Intramolecular Homolytic Substitution at Selenium: Synthesis of Novel Selenium-Containing Vitamin E Analogues

Nawaf Al-Maharik,[†] Lars Engman,*[,†] Jonas Malmström,[†] and Carl H. Schiesser*[,‡]

Institute of Chemistry, Department of Organic Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden, and School of Chemistry, The University of Melbourne, Victoria 3010, Australia

Lars.Engman@kemi.uu.se

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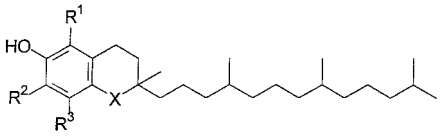
Treatment of 1-(benzylselenenyl)-5-butyl-5-nonanol (**10**) with oxalyl chloride followed by the sodium salt of *N*-hydroxypyridine-2-thione afforded the corresponding pyridine-2-thione-*N*-oxycarbonyl (PTOC) oxalate ester which was not isolated but immediately heated to provide 2,2-dibutylselenane (**7**). This transformation presumably involves a tertiary alkyl radical that undergoes intramolecular homolytic substitution at selenium with loss of the benzyl radical to provide the selenium-containing ring system (**7**). A similar protocol, when applied to 1-(2-benzylselenenyl-5-methoxyphenyl)-3-methyl-3-heptanol (**18**) and 1-(2-benzylselenenyl-5-methoxyphenyl)-3,7,11,15-tetramethyl-3-hexadecanol (**19**), followed by deprotection, afforded the selenium-containing α-tocopherol analogues **4** and **1f**, respectively, in moderate yields. To the best of our knowledge, these transformations represent the first examples of tertiary radicals involved in homolytic substitution chemistry at selenium.

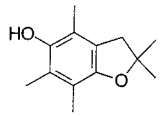
Introduction

Antioxidants are of great interest in biological and polymeric systems. In biological systems, they protect cell components from oxidative damage, whereas in polymeric systems, they act as stabilizers to prevent oxidative, photochemical, and thermal degradation of the material. Vitamin E is a well-known lipid-soluble antioxidant in biological systems.[1] It protects cell membranes from oxidative degradation by acting as a chain-breaking donating antioxidant. The term vitamin E refers to one or more structurally related phenolic compounds called tocopherols (compounds **1a**−**d**), among which α-tocopherol is the most active.



1a X= O, R^1= R^2= R^3= CH_3 α-tocopherol
1b X= O, R^1= R^3= CH_3, R^2= H β-tocopherol
1c X= O, R^2= R^3= CH_3, R^1= H γ-tocopherol
1d X= O, R^1= R^2= H, R^3= CH_3 δ-tocopherol
1e X= S, R^1= R^2= R^3= CH_3
1f X= Se, R^1= R^2= R^3= H
1g X= Se, R^1= R^2= R^3= CH_3

Several efforts have been made to develop antioxidants with better antioxidative properties than vitamin E. For example, Ingold and co-workers prepared the analogue **2**, which has a five-membered fused heterocyclic ring instead of a six-membered one.[2] They reported that this compound, because of stereoelectronic effects, had an



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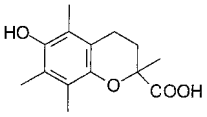
inhibition rate 1.8 times higher than that of α-tocopherol. Water-soluble α-tocopherol analogues have also been prepared to increase bioavailability.[3] The most notable example is Trolox (**3**). However, not so much attention



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has been paid to the heteroatom in the fused heterocyclic ring. Ingold and co-workers prepared the sulfur analogue (**1e**) of α-tocopherol,[4] but it turned out to be slightly less efficient as an antioxidant than the parent.[5]

We have demonstrated that various sulfur-, selenium-, and tellurium-containing compounds show promising antioxidative properties in different models[6] and polymeric systems.[7] Divalent organoselenides and tellurides react readily with many types of oxidants, and the resulting tetravalent compounds can be reduced by mild reducing agents. Thus, in the presence of a stoichiometric reductant, the Se/Te-containing materials can act as catalytic antioxidants. Because of this facile redox cycling, we believe selenium- and tellurium-containing α-toco-

* Correspondence may be addressed to either author.
[†] Uppsala University.
[‡] The University of Melbourne.

