Synthesis and Inhibition Studies of Sulfur-Substituted Squalene Oxide Analogues as Mechanism-Based Inhibitors of 2,3-Oxidosqualene−Lanosterol Cyclase†

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The synthesis and biological evaluation of three new sulfur-substituted oxidosqualene (OS) analogues (**1**−**3**) are presented. In these analogues, C-11, C-15, or C-18 in the OS skeleton was replaced by sulfur. The sulfur position in the OS skeleton was chosen to disrupt one or more key processes involved in cyclization: (a) the folding of the B-ring into a boat conformation, (b) the *anti*-Markovnikov cyclization leading to the C-ring, or (c) the formation of the D-ring during the lanosterol biosynthesis. Enzyme inhibition kinetics using homogeneous mammalian oxidosqualene cyclases (OSC) were also examined for the previously reported S-19 analogue **4**. The four analogues were potent inhibitors of mammalian OSCs (IC_{50} = 0.05−2.3 μM for pig and rat liver OSC) and fungal cell-free *Candida albicans* OSC (submicromolar IC_{50} values). In particular, the S-18 analogue **3** showed the most potent inhibition toward the rat liver enzyme (IC_{50} = 50 nM) and showed potent, selective inhibition against the fungal enzyme (IC_{50} = 0.22 nM, 10-fold more potent than the S-19 analogue **4**). Thus, **3** is the most potent OSC inhibitor known to date. The K_i values ranged from 0.5 to 4.5 μM for pig OSC, with **3** and **4** showing about 10-fold higher potency for rat liver OSC. Interestingly, the S-18 analogue **3** showed time-dependent irreversible inhibition with homogeneous pig liver OSC (k_{inact} = 0.06 min^{-1}) but not with rat OSC.

Introduction

Cyclization of 2,3-oxidosqualene (OS) to lanosterol mediated by 2,3-oxidosqualene−lanosterol cyclase (OSC) involves formation of the protosterol cation and its backbone rearrangement to lanosterol and proceeds *via* distinct carbocationic intermediates (Scheme 1).[1,2] Johnson and co-workers[3] hypothesized that a stereocontrolled delivery of "point-charge" nucleophiles by the enzyme could stabilize each cationic intermediate. The cyclization process has been the subject of numerous biomimetic studies.[1]

Lanosterol synthases have been cloned and sequenced from several sources.[4] Rat liver OSC, an 83-kDa membrane-associated protein, has been cloned and functionally expressed.[4e] The deduced amino acid sequence of the rat enzyme showed significant homology to the known OSCs from yeast and plant (39−44% identity) and still retained 17−26% identity with bacterial squalene cyclases (SCs). Sequence comparisons of eukaryotic OSCs and bacterial SCs have revealed the presence of the QW motif, a highly-conserved motif rich in aromatic amino acids (six repeats in both OSCs and SCs).[5] The β-strand turn motif was well-conserved, and it has been postulated that the aromatic amino acids of the QW motif might play a structural or functional role in catalysis by stabilizing the carbocationic intermediates through cation−π-interactions.[4d,e]

For several decades, OSCs have been the targets of inhibition studies.[6] Inhibition of OSCs has been achieved by substrate analogues[7] as well as mimics of the presumed carbocationic intermediates.[8] Recently, attention has focused on the design of mechanism-based inactivators.[1,9] Ceruti *et al.*[10] examined squalenoid epoxide vinyl ethers as possible "suicide" inhibitors. The authors suggested that cyclization of such substrates would form a C-20 carbocation, which could be stabilized through formation of an oxocarbenium ion. The latter could interact with an active site nucleophile producing irreversible enzyme inhibition. In fact, the vinyl ether-containing squalene oxides were competitive inhibitors, *i.e.*, 22,23-dihydro-20-oxa-2,3-oxidosqualene showed a K_i of 60 μM and an IC_{50} of 80 μM for rat liver OSC. A potent irreversible inactivator of pig liver OSC, 29-methylidene-2,3-oxidosqualene (29-MOS),[11] exhibited an IC_{50} value of 0.5 μM and a k_{inact} of 221 min^{-1}. The reactive intermediate partitioned to give a product, 21-methylidenelanosterol, that could be isolated in low yield as a cyclization product of 29-MOS.[11c] Both inhibition and cyclization appear to occur *via* a common

† Dedicated to the memory of Professor William S. Johnson, friend and mentor.

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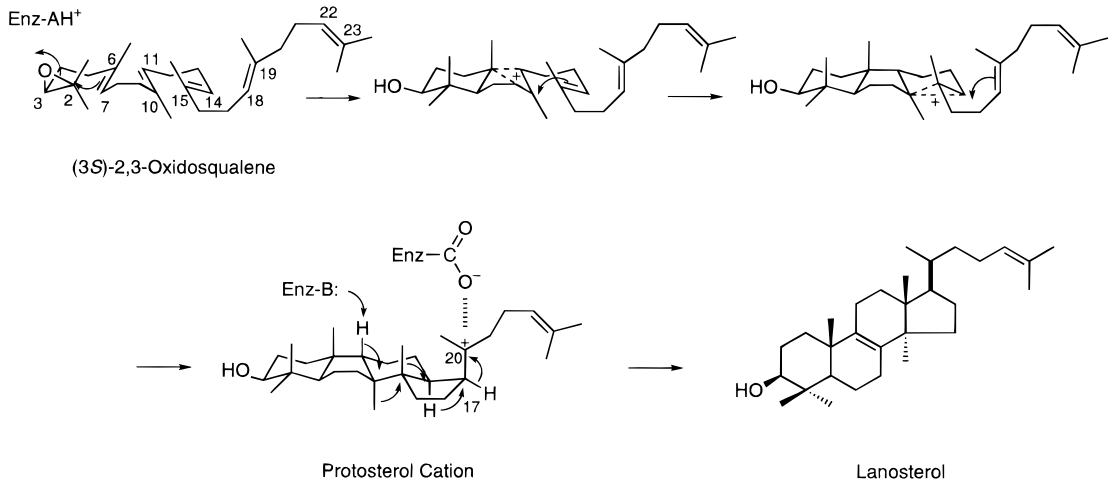
Scheme 1. Proposed Cyclization Mechanism of Oxidosqualene into Lanosterol



cationic intermediate.[11,12] An Asp residue (D456 in rat OSC) in a highly-conserved sequence (DCTAE motif) was covalently modified by [^{3}H]-29-MOS.[4e,12] Corey *et al.*[13] found 10,15-didesmethyl-OS to be a time-dependent irreversible inhibitor of yeast cyclase, but the covalent modification of protein was not confirmed. Abad *et al.*[14] found that 2,3:18,19-dioxidosqualene was a potent noncompetitive inhibitor (IC_{50} = 0.11 μM) of rat liver OSC.

More recently, Zheng *et al.* described a series of sulfur and sulfoxide OS analogues in which sulfur has replaced carbon C-5, C-6, C-8, C-9, C-10, C-13, C-14, C-16, C-19, or C-20; many are good inhibitors of OSC.[15,16] Among them, the S-19 analogue **4** resulted in extremely potent inhibition (IC_{50} = 0.0023 μM) of *Candida albicans* OSC.[15b] Here we now report the synthesis and biological activity of a new set of thia-OS analogues (**1**−**3**), in which C-11, C-15, or C-18 in the OS skeleton was replaced by sulfur (Figure 1). The sulfur position in the OS skeleton was chosen to interfere with (a) the folding of the B-ring into a boat conformation, (b) the *anti*-Markovnikov cyclization leading to the C-ring, and (c) the formation of the D-ring during the lanosterol biosynthesis. We propose that inhibition could occur *via* interruption of the cyclization process, trapping the generated carbocations as sulfonium intermediates. Our strategy employs the sulfur atom as a π-donor that mimics a double bond. Enzyme inhibition kinetics using homogeneous mammalian OSC are also presented for the S-19 analogue **4**, and implications for the enzyme inhibition mechanism are discussed.

