Novel Antioxidants: Unexpected Rearrangements in the Radical Cyclization Approach to 2,3-Dihydrobenzo[*b*]thiophene-5-ol Derivatives

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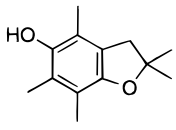
Received November 13, 1997

The novel α-tocopherol analogue 3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene-5-ol (**4a**) was prepared by cyclodehydration of the aryl 2-hydroxyalkyl sulfide **6** in concentrated sulfuric acid. Aromatic bromination and dehydration of alcohol **6** furnished the 2-bromoaryl methallyl sulfide **10a** as the kinetic product and the 2-bromoaryl 2-methyl-2-propenyl sulfide **11a** as the thermodynamic one. Radical cyclization of these compounds afforded the desired 2,3-dihydrobenzo[*b*]-thiophene derivative **12** in addition to a rearranged isomer **13** thereof. It is proposed that the transformation of compound **10a** to **13** occurs via 6-endo cyclization, *β*-scission, and subsequent 5-exo cyclization. The radical cyclization of the 2-bromoaryl allyl sulfide **16**, unsubstituted in the allylic moiety, furnished only 2,3-dihydrobenzo[*b*]thiophene-5-ol derivative **17**.

Introduction

α-Tocopherol, a component of vitamin E, is the major lipid-soluble antioxidant present in human blood.[1] The antioxidant properties of the tocopherols have been ascribed to their capacity to rapidly transfer a hydrogen atom to peroxyl radicals. The tocopheryl radicals formed in this process are then known to combine with another peroxyl radical. Thus, tocopherols scavange peroxyl radicals and act as chain-breaking antioxidants.[2] Since the pioneering work on vitamin E analogues by Ingold and co-workers in the 1980s,[3−7] there has been a continuous search[8] for structures with improved or modified antioxidative properties. Some of the modifications were introduced to increase hydrophilicity and bioavailability of the parent chromanol system.[9,10] The most notable improvments in antioxidant efficiency emerged from the idea that the antioxidant capacity critically depends on the steric and stereoelectronic effects stabilizing the aryloxy radical (ArO•) formed in the hydrogen atom transfer step.[5] Thus, the better overlap between the nonphenolic oxygen 2p-type lone pair and the aromatic *π*-system in the 2,3-dihydrobenzofuran derivative **1**, as compared to α-tocopherol, seems to explain the 1.8-fold



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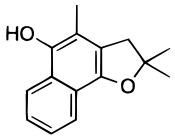

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increase in the $k_{inhibition}$ in the inhibited autoxidation of styrene method. Barclay has recently prepared a 2,3-dihydronaphthofuran derivative **2** that shows a $k_{inhibition}$ value 10 times that of α-tocopherol.[11,12] The higher antioxidant activity in this case was attributed to additional delocalization of the phenoxyl radical into the fused aromatic ring.

Sulfur is generally considered to be more effective than oxygen at stabilizing a neighboring radical center.[13] However, 1-thio-α-tocopherol and related 6-hydroxythiochromans turned out to be slightly less reactive toward peroxyl radicals than structurally related 6-hydroxychromans.[6,7] To the best of our knowledge, the corresponding 1-seleno- and 1-tellurochromanols were never prepared. Nishiyama and co-workers[14,15] observed the high antioxidant capacity of phenolic compounds carrying a sulfur atom para to the hydroxyl group. We recently reported that bis(4-hydroxyphenyl) telluride (**3**) was a better inhibitor of azo-initiated peroxidation of linoleic acid than the corresponding organosulfur compound.[16]

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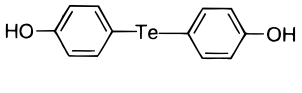
S0022-3263(97)02087-2 CCC: $15.00
Published on Web 04/28/1998



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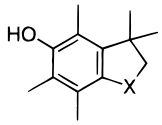


4 a X=S
b X=Se
c X=Te

In view of the above structure−activity relationships, we thought it would be interesting to synthesize a series of tocopherol analogues **4**, where the heteroatom X could be sulfur, selenium, or tellurium. In this paper, we describe a radical cyclization approach to the sulfur analogue **4a** and some closely related compounds.

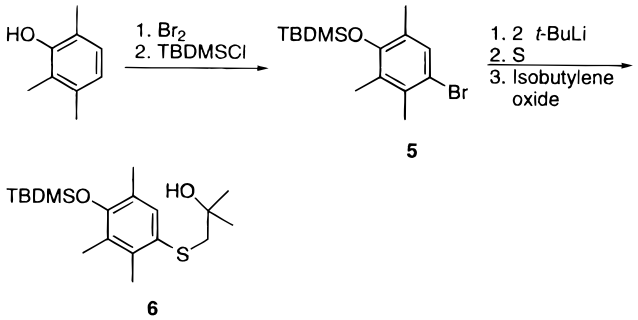
Results

There is evidence that the 2,3-dihydrobenzothiophene as well as the 2*H*-1-benzothiopyran systems can be assembled by cyclodehydration of the corresponding aryl hydroxyalkyl sulfides.[17] It occurred to us that the tertiary alcohol required for such an approach toward compound **4a** can be obtained in few steps from the commercialy available 2,3,6-trimethylphenol. As shown in Scheme 1, bromination of the phenol occurred regiospecifically[18] in the 4-position (97% yield). Protection of the phenol as a TBDMS ether **5** (95% yield) was performed to increase the yield in the following one-pot sequence involving lithiation, sulfur insertion, and thiolate ring opening of isobutylene oxide. The epoxide was selectively attacked from the terminus, affording the tertiary alcohol **6** as an oil in 74% isolated yield.

