JOC Article

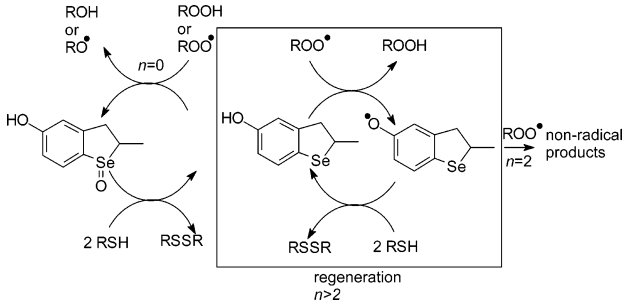
Regenerable Chain-Breaking 2,3-Dihydrobenzo[*b*]selenophene-5-ol Antioxidants

Sangit Kumar,[†] Henrik Johansson,[†] Lars Engman,*[,†] Luca Valgimigli,[‡] Riccardo Amorati,[‡] Maria Grazia Fumo,[‡] and Gian Franco Pedulli[‡]

Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, SE-751 23 Uppsala, Sweden, and Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Via S. Giacomo 11, 40126 Bologna, Italy

lars.engman@biorg.uu.se

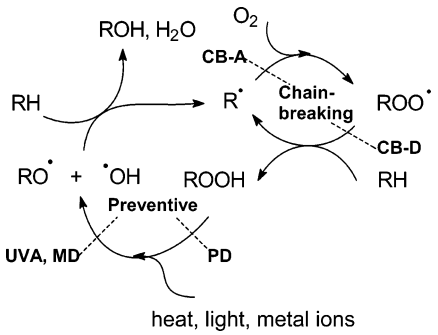
Received January 2, 2007



A series of 2,3-dihydrobenzo[*b*]selenophene-5-ol antioxidants was prepared by subjecting suitably substituted allyl 4-methoxyphenyl selenides to microwave-induced seleno-Claisen rearrangement/intramolecular Markovnikov hydroselenation followed by boron tribromide-induced O-demethylation. The novel antioxidants were assayed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water/chlorobenzene two-phase system containing *N*-acetylcysteine as a thiol reducing agent in the aqueous phase. Antioxidant efficiency as determined by the inhibited rate of peroxidation, R_{inh}, increased with increasing methyl substitution (R_{inh} = 46−26 μM/h), but none of the compounds could match α-tocopherol (R_{inh} = 22 μM/h). Regenerability as determined by the inhibition time, T_{inh}, in the presence of the thiol regenerating agent decreased with increasing methyl substitution. Thus, under conditions where the unsubstituted compound **5a** inhibited peroxidation for more than 320 min, α-tocopherol worked for 90 min and the trimethylated antioxidant **5g** for 60 min only. Sampling of the aqueous phase at intervals during peroxidation using antioxidant **5a** showed that *N*-acetylcysteine was continuously oxidized with time to the corresponding disulfide. In the absence of the regenerating agent, compounds **5** inhibited peroxidation for 50−60 min only. A (RO)B3LYP/LANL2DZdp//B3LYP/LANL2DZ model was used for the calculation of homolytic O−H bond dissociation enthalpies (BDE) and adiabatic ionization potentials (IP) of phenolic antioxidants **5**. Both BDE (80.6−76.3 kcal/mol) and IP (163.2−156.0 kcal/mol) decrease with increasing methyl substitution. The phenoxyl radical corresponding to phenol **5g** gave an intense ESR signal centered at g = 2.0099. The H−O bond dissociation enthalpy of the phenol was determined by a radical equilibration method using BHA as an equilibration partner. The observed BDE (77.6 ± 0.5 kcal/mol) is in reasonable agreement with calculations (76.3 kcal/mol). As judged by calculated log P values, the lipophilicity of compounds **5** increased slightly when methyl groups were introduced into the phenolic moiety (2.9 > C log P < 4.2). The capacity of compounds **5a** (k_{inh} = 3.8 × 10^5 M^{-1} s^{-1}) and **5g** (k_{inh} = 1.5 × 10^6 M^{-1} s^{-1}) to inhibit azo-initiated autoxidation of styrene in the homogeneous phase (chlorobenzene) was also studied. More efficient regeneration at the lipid−aqueous interphase is the most likely explanation why the intrinsically poorest antioxidant **5a** can outperform its analogues as well as α-TOC in the two-phase system. Possible mechanisms of regeneration are discussed and evaluated.

10.1021/jo0700023 CCC: $37.00
Published on Web 03/03/2007

SCHEME 1. Antioxidant Mechanisms



Introduction

All organic materials exposed to air undergo oxidative degradation. Reducing the rate of such processes by utilizing low concentrations of "antioxidants" is of paramount importance for aerobic organisms as well as for producers of most kinds of commercial products. In medicine, the term "oxidative stress" has been introduced to describe a situation characterized by an elevation in the cellular steady-state concentration of reactive oxygen-derived species. This condition occurs if the balance between oxidants and various antioxidant defenses is impaired. The recent interest in pharmaceutical antioxidants[1] and "antioxidant pharmacotherapy"[2] has emerged as a remedy for pathological conditions characterized by oxidative stress (chronic inflammatory disorders, atherosclerosis, cataract, etc.). Food technologists use antioxidants to inhibit lipid peroxidation and, thus, rancidity in food materials.[3] Polymer chemists use antioxidants to control polymerization in the manufacture of rubber, plastics, and paint and for the stabilization of polymeric materials during processing and use.[4] The oil industry makes extensive use of antioxidants in the design of better automobile fuels and lubricating oils.[5] Provided toxicity/environmental problems associated with increasing antioxidant use can be coped with, disease prevention/extending the lifetime of various materials is obviously of significant benefit to man and society.

Mechanistically, the chemical processes responsible for oxidative damage to biological material and the deterioration of the mechanical properties of a polymer during processing and use are very similar (Scheme 1[6]). The catalytic cycle in the upper right of the scheme is a free radical chain process known as autoxidation. If not intercepted, this will in short time convert organic material (RH) to the corresponding alkylhydroperoxide (ROOH). Chain-breaking accepting antioxidants (CB-A) trap carbon-centered radicals in competition with dioxygen. Chain-breaking donating antioxidants (CB-D) donate hydrogen atoms to peroxyl radicals before they can propagate the peroxidation reaction.[6] The cycle to the left in Scheme 1 shows different ways of initiation of the autoxidation process. Preventive antioxidants keep initiation of new chains to a minimum either by destroying hydroperoxides (PD = peroxide decomposer) by absorbing ultraviolet light (UVA = UV absorbers) or by complexing transition metals which would otherwise give rise to radicals via Fenton-like chemistry of hydroperoxides (MD = metal deactivator).

In vivo, peroxide decomposition is brought about by enzymatic systems: Catalase containing ferric heme groups catalyze decomposition of hydrogen peroxide into oxygen and water. A family of closely related selenium-containing glutathione peroxidases (GPxs) catalyzes the reduction of hydrogen peroxide and organic hydroperoxides into water and alcohols, respectively.[7] The stoichiometric reducing agent in these processes is the tripeptide glutathione, GSH (γ-glutamyl cysteinyl glycine) which is oxidized to the corresponding disulfide, GSSG (eq 1).[8]

$$\mathrm{ROOH/HOOH} + 2\ \mathrm{GSH} \xrightarrow{\mathrm{GPxs}} \mathrm{ROH/H_2O} + \mathrm{GSSG} + \mathrm{H_2O} \quad (1)$$

With drug and other antioxidant applications in mind, some of us[9] and others[10] have developed simple organochalcogen compounds that could mimic the properties of the GPxs and catalyze the decomposition of hydroperoxides in the presence of suitable stoichiometric reductants.

Vitamin E is the most important lipophilic, chain-breaking antioxidant in vivo.[11] Thus, it serves to protect DNA, proteins, lipids, carbohydrates, and other important biomolecules from becoming oxidatively damaged by radical processes involving reactive oxygen and nitrogen species. α-Tocopherol (α-TOH), the most reactive component of vitamin E, is known to trap two peroxyl radicals before it is converted into nonradical products. It would therefore seem wise for Nature to provide a system for its regeneration and catalytic mode of action, especially within biological membranes where it is the only protective agent. Although it has been hard to establish conclusively that this regeneration process occurs in vivo,[12] it is generally accepted[13] that ascorbate as a co-antioxidant (CoAH) could donate a hydrogen atom to the α-tocopheryl radical,

† Uppsala University.
‡ Università di Bologna.

(1) Andersson, C. M.; Hallberg, A.; Högberg, T. *Adv. Drug Res.* **1996**, *28*, 65−180.
(2) (a) Rice-Evans, C. A.; Diplock, A. T. *Free Radical Biol. Med.* **1993**, *15*, 77−96. (b) Bast, A. *Drug News Persp.* **1994**, *7*, 465.
(3) Pokorny, J.; Yanishlieva, N.; Gordon, M. *Antioxidants in Foods*; Woodhead Publishing: Cambridge, 2001.
(4) Zweifel, H. *Stabilization of Polymeric Materials*; Springer: Berlin, 1997.
(5) Mortier, R. M., Orszulik, S. T., Eds. *Chemistry and Technology of Lubricants*; Blackie Academic & Professional: London 1997.
(6) Scott, G. In *Free Radicals: Chemistry, Pathology and Medicine*; Rice-Evans, C., Dormandy, T., Eds; Richelieu Press: London, 1988; p 103.
(7) (a) Spallholz, J. E.; Boylan, L. M. In *Peroxidases in Chemistry and Biology*; Everse, J., Everse, K. E., Grisham, M. B., Eds.; CRC Press: Boca Raton, FL, 1991; Vol. 1, Chapter 12. (b) Sunde, R. A. In *Handbook of Nutritionally Essential Mineral Elements*; O'Dell, B., Sunde, R. A., Eds.; Marcel Dekker: New York, 1997; Chapter 18. (c) Birringer, M.; Pilawa, S.; Flohé, L. *Nat. Prod. Rep.* **2002**, *19*, 693−718.
(8) See: Prabhakar, R.; Vreven, T.; Morokuma, K.; Musaev, D. G. *Biochemistry* **2005**, *44*, 11864−11871 and refs cited therein.
(9) (a) Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 9737−9743. (b) Andersson, C.-M.; Hallberg, A.; Brattsand, R.; Cotgreave, I. A.; Engman, L.; Persson, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2553−2558. (c) Engman, L.; Stern, D.; Pelcman, M. Andersson, C.-M. *J. Org. Chem.* **1994**, *59*, 1973−1979. (d) Kanda, T.; Engman, L.; Cotgreave, I. A.; Powis, G. *J. Org. Chem.* **1999**, *64*, 8161−8169. (e) McNaughton, M.; Engman, L.; Birmingham, A.; Powis, G., Cotgreave, I. A. *J. Med. Chem.* **2004**, *47*, 233−239.
(10) (a) Mugesh, G.; Singh, H. B. *Chem. Soc. Rev.* **2000**, *29*, 347−357. (b) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125−2179.
(11) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194−201.
(12) Halliwell, B.; Gutteridge, J. M. C. *Free Radicals in Biology and Medicine*, 3rd ed.; Oxford University Press: Oxford, 1999; p 215.
(13) (a) Kamal-Eldin, A.; Appelquist, L.-Å. *Lipids* **1996**, *31*, 671−701. See refs 266−286. See also: (b) Sato, K.; Niki, E.; Shimasaki, H. *Arch. Biochem. Biophys.* **1990**, *279*, 402−405. (c) Bisby, R.; Parker, A. W. *Arch. Biochem. Biophys.* **1995**, *317*, 170−178. (d) Noguchi, N.; Niki, E. *Free Radical Res.* **1998**, *28*, 561−572. (e) Niki, E.; Noguchi, N. *Acc. Chem. Res.* **2004**, *37*, 45−51.