Results and Discussion

Synthesis of 2,3-OS Analogues. The candidate inhibitors **1**−**3** were prepared through coupling of a suitable alkylthiolate anion and an electrophile as described previously.[15a] Thus, for the synthesis of **1**, geranylacetone (**5**) (Scheme 2) was reduced, protected as a *tert*-butyldimethylsilyl ether, and then converted with *N*-bromosuccinimide in THF−H_2O (4:1)[17] into the corresponding terminal bromohydrin **8** (39% yield for two steps). The latter was transformed to epoxide **9** using K_2CO_3/MeOH (96% yield) and deprotected using tetrabutylammonium fluoride to give the epoxy alcohol **10** (98% yield), which was converted into the corresponding mesylate **11**. After workup, **11** was used for further reaction without purification.

Introduction of sulfur (Scheme 3) was achieved through reaction of homofarnesol[8a] (**12**) with thiolacetic acid *via* a modified Mitsunobu reaction[18] to give the thioacetate **13**. The resulting thioacetate was reduced to the desired thiol **14** with $LiAlH_4$ (85% yield). Coupling of thiol **14** and mesylate **11** was carried out using 50% NaOH in aqueous toluene in the presence of tetraoctylammonium bromide as a phase transfer catalyst,[19] giving product **1** in 29% yield.

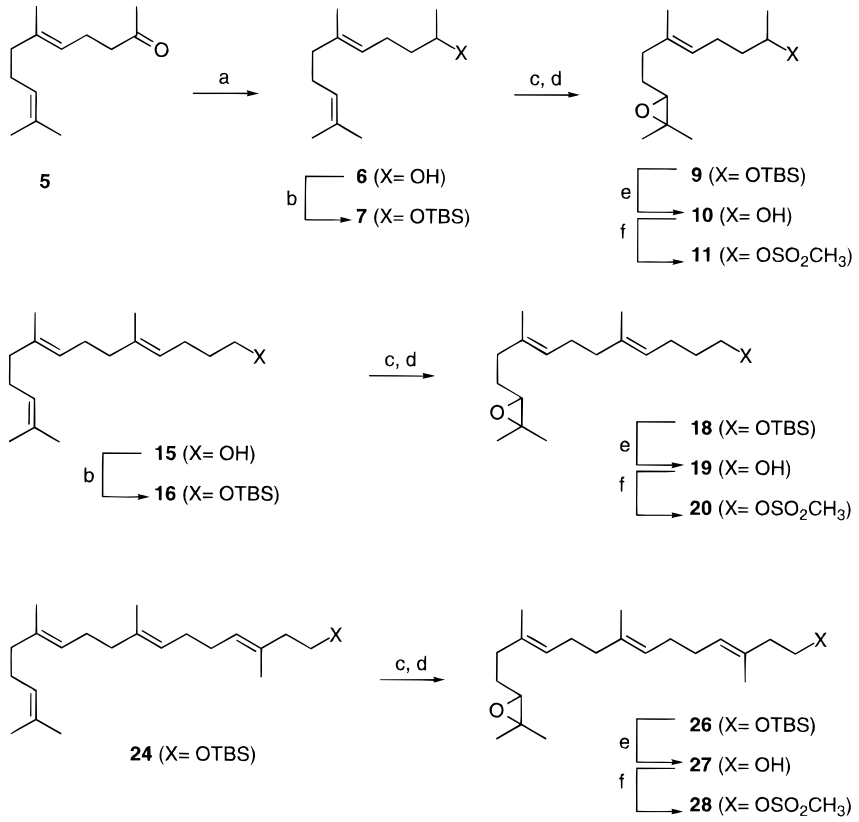
The low yield of the coupling reaction can be attributed to low reactivity of the secondary mesylate **11** toward the thiol anion. Attempts to improve the yield of the coupling by use of the triflate of **10** failed. Although the triflate could be formed, coupling conditions led primarily to alcohol **10** with <5% coupling. The structure of **1** was confirmed by appearance in the ^{1}H NMR spectrum of signals attributable to the protons α to the sulfur, δ 2.75 (m, CH_3CHS) and 2.50 (t, J = 8 Hz, CH_2S), as well as a signal at δ 2.70 (t, J = 6.5 Hz) confirming the presence of the epoxide.

A similar strategy was applied to the synthesis of **2**. As shown in Scheme 2, 4,8,12-trimethyl-(3*E*,7*E*),11-tridecatrien-1-ol (**15**)[20] was protected as the *tert*-butyldimethylsilyl ether in CH_2Cl_2 and then converted to the terminal bromohydrin **17**. Reaction of **17** with 2.5% K_2CO_3 in methanol afforded **18** (35% yield for three steps). Deprotection of **18** was achieved with Bu_4NF in THF to give epoxy alcohol **19** in 94% yield. Subsequent mesylation gave **20**, which was used without further purification.

Homogeraniol (**21**) (Scheme 3) was prepared in good yield by the method of Leopold.[21] Reaction of homogeraniol (**21**) with thiolacetic acid followed by reduction with $LiAlH_4$ gave thiol **23** in good yield. Coupling of crude mesylate **20** with thiol **23** was carried out as described above for the synthesis of **1**. Thus, thiol **23** was treated with 50% aqueous NaOH in toluene, tetraoctylammonium bromide, and mesylate **20**. After 15 h at 40 °C the desired compound **2** was isolated in 65% yield. A signal in the ^{1}H NMR spectrum of **2** at δ 2.50 (m, 4H, 2 × S-CH_2) indicated successful coupling, while a signal at δ 2.70 (t, J = 6 Hz) confirmed the presence of the epoxide structure.

Preparation of **3**, in which sulfur replaces the nucleophilic carbon at position 18 of the 2,3-OS skeleton, is also outlined in Schemes 2 and 3. Reaction of **24**[9a] with NBS in THF−H_2O gave the terminal bromohydrin **25**,

Scheme 2[a]



[a] Reagents: (a) LAH, THF; (b) TBSCl, DMAP, Et_3N, CH_2Cl_2; (c) NBS, THF, H_2O, 0 °C; (d) 2.5% K_2CO_3, MeOH; (e) Bu_4NF, THF, H_2O; (f) CH_3SO_2Cl, DMAP, Et_3N, CH_2Cl_2.