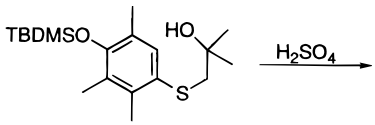
Cyclodehydration of compound **6** was unsuccessful in polyphosphoric, perchloric, and formic acid. Various Lewis acids also failed to cause cyclization in nitromethane or toluene. However, when compound **6** was kept in concentrated sulfuric acid for 30 min at 0 °C, the desired compound **4a** was formed together with the benzo[*b*]thiophene derivative **7** (27% isolated yield of a 1/1 mixture; eq 1). The separation of these materials by flash chromatography was conveniently performed after *m*-CPBA oxidation to the respective sulfoxides.

Various radical routes to the 2,3-dihydrobenzothiophene system were also considered. Crich[19] recently reported the efficient formation of the sulfur−aryl bond of 3,3-dimethyl-2,3-dihydrobenzo[*b*]thiophene by intramolecular homolytic substitution at sulfur.[20] With some functional group modification (aromatic halogenation, elimination), compound **6** could be transformed into a precursor for a radical cyclization approach to the target

Scheme 1



5 **6**



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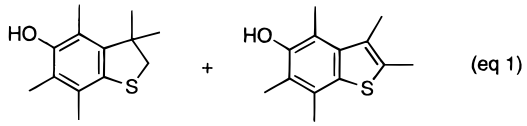
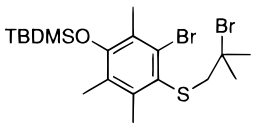


4a **7**

compound **4a**. Bromination in acetic acid not only introduced an aromatic bromide but also caused substitution of the very labile tertiary alcohol. However, on chromatographic purification, the dibromide **8** was partly hydrolyzed to the tertiary alcohol **9**. In the most practical



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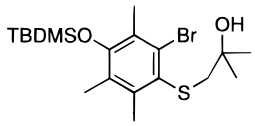

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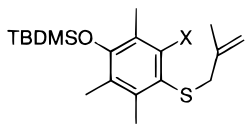
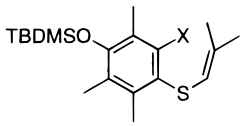


10 a X=Br
b X=H



11 a X=Br
b X=H

approach, the crude dibromide **8** was therefore treated in aqueous tetrahydrofuran with triethylamine to afford pure alcohol **9** in 67% overall yield from compound **6.** *p*-Toluenesulfonic acid-catalyzed dehydration of alcohol **9** in refluxing toluene afforded the terminal olefin **10a** as the kinetic product (1 h reflux; 68% isolated yield) and the vinylic sulfide **11a** as the thermodynamic product (24 h reflux; 74% isolated yield).

5-Endo-trig-cyclization of compound **11a** was attempted by syringe pump addition of tris(trimethylsilyl)-silane and AIBN initiation. In addition to reduced starting material **11b** (50%), a 1:1 mixture of the desired 2,3-dihydrobenzo[*b*]thiophene **12** and an isomer **13** thereof was isolated (41% yield). As indicated, the structural assignments of these materials were supported by NOE-difference experiments and further corroborated by selective INEPT experiments. In the case of compound **13**, the experiments were done on the corresponding sulfoxide **14**. The sulfoxide produced on desilylation and *m*-CPBA oxidation of compound **12** was identical to the sulfoxide of product **4a** obtained in the above cyclodehydration approach.

Compound **10a** was also subjected to radical cyclization. In this case, slow addition of hydride donor and the use of tris(trimethylsilyl)silane instead of tributylstannane were not necessary to avoid formation of a reduction product (**10b**). Heating of compound **10a** with

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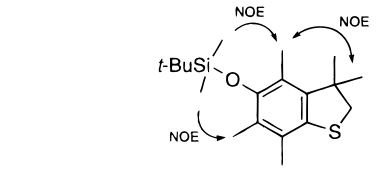

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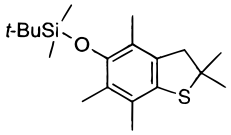

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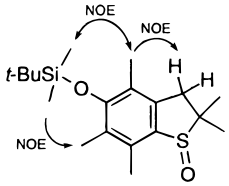

