# A Novel Camphor-Derived Selenenamide That Acts as a Glutathione Peroxidase Mimetic

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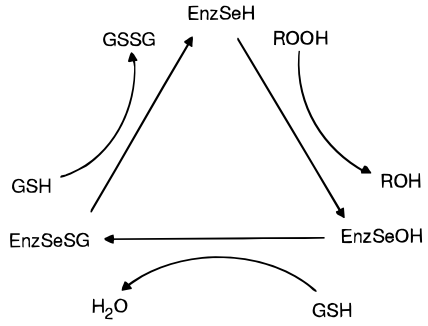
**Abstract:** A novel cyclic selenenamide **6** was prepared from the corresponding amido-substituted diselenide **5** by brominolysis and treatment with silver triflate. The selenenamide promotes the oxidation of phenylmethanethiol to the corresponding disulfide with *tert*-butyl hydroperoxide. It functions by reacting with the thiol to afford selenenyl sulfide **8**, which undergoes further attack by the thiol to produce dibenzyl disulfide and selenol **9**. The latter compound is oxidized by the hydroperoxide to the selenenic acid **10**, which in turn reacts with additional thiol, thus regenerating the selenenyl sulfide and forming water as the byproduct. The original selenenamide therefore acts as a procatalyst in this process and is not regenerated, whereas the selenenyl sulfide is the true catalyst. The selenenyl sulfide was isolated in the absence of the hydroperoxide and was fully characterized. The selenol was not observed in the catalytic cycle, but its transient formation was supported by a crossover experiment in which selenenyl sulfide **8** underwent thiol interchange with (4-methoxyphenyl)methanethiol. The catalytic cycle strongly resembles the mechanism by which the selenium-containing enzyme glutathione peroxidase catalyzes the destruction of hydroperoxides *in vivo* through the concomitant oxidation of glutathione to the corresponding disulfide.

Reduced oxygen species such as hydroperoxides are normal products of aerobic metabolism. However, they are known to generate highly reactive free radicals that destroy key biological molecules and cause damage to cell membranes. This in turn has been implicated in a variety of phenomena, including aging, Alzheimer's disease, inflammation, and certain cancers.[1] Living organisms have evolved a number of defense mechanisms to cope with oxidative stress, including the selenium-containing enzyme glutathione peroxidase (GSH-Px) that catalytically destroys hydroperoxides.[2] GSH-Px consists of four identical subunits of approximately 21 000 Da, each containing an essential selenocysteine residue.[2,3] It is the redox chemistry of the selenium atom that is responsible for the enzyme's catalytic activity.

The mechanism by which GSH-Px destroys hydroperoxides is shown in Scheme 1.[4] The selenol of a reduced selenocysteine moiety (EnzSeH) is oxidized by the hydroperoxide to generate a selenenic acid (EnzSeOH). The tripeptidic cofactor glutathione (GSH) then reacts with the selenenic acid, affording the corresponding selenenyl sulfide (EnzSeSG) and water. A second molecule of glutathione attacks at the sulfur atom of the latter species, producing glutathione disulfide (GSSG) and regenerating the selenol EnzSeH to complete the catalytic cycle. Thus, in the overall process, 2 equiv of glutathione are oxidized to the disulfide and water, while the hydroperoxide is reduced to the corresponding alcohol. At higher peroxide concentrations, a seleninic acid ($EnzSeO_2H$) may also be involved.

**Scheme 1**




Recently, much attention has been devoted to the discovery of compounds that mimic the action of GSH-Px. In particular, the cyclic selenenamide Ebselen (**1**)[5] has been shown to be a good catalyst for the reduction of peroxides and hydroperoxides with thiols. This property, when combined with Ebselen's relatively low toxicity, has led to interest in its therapeutic potential for a number of disease states,[6] and it has undergone evaluation in clinical trials as an antiinflammatory agent. Other mimetics incude the Ebselen homologue **2**,[6b] various other