α-TO•, which results from the interaction of α-TOH with peroxyl radicals (eqs 2 and 3).

$$ROO^{\bullet} + \alpha\text{-TOH} \rightarrow ROOH + \alpha\text{-TO}^{\bullet} \quad (2)$$

$$\alpha\text{-TO}^{\bullet} + CoAH \rightarrow \alpha\text{-TOH} + CoA^{\bullet} \quad (3)$$

Niki and co-workers showed that vitamin E, although it is intrinsically a better scavenger of peroxyl radicals, is spared by vitamin C when both antioxidants were present in the homogeneous phase.[14] Also, when a lipid-soluble radical initiator was used in liposomes, both Niki and Ingold found that ascorbate in the aqueous phase was able to spare lipid-soluble α-TOH in the lipid phase.[15] α-Tocopherol has also been shown to catalyze the reduction of peroxyl radicals (eq 4)

$$ROO^{\bullet} + CoAH \xrightarrow{\alpha\text{-TOH}} ROOH + CoA^{\bullet} \quad (4)$$

in the presence of lipid-soluble co-antioxidants such as ubiquinols,[16,17] α-tocopheryl hydroquinone,[17] flavonoids,[18] phenothiazines,[19] catechols,[19] and phenols[20] with sufficiently low O−H bond dissociation energies. A kinetic model for the recycling of α-TOH by co-antioxidants in homogeneous solution has been proposed by Pedulli and co-workers.[19,20]

Other water-soluble co-antioxidants than ascorbate have also been considered for the regeneration of α-TOH across the lipid aqueous interphase. Although both urate and glutathione are often present in much higher concentrations than ascorbate in human plasma, it seems they are incapable[21,22] of regenerating α-tocopherol from tocopheryl radicals produced in a lipid environment.

In the present study, we have systematically investigated the regeneration of a series of 2,3-dihydrobenzo[*b*]selenophene-5-ol derivatives by water-soluble *N*-acetylcysteine in a two-phase model system for lipid peroxidation. As it turns out, regeneration and catalytic performance is largely dictated by the number and position of methyl substituents contained in the phenolic ring of the antioxidant.

Results

Azo-initiated peroxidation of linoleic acid or derivatives thereof has frequently been used for studying the antioxidative properties of synthetic and natural compounds.[23] Some time ago, we designed a two-phase variant of this system which allows the study of antioxidant regeneration by water-soluble co-antioxidants.[24] In the experimental setup used (schematically shown in Figure 1), linoleic acid and the antioxidant to be evaluated were vigorously stirred in chlorobenzene at 42 °C with an aqueous solution of *N*-acetylcysteine (NAC). 2,2′-Azobis(2,4-dimethylvaleronitrile) (AMVN) was added as an initiator in the organic phase and the progress of peroxidation monitored by HPLC (conjugated diene hydroperoxide formation). For comparison of catalyst efficiency, the inhibited rate of peroxidation, R_{inh}, was determined by least-squares methods from absorbance/time plots. The progress of peroxidation was followed for 320 min and the duration of the inhibited phase, T_{inh}, determined graphically as the cross-point for the inhibited and the uninhibited lines. We previously reported[25] that, whether (T_{inh} = 90 min) or not (T_{inh} = 80 min) NAC (1 mM) was present in the aqueous phase, α-tocopherol (40 μM) inhibited peroxidation of linoleic acid for almost the same time in the lipid phase. This is in line with Barclay's[22] results from liposome studies which indicated that water-soluble glutathione could not regenerate α-TOH. In the same study, we compared the antioxidant profile of 2,3-dihydrobenzo[*b*]furan-5-ol (**1a**) and its 1-thio (**1b**), 1-seleno (**1c**), and 1-telluro (**1d**) analogues. Interestingly, the inhibition time for all compounds was significantly prolonged if NAC was present in the aqueous phase. The effect of the thiol reducing agent was particularly noteworthy with the selenium analogue **1c** (T_{inh} = 50 and >300 min, respectively, in the presence and absence of NAC).

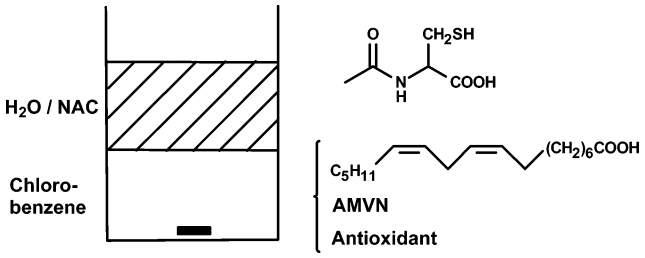
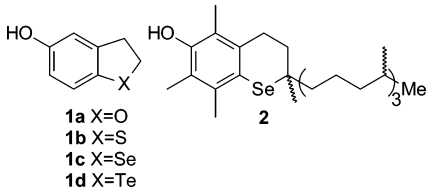


FIGURE 1. Two-phase model used for studying regeneration of chain-breaking antioxidants.



Encouraged by this result, but still largely ignorant about the parameters relevant for catalyst regeneration, we recently embarked on a total synthesis of all-*rac*-α-selenotocopherol (**2**), the selenium analogue of TOH.[26] However, we were rather

(14) Niki, E.; Saito, T.; Kawakami, A.; Kamiya, Y. *J. Biol. Chem.* **1984**, *259*, 4177−4182.

(15) (a) Niki, E.; Kawakami, A.; Yamamoto, Y.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1971−1975. (b) Doba, T.; Burton, G. W.; Ingold, K. U. *Biochem. Biophys. Acta* **1985**, *835*, 298−303.

(16) Frei, B.; Kim, M. C.; Ames, B. N. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 4879−4883.

(17) Shi, H.; Noguchi, N.; Niki, E. *Free Radical Biol. Med.* **1999**, *27*, 334−346.

(18) (a) Jia, Z.-S.; Zhou, B.; Yang, L.; Wu, L.-M.; Liu, Z.-L. *J. Chem. Soc., Perkin Trans. 2* **1998**, 911−915. (b) Zhou, B.; Jia, Z.-S.; Chen, Z.-H.; Yang, L.; Wu, L.-M.; Liu, Z.-L. *J. Chem. Soc., Perkin Trans. 2* **2000**, 785−791. (c) Chen, Z.-H.; Zhou, B.; Yang, L.; Wu, L.-M.; Liu, Z.-L. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1835−1839. (d) Pedrielli, P.; Skibsted, L. H. *J. Agric. Food Chem.* **2002**, *50*, 7138−7144.

(19) Amorati, R.; Ferroni, F.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2002**, *67*, 9295−9303.

(20) Amorati, R.; Ferroni, F.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **2003**, *68*, 9654−9658.

(21) Niki, E.; Saito, M.; Yoshikawa, Y.; Yamamoto, Y.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 471−477.

(22) (a) Barclay, L. R. C. *J. Biol. Chem.* **1988**, *263*, 16138−16142. (b) However, there is esr evidence that glutathione may regenerate α-TOH from the α-tocopheryl radical, α-TO•:[22a] Niki, E.; Tsuchiya, J.; Tanimura, R.; Kamiya, Y. *Chem. Lett.* **1982**, 789−792.

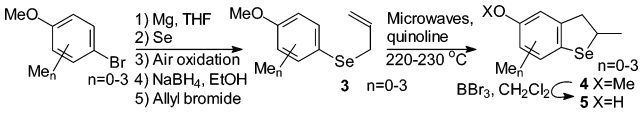
(23) (a) Cosgrove, J. P.; Church, D. F.; Pryor, W. A. *Lipids* **1987**, *22*, 299−304. (b) Braughler, J. M.; Pregenzer, J. F. *Free Radical Biol. Med.* **1989**, *7*, 125−130. (c) Pryor, W. A.; Cornicelli, J. A.; Devall, L. J.; Tait, B.; Trivedi, B. K.; Witiak, D. T.; Wu, M. *J. Org. Chem.* **1993**, *58*, 3521−3532.

(24) Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461−4467.

(25) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434−3440.

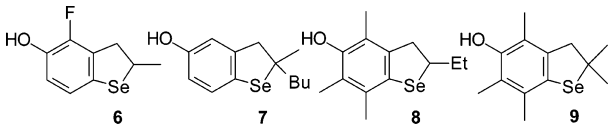
(26) Shanks, D.; Amorati, R.; Fumo, M. G.; Pedulli, G. F.; Valgimigli, L.; Engman, L. *J. Org. Chem.* **2006**, *71*, 1033−1038.

SCHEME 2



disappointed to find that compound **2**, just like α-TOH, was not regenerable in our two-phase model for lipid peroxidation (T_{inh} = 58 min whether NAC was present or not).

Synthesis. In order to carry out a more systematic investigation of catalyst regenerability, we needed ready access to selenochromanol or 2,3-dihydrobenzo[*b*]selenophene-5-ol derivatives substituted in the aromatic moiety with a variable number of methyl groups. It occurred to us that the seleno-Claisen rearrangement reported by Stefani and co-workers[27] some time ago could provide the desired organoselenium antioxidants with relatively little effort (Scheme 2). The allyl aryl selenides **3** required for this approach were prepared from commercially available 4-bromoanisoles via conversion to a Grignard reagent, insertion of elemental selenium into the carbon−magnesium bond, air oxidation, borohydride reduction of the crude resulting diaryl diselenide, and, finally, areneselenolate allylation. Compounds **3** were isolated in yields ranging from 32 to 96%. According to the literature procedure for seleno-Claisen rearrangement,[27] 2,3-dihydrobenzo[*b*]selenophenes unsubstituted in the aromatic moiety were obtained in low yields by heating for 2−3 h with quinoline at 210 °C. Obviously, the 2-allylbenzeneselenol product of the seleno-Claisen rearrangement undergoes intramolecular hydroselenation in a Markovnikov fashion under the harsh reaction conditions. For the preparation of compounds **4**, we found it optimal to perform the reaction in a microwave reactor at 220−230 °C for ca. 45 min. Still, isolated yields were only modest (13−59%). The higher reaction temperature was crucial for obtaining the sterically encumbered compounds **4** carrying methyl groups in either or both positions 4 and 7 of the dihydrobenzo[*b*]-selenophene. O-Demethylation to give the desired phenolic compounds **5** proceeded in good yields (47−98%) by treatment with boron tribromide in dichloromethane. Compounds prepared carry none (**5a**), one (**5b**, **5c**), two (**5d**, **5e**, **5f**), or three (**5g**) methyl substituents in the aromatic moiety (for structures, see Table 1). In addition, mostly in analogy with the chemistry shown in Scheme 2, we have also prepared dihydrobenzo[*b*]-selenophene-5-ol derivatives carrying a fluorine in the aromatic ring (compound **6**) and a few compounds (**7**, **8**, and **9**) where the substitution in the 2-position of the dihydrobenzo[*b*]-selenophene system has been varied.