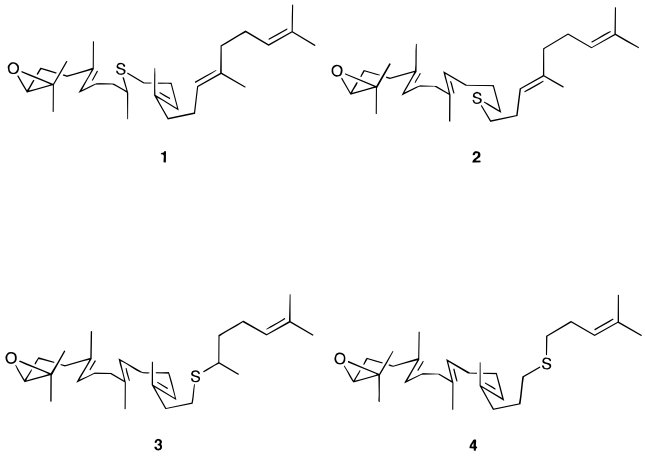


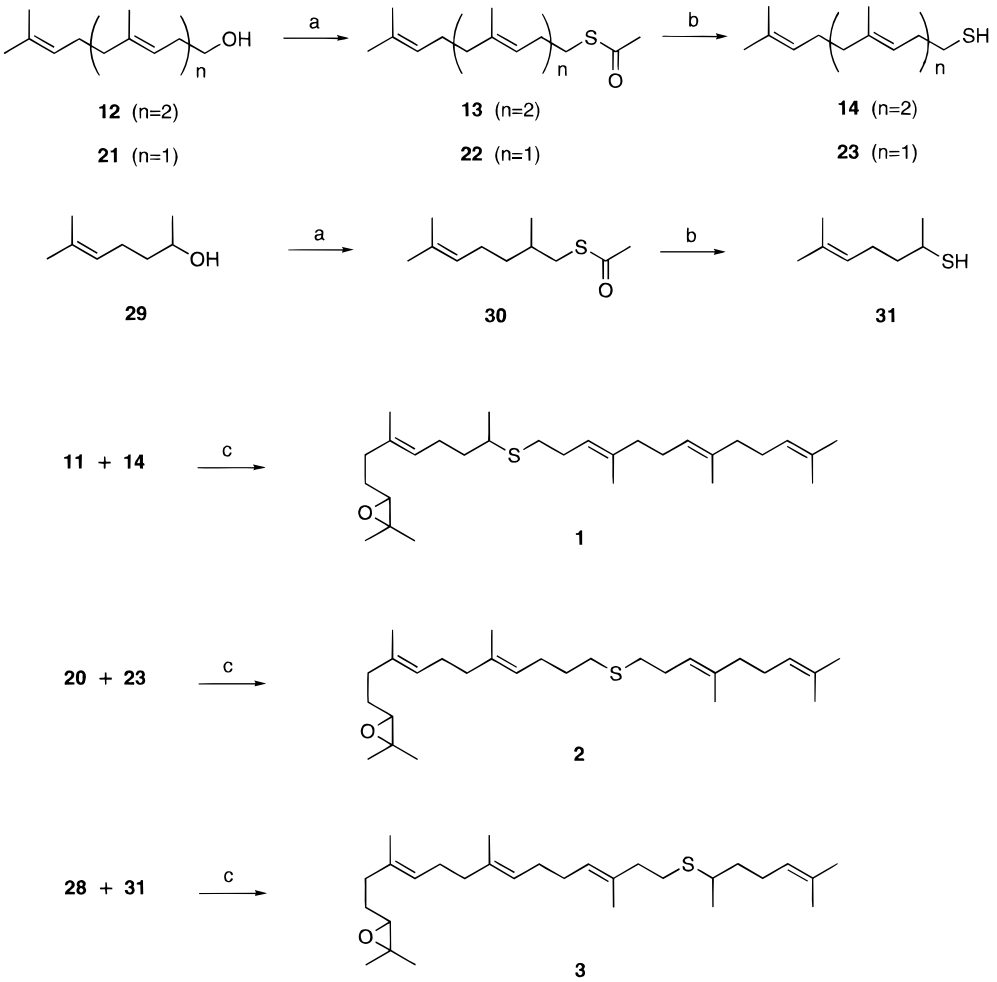
Figure 1. Sulfur-substituted 2,3-oxidosqualene analogues.

which was converted to the terminal epoxide **26** by K_2CO_3/MeOH in 37% yield for two steps. Removal of the silyl protecting group of **26** followed by mesylation provided **28**. The required thiol **31** was prepared from alcohol **29** in 76% yield for two steps. Synthesis of **3** was completed by coupling **28** and **31** in 74% yield. ^1H NMR spectral analysis confirmed the structure of **3**. The sulfur-containing OS analogue **4** (sulfur replaces C-19 in OS) was available from previous work.[15a]

Biological Results. Compounds **1**−**4** (all prepared in racemic form) were quite potent inhibitors of cell-free *C. albicans* and homogeneous rat and pig liver OSCs[22] (Table 1). In particular, the S-18 analogue **3** showed the most potent inhibition toward rat liver (IC_{50} = 0.050 μM) and *C. albicans* OSC (IC_{50} = 0.000 22 μM, 10-fold more potent than the previously reported S-19 analogue **4**) in the series of sulfur-containing analogues prepared so far.[15,16] This was the best OSC inhibition known so far. For rat OSC, compound **3** is in fact far more potent than inhibitors such as 29-MOS (IC_{50} = 0.3 μM)[11] and 2,3:18,19-dioxidosqualene (IC_{50} = 0.11 μM).[14] Interestingly, compounds **3** and **4** showed extremely low IC_{50} values (0.000 22 and 0.0023 μM, respectively) toward the fungal OSC compared with those for mammalian OSCs (2.3 and 1.0 μM, respectively, for pig OSC), suggesting striking species selectivity of the inhibition activities between fungal and mammalian OSCs.[15b] The 1000-fold selectivity between fungal and pig OSC observed for compound **3** has never been achieved before.[23] Compounds **3** and **4** thus have potential for development as potential antifungal agents. These observations support the idea that small changes in the amino acid sequence substantially affect the susceptibility of these enzymes to inhibitors. The deduced amino acid sequence of *C. albicans* OSC showed *ca.* 40% identity with that of rat OSC.[8e] Furthermore, as mentioned above, in the entire series of sulfur-containing OS analogues, compounds **3** (S-18) and **4** (S-19) showed the most potent inhibition, which supports the suggestion by Zheng *et al.*[15a] that modifications of the prering D region of OS should yield potent inhibition.

Kinetic analyses revealed that **1**−**4** are competitive inhibitors of pig liver OSC[22] with K_i values of 0.5, 4.5, 1.5, and 1.4 μM, respectively (Table 1). For rat liver OSC, **3** and **4** showed potent inhibition with K_i values of 0.037 and 0.18 μM, respectively. Further, for both enzymes, the time dependency of inactivation was measured, and the rates of inactivation (k_{inact}) were calculated (Table 1).

Scheme 3[a]



[a] Reagents: (a) PPh_3, DIAD, CH_3COSH, THF; (b) LAH, Et_2O; (c) 50% NaOH, Oct_4NBr, $PhCH_3$, H_2O, 40 °C.

Table 1

compd	IC_{50} (μM)	K_i (μM)	k_{inact} (min^{-1})
	Rat Liver (Purified)[15b]		
3	0.050	0.037	0.0001
4	0.26	0.18	0.0001
29-MOS	0.3	2.5	ND[a]
	Pig Liver (Purified)		
1	0.7	0.5	0.04
2	2.3	4.5	0.13
3	2.3	1.5	0.06
4	1.0	1.4	0.0001
29-MOS	0.5	4.4	221
	C. albicans (Cell-free)		
1	0.54		
2	8.4		
3	0.00022		
4	0.0023[15a]		

[a] ND, not determined.

The time dependency of inactivation of pig liver OSC by compounds **3** and **4** is shown in Figure 2. The S-18 analogue **3** showed a significant ability to decrease the activity of pig liver OSC. Its ability to inactivate the enzyme was comparable to that of 29-MOS,[11] although its time course was 3 orders of magnitude slower. In contrast, inhibition by the S-19 analogue **4** did not show time dependency. Small changes in the location of sulfur (C-19 or C-18), therefore, can significantly affect the inhibitory activity. Indeed, **3** acted as a time-dependent, mechanism-based inhibitor for pig liver OSC, while **4** acted only as a competitive inhibitor. Interestingly, for rat liver OSC, both compounds **3** and **4** showed inhibition that was independent of preincubation time (Table 1). Furthermore, we have recently found that inhibition of pig OSC by **3** was irreversible and that tritium-labeled S-18 analogue **3** covalently modified the enzyme.[15c] Rat OSC was not covalently modified by radiolabeled **3**, confirming the species selectivity observed in the kinetic behavior.

In inhibitors **1**−**4**, sulfur atoms were positioned to interfere with cyclization leading to rings B, C, and D. It is possible that **1**−**4** could bind to OSCs and could be cyclized to **32**−**35**, respectively (Figure 3). Inhibition could result from partially-cyclized intermediates such as these or from a conformational change of the substrate, a conformational change in the enzyme, or a reaction of the substrate mimic with OSC.[25] In any case, it seems reasonable that bicyclic, tricyclic, or tetracyclic sulfonium ions, if formed, could be stabilized by nucleophilic residues at the active sites of the cyclases.

