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Synthesis of Vinyl Sulfide Analogs of 2,3-Oxidosqualene and Their Inhibition of 2,3-Oxidosqualene Lanosterol-Cyclases

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Abstract: Syntheses of all *trans* (6*E*)-5-, (10*E*)-9-, (14*E*)-16- and (18*E*)-20-thia-2,3- oxidosqualenes as inhibitors of 2,3-oxidosqualene-lanosterol cyclase (OSC) are reported. To mimic the natural geometry of 2,3-oxidosqualene (2,3-OS), we required *E*-vinyl sulfides which were prepared by condensation of sulfur-substituted Wittig-Horner reagents (α -thioterpenoidyl diphenylphosphine oxides) with appropriate aldehydes. Mixtures of *syn* and *anti* α -hydroxydiphenylphosphine adducts were separated by chromatography and the *syn* isomers were transformed to the *E*-vinyl sulfides. Both (6*E*)-5- and (18*E*)-20-thia-2,3-OS inhibited OSC from *Candida albicans* (IC₅₀ = 47 and 0.2 μ M, respectively) and rat liver (IC₅₀ = 7.7 and 0.32 μ M, respectively). Their activities were compared with those of previously synthesized (6*E*)-8- and (14*E*)-13-thia-2,3-OSs (IC₅₀ = 0.68 and 45 μ M, *C. albicans*, IC₅₀ = 34 and 61 μ M, rat liver, respectively). The best inhibitor among these compounds for the OSC of *C. albicans* and rat liver is the (18*E*)-20-thia-2,3-OS. This result suggests that modification of C-20 region of the 2,3-OS skeleton is an attractive strategy for development of OSC inhibitors.

Introduction

2,3-Oxidosqualene-lanosterol cyclases (OSCs) catalyze the cyclization of (3*S*)-2,3-oxidosqualene (2,3-OS), **1**, to a number of tetracyclic triterpenes.¹⁻⁴ In addition, some monocyclic^{5a} and bicyclic^{5b} terpenoids found in nature are envisioned to have arisen from partial cyclization of 2,3-OS. During the formation of tetracyclic triterpenoids, OSCs are considered to bind 2,3-OS, **1**, in a chair-boat-chair conformation then mediate the sequential formation of four new C-C bonds leading to tetracyclic protosterol. Backbone rearrangement of this cation by OSC leads to lanosterol in fungi and mammalian systems. The mechanism of

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these cyclizations is believed to involve a set of conformationally rigid, partially cyclized carbocationic intermediates⁴ Since OSCs are rich in tryptophan and tyrosine and these residues occur at nearly identical positions in the OSCs for which sequences are known, it is considered that these residues are involved in the stabilization of the presumptive cation intermediates.^{5c, d}

Because of their function in sterol biosynthesis as catalysts mediating the formation of the sterol nucleus, much attention has been centered on the design of inhibitors of OSCs.⁶ Among the more effective OSC inhibitors are substrate mimics,⁷⁻¹¹ the most potent of which are 2,3,18,19-dioxidosqualene⁸ and analogs of 2,3-OS in which sulfur is located at positions normally occupied by the presumptive cationic carbons.¹¹

