35: ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.40 (m, 3 H), 6.36, 6.06 (s, 1 H), 3.70 (s, 3 H), 2.33 (s, 3 H); IR (KBr) 1660 cm^{-1}; FDMS, m/e 176 ($C_{11}H_{12}O_2$).

Addition of Sodium Thiophenoxide to 9. Thiophenol (0.17 g, 1.5 mmol) was added to 5 mL of 1 M sodium methoxide in methanol. The resulting solution was added to a solution of **9** (0.35 g, 0.61 mmol) in 10 mL of CH_2Cl_2, giving an exothermic reaction that precipitated Te metal. The reaction mixture was diluted with ether (75 mL). The resulting solution was washed with water (2 × 50 mL), filtered through Celite, dried over sodium sulfate, and concentrated. Recrystallization from hexanes gave 0.14 g (74%) of **37**: mp 106.5–108.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2 H), 7.53 (s, 1 H), 7.50 (m, 2 H), 7.17 (m, 6 H); IR (KBr) 1640, 1510, 1493, 1240, 950 cm^{-1}; FDMS, m/e 316 ($C_{21}H_{16}OS$). Anal. Calcd for $C_{21}H_{16}OS$: C, 79.7; H, 5.1; S, 10.1. Found: C, 79.4; H, 5.2; S, 10.6.

Addition of Sodium Thiophenoxide to 27. The procedure described for **9** was repeated with 0.30 g (0.50 mmol) of **27**. Crude **38** was recrystallized from hexanes to give 0.14 g (82%) of **38**: mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 3 H), 7.6–7.0 (m, 11 H), 7.35 (s, 1 H); IR (KBr) 1640 cm^{-1}; FDMS, m/e 334 ($C_{21}H_{15}OS$).

Lithium Triethylborohydride Reduction of 21. Oxatellurolylium chloride **21** (0.293 g, 1.00 mmol) was dissolved in 5 mL of dry THF. Lithium triethylborohydride (1.10 mL, 1 M in THF) was added via syringe. The resulting solution was stirred for 2.0 h at ambient temperature. The reaction mixture was concentrated. The residue was purified by chromatography on silica gel to give 0.18 g (92%) of **41**: mp 215–216 °C; ^{1}H NMR ($CDCl_3$) δ 9.00 (d, 2 H, J = 9 Hz), 8.30 (d, 2 H, J = 9 Hz), 8.10 (m, 4 H), 7.53 (m, 6 H); IR (KBr) 1610, 1500, 1240, 1010, 742 cm^{-1}; λ_{max} (CH_2Cl_2) (log ϵ) 425 nm (4.77); FDMS, m/e 392 ($C_{18}H_{14}O_2{}^{130}Te$). Anal. Calcd for $C_{18}H_{14}O_2Te$: C, 55.4; H, 3.6; Te, 32.7. Found: C, 55.3; H, 3.6; Te, 33.3.

Lithium Triethylborohydride Reduction of 14. The procedure described for **21** was repeated with 0.29 g (0.78 mmol) of **14**, giving 0.11 g (53%) of **40** as an orange solid: mp 160–163 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 4 H), 7.77 (s, 2 H), 7.52 (m, 6 H), 7.4–6.8 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 190.7, 151.3, 137.6, 133.0, 128.8, 128.4, 127.3; IR (KBr) 1610, 1595, 1570, 1500, 1480, 1225, 745, 685 cm^{-1}; λ_{max} (CH_2Cl_2) (log ϵ) 452 nm (4.36); FDMS, m/e 544 ($C_{30}H_{22}O_2{}^{130}Te$). Anal. Calcd for $C_{30}H_{22}O_2Te$: C, 66.5; H, 4.1; Te, 23.6. Found: C, 66.6; H, 4.1; Te, 23.9.