As described above, the S-18 analogue **3** is an extremely potent, time-dependent, and irreversible inhibitor of pig OSC. If it is assumed that **3** is cyclized to a tricyclic sulfonium ion (**34**), reaction with the OSC could then occur in several ways:[26] (i) nucleophilic attack at the α-carbon to give a thioether with alkylation of OSC, (ii) β-elimination by a basic residue to give the thioether and an alkene, or (iii) proton abstraction α to the sulfonium to form an ylide, with possible subsequent

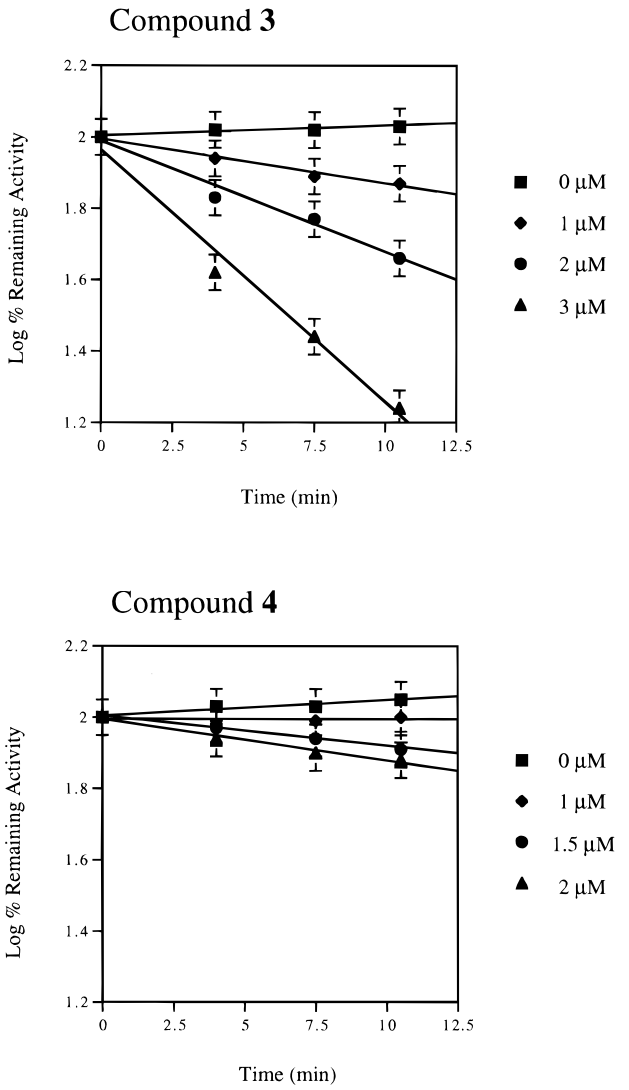


Figure 2. Time-dependent inactivation of pig liver OSC by compounds **3** and **4**.

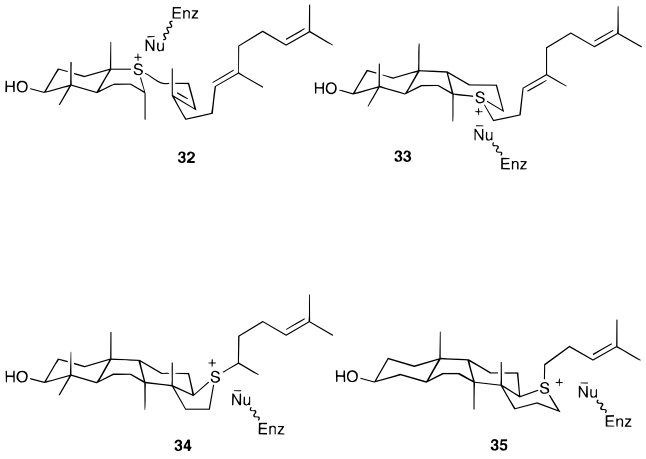


Figure 3. Putative sulfonium ions resulting from participation of S-11, S-15, S-18, or S-19 in cyclization of analogues **1**−**4**.

alkylation. Recently, we have prepared both [17-^{3}H]- and [22-^{3}H]-**3** and found that both of the labeled regioisotopomers covalently modified the enzyme.[15c] The retention of the tritium label for both isotopomers excluded the possibility of an attack at C-20 with transfer of the side chain to the active site. Nucleophilic trapping could alternatively occur on a bicyclic or tricyclic intermediate.[15c] Elucidation of the covalently-modified amino acid, the pendant partially-cyclized derivative of **3**, and the partitioning to released cyclization products of **3** are currently under investigation.

Experimental Section

General Chemical Procedures. Nuclear magnetic resonance (NMR) spectroscopy was conducted on a Bruker AMX-400 spectrometer at 400.13 and 100.62 MHz for ^{1}H and ^{13}C NMR spectra, respectively. All spectra were run in deuteriochloroform. ^{1}H NMR chemical shifts are reported in parts per million (ppm, δ) relative to TMS (0.00 ppm). ^{13}C NMR spectra are referenced to $CDCl_3$ (77.0 ppm). Mass spectra were obtained using a Hewlett-Packard 5985B GC−MS instrument equipped with a DB-1 coated column (30 m × 0.32 mm i.d., 0.25 μm film) operating at 70 eV for electron impact (EI) ionization. Chemical ionization (CI) was performed using isobutane as a proton source, and data are quoted in relative intensity. IR spectra were recorded on a Perkin-Elmer Model FT 1605 spectrophotometer. Elemental analyses were obtained using a Carbo Erba Model-1106 elemental analyzer. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium benzophenone-ketyl. Diisopropylamine and triethylamine were distilled from CaH_2 and stored under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2 prior to use. *N*-Bromosuccinimide was recrystallized from water and dried under high vacuum. Chemicals obtained from commercial sources were used without further purification. All moisture- and air-sensitive reactions were conducted under a positive pressure of argon in glassware that was flame-dried under vacuum. A nitrogen glovebag was used to weigh all the moisture- and oxygen-sensitive compounds. Syringes and cannulas were used to transfer oxygen- and water-sensitive liquid reagents. Standard workup refers to the combining of organic extracts, washing with ice-cold brine, and drying over $MgSO_4$. This is followed by filtration and solvent removal under reduced pressure. Chromatography refers to flash chromatography using Merck silica gel 60, mesh 230−400.

Biological Procedures. 1. Enzyme Inhibition Assay (*C. albicans*). The assay procedure is that reported by Zheng *et al.*[15a]

2. Enzyme Inhibition Assay and Kinetics Determinations (Pig liver OSC). Inhibitors were preincubated for 10 min at 37 °C in a mixture of phosphate buffer, pH 7.40, and [^{14}C]-(3*S*)-2,3-oxidosqualene[27] before addition of the enzyme solution (specific activity = 2643 nmol of lanosterol formation/h/mg)[22] and then incubated for 1 h. The reaction was stopped by addition of 0.1% lanosterol solution. The sample was then spotted (2 × 50 μL) on TLC plates (Whatman silica gel 60 Å with preabsorbant strip), developed with CH_2Cl_2, and analyzed by radio-TLC scanning using an imaging scanner (BioScan System 500). The K_i values were determined using the same conditions as above. Substrate concentration was adjusted to final concentrations of 20, 25, 33, and 50 μM. Inhibitor concentrations were adjusted to (**1**) 0.0, 0.5, and 1.0 μM; (**2**) 0.0, 1.5, and 2.5 μM; (**3**) 0.0, 1.0, and 2.0 μM; and (**4**) 0.0, 0.5, and 1.0 μM. The K_i calculation was done using the BMDP Statistical Software for derivative-free nonlinear regression.[24]

3. Time Dependency. The assays were conducted at 37 °C in glass microtubes. The tubes containing 60 μL of 0.1% Triton X-100 in 0.1 M phosphate buffer, pH 7.40, 39 μL of phosphate buffer, pH 7.40, and 1 μL of [^{14}C]-(3*S*)-2,3-oxidosqualene were preincubated for 10 min. A preincubated 20-μL aliquot from a mixture of 119 μL of homogeneous pig liver OSC and 1 μL of each inhibitor (**1**, 0.0, 0.5, 1.0, and 1.5 μM; **2**, 0.0, 0.6, 1.2, and 2.4 μM; **3**, 0.0, 1.0, 2.0, and 3.0 mM; **4**, 0.0, 0.5, 0.75, and 1.0 μM) was added at 0, 3, 5, and 7 min for inhibitors **1** and **2** and at 0, 4, 7.5, and 10.5 min for inhibitors **3** and **4**. The samples were incubated for 1 h prior to TLC analyses.

