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Synthesis and Antioxidant Profile of all-*rac*-α-Selenotocopherol

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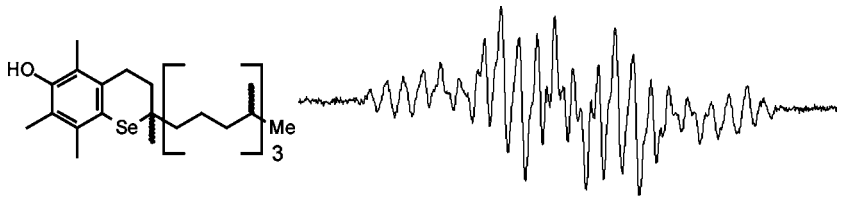
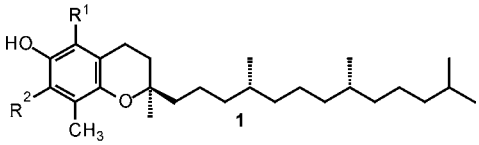


all-*rac*-α-Selenotocopherol (**6c**) has been synthesized in 11 steps in 6.6% total yield. Key steps include chloromethylation to approach the persubstituted aromatic **9b** and cyclization of alcohol precursor **10** by radical homolytic substitution at selenium to form the selenotocopherol heterocycle. Determination of the OH bond dissociation enthalpy (BDE) of **6c** by electron paramagnetic resonance (EPR) equilibration techniques gave a value of 78.1 ± 0.3 kcal mol^{-1}, approximately 1 kcal mol^{-1} higher than that of α-tocopherol. Kinetic studies performed by measuring oxygen uptake of the induced oxidation of styrene in the presence of an antioxidant showed that selenotocopherol (**6c**) was a slightly poorer inhibitor than α-tocopherol, in agreement with the BDE values. In contrast to simpler selenotocopherol analogues, **6c** was not regenerable in the presence of a stoichiometric coreductant in a two-phase lipid peroxidation model.

Introduction

Oxidative stress is a contributing factor in many of the so-called "diseases of aging" which include, for example, conditions such as atherosclerosis and Alzheimer's disease.[1] Our bodies have an endogenic arsenal of enzymatic and nonenzymatic antioxidants to combat oxidative degradation, but because it is apparent that these defenses are sometimes breached, there is a current interest in the development and application of new synthetic antioxidants for "antioxidant therapy". In cell membranes, the most important antioxidant is Vitamin E, which is a collective term for a series of structurally related chromanols named tocopherols (**1a**−**d**), differing only in the number and position of the aromatic methyl groups, where α-tocopherol is the most abundant.[2]



R^1=R^2=CH_3	α-tocopherol
R^1=CH_3, R^2=H	β-tocopherol
R^1=H, R^2=CH_3	γ-tocopherol
R^1=R^2=H	δ-tocopherol

In the development of new antioxidants to bolster our defense against oxidative stress, the α-tocopherol structure is therefore a natural starting point. The possibilities for variation of the structure are numerous. Two decades ago, Ingold and coworkers discovered that decreasing the size of the nonaromatic ring from six- to five-membered (**2**) resulted in a significant increase in antioxidant activity, presumably due to a better lp SOMO overlap in the phenoxyl radical.[3] The side chain of α-tocopherol has been varied to provide water-soluble analogues

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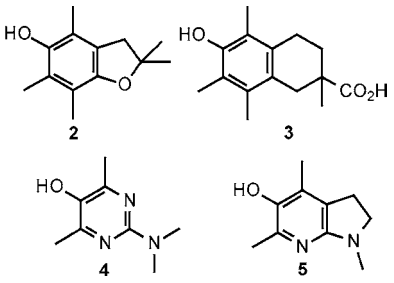
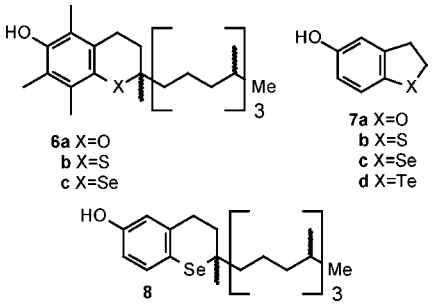
with altered pharmacokinetic properties (**3**).[4] Recently, variations in the phenolic ring, as exemplified by pyrimidin-5-ol **4** and pyridin-3-ol **5**, were found to produce antioxidants with improved air stability and hydrogen-atom donating capacity.[5,6]



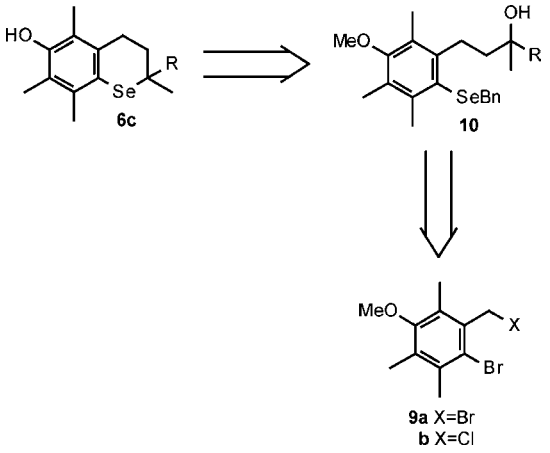
The nature of the heteroatom in the fused heterocyclic ring is another target for investigation. The aforementioned pyridinol- and pyrimidinol-based antioxidants use amine substituents to improve potency. Ingold has prepared the racemic sulfur analogue of α-tocopherol (**6b**), which proved to be less effective as a hydrogen-atom donor than the parent tocopherol (**6a**).[7] Within our group, a series of simple chalcogen-substituted analogues (**7a**−**d**) were tested, and the selenium-substituted analogue (**7c**) seemed particularly promising, being catalytically regenerated by a stoichiometric coreductant.[8] We have also previously synthesized a selenium-substituted α-tocopherol analogue lacking only aromatic methyl groups (**8**), although this compound was never tested for antioxidant activity.[9] To further assess the true potential of selenium-substituted antioxidants, we have now synthesized the full selenium analogue of racemic α-tocopherol (**6c**) and investigated its antioxidant activity.