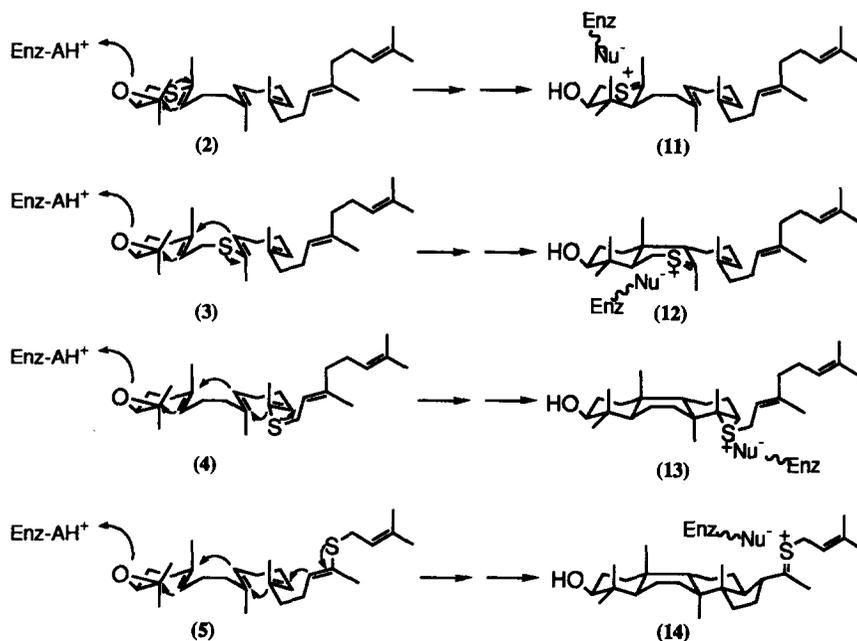


Figure 1

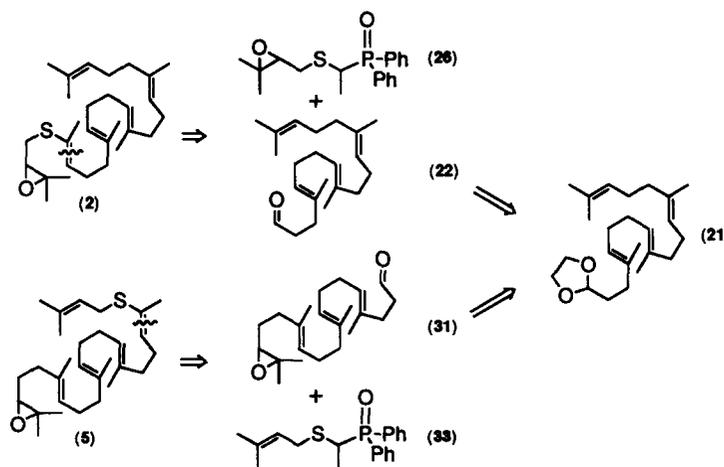
In the present study, we have prepared four analogs of 2,3-OS (2-5) in which a vinyl sulfur has been placed at chain position α to those carbons presumed to possess a positive charge during the normal cyclization of 2,3-OS. Theoretical studies have shown that sulfur is an efficient π - and σ -donor to electron deficient α -carbon.¹² Our presumption was that these 2,3-OS analogs would cyclize to the point that the

carbocation formed could be stabilized by an adjacent sulfur. We reasoned that this stabilization would decrease the reactivity of the cation interrupting further cyclization. Charge in the partially cyclized cations would be distributed between the carbon normally bearing the positive charge and the adjacent sulfur. The presumptive thiocarbenium ions might react with residues normally stabilizing the natural carbocations (Figure 1).

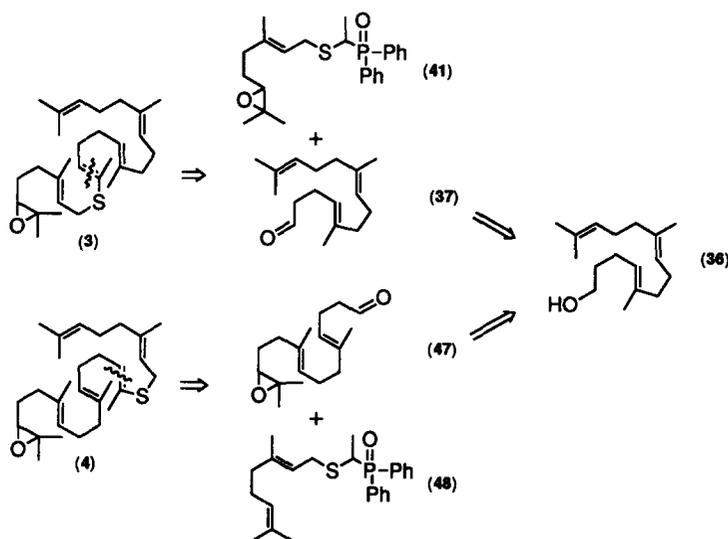
We report the synthesis of **2-5**, their inhibition of selected OSCs and comparison of their inhibitory power with previously synthesized vinyl sulfur 2,3-OS analogs.¹³