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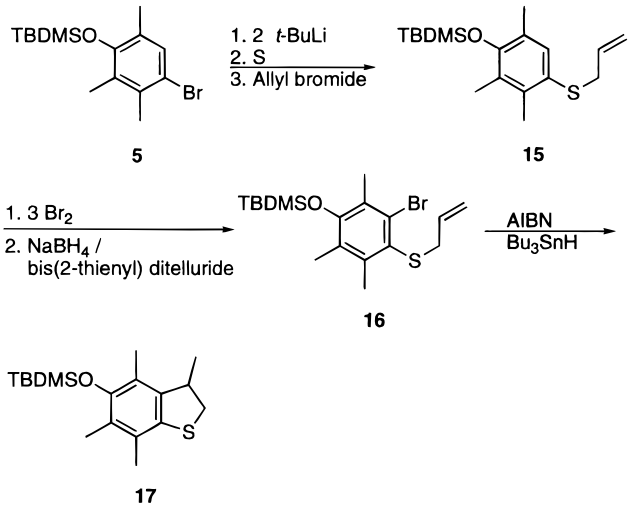
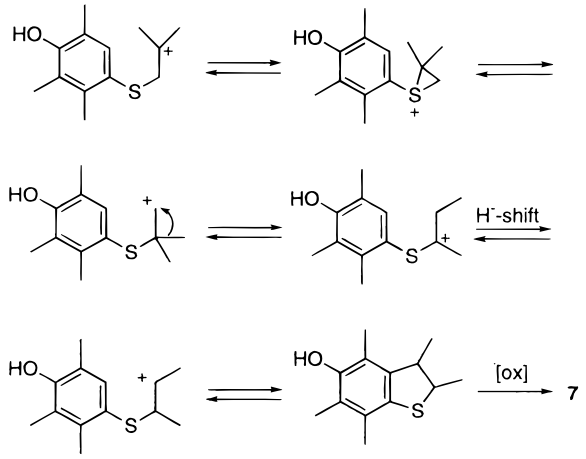
1.2 equiv of tributylstannane and a trace of AIBN in benzene for 3 h resulted in the formation of a 3/1 mixture of compounds **12** and **13** (40% isolated yield). The reaction was also tried using an excess of the hydride donor. With a 5-fold excess, compound **12** was isolated as the only cyclized product in low (17%) yield.

The radical cyclization approach to the 2,3-dihydrobenzo[*b*]thiophene-5-ol system was also tried using a 2-bromoaryl allyl sulfide unsubstituted in the allyl moiety. Unfortunately, propylene oxide was ring-opened with poor yield and regioselectivity using the procedure described in Scheme 1. Therefore, the lithium arenethiolate derived from compound **5** was alkylated with allyl bromide (43% overall yield) and the resulting sulfide **15** treated with 3 equiv of bromine in acetic acid (Scheme 2). The double bond was regenerated by treatment of the crude reaction mixture with sodium borohydride/bis-(2-thienyl) ditelluride according to a literature method[21] to give radical precursor **16** in 50% yield. Heating of compound **16** with tributyltin hydride and AIBN initiation afforded 2,3-dihydrobenzo[*b*]thiophene **17** in 55% yield, uncontaminated by any isomer thereof.

Scheme 2



Scheme 3



Discussion

The cyclodehydration route to 2,3-dihydrobenzo[*b*]-thiophenes (eq 1) has previously been high yielding with tertiary alcohols and unsubstituted aryl groups.[17] The low yield of compound **4a** obtained in the attempted cyclization of compound **6** can probably be ascribed to unfavorable steric interactions between the *gem*-dimethyl groups and the methyl substituent in the 4-position. Recently, an analogue of vinylic sulfide **11b**, lacking substituents in the aryl ring, was induced to rearrange to 3,3-dimethyl-2,3-dihydrobenzo[*b*]thiophene in methylene chloride in the presence of an excess of aluminum chloride.[22] The similar treatment of compound **11b** induced desilylation but essentially no cyclization.

The transformation of sulfide **6** to dibenzo[*b*]thiophene derivative **7** probably occurs via carbocation and episulfonium ion intermediates. It also has to involve methyl and hydride shifts and finally oxidation (Scheme 3). The aromaticity of the heterocyclic ring formed provides a driving force for this kind of reorganization.

The formation of isomeric mixtures of 2,3-dihydrobenzo[*b*]thiophenes **12** and **13** in the radical cyclization of compounds **10a** and **11a** is mechanistically intriguing. Compound **12** results from 5-exo cyclization of radical **18**, followed by hydrogen atom abstraction (Scheme 4). The formation of "rearranged" product **13** can be accounted for by assuming 6-endo cyclization of the initially formed aryl radical, followed by β-scission and 5-exo cyclization. In fact, it is well established that a methyl substituent at the 5-position in a hexenyl radical makes the 6-endo mode of cyclization more competitive.[23] An alternative mechanism, involving a neophyl rearrangement of compound **19** to **20**, appears unlikely. Unless electron-withdrawing substituents are present in the aromatic, such processes are usually slow.[24] Also, in contrast to cases where the neophyl rearrangment is likely to be operative,[25] the ratio **12**/**13** ratio was invariant of the concentration of the radical precursor (0.35 or 0.05 M). In the presence of an excess of the hydrogen atom donor, isomer-free compound **12** was isolated in much lower yields than those obtained in the stoichiometric reaction. We hypothesize that this selectivity is due to suppression of the 6-endo route to product. Compound **16**, lacking substituents in the allylic moiety, failed to give a "rearranged" radical cyclization product. In this case, the endo