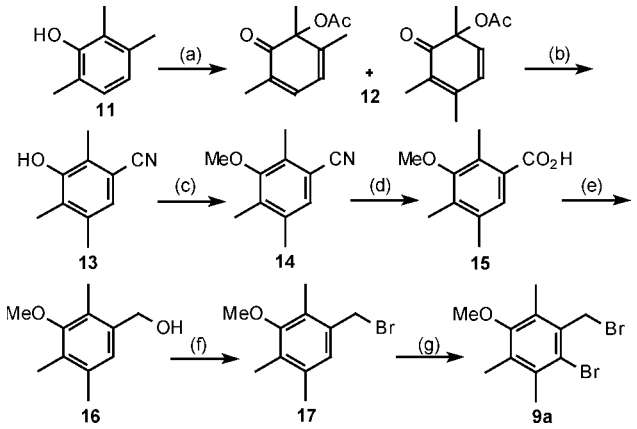
Results and Discussion

Synthesis. Homolytic substitution at selenium is now a well-established tool for the construction of selenacycles. Within our group, this technique has been applied to the synthesis of simple α-tocopherol analogues,[9] and Schiesser has recently used it for the construction of selenacycle-fused pyridines[10] and selenapenams.[11] This was therefore the method of choice for synthesizing selenotocopherol (**6c**) (Scheme 1). If the persubstituted aromatic **9** could be made, it was expected that radical precursor **10** could be approached by the same means as those previously reported for the synthesis of analogue **8**.[9]

SCHEME 1



SCHEME 2[a]



[a] Conditions: (a) $Pb(OAc)_4$, CH_2Cl_2, quantitative; (b) NaCN, MeOH, reflux, 47%; (c) MeI, K_2CO_3, acetone, quantitative; (d) KOH, H_2O, ethylene glycol, 140 °C, 90%; (e) $LiAlH_4$, THF, reflux, 97%; (f) PBr_3, Et_2O, 97%; (g) Br_2, CH_2Cl_2, quantitative.

Our initial approach toward structure **9** from phenol **11** involved oxidation to the *ortho*-quinol acetates **12** (Scheme 2).[12] The resulting mixture of regioisomers was used directly for conjugate addition/rearomatization to give benzonitrile **13** in moderate yields.[13] This was converted to benzyl bromide **9a** in high yield via O-methylation to give **14**, via nitrile hydrolysis to give **15**, via reduction of the carboxylic acid to give **16**, via benzylic substitution to give **17**, and, finally, via aromatic bromination.

A more expedient route, giving benzyl chloride **9b** in three steps, entailed bromination of phenol **11** to give **18** and methylation to give **19**, followed by microwave-assisted chloromethylation of the product anisole (Scheme 3). Subsequent synthesis toward ketone **24** proceeded as expected, in good yields, following procedures developed for the synthesis of **8**.[9] Thus, the hexa-substituted aromatic was subjected to benzylic substitution with the enolate of *tert*-butyl acetoacetate to give

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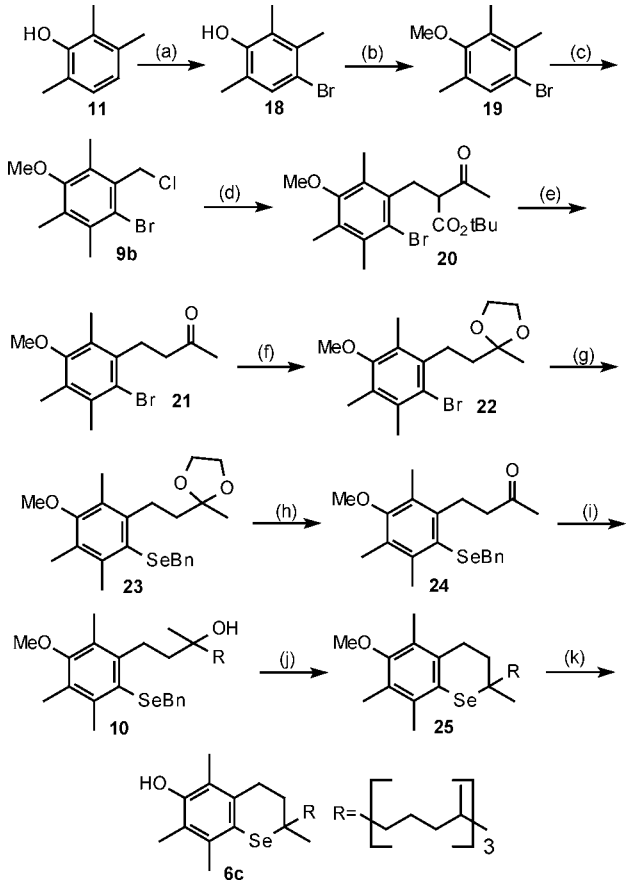
SCHEME 3[a]