Results and Discussion

Preparation of 2,3-OS analogs (**2-5**) containing vinyl sulfur at C-5, C-9, C-16 and C-20 positions required construction of trisubstituted *E*-vinyl sulfides. Synthesis of the target molecules involved Wittig-Horner methodology developed by Cattel¹⁴ and Corey¹⁵ for the synthesis of (*E*)-20-oxa-2,3-OS analogs. This method is effective for the synthesis of compounds **2-5** because it utilizes a set of common intermediates. Retrosynthetic analysis of **2** and **5** reveals that both can be derived from **21** (Scheme 1). Similarly, both **3** and **4** can be obtained from **36** (Scheme 2).

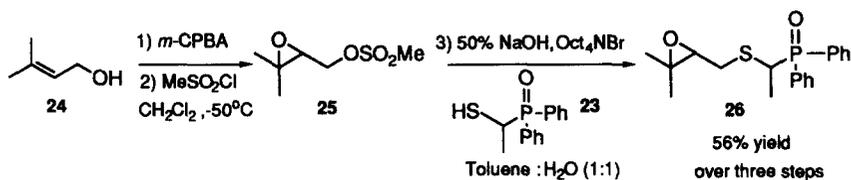
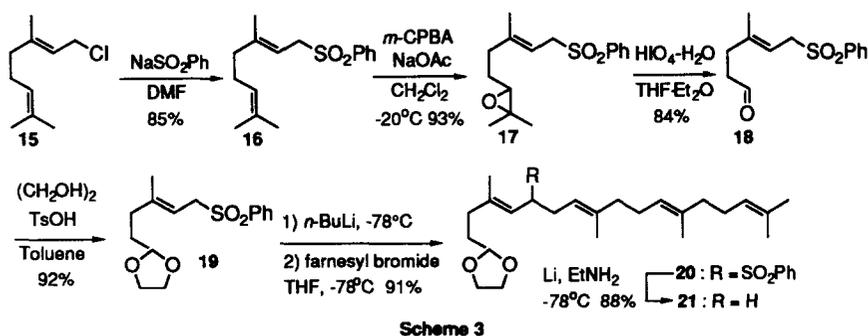


