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Aromatic Derivatives and Tellurium Analogues of Cyclic Seleninate Esters and Spirodioxyselenuranes That Act as Glutathione Peroxidase Mimetics

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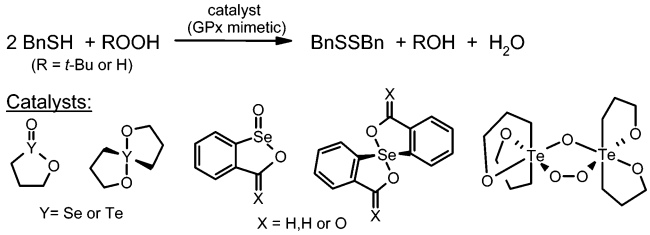
Received June 21, 2005



Several novel organoselenium and tellurium compounds were prepared and evaluated as mimetics of the selenoenzyme glutathione peroxidase, which protects cells from oxidative stress by reducing harmful peroxides with the thiol glutathione. The compounds were tested for catalytic activity in a model system wherein *tert*-butyl hydroperoxide or hydrogen peroxide were reduced with benzyl thiol and the rate of the reaction was measured by monitoring the formation of dibenzyl disulfide. Thus, aromatic derivatives **19**, **22**, **24**, and **25** proved to be inferior catalysts compared to the parent cyclic seleninate ester **14** and spirodioxyselenurane **16**. In the case of **19** and **22**, this was the result of their rapid conversion to the relatively inert selenenyl sulfides **31** and **32**, respectively. In general, hydrogen peroxide was reduced faster than *tert*-butyl hydroperoxide in the presence of the selenium-based catalysts. The cyclic tellurinate ester **27** and spirodioxytellurane **29** proved to be superior catalysts to their selenium analogues **14** and **16**, respectively, resulting in the fastest reaction rates by far of all of the compounds we have investigated to date. Oxidation of **29** with hydrogen peroxide produced the unusual and unexpected peroxide **33**, in which two hypervalent octahedral tellurium moieties are joined by ether and peroxide bridges. The structure of **33** was confirmed by X-ray crystallography. Although **33** displayed strong catalytic activity when tested independently in the model system, its relatively slow formation from the oxidation of **29** rules out its intermediacy in the catalytic cycle of **29**.

Introduction

The formation of peroxide byproducts during the course of normal aerobic metabolism contributes to oxidative stress in living organisms.[1] Peroxides, as well as free radicals derived from them,[2] have been implicated in a variety of degenerative processes and diseases, including inflammation, cardiovascular disease, mutagenesis and cancer, dementia, and the aging process. Fortunately, oxidative stress is mitigated by dietary antioxidants, as well as by endogenous enzymes that catalyze the destruction of peroxides and other reactive oxygen species.[1,3] The latter include glutathione peroxidase (GPx),[4] which promotes the reduction of peroxides with the stoichiometric reductant glutathione (GSH), a tripeptide thiol that is ubiquitous in the cells of higher organisms. The structure[5] and catalytic mechanism[4] of GPx have been

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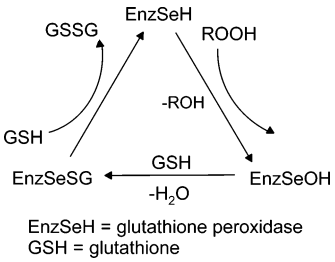
10.1021/jo0512711 CCC: $30.25
Published on Web 10/12/2005

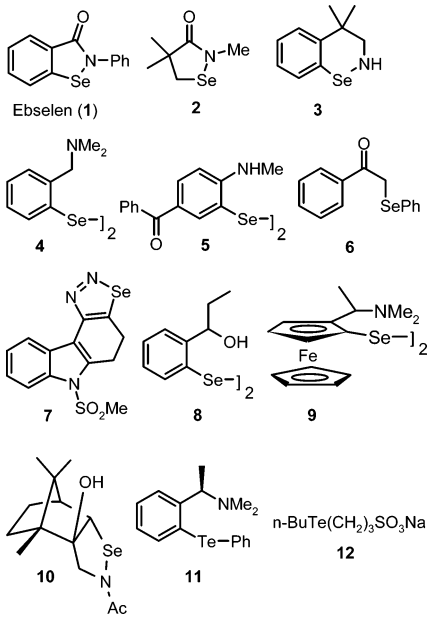
SCHEME 1



extensively studied. The tetrameric enzyme contains a selenocysteine residue in each of its four subunits, and the catalytic activity of GPx results from the redox properties of the selenocysteine selenol moieties. As shown in Scheme 1, the selenol functionality (EnzSeH) reacts with a peroxide molecule to generate the corresponding selenenic acid (EnzSeOH). The latter then reacts in succession with two molecules of glutathione to regenerate the original selenol via the corresponding selenenyl sulfide (EnzSeSG). Seleninic acid intermediates ($EnzSeO_2H$) have also been postulated at high peroxide concentrations.