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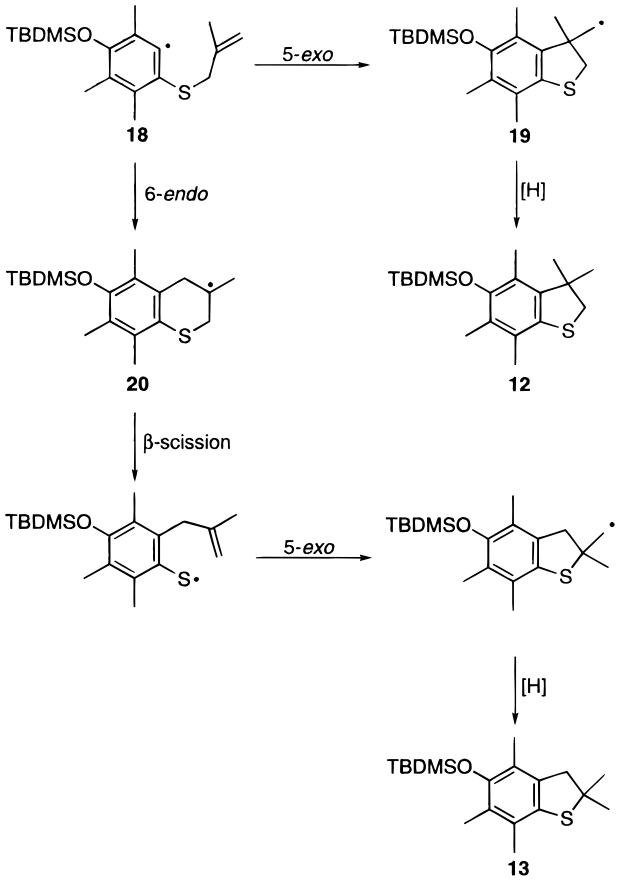
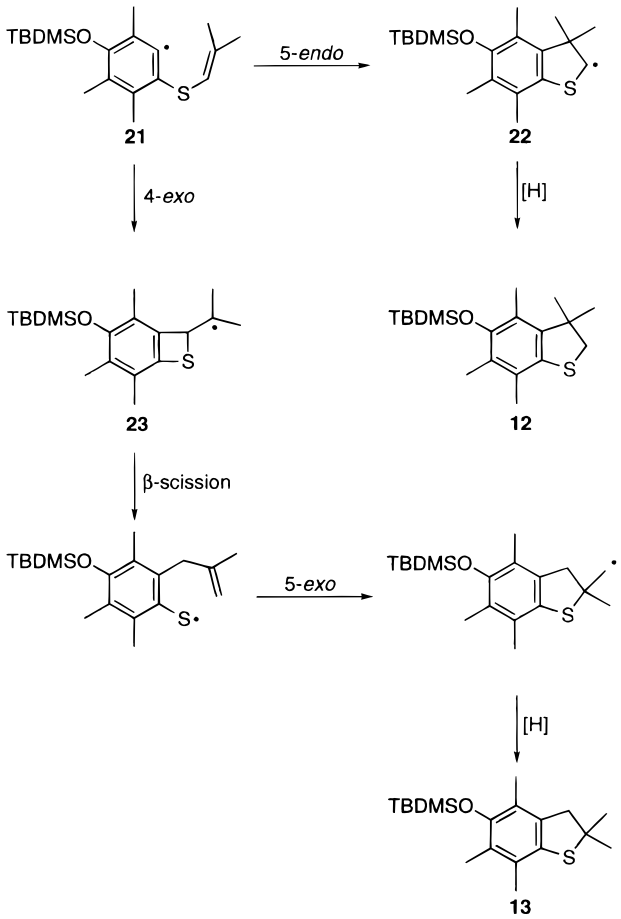
Scheme 4



Scheme 5



mode of cyclization is too slow to become an effective competing reaction.[26]

The analogous mechanism (Scheme 5) for formation of compounds **12** and **13** from compound **11b** is more speculative. Synthetically useful 4-exo and 5-endo pentenyl radical cyclizations are rarely seen.[26] However, since radical **21** is an aryl radical, it could be expected to undergo cyclization 2−3 orders of magnitude faster than a corresponding alkyl radical. Furthermore, the products of 4-exo and 5-endo cyclization are both stabilized, the latter (radical **22**) by interaction with sulfur, the former (radical **23**) by being tertiary. In combination, these factors may serve to make radical cyclization become competitive to hydrogen atom abstraction.

In conclusion, we have prepared new 2,3-dihydrobenzo[*b*]thiophene-5-ol derivatives in few steps from 2,3,6-trimethylphenol by using a radical cyclization approach. The antioxidative properties of the novel α-tocopherol analogues are presently being evaluated.

Experimental Section

Melting points are uncorrected. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded in $CDCl_3$ on Varian XL-300 or VXR unity 400 spectrometers. 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. Merck 60 silica gel was used for flash column chromatography. Bis(2-thienyl) ditelluride was prepared according to a literature procedure.[27] Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone. Benzene and dichloromethane were distilled under nitrogen from calcium hydride. Elemental analyses were performed by Analytical Laboratories, Lindlar, Germany.