Scheme 1

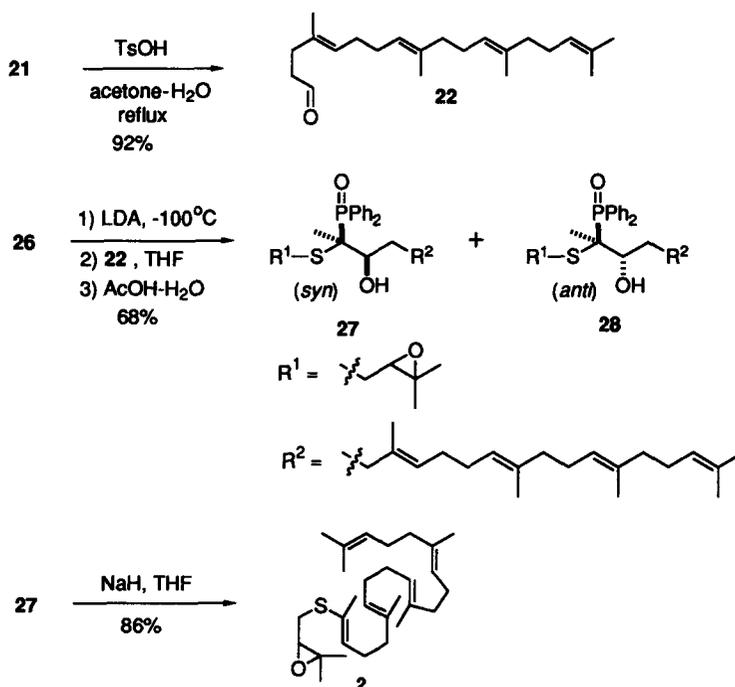


Scheme 2

Syntheses of 2 and 5. Synthesis of 2 in which sulfur replaces C-5 in 2,3-OS commenced with construction of key intermediate 21 (Scheme 3).¹⁶ In comparison with the previously reported procedure,¹⁶ the synthetic route to 21 was shortened by two steps. Reaction of geranyl chloride 15 with NaSO₂Ph in DMF gave sulfone, 16. Selective epoxidation of 16 gave epoxide 17 in 93% yield, and the latter was oxidatively cleaved to 18 which was converted to acetal, 19. The latter was subjected to a metalation-alkylation sequence to furnish tetraen-sulfone, 20. Reductive elimination of the sulfone moiety gave the key tetraen-acetal, 21 (Scheme 3). The required diphenylphosphinoyl-ethane-1-thiol, 23, was prepared by a procedure analogous to that used for the synthesis of diethyl-phosphorylthiol.¹⁷ Conversion of alcohol, 24, to its corresponding epoxy mesylate, 25, was executed by epoxidation followed by mesylation (Scheme 4). The required Wittig-Horner agent, 26, was obtained in overall 56% yield by coupling thiol, 23, with mesylate, 25, under phase-transfer conditions¹⁸ (Scheme 4).

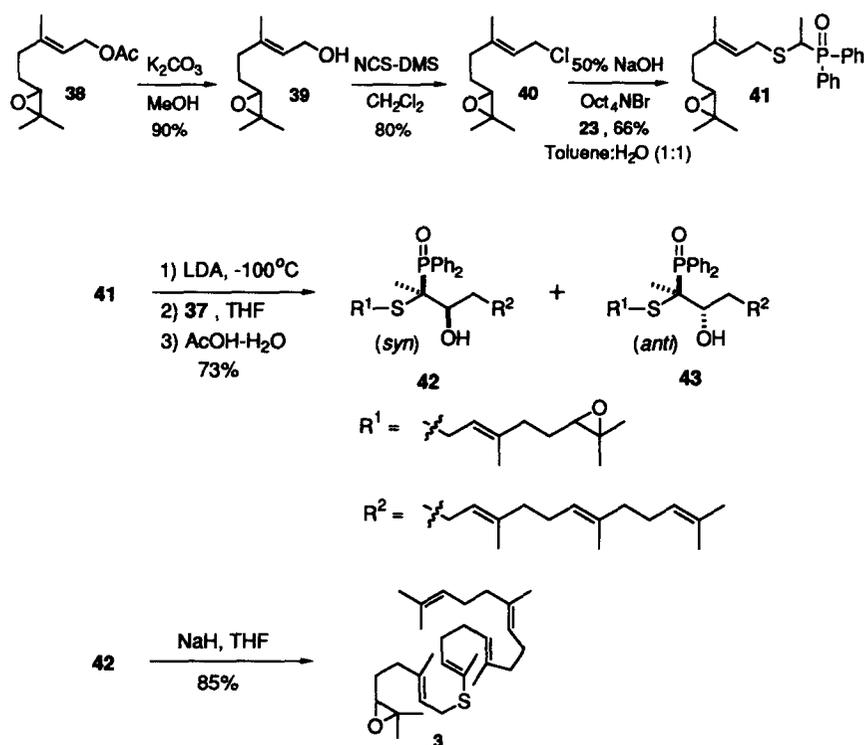


Deacetalization of **21** in aqueous acetone generated **22** (Scheme 5). Metalation of **26** followed by addition of aldehyde, **22**, gave a mixture of *syn* and *anti* (~60/40; by $^1\text{H-NMR}$ analysis) α -hydroxydiphenylphosphinoyl isomers (**27** and **28**, Scheme 5). Analysis of this mixture by thin layer chromatography revealed two overlapping spots. Repeated flash column chromatography partially separated the two isomers to give pure **27** (*syn*) in 31% yield. The *anti* isomer, **28**, was contaminated with ~15% of **27**. Reaction of **27** with NaH in THF gave isomerically pure (6*E*)-5-thia-2,3-OS, **2**, in 86% yield (Scheme 5). $^1\text{H-NMR}$ of **2** revealed a triplet of quartets at δ 5.55 ($J = 7.1, 1.21$ Hz) for the vinyl hydrogen attached to C-7. The nOe difference $^1\text{H-NMR}$ spectrum of **2** confirmed the *E*-stereochemistry of the vinyl sulfide. A nOe enhancement was observed between the C-7 vinyl hydrogen (δ 5.55, $J = 7.1, 1.21$ Hz) and C-4 hydrogens (δ 2.92), but not between the C-7 vinyl hydrogen and methyl attached to C-6. This indicates the C-7 vinyl hydrogen and C-6 methyl are *trans*.^{13, 15}