Registry No. **8**, 99654-55-4; **9**, 99654-54-3; **10**, 87761-70-4; **11**, 87761-67-9; **14**, 99654-54-3; **15**, 99654-53-2; **16**, 82531-87-1; **17**, 82531-84-8; **18**, 99654-57-6; **19**, 99654-58-7; **20**, 82531-97-3; **21**, 82531-88-2; **22**, 100993-57-5; **23**, 99654-61-2; **24**, 99654-62-3; **25**, 99654-59-8; **26**, 99654-56-5; **27**, 99654-60-1; **28**, 100993-53-1; **29**, 100993-54-2; **30**, 100993-55-3; **31**, 100993-56-4; **32**, 101009-43-2; **33**, 100993-60-0; **34**, 99654-63-4; (*E*)-**35**, 50487-01-9; (*Z*)-**35**, 50515-43-0; (*E*)-**36**, 101009-45-4; (*Z*)-**36**, 101009-48-7; **37**, 53656-87-4; **38**, 101009-46-5; **40**, 101009-44-3; **41**, 100993-58-6; 3-(*p*-methoxyphenyl)-5-phenyl-1,2-oxatellurolyl-1-ium chloride, 84280-84-2; 3-(*p*-*tert*-butylphenyl)-5-phenyl-1,2-oxatellurolyl-1-ium chloride, 100993-59-7; 3-methyl-5-(*p*-(*N*,*N*-dimethylamino)-phenyl)-1,2-oxatellurolyl-1-ium chloride, 101009-47-6; 3-phenyl-5-(α-methylphenyl)-1,2-oxatellurolyl-1-ium chloride, 84281-07-2.

Supplementary Material Available: Tables VII–X, showing crystal data for **9**, positional and thermal parameters, general temperature factor expressions, and bond angles involving Te (3 pages). Ordering information is given on any current masthead page.

Synthesis of 2-Substituted 5,7,8-Trimethyl-6-hydroxythiochromans and Purported Syntheses of Sulfur-Containing Analogues of Vitamin E[1]

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The syntheses of 5,7,8-trimethyl-, 2,5,7,8-tetramethyl-, and 2,2,5,7,8-pentamethyl-6-hydroxythiochromans have been achieved by a Michael-type condensation of methyl acrylate and related methyl esters with 2,3,5-trimethyl-4-hydroxythiochromans followed by cyclization of the free acid and reduction. These three previously unknown compounds can serve as simple models for the still unknown 1-thia-α-tocopherol (**1**), which could not be prepared by this route. Indeed, two purported syntheses of **1**[8,9] have been shown to yield an essentially identical mixture of five isomers of the desired compound. For three components in this mixture, including the two major products, it is highly probable that the initial condensation at sulfur has not been followed by ring closure.

Vitamin E is the major lipid-soluble, chain-breaking antioxidant present in human blood.[3,4] α-Tocopherol, the main component of vitamin E, and other alkylated 6-hydroxychromans are excellent antioxidants in vitro.[5] Detailed structure–activity studies led us to synthesize alkylated 5-hydroxydihydrobenzofurans which were found, as predicted, to be even better antioxidants than the 6-hydroxychromans.[6,7] We wished to extend these studies to the sulfur-containing analogue of α-tocopherol, **1**, since this compound would also be expected to be an excellent antioxidant. The purported synthesis of **1** and related compounds was first reported in 1944[8] and again in 1982.[9] We repeated both syntheses and found that they do not yield **1** in significant amounts (vide infra). We therefore developed, and report herein, a short synthesis of three model 6-hydroxythiochromans **2** (R_1 and R_2 = H or CH_3).

Although there are various potential synthetic approaches to **1** and **2**[10–14] reagents containing a free phenolic

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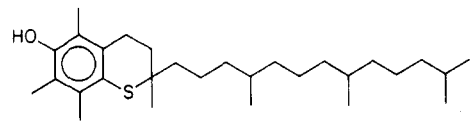
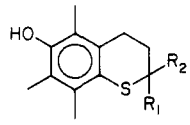