Inhibition Studies. Inhibition studies with newly prepared antioxidants were performed in the model system described in Figure 1. The inhibition time, T_{inh}, and the inhibited rate of peroxidation, R_{inh}, in the presence/absence of NAC in the aqueous phase are shown in Table 1 for compounds studied. The results with α-tocopherol are included for comparison. There are several interesting trends in the data: Some of the antioxidants inhibit peroxidation for considerably longer times in the presence of the thiol reducing agent in the aqueous phase (regeneration conditions). The inhibition time in the presence of NAC is highly dependent on the number and position of methyl groups contained in the aromatic moiety of the antioxidant. The best regenerability is found with the unsubstituted compound **5a** (T_{inh} > 320 min) and fluoro derivative **6** (T_{inh} = 300 min). Antioxidants **5b** and **5c** carrying one methyl group in positions 6 and 7, respectively, showed markedly poorer catalytic performance (T_{inh} = 230 and 190 min). Regenerability continued to decrease when two methyl groups were introduced into the phenolic ring (compounds **5d**, **5e**, and **5f**). The effect was particularly noteworthy in the case of 4,6-disubstitution (T_{inh} = 80 min for compound **5d**). The fully ring-methylated antioxidant **5g**, just like α-TOH, could not be regenerated by NAC under the experimental conditions used. The peroxidation traces recorded with the most regenerable antioxidant **5a** and α-TOH are shown in Figure 2. The peroxyl radical quenching ability of the antioxidant is reflected in the inhibited rate of peroxidation. Although α-TOH (R_{inh} = 22 μM/h in the absence of thiol reducing agent) is intrinsically a better chain-breaking antioxidant than any of the synthetic compounds, it is clearly outperformed by compound **5a** (R_{inh} = 46 μM/h in the absence of thiol) after ca. 100 min. In fact, antioxidant **5a** is the least efficient peroxyl radical quencher in the series of new organoseleniums prepared. As could be expected,[28] introduction of methyl groups (especially into the *ortho*- and *para*-positions) of phenolic antioxidants would serve to increase the antioxidant activity. This trend is reflected in the observed inhibited rates of peroxidation for compounds **5** in the absence of NAC. Thus, compound **5b** carrying a *meta*-methyl group is only slightly more efficient than compound **5a**. Compounds **5b** (*ortho*-methyl) and **5e** and **5f** (*ortho*,*meta*-dimethyl) are clearly more efficient, and compound **5g** (*ortho*, *ortho*,*meta*-trimethyl) is the most efficient peroxyl radical quencher in the series. The trend seen in the inhibition data without NAC in the aqueous phase is largely reflected in the data obtained under regeneration conditions. It might be noted that all the antioxidants tested appear to be slightly more efficient when evaluated in the absence of thiol. This could be due to differences in pH (neutral in purely aqueous solution as compared with pH ca. 3.8 in a 1 mM aqueous solution of NAC) or ionic strength in the aqueous phase. More likely, however, this is due to different kinetic pathways of inhibition in the presence and absence of the co-antioxidant.[29]

Inhibition times for organoselenium antioxidants **5** and **6** in the absence of NAC in the aqueous phase were all shorter (50−70 min) than that recorded for α-TOH (80 min). α-TOH has a capacity to trap two peroxyl radicals before it is converted into nonradical products (the stoichiometric factor *n* equals 2). Thus, the stoichiometric factor for most of the synthetic antioxidants (**5a**, **5b**, **5e**, **5f**, **5g**) is only 1.25. Only fluoro derivative **6** showed a significantly higher value (n = 1.75).

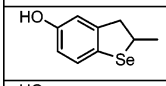
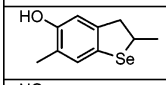
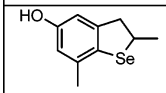
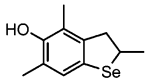
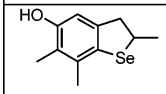
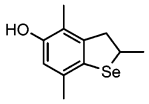
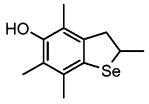
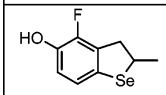
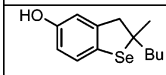
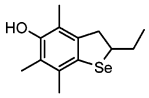
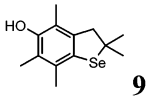
Compound **7**, unsubstituted in the phenolic ring just like compound **5a**, but carrying an additional butyl group in position

(27) Stefani, H. A.; Petragnani, N.; Ascenso, M. F. C.; Zeni, G. *Synth. Commun.* **2003**, *33*, 2161−2166.

(28) (a) Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *J. Org. Chem.* **1996**, *61*, 9259−9263. (b) Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173−1183.

(29) In the absence of thiol and under conditions where n = 2, the slope of the inhibited period is proportional to $1/2k_{inh}$, unlike when regeneration takes place. In this case, the phenoxyl radical is recycled before trapping the second peroxyl radical, and the slope of the inhibited trace is proportional to $1/k_{inh}$.

TABLE 1. Inhibition Times (T_{inh}) and Inhibited Rates of Peroxidation (R_{inh}) in the Presence and Absence of 1 mM *N*-Acetylcysteine in the Aqueous Phase, Calculated O−H Bond Dissociation Enthalpies, Ionization Potentials, and Lipophilicities for Compounds 5−9 and α-Tocopherol

Antioxidant	R_{inh}[a] (μM·h^{-1})	T_{inh}[b] (min)	Without NAC in aqueous phase		BDE[c] (kcal·mol^{-1})	IP[d] (kcal·mol^{-1})	*C*log*p*[e]
			R_{inh}[a] (μM·h^{-1})	T_{inh}[b] (min)			
 **5a**	69	>320	46	50	80.8	163.2	2.9
 **5b**	44	230	31	50	78.6	160.6	3.3
 **5c**	51	190	43	60	80.7	163.2	3.4
 **5d**	30	80	25	60	77.1	158.2	3.8
 **5e**	34	130	29	50	78.1	158.4	3.8
 **5f**	39	130	29	50	78.8	158.6	3.8
 **5g**	30	60	26	50	76.3	156.0	4.2
 **6**	93	300	51	70	79.7	169.5	3.1
 **7**	59	>320	45	70	-	-	5.0
 **8**	35	80	30	60	-	-	4.7
 **9**	29	100	28	60	-	-	4.7
α-TOH	24	90	22	80	-	-	-

[a] Rate of peroxidation during the inhibited phase (uninhibited rate = ca. 650 μM/h). [b] Duration of the inhibited phase of peroxidation. Reactions were monitored for ≤320 min. [c] Calculated O−H bond dissociation enthalpies. [d] Calculated ionization potential. [e] Calculated log *P* values.

2, inhibited peroxidation for a similarly long time (Table 1; T_{inh} > 320 min) under regeneration conditions. In the absence of NAC, the compound showed similar antioxidant efficiency (R_{inh} = 45 μM/h) but slightly longer inhibition time (T_{inh} = 70 min). As compared with antioxidant **5g**, variation in the 2-substitution (compounds **8** and **9**) did not affect the inhibition characteristics much (T_{inh} = 80 and 60 min, respectively, with and without NAC for both compounds; R_{inh} = 30 and 28 μM/h, respectively, without NAC in the aqueous phase).

The consumption of thiol in the aqueous phase was not routinely monitored with time for experiments carried out in the two-phase system. However, we have confirmed that the only chemical process occurring in the aqueous phase during peroxidation is oxidation of NAC to the corresponding disulfide. In the evaluation of the most regenerable antioxidant **5a**, the aqueous phase was sampled at intervals and the thiol/disulfide concentrations were monitored by reversed phase HPLC. As shown in Figure 3, the concentration of NAC drops more or less linearly with time and can be extrapolated to reach zero after ca. 390 min. Inhibition times were also recorded in the presence of less (0.5−0.0625 mM) than the standard (1 mM) concentration of NAC. As shown in Figure 4, T_{inh} decreases in a more or less linear fashion to the limiting value under non-regenerating conditions as the NAC concentration is lowered.

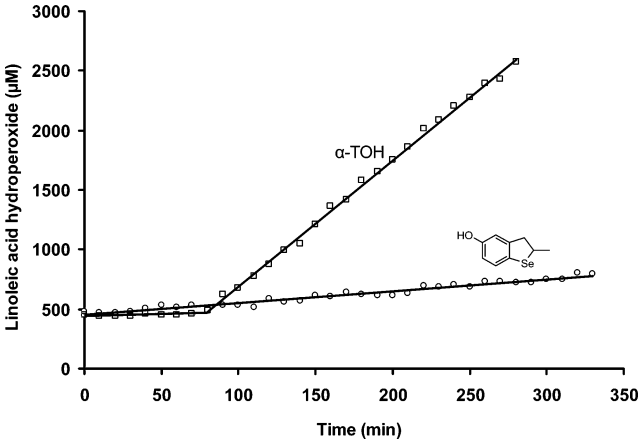


FIGURE 2. Peroxidation traces (linoleic acid hydroperoxide concentration vs time) recorded using compound **5a** or α-TOH as antioxidants in the chlorobenzene layer in the presence of NAC (1 mM) in the aqueous phase.

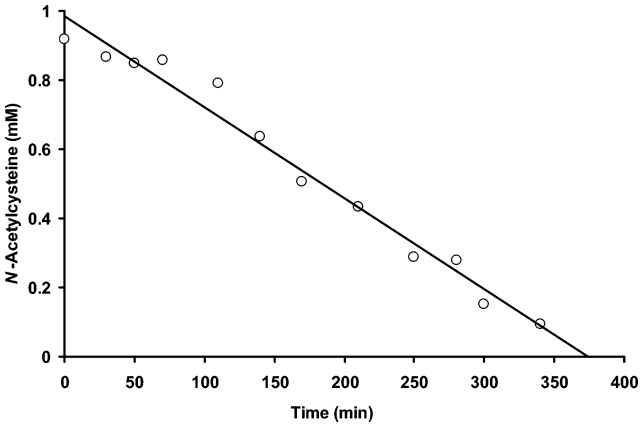


FIGURE 3. Concentration of *N*-acetylcysteine in the aqueous phase with time during a normal peroxidation experiment using antioxidant **5a**.

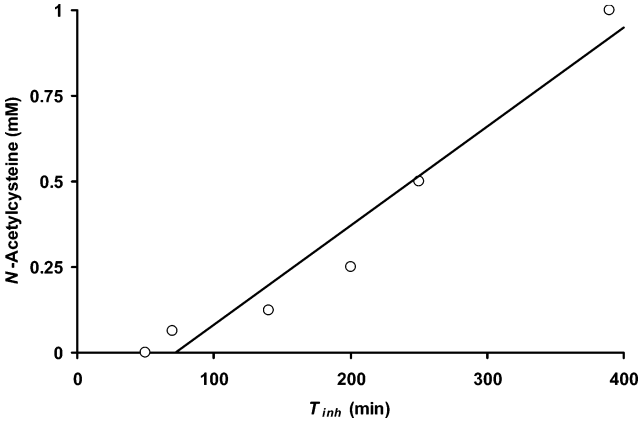


FIGURE 4. Inhibition time recorded with compound **5a** in the presence of various amounts of *N*-acetylcysteine (1, 0.5, 0.25, 0.125, 0.0625, and 0 mM) in the aqueous phase.

Inhibition studies with two of the novel antioxidants (**5a** and **5g**) and α-TOC as a reference have also been performed in the homogeneous phase (inhibited autoxidation of styrene in chlorobenzene at 303 K with AIBN initiation). The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus built in one of our laboratories and based on a Validyne DP15 differential pressure transducer, which has been previously described.[30] The observed kinetics are in accord with eqs 5−10. Both compounds **5a** and **5g** showed in styrene a neat inhibition period, T_{inh}, whose length provided the stoichiometric factor, which is the number of peroxyl radicals trapped by each molecule of antioxidant. This is given by $n = R_i T_{inh}/[AH]$, where R_i is the initiation rate, measured in a preliminary set of experiments using α-TOH, and [AH] is the initial concentration of antioxidant.