The design, synthesis, and evaluation of small-molecule selenium compounds that mimic the biological activity of GPx have been investigated by several groups,[6] and representative examples **1**,[7] **2**,[8] **3**,[9] **4**,[10] **5**,[11] **6**,[12] **7**,[13] **8**,[14] **9**,[15] and **10**[16] are shown in Chart 1. Ebselen (**1**) has undergone clinical trials as an antioxidant.[17] Certain types of tellurium compounds (e.g. **11**[18] and **12**[19]) as well

CHART 1



as dendrimeric[20] and cyclodextrin-derived[21] organochalcogen catalysts that emulate GPx have also been reported. Several distinct mechanisms, including the one in Scheme 1, have been identified in the catalytic cycles of these mimetics. In general, substituents that are capable of coordinating or covalently bonding with the selenium or tellurium atom can be employed to modulate the redox behavior and therefore the catalytic activity of the compounds. While coordinating amino groups have been widely studied for this purpose,[22] oxygen substituents have been much less investigated.[14,23] We recently reported[24] that the oxidation of allyl 3-hydroxypropyl selenide (**13**) with *tert*-butyl hydroperoxide produces the novel cyclic seleninate ester (**14**) rapidly and quantitatively by a series of oxidation and [2,3]sigmatropic rearrangement steps. In the presence of a sacrificial thiol, the latter then functions as an unusually effective catalyst for the destruction of the peroxide via the mechanism in Scheme 2. More recently, we demonstrated that the similar oxidation of bis(3-hydroxypropyl) selenide (**15**) produces the novel dialkoxyspiroselenurane (**16**), which again displays exceptionally high catalytic activity in this process via Scheme 3.[25]

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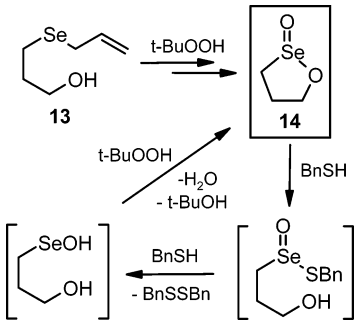
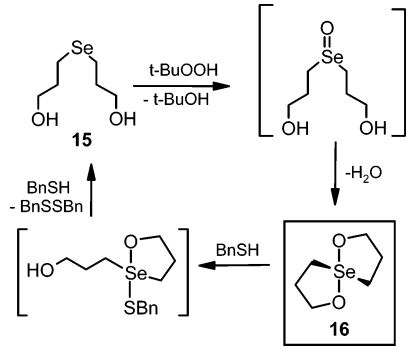
SCHEME 2



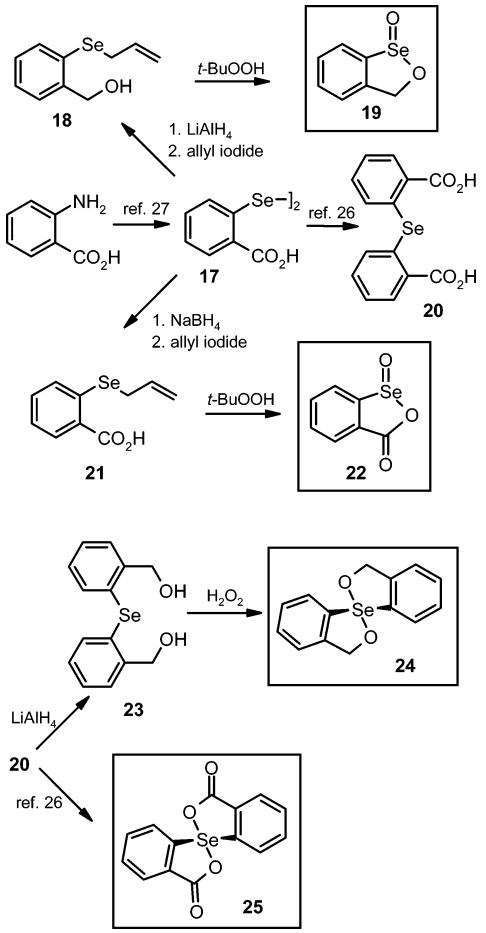
SCHEME 3



To compare the catalytic activity of various GPx mimetics, we have developed a convenient protocol based on the reduction of *tert*-butyl hydroperoxide with benzyl thiol (BnSH).[16,24,25] This peroxide was chosen because it is readily available and convenient to handle. The thiol and its corresponding disulfide (BnSSBn) contain chromophores that make their concentrations easy to monitor by HPLC during the course of each reaction, while their methylene groups provide convenient NMR signals for further investigations of possible intermediates. The assays were typically run with excess peroxide and 10 mol % of the catalyst in a mixture of dichloromethane−methanol that was found to dissolve the peroxide, the thiol, and a large variety of the catalysts that we investigated. Assays were conducted at 18 °C in order to facilitate monitoring some of the faster reactions, without unduly retarding the slower ones. Since the kinetic profiles of some of our earlier GPx mimetics were found to include irregularities such as induction periods during the initial oxidation step or unusually rapid early stage kinetics (presumably due to the rapid conversion of the catalyst to an intermediate that then reacts more slowly in a subsequent step), we chose to compare the catalytic activities of various GPx mimetics by means of half-lives ($t_{1/2}$), representing the time required to oxidize half of the thiol to its disulfide. For example, when 90% *tert*-butyl hydroperoxide was used under these conditions, **14** and **16** displayed $t_{1/2}$ of 2.5 and 2.9 h, respectively, as compared to 42 h for ebselen (**1**).[24,25]

Since aliphatic organoselenium compounds tend to be generally more toxic than aromatic analogues,[6b] we now report an extension of our earlier investigation to aromatic congeners of **14** and **16**, namely **19**, **22**, **24**, and **25**, as well as the novel tellurium analogues **27** and **29**. We also measured the catalytic activity of these compounds with hydrogen peroxide in place of *tert*-butyl hydroperoxide, to compare the reactivities of the two oxidants. These new results, when taken in conjunction with the previous studies of **14** and **16**,[24,25] provide new insight into the structure−activity relationships of the catalysts and their mechanisms.

SCHEME 4



Results and Discussion

The preparations of the cyclic seleninates **19** and **22**, as well as the spirodioxyselenuranes **24** and **25**, are shown in Scheme 4. With the exception of **25**,[26] these compounds are novel, but all were easily obtained from anthranilic acid via the known diselenide **17**[27] and selenide **20**.[26] The novel tellurium compounds **27** and **29** were prepared as shown in Scheme 5.

