Synthesis of Sulfur- and Sulfoxide-Substituted 2,3-Oxidosqualenes and Their Evaluation as Inhibitors of 2,3-Oxidosqualene-Lanosterol Cyclase

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Abstract: 2,3-Oxidosqualene (23-OS) analogs that contain thioether (**52**−**55**) and sulfoxide (**56**−**60**) at positions normally occupied by carbons considered to be cationic during 2,3-oxidosqualene-lanosterol cyclase (OSC) cyclization (C-6, C-10, C-14, and C-19) were synthesized and tested as substrate mimic inhibitors of fungal and mammalian OSC. The analogs were found to be potent inhibitors of cyclase in cell-free extracts of *Candida albicans* and rat liver. Thioether analogs were more potent than the corresponding sulfoxides. In both series, those 2,3-OS analogs containing a sulfur at the position normally occupied by C-19 were the most potent. With *C. albicans* cyclase, the IC_{50} for thioether **55** was 0.0023 μM while **60** exhibited an IC_{50} of 0.065 μM, which are the lowest values reported for a inhibitor of this enzyme. Similarly, thioether **55** displayed an IC_{50} of 0.00082 μM for rat liver cyclase which is the best inhibitor up to date for this enzyme. These results suggest that mimics with modification in the region of C-19 of 2,3-OS have a high affinity for the active site of these enzymes. The same series of analogs (**52**−**60**) were also tested for inhibition of cholesterol biosynthesis in intact MDBK (Madin Darbin bovine kidney) cells and for *in vitro* antifungal activity against *C. albicans*.

Introduction

Cyclizations of (3*S*)-2,3-oxidosqualene (2,3-OS, **1**) by 2,3-oxidosqualene-lanosterol cyclases (OSCs) are among the most complex reactions in nature.[1,2] OSCs are considered to initially bind **1** in a chair-boat-chair conformation and then catalyze the sequential formation of four new C−C bonds leading *via* cations **2**−**5** to a tetracyclic protosterol cation, **6**. Assisted rearrangement of **6** gives lanosterol (**7**) in fungi and mammalian systems. The mechanism of cyclization of **1** to lanosterol (**7**) has been a matter of debate and is still the subject of conjecture. Although early suggestions were for a "synchronous" process,[3] current hypotheses center on a "stepwise" process, proceeding through a series of discrete, conformationally rigid, partially cyclized carbocationic intermediates (**2**−**5**, Scheme 1). Prominent in providing evidence supporting the stepwise process has been the van Tamelen group.[4a−d] The natural occurrence of monocyclic[5a] and bicyclic[5b] triterpenes, obviously derived from **1**, has also been viewed as evidence for the "stepwise" mechanism.

Recent advances in characterization and purification have spurred mechanistic studies of OSCs. Several cyclases have been purified to homogeneity from vertebrate,[6] plant,[7] yeast,[8] and bacterial[9] sources. *Candida albicans* OSC has been cloned and sequenced.[10] Corey *et al.* transformed (18*E*)-20-oxa-2,3-OS and (20*E*)-20,21-didehydro-2,3-OS to their respective protosterols, clearly establishing that these derivatives have 17β stereochemistry.[11] Xiao and Prestwich reported 29-methylidene-2,3-OS as the first mechanism-based irreversible inhibitor of an OSC.[12] Inhibition occurred through covalent binding of the presumptive C-21 cation to the active site of the enzyme.[12] Numerous inhibitors of OSC have displayed potent activity.[13]

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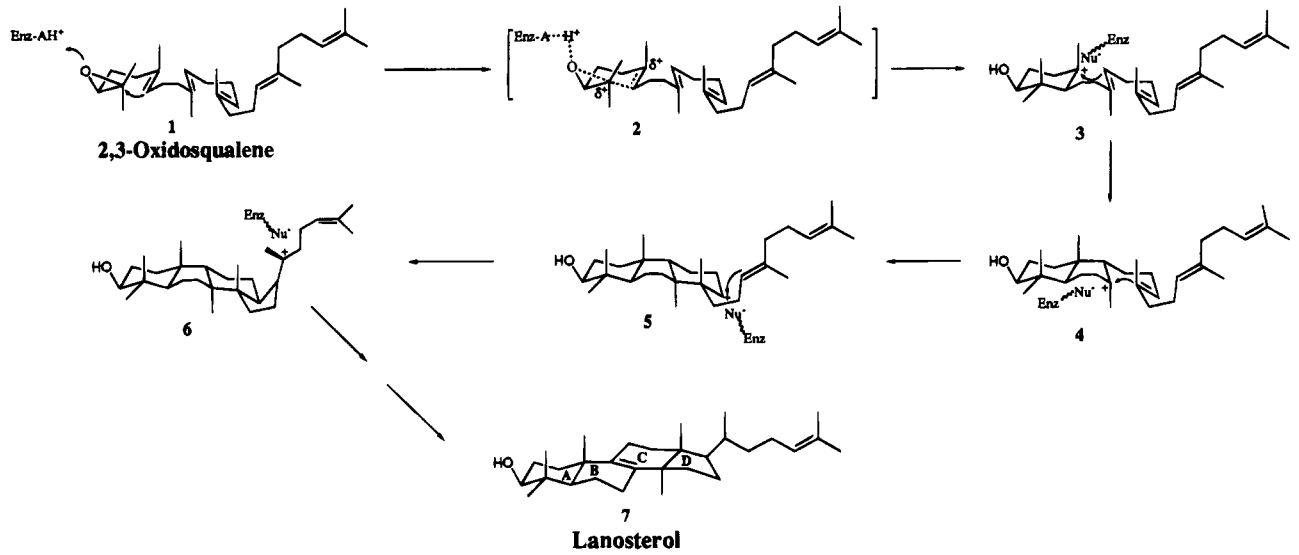
Scheme 1



Among the most effective are substrate mimics such as 2,3-iminosqualene,[14] 2,3,18,19-dioxidosqualene,[15] 10-aza-10,11-dihydro-2,3-OS,[16] 19-aza-18,19-dihydro-2,3-OS,[2a] and vinyl sulfur 2,3-OS analogs.[17] Intermediate mimics such as 2-aza-2,3-dihydrosqualene,[18] monocyclic derivatives of **1** such as *N*-alkyl-3,3-dimethyl-4-hydroxypiperidine[19] and 2-alkyl-1,3,3-trimethyl-4-hydroxypiperidine,[20] and bicyclic compounds such as *N*-(1-oxododecyl)-4α,10-dimethyl-8-aza-*trans*-decal-3β-ol[21] and aminobenzophenone analogs[22] are also potent. The best inhibitor among these compounds was 2,3,18,19-dioxidosqualene which exhibited noncompetitive, time-dependent kinetics.[15] This result has highlighted substrate mimics as attractive synthetic targets.

This paper reports the synthesis and inhibitory activity of 2,3-OS analogs in which sulfur or sulfoxide has replaced carbons C-6, C-10, C-14, or C-19 in **1** that are considered to become positively charged during OSC cyclization.

Our choice of sulfur-substituted 2,3-OS analogs was guided by several considerations. In the native cyclization, π bonds are the intramolecular nucleophiles that react with each cation. The excellent nucleophilic properties of sulfur[23] compared to candidates such as nitrogen and oxygen was considered to be an advantage if **52**−**55** acted as substrate mimics. We reasoned that initial enzymatic interaction with 2,3-OS would be primarily with the π orbital of the sp^2 carbons normally at the sites now occupied by sulfur and the latter could mimic these interactions.

As each ring is formed in the native cyclization, the carbon positions occupied by sulfur normally become positively charged and require an enzymatic nucleophile for stabilization. A further beneficial feature of sulfur is its stability as a sulfoxide. Sulfoxide analogs **56**−**60** provide electron-deficient centers at the relevant locations which could take advantage of this interaction to inhibit OSC.

Finally, it is possible that **52**−**55** could bind to OSCs and cyclize to **8**−**11** respectively (Figure 1). In this event the new sulfonium ions formed would each be positioned near the OSC nucleophilic sites normally stabilizing **3**−**6**. Since formation of rings A[4a] and B[24] has been shown to be the rate-determining step in the biomimetic polyene cyclization of analogs of **1**, one might reasonably expect that analogs **52** and **53** leading to **8** and **9**, respectively, would be the most potent inhibitors in this event. If cyclization of **52**−**55** occurred, one would expect the thioethers to be stronger inhibitors than their sulfoxide analogs **56**−**60** since both would be mimicking enzyme−intermediate complexation and the cyclized derivatives of **52**−**55** should be better intermediate mimics.

If both the thioether and sulfoxide analogs of **1** behave as substrate mimics, the sulfoxides should be the more potent inhibitors. While interactions between OSC and the sulfoxides mimic enzyme−intermediate complexation, the interactions between OSC and the corresponding thioethers mimic enzyme−substrate complexation, which is generally weaker.

Results and Discussion

Syntheses of Sulfur and Sulfoxide 2,3-OS Analogues. The preparation of **52** and **56** in which the sulfur atom and sulfoxide replaces C-6 in 2,3-OS was achieved by coupling epoxy mesylate **16** and tetraenic thiol **25** (Scheme 2). The former was prepared from alcohol **12** *via* protection to give **13**, epoxidization to **14**, deprotection to **15**, and mesylation to **16** in 55% overall yield. Tetraenic thiol **25** was prepared from the corresponding alcohol **23**, which was derived from coupling farnesyl chloride (**21**) and allylic bromide **20**. Synthesis of **20** commenced with