(1) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194.
(2) 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.
(3) Bolkenius, F. N.; Grisar, J. M.; De Jong, W. *Free Radical Res. Commun.* **1991**, *14*, 363. Grisar, J. M.; Petty, M. A.; Bolkenius, F. N.; Dow, J.; Wagner, J.; Wagner, E. R.; Haegele, K. D.; De Jong, W. *J. Med. Chem.* **1991**, *34*, 257.
(4) Robillard, B.; Ingold, K. U. *Tetrahedron Lett.* **1986**, *27*, 2817.
(5) Robillard, B.; Hughes, L.; Slaby, M.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1986**, *51*, 1700. Zahalka, H. A.; Robillard, B.; Hughes, L.; Lusztyk, J.; Burton, G. W.; Janzen, E. G.; Kotake, Y.; Ingold, K. U. *J. Org. Chem.* **1988**, *53*, 3739.

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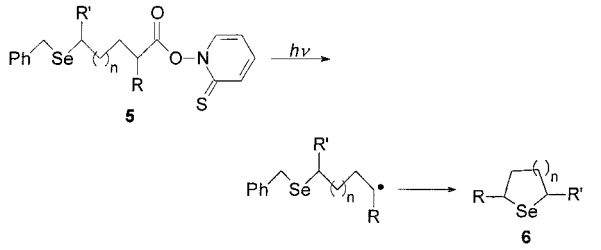
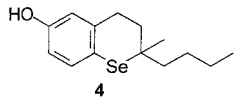
Scheme 1



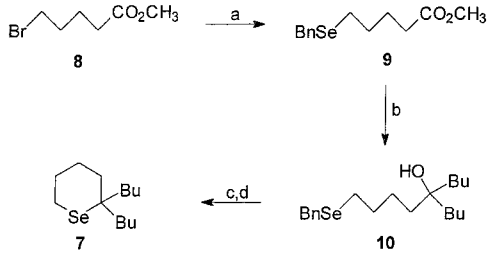
pherols will be more efficient than the corresponding oxygen and sulfur analogues. As model compounds of increasing complexity, we decided to synthesize the selenium-containing analogues **4** and **1f**.



Intramolecular homolytic substitution is now a proven synthetic method for the preparation of various heterocycles.[8] Intramolecular homolytic substitution at sulfur has been used in the preparation of sulfur-containing heterocycles.[9] We have recently demonstrated that intramolecular homolytic substitution at selenium or tellurium is a convenient method for the preparation of selenium or tellurium heterocycles.[10] For example, irradiation of radical precursor **5** (Scheme 1) leads to rapid and efficient intramolecular homolytic substitution at selenium to give substituted and saturated selenium-containing heterocycles **6** in good yield.[11]

We now describe, to the best of our knowledge, the first examples of tertiary radicals undergoing intramolecular homolytic substitution reactions at selenium to afford selenium-containing heterocycles.

Scheme 2[a]

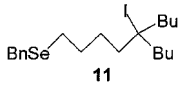


[a] Key: (a) Bn_2Se_2, $NaBH_4$, EtOH, 95%. (b) Mg, *n*-BuBr, Et_2O, 76%. (c) Oxalyl chloride, C_6H_6. (d) Sodium salt of 2-mercaptopyridine *N*-oxide, DMAP, C_6H_6, 40% from **10**.

Results and Discussion

Synthesis of 2,2-Dibutylselenane (7), a Model Compound. To explore methods for the preparation of the required selenium-containing ring systems (e.g., **1f**), we first turned our attention to the preparation of 2,2-dibutylselanane (**7**), a model compound. Barton, Crich, and co-workers reported some time ago a convenient way to generate radicals from tertiary alcohols by the use of PTOC oxalates (anhydrides of an oxalic acid monoester and *N*-hydroxypyridine-2-thione).[12] It was envisaged that free-radical homolytic substitution chemistry involving an appropriately substituted tertiary radical would produce the desired selenacycle. Model compound **7** was prepared from commercially available methyl 5-bromovalerate (**8**) as indicated in Scheme 2. Thus, treatment of bromide **8** with sodium benzylselenolate afforded selenide **9** in 95% isolated yield. The required tertiary alcohol **10** was prepared in 76% isolated yield by treatment of ester **9** with 2.1 equiv of *n*-butylmagnesium bromide. The alcohol was then treated with oxalyl chloride, followed by the sodium salt of 2-mercaptopyridine *N*-oxide and DMAP, to afford the desired selenide **7** in 40% yield from compound **10**.

Interestingly, attempted intramolecular homolytic substitution using the tertiary iodide **11** as a starting



material under standard free-radical conditions [(tris-(trimethylsilyl)silane (TTMSS) and AIBN, *n*-Bu_3SnH and AIBN, $(n\text{-}Bu_3Sn)_2$ and *hν*] gave only low yields of the desired selenacycle **7**. Elimination seems to be the predominant competing reaction in these cases.