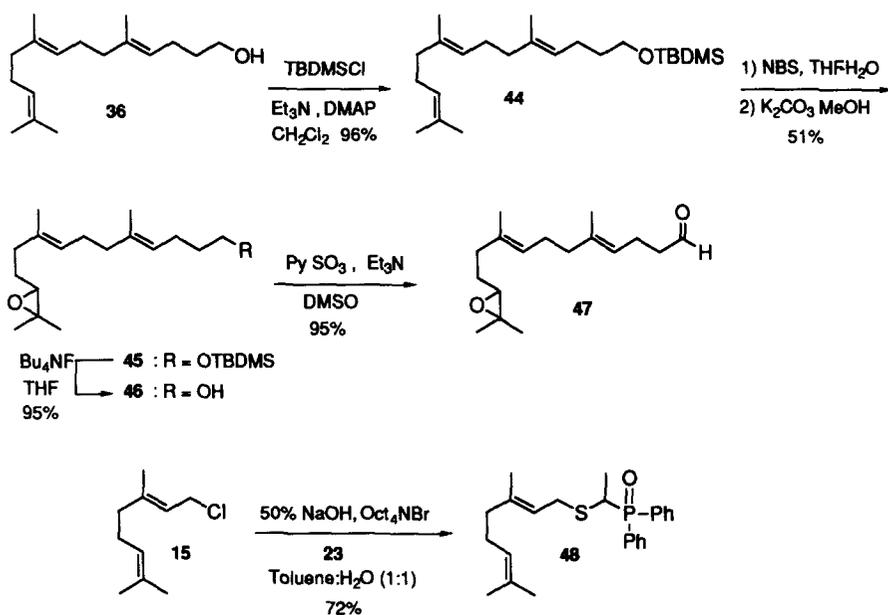
Scheme 5

Synthesis of **5** in which sulfur replaces C-20 in 2,3-OS commenced with conversion of **21** to terminal bromohydrin, **29**, in 38% yield.¹⁹ Removal of the acetal of latter compound followed by treatment with K_2CO_3 in methanol gave epoxy aldehyde, **31**,¹⁵ in 37% yield over two steps (Scheme 6). Coupling of thiol, **23**, with allylic chloride, **32**, under phase transfer conditions¹⁸ gave the required Wittig-Horner reagent, **33**, in 73% yield. Reaction of **31** with the lithium anion of **33** at -100°C in THF followed by addition of acetic acid gave a mixture of *syn* and *anti* (~65/35; by ^1H NMR analysis) α -hydroxy-diphenylphosphinoyl isomers (**34** and **35**) in 71% yield (Scheme 6). Partial separation using flash column chromatography gave pure **34** (*syn*) in 33% yield. The *anti* isomer, **35**, was contaminated with ~15% of **34**. Treatment of **34** with NaH/THF gave isomerically pure (18*E*)-20-thia-2,3-OS, **5**, in 89% yield (Scheme 6). The structure of **5** was confirmed by ^1H NMR analysis, which revealed a triplet of quartets at δ 5.35 ($J = 7.0, 1.24$ Hz) for the vinyl hydrogen attached to C-18. The *E*-geometry of the vinyl sulfide was confirmed by observation of a nOe enhancement between the C-18 vinyl hydrogen and the C-21 hydrogen.^{13, 15}