TABLE 2. Rate Constants, k_{inh}, for the Reaction of Compounds 2, 5a, and 5g with Peroxyl Radicals in Styrene/Chlorobenzene at 303 K, Number of Radicals Trapped by Each Antioxidant Molecule, *n*, and Experimental Bond Dissociation Enthalpies, BDE_{OH}, Measured by Radical Equilibration EPR in Benzene at 298 K[a]

compound	k_{inh} ($M^{-1}s^{-1}$)	*n*	BDE_{OH} (kcal/mol)
2[b]	1.2×10^6	1.9	78.1 ± 0.3
5a	$3.8 \pm 0.4 \times 10^5$	2.0	81.6[d]
5g	$1.5 \pm 0.3 \times 10^6$	1.7	77.6 ± 0.5
BHA	1.2×10^5[c]	2[c]	77.2 ± 0.2[e]
α-TOH	3.2×10^6[c]	2[c]	$77.1_5 \pm 0.3$[e]

[a] Data obtained under identical experimental settings with reference antioxidants BHA (2,6-di-*tert*-butyl-4-methoxyphenol), and α-tocopherol are shown for comparison. [b] Data from ref 26. [c] Reference values from ref 20 re-measured here to calibrate the instrumental settings. [d] Estimated value. [e] Data from ref 28a, corrected for the revised BDE of 2,4,6-tri-*tert*-butylphenol.[31]

$$\text{initiator} \xrightarrow{R_i} R^\bullet \quad (5)$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \quad (6)$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \quad (7)$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{products} \quad (8)$$

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \quad (9)$$

$$ROO^\bullet + ArO^\bullet \rightarrow \text{products} \quad (10)$$

Integration of the oxygen consumption trace affords the rate of reaction with peroxyl radicals, k_{inh}, provided k_p is known (eq 11).

$$\Delta[O_2]_t = -k_p/k_{inh}[RH]\ln(1 - t/T_{inh}) \quad (11)$$

As can be seen from the inhibition data in Table 2, compound **5a** is much less reactive toward peroxyl radicals than the fully methylated analogue **5g**. The stoichiometric factor *n* equals the theoretical value for a phenol. The peroxyl radical quenching ability of compound **5g** is very similar to that previously reported for selenotocopherol **2**. This is not surprising if the small difference in BDE_{OH} (vide infra) is considered not significant. However, the stoichiometric factor obtained experimentally for a freshly prepared solution of compound **5g** ($n = 1.7$) was lower than that recorded for the more tocopherol-like analogue **2** ($n = 1.9$). Furthermore, if the solution of **5g** was left for some time at room temperature before the peroxidation experiment, the recorded stoichiometric factor was even lower ($n = 1.3-$

(30) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142−2146.

1.4 after 4 h). This lower value of *n* possibly indicates that the antioxidant is partly degraded by air in solution.

In order to evaluate the possible synergism between compounds **5a** and **5g** with thiol under homogeneous phase conditions, we have studied the inhibited autoxidation of styrene (4.3 M in chlorobenzene) under identical experimental conditions as described above using a fixed concentration of 6.25×10^{-6} M of **5a** or **5g** and variable amounts of 1-octylmercaptan. The use of styrene at such concentration cancelled out the minor antioxidant activity of the mercaptan up to 1 mM. Therefore, we could safely use the co-antioxidant in concentrations up to 160 times those of the organoselenium. Interestingly, as compared with compound **5a** or **5g** alone (no thiol added), no difference in the oxygen consumption traces was ever observed with any concentration of co-antioxidant used. This shows that 1-octylmercaptan cannot regenerate compounds **5a** and **5g** from the corresponding phenoxyl radicals under homogeneous phase conditions.

Calculations. Recently, the introduction of easily applicable DFT models for the prediction of relative bond dissociation energies (BDEs) and ionization potentials (IPs) by Wright and co-workers[28b] has greatly facilitated the design of novel antioxidants. However, these DFT methods are not directly applicable to antioxidants containing heavy elements such as selenium. This is because relativistic effects upon the core electrons become too great to ignore for these atoms, precluding the use of the standard all-electron basis set these models are based upon. Therefore, we recently developed DFT models closely resembling those by Wright but utilizing a basis set incorporating relativistic effective core potentials for the core electrons.[35] These inherently take care of the relativism problem and drastically reduce the number of electrons to be calculated upon and, thus, the cost of calculation. This (RO)B3LYP/LANL2DZdp//B3LYP/LANL2DZ model was used for the calculation of homolytic OH bond dissociation enthalpies and adiabatic ionization potentials of phenolic antioxidants **5** and **6**, and the results are shown in Table 1. Not unexpectedly, both BDE and IP for compounds **5** decrease with increasing methyl substitution as one traverses the table from top to bottom (BDE = 80.8 kcal/mol and IP = 163.2. kcal/mol for compound **5a**; BDE = 76.3 kcal/mol and IP = 156.0 kcal/mol for compound **5g**). Introduction of fluorine into the 4-position of the dihydrobenzo[*b*]selenophene-5-ol system (compound **6**) also has a weakening effect on the OH bond (in line with the predicted effects of *ortho*-chlorine substitution[28b] in phenolic compounds). On the other hand, the electron-withdrawing fluorine caused a significant increase in the ionization potential of compound **6** (IP = 169.5 kcal/mol). Interestingly, the inhibited rates of peroxidation for compounds **5** showed a good correlation both with calculated bond dissociation enthalpies ($R^2 = 0.87$) and ionization potentials ($R^2 = 0.87$).

Depending on the number and position of aromatic methyl groups, the organoselenium phenolic antioxidants **5**−**9** are more or less readily regenerated at the aqueous lipid interphase. We therefore thought it would be interesting to see how structural modifications in the series affected lipophilicities of the compounds. Shown in Table 1 are calculated log *P* values. As expected, lipophilicity in the series of compounds **5** increases steadily as one, two, or three aromatic methyl groups are introduced. The introduction of additional alkyl groups in the 2-position of the dihydrobenzo[*b*]selenophene moiety results in a further increase in lipophilicity (compounds **7**−**9**).

EPR and Experimental Bond Dissociation Enthalpy Data. Out of the various methods available for determination of phenolic O−H bond strengths, the electron paramagnetic resonance (EPR) equilibration technique presently seems to afford the most accurate values.[28a,32] In this method, the equilibrium constant, K_e, for the hydrogen atom transfer reaction between a reference phenol (Ar′OH) and the compound under investigation (ArOH) is measured (eq 12). In order to check the accuracy of our H−O BDE calculations, we tried to obtain experimental values for the two extremes of compounds **5** (**5a** and **5g**).

$$\mathrm{ArOH} + \mathrm{Ar'O^{\bullet}} \rightleftarrows \mathrm{ArO^{\bullet}} + \mathrm{Ar'OH} \qquad (12)$$

Whereas compound **5a** produced only a weak signal when reacted at room temperature inside the cavity of an EPR spectrometer with alkoxyl radicals generated photolytically from di-*tert*-butyl peroxide in deoxygenated benzene, compound **5g** produced an intense spectrum centered at $g = 2.0099$ (referenced to the DPPH radical[36] $g = 2.0036_4$). This spectrum is shown in Figure 5 together with a computer simulation and was interpreted in terms of the following hyperfine splitting constants of 4.61 G (3H), 6.11 G (3H), 1.25 G (3H), 1.00 G (2H), and 1.60 G (1H). For obtaining the H−O BDE of compound **5g**, butylated hydroxyanisole (BHA; BDE = 77.2 kcal/mol in benzene[31]) was used as a reference. In the calculation of K_e, the initial concentrations of **5g** and BHA were used, while the relative radical concentrations were determined by means of EPR spectroscopy. The BDE for the species ArOH was calculated, in the assumption that the entropic term can be neglected,[28a] by means of eq 13 from K_e and the BDE value of the reference phenol. From these measurements, repeated under different light intensities in order to check the constancy of K_e, a BDE value of 77.6 ± 0.5 kcal/mol was obtained, a value reasonably well reproduced by calculations (1.3 kcal/mol higher).

$$\mathrm{BDE(ArO{-}H)} \cong \mathrm{BDE(Ar'O{-}H)} - RT\ln(K_e) \qquad (13)$$

Due to the short persistence of the phenoxyl radical corresponding to phenol **5a** (which would introduce a large error in the radical equilibration measurement), the $\mathrm{BDE_{OH}}$ value was instead obtained from the measured value for **5g** by considering the additive contribution of ring substituents.[28a,32] Indeed, two *ortho*-methyls are known to lower the $\mathrm{BDE_{OH}}$ of a phenol by 3.5 kcal/mol, while a methyl in the *meta*-position contributes

(31) All the BDE values determined in benzene solution by means of the EPR radical equilibration technique,[32] based on the O−H BDE of 2,4,6-tri-*tert*-butylphenol determined many years earlier by Mahoney et al.[33] using calorimetric measurements, must be downscaled by 1.1 kcal/mol due to the revision of the heat of formation of (*E*)-azobenzene.[34]

(32) (a) Brigati, G.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 4828−4832. (b) Pratt, A. D.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 11085−11092. (c) Valgimigli, L.; Brigati, G.; Pedulli, G. F.; DiLabio, G.; Mastragostino, M.; Arbizzani, C.; Pratt, D. A. *Chem.—Eur. J.* **2003**, *9*, 4997−5010.

(33) Mahoney, L. R.; Ferris, F. C.; DaRooge, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3883−3889.

(34) Mulder, P.; Korth, H.-G.; Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Phys. Chem. A* **2005**, *109*, 2647−2655.

(35) Shanks, D.; Frisell, H.; Ottosson, H.; Engman, L. *Org. Biomol. Chem.* **2006**, *4*, 846−852.

(36) Valgimigli, L.; Ingold, K. U.; Lusztyk, J. *J. Org. Chem.* **1996**, *61*, 7947−7950.

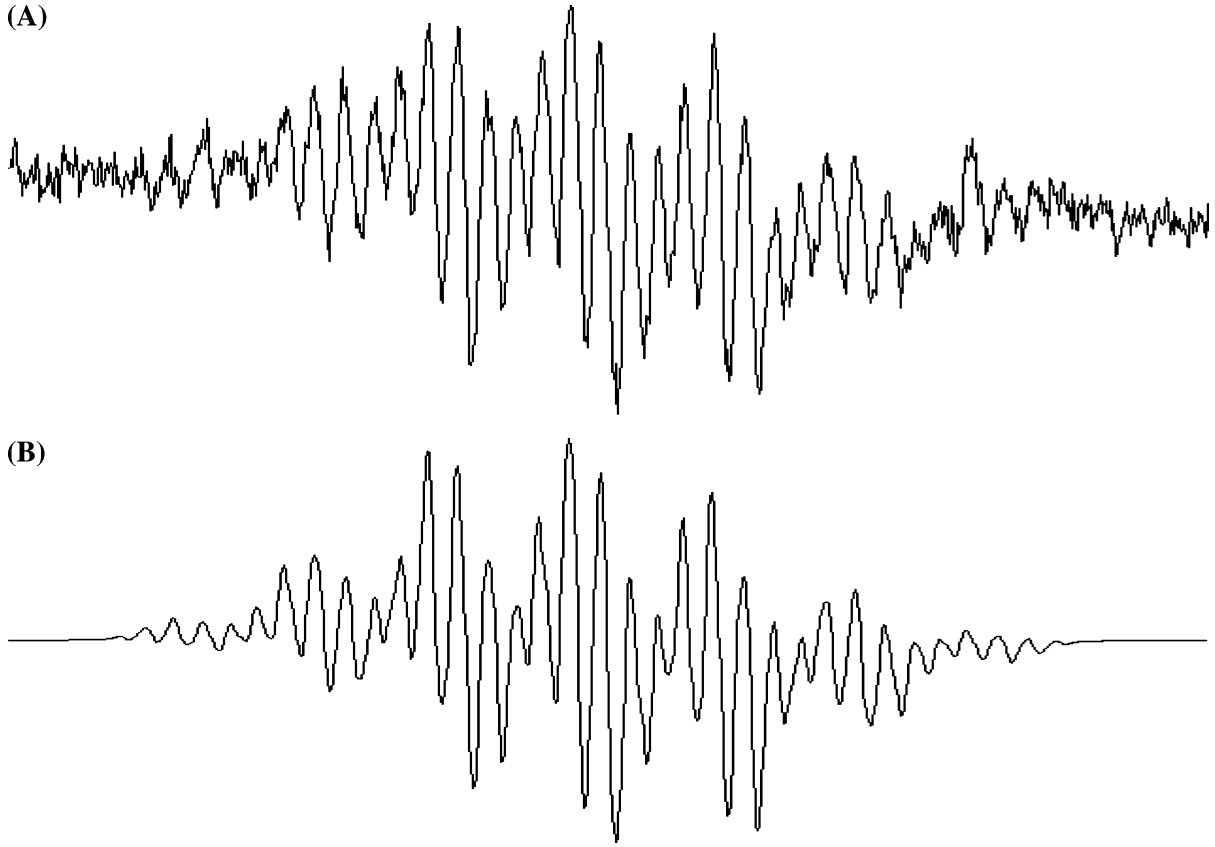
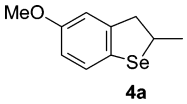


FIGURE 5. Experimental (A) and computer-simulated (B) spectra obtained by irradiating compound **5g** in benzene containing 10% v/v di-*tert*-butyl peroxide at 298 K.