Synthesis of the Selenium-Containing Vitamin E Analogues 4 and 1f. The selenochromane **4** was prepared as outlined in Scheme 3. Bromination of 3-methoxybenzyl bromide, **12**,[13] gave the dibromide **13** in 97% yield. Subsequent treatment of compound **13** with the enolate of *tert*-butyl acetoacetate, followed by hydrolysis and decarboxylation, furnished the desired ketone **15** quantitatively. Further protection as the 1,3-dioxolane

(6) Cotgreave, I. A.; Moldéus, P.; Engman, L.; Hallberg, A. *Biochem. Pharmacol.* **1991**, *42*, 1481. Cotgreave, I. A.; Moldéus, P.; Brattsand, R.; Hallberg, A.; Andersson, C.-M.; Engman, L. *Biochem. Pharmacol.* **1992**, *43*, 793. Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C.-M. *J. Am. Chem. Soc.* **1992**, *114*, 9737. Andersson, C.-M.; Hallberg, A.; Brattsand, R.; Cotgreave, I. A.; Engman, L.; Persson, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2553. Engman, L.; Stern, D.; Pelcman, M.; Andersson, C.-M. *J. Org. Chem.* **1994**, *59*, 1973. Andersson, C. M.; Brattsand, R.; Hallberg, A.; Engman, L.; Persson, J.; Moldéus, P.; Cotgreave, I. A. *Free Radical Res.* **1994**, *20*, 401. Engman, L.; Andersson, C.; Morgenstern, R.; Cotgreave, I. A.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 2929. Engman, L.; Persson, J.; Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M. *Free Radical Biol. Med.* **1995**, *19*, 441. Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C.-M.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461. Wieslander, E.; Engman, L.; Svensjö, E.; Erlansson, M.; Johansson, U.; Linden, M.; Andersson, C.-M.; Brattsand, R. *Biochem. Pharmacol.* **1998**, *55*, 573. Kanda, T.; Engman, L.; Cotgreave, I. A.; Powis, G. *J. Org. Chem.* **1999**, *64*, 8161.

(7) Engman, L.; Stern, D.; Stenberg, B. *J. Appl. Polym. Sci.* **1996**, *59*, 1365. Malmström, J.; Engman, L.; Bellander, M.; Jacobsson, K.; Stenberg, B. *J. Appl. Polym. Sci.* **1998**, *70*, 449.

(8) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265.

(9) See, for example: Kampmeier, J. A.; Evans, T. R. *J. Am. Chem. Soc.* **1966**, *88*, 4096. Benati, L.; Montevecchi, P. C.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1272. Beckwith, A. L. J.; Boate, D. R. *J. Chem. Soc., Chem. Commun.* **1986**, 189. Beckwith, A. L. J.; Boate, D. R. *J. Org. Chem.* **1988**, *53*, 4339. Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143. Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566.

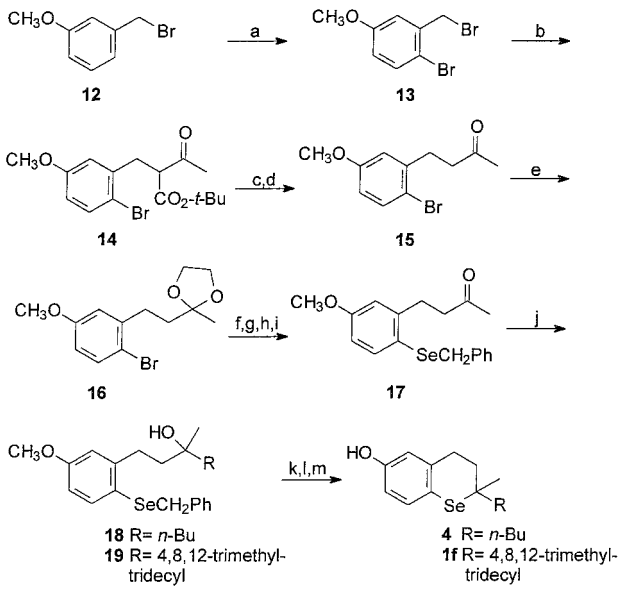
(10) Schiesser, C. H.; Sutej, K. *Tetrahedron Lett.* **1992**, *33*, 5137. Lyons, J. E.; Schiesser, C. H.; Sutej, K. *J. Org. Chem.* **1993**, *58*, 5632. Fong, M. C.; Schiesser, C. H. *Tetrahedron Lett.* **1995**, *36*, 7329. Fong, M. C.; Schiesser, C. H. *J. Org. Chem.* **1997**, *62*, 3103. Lucas, M. A.; Schiesser, C. H. *J. Org. Chem.* **1998**, *63*, 3032. Laws, M. J.; Schiesser, C. H. *Tetrahedron Lett.* **1997**, *38*, 8429. Schiesser, C. H.; Zheng, S.-L. *Tetrahedron Lett.* **1999**, *40*, 5095. Engman, L.; Laws, M. J.; Malmström, J.; Schiesser, C. H.; Zugaro, L. M. *J. Org. Chem.* **1999**, *64*, 6764. Lucas, M. A.; Nguyen, O. T. K.; Schiesser, C. H.; Zheng, S.-L. *Tetrahedron* **2000**, *56*, 3995.