[a] Conditions: (a) Br_2, CH_2Cl_2, quantitative; (b) MeI, K_2CO_3, acetone, quantitative; (c) $(CH_2O)_n$, HCl, AcOH, 154 °C, 57%; (d) *tert*-butyl acetoacetate, NaH, THF, 78%; (e) HCl, H_2O, reflux, 98%; (f) ethylene glycol, *p*-TsOH, benzene, reflux, quantitative; (g) (i) *t*-BuLi, THF, −78 °C, (ii) Se, −78 °C to room temperature, (iii) BnBr, room temperature, 66% overall; (h) HCl, H_2O, THF, room temperature, 98% (i) Mg, 4,8,12-trimethyltridecyl bromide, THF, reflux, 47%; (j) (i) oxalyl chloride, toluene, (ii) 2-mercaptopyridine *N*-oxide, DMAP, toluene, reflux, 49%; (k) BBr_3, CH_2Cl_2, −78 °C, quantitative.

20, decarboxylative hydrolysis to give **21**, protection as the glycol ketal to give **22**, lithiation, selenium insertion and benzylation to give **23**, and, finally, deprotection to give **24**. Grignard addition to ketone **24** proved troublesome, and significant quantities of starting material and aldol-type byproducts were isolated in addition to alcohol **10**. It was found that addition of borontrifluoride etherate suppressed formation of the aldol byproducts, although the yield remained moderate. Cyclization according to the Barton−Crich protocol formed selenochroman **25**, which was smoothly deprotected using BBr_3 to provide selenotocopherol (**6c**).

Electron Paramagnetic Resonance (EPR) Spectra of the Free Radical Obtained from Selenotocopherol (6c). Radicals were produced at room temperature inside the cavity of an EPR spectrometer by reacting selenotocopherol (**6c**) with alkoxyl radicals generated photolytically from di-*tert*-butyl peroxide in deoxygenated benzene solutions. By photolyzing solutions of **6c**, an intense spectrum centered at $g = 2.0101$ was observed, as shown in Figure 1 together with its computer simulation. Hyperfine splitting constants of 4.94 G (3H), 5.68 G (3H), 1.75 G (3H), and 1.37 G (2H) were extracted. These spectral parameters are consistent with the structure of the selenotocopheroxyl radical.

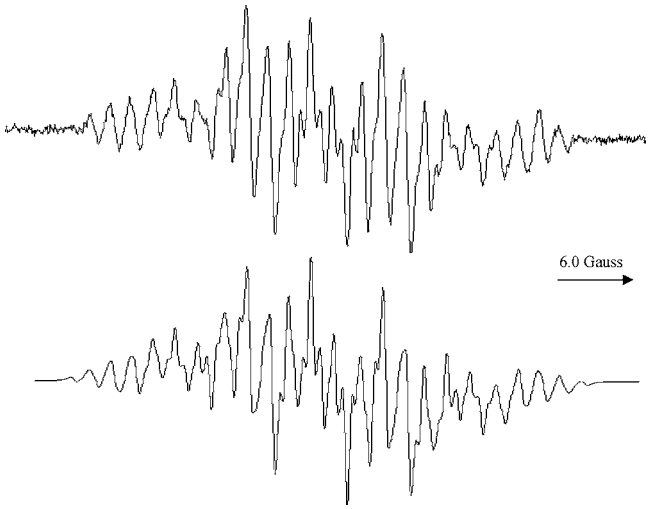


FIGURE 1. Experimental (top) and computer-simulated (bottom) spectra obtained by irradiating compound **6c** in benzene containing 10% v/v di-*tert*-butyl peroxide at 298 K.

OH Bond Dissociation Enthalpy (BDE). To measure the OH BDE value for selenotocopherol (**6c**), we used the EPR radical equilibration technique. Of the various methods used for the determination of bond strengths, this one seems at present to guarantee the best accuracy.[14−17] For this purpose, we measured the equilibrium constant, K_e, for the hydrogen-atom transfer among a reference phenol (ArOH), in this case BHA (BDE = 77.2 kcal mol^{-1}),[14,18] the selenotocopherol (**6c**, SeTocOH), and the corresponding phenoxyl radicals (eq 1) generated under continuous photolysis in deoxygenated benzene at room temperature (25 °C).

$$\text{SeTocOH} + \text{ArO}^{\bullet} \rightleftharpoons \text{SeTocO}^{\bullet} + \text{ArOH} \qquad (1)$$

In the calculation of K_e, the equilibrium constant for eq 1, the initial concentrations of SeTocOH and ArOH were used, and the relative radical concentrations were determined by means of EPR spectroscopy. The BDE for selenotocopherol (**6c**) was calculated, in the assumption that the entropic term can be neglected,[15] by means of eq 2 from K_e and the BDE value of the reference phenol.

$$\text{BDE(SeTocO−H)} \cong \text{BDE(ArO−H)} - RT\ln(K_e) \qquad (2)$$

From these measurements, repeated under different light intensities to check the constancy of K_e, we obtained a BDE value of 78.1 ± 0.3 kcal mol^{-1} for selenotocopherol (**6c**). The BDE of