−0.5 kcal/mol. Thus, the resulting estimated BDE_{OH} of compound **5a** is 81.6 kcal/mol, which is in good agreement with the calculated value of 80.8 kcal/mol (Table 1). Measured and estimated BDE_{OH} data are shown in Table 2.

Discussion

Nature is using thiols for regeneration of some of its most efficient antioxidant enzymes. Our interest in regenerable chain-breaking organoseleniums stems from the observation that organoselenium antioxidant **1c** was active for a much longer time than the corresponding oxygen (**1a**) and sulfur (**1b**) analogues in the presence of a water-soluble thiol when evaluated in the two-phase model for lipid peroxidation. However, since neither α-TOC nor selenotocopherol (**2**) are regenerable by thiol, replacement of oxygen for selenium in general is not enough, at least in the chromanol series, for imposing regenerability on the catalyst. The microwave-assisted seleno-Claisen rearrangement offered a facile route to a variety of dihydrobenzo[*b*]selenophene-5-ol derivatives **5** where the number and position of methyl groups in the aromatic moiety could be varied. Among compounds prepared and evaluated, the unsubstituted derivative **5a** was clearly the more easily regenerable, whereas the fully methylated compound **5g** acted only on a slightly more than stoichiometric basis ($n = 1.25$). Introduction of methyl groups is likely to both weaken the phenolic OH bond and lower the oxidation potential. Thus, whether the peroxyl radical quenching by these antioxidants involves hydrogen atom transfer, proton-coupled electron transfer,[37] or proton tunneling,[38] the process is expected to be facilitated by increasing methyl substitution. This is what we observe experimentally. More efficient regeneration at the lipid−aqueous interphase is the most likely explanation why the intrinsically poorest antioxidant **5a** can outperform its analogues as well as α-TOC in the two-phase system. Some speculation as to the mechanisms of antioxidant action and regeneration are presented in the following: The synthetic precursor of the efficient antioxidant **5a**, the O-methylated compound **4a**, did not show any antioxidant activity when evaluated in the two-phase model.



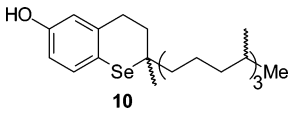
4a

This suggests that the phenolic organoselenium antioxidants are transformed into the corresponding phenoxyl radicals by one of the mechanisms mentioned above. A mechanism involving electron transfer only, followed by disproportionation of the resulting (selenium-centered) radical cation into selenium(II)/(IV) compounds, followed by thiol-mediated reduction of the tetravalent species (selenoxide), appears unlikely considering the lower calculated (by 3.8 kcal/mol) oxidation potential of compound **4a** as compared with that of **5a**.

(37) Costentin, C.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **2006**, *128*, 4552−4553.

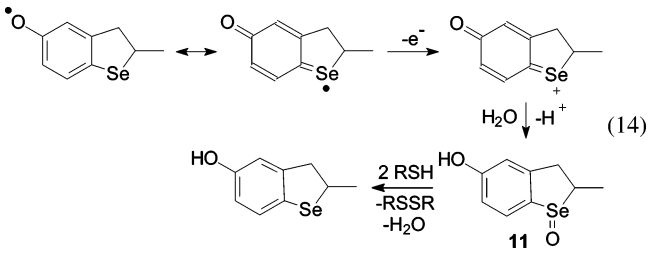
(38) Nagaoka, S.; Inoue, M.; Nishioka, C.; Nishioku, Y.; Tsunoda, S.; Ohguchi, C.; Ohara, K.; Mukai, K.; Nagashima, U. *J. Phys. Chem. B* **2000**, *104*, 856−862.

If regeneration is occurring in the aqueous phase or at the aqueous lipid interphase, one may argue that regenerability would simply depend on the relative lipophilicities of the antioxidants investigated. Admittedly, as shown in Table 1, compounds **5** become more lipid soluble as the number of aromatic methyl groups increase. However, since the two most readily regenerable antioxidants **5a** (*C* log *P* = 2.9) and **7** (*C* log *P* = 5.0) show a more than 2 orders of magnitude difference in water solubility, lipophilicity cannot explain the observed differences in regenerability. Rather, it seems that the presence/absence of methyl groups flanking the phenolic moiety has a much stronger influence on regenerability. In support of this view, we found that the selenochromanol derivative **10**, prepared by us some time ago,[39] showed a significantly better regenerability (T_{inh} = 150 min in the presence and T_{inh} = 70 min in the absence of *N*-acetylcysteine) than selenotocopherol (**2**).



10

As one traverses group 16 of the periodic table from top to bottom, the chalcogens become more readily oxidized. This trend is also seen when these elements are incorporated into organic molecules. Thus, the oxidation potential of compound **1c**, as determined by cyclic voltammetry, was 0.22 V lower than that recorded for the sulfur and oxygen analogues.[25] Sulfur and selenium can easily expand their valence shells to accommodate 10 or 12 electrons. Tetravalent sulfur and selenium derivatives such as sulfoxides and selenoxides are therefore perfectly stable compounds. In contrast to sulfoxides, selenoxides are readily reduced to the divalent state by a variety of mild reducing agents such as thiols and ascorbate. It is therefore tempting to try to involve a selenoxide in the mechanism responsible for regeneration of compound **5a**. Such a species (**11**) could form (eq 14) if the resonance-stabilized phenoxyl radical is further oxidized and the resulting selenonium ion reacts with water with loss of a proton. Regeneration is then induced by thiol and accompanied by disulfide formation. Although the mechanism proposed in eq 14 nicely explains why selenium compounds would be expected to be superior to their sulfur and oxygen counterparts when it comes to regeneration, it does not seem to explain the trends seen in Table 1.



(14)

Thus, an increasing number of electron-donating alkyl groups in the aromatic moiety is likely to facilitate one-electron oxidation of the phenoxyl radical. Also, since compound **5d** shows such poor regenerability, steric hindrance around the selenoxide (which could be a reason why this mechanism does not come into play with 7-substituted derivatives) does not seem to be an important issue.

In the absence of *N*-acetylcysteine, organoselenium antioxidants **1c**, **2**, and **5**−**10** inhibit peroxidation for shorter times than α-tocopherol in the two-phase model for lipid peroxidation. Thus, the stoichiometric factors for all these compounds are lower than the theoretical value $n = 2$ expected for chain-breaking phenolic antioxidants. The reason for this may be that a fraction of the antioxidant is converted to an inactive form, probably a selenoxide. The small amount of linoleic acid hydroperoxide which is always present in the commercially available linoleic acid is likely to convert the organoseleniums to the corresponding selenoxides before and during the experiment. Also, peroxyl radicals may transfer an oxygen atom to the organoseleniums to produce an alkoxyl radical and selenoxide. Such oxygen transfer processes have previously been observed with organotelluriums[40] as well as other organochalcogen compounds. Since the alkoxyl radical is also chain-carrying, this reaction will not affect the rate of peroxidation of the substrate. Under regeneration conditions, the two selenoxide forming reactions will be unproblematic. As indicated in eq 14, selenoxides are likely to be rapidly reduced by aqueous thiol to give the active selenide form of the antioxidant.

The simplest process for regeneration of antioxidants **5** would involve hydrogen atom transfer from thiol contained in the aqueous phase to phenoxyl radicals formed in the chlorobenzene layer. The decrease in regenerability on increasing methyl substitution, especially in the 4- and 6-positions, could then be due to steric hindrance around the phenoxyl radical. This mechanism is likely to be operative only if the bond dissociation enthalpy of the thiol is lower or at least comparable to that of the phenolic O−H bond and if the rate of H-atom transfer is significant.[20] Experimental S−H bond dissociation enthalpy data are not abundant in the literature, and the methodology used in calculating them seems to be critical for obtaining reliable results.[41] Although we have not been able to find a useful value for *N*-acetylcysteine, it seems reasonable to assume that the S−H BDE would be in the range of 85−90 kcal/mol.[41,42] The predicted value for cysteine in proteins is 87.8 ± 2.4 kcal/mol.[43] Thus, considering that the H−O BDEs of compounds **5** are in the range of 76−81 kcal/mol, NAC is not likely to act as a regenerating agent by donation of a thiol-derived hydrogen atom. However, due to captodative stabilization of the resulting carbon-centered radical, the $^{\alpha}$C−H bond of NAC is probably weaker than the S−H bond. The corresponding BDE for cysteine in proteins was estimated to 82.7 ± 2.4 kcal/mol.[43] The calculated H−O BDEs of compounds **2a**−**d** are all very similar (81.3, 80.5, 80.3, and 80.5, respectively[25]). Yet, the organoselenium compound **2c** was found to be considerably more regenerable than its analogues in the two-phase model. This also suggests that regeneration occurs by some other mechanism than hydrogen atom transfer to a phenoxyl radical.

In the light of these thermodynamic considerations, the failure of 1-octylmercaptan to regenerate compounds **5a** and **5g** from their corresponding phenoxyl radicals under homogeneous phase conditions is not surprising. The S−H BDE of 1-octylmercaptan

(39) Al-Maharik, N.; Engman, L.; Malmström, J.; Schiesser, C. H. *J. Org. Chem.* **2001**, *66*, 6286−6290.

(40) Engman, L.; Persson, J.; Merényi, G.; Lind, J. *Organometallics* **1995**, *14*, 3641−3648.

(41) Cabral do Couto, P.; Costa Cabral, B. J.; Martinho Simoes, J. A. *Chem. Phys. Lett.* **2006**, *421*, 504−507.

(42) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *Eur. J. Org. Chem.* **2006**, 3242−3250.

(43) Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 8848−8855.

can be considered similar to that of ethanethiol for which the values of 88.1 and 88.7 can be found in the literature.[44,45] These values are ~7 and ~ 11 kcal/mol, respectively, higher than the H−O BDE of compounds **5a** and **5g**, making regeneration by hydrogen atom transfer practically impossible. However, in water or very polar solvents such as acetonitrile or in two-phase systems, regeneration by thiols may still be possible if it occurs by electron transfer rather than hydrogen atom transfer. To get a rough idea about the feasibility of such a process (eq 15), one could compare the standard reduction potential of the thiol in water with those for the redox couple $ArO^{\bullet}/ArO^{-}$.