The catalytic activities of the compounds investigated are shown in Table 1, and kinetic plots are provided in the Supporting Information. For comparison, control experiments run in the absence of any selenium- or tellurium-based catalyst produced $t_{1/2} > 300$ h with 90% or 56% *tert*-butyl hydroperoxide and $t_{1/2} = 116$ h with 29% hydrogen peroxide. A reinvestigation of **14** with different concentrations of *tert*-butyl hydroperoxide (entries 1−3), as well as with hydrogen peroxide (entry 4), revealed that its catalytic activity is highly dependent on the identity and concentration of the oxidant. When the hydroperoxide was employed, a dramatic increase in $t_{1/2}$ from 2.5 to

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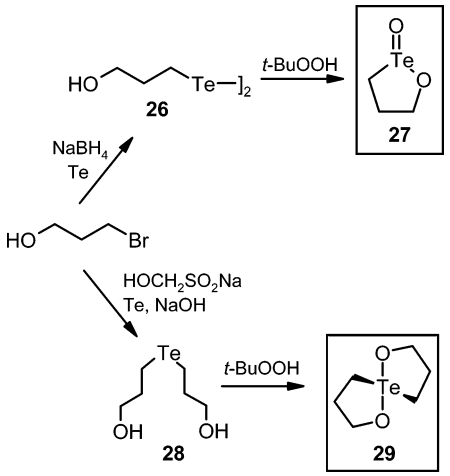
(27) Lesser, R.; Weiss, R. *Ber. Dtsch. Chem. Ges.* **1913**, 2640.

SCHEME 5



167 h was observed, as the concentration of the hydroperoxide reagent was changed from 90% to 38%. We also noted that, as the hydroperoxide concentration was lowered, an increasing accumulation of the corresponding selenenyl sulfide **30** occurred (Scheme 6). The latter compound had been previously identified as a minor byproduct at high hydroperoxide concentrations, and it was established that its formation comprises a competing deactivation pathway because of its low catalytic activity compared to that of the cyclic seleninate ester **14** itself.[24] At low concentrations of the hydroperoxide, or in its complete absence, **14** reacted with benzyl thiol to afford **30** quantitatively. By comparison, the $t_{1/2}$ measured with **14** in the presence of 29% hydrogen peroxide was considerably shorter than with a comparable concentration of the hydroperoxide (cf. entries 3 and 4).

Examination of the benzo analogue **19** revealed that it displays lower catalytic activity than the parent seleninate ester **14** with *tert*-butyl hydroperoxide (entry 2 vs 5) but identical activity in the reduction of hydrogen peroxide (entry 4 vs 6). Introduction of the electron-withdrawing carbonyl group in **22** decreased the catalytic activity in the case of both *tert*-butyl hydroperoxide (entry 5 vs 7) and hydrogen peroxide (entry 6 vs 8), affording $t_{1/2}$ values only slightly shorter than control reactions run in the absence of catalyst (vide supra). Further examination of the reactions catalyzed by **19** and **22** showed that the two compounds were gradually converted into the selenenyl sulfides **31** and **32**, respectively, in the presence of benzyl thiol and 56% *tert*-butyl hydroperoxide (entries 5 and 7, respectively). These compounds were isolated, characterized, and assayed independently with 56% *tert*-butyl hydroperoxide, revealing very poor catalytic activities ($t_{1/2}$ = 192 and >300 h, respectively). Similarly, the reduction of 29% hydrogen peroxide with benzyl thiol in the presence of **32** produced an unusually slow reaction with $t_{1/2}$ = 89 h. It therefore appears that, as in the case of **30** derived from **14**, the formation of the corresponding selenenyl sulfides **31** and **32** again comprises a deactivation pathway.

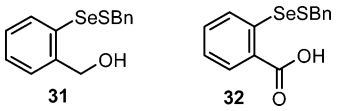
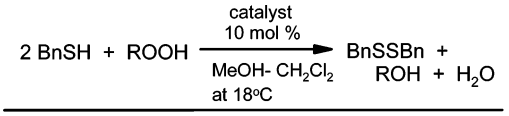
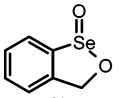
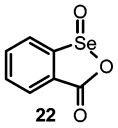
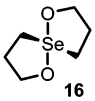
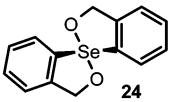
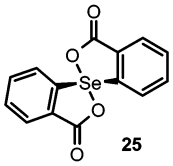


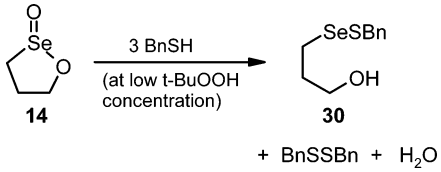
TABLE 1. Catalytic Activities of GPx Mimetics[a]



Entry	Catalyst	$t_{1/2}$ (h)	Oxidant
1		2.5	90% t-BuOOH[b]
2		90	56% t-BuOOH
3		167	38% t-BuOOH
4	**14**	18	29% H_2O_2
5		162	56% t-BuOOH
6	**19**	18	29% H_2O_2
7		252	56% t-BuOOH
8	**22**	73	29% H_2O_2
9		2.9	90% t-BuOOH[c]
10		1.9	56% t-BuOOH
11		2.1	38% t-BuOOH
12	**16**	0.2	29% H_2O_2
13		62	56% t-BuOOH
14	**24**	5.5	29% H_2O_2
15		113	56% t-BuOOH
16	**25**	35	29% H_2O_2
17		0.05	56% t-BuOOH
18	**27**	<0.05	29% H_2O_2
19		0.06	56% t-BuOOH
20	**29**	0.08	29% H_2O_2