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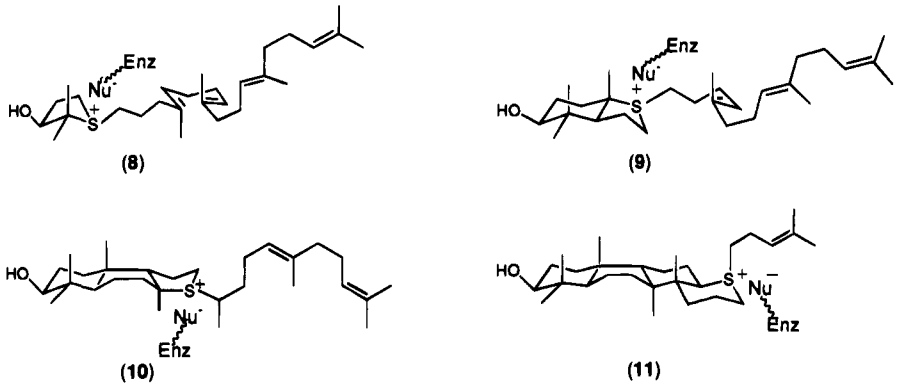
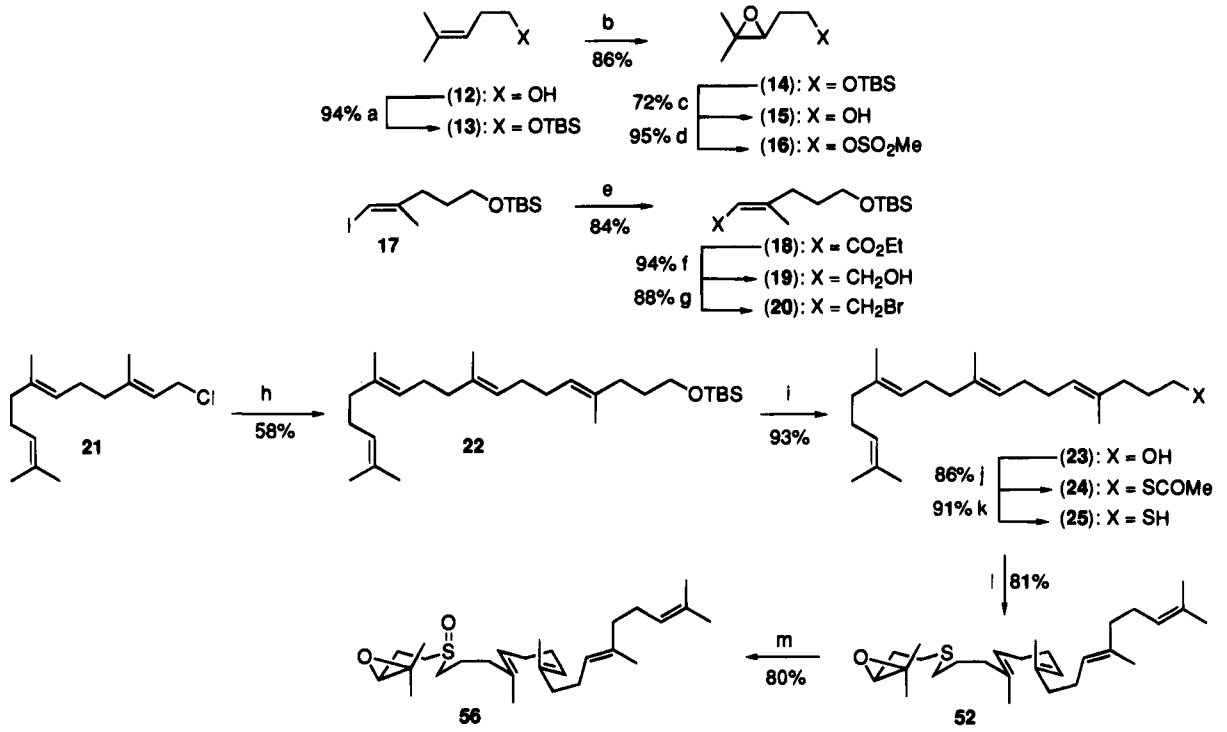


Figure 1.

Scheme 2



[a] (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) MCPBA, CH_2Cl_2; (c) Bu_4NF, THF; (d) $MeSO_2Cl$, Et_3N, −50 °C, CH_2C_12; (e) *n*-BuLi, −78 °C, THF; then $ClCO_2Et$; (f) DIBAL-H, ether; (g) $MeSO_2Cl$, Et_3N, −40 °C, LiBr, CH_2Cl_2; (h) Li, Ph_2, 2 h, THF, then BaI_2, 0.5 h, then **21**, 0.5 h, −78 °C, THF, then **20**, 12 h, THF; (i) Bu_4NF, THF; (j) PPh_3, *i*-$PrO_2CN{=}CNCO_2Pr$-*i*, MeCOSH, 0 °C, THF; (k) $LiAlH_4$, ether; (l) 50% NaOH, **16**, Oct_4NBr, 40 °C, H_2O−toluene; (m) $KHSO_5$, 2 min, −5 °C, MeOH.

conversion of **17**[17] to the vinyllithium with 1.1 equiv of *n*-BuLi at −78 °C followed by addition of ethyl chloroformate. This procedure gave conjugated ester **18** which was reduced with DIBAL-H to alcohol **19**, which was, in turn, converted to allylic bromide **20**. Coupling with farnesyl chloride (**21**) was achieved by the barium derivative of **21**[25] to give the protected tetraenol **22** in 58% yield. Deprotection and reaction of **23** with thiolacetic acid gave **24**, which was reduced to thiol **25** in 73% yield over three steps.[26] Coupling of mesylate **16** and thiol **25** to give **52** was achieved in 81% yield by treatment with 50% NaOH in toluene:H_2O (1:1) in the presence of tetraoctylammonium bromide as a phase-transfer agent.[27] Oxidation of **52** with $KHSO_5$ in MeOH gave sulfoxide **56** in 80% yield.[28] Structures of **52** and **56** were confirmed by ^1H NMR COSY spectra.

The synthesis of **53** and **57** in which the sulfur replaces C-10 of 2,3-OS involved coupling of epoxy mesylate **31** with trienic thiol **34** (Scheme 3). The former was prepared from homogeraniol (**26**)[29] which was initially protected (to **27** and converted via NBS in THF−H_2O (3.8:1)[30] to bromohydrin **28** and then to epoxide **29**. Deprotection of **29** using Bu_4NF gave epoxy alcohol **30**, which was converted to mesylate **31**. Preparation of trienic thiol **34** involved Mitsunobu reaction of **32**[31] with thiolacetic acid to give **33**, which was reduced to the thiol **34**.[26] Coupling of **31** and **34** to give **53** in 73% yield was carried out with the aid of a phase-transfer agent.[27] Oxidation of **53** with $KHSO_5$ in MeOH gave sulfoxide **57** in 84% yield.[28] Structures of **53** and **57** were confirmed by ^1H NMR COSY spectra.

The synthesis of **54**, **58**, and **59** in which sulfur replaces C-14

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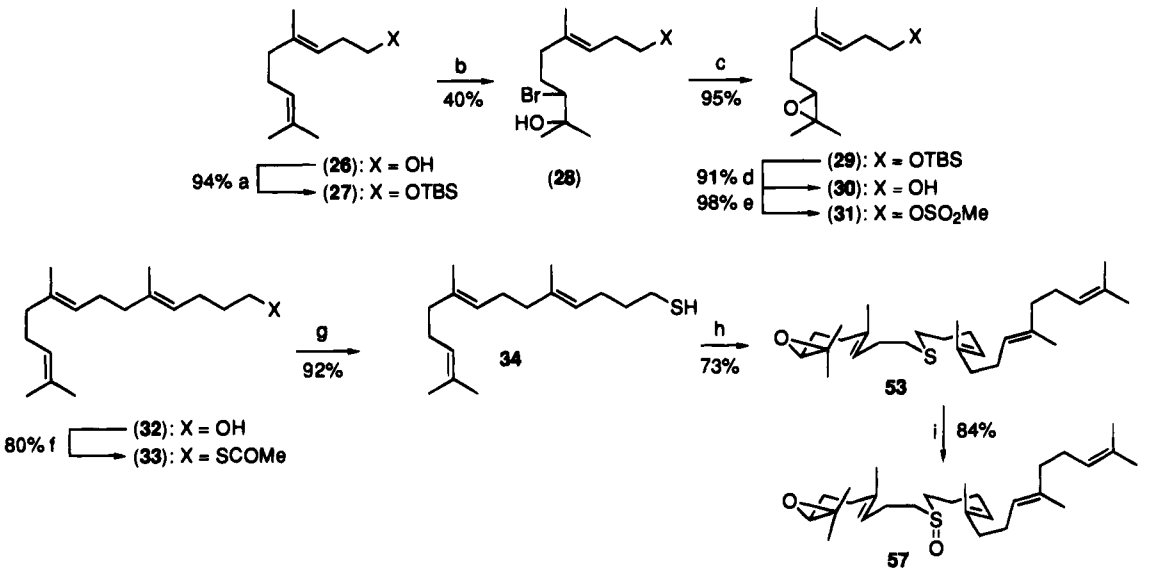
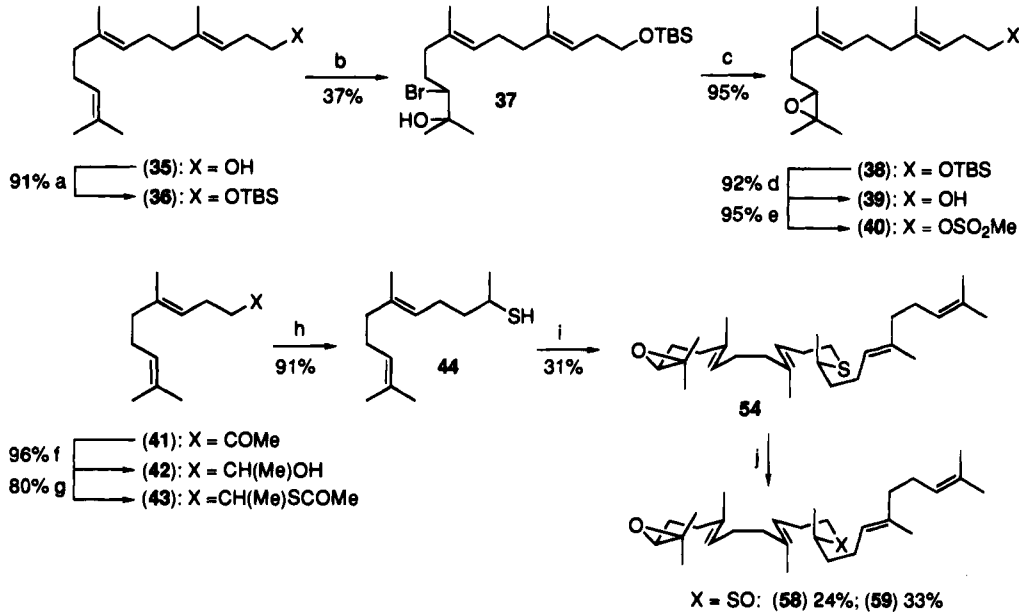
Scheme 3



[a] (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) 1.0 equiv of NBS, 0 °C, THF−H_2O; (c) K_2CO_3, MeOH; (d) Bu_4NF, THF; (e) $MeSO_2Cl$, Et_3N, −50 °C, CH_2Cl_2; (f) PPh_3, *i*-$PrO_2CN{=}CNCO_2Pr$-*i*, MeCOSH, 0 °C, THF; (g) $LiAlH_4$, 0 °C, ether; (h) 50% NaOH, **31**, Oct_4NBr, 40 °C, H_2O−toluene; (i) $KHSO_5$, 2 min, −5 °C, MeOH.

Scheme 4



[a] (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) 1.0 equiv of NBS, 0 °C, THF−H_2O; (c) K_2CO_3, MeOH; (d) Bu_4NF, THF; (e) $MeSO_2Cl$, Et_3N, −50 °C, CH_2Cl_2; (f) $LiAlH_4$, (g) PPh_3, *i*-$PrO_2CN{=}CNCO_2Pr$-*i*, MeCOSH, 0 °C, THF; (h) $LiAlH_4$, 0 °C, ether; (i) 50% NaOH, **40**, Oct_4NBr, 40 °C, H_2O−toluene; (j) $KHSO_5$, 2 min, −5 °C, MeOH.

of 2,3-OS involved coupling of epoxy mesylate **40** and dienic thiol **44** (Scheme 4). The former was prepared from homofarnesol (**35**) by a sequence involving hydroxyl protection to **36**, hydrobromination to **37**, dehydrobromination to **38**, hydroxyl deprotection to **39**, and mesylation to **40**. Dienic thiol **44** was prepared from geranylacetone (**41**) via reduction to **42**, reaction of the latter with thiolacetic acid to give thioacetate **43**, and reduction. Coupling of mesylate **40** and thiol **44** under phase-transfer conditions was more difficult than for previous cases because coupling involved a secondary sulfide. The maximum yield in several coupling experiments was 31% of **54**. Oxidation[28] of **54** with $KHSO_5$ in MeOH gave two diastereoisomers, **58** and **59**, which were obtained separately after column chromatography in 24% and 33% yields, respectively.[32] ^1H NMR spectra of **58** and **59** show identical features except signals attributable to a methyl and a hydrogen attached to C-15 of **58** and **59**. Thus, the less polar (TLC) diastereoisomer **58** is the *threo* isomer with $\delta = 1.23$ (d, $J = 6.9$ Hz) for the CH_3 and $\delta = 2.73$ for the hydrogen attached to C-15 while the more polar diastereomer **59** is the *erythro* isomer with $\delta = 1.27$ (d, $J = 6.9$ Hz) for the CH_3 and $\delta = 2.67$ for the hydrogen attached to this carbon. Structures of **54**, **58**, and **59** were confirmed by ^1H NMR COSY spectra.