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(18) All the BDE values determined in benzene solution by means of the EPR radical equilibration technique,[14] based on the O−H BDE of 2,4,6-tri-*tert*-butylphenol determined many years earlier by Mahoney et al.[19] using calorimetric measurements, must be downscaled by 1.1 kcal mol^{-1} because of the revision of the heat of formation of *E*-azobenzene.[20]
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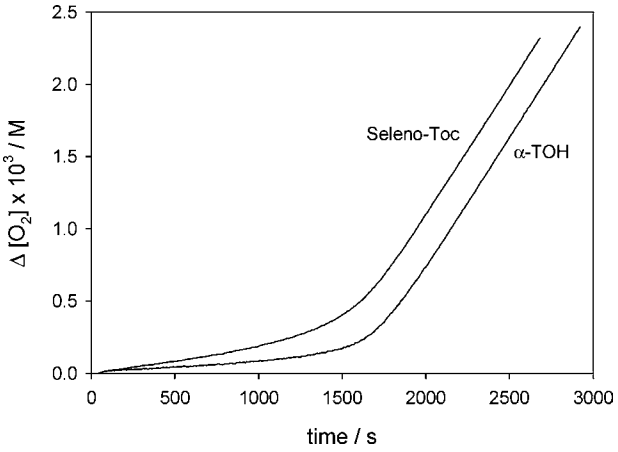

FIGURE 2. Oxygen consumption recorded during the thermally initiated autoxidation of styrene (4.7 M) in air-saturated chlorobenzene at 30 °C, in the presence of AMVN (5×10^{-3} M) as the initiator and selenotocopherol (**6c**) or α-tocopherol (**6a**), at 5.0×10^{-6} M.

α-tocopherol is valued at 77.15 kcal mol^{-1} by the same technique,[18] and thus, it can be seen that the BDE in the selenium-containing analogue is approximately 0.95 kcal mol^{-1} higher than in α-tocopherol. This is in good agreement with the calculated difference of 0.94 kcal mol^{-1}.[21]

Kinetic Measurements. Kinetic measurements with peroxyl radicals have been performed by studying the inhibited autoxidation of a standard oxidizable substrate (styrene) at 303 K in chlorobenzene, initiated by 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN), in the presence of selenotocopherol (**6c**) or α-tocopherol (α-TOH) as the reference antioxidant (Figure 2).

The autoxidation was followed by monitoring the oxygen consumption in an oxygen-uptake apparatus built in our laboratory and based on a Validyne DP15 differential pressure transducer, which has been previously described.[22] The observed kinetics are in accord with equations 3−8.

$$\text{initiator} \xrightarrow{R_i} R^\bullet \tag{3}$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \tag{4}$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \tag{5}$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{products} \tag{6}$$

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \tag{7}$$

$$ROO^\bullet + ArO^\bullet \rightarrow \text{products} \tag{8}$$

Compound **6c** showed a neat inhibition period, τ, in styrene, whose length provided the stoichiometric coefficient, i.e., the number of peroxyl radicals trapped by one molecule of antioxidant, $n = R_i\tau/[AH]$, where R_i is the initiation rate measured in a preliminary set of experiments using α-tocopherol and [AH] is the initial concentration of antioxidant. Integration of the oxygen consumption trace affords the rate of reaction with peroxyl radicals, k_{inh}, provided k_p is known (eq 9).

$$\Delta[O_2]_t = -k_p/k_{inh}\,[AH]\ln(1 - t/\tau) \tag{9}$$

It transpires that selenotocopherol has an inhibition rate, $k_{inh} = 1.2 \times 10^6$ M^{-1} s^{-1}, and a stoichiometric coefficient, $n = 1.9$, similar to those of α-tocopherol, which has $k_{inh} = 3.2 \times 10^6$ M^{-1} s^{-1} and $n = 2.0$. Thus, the selenotocopherol (**6c**) is only slightly less effective than its oxygen-containing analogue α-tocopherol, in agreement with the slightly higher value of the OH BDE. This, and the fact that the stoichiometric coefficients are nearly identical, implies that both antioxidants act by the same mechanism.

Evaluation of the Regenerability of Selenotocopherol (6c). To evaluate whether selenotocopherol (**6c**) was regenerable by a stoichiometric coreductant, it was tested in a two-phase lipid peroxidation model similar to that previously described.[8] In brief, a thermostated vial is charged with a chlorobenzene solution of linoleic acid. First, the antioxidant to be tested is added, followed by an aqueous solution of the coreductant (*N*-acetyl cysteine). The mixture is stirred and allowed to come to equilibrium for 30 min before oxidation is induced by addition of a solution of an azo initiator. The oxidation is followed by sampling the organic phase every 10 min, separating the components by high-pressure liquid chromatography (HPLC), and monitoring the formation of conjugated dienes at 234 nm. In the absence of NAC, selenotocopherol had an inhibition period of 58 min, compared to α-tocopherol (**6a**), which had a $t_{inh} = 80$ min. We expected, in analogy to selenide **7c**, that the inhibition period of selenotocopherol would be significantly increased in the presence of NAC, but to our surprise, no difference was observed. Hence, although the simple selenotocopherol analogue **7c** is catalytically regenerable, the full selenotocopherol (**6c**) is not. At the moment, we can only speculate as to the origin of this difference in reactivity. Possible reasons include steric hindrance at the redox-active site or a changeover in mechanism from electron transfer to hydrogen-atom transfer with increasing substitution of the selenide. Methyl-protected selenotocopherol **25** was also tested and was shown to have no inhibiting effect whatsoever, demonstrating the necessity of the phenolic hydrogen for activity. In analogy to selenide **7c**, selenotocopherol is not expected to possess any hydroperoxide-decomposing activity. Further studies into the antioxidant and regeneration mechanisms are underway in our laboratories.