6,10-Dimethyl-(5*E*),9-undecadien-2-ol (6). To a slurry of $LiAlH_4$ (1.0 g, 26.0 mmol) in 30 mL of THF, under an atmosphere of argon, was added dropwise a solution of ketone **5** (5.0 g, 26.0 mmol) in 15 mL of THF. The reaction was refluxed for 30 min, at which time excess $LiAlH_4$ was destroyed at 0 °C by slow addition of 1.0 mL of water followed by 1.0 mL

of 15% NaOH followed by 3.0 mL of water. The resulting solids were filtered and rinsed thoroughly with small portions of Et_2O (5 × 20 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (2/1) as an eluant afforded **6** (4.8 g, 94%) as an oil. IR (neat): 3342 (b), 2922, 2895, 2884, 1449, 1384, 1119, 1061, 826, 737 cm^{-1}. ^1H NMR: δ 5.10 (m, 2H), 3.80 (m, 1H), 2.07 (m, 4H), 1.98 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.49 (m, 2H), 1.18 (d, J = 6 Hz, 3H). ^{13}C NMR: δ 135.4, 131.1, 124.2, 123.9, 67.6, 39.62, 39.1, 26.5, 25.5, 24.2, 23.2, 17.5, 15.8. CIMS: m/z 196 (M^+, 1), 178 (0.5), 163 (3), 153 (37), 135 (25), 123 (11), 109 (75), 107 (11), 95 (19), 93 (11), 81 (32), 69 (100), 67 (82), 55 (19). Anal. ($C_{13}H_{24}O$) H; C: calcd, 79.52; found, 79.10.

1,5,9-Trimethyl-(4*E*),9-decadienyl *tert*-Butyldimethylsilyl Ether (7). To a solution of **6** (4.0 g, 20.4 mmol) in 50 mL of CH_2Cl_2 were added Et_3N (2.91 g, 30.6 mmol), *tert*-butyldimethylsilyl chloride (3.67 g, 24.3 mmol), and 4-(dimethylamino)pyridine (0.05 g, 0.4 mmol) as a catalyst. The mixture was stirred overnight at room temperature. Standard workup followed by chromatography using ethyl acetate/hexanes (1/2) as eluant afforded the protected alcohol **7** (6.0 g, 95%) as an oil. IR (neat): 2960, 2882, 2860, 1454, 1372, 1249, 1137, 1090, 1037, 831, 767 cm^{-1}. ^1H NMR: δ 5.10 (m, 2H), 3.78 (m, 1H), 2.05 (m, 2H), 1.96 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.11 (d, J = 6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR: δ 135.0, 124.5, 124.4, 68.4, 39.9, 39.8, 26.8, 25.9, 25.6, 24.3, 23.7, 18.2, 17.6, 16.0, −4.4, −4.7. CIMS: m/z 310 (M^+, 1), 253 (20), 177 (15), 143 (2), 135 (10), 109 (70), 75 (100), 59 (10). Anal. ($C_{19}H_{38}OSi$) C,H.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-bromo-2,6-dimethyl-(6*E*)-undecen-2-ol (8). A solution of the protected alcohol **7** (6.0 g, 19.3 mmol) in THF (370 mL) and water (100 mL) was treated with *N*-bromosuccinimide (3.44 g, 19.3 mmol) in THF (60 mL) and water (20 mL), while the temperature was kept at 0 °C. After the reaction mixture was stirred for 1 h at 0 °C, THF was removed *in vacuo*. Standard workup followed by column chromatography using ethyl acetate/hexanes (20/1) as the eluant afforded the bromohydrin **8** (5.9 g, 76%, two cycles) as a colorless oil. IR (neat): 3451 (b), 2956, 2856, 1471, 1373, 1254, 1134, 1090, 1035, 906, 835, 774 cm^{-1}. ^1H NMR: δ 5.20 (t, J = 6 Hz, 1H), 3.96 (m, 1H), 3.75 (m, 1H), 1.90−2.35 (m, 8H), 1.59 (s, 3H), 1.55 (s, 6H), 1.33 (d, J = 7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 133.1, 126.1, 72.4, 70.7, 68.3, 39.7, 38.2, 32.2, 26.6, 25.9, 24.3, 23.7, 23.7, 18.1, 15.8, −4.4, −4.7. CIMS: m/z 409/407 ($M^+ + 1$, 12/12), 391 (3), 327 (5), 277 (65), 276 (15), 275 (54), 274 (8), 259 (16), 257 (18), 195 (46), 177 (100). Anal. ($C_{19}H_{39}BrO_2Si$) C,H.

2-[(*tert*-Butyldimethylsilyl)oxy]-6,10-dimethyl-9,10-epoxy-(5*E*)-undecene (9). To a solution of powdered K_2CO_3 (3.6 g, 26.0 mmol) in 50 mL of methanol was added the bromohydrin **8** (5.3 g, 13.0 mmol), and the reaction mixture was stirred for 1 h at room temperature. Methanol was removed *in vacuo*; the resulting slurry was diluted with water (50 mL) and extracted with ether (3 × 50 mL). Standard workup and chromatography using ethyl acetate/hexanes (1/5) as an eluant afforded **9** (4.1 g, 96%) as an oil. IR (neat): 2958, 2856, 1461, 1376, 1253, 1134, 1087, 1039, 835, 774 cm^{-1}. ^1H NMR: δ 5.15 (t, J = 6 Hz, 1H), 3.76 (m, 1H), 2.70 (t, J = 6 Hz, 1H), 1.90−2.21 (m, 8H), 1.57 (s, 3H), 1.29 (s, 3H), 1.22 (3H), 1.12 (d, J = 7 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 134.1, 125.0, 68.3, 58.2, 39.8, 36.3, 27.5, 25.9, 25.7, 24.8, 24.2, 23.7, 18.7, 18.1, 15.9, −4.3, −4.6. CIMS: m/z 327 ($M^+ + 1$, 26), 309 (16), 269 (8), 196 (13), 195 (100), 178 (11), 177 (79), 153 (8). Anal. ($C_{13}H_{38}O_2Si$) C,H.

6,10-Dimethyl-9,10-epoxy-(5*E*)-undecen-2-ol (10). Silyl ether **9** (4.1 g, 12.5 mmol) was dissolved in 30 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF, and the solution was stirred for 4 h at room temperature. The solution was diluted with water (100 mL) and extracted with ether (4 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (1/1) as the eluant yielded **10** (2.6 g, 98%) as a colorless oil. IR (neat): 3427 (b), 2963, 2925, 1741, 1451, 1378, 1248, 1124, 953, 868 cm^{-1}. ^1H NMR: δ 5.18 (t, J = 6 Hz, 1H), 3.80 (m, 1H), 2.69 (t, J = 6 Hz, 1H), 2.02 −2.20 (m, 8H), 1.62 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 1.19 (d, J = 7 Hz, 3H); ^{13}C NMR: δ 134.1, 124.6, 67.2, 63.9, 58.0, 39.0, 36.1, 27.2, 24.6, 24.1, 23.2, 18.4, 15.6. CIMS: m/z 212 (M^+, 0.4), 194 (1), 153 (4), 123 (10), 121 (11), 112 (12), 85 (100), 81 (79), 77 (17), 72 (30), 71 (62), 69 (56), 68 (19), 67 (78), 59 (64). Anal. ($C_{13}H_{24}O_2$) C,H.