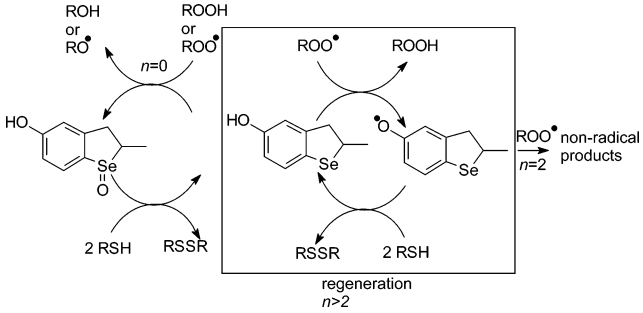
$$2\ RSH + 2\ ArO^{\bullet} \rightarrow RSSR + 2\ ArOH \qquad (15)$$

The reduction potential for NAC has recently been reported to be slightly more positive ($\Delta E^{\circ} = +63$ mV) than that for glutathione,[46] whose standard potential in water at 25 °C and pH 7 is known as $E^{\circ} = -240$ mV versus NHE.[47,48] This corresponds to $E^{\circ} = -145$ mV versus NHE at pH 3.8[48] (which is the pH in the aqueous phase under our experimental conditions). This redox potential for the thiol/disulfide couple should be matched with the potential for the couple $ArO^{\bullet}/ArO^{-}$, which for most phenoxyl radicals fall in the range $0.1 < E^{\circ} < 1.4$ V versus NHE, depending on the substituents in the aromatic ring.[49]Although standard reduction potentials for aryloxyl radicals corresponding to phenols **5**−**9** are not available, a value for the closely related compound **1c** is known as $E^{\circ} = +0.49$ V (vs NHE at pH 12[25]) and, considering the reported $pK_a = 9.9$,[25] it is expected to increase by about 0.36 V at pH 3.8.[50] E° is also expected to vary linearly with Hammett $\sigma+$ parameter[51] of ring substituents.[25,49] A quantitative estimation of the EMF (ΔE) for the cell arising from eq 15, according to Nernst's equation at 25 °C (eq 16), would clearly require several parameters which are presently not known (e.g., the actual concentration of transient species at the aqueous lipid interface to be inserted in the reaction quotient Q). However, on a qualitative basis, regeneration of all compounds **5** from their corresponding phenoxyl radicals in the aqueous phase by electron transfer from NAC is expected to be thermodynamically favored.

$$\Delta E = \Delta E^{\circ} - (59.1\ \text{mV}/2) \log Q \qquad (16)$$

The success of the regeneration process would also depend on the rate of electron transfer as compared with those of other reactions that the phenoxyl radical could undergo (such as trapping of a second peroxyl radical). Overall, the successful regeneration of phenolic antioxidants such as compound **5a** is due to the favorable interplay and balance between several redox and other processes as summarized in Scheme 3. Considering that the purported electron transfer is occurring at the lipid aqueous interphase, it may be essential that phenoxyl radicals are sterically unhindered for the process to be efficient.

SCHEME 3. Reactions Involved in the Antioxidant Activity of Compounds 5 in the Two-Phase System, Including (Box) the Regeneration of Phenoxyl Radical at the Organic−Aqueous Interface[a]



[a] Stoichiometric factors n (the number of peroxyl radicals that each antioxidant molecule can destroy) are indicated when appropriate.

Experimental Section

Typical Procedure for the Preparation of Allyl Aryl Selenides. Allyl 4-Methoxyphenyl Selenide (3a). To a dry 100 mL three-necked flask containing Mg turnings (720 mg, 30 mmol) and anhydrous tetrahydrofuran (50 mL) was added 4-bromoanisole (3.9 mL, 30 mmol) dropwise with stirring. The reaction mixture was heated at reflux, and stirring continued until all magnesium had disappeared. Selenium powder (2.40 g, 30 mmol) was then added in portions over a period of 30 min. After another 2 h, the resulting solution of magnesium areneselenolate was poured into a beaker and kept in the open air overnight. Diaryl diselenide formed was extracted with Et_2O (4 × 25 mL). The ether solution was washed with water, and the organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure to give a brown solid. To this crude product in EtOH (30 mL) was added $NaBH_4$ (0.945 g, 25 mmol) at 0 °C under N_2. The reaction mixture was warmed to room temperature and stirred for 30 min. During this process, the yellow color of the reaction mixture had faded away. Allyl bromide (2.11 mL, 25 mmol) was added to the cooled (0 °C) reaction mixture, and stirring continued for an additional 30 min at room temperature. After aqueous workup, ether extraction (3 × 20 mL), drying over Na_2SO_4, and evaporation, column chromatography using pentane/CH_2Cl_2 (85:15) as an eluent afforded the pure title compound (4.85 g, 71%): ^{1}H NMR δ 7.48 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.92 (m, 1H), 4.90 (t, J = 15.1 Hz, 2H), 3.80 (s, 3H), 3.44 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 136.4, 134.8, 132.3, 116.6, 115.8, 114.7, 55.3, 31.8.

The following compounds were analogously prepared starting from the appropriately substituted 4-bromoanisole.

Allyl 4-Methoxy-3-methylphenyl Selenide (3b): Yield 32%; ^{1}H NMR δ 7.31−7.36 (several peaks, 2H), 6.73 (d, J = 8.0 Hz, 1H), 5.93 (m, 1H), 4.92−4.88 (several peaks, 2H), 3.82 (s, 3H), 3.43 (dm, J = 8.0 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR δ 157.8, 137.2, 134.9, 133.6, 127.6, 119.3, 116.5, 110.6, 55.4, 31.8, 16.2.

Allyl 4-Methoxy-2-methylphenyl Selenide (3c): Yield 96%; ^{1}H NMR δ 7.46 (dm, J = 8.5 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 6.66 (dm, J = 8.5 Hz, 1H), 5.93 (m, 1H), 4.94−4.89 (several peaks, 2H), 3.79 (s, 3H), 3.41 (d, J = 7.6 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR δ 159.7, 142.8, 136.8, 134.7, 121.1, 116.6, 115.8, 112.0, 55.3, 30.8, 23.4.

Allyl 3,5-Dimethyl-4-methoxyphenyl Selenide (3d): Yield 76%; ^{1}H NMR δ 7.20 (s, 2H), 5.97 (m, 1H), 4.98 (m, 2H), 3.73 (s, 3H),

(44) Orlov, Y. D.; Lebedev, Y. A. *Bull. Acad Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1984**, *33*, 1227−1230.
(45) Janousek, B. K.; Reed, K. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 3125−3129.
(46) Noszál, B.; Visky, D.; Kraszni, M. *J. Med. Chem.* **2000**, *43*, 2176−2182.
(47) Scott, E. M.; Duncan, I. W.; Ekstrand, V. *J. Biol. Chem.* **1963**, *238*, 3928−3933.
(48) (a) Schafer, F. Q.; Buettner, G. R. *Free Radical Biol. Med.* **2001**, *30*, 1191−1212. (b) Shen, D.; Dalton, T. P.; Nebert, D. W.; Shertzer, H. G. *J. Biol. Chem.* **2005**, *280*, 25305−25312.
(49) (a) Jonsson, M.; Lind, J.; Merényi, G. *J. Phys. Chem. A* **2002**, *106*, 4758−4762. (b) Lind, J.; Shen, X.; Eriksen, I. E.; Merényi, G. *J. Am. Chem. Soc.* **1990**, *112*, 479−482. (c) Armstrong, D. A.; Sun, Q.; Schuler, R. H. *J. Phys. Chem.* **1996**, *100*, 9892−9899.
(50) Li, C.; Hoffman, M. Z. *J. Phys. Chem. B* **1999**, *103*, 6653−6656.
(51) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.

3.50 (d, J = 7.4 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR δ 156.7, 134.7, 134.3, 131.7, 123.9, 116.7, 59.8, 31.1, 16.0.

Allyl 2,3-Dimethyl-4-methoxyphenyl Selenide (3e): Yield 62%; ^{1}H NMR δ 7.45 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 5.97 (m, 1H), 5.00−4.93 (several peaks, 2H), 3.84 (s, 3H), 3.42 (d, J = 7.4 Hz, 2H), 2.51 (s, 3H), 2.24 (s, 3H); ^{13}C NMR δ 157.5, 140.7, 134.7, 133.7, 125.8, 121.8, 116.4, 108.4, 55.5, 31.0, 20.1, 12.7.

Allyl 2,5-Dimethyl-4-methoxyphenyl Selenide (3f): Yield 65%; ^{1}H NMR δ 7.34 (s, 1H), 6.72 (s, 1H), 5.95 (m, 1H), 4.99 (several peaks, 2H), 3.83 (s, 3H), 3.43 (d, J = 7.6, 2H), 2.49 (s, 3H), 2.20 (s, 3H). ^{13}C NMR δ 157.7, 139.9, 137.6, 134.8, 124.6, 120.2, 116.4, 111.7, 55.3, 30.8, 23.1, 15.6.

Allyl 4-Methoxy-2,3,5-trimethylphenyl Selenide (3g): Yield 70%; ^{1}H NMR δ 7.39 (s, 1H), 5.98 (m, 1H), 4.95−5.07 (several peaks, 2H), 3.71 (s, 3H), 3.47 (d, J = 7.6 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H); ^{13}C NMR δ 156.6, 138.0, 134.6, 134.0, 130.3, 128.5, 125.8, 116.8, 60.0, 30.6, 19.8, 16.0, 13.4.

Allyl 3-Fluoro-4-hydroxyphenyl Selenide. To a solution of 3-fluoro-4-hydroxybromobenzene (0.91 mL, 8.33 mmol) in THF (20 mL) was added *t*-BuLi (15.9 mL of a 1.7 M solution in pentane, 27 mmol) dropwise at −78 °C under N_2. The resulting yellowish reaction mixture was stirred for 15 min when selenium powder (2.16 g, 27 mmol) was added in two portions under a brisk flow of N_2. After another 30 min at −78 °C, the reaction was brought to room temperature and stirred for 2 h. All selenium had reacted to give a brownish-red reaction mixture which was poured over ice (25 g) and kept for 1 h before addition of aqueous HCl (4 M). After ether extraction (4 × 30 mL), drying over Na_2SO_4, and concentration in vacuo, a yellowish liquid (2.25 g) was obtained. Crystallization from pentane/ether gave almost pure, light yellow crystals (1.457 g) of bis(2-fluoro-4-hydroxyphenyl)diselenide. This diselenide (1.14 g) was dissolved in EtOH (30 mL), and $NaBH_4$ (230 mg, 6 mmol) was added under N_2 at 0 °C. After additional stirring for 40 min at this temperature and for 30 min at room temperature, allyl bromide (0.58 mL, 6.7 mmol) was added dropwise. After stirring at 0 °C for 5 min and at room temperature for 1 h, workup including ether extraction (3 × 15 mL), drying over Na_2SO_4, and concentration in vacuo gave a colorless liquid which was purified by column chromatography using pentane/ethyl acetate (95:5) as an eluent. The yield of the title compound was 787 mg (57%): ^{1}H NMR δ 7.26 (ddd, J = 0.9, 2.0, 10.2 Hz, 1H), 7.20 (dm, J = 8.3 Hz, 1H), 6.91 (td, J = 8.3 Hz, 0.9, 1H), 5.90 (m, 1H), 5.41 (br s, 1H), 4.91 (m, 2H), 3.46 (dm, J = 7.6 Hz, 2H); ^{13}C NMR δ 150.6 (d, J_{C-F} = 240.5 Hz), 143.5 (d, J_{C-F} = 14.3 Hz), 134.4, 131.7 (d, J_{C-F} = 3.5 Hz), 121.9 (d, J_{C-F} = 18.2 Hz), 119.9 (d, J_{C-F} = 5.6 Hz), 117.8 (d, J_{C-F} = 2.0 Hz) 117.1, 31.9.

3-Methyl-2-propen-1-yl 4-Methoxy-2,3,5-trimethylphenyl Selenide (*E*/*Z* ca. 3/1) was prepared according to the typical procedure using (*E*/*Z*)-3-methyl-2-propen-1-yl bromide instead of allyl bromide: Yield 97%; ^{1}H NMR δ 7.34, 7.30 (s, 1H), 5.73−5.45 (m, 2 H), 3.77 (s, 3H), 3.58, 3.51 (d, J = 7.6 Hz, 2H), 2.50, 2.47 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.72, 1.62 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 156.5, 156.4, 137.9, 137.8, 134.1, 134.0, 130.0, 128.3, 128.3, 128.0, 127.0, 126.7, 126.2, 126.1, 126.0, 59.8, 30.0, 24.1, 19.7, 19.6, 17.7, 15.8, 15.8, 13.2, 12.3.

2-Methyl-2-propen-1-yl 4-Methoxy-2,3,5-trimethylphenyl Selenide was prepared according to the typical procedure using 2-methyl-2-propen-1-yl bromide instead of allyl bromide: Yield 60%; ^{1}H NMR δ 7.24 (s, 1H), 4.71 (several peaks, 2H), 3.68 (s, 3H), 3.43 (m, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 2.23 (s, 3H), 1.88 (m, 3H); ^{13}C NMR δ 156.6, 142.1, 138.2, 134.1, 130.2, 128.6, 126.4, 113.4, 60.1, 35.9, 21.7, 19.8, 16.0, 13.4.