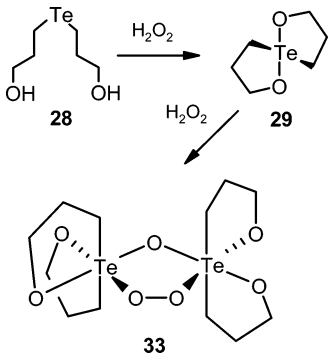
[a] Reactions were performed with BnSH (0.029 M), the catalyst (0.0029 M), and either 56% TBHP (0.038 M), 38% TBHP (0.023 M), or 29% H_2O_2 (0.040 M) in CH_2Cl_2–MeOH (95:5) at 18 °C, except for entries 7, 8, 17, and 18, where the solvent was CH_2Cl_2–MeOH (4:1). [b] Data taken from ref 24. [c] Data taken from ref 25.

SCHEME 6



The spirodioxyselenurane **16** displayed lower sensitivity toward hydroperoxide concentration, affording strong and comparable catalytic activity from 90% to 38% concentration (entries 9–11). Catalytic activity increased by a further ca. 1 order of magnitude when hydrogen peroxide was employed as the oxidant. At the end of the catalytic cycle, when the benzyl thiol had been consumed,

SCHEME 7



16 was the principal selenium-containing product present in the mixture. On the other hand, when the reactions were carried out in the presence of excess thiol, selenide **15** was recovered. This is consistent with the mechanism shown in Scheme 3, although we cannot rule out that the intermediate selenoxide catalyzes the reduction of the hydroperoxide by an independent pathway when both the hydroperoxide and thiol are present. The benzo analogue **24** showed much weaker catalytic activity (entry 13 and 14) than **16**, while its benzoyl counterpart **25** proved to be even more debilitated (entry 15 and 16) when employed with either oxidant.

We next investigated the novel tellurium analogues **27** and **29**. These compounds afforded by far the strongest catalytic activity of all of the GPx mimetics that we have examined to date,[16,24,25] with $t_{1/2}$ values of <5 min, using either 56% *tert*-butyl hydroperoxide (entry 17 and 19) or 29% hydrogen peroxide (entry 18 and 20). Although the reactions catalyzed by **27** and **29** were too rapid to permit a more detailed analysis of intermediates by NMR techniques, control experiments indicated that **27** and **29** are inert to *tert*-butyl hydroperoxide for at least several hours but that they react rapidly with benzyl thiol. This is consistent with the mechanisms shown in Schemes 2 and 3, where thiolysis, rather than oxidation of the catalyst, provides entry into the catalytic cycle. However, it is also possible that the corresponding tellurenyl sulfide was produced during the catalytic cycle of **27** but that, in contrast to its selenenyl sulfide counterpart **30**, it served as an efficient catalyst for the reduction of the hydroperoxide. Unfortunately, the tellurenyl sulfide proved relatively unstable and it was not possible to isolate it in a pure state and measure its $t_{1/2}$ in an independent experiment.

When the spirodioxytellurane **29** was treated with excess 29% hydrogen peroxide in the absence of the thiol, we unexpectedly obtained a new compound that was isolated, characterized, and subjected to X-ray crystallography (Scheme 7). It proved to have the highly unusual peroxide structure **33**, whose ORTEP diagram is shown in Figure 1. The product is dimeric, where each hypervalent tellurium atom occupies the center of a distorted octahedron, bonded to four oxygen atoms in a roughly square planar arrangement. The central ring comprises a 1,2,4-trioxa-3,5-ditellurolane moiety that includes the peroxide linkage. Full details of the crystal structure are contained in the Supporting Information. An independent assay of **33** indicated that it too has very strong catalytic activity ($t_{1/2}$ < 3 min with 29% hydrogen peroxide or 56% *tert*-butyl hydroperoxide). However, its relatively slow formation from **29** via Scheme 7 (ca. 50% complete after 6 h) indicates that it does not play a significant role in the catalytic cycle of **29**.

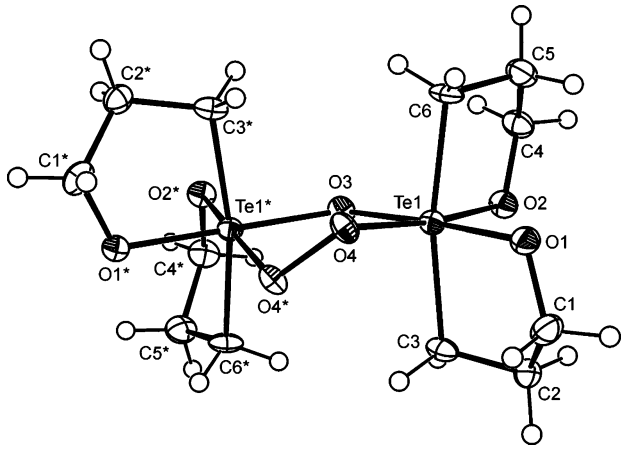


FIGURE 1. ORTEP diagram of peroxide **33**.