1



2

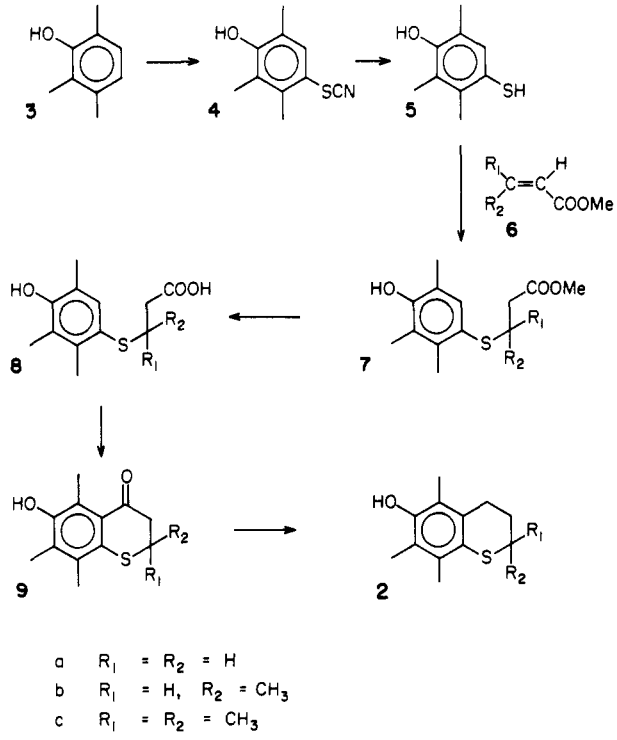
OH groups have not been employed. Our route to **2**, which is outlined in Scheme I, does not involve protection and subsequent deprotection[15] of this hydroxyl group. Our key intermediate is 2,3,5-trimethyl-4-hydroxybenzenethiol (**5**), which was obtained in an overall yield of 60% from 2,3,6-trimethylphenol (**3**). This phenol was dissolved in dry methanol containing ammonium thiocyanate; the solution was cooled to 0 °C and bubbled with chlorine.[16] Removal of the ammonium chloride (filtration) and solvent (reduced pressure) yielded the thiocyanate **4**, which was reduced to **5** with $LiAlH_4$,[17] without further purification. Compound **5** was shown to be the authentic material by comparison with a sample prepared by the procedure of Karrer and Leiser.[8]

The esters **7a–c** were obtained by a Michael-type addition of **5** to **6a–c** in deoxygenated methanol containing catalytic amounts of concentrated H_2SO_4 and trimethyl orthoformate. Our attempts to cyclize these esters directly to the thiochromanones **9** were not very successful. The esters were therefore first converted to the free acids **8** by a basic hydrolysis in methanol, and the acids were then cyclized using concentrated H_2SO_4. The desired compounds **2a–c** were obtained by reduction of the corresponding **9** in a mixture of toluene/aqueous HCl containing Zn/Hg amalgam (the Clemmensen–Martin method[18]). Analyses, yields and some spectroscopic data for **7a–c**, **8a–c**, **9a–c**, and **2a–c** are given in the Experimental Section.

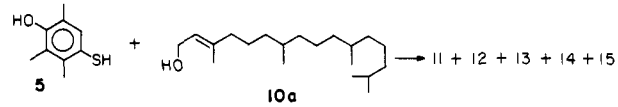
The condensation of **5** with **6** ($R_1 = CH_3$, R_2 = phytyl) did not occur under the conditions described above nor were we able to effect this condensation under a variety of other conditions. We are therefore attempting to develop a new synthetic route to the desired 1-thia-α-tocopherol. The absolute in vitro antioxidant activities of **2a–c** and certain related compounds will be measured by our usual procedure[5,7] and will be reported at a later date.

Purported Syntheses of 1. Karrer and Leiser[8] reported in 1944 that **1** was obtained by reaction of **5** with phytol (**10a**) in formic acid. We repeated this reaction exactly as it is described[8] and isolated and purified a fraction corresponding to the described product. Although this fraction gave only a single spot by thin-layer chromatography, an analysis by GC/MS shows that it is actually a mixture of five isomers, **11–15**, with compounds **11** and **13** being the major components in the mixture.

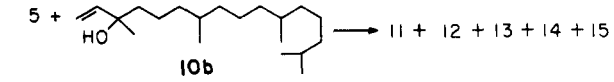
Scheme I



a $R_1 = R_2 = H$
b $R_1 = H$, $R_2 = CH_3$
c $R_1 = R_2 = CH_3$

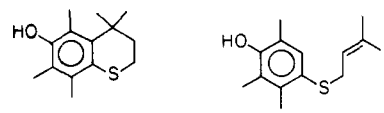


In 1982, Valashek et al.[9] reported that **1** was obtained by reaction of **5** with isophytol (**10b**) in butyl acetate containing $ZnCl_2$ and $Na_2S_2O_4$. Upon isolation and analysis of the fraction corresponding to that described as **1**,[9] we found that this fraction was also a mixture of the same five compounds, **11–15**, and that its composition was essentially



the same as that obtained following the 1944 procedure (see Table I). The earlier claims that **1** had been synthesized and isolated relied either wholly on the elemental analysis[8] or on the elemental analysis and mass spectrum.[9]

The five compounds that we have detected by GC/MS fall into two well defined classes. Comparison of their mass spectra (see Table II) with those of model compounds **2a–c**, **7a–c**, **16**,[7] and **17** reveal whether or not the heterocyclic ring has or has not been formed.