(11) Schiesser, C. H.; Sutej, K. *J. Chem. Soc., Chem. Commun.* **1992**, 57. Benjamin, L. J.; Schiesser, C. H.; Sutej, K. *Tetrahedron* **1993**, *49*, 2557.

(12) Barton, D. H. R.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1984**, 774. Barton, D. H. R.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1603. Barton, D. H. R.; Crich, D.; *Tetrahedron Lett.* **1985**, *26*, 757. Crich, D.; Fortt, S. M. *Synthesis* **1987**, 35.

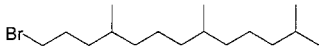
(13) Beard, W. Q., Jr.; van Eenam, D. N.; Hauser, C. R. *J. Org. Chem.* **1961**, *26*, 2310.

Scheme 3[a]



[a] Key: (a) Br_2, $CHCl_3$, 97%. (b) *tert*-Butyl acetoacetate, NaH, THF, 71%. (c) 6 M HCl. (d) heat, quantitative from **14**. (e) Ethylene glycol, *p*-TsOH·H_2O, C_6H_6, 97%. (f) *t*-BuLi, THF. (g) Elemental Se. (h) Benzyl bromide. (i) 3 M HCl, 78% from **16**. (j) Mg, *n*-BuBr, Et_2O, 74% of **18**; Mg, 4,8,12-trimethyltridecyl bromide, Et_2O, 54% of **19. (**k) Oxalyl chloride, C_6H_6. (l) Sodium salt of 2-mercaptopyridine *N*-oxide, DMAP, C_6H_6. (m) BBr_3, CH_2Cl_2, 48 % of **4** from **18**; 62% of **1f** from **19**.

16 proceeded in excellent yield (97%). Compound **16** was lithiated, selenium was inserted into the carbon−lithium bond, and the lithium selenolate was benzylated in situ. After workup, the crude material was subjected to deprotection with hydrochloric acid to furnish selenide **17** in 78% isolated yield from compound **16**. The desired tertiary alcohol **18** was conveniently prepared in 74% yield by treatment of ketone **17** with *n*-butylmagnesium bromide under standard Grignard conditions. Ring closure was achieved as described previously for compound **10**. Accordingly, the alcohol **18** was treated with oxalyl chloride in benzene, followed by the sodium salt of 2-mercaptopyridine *N*-oxide and DMAP, to obtain the desired cyclized selenide in moderate yield. The crude product was subjected to treatment with boron tribromide in CH_2Cl_2 to furnish the desired selenochromane **4** in 48% isolated yield from compound **18**. The selenium-containing analogue **1f** was prepared as outlined in Scheme 3. To introduce the racemic vitamin E side chain, bromide **20** was first prepared following a modified literature



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procedure from commercially available farnesol.[14] Subsequent conversion of **20** into the corresponding Grignard reagent and treatment with ketone **17** afforded the tertiary alcohol **19** in 54% isolated yield. This compound was then subjected to the Barton/Crich procedure as described previously; selenide **1f** was isolated in 62% yield from compound **19** as a mixture of diastereomers.

(14) Aldrich, J. R.; Oliver, J. E.; Lusby, W. R.; Kochansky, J. P.; Borges, M. *J. Chem. Ecol.* **1994**, *20*, 1103. Cohen, N.; Schaer, B. *J. Org. Chem.* **1992**, *57*, 5783.

In summary, we have demonstrated the first examples of intramolecular homolytic substitution of tertiary radicals at selenium by employing the Barton/Crich protocol for the preparation of 2,2-dibutylselenane and two selenochromane tocopherol analogues. Currently, we are exploring this chemistry for the preparation of the selenium-containing α-tocopherol analogue **1g**.