4-Bromo-2,3,6-trimethylphenol.[18] A solution of bromine (3.80 mL, 73.4 mmol) in acetic acid (40 mL) was added dropwise to a magnetically stirred solution of 2,3,6-trimethylphenol (10.0 g, 73.4 mmol) in acetic acid (70 mL) maintained at 15 °C. After addition, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Water was added, and the mixture was neutralized with NaOH (2 M (aq)). The aqueous phase was extracted with diethyl ether (3 × 100 mL), and the combined organic phases were washed with water and saturated sodium chloride. The organic phase was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the title compound (15.3 g, 97%) as light yellow crystals, which were used in the next step without further purification. Recrystallized material melted at 83−85 °C (lit.[18] mp 85−86 °C).

***tert*-Butyldimethylsilyl 4-Bromo-2,3,6-trimethylphenyl Ether (5).** To a solution of *tert*-butylchlorodimethylsilane (12.2 g, 80.9 mmol) in DMF (35 mL) at ambient temperature were added imidazole (11.5 g, 169 mmol) and 4-bromo-2,3,6-trimethylphenol (14.5 g, 67.4 mmol). The resulting mixture was then stirred at ambient temperature for 66 h. Water (50 mL) was added, and the solution was extracted with pentane (4 × 80 mL). The combined organic phases were washed with water and saturated sodium chloride. The organic phase was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the title compound (21.1 g, 95%) as white crystals, mp 48−49 °C, which were used in the next step without further purification: ^{1}H NMR δ 0.15 (s, 6H), 1.04 (s, 9H), 2.16 (s, 3H), 2.17 (s, 3H), 2.31 (s, 3H), 7.19 (s, 1H); ^{13}C NMR δ −3.2, 15.3, 17.4, 18.7, 20.0, 26.0, 116.9, 127.9, 129.2, 131.3, 134.5, 151.1. Anal. Calcd for $C_{15}H_{25}BrOSi$: C, 54.70; H, 7.65. Found: C, 54.83; H, 7.54.

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2-Methyl-2-hydroxypropyl 4-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (6). *tert*-Butyllithium (19.6 mL, 1.7 M, 32.2 mmol) was added, dropwise, to a stirred solution of compound **5** (5.31 g, 16.1 mmol) in dry THF (100 mL) maintained at −78 °C under an atmosphere of dry nitrogen. After 0.5 h, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Sulfur (0.52 g, 16.3 mmol) was added, in one portion, and the reaction was stirred at room temperature for 20 min. Finally, isobutylene oxide (1.45 mL, 16.1 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with a saturated NH_4Cl solution, and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 100 mL), and the combined organic phases were washed with water and brine and then dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc/pentane 15/85) to afford 4.22 g (74%) of the title compound as a light yellow oil: ^{1}H NMR δ 0.15 (s, 6H), 1.03 (s, 9H), 1.28 (s, 6H), 2.13 (s, 3H), 2.16 (s, 3H), 2.32 (s, 1H), 2.38 (s, 3H), 2.96 (s, 2H), 7.15 (s, 1H); ^{13}C NMR δ −3.1, 14.9, 17.6, 17.7, 18.7, 26.0, 28.7, 50.2, 70.8, 126.7, 127.0, 128.4, 132.3, 137.1, 151.5. Anal. Calcd for $C_{19}H_{34}O_2SSi$: C, 64.35; H, 9.66. Found: C, 64.16; H, 9.61.

3,3,4,6,7-Pentamethyl-2,3-dihydrobenzo[*b*]thiophene-5-ol (4a) and 2,3,4,6,7-Pentamethylbenzo[*b*]thiophene-5-ol (7). Neat concentrated sulfuric acid (12 mL) was added to compound **6** (1.00 g, 2.82 mmol), and the reaction was stirred at ambient temperature for 35 min. The reaction mixture was poured onto ice and neutralized with potassium hydroxide. The residue was then extracted with diethyl ether (3 × 50 mL), and the combined organic phases were washed with water and saturated sodium chloride. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure and the residue purified by flash chromatography (EtOAc/pentane 5/95) to afford an inseparable 1:1 mixture of the title compounds **4a** and **7** (0.172 g, 27%). To a stirred solution of the mixture in dichloromethane (40 mL) was added *m*-chloroperbenzoic acid (0.18 g, 0.808 mmol) at 0 °C under nitrogen. Stirring was then continued at 0 °C for 35 min, whereupon water was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic phases were washed with $NaHCO_3$ (5% (aq)), water, and brine. After drying (Na_2SO_4), evaporation of the solvent, and flash chromatography (EtOAc/pentane 80/20), the pure sulfoxides (0.164 g, 85%) were obtained.

2,3,4,6,7-Pentamethylbenzo[*b*]thiophene-5-ol 1-oxide: mp 193−196 °C; ^{1}H NMR δ 2.07 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.28 (s, 3H), 2.46 (s, 3H), 6.80 (s, 1H); ^{13}C NMR δ 10.8, 12.3, 12.7, 16.8, 16.9, 121.3, 124.7, 132.8, 134.4, 135.7, 139.1, 139.4, 156.4. Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 65.35; H, 6.41.