6,10-Dimethyl-9,10-epoxy-(5*E*)-undecen-2-yl Methanesulfonate (11). To a solution of epoxy alcohol **10** (0.20 g, 0.94 mmol) in CH_2Cl_2 (30 mL) at −50 °C were added triethylamine (0.15 g, 1.48 mmol) and methanesulfonyl chloride (0.14 g, 1.22 mmol). The mixture was stirred at −50 °C for 5 min and then warmed to 0 °C. The reaction mixture was poured into water, the organic layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). After the combined extracts were dried over $MgSO_4$, the solvents were removed *in vacuo* and the resulting product **11** was used in the next reaction without further purification.

4,8,12-Trimethyl-(3*E*,7*E*),11-tridecatrienyl Thioacetate (13). To a stirred solution of triphenylphosphine (7 g, 26.7 mmol) in THF (70 mL) was added diisopropyl azodicarboxylate (5.6 g, 26.7 mmol) at 0 °C. The mixture was stirred for 0.5 h, after which time a mixture of thioacetic acid (2.0 g, 26.6 mmol) and homofarnesol (**12**)[8a] (3.1 g, 13.3 mmol) in THF (30 mL) was added, while the temperature was maintained below 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and overnight at room temperature. After standard workup, chromatography using ethyl acetate/hexanes (1/20) as eluant afforded **13** (3.28 g, 80%) as a yellow liquid. IR (neat): 2965, 2925, 2854, 1694, 1442, 1381, 1352, 1134, 1107, 950, 835 cm^{-1}. ^1H NMR: δ 5.10 (m, 3H), 2.82 (t, J = 8 Hz, 2H), 2.30 (s, 3H), 2.21 (m, 2H), 2.05−1.96 (m, 8H), 1.69 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H). ^{13}C NMR: δ 195.7, 137.5, 135.0, 131.1, 124.3, 123.9, 121.7, 39.6, 39.5, 30.5, 29.4, 27.9, 26.7, 26.4, 25.6, 23.2, 17.6, 16.1, 15.5. CIMS: m/z 294 (M^+, 2), 251 (9), 218 (2), 183 (5), 175 (3), 115 (17), 81 (52), 69 (100). Anal. ($C_{18}H_{30}OS$) C,H.

4,8,12-Trimethyl-(3*E*,7*E*),11-tridecatriene-1-thiol (14). To a solution of $LiAlH_4$ (0.61 g, 16 mmol) in THF (20 mL) was added dropwise a solution of **13** (0.62 g, 2 mmol) in THF (10 mL) at 0 °C. After 0.5 h excess $LiAlH_4$ was destroyed at 0 °C by slow addition of 1.0 mL of water followed by 1.0 mL of 15% NaOH followed by 3.0 mL of water. The resulting solids were filtered and rinsed thoroughly with small portions of Et_2O (5 × 20 mL). Standard workup followed by chromatography using hexanes as an eluant afforded **14** (0.43 g, 85%) as a yellow liquid. IR (neat): 2920, 2560, 1736, 1670, 1450, 1275, 1100, 970, 835 cm^{-1}. ^1H NMR: δ 5.10 (m, 3H), 2.83 (t, J = 8 Hz, 2H), 2.23 (m, 2H), 2.10−1.95 (m, 8H), 1.66 (s, 3H), 1.61 (s, 3H), 1.59 (s, 6H). ^{13}C NMR: δ 137.5, 134.9, 131.0, 124.4, 123.9, 121.8, 39.7, 39.6, 31.9, 30.5, 29.4, 28.0, 26.7, 26.4, 25.6, 17.6, 16.1, 15.9. CIMS: m/z 252 (M^+, 15), 237 (20), 209 (70), 169 (55), 136 (74), 115 (37), 81 (90), 69 (100). HRMS Calcd for $C_{16}H_{28}Si$: 252.1912. Found: 252.1867.

6,10-Dimethyl-9,10-epoxy-(5*E*)-undecenyl 4′,8′,12′-Trimethyl-(3*E*,7*E*),11-tridecatrienyl Sulfide (1). To a solution of NaOH (5 g, 0.12 mol) in H_2O (10 mL) and toluene (10 mL) were added tetraoctylammonium bromide (0.05 g, 0.1 mmol), thiol **14** (0.25 g, 1 mmol), and mesylate **11** (0.29 g, 1 mmol) at room temperature. The mixture was then warmed to 40 °C and stirred overnight. Standard workup followed by chromatography using ethyl acetate/hexanes (1/20) as the eluant yielded **1** (0.13 g, 29%). IR (neat): 2960, 2923, 2855, 1449, 1376, 1248, 1121, 835 cm^{-1}. ^1H NMR: δ 5.12 (m, 4H), 2.75 (m, 1H), 2.69 (t, J = 6.5 Hz, 1H), 2.50 (t, J = 8 Hz, 2H), 2.25 (m, 2H), 2.18−1.94 (m, 20H), 1.77 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H), 1.57 (s, 3H), 1.29 (s, 3H), 1.27 (d, J = 8.5 Hz, 3H), 1.25 (s, 3H). ^{13}C NMR: δ 136.6, 135.0, 134.7, 131.2, 124.5, 124.1, 123.5, 122.7, 64.1, 58.2, 39.9, 39.7, 37.1, 36.4, 33.9, 32.0, 30.6, 28.7, 27.5, 26.6, 25.6, 25.5, 24.9, 23.4, 22.6, 18.7, 17.7, 16.7, 16.2. CIMS: m/z 447 ($M^+ + 1$, 55), 269 (23), 253 (100), 227 (71), 211 (46), 195 (38), 177 (31), 137 (35). HRMS Calcd for $C_{29}H_{50}OS$: 446.3582. Found: 446.3588.

1-[(*tert*-Butyldimethylsilyl)oxy]-5,9,13-trimethyl-(4*E*,8*E*),12-tetradecatriene (16). To a solution of alcohol **15** (4.0 g, 16.0 mmol) in 50 mL of CH_2Cl_2 was added Et_3N (2.5 g, 24.7 mmol), *tert*-butyldimethylsilyl chloride (3.0 g, 20.0 mmol), and 4-(dimethylamino)pyridine (0.1 g, 0.8 mmol). The mixture was stirred overnight at room temperature. Standard workup

followed by chromatography using ethyl acetate/hexanes (1/15) as eluant afforded the protected alcohol **16** (5.06 g, 87%) as an oil. IR (neat): 2928, 2851, 1444, 1383, 1255, 1099, 836, 775 cm^{-1}. ^1H NMR: δ 5.12 (m, 3H), 3.60 (t, J = 6.0 Hz, 2H), 2.10−1.95 (m, 10H), 1.68 (s, 3H), 1.60 (s, 9H), 1.55 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 135.3, 134.9, 124.5, 124.3, 124.1, 62.7, 39.7, 33.1, 26.8, 26.7, 26.0, 24.6, 24.2, 18.3, 17.6, 16.0, −5.3. CIMS: m/z 365 ($M^+ + 1$), 307 (6), 234 (18), 233 (100), 231 (24). Anal. ($C_{23}H_{44}OSi$) C,H.

3-Bromo-2,6,10-trimethyl-14-[(*tert*-butyldimethylsilyl)oxy]-(6*E*,10*E*)-tetradecadien-2-ol (17). A solution of the protected alcohol **16** (5.0 g, 13.7 mmol) in THF (370 mL) and water (100 mL) was treated with *N*-bromosuccinimide (2.55 g, 14.4 mmol) in THF (60 mL) and water (20 mL), while the temperature was kept at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, THF was removed *in vacuo*, and standard workup followed by filtration over SiO_2 using ethyl acetate/hexanes (20/1) as an eluant afforded the bromohydrin **17** (3.1 g, 48%) as an oil. IR (neat): 3429, 2930, 2856, 1741, 1726, 1426, 1375, 1253, 1101, 1047, 836, 775 cm^{-1}. ^1H NMR: δ 5.14 (m, 2H), 3.98 (m, 1H), 3.59 (t, J = 6 Hz, 2H), 2.18−1.95 (m, 12H), 1.61 (s, 6H), 1.37 (s, 3H), 1.34 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H). The product was used without further purification in the next reaction.