Experimental Section

3-(Bromomethyl)-1-methoxybenzene[13] and 4,8,12-trimethyltridecyl bromide[14] were prepared according to literature procedures. Melting points are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Varian unity 400 spectrometer. For proton spectra, the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm), while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. ^{77}Se NMR chemical shifts are given in ppm relative to externally referenced diphenyl diselenide (δ 464). EI mass spectra were recorded at 70 eV. M^+ ions are given for ^{80}Se. Unless otherwise stated, the mass spectra were recorded via direct inlet. Merck 60 or MATREX LC 60A/35-70MY 80/25 85040 (GRACE Davison) silica gel was used for flash column chromatography. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium/benzophenone. Benzene and pyridine were distilled under nitrogen from calcium hydride. Elemental analyses were performed by Chemical and Micro Analytical services Pty. Ltd, Geelong, Victoria, Australia, or by Analytical Laboratories, Lindlar, Germany.

Methyl 5-Benzylselenenylvalerate (9). Sodium borohydride was added, in portions under nitrogen, to a suspension of dibenzyl diselenide (1.81 g, 5.32 mmol) in absolute ethanol (150 mL) until the characteristic yellow color of the diselenide had disappeared. Methyl 5-bromovalerate (**8**) (2.00 g, 10.3 mmol) was added, and the reaction mixture was stirred at ambient temperature for 18 h. Water and diethyl ether were added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (pentane/EtOAc 97.5:2.5) gave the title compound (2.79 g, 95%) as a colorless oil. ^{1}H NMR: δ 1.66 (4H, m), 2.29 (2H, m), 2.47 (2H, m), 3.66 (3H, s), 3.77 (2H, s), 7.16−7.30 (5H, m). ^{13}C NMR: δ 23.2, 25.1, 26.9, 29.6, 33.4, 51.5, 126.6, 128.4, 128.7, 139.4, 173.7. ^{77}Se NMR: δ 255. Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.36. Found: C, 54.37; H, 5.97.

1-Benzylselenenyl-5-butyl-5-nonanol (10). To a suspension of magnesium (442 mg, 18.2 mmol) in dry diethyl ether (50 mL), under nitrogen, was added *n*-butyl bromide (2.0 mL, 18.2 mmol) under reflux. The reaction mixture was then stirred at reflux for 3 h. Compound **9** (2.47 g, 8.66 mmol) dissolved in diethyl ether (15 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at ambient temperature for 18 h. NH_4Cl was added, and the layers were separated. The aqueous phase was extracted with diethyl ether (3×), and the combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (pentane and then pentane/EtOAc 95:5) gave the title compound (2.43 g, 76%) as a pale yellow oil. ^{1}H NMR: δ 0.91 (6H, t, J = 6.7 Hz), 1.12 (1H, br s), 1.19−1.42 (16H, m), 1.60 (2H, t, J = 7.4 Hz), 2.50 (2H, m), 3.77 (2H, s), 7.16−7.30 (5H, m). ^{13}C NMR: δ 14.1, 23.3, 23.8, 23.9, 25.7, 26.9, 30.8, 38.7, 38.9, 74.2, 126.6, 128.4, 128.8, 139.5. ^{77}Se NMR: δ 254. Anal. Calcd for $C_{20}H_{34}OSe$: C, 65.02; H, 9.28. Found: C, 64.98; H, 9.09.

2,2-Dibutyl Selenane (7). The alcohol **10** (199 mg, 0.538 mmol) was treated with oxalyl chloride (1 mL) in benzene (3 mL) for 18 h at ambient temperature under an atmosphere of dry nitrogen. After the reaction mixture was evaporated to dryness under reduced pressure, the residue was taken up in benzene (2 mL) and added over 10 min to a stirred suspension of the sodium salt of 2-mercaptopyridine *N*-oxide (88 mg, 0.65 mmol) and DMAP (7 mg, 0.057 mmol) in benzene (4 mL) at

reflux, under nitrogen. The reaction mixture was then stirred at reflux for 2 h. After the reaction mixture was filtered through a plug of Celite, the crude material was purified by flash chromatography (hexane) to give the title compound (56 mg, 40%) as a pale yellow oil. ^{1}H NMR: δ 0.93 (6H, m), 1.18−1.38 (8H, m), 1.54−1.72 (6H, m), 1.81 (2H, m), 1.88 (2H, m), 2.66 (2H, m). ^{13}C NMR: δ 14.1, 18.3, 22.6, 23.2, 26.2, 27.9, 38.5(3), 38.5(6), 44.7. ^{77}Se NMR: δ 303. GC−MS *m*/*z* (relative intensity): 262 (M^+, 85.1). HRMS: calcd for $C_{13}H_{26}Se$, 262.1199; found, 262.1168.