Conclusions

These experiments indicate that the benzo analogues **19** and **24** have diminished, or at best comparable, catalytic activity relative to the original selenium-based catalysts **14** and **16**. The activity is further decreased when electron-withdrawing carbonyl groups are introduced in the benzoyl derivatives **22** and **25**. Furthermore, the diminished activity of **14** at low concentrations of *tert*-butyl hydroperoxide, as well as the generally lower catalytic activity of the benzo and benzoyl compounds **19** and **22**, can be attributed to the formation of the respective selenenyl sulfides **30**−**32**. Thus, although selenenyl sulfide intermediates have been postulated to play a key role in the catalytic cycles of GPx (see Scheme 1) and of some of the mimetics reported earlier,[6] their formation in the present case represents a deactivation pathway. This was unequivocally confirmed by the measurement of their catalytic activities in independent assays using authentic samples.

Our present results also indicate that the catalytic reduction of hydrogen peroxide proceeds more rapidly by up to an order of magnitude compared to that of *tert*-butyl hydroperoxide when the selenium-containing catalysts **14**, **16**, **19**, **22**, **24**, and **25** are employed. Perhaps most noteworthy of all is the observation that the novel tellurium analogues **27** and **29** displayed remarkable catalytic activity, affording $t_{1/2}$ values in our model assay of <5 min compared to 0.2−90 h for the corresponding selenium analogues **14** and **16** under comparable conditions of oxidant and concentration.

Finally, while spirodioxyselenurane **16** was stable toward both oxidants in the absence of benzyl thiol, the corresponding tellurane **29** was only resistant toward *tert*-butyl hydroperoxide. When treated with hydrogen peroxide, **29** was slowly converted into the unusual and unexpected dimeric tellurium peroxide species **33**. While the latter displayed strong catalytic activity of its own in an independent assay, its formation from **29** was too slow for it to contribute significantly to the reduction of hydrogen peroxide with benzyl thiol in the presence of **29**.

These experiments further illustrate that diverse mechanisms are possible in the reduction of peroxide species with sacrificial thiols in the presence of small-molecule organoselenium and tellurium compounds that serve as catalysts for the process.

Experimental Section

Diselenide **17**,[27] selenide **20**,[26] and spirodioxyselenurane **25**[26] were prepared by literature procedures. Experimental details for the preparation of **14** and **16** can be found in the Supporting Information of refs 24 and 25, respectively. NMR spectra were run in $CDCl_3$ unless otherwise indicated. Chemical shifts for ^{77}Se and ^{125}Te NMR spectra are reported relative to dimethyl selenide and dimethyl telluride, respectively (δ 0.00). The spectra were recorded by using diphenyl diselenide in $CDCl_3$ (δ 463 ppm[28]) or selenium dioxide in D_2O (δ 1302.6 ppm[29]), for ^{77}Se NMR spectra, and diphenyl ditelluride in $CDCl_3$ (δ 420.8 ppm[30]), for ^{125}Te NMR spectra. Benzyl thiol was distilled prior to use and the concentrations of *tert*-butyl hydroperoxide and hydrogen peroxide were determined by iodometric analysis.[31]

Glassware used in the measurement of catalytic activity (Table 1) was washed only with water followed by acetone, and was flame-dried prior to use. Contamination with traces of detergent or alkali produced abnormal kinetic results.

Allyl (2-Hydroxymethyl)phenyl Selenide (18). Diselenide **17** (1.43 g, 3.57 mmol) in 50 mL of dry THF was added dropwise to a stirred solution of 0.69 g (18 mmol) of lithium aluminum hydride in 20 mL of dry THF at 0 °C. After the initial vigorous reaction subsided, the mixture was warmed to room temperature, stirred for 6 h, and treated with 0.7 mL (8 mmol) of allyl iodide. Stirring was continued overnight, the mixture was quenched with 100 mL of water and filtered, and the residue was washed thoroughly with ether. The filtrate was extracted repeatedly with ether. The combined organic layers were dried and concentrated in vacuo. The crude product was chromatographed (elution with hexanes−ethyl acetate 3:2) to afford 816 mg (50%) of **18** as a yellow oil: IR (neat) 3350 (br), 1028, 750 cm^{-1}; ^1H NMR (300 MHz) δ 7.54 (dd, J = 7.4, 1.3 Hz, 1 H), 7.40 (dd, J = 7.4, 1.3 Hz, 1 H), 7.31−7.18 (m, 2 H), 6.00−5.86 (m, 1 H), 4.99−4.92 (m, 2 H), 4.76 (s, 2 H), 3.51 (d, J = 7.7 Hz, 2 H), 2.40 (br s, 1 H); ^{13}C NMR (75 MHz) δ 143.0, 134.8, 134.3, 129.7, 128.5, 128.4, 128.0, 117.3, 65.6, 31.1; mass spectrum, *m/z* (relative intensity) 228 (10, M^+), 187 (38), 157 (17), 129 (26), 105 (17), 78 (100); exact mass calcd for $C_{10}H_{12}O^{80}Se$ 228.0053, found 228.0060.

Benzo-1,2-oxaselenolane *Se*-Oxide (19). *tert*-Butyl hydroperoxide (0.96 mL of 38% aqueous solution, 3.9 mmol) was added to 448 mg (1.97 mmol) of selenide **18** in 15 mL of dichloromethane. The mixture was stirred at room temperature overnight, concentrated in vacuo, and chromatographed (elution with 20% methanol−ethyl acetate) to afford 351 mg (88%) of **19** as a white solid: mp 139−140 °C (from ethyl acetate); IR (KBr) 1462, 1260, 966 cm^{-1}; ^1H NMR (300 MHz) δ 7.81 (d, J = 7.7 Hz, 1 H), 7.61−7.47 (m, 3 H), 5.97 (d, J = 13.8 Hz, 1 H), 5.61 (d, J = 13.6 Hz, 1 H); ^{13}C NMR (75 MHz) δ 148.3, 143.7, 132.2, 129.3, 125.5, 122.9, 78.6; ^{77}Se NMR (76 MHz) δ 1349.1; mass spectrum, *m/z* (relative intensity) 202 (30, M^+), 106 (74), 78 (100); exact mass calcd for $C_7H_6O_2{}^{80}Se$ 201.9533, found 201.9540. Anal. Calcd for $C_7H_6O_2Se$: C, 41.81; H, 3.01. Found: C, 41.54; H 2.97.