Typical Procedure for Microwave-Assisted Seleno-Claisen Rearrangement/Intramolecular Hydroselenation. 5-Methoxy-2-methyl-2,3-dihydrobenzo[*b*]selenophene (4a). Freshly prepared allylic selenide **3a** (4.62 g, 20.3 mmol) in quinoline (10 mL) was charged into a glass tube (20 mL), and the sealed vial was heated in a microwave reactor for 1 h at 220 °C. The reaction mixture was then treated with HCl (300 mL of 4 M aqueous solution) and the organic phase extracted into diethyl ether (3 × 30 mL). After drying (Na_2SO_4), evaporation, and purification by column chromatography using pentane/CH_2Cl_2 (80:25) as an eluent, the pure title compound was isolated as a light yellow oil (2.74 g, 59%): ^{1}H NMR δ 7.20 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 2.6 Hz, 1H), 6.71 (dd, J = 2.6, 8.4 Hz, 1H), 4.17 (m, 1H), 3.78 (s, 3H), 3.41 (dd, J = 6.8, 15.2 Hz, 1H), 3.03 (dd, J = 6.6, 15.2 Hz, 1H), 1.61 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 158.0, 143.9, 137.3, 126.3, 113.0, 111.7, 55.3, 47.4, 41.5, 22.6.

The following compounds were analogously prepared starting from the appropriately substituted allyl phenyl selenides.

2,6-Dimethyl-5-methoxy-2,3-dihydrobenzo[*b*]selenophene (4b): Yield 35%; ^{1}H NMR δ 7.05 (s, 1H), 6.70 (s, 1H), 4.15 (m, 1H), 3.76 (s, 3H), 3.40 (dd, J = 6.6, 15.2 Hz, 1H), 3.00 (dd, J = 6.8, 15.2 Hz, 1H), 2.16 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 156.2, 140.9, 127.8, 126.5, 126.3, 108.2, 55.7, 47.7, 41.7, 22.8, 16.2.

2,7-Dimethyl-5-methoxy-2,3-dihydrobenzo[*b*]selenophene (4c): Yield 13%; ^{1}H NMR δ 6.22 (d, J = 2.5 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 4.11 (m, 1H), 3.78 (s, 3H), 3.43 (dd, J = 6.8, 15.4 Hz, 1H), 3.03 (dd, J = 6.8, 15.4 Hz, 1H), 2.22 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 158.5, 143.4, 135.5, 128.6, 113.6, 109.1, 55.6, 47.9, 40.7, 23.2, 22.9.

5-Methoxy-2,4,6-trimethyl-2,3-dihydrobenzo[*b*]selenophene (4d): Yield 46%; ^{1}H NMR δ 6.98 (s, 1H), 4.18 (m, 1H), 3.70 (s, 3H), 3.38 (dd, J = 7.0, 15.3 Hz, 1H), 3.00 (dd, J = 6.6, 15.3 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 154.8, 140.4, 131.0, 130.0, 127.9, 125.1, 60.0, 45.8, 40.6, 23.1, 16.2, 13.8.

5-Methoxy-2,6,7-trimethyl-2,3-dihydrobenzo[*b*]selenophene (4e): Yield 39%; ^{1}H NMR δ 6.63 (s, 1H), 4.09 (m, 1H), 3.78 (s, 3H), 3.45 (dd, J = 6.9, 15.2 Hz, 1H), 3.05 (dd, J = 6.5, 15.2 Hz, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 156.3, 139.2, 134.0, 129.1, 124.0, 106.2, 56.0, 48.2, 40.3, 22.9, 21.2, 12.1.

5-Methoxy-2,4,7-trimethyl-2,3-dihydrobenzo[*b*]selenophene (4f): Yield 26%; ^{1}H NMR δ 6.54 (s, 1H), 4.12 (m, 1H), 3.78 (s, 3H), 3.46 (dd, J = 7.4, 15.8 Hz, 1H), 3.01 (dd, J = 6.9, 15.8 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.60 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 156.5, 142.2, 131.9, 128.2, 121.1, 110.7, 56.0, 46.1, 39.6, 23.3, 23.2, 13.3.

5-Methoxy-2,4,6,7-tetramethyl-2,3-dihydrobenzo[*b*]selenophene (4g): Yield 26%; ^{1}H NMR δ 7.39 (s, 1H), 4.08 (m, 1H), 3.64 (s, 3H), 3.43 (dd, J = 7.1, 15.5 Hz, 1H), 3.00 (dd, J = 7.0, 15.5 Hz, 1H), 2.19 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H), 1.59 (d, J = 6.8 Hz, 1H); ^{13}C NMR δ 155.2, 139.01, 133.2, 131.2, 128.2, 125.2, 60.3, 46.2, 39.2, 23.3, 21.1, 13.9, 12.8.

2-Ethyl-5-methoxy-4,6,7-trimethyl-2,3-dihydrobenzo[*b*]selenophene: Yield 19%; ^{1}H NMR δ 3.95 (m, 1H), 3.65 (s, 3H), 3.43 (dd, J = 7.7, 15.4 Hz, 1H), 3.05 (dd, J = 7.7, 15.4 Hz, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.87 (m, 2H), 1.04 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 155.3, 139.6, 139.4, 128.2, 125.2, 114.6, 60.5, 48.1, 44.0, 30.6, 21.2, 14.2, 14.0, 12.9.

5-Methoxy-2,2,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]selenophene: Yield 21%; ^{1}H NMR δ 3.64 (s, 3H), 3.12 (s, 2H), 2.18 (s, 6H), 2.13 (s, 3H), 1.68 (s, 6H); ^{13}C NMR δ 155.2, 139.1, 134.1, 131.3, 128.1, 125.4, 60.3, 53.3, 52.5, 31.7, 21.0, 13.9, 12.8.

Typical Procedure for O-Demethylation. 2-Methyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5a). To a cooled (−78 °C), stirred solution of dihydrobenzo[*b*]selenophene **4a** (1.14 g, 5 mmol) in CH_2Cl_2 (10 mL) kept under N_2 was added BBr_3 (6 mL of a 1 M solution in CH_2Cl_2; 6 mmol) dropwise. The mixture was then allowed to warm to room temperature and stirred for another 20 h when it was poured into water and extracted with additional CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by column chromatography using pentane/ethyl acetate (85:15) as an eluent afforded the title compound in

the form of colorless crystals (1.00 g, 94%): mp 89−90 °C; ^{1}H NMR δ 7.11 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.6 Hz, 1H), 6.60 (dd, J = 2.6, 8.2 Hz, 1H), 4.89 (s, 1H), 4.15 (m, 1H), 3.37 (dd, J = 7.0, 15.4 Hz, 1H), 2.98 (dd, J = 6.8, 15.4 Hz, 1H), 1.58 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 153.8, 144.4, 127.2, 126.6, 114,7, 113.1, 47.4, 41.8, 22.7; ^{77}Se NMR δ 415. Anal. Calcd for $C_9H_{10}OSe$: C, 50.74; H, 4.73. Found: C, 50.52; H, 4.69.

The following compounds were analogously prepared starting from the appropriately substituted 5-methoxy-2,3-dihydrobenzo[*b*]-selenophenes.

2,6-Dimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5b): Yield 65%; mp 106−107 °C; ^{1}H NMR δ 7.02 (s, 1H), 6.64 (s, 1H), 4.42 (br s, 1H), 4.14 (m, 1H), 3.36 (dd, J = 6.7, 15.3 Hz, 1H), 2.96 (dd, J = 6.7, 15.3 Hz, 1H), 2.19 (s, 3H), 1.57 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 151.9, 141.6, 127.9, 127.1, 123.2, 112.6, 47.2, 41.8, 22.8, 15.8; ^{77}Se NMR δ 416. Anal. Calcd for $C_{10}H_{11}OSe$: C, 52.89; H, 5.32. Found: C, 52.59; H, 5.20.

2,7-Dimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5c): Yield 47%; mp 81−82 °C; ^{1}H NMR δ 6.54 (s, 1H), 6.49 (s, 1H), 4.49 (s, 1H), 4.11 (m, 1H), 3.4 (dd, J = 6.9, 15.4 Hz, 1H), 3.01 (dd, J = 6.9, 15.4 Hz, 1H), 2.19 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 154.1, 143.7, 135.8, 128.6, 115.0, 110.3, 47.7, 40.7, 23.0, 22.9; ^{77}Se NMR δ 390. Anal. Calcd for $C_{10}H_{11}OSe$: C, 52.87; H, 5.32. Found: C, 52.90; H, 5.21.

2,4,6-Trimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5d): Yield 98%; mp 121−122 °C; ^{1}H NMR δ 6.91 (s, 1H), 4.53 (s, 1H), 4.15 (m, 1H), 3.39 (dd, J = 7.2, 15.6 Hz, 1H), 2.98 (dd, J = 7.0, 15.6 Hz, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 150.0, 140.2, 126.4, 124.8, 122.5, 121.1, 45.9, 40.5, 23.1, 16.1, 13.5; ^{77}Se NMR δ 416. Anal. Calcd for $C_{11}H_{14}$-OSe: C, 54.78; H, 5.85. Found: C, 54.92; H, 5.88.

2,6,7-Trimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5e): Yield 92%; mp 133−134 °C; ^{1}H NMR δ 6.52 (s, 1H), 4.66 (s, 1H), 4.07 (m, 1H), 3.38 (dd, J = 7.1, 15.1 Hz, 1H), 2.98 (dd, J = 6.7, 15.1 Hz, 1H), 2.19 (s, 3H), 2.14 (s, 3H), 1.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 152.0, 139.7, 134.2, 129.2, 121.4, 110.3, 47.7, 40.4, 22.8, 21.2, 12.0; ^{77}Se NMR δ 398. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.58; H, 5.72.

2,4,7-Trimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5f): Yield 81%; mp 122−124 °C; ^{1}H NMR δ 6.46 (s, 1H), 4.58 (s, 1H), 4.12 (m, 1H), 3.40 (dd, J = 7.0, 15.6 Hz, 1H), 3.00 (dd, J = 6.9, 15.6 Hz, 1H), 2.16 (s, 6H), 1.60 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 152.2, 142.4, 132.4, 128.4, 118.7, 115.0, 46.2, 39.7, 23.3, 22.7, 13.2; ^{77}-Se NMR δ 392. Anal. Calcd for $C_{11}H_{14}OSe$: C, 54.78; H, 5.85. Found: C, 54.65; H, 5.92.

2,4,6,7-Tetramethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (5g): Yield 78%; mp 124−125 °C; ^{1}H NMR δ 4.44 (s, 1H), 4.06 (m, 1H), 3.44 (dd, J = 6.9, 15.3 Hz, 1H), 3.02 (dd, J = 6.9, 15.3 Hz, 1H), 2.18 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 150.4, 138.5, 130.9, 128.8, 121.0, 118.3, 46.5, 39.0, 23.3, 21.3, 13.7, 12.4; ^{77}Se NMR δ 398. Anal. Calcd for $C_{11}H_{14}OSe$: C, 56.49; H, 6.27. Found: C, 56.27; H, 6.14.

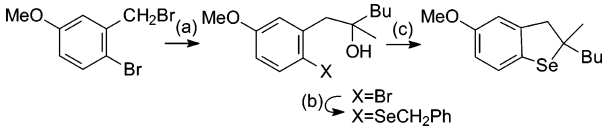
4-Fluoro-2-methyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (6) was prepared from allyl 3-fluoro-4-hydroxyphenyl selenide (247 mg, 1.07 mmol) according to the typical procedure for preparation of compounds **4**: Yield 18%; ^{1}H NMR δ 6.90 (dm, J = 8.2 Hz, 1H), 6.79 (tm, J = 8.2 Hz, 1H), 4.88 (br s, 1H), 4.23 (m, 1H), 3.46 (dd, J = 6.9, 15.7 Hz, 1H), 3.08 (dd, J = 6.7, 15.7 Hz, 1H), 1.61 (d, J = 6.9 Hz, 3H); MS *m*/*z* 232 (M+, 100), 150 (50). Anal. Calcd for C_9H_9OFSe: C, 46.77; H, 3.92. Found: C, 46.55; H, 4.02.