Similar chemistry was applied to the synthesis of **55** (and **60**) in which sulfur replaced C-19 of 2,3-OS (Scheme 5). Thus, **55** was prepared by coupling of epoxy mesylate **48** and thiol **51**. The former was prepared from **22** by hydrobromination to **45**,[30] deprotection and dehydrobromination to **47** and mesylation

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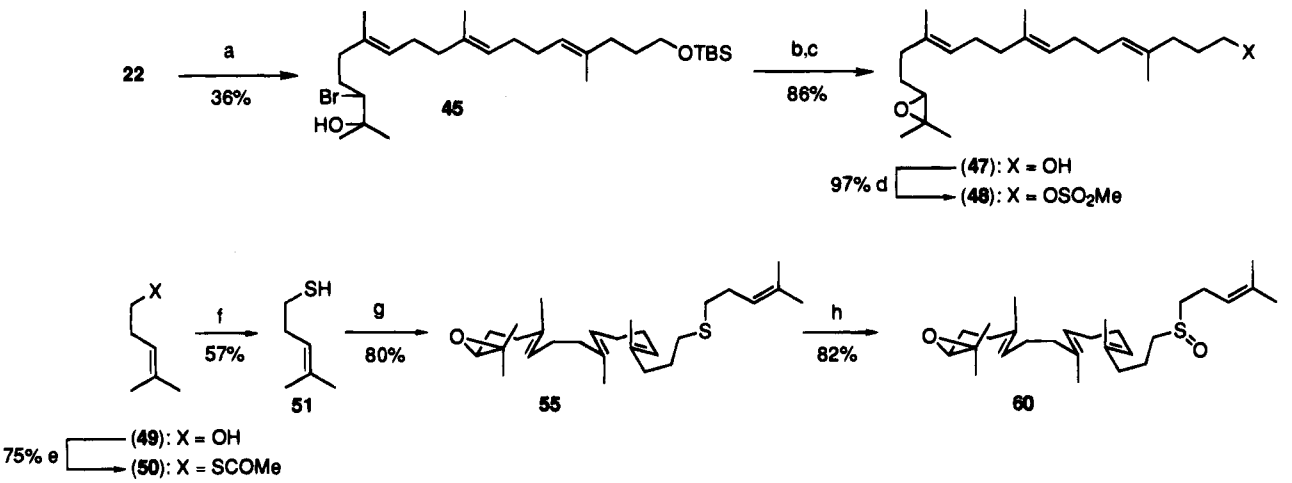
Scheme 5



[a] (a) 1.0 equiv of NBS, 0 °C, THF−H_2O; (b) K_2CO_3, MeOH; (c) Bu_4NF, THF; (d) $MeSO_2Cl$, Et_3N, −50 °C, CH_2Cl_2; (f) PPh_3, *i*-$PrO_2CCN{=}CNCO_2Pr$-*i*, MeCOSH, 0 °C, THF; (f) $LiAlH_4$, 0 °C, ether; (g) 50% NaOH, **48**, Oct_4NBr, 40 °C, H_2O−toluene; (h) $KHSO_5$, 2 min, −5 °C, MeOH.

Table 1

compd	IC_{50}[a] (μM) *C. albicans* cyclase (cell-free)	rat liver cyclase (cell-free)	MDBK[b] (intact cells)
52	0.069	0.0084	1.16
53	0.069	0.55	2.31
54	2.24	5.15	76.2
55	0.0023	0.00082	4.62
56	0.16	1.22	1.11
57	0.26	ND[e]	0.45
58	3.90	1.73	0.87
59	5.41	7.78	0.87
60	0.065	0.29	0.45
Keto[c]	ND[e]	ND[e]	0.94
Nafti[d]	ND[e]	ND[e]	10.4

[a] IC_{50}, concentration of inhibitor required to reduce enzyme activity by 50%. [b] MDBK, Madin Darbin bovine kidney cells. [c] Keto, ketoconazole. [d] Nafti, naftifine. [e] ND, not determined.

to **48**. Thiol **51** was prepared from the corresponding alcohol **49**.[26] Coupling of **48** and **51** to **55** was achieved in 80% yield.[27] Oxidation[28] of **55** with $KHSO_5$ in MeOH gave sulfoxide **60** in 82% yield. Structures of **55** and **60** were confirmed by ^1H NMR COSY spectra.

An attempt to prepare all of the sulfonium compounds from their corresponding sufides (**52**−**55**) for biological testing failed due to the instability of the sulfonium compounds.

Biological Results. 2,3-Oxidosqualene analogs **52**−**60** were examined for their ability to inhibit *C. albicans* and rat liver OSC in cell-free extracts as well as cholesterol biosynthesis in intact MDBK cells (Table 1). Comparison of activity is best measured in cell-free systems since adventitious adsorption and differing penetration into the cells distorts relative activities to a larger degree in whole-cell systems. All 2,3-OS analogs prepared in this study possess sufficient conformational flexibility to assume conformations that should allow them to be recognized by OSCs as substrates.

2,3-OS analogs **52** and **56**, which situate sulfur at the position normally occupied by C-6, designed to interfere with the formation of the A ring, showed more potent inhibition in fungal and rat liver OSC [for **52**, IC_{50} = 0.069 μM, *C. albicans;* 0.0084 μM, rat liver, Table 1] than previously reported inhibitors.[13] It is remarkable that thioether **52** is 2.3-fold more potent in *C. albicans* and 145-fold more potent in rat liver cyclase than the sulfoxide **56**. If **52** and **56** are acting as unmodified substrate analogs, these relative activities reveal a stronger interaction for **52** with OSC binding sites normally stabilizing the initially formed cation **3**.

2,3-OS analogs **53** and **57** possess sulfur at the position normally occupied by C-10 and were designed to interfere with B ring formation. Again, the thioether **53** was more potent (3.7-fold in *C. albicans*) than the sulfoxide **57**. For *C. albicans* OSC, **53** was as potent as **52** which qualified it as a more potent inhibitor than any previously reported (Table 1).[13] In rat liver OSC, **53** was 65-fold less potent than **52**. Thioether **53** was the only thioether examined in this study to be more active in *C. albicans* than rat liver cyclase (~8-fold). The higher inhibition of **52** compared to **53** in *C. albicans* OSC is consistent with the stronger interaction of cation **3** compared with **4** which would be expected if formation of ring A is slower than for ring B.

2,3-OS analogs **54** and **58** possess sulfur at the position normally occupied by C-14 and were expected to interfere with the anti-Markovnikov cyclization leading to the C ring. Inhibition observed for thioether **54** in the cell-free *C. albicans* OSC reveals that it is 32-fold less potent than **52** or **53** and 613-fold less potent than **52** in rat liver cyclase (Table 1). The low activity of **54** compared to **52** or **53** could be due to misplacement of the sulfur in **54**. Thus, formation of ring C could proceed via cyclization to a five-membered ring and formation of a tertiary carbonium ion followed by a 1,2 shift.[4e,f] In this event, the sulfurs in **54** and **58** should be more effective at the position normally occupied by C-15. The van Tamelen and Krief groups have examined this question by cyclization of 2,3-OS analogs lacking Δ^{18} unsaturation and possessing *Z* geometry of Δ^{18}. These derivatives cyclized to produce a five-membered C ring, suggesting preferential cation formation at C-15 if one interfered with subsequent ring D formation.[4e,f] For both *C. albicans* and rat liver cyclases, thioether **54** exhibited activity similar to that of the corresponding sulfoxides **58** and **59** with **58** being slightly more inhibitory (~3-fold) than **54** in the latter. This is the only case in which a sulfoxide was more inhibitory than the corresponding thioether and is consistent with action of both 2,3-OS analogs as unmodified substrate mimics.

2,3-OS analogs **55** and **60**, possessing sulfur at C-19, were designed to interfere with the formation of the protosterol cation **6** (Scheme 1). Analog **55** is the most powerful inhibitor prepared in this study [IC_{50} = 0.0023 μM, *C. albicans;* 0.00082 μM, rat liver (Table 1)]. This 2,3-OS mimic is some 30-fold

more potent than **52** or **53** and 974-fold more potent than **54** in *C. albicans* and 102-, 670-, and 6,280-fold more active than **52**, **53**, and **54**, respectively in rat liver cyclase. It is the most powerful OSC inhibitor reported to date and suggests that 2,3-OS modifications in the region of C-19 are good candidates for further investigation.

Sulfoxides were generally less active than their corresponding thioethers. In *C. albicans* cyclase, sulfoxide analogs of the thioethers were 2- to 3-fold less potent except for **60** which was 28-fold less potent than its thioether analog **55**. In rat liver cyclase the differences between thioethers and the corresponding sulfoxides were more striking. Thioether **52** was 145-fold more active than sulfoxide **56**, whereas differences between **54** and its sulfoxides **58** and **59** were less than 3-fold. The largest difference between a thioether and the corresponding sulfoxide was observed for **55** *vs* **60**. The former was 353-fold more active than the latter in rat liver cyclase. An interesting feature of sulfoxide activity is the relative activity of diastereoisomeric **58** and **59**. In rat liver cyclase they exhibited noticeably different activities which actually bracket the activity of the corresponding thioether (0.33- and 1.5-fold differences compared with **54**). We attribute the activity of the sulfoxides to coulombic interactions of the electron-deficient sulfurs with the sites normally stabilizing cationic intermediates **3**−**6** (Scheme 1). It is noteworthy that **60**, which possesses a sulfoxide in place of C-19 of 2,3-OS, exhibited the strongest inhibitory activity of any sulfoxide in both *C. albicans* and rat liver cyclases.

The superior activity of thioethers in comparison to their sulfoxide analogs is puzzling if both types of analogs behave as unmodified substrate mimics. In the event that **52**−**55** are cyclized to the sulfonium ions **8**−**11** (Figure 1) or close structural relatives, one would expect the observed stronger inhibition for thioethers than for the corresponding sulfoxides. The mode of action of **55** with pig liver OSC[6b] has been probed in preliminary kinetic studies[33] (I. Abe and G. D. Prestwich, unpublished results). With this mammalian OSC, **55** acts as a competitive inhibitor and its inhibition is reversible in comparison with 29-methylidene-2,3-OS.[12] This result suggests that **55** is recognized as a pseudo substrate and competes with the substrate for the same binding site.

