 (s), 3.38 (d, J = 8.4 Hz), 1.28 (d, J = 6.4 Hz); ^{13}C NMR (101) MHz, $CDCl_3$) δ 145.8, 129.6, 128.9, 127.8, 126.9, 66.0, 31.6, 17.6; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 173.9; mass spectrum (EI-TOF), m/z (relative intensity) 272 (20, M^+), 198 (65), 91 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{16}O_2{}^{80}Se$ 272.0316; found 272.0317.

7-[(But-3-en-2-yloxy)methyl]-3*H*-2,1λ^4-benzoxaselenol-1-one (26). Selenide **25** (100 mg, 0.369 mmol) was dissolved in 18 mL of acetonitrile. Hydrogen peroxide (0.090 mL, 29%, 0.85 mmol) was added, and the solution was heated at 70 °C for 24 h. The solution was concentrated in vacuo to afford a white solid, which was chromatographed immediately over silica gel (elution with 10% methanol−ethyl acetate) to give 53 mg (50%) of the cyclic seleninate **26** as a white solid as a 1:1 mixture of diastereomers: mp 69−71 °C; IR (film) 1192, 1179, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (td, J = 7.5, 1.0 Hz, 1 H), 7.32 (d, J = 7.6 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 5.98 (ddd, J = 17.2, 10.3, 7.9 Hz, 1 H), 5.87−5.80 (m, 1 H), 5.49 (dd, J = 13.9, 2.4 Hz, 1 H), 5.35−5.24 (m, 2 H), 4.90 (d, J = 13.4 Hz, 0.5 H), 4.77 (d, J = 13.4 Hz, 0.5 H), 4.67 (d, J = 13.3 Hz, 0.5 H), 4.60 (d, J = 13.6 Hz, 0.5 H), 4.26−4.18 (m, 1 H), 1.53 (d, J = 6.3 Hz, 1.5 H), 1.49 (d, J = 6.4 Hz, 1.5 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.59, 144.55, 144.2, 138.83, 138.75, 138.6, 138.4, 131.73, 131.67, 124.91, 124.89,

121.34, 121.27, 118.2, 117.9, 79.5, 79.3, 76.3, 76.2, 67.5, 67.0, 21.6, 21.4; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 1331.6, 1331.1; mass spectrum (EI-TOF), m/z (relative intensity) 286 (10, M^+), 270 (30), 213 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{14}O_3{}^{80}Se$ 286.0108; found 286.0108. Anal. Calcd for $C_{12}H_{14}O_3Se$: C, 50.54; H, 4.95. Found: C, 50.47; H, 5.03.

2-Bromo-1,3-bis[(methoxymethoxy)dideuteriomethyl]-benzene (8-d_4). The product was obtained from the reduction of 2-bromo-1,3-benzenedicarboxylic acid by a literature procedure.[30] Protection with MOM chloride was performed as in the conversion of the nondeuterated derivative **7** to **8**: clear oil; IR (film) 1219, 1152, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.4 Hz, 2 H), 7.33 (dd, J = 8.3, 6.9 Hz, 1 H), 4.76 (s, 4 H), 3.43 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.9, 128.5, 127.4, 123.5, 96.2, 68.5 (quintet, J = 22.3 Hz), 55.6; mass spectrum (EI-TOF), m/z (relative intensity) 308 (100, M^+), 277 (75); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{13}D_4O_4{}^{79}Br$ 308.0561; found 308.0562.

The deuterated crotyl selenide **27** and seleninate ester **28** were prepared from 2-bromo-1,3-bis[(methoxymethoxy)dideuteriomethyl]-benzene in the same manner as their nondeuterated analogues.

2-({2,6-Bis[(methoxymethoxy)dideuteriomethyl]phenyl}-diselanyl)-1,3-bis[(methoxymethoxy)dideuteriomethyl]-benzene (9-d_8): Red gel; IR (film) 1205, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.34 (m, 6 H), 4.58 (s, 8 H), 3.35 (s, 12 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 130.1, 129.4, 127.8, 96.2, 69.0 (m, very weak), 55.6; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 353.5; mass spectrum (EI-TOF), m/z (relative intensity) 618 (10, M^+), 203 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{24}H_{26}D_8O_8{}^{80}Se_2$ 618.1086; found 618.1085.