1-[(*tert*-Butyldimethylsilyl)oxy]-12,13-epoxy-5,9,13-trimethyl-(4*E*,8*E*),12-tetradecatriene (18). The bromohydrin **17** (3.0 g, 6.5 mmol) was added to K_2CO_3 (1.8 g, 13.0 mmol), dissolved in methanol (40 mL), and stirred for 1 h. Next, most of the methanol was removed *in vacuo*, and the resulting slurry was diluted with water (20 mL). After extraction with Et_2O (4 × 30 mL), standard workup followed by chromatography using ethyl acetate/hexanes (1/10) as the eluant yielded the epoxide **18** (2.3 g, 90%) as a colorless oil. IR (neat): 2928, 2856, 1462, 1378, 1253, 1100, 1006, 836, 775 cm^{-1}. ^1H NMR: δ 5.15 (2H), 3.58 (t, J = 6.5 Hz, 2H), 2.70 (t, J = 6.0 Hz, 1H), 2.15−1.96 (m, 10H), 1.59 (s, 3H), 1.54 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 0.95 (s, 9H), 0.05 (s, 6H). ^{13}C NMR: δ 135.2, 134.0, 124.9, 124.2, 64.1, 62.7, 58.2, 39.6, 36.3, 33.0, 27.5, 26.7, 25.9, 24.9, 24.2, 18.7, 18.3, 16.0, 15.9, −5.4. CIMS: m/z 382/281 ($M^+ + 1$, 12/41), 363 (15), 250 (10), 249 (53), 232 (17), 231 (100). Anal. ($C_{23}H_{44}O_2Si$) C,H.

12,13-Epoxy-5,9,13-trimethyl-(4*E*,8*E*)-tetradecatrien-1-ol (19). Silyl ether **18** (2.28 g, 6.0 mmol) was dissolved in 20 mL of a 1.0 M solution of tetrabutylammonium fluoride in THF, and the solution was stirred for 4 h at room temperature. The solution was diluted with water (30 mL) and extracted with ether (4 × 20 mL). Standard workup followed by chromatography using ethyl acetate/hexanes (1/1) as the eluant yielded **19** (1.5 g, 94%) as a colorless oil. IR (neat): 3386, 2929, 1461, 1379, 1250, 1122, 1059, 873, 773 cm^{-1}. ^1H NMR: δ 5.13 (m, 2H), 3.63 (t, J = 6.5 Hz, 2H), 2.70 (t, J = 6.5 Hz, 1H), 2.18−1.98 (m, 10H), 1.60 (m, 8H), 1.29 (s, 3H), 1.25 (s, 3H). ^{13}C NMR: δ 135.6, 134.1, 124.8, 123.9, 64.2, 62.7, 58.3, 39.6, 36.3, 32.8, 27.5, 26.5, 24.8, 24.2, 18.7, 16.0, 15.9. CIMS: m/z 268/267 ($M^+ + 1$, 19/100), 250 (17), 249 (95), 153 (30), 137 (11), 135 (27), 127 (16), 123 (15), 111 (16), 109 (27). Anal. ($C_{17}H_{30}O_2$) C,H.

12,13-Epoxy-5,9,13-trimethyl-(4*E*,8*E*)-tetradecadienyl Methanesulfonate (20). To a solution of epoxy alcohol **19** (0.20 g, 0.75 mmol) in CH_2Cl_2 (30 mL) at −50 °C were added triethylamine (0.15 g, 1.48 mmol) and methanesulfonyl chloride (0.14 g, 1.2 mmol). The mixture was stirred at −50 °C for 5 min and then warmed to 0 °C. The reaction mixture was poured into water, the organic layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). After the combined extracts were dried over $MgSO_4$, the solvent was removed *in vacuo* and the crude mesylate **20** was used for the next reaction without further purification.

4,8-Dimethyl-(3*E*),7-nonadienyl Thioacetate (22). To a stirred solution of triphenylphosphine (1.56 g, 6.0 mmol) in THF (15 mL) was added diisopropyl azodicarboxylate (1.2 g, 6.0 mmol) at 0 °C. The mixture was stirred for 0.5 h, after which time a mixture of thioacetic acid (0.46 g, 6.0 mmol) and homogeraniol (**21**)[21] (0.5 g, 3.0 mmol) in THF (30 mL) was added, while the temperature was maintained below 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then overnight at room temperature. Standard workup with SiO_2 chromatography using ethyl acetate/hexanes (1/20) as eluant afforded **22** (0.54 g, 80%). IR (neat): 3350, 2910, 1690, 1435, 1350, 1130, 1100, 950, 830, 735 cm^{-1}. ^1H NMR: δ 5.10 (m, 2H), 2.85 (t, J = 7 Hz, 2H), 2.31 (s, 3H), 2.25 (m, 2H), 2.06−1.95 (m, 4H), 1.67 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H). The ^1H NMR spectrum was in agreement with that reported in ref 28.

4,8-Dimethyl-(3*E*),7-nonadienethiol (23). To a stirred solution of 2.5% KOH in methanol (10 mL) was added thiol **22** (0.5 g, 1.9 mmol) at room temperature. The mixture was stirred for 4 h, after which time most of the methanol was removed *in vacuo*. The resulting slurry was diluted with water (20 mL) and extracted with Et_2O (3 × 20 mL). Standard workup and chromatography using hexanes as the eluant afforded **23** (0.31 g, 88%) as a yellow liquid. ^1H NMR: δ 5.10 (m, 2H), 2.51 (dt, J = 7.0, 7.5 Hz, 2H), 2.30 (m, 2H), 2.05 (m, 2H), 2.00 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.41 (t, J = 7.5 Hz, 1H). The ^1H NMR spectrum was in agreement with that reported in ref 28.

12,13-Epoxy-5,9,13-trimethyl-(4*E*,8*E*)-tetradecadienyl 4′,8′-Dimethyl-(3′*E*),7′-nonadienyl Sulfide (2). To a solution of NaOH (5.0 g, 0.12 mol) in H_2O (10 mL) and toluene (10 mL) were added tetraoctylammonium bromide (0.05 g, 0.1 mmol), thiol **23** (0.24 g, 1.3 mmol), and mesylate **20** (0.30 g, 0.87 mmol) at room temperature. The mixture was then warmed to 40 °C and stirred overnight. Standard workup followed by chromatography using ethyl acetate/hexanes (1/20) as the eluant yielded **2** (0.24 g, 64%). IR (neat): 2926, 2856, 1666, 1448, 1377, 1250, 1105, 910, 836, 776, 733 cm^{-1}. ^1H NMR: δ 5.13 (m, 4H), 2.70 (t, J = 6 Hz, 1H), 2.50 (m, 4H), 2.25 (m, 2H), 2.19−1.96 (m, 16H), 1.66 (s, 3H), 1.61 (sb, 9H), 1.59 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H). ^{13}C NMR: δ 136.5, 135.7, 135.1, 134.1, 124.8, 124.2, 123.6, 122.6, 39.6, 36.3, 33.0, 32.2, 31.2, 29.8, 28.5, 27.5, 27.1, 26.6, 25.9, 24.8, 18.7, 15.9. CIMS: m/z 433 ($M^+ + 1$, 20), 381 (50), 363 (24), 249 (63), 231 (100). HRMS Calcd for $C_{28}H_{48}OS$: 432.3425. Found: 432.3434.