Activity of **52**−**60** in intact mammalian MDBK cells was significantly lower than that in the cell-free systems. Thioethers **52**−**54** exhibited the same relative order of activity in this system as they did in the cell-free systems. Thus, **52** was more potent than **53** and the latter was more potent than **54**. In MDBK cells, **55** was observed to be less active than both **52** and **53**. Indeed, in this system sulfoxides were either as active as (**52** *vs* **56**) or more active (**53** *vs* **57**, **54** *vs* **58** and **59**, **55** *vs* **60**) than their thioether analogs. We suspect that the lower activity of **52**−**60** in MDBK cells is due to low permeability of the thioethers relative to the sulfoxides and possibly also to adventitious adsorption. Interestingly, none of the compounds were toxic to MDBK cells up to 100 μg/mL. Several of the compounds prepared in this study were more potent inhibitors of cholesterol synthesis in MDBK cells than ketoconazole[34] (a 14α-demethylase inhibitor) and all except **54** were more active than naftifine[35] (a squalene epoxidase inhibitor) (Table 1).

(33) Compound **55** and related sulfur 2,3-oxidosqualenes have been tested on purified pig liver OSC in collaboration with Professor G. D. Prestwich at State University of New York at Stony Brook, Stony Brook, NY. The detailed mechanistic features of the inhibition will be the subject of future publication. Stack, D.; Zheng, Y. F.; Perez, A. L.; Abe, I.; Prestwich, G. D.; Oehlschlager, A. C. Unpublished results.

(34) Heel, R. C.; Brogden, R. N.; Carmine, A.; Morley, P. A.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *23*, 1.

(35) Ryder, N. S.; Dupont, M. C. *Biochem. J.* **1985**, *230*, 765.

2,3-OS analogs **52**−**60** were examined for their antifungal activity against *C. albicans*. All exhibited MIC values over 100 μg/mL compared to the presently used commercial antifungals ketoconazole (*C. albicans* MIC 20 μg/mL). Further, none inhibited ergosterol synthesis in growing *C. albicans* cells up to 100 μg/mL (data not shown). We suspect that the poor activity of **52**−**60** in growing *C. albicans* cells is due to low permeability of these compounds.[20b]

In summary, efficient routes have been developed for preparation of 2,3-oxidosqualenes with sulfur or sulfoxide replacing those carbons considered to develop cationic character during the OSC-mediated cyclization. Thioethers **52**−**55** showed powerful inhibitory activity in fungal and mammalian OSC while the corresponding sulfoxides were less potent. It is difficult to rationalize the superior inhibition of thioethers **52**−**55** when compared to that of the sulfoxides **56**−**60** unless one assumes cyclization of the former to sulfonium ions **8**−**11** (Figure 1) or structural relatives. The relative activity of **52**−**55** suggests that placement of heteroatoms near C-19 of 2,3-OS results in the most significant inhibition. Thioether **55** exhibits IC_{50} values of 0.0023 and 0.00082 μM in *C. albicans* and rat liver cyclase, respectively, and is the most potent OSC inhibitor reported to date. Preliminary kinetic studies of the inhibition of pig liver OSC of **55** (I. Abe and G. D. Prestwich, unpublished work) reveal that it is a competitive inhibitor. This is consistent with its activity in an unmodified form and supports the fact that **55** may act as a substrate mimic.

Experimental Section

A. General Chemical Methods. NMR spectra were recorded on a Bruker AMX-400 spectrometer for ^1H and ^{13}C NMR spectra, respectively. Mass spectra were obtained on a Hewlett-Packard 5985B GC/MS equipped with a DB-1 capillary column (30 mm × 0.32 mm i.d.; with 0.25 μM) system operating at 70 eV for electron impact (EI) ionization. Chemical ionization (CI) was performed using isobutane as the proton source. IR spectra were recorded on a Perkin-Elmer Model FT 1605 spectrophotometer. Elemental analyses were performed using a Carlo Erba Model-1106 elemental analyzer.

Tetrahydrofuran and diethyl ether were distilled from sodium−benzophenone−ketyl. Triethylamine, acetonitrile, and dichloromethane were all freshly distilled from CaH_2 prior to use. *N*-Bromosuccinimide and *N*-chlorosuccinimide were recrystallized from glacial acetic acid, washed with ice−water, and dried under high vacuum prior to use. Triphenylphosphine was dried over phosphorus pentoxide under high vacuum for 4 h in a heating pistol using acetone as solvent. Anhydrous BaI_2 was prepared by drying $BaI_2 \cdot H_2O$ (Aldrich, 95%) at 160 °C for 2 h under high vacuum (<5 Torr). Ethyl chloroformate (Sigma) was freshly distilled under argon prior to use. Other chemicals obtained from commercial sources were used without further purification. All moisture- and air-sensitive reactions were conducted under argon in vacuum-dried glassware. A nitrogen glovebag was used to weigh all the moisture-sensitive compounds. Syringes and canulas were used to transfer reagents. Unless otherwise stated, standard workup refers to the combined organic extracts being washed with ice-cold brine, dried over anhydrous $MgSO_4$, amd filtered, with the filtrate being concentrated *in vacuo*.

B. Biological Methods. 1. Cells and Culturing Conditions. *C. albicans* SC5314 was from the Squibb Culture Collection (Princeton, NJ). It was grown in casein hydrolysate−yeast extract−glucose (5 g each per liter water) medium at 30 °C. Madin Darbin bovine kidney (NBL-1) epithelial cells (MDBK cells) ATCC CCL.22, originally obtained from the American Type Culture Collection (Rockville, MD), were grown as a monolayer and used between the 130 and 150 passages. Stock cultures were maintained in a humidified incubator (5% CO_2) at 37 °C in 250 mL (75 cm^2) flasks containing 15 mL of Dulbecco's modified Eagle medium (D-MEM; high glucose, with L-Gln but no sodium pyruvate) (GIBCO, Grand Island, NY) supplemented with 10% fetal calf serum (FCS) (GIBCO). Cells were split (1:5 ratio) every 3 days.

2. *In-Vitro* Antifungal Activity and Mammalian Cell Toxiciity. The minimum inhibitory concentrations (MIC, concentration of inhibitor required to completely inhibit growth of the organism *in vitro*) of **52**–**60** were measured in casein hydrolysate–yeast extract–glucose (5 g each per liter of water) medium (96-well plates) against standard strains of *C. albicans* after overnight incubation at 35 °C. On day 0, MDBK cells were washed with 10 mL of Dulbecco's phosphate-buffered saline (D-PBS) (GIBCO) and then dissociated by being incubated for 10 min at 37 °C with 5 mL of 0.05% trypsin–0.53 mM EDTA (GIBCO). After the reaction was quenched with 19 mL of D-MEM–FCS, 4 mL of the cell suspension was removed, diluted with 46 mL of D-MEM–FCS (~25 000 cells/mL), and transferred (0.5 mL samples) to 11.3 mm wells of a 48-well plate (Costar Corp., Cambridge, MA). On day 3, test compounds were added and cells were incubated for an additional 24 h. On day 4, D-MEM–FCS was removed from the wells and 0.2 mL of D-PBS was added to each well followed by 0.05 mL of 0.1% Trypan blue (GIBCO) in water. Cells were inspected immediately under an inverted phase microcope (Zeiss IM 35) for dye exclusion and morphology.

3. Cholesterol Biosynthesis Inhibition Assays in MBDK Cells. MDBK cells in 75 mL flasks were washed with 10 mL of Dulbecco's phosphate-buffered saline (D-PBS) (GIBCO) and then dissociated by being incubated with 5 mL of trypsin (0.05%)–0.53 mM EDTA for 10 min at 37 °C. After the reaction was quenched with 19 mL of D-MEM–FCS, 2 mL of the resulting suspension was transferred to 35 mm wells of a 6-well plate. After 3 days, D-MEM–FCS was replaced by 1 mL of D-MEM in each well. After 4 days, 5 μmol of [1,2-^{14}C]-AcONa (New England Nuclear, Boston Mass., specific activity 55 μCi/μmol; 250 μCi/2.5 mL of EtOH) and 5 μL of test compound (100-fold concentrated in 10% DMSO) were added. After 10 h at 37 °C, the medium was removed from the wells, 1 mL of cold TCA (5%) was added to each well, and after 15 min at 4 °C, the cells were scraped with a disposable plastic cell scraper (Costar Corp.). The suspension was transferred to a glass tube (13 × 100 mm), and the well was washed twice with 1 mL of H_2O which was also transferred to the tube. After centrifugation at 3000 rpm for 3 min (Savant centrifuge), the supernatant was removed and the pellets were lyophilized. They were then extracted once with 1.5 mL of MeOH and once with 1 mL of MeOH:C_6H_6 (1:1, v:v). The combined extracts were placed under a stream of nitrogen to remove the solvent, and the residue was redissolved in 20 μL of CH_3Cl:MeOH (2:1, v:v). Then 10 μL of the resulting extract was spotted on silica gel TLC plates and developed with petroleum ether:Et_2O:AcOH (85:15:1, v:v:v). The cholesterol and lanosterol bands were localized by autoradiography (1–2 d exposure), scraped, and counted. Inhibition of cholesterol biosynthesis was determined for several concentrations of inhibitor and that which reduced it to 50% of control was reported as the IC_{50}.

4. Enzyme Inhibition Assay. This was carried out as previously described in ref 36. IC_{50} values were measured using a cell-free preparation of *C. albicans*. Cells collected from an 8 h culture in TYG medium were digested for 30 min with Zymolase 100T (Seikagaku Kogyo, Japan). For each gram cell mass were used 1 mg of Zymolase, 12.5 μL of 2-mercaptoethanol, and 5 mL of a digestion buffer (50 mM phosphate, pH 7.4, containing 1 M mannitol). The resulting protoplasts were collected by centrifugation and lysed in 100 mM phosphate buffer, pH 6.9. The supernatant after centrifugation at 15000*g* is the cell-free extract which retains full cyclase activity as shown by a 42% incorporation of racemic [^{14}C]-2,3-oxidosqualene in the presence of the nonionic detergent Decyl Poe (*n*-decylpentaoxyethylene, Bachem, Switzerland). This detergent inhibits the further metabolization of lanosterol to fungal sterols by the cell-free preparation and thus allows an accurate measurement of the inhibitory activity of test compounds. The nonsaponifiable lipids were extracted and applied to TLC plates (silica gel F-254, Merck, Germany) which were developed twice in dichloromethane. The radiolabeled spots, in this case only oxidosqualene and lanosterol, were quantified with an automatic TLC scanner (Rita 3200, Raytest, Germany). The % activity was plotted against log inhibitor concentration to determine the IC_{50}.

The IC_{50} values against the rat liver cyclase were measured in a cell-free system in an analogous manner. The chopped, fresh or frozen, livers were homogenized in a loose-fitting potter homogenizer with 4 mL per gram of a 100 mM phosphate buffer, pH 7.4, containing 0.5 mM dithiothreitol and 10 mM nicotinamide. After filtering through glass wool and centrifuging for 30 min at 15 000 rpm, the supernatant was diluted with 20% glycerol, shock frozen in liquid nitrogen, and stored at −70 °C until use. The experimental procedure was as for *C. albicans*, although it was found that better incorporation of radiolabeled oxidosqualene was obtained if the reaction was performed without detergent, with the substrate added as an alcoholic solution. This is presumably due to the different composition of the rat liver extract.