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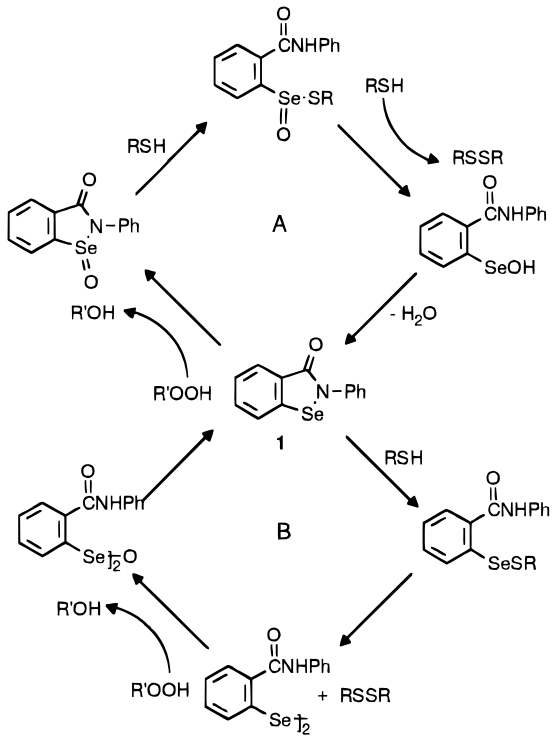
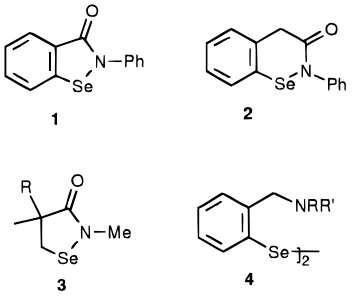
**Scheme 2**

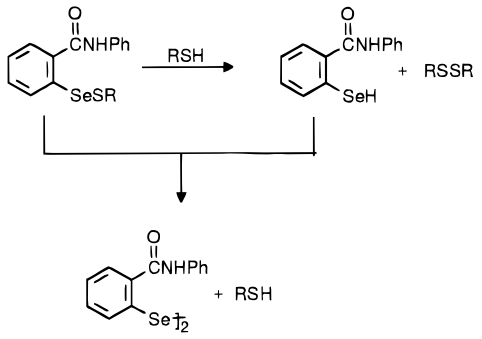



benzoselenazolinones,[6c] selenenamides **3**,[7] diaryl diselenides, especially ones containing proximal amino groups such as **4**,[6c,8] various ditellurides[9] and tellurides,[10] α-phenylseleno ketones,[11] certain organotellurium(IV) and organoselenium(IV) species,[12] and the artificial selenoenzyme, selenosubtilisin.[13]

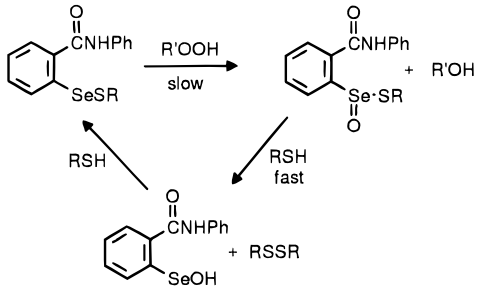



The mechanism by which Ebselen and other related GSH-Px mimetics catalyze the reduction of peroxides has been the subject of several studies. Fischer and Dereu[14] proposed that at high peroxide concentrations, Ebselen is first oxidized to its seleninamide [R(Se═O)NR′$_2$], which then reacts with 1 equiv of thiol to form the corresponding thioseleninate [RSe(═O)SR′]. The further reaction of the latter species with a second equivalent of the thiol then regenerates the original selenenamide **1**, via a selenenic acid (RSeOH), along with 1 mol of the disulfide (Scheme 2, path A). Under conditions of excess thiol, which represents a more realistic scenario *in vivo*, **1** reacts directly with the thiol to afford a selenenyl sulfide (RSeSR′) intermediate