3,8,12,16-Tetramethyl-(3*E*,7*E*,11*E*),15-heptadecatetraenyl *tert*-Butyldimethylsilyl Ether (24). This was prepared by the method of Dodd and Oehlschlager.[8a]

3-Bromo-17-[(*tert*-butyldimethylsilyl)oxy]-2,6,10,16-tetramethyl-(6*E*,10*E*,14*E*)-heptadecatrien-2-ol (25). This was prepared in 39% yield from **24** by the same procedure described for **8**. IR (neat): 3454, 1666, 1462, 1383, 1255, and 1098 cm^{-1}. CIMS: m/z 517/515 ($M^+ + 1$, 9.7/10.2), 385 (33.5), 383 (37.4), 367 (38.4), 365 (40.4), 303 (47.2), 285 (100), 231 (14.3), 229 (11), 205 (11.9), 203 (16.6), 191 (13.4), 189 (8.1), 135 (30.2), 133 (42.4). ^1H NMR: δ 5.22−5.10 (m, 3H), 3.98 (dd, J = 11.3, 1.6 Hz, 1H), 3.65 (t, J = 7.2 Hz, 2H), 2.36−2.28 (m, 1H), 2.19 (t, J = 7.2 Hz, 2H), 2.16−1.90 (m, 10H), 1.84−1.73 (m, 1H), 1.68 (m, 1H), 1.61 (s, 3H), 1.59 (s, 6H), 1.34 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.041 (s, 6H). ^{13}C NMR: δ 135.0, 133.1, 132.273, 126.2, 126.0, 124.5, 72.4, 70.8, 62.6, 43.1, 39.7, 38.2, 32.3, 28.3, 28.2, 26.7, 26.0, 25.9, 18.3, 16.4, 16.0, 15.9, −5.2. Anal. ($C_{27}H_{51}BrO_2Si$) C,H.

1-[(*tert*-Butyldimethylsilyl)oxy]-15,16-epoxy-3,8,12,16-tetramethyl-(3*E*,7*E*,11*E*)-heptadecatriene (26). This was prepared in 96% yield by the same procedure as described for **9**. IR (neat): 2957, 2928, 2856, 1666, 1462, 1378, 1252, 1096, 836 cm^{-1}. CIMS: m/z 435 ($M^+ + 1$, 6.3), 418 (6.3), 303 (62.9), 285 (100), 259 (12.6), 191 (28.0), 163 (37.2), 155 (22.7), 149 (30.5), 135 (38.2), 123 (16.3). ^1H NMR: δ 5.20−5.10 (m, 3H), 3.65 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 6.3 Hz, 1H), 2.19 (t, J = 7.2 Hz, 2H), 2.16−1.95 (m, 12H), 1.61 (s, 6H), 1.59 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR: δ 135.3, 134.3, 132.5, 126.5, 125.2, 124.6, 64.4, 62.8, 58.4, 43.4, 39.9, 36.6, 28.6, 28.4, 27.8, 27.0, 26.2, 25.1, 19.0, 18.6, 16.7, 16.2, −5.0. Anal. ($C_{27}H_{50}O_2Si$) C,H.

15,16-Epoxy-3,8,12,16-tetramethyl-(3*E*,7*E*,11*E*)-heptadecatrien-1-ol (27). This was prepared in 92% yield by the procedure described for **10**. IR (neat): 3418, 2955, 2927, 2852, 1667, 1448, 1379, 1250, 1049, 875 cm^{-1}. CIMS: m/z 321 ($M^+ + 1$, 61.1), 303 (100), 285 (15.6), 221 (11.7), 217 (10.6), 207 (12.6), 191 (37.1), 163 (27.5), 153 (50.3), 149 (30.4). ^1H NMR: δ 5.24 (dt, J = 1.2, 6.3 Hz, 1H), 5.18−5.08 (m, 2H), 3.64 (dt, J = 5.9, 6.0 Hz, 2H), 2.70 (t, J = 6.3 Hz, 1H), 2.24 (t, J = 6.0

Hz, 2H), 2.20−1.95 (m, 12H), 1.63 (d, J = 1.2 Hz, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H). ^{13}C NMR: δ 135.4, 134.1, 131.4, 127.8, 124.9, 122.5, 64.2, 60.2, 58.2, 42.8, 39.6, 36.3, 28.3, 28.1, 27.5, 26.6, 24.9, 21.0, 18.7, 16.0, 16.0, 15.8. Anal. ($C_{21}H_{36}O_2$) C,H.

15,16-Epoxy-3,8,12,16-tetramethyl-(3*E*,7*E*,11*E*)-heptadecatrienyl Methanesulfonate (28). This was prepared in 97% yield by the procedure described for **11**. Compound **28** was used in the next reaction without further purification. ^{1}H NMR: δ 5.30−5.00 (m, 3H), 4.27 (t, J = 6.8 Hz, 2H), 3.00 (s, 3H), 2.70 (t, J = 6.3 Hz, 1H), 2.42 (t, J = 6.8 Hz, 2H), 2.25−1.86 (m, 12H), 1.66 (s, 3H), 1.58 (s, 6H), 1.30 (s, 3H), 1.26 (s, 3H).

6-Methyl-5-heptenyl-2-thioacetate (30). This was prepared in 84% yield by the procedure described for **13**. IR (neat): 2965, 2924, 2856, 1692, 1450, 1378, 1353, 1115, 952 cm^{-1}. CIMS: m/z 187 (M^+ + 1, 13.4), 186 (M^+, 2.3), 146 (10.3), 145 (100), 101 (3.9). ^{1}H NMR: δ 5.07 (tq, J = 7.2, 1.3 Hz, 1H), 3.54 (sextet, J = 6.9 Hz, 1H), 2.30 (s, 3H), 2.04 (dt, J = 7.4, 7.4 Hz, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.61−1.50 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H). ^{13}C NMR: δ 195.6, 132.1, 123.4, 39.3, 36.4, 30.6, 25.6, 23.9, 21.4, 17.6. Anal. ($C_{10}H_{18}OS$) C,H.

6-Methyl-5-heptene-2-thiol (31). This was prepared in 91% yield by the procedure described for **14**. IR (neat): 2966, 2921, 2850, 1667, 1449, 1376, 1115, 826 cm^{-1}. CIMS: m/z 147/145 (M^+ + 1, 5.6/100), 111 (12.2), 109 (1.4), 103 (4.5), 101 (19.8). ^{1}H NMR: δ 5.07 (tq, J = 7.2, 1.3 Hz, 1H), 2.92 (septet, J = 6.7 Hz, 1H), 2.09 (dt, J = 7.2, 7.2 Hz, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59−1.49 (m, 2H), 1.47 (d, J = 6.3 Hz, 1H), 1.33 (d, J = 6.7 Hz, 3H). ^{13}C NMR: δ 131.9, 123.4, 40.9, 35.0, 25.8, 25.5, 22.0, 17.57. Anal. ($C_8H_{16}S$) C,H.

15,16-Epoxy-3,8,12,16-tetramethyl-(3*E*,7*E*,11*E*)-heptadecatrienyl 1′,5′-Dimethyl-4′-hexenyl Sulfide (3). This was prepared in 74% yield by coupling of **28** and **31** according to the procedure described for **1**. IR (neat): 2960, 2922, 2855, 1667, 1449, 1376, 1248, 1119, 826 cm^{-1}. CIMS: m/z 447 (M^+ + 1, 100), 429 (48.8), 335 (11.4), 293 (26.8), 285 (14.6), 145 (9.2). ^{1}H NMR: δ 5.22−5.05 (m, 4H), 2.75 (sextet, J = 6.7 Hz, 1H), 2.70 (t, J = 6.3 Hz, 1H), 2.57 (t, J = 7.3 Hz, 2H), 2.23 (t, J = 7.3 Hz, 2H), 2.20−1.95 (m, 12H), 1.68 (s, 3H), 1.65−1.58 (m, 2H), 1.61 (s, 9H), 1.59 (s, 3H), 1.51−1.44 (m, 2H), 1.29 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H), 1.25 (s, 3H). ^{13}C NMR: δ 135.1, 134.1, 133.8, 131.9, 125.7, 125.0, 124.3, 124.0, 64.2, 58.2, 40.2, 39.7, 39.6, 37.2, 36.4, 29.1, 28.3, 28.1, 27.6, 26.7, 25.6, 24.9, 21.4, 18.7, 17.7, 16.0, 15.9, 15.8. Anal. ($C_{29}H_{50}OS$) C,H.

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