16 **17**

With the exception of **7a**, the ring-opened model compounds, **7a–c**, and **17**, give intense peaks at m/e 168 (which corresponds to the molecular ion of **2**) and significant peaks at m/e 167. By contrast, both of these peaks have a negligible relative intensity (≤1%) for the ring-closed model compounds **2a–c** and **16**. It seems probable that compounds **11–13** with their principal ion having m/e 168 are ring-opened adducts of **5** and **10a** (or **10b**) and that **14**

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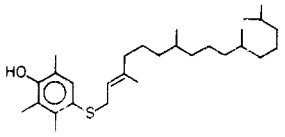
Table I. Products Formed by Reaction of 5 with 10a or 10b

reagents	reacn conditions	ref	overall yield,[a] %	VPC analysis, %[b] 11	12	13	14	15
5 + 10a	HCOOH, reflux, 5 h	8	52	26	8	44	10	12
5 + 10b	HCOOH, reflux, 5 h	c	55	25	8	44	11	12
5 + 10b	BuOAc, H^+ cat., $ZnCl_2$, $Na_2S_2O_4$, reflux, 30 min	9	82	28	9	42	10	11
			Retention Times[d]	5.95	6.65	7.30	7.75	8.0

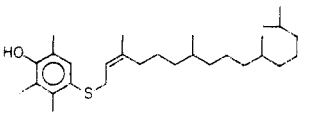
[a] Based on starting 5. [b] Based on integrated peak area. [c] This work. [d] In min.

and 15 are ring-closed adducts.

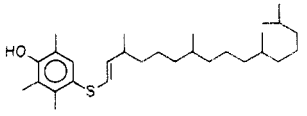
The 500-MHz ^1H NMR spectrum of the 11–15 product mixture formed by reaction of 5 with 10b (see supplementary material) allowed us to identify the two major products, 11 and 13, and served to confirm the conclusions reached from analysis of the GC/MS data. The spectrum showed two singlets at 7.125 and 7.116 ppm, which indicated that two major products were formed, both of which contained an aromatic proton and hence had not undergone ring closure. The intensities of these two NMR signals indicated that these two compounds were present in a ratio of ca. 1.0:1.7, which corresponds to the GC and GC/MS ratio of [11]:[13] Table I). The spectrum also showed a doublet at 3.34 ppm (corresponding to two protons), which is at the position expected for $ArSCH_2R$ protons,[19] and two multiplets centered at 5.15 and 5.27 ppm which must be due to two different vinylic protons. The latter were shown to be coupled to the protons centered at 3.34 ppm by proton decoupling. Integration of the various signals showed that the two single aromatic protons at 7.125 and 7.116 ppm correspond to the two single vinylic protons at 5.15 and 5.27 ppm, respectively. On the above evidence we identify the two main products, 11 and 13, as the *E* and *Z* (or *Z* and *E*) ring-opened isomers shown. We believe that the third ring-opened compound, 12, is most likely to be an isomer of 11 and 13 in which the double bond has migrated.



11 (or 13)

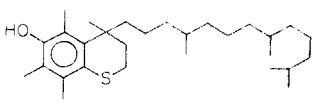


13 (or 11)



12

Comparison of the mass spectra of the two ring-closed adducts 14 and 15 with those of the model ring-closed compounds, particularly 2c and 16 (see Table II) suggests that 14 might be the desired product, i.e., 1, and that 15 is an isomer with the phytyl and methyl groups attached to the carbon at position 4.



15

We are currently attempting to develop an efficient synthesis of 1-thia-α-tocopherol.

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Experimental Section

General. Reactions were carried out under an atmosphere of argon or nitrogen and their progress was monitored by TLC or GC. Thin-layer chromatography was performed on BDH silica gel 60F-254 plates eluted with hexane/ethyl acetate in the v/v ratio given in parenthesis after the R_f value. Spots were visualized by UV (254 nm) and by spraying with phosphomolybdic acid (3.5% in ethanol) and heating at 80 °C. Column chromatography was carried out under pressure (2–5 psi—flash chromatography) on silica gel, Merck 60 (230–400 mesh). ^1H NMR spectra were recorded on a Varian 60-MHz instrument in $CDCl_3/Me_4Si_{int}$ solvent unless otherwise noted. Gas chromatographs and mass spectra (electron impact, 70 eV) were recorded on a Hewlett-Packard 5970B mass selective detector using a 10-m, 0.2-mm i.d. Ultra I (cross-linked methyl silicone) column with column temperature = 280 °C, injection port = 320 °C, He flow = 1 cm^3/min. Melting points were determined on a Fisher 355 melting point apparatus and are uncorrected. Yields refer to isolated pure materials.