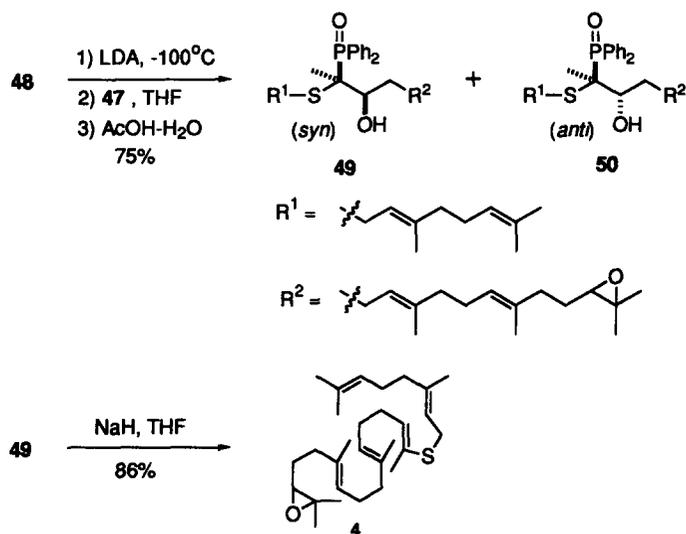
Scheme 7

Syntheses of 3 and 4. Synthesis of 3 in which sulfur replaces C-9 in 2,3-OS involved similar chemistry. The required triene alcohol, 36, and aldehyde, 37, (Scheme 2) were prepared according to the procedure described by Coates.²⁰ Hydrolysis of available epoxy geranyl acetate, 38,¹⁶ gave epoxy alcohol, 39, which was converted with NCS-DMS²¹ to epoxy-geranyl chloride, 40, in 72% yield over two steps. Reaction of chloride, 40, with thiol, 23, under phase-transfer conditions¹⁸ furnished 41 in 66% yield (Scheme 7). Addition of aldehyde, 37, to the lithium anion of 41 at -100°C , followed by addition of acetic acid, gave the α -hydroxydiphenylphosphinoyl isomers, 42 and 43, as a ($\sim 60/40$ by ^1H NMR analysis) mixture of diastereoisomers in 73% yield (Scheme 7). Repeated flash chromatography achieved separation of the isomers, and elimination was then carried out as described above furnished isomerically pure (10*E*)-9-thia-2,3-OS, 3 (Scheme 7). The structure of 3 was confirmed by ^1H NMR which revealed a triplet of quartets for the C-11 vinyl hydrogen at δ 5.38 ($J = 6.70, 1.19$ Hz). A nOe enhancement between the C-11 vinyl hydrogen and the C-8 hydrogen of 3 was observed and confirmed the geometry of the *E*-vinyl sulfide.^{13,15}



Scheme 8

Synthesis of **4** in which sulfur replaces C-16 in 2,3-OS was similarly accomplished by the condensation of epoxy-aldehyde, **47**, with the lithium anion of **48**. Preparation of epoxy-aldehyde, **47**, began with protection of alcohol, **36**, as a silyl ether, **44**, in 96% yield (Scheme 8). Reaction of **44** with NBS¹⁹ followed by treatment with K₂CO₃ in MeOH gave epoxide, **45**, in 51% overall yield for two steps. Deprotection of **45** using *n*-Bu₄NF followed by oxidation of **46** gave epoxy aldehyde, **47**, in 90% overall yield. The required **48** was prepared by coupling of geranyl chloride, **15**, with thiol, **23**, under phase-transfer conditions¹⁸ in 72% yield (Scheme 8).



Scheme 9

Addition of aldehyde **47** to the lithium anion of **48** at -100°C gave, after acetic acid quench, α -hydroxy diphenylphosphinoyl isomers, **49**, and **50**, as a ~65/35 mixture (by ^1H NMR analysis) (Scheme 9). Repeated flash chromatography and elimination as described above furnished the *E*-vinyl sulfide, **4**, **13**, **15** (Scheme 9).