4-Methyl-3-pentenyl *tert*-Butyldimethylsilyl Ether (13). To a solution of **12** (0.45 g, 4.5 mmol) in CH_2Cl_2 (30 mL) and Et_3N (0.485 g, 4.8 mmol) at 0 °C were added *tert*-butyldimethylsilyl chloride (0.694 g, 4.6 mmol) and 4-(dimethylamino)pyrine (0.02 g). This was stirred at 0 °C for 0.5 h and at room temperature for 6 h. The reaction mixture was poured into water (20 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (4 × 30 mL). Standard workup followed by flash column chromotography using diethyl ether:pentane (1:9) gave **13** (0.91 g, 94% yield) as colorless oil: IR (film) 1672, 1473, 1257, and 1100 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 215 (M^+ + 1, 1.0), 157 (6.2), 95 (2.9), 91 (2.4), 89 (2.2), 85 (9.1), 84 (7.4), 83 (100), 81 (9.0); ^{1}H NMR ($CDCl_3$, ppm) 5.12–5.08 (m, 1H), 3.57 (t, J = 7.2 Hz, 2H), 2.21 (dt, J = 7.2, 7.2 Hz, 2H), 1.69 (s, 3H), 1.59 (s, 3H), 0.89 (s, 9H), 0.048 (s, 6H). Anal. Calcd for $C_{12}H_{26}OSi$: C, 67.22; H, 12.22. Found: C, 67.36; H, 12.30.

4-Methyl-3,4-epoxypentyl *tert*-Butyldimethyl Ether (14). To a stirred solution of **13** (0.91 g, 4.25 mmol) in CH_2Cl_2 (35 mL) at −40 °C was added *m*-CPBA (1.08 g, 5.0 mmol, 80% by weight) in one portion. The reaction mixture was stirred for 0.5 h at this temperature and warmed to 0 °C over 1 h. The mixture was poured into saturated aqueous NaS_2O_3 solution (10 mL), and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phase was washed with saturated $NaHCO_3$ (2 × 20 mL). Standard workup followed by flash column chromotography using diethyl ether:pentane (3:7) gave pure **14** (0.843 g, 86% yield): IR (film) 1775, 1256, 1097, and 1005 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 231 (M^+ + 1, 100), 213 (44), 173 (44.3), 145 (32.6), 133 (4.1), 115 (2.2), 99 (79.2), 89 (23.4); ^{1}H NMR ($CDCl_3$, ppm) 3.79–3.75 (m, 2H), 2.84 (t, J = 6.2 Hz, 1H), 1.86–1.68 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 0.89 (s, 9H), 0.059 (s, 6H). Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.68; H, 11.45.

4-Methyl-3,4-epoxypentan-1-ol (15). To a solution of **14** (0.81 g, 3.52 mmol) in THF (10 mL) at room temperature was added tetrabutylammonium fluoride (10 mL, 1 M solution in THF, 10 mmol). This was stirred for 8 h at room temperature. Then water (10 mL) was added, and the mixture was extracted with ether (4 × 20 mL). Standard workup followed by flash chromatography using diethyl ether:pentane (9:1) afforded (GC purity 91%) **15** (0.295 g, 72% yield): IR (film) 3428 and 1064 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 117 (M^+ + 1,100), 99 (43), 85 (4.2), 81 (4.0); MS *m/z* (rel intensity) 116 (M^+, trace), 101 (4.0), 85 (100), 73 (4.6), 71 (4.2), 59 (97), 57 (25.5), 45 (15.5), 43 (40.6), 42 (20.3), 41 (47.2); ^{1}H NMR ($CDCl_3$, ppm) 3.88–3.79 (m, 2H), 2.90 (dd, J = 4.7, 7.8 Hz, 1H), 1.92–1.84 (m, 2H), 1.74–1.66 (m, 1H), 1.32 (s, 3H), 1.29 (s, 3H).

3,4-Epoxy-4-Methylpentyl Methanesulfonate (16). To a solution of **15** (0.174 g, 1.5 mmol) in CH_2Cl_2 (20 mL) at −50 °C were added triethylamine (0.202 g, 2.0 mmol) and methanesulfonyl chloride (0.208 g, 1.8 mmol). This was stirred at −50 °C for 10 min, warmed to 0 °C over 1 h, and then poured into water (10 mL), and the organic phase was separated. The aqueous phase was extracted with ether (3 × 20 mL). Standard workup followed by high vaccum gave **16** (0.276 g, 95% yield) of sufficient purity (GC purity >99%) for use in the subsequent reaction without further purification: CIMS *m/z* (isobutane, rel intensity) 195 (M^+ + 1, 100), 177 (10.2); ^{1}H NMR ($CDCl_3$, ppm) 4.43–4.32 (m, 2H), 3.03 (s, 3H), 2.86 (dd, J = 4.9, 7.4 Hz, 1H), 2.13–2.05 (m, 1H), 1.91–1.81(m, 1H), 1.33 (s, 3H), 1.29 (s, 3H).

Ethyl 6-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*E*)-hexenoate (18). To a stirred solution of **17** (0.681g, 2.0 mmol) in THF (30 mL) under argon at −78 °C was added dropwise *n*-BuLi (0.8 mL, 2.0 mmol, 2.5 M solution in hexane). The reaction was stirred for 20 min. Then freshly distilled ethyl chloroformate (0.21 mL, 2.2 mmol) was added dropwise and the mixture was allowed to stand at −78 °C for 1 h and

(36) Jolidon, S.; Polak, A. M.; Guerry, P.; Hartman, P. G. *Biochem. Soc. Trans.* **1990**, *18*, 47.

warmed to room temperature over 3 h before it was quenched by being poured into water (10 mL) and extracted with ether (3 × 20 mL). Standard workup followed by flash colunm chromatography using ethyl acetate:hexane (1:9) gave **18** (0.48 g, 84% yield): IR (film) 1719, 1649, 1256, 1223, 1148, and 1105 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 288 (M^+ + 2, 22.1), 287 (M^+ + 1, 100), 242 (3.6), 230 (2.2), 229 (13.3), 155 (16.8); ^1H NMR ($CDCl_3$, ppm) 5.65 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H), 2.19 (t, J = 7.7 Hz, 2H), 2.15 (s, 3H), 1.71−1.64 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 166.75, 159.73, 115.71, 62.31, 59.38, 37.26, 30.60, 25.90, 18.75, 18.22, 14.30, −5.37. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 63.01; H, 10.75.

6-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2(*E*)-hexen-1-ol (19). To a solution of **18** (0.45 g, 1.57 mmol) in ether (20 mL) at −78 °C under argon was added diisobutylaluminum hydride (DIBAL-H) (4 mL, 4 mmol, 1 M solution in hexane). The reaction was warmed to 0 °C and stirred for 1.5 h. Then excess DIBAL-H was destroyed by addition of water (1 mL), and the resulting mixture was poured into an ice-cold 5% aqueous solution of tartaric acid (10 mL). The mixture was extracted with ether (3 × 30 mL), and the combined organic phase was washed with $NaHCO_3$ solution. Standard workup followed by flash column chromatography using ethyl acetate:hexane (1:4) gave **19** (0.36 g, 94% yield) as colorless liquid: IR (film) 3344, 1669, 1255, and 1101 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 245 (M^+ + 1, 3.8), 227 (100), 228 (17.9), 133 (2.0); ^1H NMR ($CDCl_3$, ppm) 5.41 (t, J = 7.0 Hz, 1H), 4.14 (d, J = 6.8 Hz, 2H), 3.59 (t, J = 6.5 Hz, 2H), 2.05 (t, J = 7.5 Hz, 2H), 1.67 (s, 3H), 1.65−1.60 (m, 2H), 0.89 (s, 9H), 0.045 (s, 6H). Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.55. Found: C, 64.05; H, 11.70.

6-Bromo-4-methyl-4(*E*)-hexenyl *tert*-Butyldimethylsilyl Ether (20). To a solution of **19** (0.244 g, 1.0 mmol) in CH_2Cl_2 (15 mL) at −50 °C under argon were added Et_3N (0.19 mL, 1.36 mmol) and methanesulfonyl chloride (0.138 g, 1.2 mmol). This was stirred at −50 °C for 30 min, and then a solution of LiBr (0.217 g, 2.5 mmol) in THF (5 mL) was added into the mixture. The mixture was warmed to 0 °C and stirred for 1 h. Water (5 mL) was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Standard workup gave **20** (0.27 g, 88% yield) as a liquid: IR (film) 1663, 1255, 1101, 836, and 661 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 309/307 (M^+ + 1, 7.8, 8.5), 263 (13.4), 261 (16), 193 (6.7), 191 (7.4); ^1H NMR ($CDCl_3$, ppm) 5.45 (t, J = 8.0 Hz, 1H), 4.09 (d, J = 8.0 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 2.09 (t, J = 7.7 Hz, 2H), 1.72 (s, 3H), 1.68−1.58 (m, 2H), 0.89 (s, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 142.60, 120.39, 62.51,41.04, 35.67, 30.75, 29.69, 25.95, 18.31, 165.05.

4,9,13,17-Tetramethyloctadeca-4(*E*),8(*E*),12(*E*),16-tetraenyl *tert*-Butyldimethylsilyl Ether (22). This was prepared by coupling of farnesylbarium and **20** according to the procedure of Corey *et al.*[25] Flash column chromatography using ethyl acetate:hexane (1:20) gave **22** in 58% yield. IR and ^1H NMR spectra are in agreement with those reported in ref 11b.

4,9,13,17-Tetramethyloctadeca-4(*E*),8(*E*),12(*E*),16-tetraen-1-ol (23). This was prepared from **22** in 93% yield by same procedure as described for the preparation of **15**. **23**: IR (film) 3330, 1107, and 1058 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 319 (M^+ + 1, 100), 318 (M^+, 11.1), 301 (10.8), 263 (7.7), 249 (10.4), 237 (26.2), 219 (21.4), 193 (20.5), 163 (19.1); ^1H NMR ($CDCl_3$, ppm) 5.21−5.16 (m, 1H), 5.13−5.08 (m, 3H), 3.64 (dt, J = 5.9, 6.2 Hz, 2H), 2.10−1.95 (m, 14H), 1.74−1.64 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 9H), 1.29 (t, J = 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 135.27, 134.92, 134.75, 131.22, 124.89, 124.44, 124.29, 124.18, 62.86, 39.74, 36.02, 30.84, 28.25, 28.19, 26.81, 26.67, 25.65, 17.65, 16.04, 15.99, 15.89. Anal. Calcd for $C_{22}H_{38}O$: C, 82.95; H, 12.02. Found: C, 82.85; H, 12.05.

4,9,13,17-Tetramethyloctadeca-4(*E*),8(*E*),12(*E*),16-tetraenyl Thioacetate (24). To a solution of triphenylphosphine (0.81 g, 3.0 mmol) in THF (30 mL) was added diisopropyl azodicarboxylate (0.63 g, 3.0 mmol) at −20 °C. The reaction was stirred efficiently and warmed to 0 °C for 1 h by which time a thick white precipatate formed. Then a mixture of thioacetic acid (0.23 g, 3.0 mmol) and **23** (0.48 g, 1.51 mmol) in THF (5 mL) was added dropwise over 20 min at −20 °C. The mixture was warmed to 0 °C from −20 °C for 0.5 h and allowed to stand at 0 °C for 1 h. The mixture was then stirred overnight at room temperature, poured into water (10 mL), and extracted with ether (3 × 40 mL). Standard workup followed by flash colunm chromatography using ethyl acetate:hexane (5:95) as eluant gave **24** (0.49 g, 86% yield) as an oil: IR (film) 1695, 1135, 1107, 954, and 836 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 377 (M^+ + 1, 100), 335 (45.2), 293 (15.1), 267 (12.6), 253 (37.4), 225 (15.9), 213 (28.3), 199 (13.1), 185 (36.2), 171 (12.8), 151 (22.4), 137 (42.8), 123 (17.7); ^1H NMR ($CDCl_3$, ppm) 5.19−5.06 (m, 4H), 2.82 (t, J = 7.3 Hz, 2H), 2.32 (s, 3H), 2.10−1.93 (m, 14H), 1.70−1.63 (m, 2H), 1.68 (s, 3H), 1.60 (s, 6H), 1.58 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 196.00, 135.24, 134.91, 133.78, 131.21, 125.42, 124.46, 124.31, 124.21, 39.75, 38.69, 30.59, 28.67, 28.26, 28.18, 27.75, 26.82, 26.69, 25.65, 17.66, 16.05, 15.80. Anal. Calcd for $C_{24}H_{40}OS$: C, 76.54; H, 10.71. Found: C, 76.38; H, 10.56.