2,3,5-Trimethyl-4-hydroxyphenyl Thiocyanate (4). Recrystallized 2,3,6-trimethylphenol (3) (Aldrich, 16 g, 118 mmol) was dissolved in 500 mL of anhydrous methanol which had been deoxygenated by bubbling with nitrogen. Ammonium thiocyanate (22 g, 290 mmol) was added to this solution which was then cooled to 0 °C and bubbled with chlorine gas. The initially colorless homogeneous solution becomes pink and then green with the formation of a white precipitate. The solution was stirred for 1 h at 0 °C and then for a further hour at 20 °C. The dissolved chlorine was removed by bubbling with nitrogen and the precipitate removed by filtration. Evaporation of the filtrate under reduced pressure followed by drying under high vacuum (0.1 torr) yielded 4 in a form pure enough for the next step in the synthesis. An analytical sample was recrystallized from hexane: white crystals, mp 100.2 °C. Anal. Calcd for $C_{10}H_{11}ONS$: C, 62.14; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.74; N, 7.39. ^1H NMR δ 7.2 (1 H, s), 5.0 (1 H, s),[20] 2.4 (3 H, s), 2.2 (6 H, s).

2,3,5-Trimethyl-4-hydroxybenzenethiol (5). The thiocyanate 4 (4 g, 24 mmol) was dissolved in 200 mL of anhydrous ether containing 50 mL of anhydrous tetrahydrofuran. This solution was added dropwise over 1 h to 200 mL of anhydrous ether containing $LiAlH_4$ (0.9 g, 24 mmol) at room temperature. After a further hour at 20 °C the unreacted $LiAlH_4$ was destroyed by cooling the heterogeneous mixture to 0 °C and adding moist ether (50 mL), H_2O (50 mL), and 1.0 N HCl (50 mL). A further 50 mL of water was added, and the organic phase was separated and washed with water (2 × 50 mL), $NaHCO_3$ solution (2 × 50 mL), water (2 × 50 mL), and saturated NaCl (50 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered and the solvent removed under reduced pressure. Column chromatography with 5% ethyl acetate in hexane gave 5 as a white powder in 60% yield based on starting 3, mp 86 °C (lit.[8] mp 87 °C).

Condensation of 5 with 6a–c To Form 7a–c. The hydroxybenzenethiol 5 (1 g, 6 mmol) was dissolved in anhydrous methanol (100 mL) containing trimethyl orthoformate (1 mL, 9 mmol), and the solution was deoxygenated by bubbling with nitrogen. Methyl acrylate 6a (2.2 mL, 14 mmol) or methyl crotonate 6b (2 mL, 13 mmol) or methyl 3,3-dimethylacrylate 6c (2 mL, 12 mmol) was then added to this solution followed by 2 drops of concentrated H_2SO_4. The solution was refluxed for 3 days and cooled, and $NaHCO_3$ (0.5 g) was added. Solvent was removed under reduced pressure, and the crude product was chromatographed with 10%

(20) OH by D_2O exchange.

Table II. Principal Ions in the Mass Spectra of Model Compounds of Known Structures and of Reaction Products 11–15

model	M_r	m/e (rel intensity)
	Ring-Opened Products	
7a	254	254 (100)
		181 (23)
		168 (16)
		167 (67)
7b	268	268 (76)
		195 (14)
		168 (100)
		167 (32)
7c	282	282 (23)
		169 (11)
		168 (100)
		167 (12)
17	236	236 (40)
		168 (100)
		167 (13)
		135 (30)
11	446	446 (63)
		181 (58)
		168 (100)
		136 (14)
12	446	446 (38)
		181 (38)
		168 (100)
		136 (10)
13	446	446 (71)
		181 (53)
		168 (100)
		136 (13)
	Ring-Closed Products	
2a	208	208 (100)
		193 (14)
		180 (19)
		178 (12)
2b	222	222 (100)
		207 (33)
		193 (20)
		178 (22)
2c	236	236 (100)
		221 (20)
		193 (67)
		181 (38)
16	236	236 (100)
		221 (39)
		206 (20)
		188 (65)
14	446	446 (100)
		221 (60)
		193 (24)
		181 (25)
15	446	446 (64)
		221 (100)
		188 (26)
		187 (24)
	Mixture[a]	
ref 9 product		446 (not given)
		221 (not given)
		168 (not given)