Allyl 2-Carboxyphenyl Selenide (21). Sodium borohydride (0.59 g, 16 mmol) was added to diselenide **17** (1.24 g, 3.10 mmol) in 60 mL of dry THF. The stirred mixture was cooled to 0 °C and 50 mL of absolute ethanol was added dropwise. The mixture was warmed to room temperature and after 15 min, 1.13 mL (12.4 mmol) of allyl iodide was added. After 1 h, the mixture was acidified with 120 mL of 1 M HCl and extracted with ether. The combined organic phases were washed with water, dried, and concentrated in vacuo. The residue was chromatographed (elution with 30% dichloromethane-ethyl acetate) to give 998 mg (67%) of **21** as a white solid: mp 137−138 °C (from benzene−petroleum ether); IR (KBr) 3200−2300 (br), 1660 cm^{-1}; ^1H NMR (300 MHz) δ 8.16 (d, J = 7.7 Hz, 1 H), 7.47−7.43 (m, 2 H), 7.29−7.23 (m, 1 H), 6.07−5.96 (m, 1 H), 5.39 (dd, J = 16.9, 1.3 Hz, 1 H), 5.15 (d, J = 10.0 Hz, 1 H), 3.59 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz) δ 172.0, 139.3, 133.4, 133.3, 132.8, 128.3, 127.4, 124.9, 118.5, 28.4; mass spectrum, *m/z* (relative intensity) 242 (19, M^+), 201 (100); exact mass calcd for $C_{10}H_{10}O_2{}^{80}Se$ 241.9846, found 241.9832. Anal. Calcd for $C_{10}H_{10}O_2Se$: C, 49.81; H, 4.18. Found: C, 49.72; H, 3.91.

Benzo-3-oxo-1,2-Oxaselenolane *Se*-Oxide (22). *tert*-Butyl hydroperoxide (0.65 mL of 56% aqueous solution, 3.8 mmol) was added to 322 mg (1.33 mmol) of selenide **21** in 40 mL of dichloromethane. The mixture was stirred at room temperature for 14 h, concentrated in vacuo, and recrystallized from acetonitrile to provide 212 mg (74%) of **22** as a white solid with mp 226−227 °C (from water): IR (KBr) 1653, 1583, 1276 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.23 (dd, J = 7.7, 1.0 Hz, 1 H), 8.11 (dd, J = 7.4, 1.3 Hz, 1 H), 7.85−7.80 (m, 1 H), 7.69−7.65 (m, 1 H); ^{13}C NMR (100 MHz, D_2O, 340 K) δ 170.8, 147.8, 134.8, 133.3, 131.6, 130.3, 125.1; ^{77}Se NMR (57 MHz, DMSO-d_6) δ 1022.3; mass spectrum, *m/z* (relative intensity) 216 (9, M^+), 200 (28), 120 (100); exact mass calcd for $C_7H_4O_3{}^{80}Se$ 215.9326, found 215.9309.

Bis[2-(hydroxymethyl)phenyl] Selenide (23). Selenide **20** (360 mg, 1.12 mmol) in 15 mL of dry THF was added dropwise to a refluxing solution of 128 mg (3.36 mmol) of lithium aluminum hydride in 20 mL of dry THF under an argon atmosphere. The resulting white slurry was refluxed for an additional 90 min, cooled to room temperature, and quenched cautiously with 50 mL of cold water. The mixture was filtered, the residue was washed thoroughly with ether and the filtrate was extracted repeatedly with ether. The combined organic layers were washed with saturated NaCl and water, dried, and concentrated in vacuo. The product was chromatographed (elution with dichloromethane−ethyl acetate 3:1) to give 174 mg (53%) of **23** as a clear oil, which solidified upon longer standing: mp 84−86 °C (from dichloromethane−hexanes); IR (neat) 3300 (br), 1006, 733 cm^{-1}; ^1H NMR (300 MHz) δ 7.47 (dd, J = 6.9, 1.5 Hz, 1 H), 7.35−7.27 m, 2 H), 7.21−7.15 (m, 1 H), 4.77 (s, 2 H), 1.89 (br s, 1 H); ^{13}C NMR (75 MHz) δ 142.2, 134.6, 130.6, 129.0, 128.9, 128.5, 65.5; ^{77}Se NMR (76 MHz) δ 316.5; mass spectrum, *m/z* (relative intensity) 294 (40, M^+), 292 (20), 246 (20), 228 (14), 195 (72), 91 (79), 77 (100); exact mass calcd for $C_{14}H_{14}O_2{}^{80}Se$ 294.0159, found 294.0139.

Spirodioxyselenurane (24). Selenide **23** (114 mg, 0.389 mmol) was dissolved in 15 mL of dichloromethane, and 80 μL (0.7 mmol) of 29% aqueous hydrogen peroxide was added. The mixture was stirred for 8 h at room temperature, the solvent was evaporated, and the crude product was chromatographed (elution with 75% ethyl acetate−hexanes) to afford 80 mg (71%) of **24** as a white solid: mp 171−173 °C (from ethyl acetate); IR (KBr) 2798, 1441, 1201, 1008 cm^{-1}; ^1H NMR (300 MHz) δ 8.03 (d, J = 7.2 Hz, 1 H), 7.41−7.34 (m, 2 H), 7.26−7.23 (m, 1 H), 5.32 (s, 2 H); ^{13}C NMR (75 MHz) δ 143.8, 134.1, 131.1, 128.2, 127.9, 124.3, 71.0; ^{77}Se NMR (76 MHz) δ 804.4; mass spectrum, *m/z* (relative intensity) 292 (20, M^+), 291 (47), 263 (68), 77 (100). Anal. Calcd for $C_{14}H_{12}O_2Se$: C, 57.74; H, 4.15. Found: C, 57.57; H, 4.18.