3,3,4,6,7-Pentamethyl-2,3-dihydrobenzo[*b*]thiophene-5-ol 1-oxide: mp 164−167 °C; ^{1}H NMR δ 1.51 (s, 3H), 1.73 (s, 3H), 2.16 (s, 3H), 2.31 (s, 3H), 2.56 (s, 3H), 2.98 (d, 1H, J = 14.0 Hz), 3.13 (d, 1H, J = 14.1 Hz), 5.54 (s, 1H); ^{13}C NMR δ 11.9, 12.1, 17.2, 28.8, 30.0, 48.9, 64.7, 118.2, 122.6, 134.8, 136.0, 147.6, 156.5.

2-Methyl-2-hydroxypropyl 6-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (9). A solution of bromine (0.745 mL, 14.4 mmol) in acetic acid (30 mL) was added dropwise to a magnetically stirred solution of compound **6** (2.55 g, 7.19 mmol) in acetic acid (55 mL) at 15 °C. After addition, the cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 3 h. Sodium thiosulfate (10% (aq)) was added, and the aqueous phase was extracted with diethyl ether (3 × 80 mL). The combined organic phases were washed with $NaHCO_3$ (5% (aq); 5 × 100 mL), water, and brine. The organic phase was dried over Na_2SO_4, and filtered and the solvent removed in vacuo. The residue was then dissolved in THF (120 mL) and stirred with triethylamine (1.25 mL) and water (60 mL) at room temperature for 2.5 h. The reaction mixture was extracted with diethyl ether (3 × 150 mL), and the combined organic phases were washed with water and brine. After drying (Na_2SO_4), filtration, removal of the solvent in vacuo, and chromatography (EtOAc/pentane 10/90), the title compound (2.05 g, 66%) was obtained as a light yellow oil: ^{1}H NMR δ 0.14 (s, 6H), 1.04 (s, 9H), 1.28 (s, 6H), 2.10 (s, 3H), 2.30 (s, 3H), 2.56 (s, 1H), 2.58 (s, 3H), 2.90 (s, 2H); ^{13}C NMR δ −3.3, 15.4, 18.6, 20.0, 20.5, 25.9, 28.5, 51.2, 70.5, 127.7, 128.2, 128.4, 132.0, 140.7, 152.5.

^{1}H NMR data for crude 2-bromo-2-methylpropyl 4-[(*tert*-butyldimethylsilyl)oxy]-6-bromo-2,3,5-trimethylphenyl sulfide (**8**): δ 0.15 (s, 6H), 1.04 (s, 9H), 1.88 (s, 6H), 2.12 (s, 3H), 2.31 (s, 3H), 2.59 (s, 3H), 3.24 (s, 2H); MS *m*/*z* (relative intensity) 496 (M^+, 46.7).

2-Methyl-2-propenyl 6-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (10a). *p*-Toluenesulfonic acid (0.019 g, 98.8 μmol) was added to a solution of alcohol **6** (0.57 g, 1.32 mmol) in toluene (20 mL). The reaction mixture was then stirred under reflux for 1 h, water was added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 80 mL). The combined organic phases were washed with $NaHCO_3$ (5% (aq)), water, and then brine. After drying (Na_2SO_4), filtration, and removal of the solvent in vacuo, the residue was purified by flash chromatography (pentane) to give 0.37 g (68%) of the title compound as white crystals: mp 37−39 °C; ^{1}H NMR δ 0.13 (s, 6H), 1.03 (s, 9H), 1.88 (s, 3H), 2.10 (s, 3H), 2.32 (s, 3H), 2.53 (s, 3H), 3.32 (s, 2H), 4.48 (m, 1H), 4.62 (m, 1H); ^{13}C NMR δ −3.3, 15.4, 18.6, 20.0, 20.4, 21.6, 26.0, 43.7, 113.5, 127.2, 127.5, 128.0, 132.8, 141.3, 141.9, 152.4. Anal. Calcd for $C_{19}H_{31}BrOSSi$: C, 54.92; H, 7.52. Found: C, 55.00; H, 7.55.

2-Methyl-1-propenyl 6-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (11a). *p*-Toluenesulfonic acid (0.066 g, 0.35 mmol) was added to a solution of alcohol **9** (1.00 g, 2.31 mmol) in toluene (55 mL). The reaction mixture was then heated under reflux for 22 h, water was added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 80 mL). The combined organic phases were washed with $NaHCO_3$ (5% (aq)), water, and then brine. After drying (Na_2SO_4), filtration, and removal of the solvent in vacuo, the residue was purified by flash chromatography (pentane) to give 0.71 g (74%) of the title compound as white crystals: mp 53−55 °C; ^{1}H NMR δ 0.14 (s, 6H), 1.05 (s, 9H), 1.76 (s, 3H), 1.87 (s, 3H), 2.11 (s, 3H), 2.32 (s, 3H), 2.49 (s, 3H), 5.46 (m, 1H); ^{13}C NMR δ −3.3, 15.3, 18.6, 19.4, 19.9, 20.3, 25.1, 26.0, 118.9, 127.6, 127.8, 128.0, 131,7, 133.6, 140.8, 152.4. Anal. Calcd for $C_{19}H_{31}BrOSSi$: C, 54.92; H, 7.52. Found: C, 54.86; H, 7.39.