2-[(2*E*)-But-2-en-1-ylselanyl]-1,3-bis[(methoxymethoxy)dideuteriomethyl]benzene (MOM-27): Pale yellow oil; IR (film) 1143, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.6 Hz, 2 H), 7.37 (dd, J = 8.3, 6.8 Hz, 1 H), 5.50 (m, 1 H), 5.17 (dqt, J = 15.1, 6.4, 1.1 Hz, 1 H), 4.75 (s, 4 H), 3.44 (s, 6 H), 3.29 (dt, J = 7.8, 1.0 Hz, 2 H), 1.54 (ddt, J = 6.4, 1.8, 1.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 130.2, 129.9, 129.0, 128.8, 127.8, 96.8, 69.8 (faint quintet, J = 22.1 Hz), 55.9, 31.8, 17.8; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 183.4; mass spectrum (EI-TOF), m/z (relative intensity) 364 (76, M^+), 276 (42), 203 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{16}H_{20}D_4O_4{}^{80}Se$ 364.1091; found 364.1081.

[2-(But-2-en-1-ylselanyl)-3-(hydroxydideuteriomethyl)-phenyl]dideuteriomethanol (27): Pale yellow oil; IR (film) 3433, 1176, 1124, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*E*-isomer) δ 7.42–7.36 (m, 3 H), 5.60–5.43 (m, 1 H), 5.31–5.18 (m, 1 H), 3.34 (dd, J = 7.9, 0.6 Hz, 2 H), 2.42 (br s, 2 H), 1.57 (dd, J = 6.5, 0.8 Hz, 3 H); (minor *Z*-isomer) δ 3.44 (d, J = 8.1 Hz), 1.30 (d, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) (*E*-isomer) δ 145.9, 129.8, 129.1, 128.34, 128.30, 126.9, 65.7 (faint quintet, J = 20.6 Hz), 31.9, 17.7; (minor *Z*-isomer) δ 129.9, 137.2, 133.2, 126.0, 25.9, 12.1; ^{77}Se NMR (76 MHz, $CDCl_3$) (*E*-isomer) δ 175.0; (minor *Z*-isomer) δ 171.6; mass spectrum (EI-TOF), m/z (relative intensity) 276 (74, M^+), 202 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{12}D_4O_2{}^{80}Se$ 276.0567; found 276.0569.

7-[(But-3-en-2-yloxy)dideuteriomethyl]-3*H*-2,1λ^4-3,3-dideuteriobenzoxaselenol-1-one (28): Clear oil, 1:1 mixture of diastereomers); IR (film) 1281, 1110, 1086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (td, J = 7.5, 1.8 Hz, 1 H), 7.33 (ddd J = 7.6, 1.8, 1.1 Hz, 1 H), 7.18 (dd, J = 7.5, 1.1 Hz, 1 H), 5.97 (ddd, J = 17.2, 10.2, 7.9 Hz, 0.5 H), 5.81 (ddd, J = 17.2, 10.2, 7.9 Hz, 0.5 H), 5.33–5.22 (m, 2 H), 4.25–4.12 (m, 1 H), 1.51 (d, J = 6.4 Hz, 1.5 H), 1.47 (d, J = 6.4 Hz, 1.5 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 144.7, 144.51, 144.48, 139.2, 139.1, 138.8, 138.6, 132.1, 132.0, 125.29, 125.27, 121.73, 121.66, 118.5, 118.2, 79.8, 79.6, 76.2 (faint multiplet), 66.7 (faint multiplet), 21.9, 21.7; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 1295.7, 1295.2; mass spectrum (EI-TOF), m/z (relative intensity) 290 (8, M^+), 123 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{10}D_4O_3{}^{80}Se$ 290.0359; found 290.0357.

{2-[(Benzylsulfanyl)selanyl)]-3-(hydroxymethyl)phenyl}-methanol (32). Cyclic seleninate ester **4** (50 mg, 0.22 mmol) was dissolved in 20 mL of dichloromethane and cooled in an ice bath. Benzyl thiol (0.074 mL, 0.63 mmol) was added to the cooled solution and stirred for 1 h. The solution was concentrated in vacuo and chromatographed immediately (elution with 50% ethyl acetate–hexanes) to afford 30 mg (40%) of the selenenyl sulfide **32** as a yellow solid: mp 99–101 °C; IR (film) 3198, 1232, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.38 (m, 3 H), 7.22–7.19 (m, 5 H), 4.90 (s, 4 H), 4.10 (s, 2 H), 2.09 (br s, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 137.1, 130.0, 128.8, 128.4, 128.0, 127.4, 65.8, 42.2; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 340.8; mass spectrum (ESI-TOF), m/z (relative intensity) 363 (100, $[M + Na]^+$); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{16}NaO_2S^{80}Se$ 362.9928; found 362.9919. Anal. Calcd for $C_{15}H_{16}O_2SSe$: C, 53.10; H, 4.75. Found: C, 53.22; H, 4.74.