[a] See text.

ethyl acetate in hexane. The products **7a–c** crystallized on concentration of the chromatography eluent under a stream of nitrogen and could be further purified by recrystallization from hexane. **7a**: yield (based on **5**), 64%; mp 68.4 °C; R_f 0.2 (8/2). Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.28; H, 7.10. ^{1}H NMR δ 7.1 (1 H, s), 4.7 (1 H, s),[20] 3.64 (3 H, s), 3.2–2.8 (2 H, m), 2.65–2.45 (2 H, m), 2.35 (3 H, s), 2.18 (6 H, s). **7b**: yield, 52%; mp 76.7 °C; R_f 0.32 (7/3). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 62.65; H, 7.56. ^{1}H NMR δ 7.1 (1 H, s), 5.3 (1 H, s),[20] 3.58 (3 H, s), 3.5–3.1 (1 H, m), 2.6–2.35 (2 H, m), 2.3 (3 H, s), 2.18 (6 H, s), 1.25 (3 H, d). **7c**: yield, 55%; mp 70.2 °C; R_f 0.57 (7/3). Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.79; H, 7.85. Found: C, 63.98; H, 7.90. ^{1}H NMR δ 7.15 (1 H, s), 5.5 (1 H, s),[20] 3.6 (3 H, s), 2.5 (2 H, s), 2.4 (3 H, s), 2.2 (6 H, s), 1.35 (6 H, s).

Conversion of the Esters 7a–c to the Acids 8a–c. To a stirred solution of **7** (**a**, 0.22 g; **b**, 0.24 g; **c**, 0.28 g; 1 mmol) dissolved in methanol (5 mL) was added 1 N NaOH (50 mL). The solution was maintained at room temperature for 1 h, following which 3 N HCl (25 mL) was added and the methanol was removed under partial vacuum. Storage at 4 °C overnight gave white crystals of **8**, which were filtered and dried. **8a**: yield (based on corresponding **7**), 83%; mp 154.5–155 °C; R_f 0.10 (7/3). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 60.45; H, 6.93. ^{1}H NMR δ 7.3 (1 H, s br),[20] 7.15 (1 H, s), 5.2 (1 H, s),[20] 3.2–2.8 (2 H, m), 2.65–2.5 (2 H, m), 2.4 (3 H, s), 2.2 (6 H, s). **8b**: yield, 72%; mp 162–164 °C; R_f 0.29 (7/3). Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13. Found: C, 61.81; H, 7.36. ^{1}H NMR δ 7.4 (2 H, s br),[20] 7.05 (1 H, s), 3.5–3.1 (1 H, m), 2.7–2.35 (5 H, s (CH_3 Ar) + m (CH_2COOMe)), 2.2 (6 H, s), 1.25 (3 H, d). **8c**: yield, 81%; mp 180 °C dec; R_f 0.30 (7/3). Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51. Found: C, 62.92; H, 7.62. ^{1}H NMR δ 6.95 (1 H, s), 6.8–6.0 (2 H, s br),[20] 2.5 (2 H, s), 2.35 (3 H, s), 2.17 (6 H, s), 1.35 (6 H, s).

Conversion of 8a–c to the Thiochromanones 9a–c. The acids **8** (**a**, 0.2 g, 0.83 mmol; **b**, 0.2 g, 0.8 mmol; **c**, 0.25 g, 0.9 mmol) were dissolved in concentrated H_2SO_4 (5 mL) to form homogeneous, dark red solutions. After 30 min at room temperature the solution was poured onto crushed ice (50 g). The resulting green mixture was extracted with ethyl acetate (100 mL), and the organic phase was washed with water (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), water (50 mL), and saturated NaCl (50 mL) and dried over anhydrous $MgSO_4$. The crude products **9a–c** obtained by filtration and solvent evaporation under reduced pressure were purified by chromatography using 12% ethyl acetate in hexane. **9a**: yield (based on corresponding **8**), 76%; mp 150.5–151 °C; R_f 0.36 (7/3). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35. Found: C, 64.64; H, 6.37. ^{1}H NMR δ 4.5 (1 H, s br),[20] 3.2–2.9 (4 H, m), 2.35 (3 H, s), 2.25 (6 H, s); MS, m/e (relative intensity) 222 (57), 194 (100), 166 (10). **9b**: yield, 75%; mp 167 °C; R_f 0.32 (8/2). Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 65.84; H, 6.75. ^{1}H NMR δ 4.0 (1 H, s),[20] 2.9–2.75 (1 H, m), 2.32 (3 H, s), 2.2–2.05 (8 H, s (2 CH_3 Ar) + m (CH_2CO)), 1.4 (3 H, d). MS, m/e (relative intensity) 236 (46), 194 (100), 166 (12). **9c**: yield, 72%; mp 131–132 °C; R_f 0.44 (8/2). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25. Found: C, 67.28; H, 7.21. ^{1}H NMR δ 4.9–4.65 (1 H, s br),[20] 2.78 (2 H, s), 2.45 (3 H, s), 2.2 (6 H, s), 1.4 (6 H, s); MS, m/e (relative intensity) 250 (34), 194 (100), 166 (8).