5-[(*tert*-Butyldimethylsilyl)oxy]-3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene (12) and 5-[(*tert*-Butyldimethylsilyl)oxy]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene (13). A. From Compound 11a. A solution of AIBN (0.045 g, 0.27 mmol) and tris(trimethylsilyl)silane (670 μL, 2.17 mmol) in dry benzene (8 mL) was injected by syringe pump over 8 h into a stirred refluxing solution of olefin **11a** (0.75 g, 1.81 mmol) in dry benzene (35 mL) kept under an atmosphere of dry nitrogen. After being heated at reflux for another 15 h, the reaction mixture was cooled and the solvent removed in vacuo. Flash chromatography (pentane) afforded a 1:1 mixture (0.25 g, 41%) of compound **12**, mp 111−113 °C, and its constitutional isomer **13**. Compound **11b** (0.30 g, 50%) was also isolated from this reaction. The use of tributyltin hydride instead of tris(trimethylsilyl)silane resulted in lower yields of cyclized products. Compound **13** could only be isolated in pure form from the mixture after conversion of the products to sulfoxides. ^{1}H NMR compound **11b**: δ 0.16 (s, 6H), 1.04 (s, 9H), 1.85 (s, 3H), 1.86 (s, 3H), 2.13 (s, 3H), 2.17 (s, 3H), 2.29 (s, 3H), 5.74 (s, 1H), 6.99 (s, 1H). ^{1}H NMR compound **12**: δ 0.12 (s, 6H), 1.04 (s, 9H), 1.44 (s, 6H), 2.08 (s, 3H), 2.14 (s, 3H), 2.20 (s, 3H), 3.06 (s, 2H); ^{13}C NMR δ −3.3, 13.8, 14.4, 18.5, 18.6, 26.0, 26.2, 47.3, 49.7, 122.9, 126.4, 128.3, 132.9, 142.0, 149.5.

B. From Compound 10a. To a solution of olefin **10a** (0.25 g, 0.61 mmol) in dry benzene (15 mL) under nitrogen was added AIBN (0.025 g, 0.15 mmol). The reaction mixture was then heated to reflux, and tributyltin hydride (203 μL, 0.76 mmol) was added dropwise. Heating was then continued at

reflux for 3.5 h and the solvent removed in vacuo after cooling of the flask. Flash chromatography (pentane) afforded a 3:1 mixture of compound **12** and **13**. The mixture (0.081 g, 40%) was oxidized with *m*-CPBA as described above (compounds **4a**/**7**), and the corresponding sulfoxides were separated by flash chromatography (EtOAc/pentane 70/30). A similar result was also obtained by using significantly less (10 mol %) AIBN. Also, the **12**/**13** ratio was invariant to the initial concentration (0.05 or 0.35 M) of the radical precursor.

5-[(*tert*-Butyldimethylsilyl)oxy]-2,2,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene 1-oxide (14): mp 129−131 °C; ^{1}H NMR δ 0.14 (s, 6H), 1.04 (s, 9H), 1.22 (s, 3H), 1.56 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.52 (s, 3H), 2.89 (d, 1H, J = 16.3 Hz), 3.44 (d, 1H, J = 16.3 Hz); ^{13}C NMR δ −3.1 (4), −3.0 (6), 14.1, 14.8, 17.6, 18.6, 21.1, 23.8, 26.0, 45.2, 60.9, 123.7, 127.5, 135.7, 136.8, 142.3, 155.0. Anal. Calcd for $C_{19}H_{32}O_2SSi$: C, 64.72; H, 9.15. Found: C, 64.60; H, 9.08.

5-[(*tert*-Butyldimethylsilyl)oxy]-3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene 1-oxide: ^{1}H NMR δ 0.15 (s, 3H), 0.16 (s, 3H), 1.04 (s, 9H), 1.49 (s, 3H), 1.70 (s, 3H), 2.13 (s, 3H), 2.27 (s, 3H), 2.54 (s, 3H), 3.00−3.14 (m, 2H); ^{13}C NMR δ −3.1, −3.0, 13.7, 14.3, 17.3, 18.7, 26.0, 28.5, 29.7, 48.8, 64.9, 123.6, 128.3, 135.1, 136.9, 147.3, 156.2.

3,3,4,6,7-Pentamethyl-2,3-dihydrobenzo[*b*]thiophene-5-ol (4a) from Compound 12. To a solution of compound **12** (0.027 g, 0.079 mmol) in dry THF (5 mL) was added tetra-*n*-butylammonium fluoride (80 μL, 1.0 M, 0.079 mmol) under an atmosphere of dry nitrogen. The reaction mixture was then stirred at ambient temperature for 1 h. Water was added, and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with water and brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Chromatography (EtOAc/pentane 5/95) afforded the title compound (0.014 g, 79%) as white crystals: mp 84−86 °C; ^{1}H NMR δ 1.47 (s, 6H), 2.14 (s, 3H), 2.19 (s, 3H), 2.27 (s, 3H), 3.07 (s, 2H), 4.43 (s, 1H); ^{13}C NMR δ 11.8, 12.3, 18.4, 26.6, 47.2, 49.6, 117.9, 121.0, 128.1, 132.0, 142.1, 149.9. Anal. Calcd for $C_{13}H_{18}OS$: C, 70.23; H, 8.16. Found: C, 70.40; H, 7.99.