**Scheme 3**




**Scheme 4**




that disproportionates to the corresponding diselenide and disulfide in the slow step. Further oxidation of the diselenide then regenerates the original selenenamide via a selenenic anhydride (RSeOSeR) (Scheme 2, path B). Peptidic nitrogen atoms may function similarly in the formation of cyclic selenenamide species in the natural enzyme GSH-Px. A variation of the Fischer and Dereu mechanism was suggested by Haenen et al.,[15] where the selenenyl sulfide reacts directly with a second mole of the thiol to produce a selenol and a disulfide, followed by attack of the selenol upon more selenenyl sulfide to afford the diselenide and thiol (Scheme 3). A third mechanism was proposed by Engman et al.,[9] wherein slow oxidation of the selenenyl sulfide to a thioseleninate occurs prior to rapid further reaction with the thiol to generate the disulfide and selenenic acid (Scheme 4). Precedence for this step with other thioseleninates was reported earlier by Kice et al.,[16] who also demonstrated that the further reaction of the selenenic acid thus produced with a second equivalent of the thiol affords the corresponding selenenyl sulfide. All three mechanisms therefore differ from the one shown in Scheme 1 for GSH-Px, where the selenenyl sulfide undergoes direct attack by GSH, followed by oxidation of the resulting selenol to its selenenic acid, without a diselenide or thioseleninate intermediate.

Studies of the analogue **3** (R = Me) were reported by Reich and Jasperse,[7] where the corresponding seleninamide, selenenyl sulfide, thioseleninate, selenol, and diselenide were implicated, with the precise mechanism dependent upon acid or base catalysis. These authors showed that thiolysis of the selenenyl sulfide in the presence of base produces the corresponding selenol, but oxidation of the latter leads to the diselenide, rather than directly to the original selenenamide **3**. Moreover, both Reich and Jasperse,[7] and Glass et al.,[17] demonstrated an alternative decomposition pathway of the thioseleninate intermediates derived from cyclic seleninamides and phenylmethanethiol by a selenoxide elimination that affords thiobenzaldehyde, which was trapped by cycloaddition with appropriate dienes.

(9) Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 9737.

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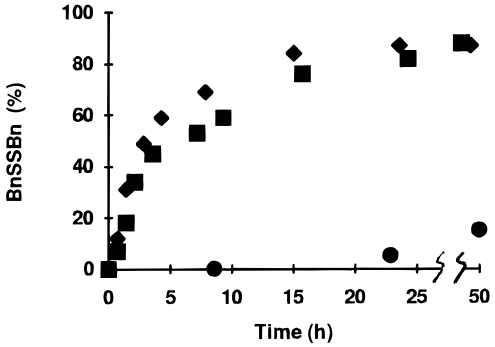
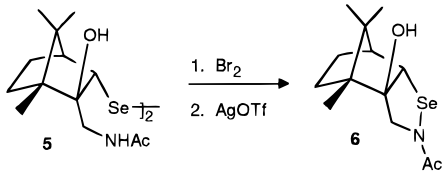



**Figure 1.** Oxidation of BnSH with TBHP in dichloromethane at 23 °C: (■) with 10 mol % of **6** present, (◆) with 10 mol % of **8** present, (●) with neither **6** nor **8** present.

**Scheme 5**




Diselenides **4**, where suitably positioned amino substituents are present, also show strong catalytic activity in the reduction of peroxides by thiols.[6c,8] Iwaoka and Tomoda[8b] proposed a mechanism similar to that of the actual enzyme GSH-Px (Scheme 1) for the model system **4** (R = Me, R′ = cyclohexyl). They also suggested that the role of the amino group is to activate the selenol intermediate toward oxidation through conversion to its conjugate base (selenolate). Moreover, hypervalent interactions between the amino nitrogen and selenium atoms stabilize the resulting selenenic acid intermediate toward further oxidation and direct thiolysis of the selenenyl sulfide toward attack at the sulfur rather than selenium atom.

During recent studies of camphor-derived auxiliary groups for use in asymmetric selenium chemistry,[18] we observed that the treatment of diselenide **5** with bromine and silver triflate resulted in its cyclization to the selenenamide **6** in high yield (Scheme 5). The product was a hydrolytically and thermally stable crystalline solid. It occurred to us that **6** might display similar mimetic behavior of GSH-Px as does Ebselen. We now report the results of our investigation of selenenamide **6**.