4-Bromo-3-(bromomethyl)-1-methoxybenzene (13). To a solution of compound **12** (2.02 g, 10.1 mmol) in chloroform (40 mL) was added bromine (525 μL, 10.1 mmol), dissolved in chloroform (20 mL), dropwise at ambient temperature. The reaction mixture was then stirred at ambient temperature for 18 h. Sodium thiosulfate (aqueous) was added, and the phases were separated. The aqueous phase was extracted with dichloromethane (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give the product (2.73 g, 97%) as white crystals, which were used in the next step without further purification. The NMR data were in good agreement with the literature.[15]

***tert*-Butyl-2-(2-bromo-5-methoxybenzyl) Acetoacetate (14).** To a suspension of NaH (80% in mineral oil) (161 mg, 5.36 mmol) in dry THF, under nitrogen, was added *tert*-butyl acetoacetate (890 μL, 5.36 mmol) at 0 °C, and the mixture was stirred for 2.5 h at ambient temperature before compound **13** (500 mg, 1.79 mmol) was added. The reaction mixture was then stirred overnight at ambient temperature. Water and diethyl ether were added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give the crude material. The excess of *tert*-butyl acetoacetate was then removed by Kugelrohr distillation. Chromatography on silica gel (hexane/EtOAc 95:5) gave the product (454 mg, 71%) as a colorless oil. ^{1}H NMR: δ 1.40 (9H, s), 2.22 (3H, s), 3.14 (1H, dd, J = 14.0, 8.3 Hz), 3.22 (1H, dd, J = 14.0, 6.6 Hz), 3.75 (3H, s), 3.84 (1H, dd, J = 8.4, 6.5 Hz), 6.65 (1H, dd, J = 8.8, 3.1 Hz), 6.80 (1H, d, J = 3.1 Hz), 7.40 (1H, d, J = 8.8 Hz). ^{13}C NMR: δ 27.9, 29.6, 34.3, 55.4, 59.8, 82.1, 114.3, 114.8, 117.1, 133.3, 138.6, 158.8, 168.0, 202.5. Anal. Calcd for $C_{16}H_{21}BrO_4$: C, 53.79; H, 5.93. Found: C, 53.96; H, 6.08.

4-(2-Bromo-5-methoxyphenyl)-2-butanone (15). To compound **14** (1.98 g, 5.55 mmol) was added 6 M hydrochloric acid (40 mL), and the reaction mixture was stirred overnight at ambient temperature. Then, another 10 mL of concentrated HCl was added, and the reaction mixture was stirred for 24 h. Because hydrolysis was not complete, another 10 mL of concentrated HCl was added, and the reaction mixture was stirred for another 24 h. During the reaction, the carboxylic acid was partly decarboxylated. Diethyl ether was added, and the phases were separated. The solvent was evaporated, and the crude material was heated neat at 130 °C for 3 h. Diethyl ether was added, and the organic phase was dried ($MgSO_4$), filtered, and evaporated to give the title compound (1.42 g, 100%) as white crystals: mp 34.0−34.5 °C. ^{1}H NMR: δ 2.16 (3H, s), 2.76 (2H, m), 2.96 (2H, m), 3.77 (3H, s), 6.63 (1H, dd, J = 8.8, 3.1 Hz), 6.79 (1H, d, J = 3.1 Hz), 7.39 (1H, d, J = 8.8 Hz). ^{13}C NMR: δ 30.0, 30.5, 43.4, 55.4, 113.6, 114.6, 116.2, 133.3, 141.2, 159.0, 207.4. Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10. Found: C, 51.25; H, 4.97.