4,9,13,17-Tetramethyl-4(*E*),8(*E*),12(*E*),16-octadecatetraene-1-thiol (25). A solution of **24** (0.475 g, 1.26 mmol) in dry ether (5 mL) was slowly added to a stirred suspension of $LiAlH_4$ (0.303 g, 8.0 mmol) in dry ether (40 mL) under argon at 0 °C. After 0.5 h at 0 °C, excess $LiAlH_4$ was destroyed at −30 °C by slow addition of water (1.0 g). The reaction mixture was filtered, and the white precipatate was washed by ether (3 × 20 mL). Standard workup followed by flash colunm chromatography using ethyl acetate:hexane (1:20) as eluant gave **25** (0.381 g, 91% yield) as an oil: IR (film) 1666 and 838 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 335 (M^+ + 1, 100), 334 (M^+, 8.5), 333 (10.6), 265 (8.9), 257 (3.0), 211 (2.0); ^1H NMR ($CDCl_3$, ppm) 5.18−5.06 (m, 4H), 2.48 (dt, J = 7.1, 7.6 Hz, 2H), 2.10−1.95 (m, 14H), 1.74−1.66 (m, 2H), 1.68 (s, 3H), 1.60 (s, 9H), 1.59 (s, 3H), 1.33 (t, J = 7.9 Hz, 1H). Anal. Calcd for $C_{22}H_{38}S$: C, 78.98; H, 11.46. Found: C, 79.10; H, 11.62.

3,4-Epoxy-4-methylpentyl 4′,9′,13′,17′-Tetramethyl-4′(*E*),8′(*E*),12′(*E*),16′-octadecatetraenyl Sulfide (52). To a solution of NaOH (2.5 g, 60 mol) in H_2O (10 mL) and toluene (10 mL) were added tetraoctylammonium bromide (0.05 g), **16** (0.194 g, 1.0 mmol), and **25** (0.244 g, 0.73 mmol) at room temperature. This mixture was warmed to 40 °C and stirred for 10 h, and then extracted with ether (3 × 20 mL). Standard workup followed by chromatography using ethyl acetate:hexane (1:20) gave pure **52** (0.255 g, 81% yield) as a colorless oil: IR (film) 1667, 1249, and 1123 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 433 (M^+ + 1, 100), 432 (M^+, 9.0), 391 (1.30), 363 (1.8), 335 (4.0), 333 (4.2), 301 (1.9), 295 (8.3), 257 (2.3); ^1H NMR ($CDCl_3$, ppm) 5.18−5.06 (m, 4H), 2.82 (t, J = 6.2 Hz, 1H), 2.78−2.58 (m, 2H), 2.56−2.48 (m, 2H), 2.10−1.93 (m, 14H), 1.86−1.77 (m, 2H), 1.76−1.66 (m, 2H), 1.68 (s, 3H), 1.59 (s, 9H), 1.58 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.22, 134.92, 134.08, 131.02, 125.16, 124.44, 124.28, 124.21, 63.25, 58.50, 39.74, 38.75, 31.85, 29.30, 29.01, 28.23, 27.91, 26.80, 26.68, 25.66, 24.76, 18.66, 17.73, 16.05, 15.89. Anal. Calcd for $C_{28}H_{48}OS$: C, 77.71; H, 11.18. Found: C, 77.50; H, 10.95.

3,4-Epoxy-4-methylpentyl 4′,9′,13′,17′-Tetramethyl-4′(*E*),8′(*E*),12′(*E*),16′-octadecatetraenyl Sulfoxide (56). This was prepared by oxidation of **52** according to the procedure of Trost *et al.*[28] for the oxidation of thioanisole to its corresponding sulfoxide. Chromatography using ethyl acetate:hexanes (7:3) gave **56** in 80% yield: IR (film) 1666, 1056, and 870 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 449 (M^+ + 1, 78), 448 (M^+, 5.0), 391 (44.5), 351 (82.7), 299 (39), 149 (100); ^1H NMR ($CDCl_3$, ppm) 5.21−5.16 (m, 1H), 5.15−5.06 (m, 3H), 2.88 (dd, J = 4.6, 7.9 Hz, 1H), 2.85−2.52 (m, 4H), 2.22−2.10 (m, 4H), 2.10−1.8 (m, 14H), 1.68 (s, 3H), 1.60 (s, 9H), 1.56 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). Anal. Calcd for $C_{28}H_{48}O_2S$: C, 74.94; H, 10.79. Found: C, 74.86; H, 10.67.

4,8-Dimethyl-3(*E*),7-nonadien-1-ol (26, Homogeraniol). This compound was prepared by the method of Leopold *et al.*[29]

4,8-Dimethyl-3(*E*),7-nonadienyl *tert*-Butyldimethylsilyl Ether (27). This was prepared in 94% yield by the procedure described for preparation of **13**. **27**: IR (film) 1663, 1255, and 1103 cm^{-1}; CIMS *m/e* (isobutane, rel intensity) 284 (M^+ + 2, 2.4), 283 (M^+ + 1, 10.3), 225 (27.2) 151 (100), 149 (9.6), 137 (4.0), 123 (4.9); ^1H NMR ($CDCl_3$, ppm) 5.12−5.09 (m, 2H), 3.58 (t, J = 7.2 Hz, 2H), 2.23 (dt, J = 7.2, 7.1 Hz, 2H), 2.08−1.98 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 0.892 (s, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.95, 131.27, 124.35, 120.35, 63.12, 39.76, 31.87, 26.71, 25.96, 25.62, 18.35,

17.61, 16.13, −5.26. Anal. Calcd for $C_{17}H_{34}OSi$: C, 72.27; H, 12.13. Found: C, 72.16; H, 12.29.

7-Bromo-8-hydroxy-4,8-dimethyl-3(*E*)-nonenyl *tert*-Butyldimethylsilyl Ether (28). To a vigorously stirred solution of **27** (1.58 g, 5.60 mmol) in THF (106 mL) and water (28 mL) at 0 °C was added dropwise over 30 min a solution of *N*-bromosuccinimide (1.0 g, 5.61 mmol) in THF (16 mL) and water (4.9 mL). The mixture was stirred for 1 h at 0 °C; then the THF was removed *in vacuo* and the aqueous phase was extracted with ether (3 × 30 mL). Standard workup followed by flash column chromatography gave recovered starting material **27** (0.42 g) and pure **28** (0.85 g, 40% yield) as a colorless oil: IR (film) 3443, 1255, and 1103 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 379 (M^+ + 1, 31.8), 321 (8.3), 249 (76.5), 247 (73.8), 229 (17.1), 167 (31.9), 149 (100); ^1H NMR ($CDCl_3$, ppm) 5.21 (t, *J* = 7.2 Hz, 1H), 3.98 (dd, *J* = 1.9, 11.3 Hz, 1H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.34 (m, 1H), 2.23 (dt, *J* = 7.1, 7.2 Hz, 2H), 2.13−2.07 (m, 1H), 2.01−1.93 (m, 2H), 1.86−1.74 (m, 1H), 1.61 (s, 3H), 1.59 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.049 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 135.13, 122.08, 72.45, 70.84, 62.97, 38.29, 31.84, 26.65, 25.85, 25.65, 18.39, 16.07, −5.24. Anal. Calcd for $C_{17}H_{35}BrO_2Si$: C, 53.81; H, 9.30. Found: C, 53.63; H, 9.34.

7,8-Epoxy-4,8-dimethyl-3(*E*)-nonenyl *tert*-Butyldimethylsilyl Ether (29). To a solution of **28** (0.5 g, 1.32 mmol) in methanol (25 mL) was added K_2CO_3 (0.365 g, 2.64 mmol) at room temperature. This mixture was stirred for 1 h, then most methanol was removed *in vacuo*. The slurry was diluted with water (20 mL), and the aquouse phase was extracted with ether (3 × 20 mL). Standard workup followed by flash column chromatography using ethyl acetate:hexane (1:9) as the eluant gave pure **29** (0.373 g, 95% yield) as an colorless oil: IR (film): 1670, 1254, and 1098 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 300 (M^+ + 2, 6.2), 299 (M^+ + 1, 27.2), 281 (25.4), 241 (12.4), 167 (63.3), 149 (100); ^1H NMR ($CDCl_3$, ppm) 5.17 (t, *J* =7.2 Hz, 1H), 3.58 (t, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.23 (dt, *J* = 7.2, 7.2 Hz, 2H), 2.18−2.04 (m, 2H), 1.71−1.64 (m, 1H), 1.63 (s, 3H), 1.62−1.56 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H), 0.89 (s, 9H), 0.049 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.06, 121.13, 64.15, 63.03, 58.24, 36.36, 31.89, 27.49, 25.98, 24.89, 18.75, 18.38, 16.17, −5.23. Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.40; H, 11.49. Found: C, 68.38; H, 11.53.

7,8-Epoxy-4,8-dimethyl-3(*E*)-nonen-1-ol (30). This was prepared by the same procedure as described for the preparation of **15**. Flash chromatography using hexane:ethyl acetate (2:3) gave **30** in 91% yield: IR (film) 3424, 1668, 1122, and 1049 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 186 (M^+ + 2, 15.9), 185 (M^+ + 1, 68.6), 167 (100), 149 (24.4), 123 (18.6), 109 (8.4); ^1H NMR ($CDCl_3$, ppm) 5.20 (t, *J* = 7.2 Hz, 1H), 3.62 (dt, *J* = 2.3, 6.3 Hz, 2H), 2.69 (dd, *J* = 5.3, 7.0 Hz, 1H), 2.36−2.11 (m, 5H), 1.74−1.61 (m, 2H), 1.66 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 137.79, 120.97, 64.34, 62.52, 58.21, 36.78, 31.66, 27.37, 24.92, 18.86, 16.27. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.60; H, 10.82.

7,8-Epoxy-4,8-dimethyl-3(*E*)-nonenyl Methanesulfonate (31). This was prepared in 98% yield by the procedure described for **16**. The **31** obtained was sufficiently pure to be used for the next reaction without purification. **31**: ^1H NMR ($CDCl_3$, ppm) 5.17 (t, *J* = 7.2 Hz, 1H), 4.18 (t, *J* = 7.0 Hz, 2H), 2.99 (s, 3H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.46 (dt, *J* = 7.1, 7.0 Hz, 2H), 2.23−2.10 (m, 2H), 1.65−1.58 (m, 2H), 1.66 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H).