2-(Butylselanyl)-1,3-bis[(methoxymethoxy)methyl]benzene (36). 2-Bromo-1,3-bis[(methoxymethoxy)methyl]benzene (**8**) (1.79 g, 5.87 mmol) was dissolved in 70 mL of dry THF under a nitrogen atmosphere. The solution was degassed with argon, cooled to −78 °C, and *n*-butyllithium (3.06 mL, 2.3 M, 7.0 mmol) was added dropwise. After 30 min, the mixture was transferred to an ice bath and elemental selenium (556 mg, 7.04 mmol) was added. After 1 h, the reaction was quenched with saturated NH_4Cl solution and ethyl acetate was added. Air was bubbled through the mixture for 30 min, followed by filtration and extraction with ethyl acetate. The combined organic layers were dried, concentrated in vacuo, and chromatographed over silica gel (elution with 15% ethyl acetate–hexanes) to afford 1.39 g (65%) of the product **36** as a yellow oil: IR (film) 1152, 1038, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 7.7 Hz, 2 H), 7.37 (dd, J = 8.6, 6.7 Hz, 1 H), 4.90 (s, 4 H), 4.77 (s, 4 H), 3.44 (s, 6 H) 2.70 (t, J = 7.5 Hz, 2 H), 1.63–1.50 (m, 2 H), 1.45–1.29 (m, 2 H), 0.87 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 129.5, 128.9, 128.0, 96.3, 70.4, 55.6, 32.6, 29.6, 23.2, 13.7; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 155.4; mass spectrum (EI-TOF), m/z (relative intensity) 362 (24, M^+), 285 (34), 199 (68), 175 (100); HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{16}H_{26}O_4{}^{80}Se$ 362.0996; found 362.0991.

[2-(Butylselanyl)-3-(hydroxymethyl)phenyl]methanol (37). Selenide **36** (1.385 g, 3.833 mmol) was dissolved in 20 mL of methanol (0.2 M), and 5 drops of concentrated HCl were added. The solution was heated to 60 °C for 20 h. The reaction was quenched with water and extracted with dichloromethane. The dichloromethane was washed with brine, dried, concentrated in vacuo, and chromatographed over silica gel (elution with a 15% to 70% gradient of ethyl acetate–hexanes) to give 996 mg (95%) of selenide **37** as a yellow oil: IR (film) 3376, 1186, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 3 H), 4.90 (s, 4 H), 2.78 (t, J = 7.4 Hz, 2 H), 2.28 (br s, 2 H), 1.68–1.55 (m, 2 H), 1.47–1.31 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 129.6, 128.1, 66.3, 32.7, 30.1, 23.2, 13.7; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 139.9; mass spectrum (CI), m/z (relative intensity) 292 $[M + NH_4]^+$; HRMS (CI-TOF) m/z $[M + NH_4]^+$ calcd for $C_{12}H_{22}NO_2{}^{80}Se$ 292.0816; found 292.0822. Anal. Calcd for $C_{12}H_{18}O_2Se$: C, 52.75; H, 6.64. Found: C, 52.94; H, 6.75.

Crossover Experiment with 12 and 27. An equimolar mixture of selenides **12** and **27** was reacted and worked up as described for the conversion of **12** into **18**. The products **18** and **28** could not be separated, and the mixture was analyzed by NMR and mass spectrometry. The ^{1}H and ^{13}C NMR spectra of the mixture provided a close match for the superimposed spectra obtained separately for the products **18** and **28**.[53] The mass spectrum of the mixture revealed parent ions corresponding to both **18** [HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{11}H_{12}O_3{}^{80}Se$ 271.9952; found 271.9953] and **28** [HRMS (EI-TOF) m/z $[M]^+$ calcd for $C_{12}H_{10}D_4O_3{}^{80}Se$ 290.0359; found 290.0370]. Parent ions corresponding to compounds **26** (m/z 286.0108) and **29** (m/z 276.0201) were not observed.

Crossover Experiment with 14 and Crotyl Alcohol. Selenurane **14** (44 mg, 0.17 mmol) was dissolved in 15 mL of acetonitrile. Hydrogen peroxide (20 μL, 29%, 0.19 mmol) was added, followed by crotyl alcohol (20 μL, 0.21 mmol). The solution was heated at 70 °C for 16 h and was then concentrated in vacuo and immediately chromatographed over silica gel (10% methanol–ethyl acetate) to provide 30 mg (65%) of **18** and 14 mg (35%) of **4**. Formation of **26** was not detected.

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of new compounds and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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