2-[2-(2-Bromo-5-methoxyphenyl)ethyl]-2-methyl-1,3-dioxolane (16). To a solution of compound **15** (1.456 g, 5.66 mmol) in benzene (40 mL) were added *p*-TsOH hydrate (108 mg, 0.566 mmol) and ethylene glycol (530 mL, 8.49 mmol). The reaction mixture was refluxed overnight with azeotropic removal of water. The solvent was evaporated, water and diethyl ether were added, and the layers were separated. The aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated to give the title compound (1.648 g, 97%) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR: δ 1.41 (3H, s), 1.94 (2H, m), 2.79 (2H, m), 3.77 (3H, s), 4.00 (4H, m), 6.62 (1H, dd, J = 8.7, 3.1 Hz), 6.79 (1H, d, J = 3.1 Hz), 7.39 (1H, d, J = 8.7 Hz). ^{13}C NMR: δ 23.9, 31.1, 39.0, 55.4, 64.8, 109.5, 113.2, 114.8, 115.8, 133.2, 142.4, 159.0.

2-(2-Benzylselenenyl-5-methoxyphenyl)ethyl Methyl Ketone (17). To a solution of compound **16** (750 mg, 2.49 mmol) in dry THF (30 mL), under nitrogen, was added *t*-BuLi (3.8 mL, 1.38 M) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, and then elemental selenium (200 mg, 2.49 mmol) was added in one portion. The reaction mixture was then stirred at ambient temperature for 30 min. Finally, benzyl bromide (325 μL, 2.74 mmol) was added, and the reaction mixture was stirred overnight at ambient temperature. NH_4Cl(aq) was added, and the aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. To a solution of crude selenide (497 mg, 1.27 mmol) in THF (6 mL) was added HCl (3 M, 5 mL). The reaction mixture was stirred at ambient temperature for 18 h. Water and diethyl ether were added, and the layers were separated. The aqueous phase was extracted with diethyl ether (3×). The combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (pentane/EtOAc 90:10) gave the title compound (674 mg, 78% from **16**) as white crystals: mp 47−48 °C. ^{1}H NMR: δ 2.07 (3H, s), 2.49 (2H, m), 2.87 (2H, m), 3.78 (3H, s), 3.95 (2H, s), 6.66 (1H, dd, J = 8.5, 2.9 Hz), 6.73 (1H, d, J = 2.9 Hz), 7.06 (2H, m), 7.20 (3H, m), 7.42 (1H, d, J = 8.5 Hz). ^{13}C NMR: δ 29.8, 30.6, 33.2, 44.8, 55.2, 112.6, 114.9, 120.5, 126.7, 128.3, 128.7, 138.0, 139.0, 146.0, 159.9, 207.8. ^{77}Se NMR: δ 319. Anal. Calcd for $C_{18}H_{20}O_2Se$: C, 62.25; H, 5.80. Found: C, 61.98; H, 5.65.

1-(2-Benzylselenenyl-5-methoxyphenyl)-3-methyl-3-heptanol (18). To a suspension of magnesium (92 mg, 3.74 mmol) in dry diethyl ether (10 mL), under nitrogen, was added *n*-butyl bromide (405 μL, 3.74 mmol) under reflux. The reaction mixture was then stirred at reflux for 5 h. Compound **17** (1.005 g, 2.89 mmol) dissolved in diethyl ether (5 mL) was added dropwise at 0 °C, and the reaction mixture was stirred at ambient temperature for 18 h. NH_4Cl(aq) was added, and the layers were separated. The aqueous phase was extracted with diethyl ether (3×), and the combined organic phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (hexane/EtOAc 90:10) gave the title compound (0.873 g, 74%) as a pale yellow oil. ^{1}H NMR: δ 0.92 (3H, m), 1.17 (3H, s), 1.31 (4H, m), 1.45 (2H, m), 1.55 (2H, m), 2.64 (2H, m), 3.79 (3H, s), 3.95 (2H, s), 6.65 (1H, dd, J = 8.5, 2.9 Hz), 6.75 (1H, d, J = 2.9 Hz), 7.08 (2H, m), 7.20 (3H, m), 7.42 (1H, d, J = 8.5 Hz). ^{13}C NMR: δ 14.1, 23.3, 26.2, 26.7, 31.1, 33.2, 41.6, 43.5, 55.2, 72.7, 112.2, 114.8, 120.7, 126.6, 128.3, 128.7, 137.9, 139.1, 147.7, 159.9. ^{77}Se NMR: δ 316. Anal. Calcd for $C_{22}H_{30}O_2Se$: C, 65.17; H, 7.46. Found: C, 65.05; H, 7.42.