2-Propenyl 4-[(*tert*-Butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (15). *tert*-Butyllithium (12.5 mL, 1.5 M, 18.3 mmol) was added, dropwise, to a stirred solution of compound **5** (3.01 g, 9.14 mmol) in dry THF (55 mL) maintained at −78 °C under an atmosphere of dry nitrogen. After 0.5 h, sulfur (0.29 g, 9.14 mmol) was added in one portion, and the reaction mixture was stirred at −78 °C for 1 h. Finally, allyl bromide (795 μL, 9.14 mmol) was added, and the mixture was allowed to slowly reach room-temperature overnight. A saturated NH_4Cl solution was then added, and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 80 mL), and the combined organic phases were washed with water and brine and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash chromatography (pentane) to afford 1.27 g (43%) of the title compound as a colorless oil: ^{1}H NMR δ 0.16 (s, 6H), 1.03 (s, 9H), 2.13 (s, 3H), 2.16 (s, 3H), 2.35 (s, 3H), 3.36−3.40 (m, 2H), 4.97−5.03 (m, 2H), 5.79−5.91 (m, 1H), 7.08 (s, 1H); ^{13}C NMR δ −3.1, 14.9, 17.5 (6), 17.6 (1), 18.7, 26.0, 38.6, 117.0, 126.0, 126.2, 128.1, 132.7, 133.9, 137.4, 151.4; MS *m*/*z* (relative intensity) 322 (M^+, 100).

2-Propenyl 6-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2,3,5-trimethylphenyl Sulfide (16). To a solution of compound **15** (0.19 g, 0.59 mmol) in acetic acid (10 mL) maintained at 15 °C was added bromine (92 μL, 1.8 mmol) dropwise. The cooling bath was then removed, and the reaction mixture was stirred at room temperature for 6 h. Sodium thiosulfate (10% (aq)) was added, and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with $NaHCO_3$ (5% (aq); 5 × 80 mL), water, and brine. The organic phase was dried over Na_2SO_4 and filtered and the solvent removed in vacuo. The residue was then dissolved in ethanol (8 mL), and bis(2-thienyl) ditelluride (0.086 g, 50 mol %) was added under an atmosphere of dry nitrogen (the use of less ditelluride[21] resulted in very poor conversion of starting material). $NaBH_4$ (5% in 5% aqueous NaOH) was then added, dropwise, until the red color of the ditelluride disappeared. The aqueous phase was then extracted with pentane (4 × 10 mL) under an atmosphere of dry nitrogen to remove most of the remaining ditelluride. The combined organic phases were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. Chromatography (pentane) afforded 0.12 g (50% from compound **15**) of the title compound as a colorless oil: ^{1}H NMR δ 0.14 (s, 6H), 1.04 (s, 9H), 2.11 (s, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 3.37−3.40 (m, 2H), 4.83−4.91 (m, 2H), 5.79−5.91 (m, 1H); ^{13}C NMR δ −3.3, 15.4, 18.6, 20.0, 20.6, 26.0, 39.2, 117.0, 126.8, 127.3, 128.0, 132.0, 133.7, 141.9, 152.5.

5-[(*tert*-Butyldimethylsilyl)oxy]-3,4,6,7-tetramethyl-2,3-dihydrobenzo[*b*]thiophene (17). To a solution of olefin **16** (0.118 g, 0.294 mmol) in dry benzene (10 mL) under nitrogen was added AIBN (0.012 g, 0.073 mmol). The reaction mixture was then heated to reflux, and tributyltin hydride (103 μL, 0.38 mmol) was added dropwise. The reaction mixture was then heated at reflux for 2.5 h and the solvent removed in vacuo after cooling of the flask. Flash chromatography (pentane) afforded 0.052 g (55%) of the title compound as white crystals: mp 69−71 °C; ^{1}H NMR δ 0.13 (s, 3H), 0.14 (s, 3H), 1.03 (s, 9H), 1.21 (d, 3H), 2.09 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.81−2.87 (m, 1H), 3.50−3.61 (m, 2H); ^{13}C NMR δ −3.2, −3.1, 14.3, 17.6, 18.6, 18.9, 26.1, 30.3, 40.0, 41.8, 122.1, 126.3, 128.2, 131.7, 141.4, 149.3. Anal. Calcd for $C_{18}H_{30}OSSi$: C, 67.02; H, 9.37. Found: C, 66.85; H, 9.55.

Acknowledgment. Financial support by the Swedish Research Council for Engineering Sciences and the Swedish Natural Science Research Council is gratefully acknowledged. We also thank professor Carl Schiesser, University of Melbourne, for valuable suggestions concerning the mechanistic discussion.

Supporting Information Available: ^{1}H NMR spectra of compounds **9**, **12**, **15**, **16**, 2,3,4,6,7-pentamethylbenzo[*b*]-thiophene-5-ol 1-oxide, and 3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[*b*]thiophene-5-ol 1-oxide (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO972087L