Conversion of 9a–c to the Thiochromans 2a–c. To a stirred solution of **9** (**a**, 0.18 g, 0.8 mmol; **b**, 0.15 g, 0.57 mmol; **c**, 0.19 g, 0.8 mmol) dissolved in toluene (5 mL) were added water (10 mL), concentrated HCl (2 mL), and the Clemmensen–Martin amalgam[18] (1 g). The heterogeneous mixture was refluxed for 2 h, at which time a further 1 mL of concentrated HCl was added and refluxing was continued for a further 3 h. The mixture was then cooled and filtered, and toluene (20 mL) was added to the filtrate. The organic phase was separated, washed with saturated $NaHCO_3$ and water, and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure yielded crude **2a–c**. These compounds, which are somewhat sensitive to air and to light, were purified by column chromatography (**2a**, using 5% ethyl acetate in hexane; **2b**, using 10% ethyl acetate in hexane) or preparative thin-layer chromatography (**2c**, using 25% ethyl acetate in hexane). **2a**: yield (based on corresponding **9**), 62%; mp 160–161 °C; R_f 0.63 (7/3). Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.54; H, 7.89. ^{1}H NMR (500 MHz) δ 4.46 (1 H, s),[20] 2.95–2.89 (2 H, m), 2.72 (2 H, t), 2.22–2.18–2.08 (11 H, 3 s (3 CH_3 Ar) + m (SCH_2CH_2)). **2b**: yield, 54%; mp 172.5 °C; R_f 0.48 (7/3). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.23; H, 8.16. Found: C, 70.31; H, 8.19. ^{1}H NMR (500 MHz) δ 4.44 (1 H, s),[20] 3.27–3.20 (1 H, m), 2.9 (1 H, t), 2.84 (1 H, t), 2.22 (3 H, s), 2.19 (2 H, t), 2.18 (3 H, s), 2.14 (3 H, s), 1.37 (3 H, d). **2c**: yield, 58%; mp 78.8 °C; R_f 0.72 (7/3). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 71.31; H, 8.61. ^{1}H NMR (500 MHz) δ 5.6–5.0 (1 H, s br),[20] 2.8 (2 H, t), 2.20 (3 H, s), 2.18 (3 H, s), 2.17 (3 H, s), 1.91 (2 H, t), 1.39 (6 H, s).

Condensation of 5 with 10a according to Ref 8 and of 5 with 10b by the Same Procedure. The hydroxybenzenethiol **5** (300 mg, 1.78 mmol) was dissolved in 5 mL formic acid, to which

was then added phytol (**10a**) or isophytol (**10b**) (620 mg, 2.09 mmol, both compounds (Aldrich) were used without purification). The solution was refluxed for 5 h, cooled, and poured onto crushed ice. Extraction with ether (50 mL) and washing of the ether extract with saturated $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), and saturated NaCl (2 × 50 mL) was followed by drying over anhydrous $MgSO_4$. The ether was removed under reduced pressure and the oily residue chromatographed with 5% ethyl acetate in hexane. The final product from both reactions was a yellow oil: yield, **5** + **10a** 415 mg (52%), **5** + **10b** 441 mg (55%). Anal. Calcd for $C_{29}H_{50}OS$: C, 77.96; H, 11.28; S, 7.17. Found (for **5** + **10a** only): C, 78.27; H, 11.48; S, 7.08. The literature[8] analysis was given only for the acetate.