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-ol (32). This was prepared according to the method of Coates *et al.*[31]

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrienyl Thioacetate (33). This was prepared in 80% yield by the procedure described for the preparation of **24**. **33**: IR (film) 1695, 1134, 1108, 936, and 835 cm^{-1}; MS *m/z* (rel intensity) 309 (M^+ + 1, 1.3), 308 (M^+, 5.2), 265 (14.1), 197 (9.3), 136 (27.0), 129 (37.4), 121 (11.1); ^1H NMR ($CDCl_3$, ppm) 5.10−5.09 (m, 3H), 2.86 (t, *J* = 7.20 Hz, 2H), 2.32 (s, 3H), 2.09−1.96 (m, 10H), 1.68 (s, 3H), 1.62 (m, 2H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, ppm) 195.89, 136.33, 135.11, 131.30, 124.53, 124.25, 123.19, 39.81, 30.67, 29.68, 28.84, 27.15, 26.88, 26.69, 25.74, 17.75, 16.14, 16.09. Anal. Calcd for $C_{19}H_{32}OS$: C, 73.97; H, 10.45. Found: C, 73.83; H, 10.34.

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatriene-1-thiol (34). This was prepared in 92% yield by the procedure described for the preparation of **25**. **34**: IR (film) 1667 and 834 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 267 (M^+ + 1, 100), 266 (M^+, 10.3), 195 (7.5), 177 (10.9), 137 (2.2), 136 (1.2), 123 (1.1); ^1H NMR ($CDCl_3$, ppm) 5.11−5.07 (m, 3H), 2.51 (dt, *J* = 7.3, 7.2 Hz, 2H), 2.12−1.95 (m, 10H), 1.68 (s, 3H), 1.65 (m, 2H), 1.61 (s, 3H), 1.60 (s, 6H), 1.32 (t, *J* = 7.82 Hz, 1H). Anal. Calcd for $C_{17}H_{30}S$: C, 76.62; H, 11.36. Found: C, 76.55; H, 11.50.

7,8-Epoxy-4,8-dimethyl-3(*E*)-nonenyl 5′,9′,13′,-Trimethyl-4′(*E*),(8′(*E*),12′-tetradecatrienyl Sulfide (53). This was prepared in 73% yield by the procedure described for the preparation of **52**. **53**: IR (film) 1681, 1249, 1122, and 834 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 435 (M^+ + 3, 9.6), 434 (M^+ + 2, 30.6), 433 (M^+ + 1, 100), 415 (9.9), 283 (6.9), 201 (11.3), 167 (14.9), 151 (1.6), 149 (14.7), 137 (4.9), 123 (3.4); ^1H NMR ($CDCl_3$, ppm) 5.21 (t, *J* = 7.0 Hz, 1H), 5.12−5.07 (m, 3H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.51 (t, *J* = 8.0 Hz, 4H), 2.28 (dt, *J* = 7.4, 7.4 Hz, 2H), 2.17−1.95 (m, 14H), 1.72−1.62 (m, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.95, 135.71, 134.99, 131.25, 124.42, 124.18, 123.49, 123.22, 64.07, 58.25, 39.72, 36.30, 32.17, 31.78, 29.84, 28.44, 27.41, 27.12, 26.79, 26.62, 25.64, 24.86, 18.74, 17.65, 16.06. Anal. Calcd for $C_{28}H_{48}OS$: C, 77.71; H, 11.18. Found: C, 77.80; H, 11.14.

7,8-Epoxy-4,8-dimethyl-3(*E*)-nonenyl 5′,9′,13′-trimethyl-4′(*E*),8′(*E*),12′-tetradecatrienyl Sulfoxide (57). This was prepared in 84% yield by oxidation of **53** using the same procedure as described for the preparation of **56**. **57**: IR (film) 1665, 1047, and 873 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 449 (M^+ + 1, 14.5), 283 (100), 265 (55), 167 (59), 149 (76); ^1H NMR ($CDCl_3$, ppm) 5.20 (t, *J* = 7.0 Hz, 1H), 5.12−5.05 (m, 3H), 2.76−2.56 (m, 5H), 2.49 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.25−1.93 (m, 14H), 1.81 (quintet, *J* = 7.2 Hz, 2H), 1.67 (s, 6H), 1.59 (s, 9H), 1.30 (s, 3H), 1.26 (s, 3H). Anal. Calcd for $C_{28}H_{48}O_2S$: C, 74.94; H, 10.79. Found: C, 74.90; H, 10.75.

4,8,12-Trimethyl-3(*E*),7(*E*),11-tridecatrien-1-ol (35). This compound was prepared by the method of Dodd and Oehlschlager.[20a]

4,8,12-Trimethyl-3(*E*),7(*E*),11-tridecatrienyl *tert*-Butyldimethylsilyl Ether (36). This was prepared in 91% yield by the procedure described for the preparation of **13**. **36**: IR (film) 1669, 1255, 1103, 836, and 775 cm^{-1}; MS *m/z* (rel intensity) 350 (M^+, 1.8), 293 (22.1), 217 (12.0), 191 (18.1), 157 (10.1), 135 (10.3), 123 (7.1), 121 (8.3), 109 (12.7); ^1H NMR ($CDCl_3$, ppm) 5.16−5.04 (m, 3H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.23 (dt, *J* = 7.1, 7.1 Hz, 2H), 2.09−1.95 (m, 8H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H), 0.89 (s, 9H), 0.049 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 137.12, 135.08, 131.31, 124.52, 124.31, 120.41, 63.73, 39.86, 31.99, 26.89, 26.72, 26.07, 25.74, 17.74, 16.25, 16.07, −5.14. Anal. Calcd for $C_{22}H_{42}OSi$: C, 75.36; H, 12.07. Found: C, 75.58; H, 12.30.

11-Bromo-12-hydroxy-4,8,12-trimethyl-3(*E*),7(*E*)-tridecadienyl *tert*-Butyldimethylsilyl Ether (37). This was prepared in 37% yield by the same procedure described for the preparation of **28**. **37**: IR (film) 3450, 1667, and 1101 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 447 (M^+ + 1, 7.9), 429 (1.2), 315 (33.3), 299 (22.4), 297 (24.8), 235 (25.3), 217 (100); ^1H NMR ($CDCl_3$, ppm) 5.20 (t, *J* = 6.4 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 3.98 (dd, *J* = 1.8, 11.9 Hz, 1H), 3.58 (t, *J* = 7.2 Hz, 2H), 2.35−2.28 (m, 1H), 2.23 (dt, *J* = 7.2, 7.2 Hz, 2H), 2.14−2.06 (m, 4H), 2.02−1.92 (m, 2H), 1.83−1.73 (m, 1H), 1.62 (s, 3H), 1.59 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.77, 133.09, 125.93, 120.52, 72.44, 70.87, 63.11, 39.65, 38.18, 32.21, 31.88, 26.67, 26.60, 25.97, 25.85, 18.36, 16.14, 15.83, −5.23. Anal. Calcd for $C_{22}H_{43}O_2BrSi$: C, 59.04; H, 9.68. Found: C, 58.98; H, 9.59.

11,12-Epoxy-4,8,12-trimethyl-3(*E*),7(*E*)-tridecadienyl *tert*-Butyldimethylsilyl Ether (38). This was prepared in 95% yield by the same procedure as described for the preparation of **29**. **38:** IR (film) 1667, 1254, and 1102 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 367 (M^+ + 1, 12), 349 (3.4), 309 (5.0), 235 (76.1), 218 (16.7), 217 (100), 191 (22.1); ^1H NMR ($CDCl_3$, ppm) 5.17−5.10 (m, 2H), 3.57 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.22 (dt, *J* = 7.1, 7.2 Hz, 2H), 2.17−2.00 (m, 6H), 1.69−1.60 (m, 2H), 1.61 (s, 6H), 1.30 (s, 3H), 1.26 (s, 3H), 0.89 (s, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.87, 134.10, 124.87, 120.44, 64.18, 63.12, 58.23, 39.69, 36.32, 31.88, 27.52, 26.64, 25.98, 24.98, 18.75, 18.37, 16.16, 15.98, −5.23. Anal. Calcd for $C_{22}H_{42}O_2Si$: C, 72.07; H, 11.56. Found: C, 72.03; H, 11.44.

11,12-Epoxy-4,8,12-trimethyl-3(*E*),7(*E*)-tridecadien-1-ol (39). This was prepared in 92% yield by the same procedure as described for **30**.

39: IR (film) 3439, 1669, 1122, and 1049 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 253 ($M^+ + 1$, 85.5), 235 (100), 217 (33.1), 191 (21.1), 167 (14.0), 153 (39.9),149 (18.7), 135 (31.1), 123 (17.2), 121 (13.4); ^1H NMR ($CDCl_3$, ppm) 5.15−5.10 (m, 2H), 3.61(dt, J = 6.3, 6.1 Hz, 2H), 2.70 (t, J = 6.3 Hz, 1H), 2.28 (dt, J = 6.6, 6.7 Hz, 2H), 2.18−2.02 (m, 6H), 1.72−1.61 (m, 2H), 1.64 (s, 3H), 1.61 (s, 3H), 1.48 (t, J = 5.84 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 138.52, 134.34, 124.69, 120.12, 64.16, 62.43, 58.29, 39.71, 36.31, 31.54, 27.46, 26.48, 24.88, 18.74, 16.19, 16.00. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.30; H, 11.23.

11,12-Epoxy-4,8,12-trimethyl-(3*E*),(7*E*)-tridecadienyl Methanesulfonate (40). This was prepared in 95% yield by the procedure described for the preparation of **16**. **40** was used for the next reaction without further purification. **40**: ^1H NMR ($CDCl_3$, ppm) 5.26−5.00 (m, 2H), 4.19 (t, J = 7.0 Hz, 2H), 3.01 (s, 3H), 2.71 (t, J = 6.4 Hz, 1H), 2.47 (dt, J = 7.3, 7.2 Hz, 2H), 2.21−2.00 (m, 6H), 1.72−1.59 (m, 2H), 1.63 (s, 6H), 1.31 (s, 3H), 1.27 (s, 3H).

1,5,9-Trimethyl-4(*E*),8-decadien-1-ol (42). A solution of **41** (2.23 g,11.4 mmol) in dry ether (10 mL) was slowly added into a stirred suspension of $LiAlH_4$ (0.95 g, 23.8 mmol) in dry ether (40 mL) at 0 °C. After 0.5 h at 0 °C, excess $LiAlH_4$ was destroyed at −30° C by slow addition of water (1.0 g) followed by 15% NaOH (1 mL). The resulting mixture was filtered, and the white precipatate was washed with ether (2 × 10 mL). Standard workup followed by flash colunm chromatography using ethyl acetate:hexane (3:7) gave **42** (2.16 g, 96% yield) as a colorless liquid: IR (film) 3346, 1128, and 1084 cm^{-1}; MS *m/z* (rel intensity) 196 (M^+, 1.4), 153 (96), 135 (52.9), 123 (20.0), 109 (100), 81 (23.8), 69 (66.4); ^1H NMR ($CDCl_3$, ppm) 5.14 (m, 1H), 5.08 (m, 1H), 3.82−3.76 (m, 1H), 2.10−1.98 (m, 6H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.52−1.46 (m, 2H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.76, 131.47, 124.38, 124.06, 68.04, 39.81, 39.32, 26.77, 25.73, 24.47, 23.56, 17.75, 16.06. Anal. Calcd for $C_{13}H_{24}O$: C, 79.52; H, 12.33. Found: C, 79.40; H, 12.29.