## Results and Discussion

For the purpose of this study, we employed a mixture containing a 2:1 molar ratio of phenylmethanethiol (BnSH) and *tert*-butyl hydroperoxide (TBHP) in dichloromethane at room temperature as our model system. Runs with and without 10 mol % of added **6** were carried out under the same conditions. Periodically, aliquots were removed, and the concentrations of the product dibenzyl disulfide (BnSSBn) were determined by HPLC, using naphthalene as an internal standard. A plot of the yield of the disulfide as a function of time for both experiments is shown in Figure 1. The plot shows that selenenamide **6** effectively accelerates the reaction of BnSH with TBHP. In the uncatalyzed experiment, extrapolation indicates that the time necessary to convert 50% of the thiol to its disulfide is ca. 6 days. In the presence of 10 mol % of **6**, however, the reaction reached its midpoint in ca. 5 h and so was 25−30 times faster than in the absence of **6**.

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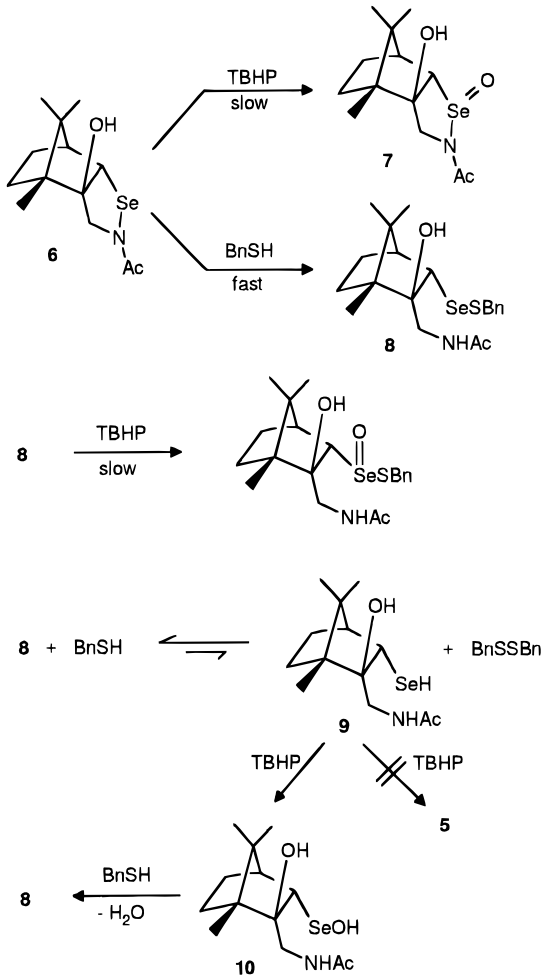
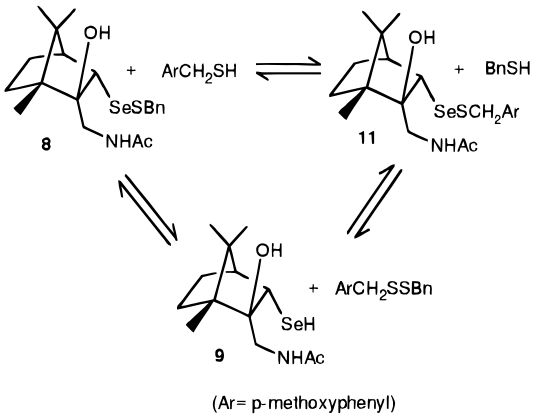
**Scheme 6**




We next set out to establish whether **6** reacts with TBHP to form the corresponding seleninamide **7**, or with the thiol to produce selenenyl sulfide **8**, in the first step. The reaction of **6** with 1 equiv each of TBHP and BnSH in deuteriochloroform led to the rapid and quantitative formation of selenenyl sulfide **8** and no detectable quantities of seleninamide **7**, or other oxidized species (Scheme 6). The identity of **8** was established by its independent synthesis and full characterization. Therefore, thiolysis rather than oxidation is unequivocally established as the first step.

The mechanisms proposed by other workers that proceed through a selenenyl sulfide intermediate (*vide supra*) can be separated into two categories, based on the sequence of its further reactions with the thiol and peroxide. When selenenyl sulfide **8** was treated with TBHP only in deuteriochloform for 16 h at room temperature, no significant reaction was observed, permitting the conclusion that the oxidation of **8** to its thioseleninate is not a viable pathway in the catalytic process. Alternatively, the reaction of **8** with BnSH would form the corresponding disulfide (BnSSBn) and selenol **9**. The oxidation of the selenol by the hydroperoxide would then be expected to generate either the selenenic acid **10** or the diselenide **5**, either of which could be recycled to the selenenyl sulfide **8** or the original selenenamide **6** via pathways similar to those in Scheme 2. However, when **8** and BnSH were combined in deuteriochloroform, we were unable to detect the appearance of the expected selenol by either $^{1}$H- or $^{77}$Se-NMR spectroscopy. An authentic sample of selenol **9** ($^{77}$Se-NMR $\delta$ −49) was obtained for comparison by reduction of diselenide **5** with sodium borohydride, followed by acidification with acetic acid. Despite