Experimental Section

Synthesis. A. 3-Cyano-2,5,6-trimethylphenol (13). To a solution of *o*-quinol acetates **12**[12] (1:1 mixture, 2 g, 10.3 mmol) in methanol (20 mL) was added sodium cyanide (1.11 g, 22.7 mmol). The mixture was stirred at room temperature for 15 min and then heated at reflux for 40 min. Water (30 mL) was added, and the methanol was removed on the rotary evaporator. The aqueous phase was extracted repeatedly with EtOAc, and the combined organic phase was washed with saturated brine, dried over $MgSO_4$, and evaporated to give a crude brown residue. This was recrystallized from CCl_4 to give the title compound as a white solid (780 mg, 47%): mp 132−133 °C; ^{1}H NMR δ 7.02 (1H, s), 4.96 (1H, s), 2.40 (3H, s), 2.26 (3H, s), 2.20 (3H, s); ^{13}C NMR δ 152.5, 136.6, 128.2, 126.0, 124.5, 118.8, 110.5, 20.1, 14.5, 12.6. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.32; H, 6.87.

B. 3-Cyano-2,5,6-trimethylanisole (14). A mixture of phenol **13** (2.26 g, 14.1 mmol), MeI (10.04 g, 70.5 mmol), and K_2CO_3 (19.55 g, 141.0 mmol) in acetone (70 mL) was stirred at room temperature for 22 h. The product slurry was filtered, and the solvent was removed in vacuo. The residue was partitioned between water

(21) Calculations performed at the (RO)B3LYP/LANL2DZdp//(U)B3LYP/LANL2DZ level. Shanks, D.; Frisell, H.; Ottosson, H.; Engman, L. *Org. Biomol. Chem.* **2006**, accepted for publication.

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and dichloromethane, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (2.46 g, quantitive) as a beige solid: mp 59−60 °C; ^{1}H NMR δ 7.17 (1H, s), 3.69 (3H, s), 2.43 (3H, s), 2.24 (3H, s), 2.23 (3H, s); ^{13}C NMR δ 157.3, 137.2, 136.2, 132.7, 129.2, 118.6, 111.1, 60.4, 20.0, 14.6, 13.1. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 75.22; H, 7.47.

C. 3-Methoxy-2,4,5-trimethylbenzoic Acid (15). A mixture of nitrile **14** (1.0 g, 5.7 mmol), KOH (960 mg, 17.1 mmol), water (1.4 mL), and ethylene glycol (11 mL) was heated (bath temp of 140 °C) for 7 h. The solution was then cooled to room temperature and treated with aqueous HCl (24 mL, 1 M). The precipitated solid was collected by filtration and dried under vacuum over P_2O_5, giving the title compound (1.0 g, 90%) as a white powder: mp 159−160 °C; ^{1}H NMR δ 11.70 (1H, br s), 7.65 (1H, s), 3.69 (3H, s), 2.55 (3H, s), 2.28 (3H, s), 2.26 (3H, s); ^{13}C NMR δ 173.2, 157.7, 135.9, 135.7, 131.8, 128.4, 127.1, 60.4, 20.1, 13.8, 13.2. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.23.

D. 3-Methoxy-2,4,5-trimethylbenzyl Alcohol (16). To a solution of the acid **15** (981 mg, 5.05 mmol) in dry THF (11 mL) at 0 °C under nitrogen was added $LiAlH_4$ (383 mg, 10.1 mmol) portionwise. After complete addition, the mixture was allowed to come to room temperature for 30 min and then heated at reflux for 20 h. Excess $LiAlH_4$ was quenched by careful addition of aqueous HCl (3 M) at 0 °C, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (880 mg, 97%) as a white powder: mp 87−88 °C; ^{1}H NMR δ 6.94 (1H, s), 4.63 (2H, s), 3.68 (3H, s), 2.27 (3H, s), 2.25 (3H, s), 2.20 (3H, s), 1.51 (1H, br s); ^{13}C NMR δ 157.2, 137.4, 135.7, 129.4, 126.7, 125.4, 64.0, 60.3, 20.1, 12.6, 11.5. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.42; H, 8.99.

E. 3-Methoxy-2,4,5-trimethylbenzyl Bromide (17). Neat PBr_3 (710 mg, 2.6 mmol) was added dropwise to a solution of alcohol **16** (860 mg, 4.77 mmol) in Et_2O (10 mL). The reaction mixture was stirred at room temperature for 4.5 h, before quenching with water. The organic phase was diluted with Et_2O, washed with water and brine, dried over $MgSO_4$, and evaporated to give the title compound (1.13 g, 97%) as a pale-blue powder: mp 70−71 °C; ^{1}H NMR δ 6.93 (1H, s), 4.49 (2H, s), 3.68 (3H, s), 2.32 (3H, s), 2.23 (3H, s), 2.20 (3H, s); in good agreement with previously published data;[23] ^{13}C NMR δ 157.4, 136.0, 134.3, 130.9, 127.9, 127.2, 60.4, 33.3, 20.0, 12.8, 11.7. Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.34; H, 6.22. Found: C, 54.23; H, 6.16.