Condensation of 5 with 10b according to Ref 9. Compound **5** (450 mg, 2.67 mmol) was dissolved in butyl acetate (1.5 mL) containing 100 mg of anhydrous, fused $ZnCl_2$ and 10 mg of $Na_2S_2O_4$. After heating for 10 min at 100 °C, isophytol (**10b**) (100 mg, 0.33 mmol) was added together with a drop of concentrated H_2SO_4. The solution was heated to 125 °C for 15 min and cooled, and a further 600 mg (2.02 mmol) of **10b** was added, followed by further heating at 125 °C for 10 min. After cooling, the oily product (yield, 1.0 g (82%)) was obtained by the addition of water. Isolation and purification were carried out as described above. Anal. Calcd for $C_{29}H_{50}OS$: C, 77.96; H, 11.28; S, 7.17. Found: C, 78.22; H, 11.48; S, 7.31. Lit.:[9] C, 77.27; H, 11.00.

3,4-Dihydro-6-hydroxy-4,4,5,7,8-pentamethyl-2*H*-1-benzothiopyran (16). The synthesis of this compound by reaction of **5** with 3-methyl-2-buten-1-ol under the conditions given in ref 8 has been reported previously.[7] Compound **2c** is a minor product (10% relative to **16**) in this reaction. The structure of **16** has been confirmed by X-ray analysis.[7]

***S*-(3,3-Dimethylallyl)-2,3,5-trimethyl-4-hydroxybenzenethiol (17).** This compound was synthesized by the condensation of **5** with isoprene essentially according to ref 21. To a heterogeneous mixture of anhydrous fused zinc chloride (0.05 g, 0.36 mmol) and of glacial acetic acid (5 mL) was added **5** (0.5 g, 2.9 mmol). The heterogeneous mixture was warmed slightly (50 °C) and cooled to 25 °C, and isoprene (2 mL, 17.6 mmol) was added at once. The reaction flask was stoppered well, and the solution was allowed to stand at 25 °C for 4 days, 1 drop of H_2SO_4 was added, and the solution was refluxed 10 min. The cooled solution was poured onto ice and extracted with ethyl acetate (2 × 20 mL). The organic phase was washed with saturated $NaHCO_3$ (20 mL), dried over Na_2SO_4, and filtered and the solvent removed under reduced pressure. The reaction mixture was subjected to column chromatography using 5% ethyl acetate in hexane as eluent. The white crystalline product had the following: yield, 350 mg (50%); mp 95.5–96.0 °C, R_f 0.32 (19/1). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 70.85; H, 8.52. ^1H NMR δ 7.1 (s br, 1 H, Ar H), 5.4–5.0 (m, 1 H, =CH), 4.6 (s, 1 H),[20] 3.2 (d, 2 H, SCH_2), 2.4 (s, 3 H, $ArCH_3$), 2.25 (s, 6 H, $ArCH_3$), 1.85–1.4 (m, 6 H, $C(CH_3)_2$).

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Supplementary Material Available: Figure showing 500-MHz ^1H NMR spectrum of the products formed by reaction of **5** with **10b**. (2 pages). Ordering information is given on any current masthead page.

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α-Nitroarylation of Ketones and Esters: An Exceptionally Facile Synthesis of Indoles, 2-Indolinones, and Arylacetic Acids†

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Silyl enol ethers and ketene silyl acetals add to aromatic nitro compounds in the presence of fluoride ion sources to give dihydroaromatic nitronates which are readily oxidized to α-nitroaryl carbonyl compounds by DDQ or Br_2. These versatile intermediates are readily converted into indoles or 2-indolinones by reductive cyclization. Since halogen substituents on the aromatic ring are not displaced in the initial alkylation reaction, nucleophilic substitution of these groups, followed by functional group manipulations of the nitro group, permits easy access to indoles, 2-indolinones, and arylacetic acids with varied substitution patterns.

Because of the very potent and diverse biological activity exhibited by various indole derivatives, this heterocyclic system has attracted considerable attention in chemistry, biology, and medicine.[1] Understandably, a very large body of chemical literature has appeared dealing with various synthetic methods for the construction of the indole nucleus. The most versatile among these are the Fischer, Bischler, Madelung, Reissert, Nenitzescu, and Gassman procedures and their various modifications.[1a,b,2] Organometallic intermediates[2c,3] as well as 2-(dimethylamino)styrenes[4] have also served as precursors for indoles. Other fundamentally new methods based on $S_{RN}1$ reactions,[5] intramolecular amidoalkylations,[6] nucleophilic[7] and free radical[8] additions, 1,5-electrocyclization of zwitterionic intermediates,[9] and aromatization of alicyclic precursors[10] are also noteworthy. By comparison, only a few methods have been reported for the synthesis of the indolinone

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