**Scheme 7**

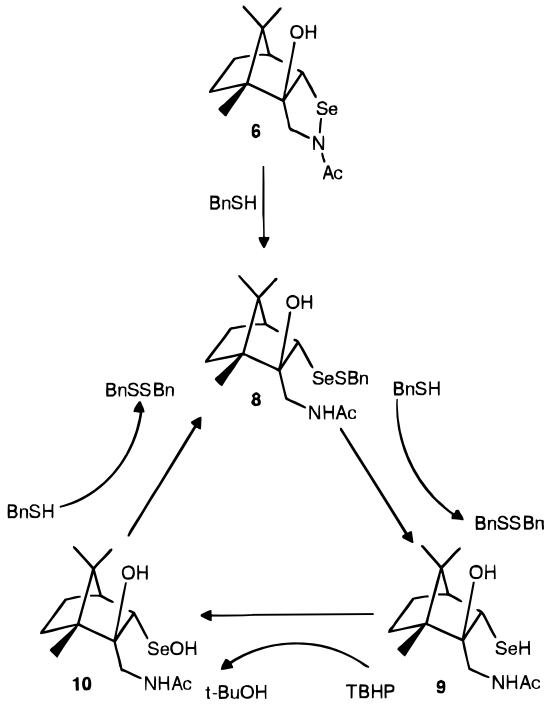



the failure to observe selenol **9** from the reaction of **8** with BnSH, the possibility remained that the latter compounds do react to form the selenol and dibenzyl disulfide but that the process is reversible and characterized by a small equilibrium constant ($K_{eq} \ll 1$). To test this hypothesis, a crossover experiment was performed in which **8** was treated with (4-methoxyphenyl)methanethiol in deuteriochloroform. After 2 h, the NMR spectrum of the reaction mixture showed the presence of the new selenenyl sulfide **11**, together with the original **8** in the ratio of ca. 1:2 (Scheme 7). The reaction of selenenamide **6** with (4-methoxyphenyl)methanethiol provided a 93% yield of authentic **11** for comparison. Although the formation of the selenenyl sulfide **11** could be explained by the nucleophilic attack of (4-methoxyphenyl)methanethiol directly at the selenium atom of **8** with the displacement of BnSH, this direct thiol interchange fails to produce a new selenium species that would be capable of reducing TBHP in the catalytic process. The formation of **8** was similarly observed when **11** was permitted to react with BnSH, thus establishing that the equilibrium can be approached from either direction (Scheme 7). The results of the crossover experiments are therefore consistent with the postulated reaction of **8** with BnSH to produce selenol **9** and dibenzyl disulfide.

On the basis of these experiments, we propose the following mechanism for the oxidation of phenylmethanethiol with TBHP in the presence of a catalytic amount of selenenamide **6**. The selenenamide is rapidly converted into the selenenyl sulfide **8** by the action of BnSH. In the presence of additional thiol, the selenenyl sulfide enters into equilibrium with BnSSBn and selenol **9**. Although **9** is not directly observed, presumably because of the small $K_{eq}$, it is rapidly oxidized in the presence of TBHP to the transient selenenic acid **10**, and this drives the process forward. The oxidation of **9** by TBHP to the diselenide **5** was ruled out in the catalytic process by the observation that **5** reacted slowly with either the thiol or TBHP in separate control experiments. Thus, if diselenide **5** had been an intermediate in the oxidation of **9** with TBHP, then it would have accumulated and been observed. The selenenic acid in turn reacts rapidly with BnSH to regenerate the selenenyl sulfide **8**,[16,19] and thus completes the catalytic cycle (Scheme 8). The latter compound is the only camphor-containing product at the end of the reaction, to the complete exclusion of the original selenenamide **6**. Furthermore, when a mixture of BnSH and TBHP was treated with 10 mol % of authentic **8**, the reaction proceeded at a comparable rate to that of the reaction where 10 mol % of **6** was added (Figure 1).