F. 2-Bromo-5-methoxy-3,4,6-trimethylbenzyl Bromide (9a). Bromine (750 mg, 4.7 mmol) dissolved in dichloromethane (8 mL) was added dropwise to a solution of aromatic **17** (1.09 g, 4.5 mmol) in dichloromethane (10 mL), and the reaction mixture was stirred for 4.5 h at room temperature. Excess bromine was destroyed by addition of saturated aqueous $Na_2S_2O_3$ (20 mL). The aqueous phase was extracted with dichloromethane, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (1.44 g, quantitative) as a white powder: mp 103−104 °C; ^{1}H NMR δ 4.77 (2H, s), 3.66 (3H, s), 2.39 (6H, s), 2.27 (3H, s); ^{13}C NMR δ 156.4, 136.4, 133.9, 132.3, 129.9, 123.9, 60.5, 33.9, 21.0, 14.3, 12.9. Anal. Calcd for $C_{11}H_{14}Br_2O$: C, 41.03; H, 4.38. Found: C, 41.05; H, 4.31.

G. 4-Bromo-2,3,6-trimethylanisole (19). Anisole **19** was prepared by the same method as that used for anisole **14**, using phenol **18**[8] as starting material: quantitative yield; ^{1}H NMR δ 7.28 (1H, s), 3.70 (3H, s), 2.36 (3H, s), 2.29 (3H, s), 2.27 (3H, s); ^{13}C NMR δ 156.3, 135.2, 131.9, 131.7, 130.1, 120.0, 60.2, 20.0, 16.0, 13.8.

H. 2-Bromo-5-methoxy-3,4,6-trimethylbenzyl Chloride (9b). A mixture of anisole **19** (800 mg, 3.5 mmol), paraformaldehyde (524 mg, 17.5 mmol), concentrated HCl (37%, 7 mL), and glacial acetic acid (3.5 mL) was heated at 154 °C for 30 min in a microwave reactor. The product was precipitated with water, and the supernatant was decanted. The crude solid was dissolved in ether, washed with water and saturated brine, and dried over $MgSO_4$, and the solvent was removed in vacuo to give a crude brown solid. This was purified by column chromatography (pentane/dichloromethane 9:1) to give the title compound (554 mg, 57%) as a white crystalline solid: mp 101−102 °C; ^{1}H NMR δ 4.87 (2H, s), 3.66 (3H, s), 2.41 (3H, s), 2.40 (3H, s), 2.28 (3H, s); ^{13}C NMR δ 156.4, 136.3, 133.9, 132.4, 130.0, 123.9, 60.5, 45.7, 21.0, 14.3, 12.9. Anal. Calcd for $C_{11}H_{14}BrClO$: C, 47.60; H, 5.08. Found: C, 47.75; H, 5.02.

I. *tert*-Butyl-2-(2-bromo-5-methoxy-3,4,6-trimethylbenzyl) Acetoacetate (20). Neat *tert*-butyl acetoactetate (475 mg, 3 mmol) was added dropwise to a stirred slurry of NaH (60% in mineral oil, 120 mg, 3 mmol) in dry THF (4 mL) at 0 °C under nitrogen. The mixture was allowed to come to room temperature over 30 min, and the solution became homogeneous. The benzyl chloride **9b** (278 mg, 1 mmol) dissolved in THF (3 mL) was added by syringe, and the mixture was heated at reflux for 15 h. The reaction was then allowed to cool to room temperature and was quenched by addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give crude product. Excess *tert*-butyl acetoactetate was removed by Kugelrohr distillation under vacuum, and the residue was subjected to column chromatography (pentane/Et_2O 85:15) to give the title compound as a colorless viscous oil (311 mg, 78%): ^{1}H NMR δ 3.93 (1H, t, J = 7.3 Hz), 3.60 (3H, s), 3.39 (1H, dd, J = 14.5, 7.3 Hz), 3.32 (1H, dd, J = 14.5, 7.3 Hz), 2.37 (3H, s), 2.27 (3H, s), 2.25 (3H, s), 2.17 (3H, s), 1.37 (9H, s); ^{13}C NMR δ 203.4, 168.9, 156.3, 135.8, 135.4, 129.8, 129.6, 124.2, 82.1, 60.3, 59.6, 31.9, 30.0, 28.0, 21.0, 14.1, 13.8. Anal. Calcd for $C_{19}H_{27}BrO_4$: C, 57.15; H, 6.82. Found: C, 57.12; H, 6.95.

J. 4-(2-Bromo-5-methoxy-3,4,6-trimethylphenyl)-2-butanone (21). A solution of acetoacetate **20** (5.0 g, 12.5 mmol) in aqueous HCl (9 M, 80 mL) was heated at reflux for 15 h. The mixture was then cooled to room temperature and extracted with diethyl ether. The organic phase was washed with water and saturated brine and then dried over $MgSO_4$ to give the title compound (3.65 g, 98%) as a white solid: mp 84−85 °C; ^{1}H NMR δ 3.63 (3H, s), 3.09 (2H, m), 2.64 (2H, m), 2.38 (3H, s), 2.26 (3H, s), 2.25 (3H, s), 2.19 (3H, s); ^{13}C NMR δ 208.3, 156.3, 137.5, 135.8, 129.4, 128.3, 123.7, 60.4, 42.5, 30.1, 28.7, 21.0, 14.1, 13.2. Anal. Calcd for $C_{14}H_{19}BrO_2$: C, 56.20; H, 6.40. Found: C, 56.31; H, 6.43.