2-Butyl-2-methylselenochroman-6-ol (4). The selenide **18** (0.18 g, 0.443 mmol) was treated with oxalyl chloride (0.5 mL) in benzene (3 mL) for 18 h at ambient temperature under an atmosphere of dry nitrogen. After the reaction mixture was evaporated 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 (79 mg, 0.532 mmol) and DMAP (5.4 mg, 0.044 mmol) in benzene (3 mL) at reflux, under nitrogen. The reaction mixture was stirred at reflux for 2.5 h. After the reaction mixture was filtered through a plug of Celite, the crude material was purified by flash chromatography (hexane/EtOAc 97.5:2.5) to give almost pure 2-butyl-6-methoxy-2-methylselenochromane (70 mg, 53%). To a solution of this material (45 mg, 0.15 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added BBr_3 (290 μL, 0.29 mmol), under nitrogen at −78 °C. The reaction was then allowed to reach ambient temperature, and the mixture was stirred for 22 h. Water and diethyl ether were added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3×), and the combined organic

(15) Hoye, T. R.; Mi, L. *J. Org. Chem.* **1997**, *62*, 8586.

phases were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Chromatography on silica gel (hexane/EtOAc 95:5) gave the title compound (39 mg, 91%) as a colorless oil. ^{1}H NMR: δ 0.91 (3H, t, J = 7.3 Hz), 1.33 (2H, m), 1.43 (2H, m), 1.54 (3H, s), 1.66−1.87 (4H, m), 2.79 (2H, m), 4.61 (1H, s), 6.59 (1H, dd, J = 8.3, 2.8 Hz), 6.66 (1H, d, J = 2.8 Hz), 7.10 (1H, d, J = 8.3 Hz). ^{13}C NMR: δ 14.1, 23.2, 27.3, 29.2, 30.0, 38.4, 44.4, 46.6, 114.2, 116.3, 120.2, 130.3, 138.8, 153.1. ^{77}Se NMR: δ 380. MS m/z (relative intensity): 284 (M^+, 100.0). HRMS: calcd for $C_{14}H_{20}OSe$, 284.0679; found, 284.0636.

1-(2-Benzylselenenyl-5-methoxyphenyl)-3,7,11,15-tetramethyl-3-hexadecanol (19). The title compound was prepared using the procedure for compound **18**. Treatment of ketone **17** (1.51 g, 4.35 mmol) with the Grignard reagent of bromide **20** gave after flash chromatography (pentane/EtOAc 90:10) compound **19** (1.36 g, 54%) as a colorless oil. ^{1}H NMR: δ 0.86 (12H, m), 1.00−1.62 (27H, m), 2.64 (2H, m), 3.79 (3H, s), 3.95 (2H, s), 6.65 (1H, dd, J = 8.4, 2.9 Hz), 6.74 (1H, d, J = 2.9 Hz), 7.08 (2H, m), 7.20 (3H, m), 7.42 (1H, d, J = 8.4 Hz). ^{13}C NMR: δ (some characteristic peaks) 55.2, 72.7, 112.2, 114.8, 120.7, 126.7, 128.3, 128.7, 137.9, 139.1, 147.7, 159.9. ^{77}Se NMR: δ 316 (0.8), 316 (0.9). MS m/z (relative intensity): 574 (M^+, 12.9). HRMS: calcd for $C_{34}H_{54}O_2Se$, 574.3289; found, 574.3276.

2-Methyl-2-(4,8,12-trimethyltridecyl)selenochroman-6-ol (1f). The title compound was prepared using the procedure for compound **4**. Treatment of selenide **19** (0.45 g, 0.784 mmol) as described gave after flash chromatography on silica gel (pentane/EtOAc 97.5:2.5) almost pure 6-methoxy-2-methyl-2-(4,8,12-trimethyltridecyl)selenochromane (235 mg, 65%). Demethylation of this material (130 mg, 0.281 mmol) afforded the title compound (121 mg, 96%) as a colorless oil. ^{1}H NMR: δ 0.86 (12H, m), 1.02−1.91 (26H, m), 2.79 (2H, m), 4.54 (1H, br s), 6.59 (1H, dd, J = 8.3, 2.8 Hz), 6.66 (1H, d, J = 2.8 Hz), 7.10 (1H, d, J = 8.3 Hz). ^{13}C NMR: δ (some characteristic peaks) 46.7, 114.2, 116.3, 120.3, 130.3, 138.8, 153.1. ^{77}Se NMR: δ 380 (0.5), 381 (0.7), 381 (0.9). MS m/z (relative intensity): 452 (M^+, 100.0). HRMS: calcd for $C_{26}H_{44}OSe$, 452.2557; found, 452.2522.

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Supporting Information Available: ^{1}H and ^{13}C spectra of compounds **1f**, **4**, **7**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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