1,5,9-Trimethyl-4(*E*),8-decadienyl Thioacetate (43). This was prepared in 80% yield by the procedure described for the preparation of **24**. **43**: IR (film) 1692, 1113, 952, and 835 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 255 ($M^+ + 1$, 26.6), 214 (15.3), 213 (100), 211 (13.4), 179 (11.7), 173 (5.3), 131 (12.7); ^1H NMR ($CDCl_3$, ppm) 5.11−5.06 (m, 2H), 3.59−3.50 (m, 1H), 2.30 (s, 3H), 2.09−2.03 (m, 6H), 1.69 (s, 3H), 1.61−1.54 (m, 2H), 1.60 (s, 3H), 1.59 (s, 3H), 1.30 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.89, 131.31, 124.32, 123.29, 39.69, 39.35, 36.43, 30.73, 26.69, 25.64, 25.51, 23.80, 21.38, 17.66, 15.97. Anal. Cacld for $C_{15}H_{26}OS$: C, 70.81; H, 10.30. Found: C, 70.94; H, 10.41.

1,5,9-Trimethyl-4(*E*),8-decadiene-1-thiol (44). This was prepared in 91% yield by the procedure described for **25**. **44**: IR (film) 1668 and 833 cm^{-1}; CIMS, *m/z* (rel intensity) 212 (M^+, 7.6), 169 (4.3), 143 (11.5), 141 (14.4), 109 (21.2), 101 (30.7), 81 (21.0), 69 (100); ^1H NMR ($CDCl_3$, ppm) 5.10−5.05 (m, 2H), 2.97−2.87 (m, 1H), 2.14−2.04 (m, 4H), 2.00−1.96 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.59−1.52 (m, 2H), 1.47 (d, J = 6.3 Hz, 1H), 1.33 (d, J = 6.7 Hz, 3H). Anal. Cacld for $C_{13}H_{24}S$: C, 73.52; H, 11.39. Found: C, 73.60; H, 11.31.

11,12-Epoxy-4,8,12-trimethyl-3(*E*),7(*E*)-tridecadienyl 5′,9′-Dimethyl-4′(*E*),8′-decadienyl Sulfide (54). This was prepared in 31% yield by the procedure described for the preparation of **52**. **54**: IR (film) 1668, 1248, 1122, and 874 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 448 ($M^+ + 2$, 34.5), 447 ($M^+ + 1$, 100),446 (M^+, 5.5), 429 (11.6), 377 (2.6), 269 (3.1), 217 (3.7); ^1H NMR ($CDCl_3$, ppm) 5.18−5.14 (m, 2H), 5.11−5.07 (m, 2H), 2.76 (sextet, J = 6.7 Hz, 1H), 2.70 (t, J = 6.2 Hz, 1H), 2.51 (t, J = 7.7 Hz, 2H), 2.26 (dt, J = 7.4, 7.6 Hz, 2H), 2.15−1.97 (m, 14H), 1.68 (s, 3H), 1.61 (s, 9H), 1.60 (s, 3H), 1.45−1.51 (m, 2H), 1.30 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 136.42, 135.61, 134.17, 131.30, 124.80, 124.36, 123.81, 122.80, 64.14, 58.24, 39.74, 38.64, 39.60, 37.15, 36.33, 30.35, 28.75, 27.53, 26.74, 26.60, 25.66, 25.49, 24.90, 23.37, 21.45, 18.76, 17.67, 16.15, 16.07. Anal. Calcd for $C_{29}H_{50}OS$: C, 77.97; H, 11.20. Found: C, 78.07; H, 11.40.

11,12-Epoxy-4,8,12-trimethyl-3(*E*),7(*E*)-tridecadienyl 5′,9′-Dimethyl-4′(*E*),8′-decadienyl Sulfoxides (58 and 59). These were prepared by the procedure described for the preparation of **56**. Chromatography using ethyl acetate:hexanes (7:3) as the eluant gave the two diastereomers **58** and **59** in 24% and 33% yields, respectively. **58**: R_f 0.44 (silica, ethyl acetate:hexanes; 7:3); IR (film) 2963, 2922, 2856, 1666, 1450, 1377, 1116, and 1047 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 463 ($M^+ + 1$, 6.5), 285 (10), 269 (14), 229 (100), 217 (30.6); ^1H NMR ($CDCl_3$, ppm) 5.20−5.11 (m, 2H), 5.11−5.03 (m, 2H), 2.73 (m, 1H), 2.70 (t, J = 6.3 Hz, 1H), 2.61−2.53 (m, 2H), 2.53−2.44 (m, 2H), 2.28−1.94 (m, 14H), 1.62−1.70 (m, 2H), 1.68 (s, 3H), 1.65 (s,3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H). Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.27; H, 10.90. Found: C, 75.26; H, 11.04. **59**: R_f 0.35 (ethyl acetate: hexanes; 7:3); IR (film) 2962, 2922, 2850, 1666, 1450, 1377, 1117, and 1047 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 463 ($M^+ + 1$, 11.6), 285 (16.3), 269 (40), 229 (100), 217 (27.7); ^1H NMR ($CDCl_3$, ppm) 5.20−5.11 (m, 2H), 5.11−5.03 (m, 2H), 2.70 (t, J = 6.3 Hz, 1H), 2.67 (m, 1H), 2.61−2.53 (m, 2H), 2.53−2.44 (m, 2H), 2.27−1.93 (m, 14H), 1.62−1.70 (m, 2H), 1.67 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.26 (s, 3H). Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.27; H, 10.90. Found: C, 75.20; H, 11.05.

16-Bromo-17-hydroxy-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*)-octadecatrienyl *tert*-Butyldimethylsilyl Ether (45). This was prepared in 36% yield from **22** by the procedure described for the preparation of **28**. IR and ^1H NMR spectra of **45** are in agreement with those reported in ref 11b.

16,17-Epoxy-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*)-octadecatrien-1-ol (47). To a solution of **45** (0.456 g, 0.86 mmol) in methanol (20 mL) was added K_2CO_3 (0.276 g, 2.0 mmol) at room temperature. This mixture was stirred for 1 h, after which time most of methanol was removed *in vacuo*. The resulting slurry was diluted with water (20 mL), and the aqueous phase was extracted with diethyl ether (3 × 20 mL). Standard workup gave **46** (0.364g). To a solution of **46** (0.364 g, 0.81 mmol) in THF (20 mL) at room temperature was added tetrabutylammonium flouride (8 mL, 1 M solution in THF, 8 mmol). The resulting mixture was stirred overnight at room temperture. Water (10 mL) was then added, and the mixture was extracted with diethyl ether (3 × 20 mL). Standard workup followed by flash column chromatography using ethyl acetate:hexane (4:6) as the eluant gave **47** (0.255 g, 89% yield, over two steps): IR and ^1H NMR spectra of **47** are in agreement with those reported in ref 11b.

16,17-Epoxy-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*)-octadecatrienyl Methanesulfonate (48). This was prepared in 97% yield by the procedure described for the preparation of **16**. **48** was used in the next reaction without further purification. **48**:^1H NMR ($CDCl_3$, ppm) 5.20−5.10 (m, 3H), 4.20 (t, J = 6.5 Hz, 2H), 3.00 (s, 3H), 2.70 (t, J = 6.2 Hz, 1H), 2.18−1.96 (m, 12H), 1.90−1.80 (m, 2H),1.76−1.60 (m, 2H), 1.61 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.30 (s, 3H), 1.25 (S, 3H).

4-Methylpent-3-enyl Thioacetate (50). This was prepared in 75% yield by the procedure described for the preparation of **24** except that the solvent was carefully distilled at atmospheric pressure using a 20 cm Vigreux column. The residue was purified by flash chromatography using diethyl ether:pentane (2:3) as eluant, and the solvent was removed again through a Vigreux column to give **50**: GC purity (96%); IR (film) 1691 and 1113 cm^{-1}; MS, *m/z* (rel intensity) 159 ($M^+ + 1$, 5.5), 158 (M^+, 59.9), 115 (2.9), 101 (2.0), 82 (100), 69 (22.8), 67 (29.1); ^1H NMR ($CDCl_3$, ppm) 5.14−5.06 (m, 1H), 2.86 (t, J = 7.4 Hz, 2H), 2.32 (s, 3H), 2.25 (dt, J = 7.2,7.4 Hz, 2H), 1.70 (s, 3H), 1.62 (s, 3H).

4-Methylpent-3-ene-1-thiol (51). This was prepared in 57% yield by the procedure described for **25** except the solvent was carefully distilled at atmospheric pressure using a Vigreux column to give **51**: GC purity (94%); IR (film) 1666 and 832 cm^{-1}; MS *m/z* (rel intensity) 117 ($M^+ + 1$, 1.0), 116 (M^+, 12.4), 101 (100), 83 (2.6), 69 (92.0), 67 (33.2), 55 (15.1), 53 (14.2), 47 (14.0), 41 (69.0); ^1H NMR ($CDCl_3$, ppm) 5.12−5.08 (m, 1H), 2.52 (dt, J = 7.2, 7.4 Hz, 2H), 2.30 (dt, J =7.1, 7.2 Hz, 2H), 1.72 (s, 3H), 1.63 (s, 3H), 1.40 (t, J = 7.7 Hz, 1H).

16,17-Epoxy-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*)-octadecatetraenyl 4′-Methylpent-3′-enyl Sulfide (55). This was prepared in 80% yield by the procedure described for the preparation of **52**. **55**: IR (film) 1666, 1281, 1122, and 875 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 433 ($M^+ + 1$, 100), 432 (M^+, 5.0), 415 (33.8), 391 (7.5), 377 (6.3), 351 (2.0), 279 (5.8), 185 (4.2), 143 (11.1), 127 (2.3); ^1H NMR ($CDCl_3$, ppm) 5.20−5.10 (m, 4H), 2.70 (t, J = 6.2 Hz, 1H), 2.50, 2.48 (overlap two triplet, J = 7.7, 7.7 Hz, 4H), 2.26 (dt, J = 7.2,

7.5 Hz, 2H), 2.16−1.96 (m, 14H), 1.70 (s, 3H), 1.67−1.62 (m, 2H), 1.62 (s, 6H), 1.59 (s, 6H), 1.30 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.07, 134.23, 134.03, 132.99, 125.02, 124.95, 124.33, 122.74, 64.18, 58.23, 39.68, 38.81, 36.33, 32.28, 31.73, 28.58, 28.26, 28.24, 28.02, 27.53, 26.70, 25.65, 24.89, 18.75, 17.78, 16.04,16.00. Anal. Calcd for $C_{28}H_{48}OS$: C, 77.71; H, 11.18. Found: C, 77.78; H, 11.04.

16,17-Epoxy-4,9,13,17-tetramethyl-4(*E*),8(*E*),12(*E*)-octadecatetraenyl 4′-Methylpent-3′-enyl Sulfoxide (60). This was prepared in 82% yield by the procedure described for the preparation of **56**. **60**: IR (film) 1667, 1112, and 1048 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 449 ($M^+ + 1$, 54.4), 448 (M^+, 52.5), 367 (67.7), 349 (68.8), 317 (10.6), 133 (100); ^{1}H NMR ($CDCl_3$, ppm) 5.20−5.08 (m, 4H), 2.70 (t, J = 6.3 Hz, 1H), 2.70−2.54 (m, 4H), 2.45 (dt, J = 7.2, 7.3 Hz, 2H), 2.20−1.95 (m, 14H), 1.92−1.80 (m, 2H), 1.71 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H). Anal. Calcd for $C_{28}H_{48}O_2S$: C, 74.94; H, 10.79. Found: C, 74.92; H, 10.73.

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