K. 2-[2-(2-Bromo-5-methoxy-3,4,6-trimethylphenyl)ethyl]-2-methyl-1,3-dioxolane (22). A mixture of ketone **21** (910 mg, 3.0 mmol), *p*-toluenesulfonic acid (60 mg, 0.3 mmol), and ethylene glycol (380 mg, 6.1 mmol) in benzene (15 mL) was heated at reflux for 13 h. The solution was then cooled to room temperature, diluted with diethyl ether, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give the title compound as a colorless oil (1.04 g, quantitive): ^{1}H NMR δ 4.04 (4H, s), 3.67 (3H, s), 2.96 (2H, m), 2.41 (3H, s), 2.33 (3H, s), 2.28 (3H, s), 1.86 (2H, m), 1.46 (3H, s); ^{13}C NMR δ 156.2, 138.6, 135.6, 128.9, 128.2, 123.8, 110.0, 65.0, 60.4, 37.5, 29.3, 23.9, 21.0, 14.1, 13.1.

L. 2-[2-(2-Benzylselenenyl-5-methoxy-3,4,6-trimethylphenyl)-ethyl]-2-methyl-1,3-dioxolane (23). To a solution of the arylbromide **22** (2.74 g, 8.0 mmol) in dry THF (80 mL) at −78 °C under nitrogen was added *t*-BuLi (8.4 mL, 8.0 mmol). The mixture was stirred at −78 °C for 5 min, and then finely ground selenium (662 mg, 8.4 mmol) was added in one portion. The mixture was allowed to approach room temperature for 15 min until all selenium had dissolved. Benzyl bromide (1.14 mL, 9.6 mmol) was added, and the reaction mixture was stirred at room temperature for a further 3 h and then quenched by addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give crude product. This was purified by flash

(23) Gruter, G. -J. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473.

chromatography (pentane/EtOAc 90:10) to give the title compound as a yellow solid (2.29 g, 66%): mp 37−39 °C; ^{1}H NMR δ 7.17 (3H, m), 7.03 (2H, m), 3.98 (2H, m), 3.95 (2H, m), 3.81 (2H, s), 3.66 (3H, s), 2.91 (2H, m), 2.48 (3H, s), 2.26 (3H, s), 2.22 (3H,s), 1.69 (2H, m), 1.38 (3H, s); ^{13}C NMR δ 157.8, 144.5, 141.3, 139.3, 128.9, 128.4, 128.0, 127.9, 127.1, 126.8, 110.1, 65.0, 60.3, 39.2, 33.0, 30.0, 23.8, 21.7, 14.1, 13.1.

M. 2-(2-Benzylselenenyl-5-methoxy-3,4,6-trimethylphenyl)-ethyl Methyl Ketone (24). A mixture of ketal **23** (2.22 g, 5.1 mmol), THF (25 mL), and aqueous HCl (25 mL, 3 M) was stirred for 15 h at room temperature. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (1.96 g, 98%) as a yellow solid: mp 80−81 °C; ^{1}H NMR δ 7.17 (3H, m), 6.99 (2H, m), 3.81 (2H, s), 3.66 (3H, s), 3.07 (2H, m), 2.49 (3H, s), 2.38 (2H, m), 2.23 (3H, s), 2.21 (3H, s), 2.10 (3H, s); ^{13}C NMR δ 208.7, 157.8, 143.4, 141.4, 139.3, 128.9, 128.5, 128.4, 127.7, 127.1, 126.9, 60.4, 44.2, 33.0, 30.0, 29.2, 21.7, 14.1, 13.2. Anal. Calcd for $C_{21}H_{26}O_2Se$: C, 64.77; H, 6.73. Found: C, 64.52; H, 6.63.

N. 1-(2-Benzylselenenyl-5-methoxy-3,4,6-trimethylphenyl)-3,7,11,15-tetramethyl-3-hexadecanol (10). To a slurry of magnesium (48 mg, 2 mmol) in dry THF (3 mL) heated at reflux under nitrogen was slowly added 4,8,12-trimethyltridecyl bromide (458 mg, 1.5 mmol) dissolved in dry THF (2 mL). The reaction mixture was heated at reflux for 5 h and then cooled to −78 °C. First, BF_3·Et_2O (114 μL, 0.9 mmol) was added, followed by ketone **24** (300 mg, 0.77 mmol) in dry THF (5 mL). The mixture was stirred at −78 °C for 15 min and then brought to room temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the crude product mixture, which was separated by column chromatography (pentane/Et_2O 85:15) to give the title compound as a pale viscous oil (227 mg, 48%) and recovered starting material (140 mg, 47%), as well as traces of aldol product: ^{1}H NMR δ 7.17 (3H, m), 7.02 (2H, m), 3.81 (2H, s), 3.67 (3H, s), 2.84 (2H, m), 2.50 (3H, s), 2.26 (3H, s), 2.53 (3H, s), 1.65−1.03 (27H, m), 0.86 (12H, m); ^{13}C NMR δ (some characteristic peaks) 157.8, 144.8, 141.3, 139.3, 128.9, 128.5, 128.0, 127.8, 127.0, 126.9, 73.3. Anal. Calcd for $C_{37}H_{60}O_2Se$: C, 72.16; H, 9.82. Found: C, 71.94; H, 9.93.