In conclusion, the mechanism in Scheme 8 is consistent with all of our observations and provides a plausible rationale for the catalytic activity of the camphorseleno system. In this

**Scheme 8**




process, selenenamide **6** is merely a procatalyst that is rapidly consumed in the first step, where it reacts with BnSH to form the selenenyl sulfide **8**. The latter functions as the true catalyst in this process via its subsequent reaction with BnSH to generate BnSSBn and the selenol **9**, followed by the rapid oxidation of the latter with TBHP to the selenenic acid **10**. Finally, the reaction of **10** with more thiol regenerates the selenenyl sulfide.

Compared to the other GSH-Px mimetics reported in the literature, the behavior of the present system as shown in Scheme 8 most closely resembles that reported by Iwaoka and Tomoda[8b] for the diselenide **4** (R = Me, R′ = cyclohexyl), although the latter compound contains a more basic tertiary amino group that can deprotonate the selenol intermediate and coordinate more strongly with the selenium center. Moreover, the mechanism in Scheme 8 is different from the catalytic cycles reported for Ebselen and related heterocycles, but appears to be identical to that established for the enzyme GSH-Px itself (Scheme 1).

## Experimental Section

Diselenide **5** was prepared by a procedure described elsewhere.[18a] All other reagents were obtained from commercial sources and purified by standard methods as necessary. The $^{77}$Se-NMR spectra were recorded using diphenyl diselenide as an external standard. Chemical shifts are reported relative to dimethyl diselenide ($\delta$ 0.0) by assuming that the resonance of the standard is at $\delta$ 461.0.[20] Elemental analyses and mass spectra were obtained by Ms. D. Fox and Ms. Q. Wu at the University of Calgary.

**Preparation of Selenenamide 6.** A 1.7 M solution of bromine in carbon tetrachloride (252 $\mu$L, 0.43 mmol) was added to a solution of diselenide **5** (235 mg, 0.39 mmol) in 5 mL of dichloromethane at −78 °C, and the resulting red solution was stirred for 45 min. A 1.1 M solution of silver trifluoromethanesulfonate in methanol (1.0 mL, 1.1 mmol) was added, which immediately discharged the red color, and the solution was stirred for 45 min at −78 °C and warmed to room temperature. The mixture was poured into 20 mL of dichloromethane,

(19) The formation of the diselenide **5** from selenol **9** would presumably proceed through the same selenenic acid intermediate **10** (or a related species such as its anhydride) that produces the selenenyl sulfide **8**. In the presence of a relatively high concentration of thiol and a low concentration of selenol, the direct formation of **8** instead of **5** from **10** is not surprising.

(20) Chivers, T.; Doxsee, D. D.; Parvez, M. *Inorg. Chem.* **1993**, *32*, 2238.

filtered, washed twice with water and aqueous NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (elution with ethyl acetate) to afford 175 mg (75%) of **6** as a white powder: mp 139−140 °C (from benzene−hexanes); IR ($CH_2Cl_2$) 3576, 1628, 1382, 1074 $cm^{-1}$; $^1$H-NMR (200 MHz) (the presence of two rotamers[21] in the ratio of 2:1 was observed) major rotamer $\delta$ 4.95 (d, $J$ = 13.2 Hz, 1 H, $NCH_2$), 4.51 (d, $J$ = 4.6 Hz, 1 H, C(3)-H), 2.83 (d, $J$ = 13.2 Hz, 1 H, $NCH_2$), 2.16 (s, 3 H), 2.10−1.92 (m, 2 H, OH and C(4)-H), 1.64−1.30 (m, 4 H), 1.25 (s, 3 H), 0.98 (s, 3 H), 0.94 (s, 3 H); minor rotamer $\delta$ 4.43−4.41 (m, C(3)-H), 4.18 (s, $J$ = 12.2 Hz, $NCH_2$), 3.23 (d, $J$ = 12.2 Hz, $NCH_2$), 1.00 (s, 3 H), 0.97 (s, 3 H); $^{77}$Se-NMR $\delta$ 885 (major rotamer), 873 (minor rotamer); mass spectrum, *m/z* (relative intensity) 303 ($M^+$, 15), 231 (14), 151 (27), 109 (52), 72 (33), 43 (100). Anal. Calcd for $C_{13}H_{21}NO_2Se$: C, 51.66; H, 7.00; N, 4.63. Found: C, 51.91; H, 6.94; N, 4.62.