Spirodioxyselenurane (25). The product was obtained in 73% yield by oxidation of selenide **20** with hydrogen peroxide as described in the literature:[26] mp 326−328 °C (from ethyl

(28) Duddeck, H. *Progr. NMR Spectrosc.* **1995**, *27*, 1.
(29) Pekonen, P.; Hiltunen, Y.; Laitinen, R. S.; Pakkanen, T. A. *Inorg. Chem.* **1990**, *29*, 2770.
(30) Granger, P.; Chapelle, S.; McWhinnie, W. R.; Al-Rubaie, A. *J. Organomet. Chem* **1981**, *220*, 149.
(31) Wagner, C. D.; Smith, R. H.; Peters, E. D. *Anal. Chem.* **1947**, *19*, 976.

acetate) (lit.[26] mp 310−322 °C); IR (KBr) 1695, 1269, 1104, 831, 743 cm^{-1}; ^1H NMR (300 MHz,) δ 8.25−8.10 (m, 4 H), 7.90−7.75 (m, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.8, 142.7, 136.2, 133.9, 130.4, 130.2, 127.1. Anal. Calcd for $C_{14}H_8O_4Se$: C, 52.68; H, 2.53. Found: C, 52.25; H 2.43.

Bis(3-hydroxypropyl) Ditelluride (26). Water (30 mL) was added dropwise to 2.08 g (16.3 mmol) of tellurium powder and 0.62 g (16 mmol) of sodium borohydride under argon. The mixture was heated until the tellurium dissolved to afford a dark red solution. After it was cooled to room temperature, 2.27 g (16.3 mmol) of 3-bromo-1-propanol and 5 mL of water were added. The solution turned orange and was stirred for an additional 3 h. The mixture was extracted with ether, and the combined organic phases were dried, concentrated in vacuo, and chromatographed (elution with 60% ethyl acetate−hexanes) to give 1.14 g (37%) of **26** as a viscous red oil: IR (neat) 3230, 1201 cm^{-1}; ^1H NMR (300 MHz) δ 3.71 (t, J = 6.1 Hz, 4 H), 3.20 (t, J = 7.2 Hz, 4 H), 2.08−1.98 (m, 4 H), 1.86 (br s, 2 H); ^{13}C NMR (75 MHz) δ 63.6, 36.1, −0.2; ^{125}Te NMR (95 MHz) δ 120.0; mass spectrum, *m/z* (relative intensity) 378 (1, M^+), 256 (10), 171 (14), 130 (49), 39 (100). The deposition of tellurium from the product was observed within a few days even when the product was stored in a refrigerator. It was used without further purification.

1,2-Oxatellurolane *Te*-Oxide (27). *tert*-Butyl hydroperoxide (750 μL of 56% solution, 4.5 mmol) was added to ditelluride **26** (241 mg, 0.646 mmol) in 35 mL of dichloromethane. The color of the ditelluride was discharged within 5 min. After an additional 30 min, the solution was concentrated in vacuo and the product was precipitated from methanol to afford 151 mg (58%) of **27** as a white solid: mp 257−260 °C; IR (KBr) 1033, 979, 664 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.23 (t, J = 5.3 Hz, 2 H), 3.11 (t, J = 6.7 Hz, 2 H), 2.21−2.16 (m, 2 H); ^{13}C NMR (100 MHz, D_2O) δ 70.2, 46.9, 27.6; ^{125}Te NMR (95 MHz, D_2O) δ 1042.0; mass spectrum, *m/z* (relative intensity); mass spectrum, *m/z* (relative intensity) 204 (5, M^+), 188 (66), 130 (100); exact mass calcd for $C_3H_6O_2{}^{130}Te$ 203.9430, found 203.9418. Anal. Calcd for $C_3H_6O_2Te$: C, 17.87; H, 3.00. Found: C, 18.19; H, 2.95.

Bis(3-hydroxypropyl) Telluride (28). Hydroxymethanesulfinic acid monosodium salt dihydrate (3.0 g, 19 mmol) was added to 0.50 g (3.9 mmol) of tellurium powder and 2.5 g (63 mmol) of sodium hydroxide in 30 mL of water. The dark red mixture was refluxed under argon until it formed a pale pink solution (ca. 30 min). The solution was cooled to room temperature and 0.69 mL (7.6 mmol) of 3-bromo-1-propanol was added. The mixture turned yellow within 5 min and was stirred for an additional 30 min. The product was extracted with ether, dried, concentrated in vacuo, and chromatographed (elution with ethyl acetate) to give 0.51 g (55%) of **28** as a yellow oil: IR (neat) 3340, 1221 cm^{-1}; ^1H NMR (300 MHz) δ 3.72 (t, J = 6.0 Hz, 4 H), 2.74 (t, J = 7.4 Hz, 4 H), 2.07−1.98 (m, 4 H), 1.80 (br s, 2 H); ^{13}C NMR (75 MHz) δ 64.0, 34.7, −1.4; ^{125}Te NMR (95 MHz) δ 229.5; mass spectrum, *m/z* (relative intensity) 248 (53, M^+), 189 (20), 172 (53), 130 (26), 57 (56), 41 (100); exact mass calcd for $C_6H_{14}O_2{}^{130}Te$ 248.0056, found 248.0044. The air-sensitive product was used directly without further purification.