O. 6-Methoxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-selenochromane (25). A solution of alcohol **10** (230 mg, 0.37 mmol) and oxalyl chloride (0.4 mL) in dry toluene (2.2 mL) was stirred at room temperature for 15 h. All volatile components were removed under vacuum, and the residue was dissolved in toluene (1.5 mL). This solution was transferred by canulla to a slurry of the sodium salt of 2-mercaptopyridine *N*-oxide (67 mg, 0.45 mmol) and DMAP (4.5 mg, 0.04 mg) and heated at reflux in toluene (3 mL). The solvent was then removed in vacuo, and the residue was purified by column chromatography (pentane/dichloromethane 80:20) to give the title compound as a colorless oil (93 mg, 49%): ^{1}H NMR δ 3.65 (3H, s), 2.83 (1H, ddd, J = 16.9, 7.4, 4.1 Hz), 2.75 (1H, ddd, J = 16.9, 8.9, 4.3 Hz), 2.23 (6H, s), 2.21 (3H, s), 1.92 (2H, m), 1.84−1.03 (24H, several peaks), 0.86 (12H, several peaks); ^{13}C NMR δ (some characteristic peaks) 154.5, 133.6, 133.4, 127.7, 127.1, 126.1, 60.5. Anal. Calcd for $C_{30}H_{52}OSe$: C, 70.97; H, 10.32. Found: C, 71.13; H, 10.48.

P. 2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)selenochroman-6-ol (6c). BBr_3 (394 μL, 1.0 M in CH_2Cl_2, 0.39 mmol) was added dropwise to a solution of the selenide **25** in dichloromethane (2.4 mL) at −78 °C under nitrogen. The mixture was brought to room temperature and stirred for 15 h. The reaction was quenched by addition of water. The aqueous phase was extracted with dichloromethane, and the combined organic phase was washed with brine, dried over $MgSO_4$, and evaporated to give the title compound (97 mg, quantitive) as a pale viscous oil: ^{1}H NMR δ 2.88 (1H, ddd, J = 16.9, 7.4, 4.1 Hz), 2.78 (1H, ddd, J = 16.9, 8.9, 4.3 Hz), 2.28 (3H, s), 2.23 (3H, s), 2.23 (3H, s), 1.93 (2H, m), 1.84−1.03 (24H, several peaks), 0.92 (12H, several peaks); ^{13}C NMR δ (some characteristic peaks) 149.6, 133.6, 133.0, 122.0, 120.6, 119.8, 45.1. Anal. Calcd for $C_{29}H_{50}OSe$: C, 70.56; H, 10.21. Found: C, 70.30; H, 10.04.

EPR and Thermochemical Measurements. Deoxygenated benzene solutions containing the phenols (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 spectrometer equipped with a microwave frequency counter for the determination of the *g*-factors, which were corrected with respect to that of the perylene radical cation in concentrated H_2SO_4 ($g = 2.0025_8$).

When using mixtures of BHA and selenotocopherol (**6c**), 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 to avoid significant consumption of the phenols during the course of the experiment.

Relative radical concentrations were determined either by double integration of the signals due to the two equilibrating species or by comparison of the digitized experimental spectra with computer-simulated ones, as previously described.[14]

Kinetic Measurements. The rate constants for the reaction of the antioxidants with peroxyl radicals have been measured by following the autoxidation of pure styrene (4.7 M) in chlorobenzene, at 303 K using AMVN (5×10^{-3} M) as an initiator . The antioxidant concentration was kept constant for all measurements (5.0×10^{-6} M) 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 the reference antioxidant: $R_i = 2[\alpha\text{-TOH}]/\tau$.[3]

HPLC Peroxidation Assay. An HPLC equipped with an autoinjector, a thermostated sample rack, a 5 μL injection loop, a photodiode array detector, and a relay-controlled stirring plate was used for the peroxidation studies. In a typical experiment, linoleic acid in chlorobenzene (7.5 mL, 36.2 mM) was stirred at 1000 rpm, 42 °C, in a 20 mL vial. To this solution was added the antioxidant in ethanol (107 μL, 3.0 mM) by micropipet, followed by an aqueous solution of NAC (8.0 mL, 1.0 mM). An injection routine, whereby every 10 min 5 μL samples of the lower organic phase were separated by a silica column (4 μ, 150 × 4.6 mm) eluted with hexane/ethanol mixtures, was commenced. Stirring (controlled by relay from the HPLC) was stopped 30 s prior to sampling to allow phase separation and immediately resumed thereafter. Prior to the fourth injection, a thermostated solution of AMVN in chlorobenzene (0.5 mL, 22.4 mM) was added to initiate oxidation. Formation of conjugated dienes was monitored at 234 nm. The inhibition period (t_{inh}) was determined by the least-squares method as the point where the uninhibited oxidation phase was projected to intersect the initial peroxide concentration.

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Supporting Information Available: General synthetic details and ^{1}H spectra of compounds **19**, **22**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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