Biological Results. Both **2** and **5** inhibited cell-free OSC of *C. albicans* with IC_{50} values of 47 and $0.2\ \mu\text{M}$, respectively. Sulfide, **5**, is 235-fold more potent than **2** in *C. albicans* cyclase. In rat liver OSC, **2** displayed an IC_{50} value of $7.7\ \mu\text{M}$ while **5** showed an IC_{50} value of $0.32\ \mu\text{M}$. Thus, **5** is 24-fold more potent than **2** in this OSC (Table 1). Compared with previously reported (6*E*)-8-thia-2,3-OS, **51**, and (14*E*)-13-thia-2,3-OS, **52**,¹³ (Figure 3, Table 1), **2** is over 69-fold less potent than **51** in the *C. albicans* OSC and showed comparable activity with **52** while **5** has the best inhibitory activity being 3.4-fold more potent than **51** and 225-fold more potent than **52**. In rat liver OSC, **2** displayed good activity being 4.4-fold and nearly 8-fold more potent than **51** and **52**, respectively. In this system, **5** again showed the best inhibitory activity being 106-fold more potent than **51** and nearly 191-fold more potent than **52**. 2,3-OS analog **5** which contains a sulfur in place of C-20 displayed the highest activity among the vinyl sulfides tested in both *C. albicans* and

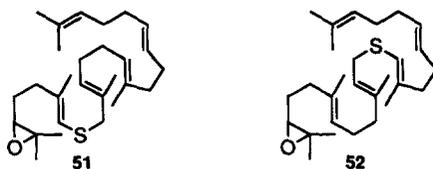


Figure 3

Table 1

| comps. | IC ₅₀ ^a (μM) | |
|-----------------|---|----------------------------------|
| | <i>C. albicans</i> cyclase (cell-free) | Rat liver cyclase (cell-free) |
| 2 | 47 | 7.7 |
| 3 ^b | <i>d</i> | <i>d</i> |
| 4 ^b | <i>d</i> | <i>d</i> |
| 5 | 0.2 | 0.32 |
| 51 ^c | 0.68 | 34 |
| 52 ^c | 45 | 61 |

^a IC₅₀: concentration of inhibitor required to reduce enzyme activity by 50%. ^b Prolonged storage of 3 and 4 resulted in decomposition. ^c 51 and 52 from ref.13. ^d Not determined.

rat liver cyclases. This result suggests that modification of the C-20 region of 2,3-OS is attractive for further development of OSC inhibitors. Although all tested vinyl sulfides showed good inhibitory activity against (*C. albicans* and rat liver) OSCs, we cannot confidently rationalize the mode of action of these inhibitors without detailed kinetic analysis. It is worth noting that vinyl sulfide, 5, showed superior activity (IC₅₀ = 0.32 μM, rat liver) in comparison to the corresponding oxygen analog 22,23-dihydro-20-oxa-2,3-OS¹⁴ (IC₅₀ = 80 μM, rat liver). The IC₅₀ value of 5 (IC₅₀ = 0.2 μM, *C. albicans*, 0.32 μM, rat liver) is comparable with 2,3-iminosqualene^{7,22} (IC₅₀ = 0.15 μM, *C. albicans*, 0.4 μM, rat liver), a potent inhibitor of 2,3-oxidosqualene-lanosterol cyclases.

Experimental

1. General Chemical Methods. ^1H NMR and ^{13}C NMR Spectra were recorded on a Bruker AMX-400 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5985B GC/MS system using a capillary column (30 mm x 0.32 mm ID; with 0.25 DB-1 coating) and 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 Perkin Elmer Model FT 1605 spectrophotometer.

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone-ketyl. Triethylamine, diisopropylamine and dichloromethane were 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. Compounds **19**, **30**, **31**, **36** and **37** were prepared by reported experimental procedures.^{13-16, 20} Chemicals obtained from commercial sources were used without purification. 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 cannulas were used to transfer reagents. Unless otherwise stated, standard work-up refers to the combined organic extracts being washed with ice-cold saturated aqueous sodium chloride, dried over anhydrous MgSO_4 , filtered and the filtrate being concentrated *in vacuo*.