2-Butyl-2-methyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (7): Yield 91%; ^{1}H NMR δ 7.09 (d, J = 8.2 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.59 (dd, J = 2.6, 8.2 Hz, 1H), 4.71 (s, 1H), 3.17 (d, J = 15.3 Hz, 1H), 3.01 (d, J = 15.3 Hz, 1H), 1.92−1.79 (several peaks, 2H), 1.62 (s, 3H), 1.29−1.50 (several peaks, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 153.6, 144.5, 127.8, 126.8, 114.6, 113.4, 61.2, 53.3, 43.2, 30.1, 28.5, 23.2, 14.2; ^{77}Se NMR δ 483. Anal. Calcd for $C_{13}H_{18}OSe$: C, 57.99; H, 6.74. Found: C, 58.11; H, 6.77.

2-Ethyl-4,6,7-trimethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (8): Yield 98%; mp 121−123 °C; ^{1}H NMR δ 4.44 (s, 1H), 3.92 (m, 1H), 3.44 (dd, J = 7.8, 15.6 Hz, 1H), 3.07 (dd, J = 7.8, 15.6 Hz, 1H), 2.18 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.86 (m, 2H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 150.3, 138.8, 130.7, 128.2, 120.9, 118.1, 47.8, 44.1, 30.5, 21.2, 14.2, 13.6, 12.4; ^{77}Se NMR δ 363. Anal. Calcd for $C_{12}H_{16}OSe$: C, 58.01; H, 6.741. Found: C, 57.84; H, 6.67.

2,2,4,6,7-Pentamethyl-2,3-dihydrobenzo[*b*]selenophene-5-ol (9): Yield 69%; mp 130−132 °C; ^{1}H NMR δ 4.42 (s, 1H), 3.14 (s, 2H), 2.16 (s, 3H), 2.15 (s, 6H), 1.68 (s, 6H); ^{13}C NMR δ 150.3, 138.7, 131.0, 129.9, 120.8, 118.5, 53.5, 52.3, 31.6, 21.2, 13.7, 12.4; ^{77}Se NMR δ 489. MS *m*/*z* 271 (M + 1, 100), 256 (39), 175 (21).

The precursor of compound **7**, 2-butyl-5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]selenophene, was prepared from 2-bromo-5-methoxybenzyl bromide as shown below. The key steps in the synthesis involve lithium tellurium exchange for benzyllithium generation and homolytic intramolecular substitution at selenium for heterocycle formation.



Reagents and conditions: (a) (i) *n*-BuTeLi, (ii) *n*-BuLi, −78 °C, (iii) 2-hexanone, −115 °C; (b) (i) *t*-BuLi, −100 °C, (ii) Se, −78 °C, (iii) air oxidation, (iv) $NaBH_4$, (v) BnBr; (c) (i) oxalyl chloride, (ii) 2-mercaptopyridine-*N*-oxide Na salt/DMAP reflux.

1-(2-Bromo-5-methoxyphenyl)-2-methyl-2-hexanol. To a solution of *n*-BuLi (3.12 mL of 1.6 M solution in hexane, 5 mmol) in THF (5 mL) was added tellurium powder (625 mg, 5 mmol) in portions, and the mixture was stirred for 15 min at room temperature under N_2. To the resulting solution of lithium butanetellurolate was added 2-bromo-5-methoxybenzylbromide (1.43 g, 5 mmol) in THF (2 mL) dropwise and stirring continued for 10 min. The red solution obtained was evaporated in vacuo, and dry Et_2O (15 mL) was added under N_2. To this solution, cooled to −98 °C, was added *n*-BuLi (3.25 mL 1.6 M, 5.2 mmol) dropwise. The resulting light yellow solution was stirred for 20 min at −78 °C and then cooled to −115 °C. 2-Hexanone (1.23 mL, 10 mmol) was added to the reaction mixture, and stirring continued for an additional 30 min at this temperature and 30 min at room temperature. After aqueous workup, extraction with CH_2Cl_2 (4 × 20 mL), drying (Na_2SO_4), evaporation, and purification by column chromatography using pentane/ethylacetate (9:1) as an eluent, the title compound was isolated as a pale yellow liquid (1.27 g, 85%): ^{1}H NMR δ 7.44 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 6.67 (dd, J = 3.2, 8.8 Hz, 1H), 3.78 (s, 3H), 2.97 (d, J = 13.6 Hz, 1H), 2.92 (d, J = 13.6 Hz, 1H), 1.56−1.33 (several peaks, 7H), 1.17 (s, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 158.6, 138.7, 133.5, 117.9, 116.8, 114.0, 73.7, 55.6, 46.8, 42.6, 26.4, 26.2, 23.4, 14.3.

Benzyl 2-(2-Hydroxy-2-methylhexyl)-4-methoxyphenyl Selenide. To a solution of 1-(2-bromo-5-methoxyphenyl)-2-methyl-2-hexanol (602 mg, 2 mmol) in THF (10 mL) was added *t*-BuLi (3.75 mL of 1.6 M solution in pentane, 6 mmol) dropwise at −100 °C under N_2. Stirring was continued for an additional 1 h at this temperature and then 20 min at room temperature. After cooling to −78 °C, selenium powder (480 mg, 6 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After 5 h, the resulting dark red reaction mixture was poured onto crushed ice and kept in the open air for 2 h. After aqueous workup, extraction with CH_2Cl_2 (4 × 20 mL), drying (Na_2SO_4), and evaporation, the crude mixture was purified by column chromatography using pentane/ethyl acetate (9:2) as an eluent to give 402 mg of a diselenide/triselenide mixture. Without further characterization, 450 mg of this product was dissolved in EtOH (20 mL), and $NaBH_4$ (378 mg, 10 mmol) was added at 0 °C under nitrogen. After

30 min, benzyl bromide (1.72 g, 10 mmol) was added to the resulting colorless reaction mixture and stirring continued for 1 h. After aqueous workup, extraction with diethyl ether (3 × 15 mL), drying (Na_2SO_4), and evaporation, the crude mixture was purified by column chromatography using pentane/ethyl acetate (9:1) as an eluent to give the title compound as a colorless oil (374 mg, 43% over two steps): ^{1}H NMR δ 7.49 (d, J = 8.5 Hz, 1H), 7.25−7.13 (several peaks, 5H), 6.88 (d, J = 2.9 Hz, 1H), 6.70 (dd, J = 2.9, 8.5 Hz, 1H), 3.97 (s, 2H), 3.82 (s, 3H), 2.89 (s, 2H), 1.55−1.34 (several peaks, 7H), 1.11 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 159.4, 142.7, 138.8, 137.6, 128.9, 128.4, 126.8, 123.5, 116.9, 113.0, 73.4, 55.4, 47.1, 42.7, 33.7, 26.4, 26.3, 23.4, 14.3.

2-Butyl-5-methoxy-2-methyl-2,3-dihydrobenzo[*b*]selenophene. Benzyl 2-(2-hydroxy-2-methylhexyl)-4-methoxyphenyl selenide (98 mg, 0.25 mmol) was stirred with oxalyl chloride (0.3 mL) in benzene (2 mL) for 18 h at ambient temperature under an atmosphere of dry N_2. After evaporation to dryness under reduced pressure, the residue was taken into benzene (3 mL) and added over 15 min to a well stirred suspension of the sodium salt of 2-mercaptopyridine *N*-oxide (53 mg, 0.35 mmol) and 4-*N*,*N*-dimethylaminopyridine (3.6 mg, 0.03 mmol) in benzene (3 mL) at reflux under N_2. After 2.5 h, the reaction mixture was filtered through a plug of Celite, evaporated, and the residue purified by flash chromatography using pentane/CH_2Cl_2 (9:1) as an eluent to give almost pure title compound (24 mg, 34%): ^{1}H NMR δ 7.15 (d, J = 8.3 Hz, 1H), 6.74 (d, J = 2.6 Hz, 1H), 6.67 (dd, J = 2.6, 8.3 Hz, 1H), 3.77 (s, 3H), 3.19 (d, J = 15.2 Hz, 1H), 3.03 (d, J = 15.2 Hz, 1H), 1.98−1.74 (several peaks, 2H), 1.62 (s, 3H), 1.32−1.54 (several peaks, 4H), 0.92 (m, 3H); ^{13}C NMR δ 158.0, 144.2, 127.7, 126.7, 112.9, 112.2, 61.1, 55.6, 53.4, 43.3, 30.0, 28.5, 23.2, 14.2.

HPLC Peroxidation Assay. The experimental setup has been recently described.[26] Inhibition times, T_{inh},[26] and inhibited rates of peroxidation, R_{inh},[25] were determined as previously described.

Kinetic Measurements. The rate constants for the reaction of the antioxidants with peroxyl radicals presented in Table 2 have been measured by following the autoxidation of styrene (4.3 M) in chlorobenzene, at 303 K using as initiator AIBN (5×10^{-2} M). The antioxidant concentration was varied in the range of 2.5×10^{-6} to 5.0×10^{-5} M. In order to evaluate the regenerability of **5a** and **5g** in homogeneous solution, 1-octanethiol (1×10^{-5} to 1×10^{-3} M) was added to the autoxidation, while the concentration of the antioxidant (**5a** or **5g**) was kept constant for all measurements (6.25×10^{-6} M) in order to compare more easily their behavior. Initiation rates, R_i, were determined for each condition in preliminary experiments by the inhibitor method using α-tocopherol as reference antioxidant: $R_i = 2[\alpha\text{-TOH}]/T_{inh}$.[52]

Calculations. Homolytic O−H bond dissociation enthalpies and adiabatic ionization potentials of phenolic antioxidants **5** and **6** were calculated as previously described.[35] The *C* log *P* values for compounds **5**−**9** were calculated by using software from BioByte Corporation together with SYbYL, version 7.2.4.

EPR and Thermochemical Measurements. Deoxygenated benzene solutions containing the phenol (0.01−0.001 M) and di-*tert*-butyl peroxide (10% v/v) were sealed under nitrogen in a suprasil quartz EPR tube. The sample was inserted at room temperature in the cavity of an EPR spectrometer and photolyzed with the unfiltered light from a 500 W high-pressure mercury lamp. The temperature was controlled with a standard variable temperature accessory and was monitored before and after each run with a copper-constantan thermocouple. The EPR spectra were recorded on a Bruker ESP 300 spectrometer equipped with a Hewlett-Packard 5350B microwave frequency counter for the determination of the *g* factors, which were corrected with respect to that of DPPH radical ($g = 2.0036_4$). When using mixtures of BHA and compound **5g**, the molar ratio of the two equilibrating radicals was obtained from the EPR spectra and used to determine the equilibrium constant, K_e. Spectra were recorded a few seconds after starting to irradiate in order to avoid significant consumption of the phenols during the course of the experiment. Relative radical concentrations were determined by comparison of the digitized experimental spectra with computer-simulated ones as previously described.[28a]

Acknowledgment. The Swedish Research Council and MIUR (Rome, Italy) are gratefully acknowledged for financial support.

Supporting Information Available: General synthetic details and ^{1}H, ^{13}C, and ^{77}Se NMR spectra of compounds prepared. Absolute energies, energy corrections, and Cartesian coordinates for compounds **4a**, **5**, and **6** and their corresponding radical cations and phenoxyl radicals. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0700023

(52) Burton, G. W.; Doba, T.; Gabe, E. J.; Hughes, L.; Lee, F. L.; Prasad, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 7053−7065.