**Reaction of BnSH and TBHP in the Presence and Absence of 10 mol % of Selenenamide 6.** TBHP (19 $\mu$L, 0.17 mmol) was added to a solution containing 0.34 mmol of phenylmethanethiol and 0.080 mmol of naphthalene (added as an internal standard) in 10 mL of dichloromethane. Selenenamide **6** (10 mg, 0.034 mmol) was added, and the progress of the reaction was monitored by HPLC. The reaction was repeated under identical conditions without **6**. The resulting data (% yield of BnSSBn vs time) are shown in Figure 1.

**Preparation of Selenenyl Sulfide 8.** Phenylmethanethiol (4 $\mu$L, 0.038 mmol) was added to a solution of 11 mg (0.037 mmol) of selenenamide **6** in 0.5 mL of deuteriochloroform. After 10 min, the thiol was consumed (NMR analysis), but traces of **6** remained, and so additional phenylmethanethiol (3 $\mu$L, 0.026 mmol) was added. After 1 h, volatile material was removed *in vacuo* to afford 15 mg (95%) of **8** as a colorless oil that solidified on standing: mp 131−132 °C (from benzene−hexanes); IR (film) 3403, 3311, 1626, 1562 $cm^{-1}$; $^1$H-NMR (200 MHz) $\delta$ 7.37−7.24 (m, 5 H, ArH), 5.98 (br s, 1 H, NH), 4.02 (s, 2 H, $SCH_2$), 3.64 (dd, $J$ = 14.2, 7.1 Hz, 1 H, $NCH_2$), 3.38−3.35 (m, 1 H, C(3)-H), 3.21 (dd, $J$ = 14.2, 4.8 Hz, 1 H, $NCH_2$), 2.71 (s, 1 H, OH), 2.01 (s, 3 H, Ac), 1.75−1.71 (m, 1 H, C(4)-H), 1.69−1.17 (m, 4 H), 0.95 (s, 3 H, C(8)-H), 0.87 (s, 3 H, C(9)-H), 0.82 (s, 3 H, C(10)-H); $^{77}$Se-NMR $\delta$ 363; mass spectrum, *m/z* (relative intensity) 303 ($M^+$, 32), 232 (22), 224 (20), 151 (42), 124 (70), 109 (69), 91 (100), 43 (72). Anal. Calcd for $C_{20}H_{29}NO_2SSe$: C, 56.33; H, 6.85; N, 3.28. Found: C, 56.43; H, 6.84; N, 3.25.

**Oxidation of Selenenyl Sulfide 8 with TBHP.** TBHP (40 $\mu$L, 0.36 mmol) was added to a solution of of **8** (150 mg, 0.35 mmol) in 3 mL of deuteriochoroforms and the reaction mixture was monitored for 24 h by $^{77}$Se-NMR and $^1$H-NMR spectroscopy. Only the starting material was detected at the end of this time.

**Reaction of Selenenyl Sulfide 8 with BnSH.** Phenylmethanethiol (24 $\mu$L, 0.20 mmol) was added to a degassed solution of selenenyl sulfide **8** (87 mg, 0.20 mmol) in 3 mL of deuteriochloroform under nitrogen, and the resulting solution was monitored for 16 h by $^{77}$Se-NMR spectroscopy. Only the starting material was present at the end of this time.

**Preparation of Selenol 9.** Sodium borohydride (10 mg, 0.26 mmol) was added to a solution of diselenide **5** (74 mg, 0.12 mmol) in 1 mL of ethanol, and the mixture was allowed to stand for 1 h with occasional shaking. Degassed deuteriochloroform (2 mL) was added and the $^{77}$Se-NMR spectrum of the sample was obtained, showing a resonance at $\delta$ −181, attributed to the borane complex of **9**.[22] Acetic acid (21 $\mu$L, 0.37 mmol) was added and the $^{77}$Se-NMR spectrum of the mixture showed a new signal at $\delta$ −49, assigned to the air-sensitive selenol **9**, which was not further characterized.