Spirodioxytellurane (29). *tert*-Butyl hydroperoxide (550 μL of 38% solution, 2.2 mmol) was added to 524 mg (2.13 mmol) of telluride **28** in 15 mL of dichloromethane. The yellow mixture turned colorless and clear within 5 min and was stirred at room temperature for an additional 30 min. The solvent was evaporated under vacuum to give a colorless oil, which solidified upon standing to give 489 mg (94%) of **29** as a waxy solid: IR (neat) 1137, 1040, 982 cm^{-1}; ^1H NMR (300 MHz) δ 4.25−4.18 (m, 2 H), 3.79−3.72 (m, 2 H), 2.90−2.73 (m, 4 H), 2.30−2.12 (m, 2 H), 1.95−1.73 (m, 2 H); ^{13}C NMR (75 MHz) δ 67.4, 28.5, 27.2; ^{125}Te NMR (126 MHz) δ 1095.8; mass spectrum, *m/z* (relative intensity) 246 (1, M^+), 188 (42), 130 (39), 43 (56); exact mass calcd for $C_6H_{12}O_2{}^{130}Te$ 245.9900, found 245.9911. Anal. Calcd for $C_6H_{12}O_2Te$: C, 29.56; H, 4.96. Found: C, 29.42; H, 5.05.

Selenenyl Sulfide 31. Cyclic seleninate ester **19** (115 mg, 0.572 mmol) was dissolved in 40 mL of dichloromethane and cooled in an ice bath. Benzyl thiol (202 μL, 1.72 mmol) was added and stirring was continued for 10 min. The solution turned dark violet and then yellow. The solvent was evaporated and the crude product was chromatographed (elution with 15% ethyl acetate−hexanes) to afford 153 mg (86%) of **31** as a pale yellow oil, which was stored in the refrigerator: IR (neat) 3356, 1258, 1198, 1023, 755, 695 cm^{-1}; ^1H NMR (300 MHz) δ 7.75 (d, J = 6.7 Hz, 1 H), 7.37−7.12 (m, 8 H), 4.77 (s, 2 H), 4.04 (s, 2 H), 1.96 (s, 1 H); ^{13}C NMR (75 MHz) δ 140.9, 137.8, 132.2, 131.8, 129.3, 128.7, 128.6, 128.5, 128.0, 127.6, 65.5, 42.3; ^{77}Se NMR (76 MHz) δ 440.2; mass spectrum, *m/z* (relative intensity) 310 (8, M^+), 186 (18), 91 (100), exact mass calcd for $C_{14}H_{14}OS^{80}Se$ 309.9931, found 309.9954. Anal. Calcd for $C_{14}H_{14}OSSe$: C, 54.37; H, 4.56. Found: C, 54.58; H, 4.81.

Selenenyl Sulfide 32. Cyclic seleninate ester **22** (22 mg, 0.10 mmol) was dissolved in 10 mL of methanol. Benzyl thiol (32 μL, 0.27 mmol) was added and the mixture was stirred for 1 h at room temperature. The product was concentrated in vacuo and recrystallized from ethyl acetate−hexanes to afford 23 mg (73%) of **32** as a white solid: mp 153−155 °C; IR (KBr) 3300−2300, 1660, 1266, 1027, 736 cm^{-1}; ^1H NMR (300 MHz) δ 8.19−8.10 (m, 2 H), 7.52−7.46 (m, 1 H), 7.47−7.18 (m, 6 H), 4.04 (s, 2 H); ^{13}C NMR (75 MHz) δ 172.2, 139.0, 138.2, 134.0, 132.6, 129.1, 128.7, 127.6, 126.3, 125.9, 42.3; ^{77}Se NMR (57 MHz) δ 566.8; mass spectrum, *m/z* (relative intensity) 324 (2, M^+), 200 (7), 91 (100). Anal. Calcd for $C_{14}H_{12}O_2SSe$: C, 52.02; H, 3.74. Found: C, 51.86; H, 3.74.

Peroxide 33. Bis(3-hydroxypropyl) telluride **28** (170 mg, 0.693 mmol) was dissolved in 15 mL of dichloromethane and treated with hydrogen peroxide (150 μL of 29% solution, 1.4 mmol). The mixture turned clear within ca. 1 min and was then stirred for an additional 16 h at room temperature. The product was concentrated in vacuo to give 185 mg (100%) of a solid, which was recrystallized from ethanol to afford 126 mg (68%) of **33**: mp 211−213 °C; IR (KBr) 1221, 1044, 989, 810 cm^{-1}; ^1H NMR (300 MHz) δ 4.20−4.08 (m, 2 H), 4.08−3.95 (m, 4 H), 3.84−3.70 (m, 2 H), 2.95−2.70 (m, 4 H), 2.68−2.53 (m, 2 H), 2.45−2.16 (m, 8 H), 2.16−1.95 (m, 2 H); ^{13}C NMR (75 MHz) δ 61.2, 60.8, 37.9, 35.1, 24.7, 24.5; ^{125}Te NMR (126 MHz) δ 1123.7. Anal. Calcd for $C_{12}H_{24}O_7Te_2$: C, 26.91; H, 4.52. Found: C, 27.04; H, 4.37. For the X-ray crystal structure of the product, see Figure 1 and the Supporting Information.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Supporting Information Available: ^1H, ^{13}C, ^{77}Se, and ^{125}Te NMR spectra, kinetic plots for the results summarized in Table 1, and X-ray crystallographic data for peroxide **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0512711