**Preparation of Selenenyl Sulfide 11.** Selenenyl sulfide **11** was prepared in 93% yield from **6** and (4-methoxyphenyl)methanethiol using the same procedure as in the preparation of **8**. Chromatography (elution with 50% ethyl acetate−hexanes) afforded **11** as a yellow oil: IR (neat) 3306, 1642, 1512, 1250 $cm^{-1}$; $^1$H-NMR (200 MHz) $\delta$ 7.28−7.23 (m, 2 H, ArH), 6.88−6.84 (m, 2 H, ArH), 6.03 (br s, 1 H, NH), 4.02 (d, $J$ = 13.0 Hz, 1 H, $SCH_2$), 3.94 (d, $J$ = 12.9 Hz, 1 H, $SCH_2$), 3.80 (s, 3 H, OMe), 3.66 (dd, $J$ = 14.2, 7.2 Hz, 1 H, $NCH_2$), 3.38−3.35 (m, 1 H, C(3)-H), 3.23 (dd, $J$ = 14.2, 4.8 Hz, 1 H, $NCH_2$), 2.83 (s, 1 H, OH), 2.01 (s, 3 H, Ac), 1.77−1.73 (m, 1 H, C(4)-H), 1.66−1.25 (m, 4 H), 0.97 (s, 3 H), 0.88 (s, 3 H), 0.82 (s, 3 H); mass spectrum, *m/z* (relative intensity) 457 ($M^+$, 1), 303 (13), 232 (8), 151 (19), 121 (100), 43 (78). Anal. Calcd for $C_{21}H_{31}NO_3SSe$: C, 55.25; H, 6.84; N, 3.07. Found: C, 55.43; H, 7.13; N, 2.88.

**Reaction of Selenenyl Sulfide 8 with (4-Methoxyphenyl)methanethiol.** Selenenyl sulfide **8** (11 mg, 0.027 mmol) and (4-methoxyphenyl)methanethiol (4 $\mu$L 0.029 mmol) were dissolved in 0.5 mL of degassed deuteriochloroform containing 5 $\mu$L of water,[23] and the mixture was allowed to stand for an additional 2 h with occasional shaking. The $^1$H-NMR spectrum then indicated that the selenenyl sulfides **8** and **11** were present in the ratio of 2:1. A mixture of both selenenyl sulfides were also observed when **11** was similarly treated with BnSH.

**Reaction of BnSH and TBHP in the Presence of 10 mol % of Selenenyl Sulfide 8.** The reaction was performed as in the case where selenenamide **6** was added and the resulting data (% yield of BnSSBn vs time) are shown in Figure 1.

**Reaction of Diselenide 5 with BnSH.** A solution of phenylmethanethiol (0.007 mmol) in 0.5 mL of deuteriochloroform was added to diselenide **5** (4 mg, 0.007 mmol) in 0.5 mL of deuteriochloroform. After 20 h, only unreacted starting material was observed by $^1$H-NMR spectroscopy.

**Reaction of Diselenide 5 with TBHP.** A solution of TBHP (0.007 mmol) in 0.5 mL of deuteriochloroform was added to diselenide **5** (4 mg, 0.007 mmol) in 0.5 mL of deuteriochloroform. After 20 h, mostly starting material was observed by $^1$H-NMR spectroscopy, along with ca. 20% of unidentified oxidized selenium species.

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(21) The presence of two sets of NMR signals for the homogeneous selenenamide **6** may be attributed to hindered rotation about the amide C−N bond. The signals did not coalesce at 50 °C in $CDCl_3$, but showed a unique set in toluene-$d_8$ at room temperature. Similar hindered rotation has been observed in *N*-acyl sulfenamides: (a) Kost, D.; Zeichner, A.; Sprecher, M. S. *J. Chem. Soc., Perkin Trans. 2* **1980**, 317. (b) Kost, D.; Egozy, H.; Elhanati, G. *Bull. Magn. Reson.* **1989**, *11*, 298.

(22) The formation of a borane selenolate complex from the reduction of diphenyl diselenide with sodium borohydride has been reported previously: Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.

(23) The crossover reaction proceeds more slowly in anhydrous deuteriochloroform for reasons that are not well understood at this time.