2. Enzyme Inhibition Assay. IC_{50} values were measured as described previously in reference 13 and 22.

3,7-Dimethyl-1-(benzenesulfonyl)-(2E)-6-octadiene (16): To a solution of geranyl chloride **15** (3.66 g, 21.2 mmol) in DMF (40 mL) at 0 °C was added NaSO_2Ph (3.78 g, 23 mmol). The reaction mixture was stirred for 12 h. Water (60 mL) was added and the aqueous layer extracted with ether (4 x 40 mL). Standard work-up followed by chromatography using ethyl acetate:hexane (4:6) as the eluant gave the sulfone **16** (5.03 g, 85%) as an oil: IR (film) 1663, 1447, 1307, 1150, 1085 and 742 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 279 (M^++1 , 2.9), 185 (1.0), 143 (11.2), 137 (100); ^1H NMR (CDCl_3 , ppm) 7.87 (d, $J = 7.0$ Hz, 2H), 7.62 (t, $J = 7.0$ Hz, 1H), 7.52 (t, $J = 7.0$ Hz, 2H), 5.18 (t, $J = 7.3$ Hz, 1H), 5.03 (m, 1H), 3.80 (d, $J = 8.0$ Hz, 2H), 1.99 (s, 4H), 1.68 (s, 3H), 1.58 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (CDCl_3 , ppm) 146.3, 138.8, 133.5, 132.0, 128.9, 128.6, 123.5, 110.4, 56.2, 39.7, 26.2, 25.7, 17.7, 16.2; Anal. calcd. for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{S}$: C, 69.03; H, 7.96. Found: C, 68.92; H, 7.89.

6,7-Oxido-3,7-dimethyl-1-(benzenesulfonyl)-(2E)-octene (17): To a solution of **16** (4.7 g, 16.9 mmol) and NaOAc (1.48 g, 18 mmol) in CH₂Cl₂ (50 mL) at -40 °C to -20 °C was added *m*-CPBA (3.66 g, 85% weight, 18 mmol) in 1.2 g portions over 1 h. The mixture was warmed to -10 °C and stirred for an additional 1.5 h. Saturated aqueous NaHCO₃ (50 mL) was added into the mixture and organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were washed with ice-cold 1N NaOH. Standard work-up followed by chromatography using ethyl acetate:hexane (1:1) as the eluant gave the epoxy sulfone **17** (4.63 g, 93%) as an oil: IR (film) 1664, 1585, 1447, 1306, 1248, 1151, 1085 and 739 cm⁻¹; CIMS *m/z*(isobutane, rel intensity) 295 (M⁺+1, 89), 277 (39), 153 (100), 143 (40.6), 135 (60); ¹H NMR (CDCl₃, ppm) 7.85 (d, *J* = 7.0 Hz, 2H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 2H), 5.21 (t, *J* = 7.9 Hz, 1H), 3.81 (d, *J* = 7.9 Hz, 2H), 2.66 (t, *J* = 6.3 Hz, 1H), 2.25-2.05 (m, 2H), 1.62-1.45 (m, 2H), 1.36 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H); ¹³C NMR (CDCl₃, ppm) 145.6, 138.9, 133.6, 129.0, 128.5, 110.9, 63.6, 58.3, 56.1, 36.4, 24.8, 21.2, 18.7, 16.2; Anal. calcd. for C₁₆H₂₂O₃S: C, 65.28; H, 7.53. Found: C, 65.36; H, 7.70.

1-(Benzenesulfonyl)-(2E)-hexen-6-al (18): To a stirred solution of **17** (4.5 g, 15.3 mmol) in diethyl ether (80 mL) at 0 °C was added dropwise a solution of HIO₄·2H₂O (3.76 g, 16.5 mmol) in THF (35 mL) over 1 h. The mixture was stirred for an additional 0.5 h and water (50 mL) was added. The organic phase was separated and the aqueous phase was extracted with ether (4 x 30 mL). The combined organic extract was washed with saturated NaHCO₃ solution (2 x 30 mL). Standard work-up followed by chromatography using ethyl acetate:hexane (6:4) as the eluant gave aldehyde **18** (3.25 g, 84%) as an oil: IR (film) 1722, 1447, 1305, 1150, 1085 and 742 cm⁻¹; CIMS *m/z*(isobutane, rel intensity) 253 (M⁺+1, 100), 235 (63), 153 (100), 143 (15.5); ¹H NMR (CDCl₃, ppm) 9.74 (t, *J* = 1.4 Hz, 1H), 7.84 (d, *J* = 7.0 Hz, 2H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.0 Hz, 2H), 5.21 (t, *J* = 8.0 Hz, 1H), 3.81 (d, *J* = 8.0 Hz, 2H), 2.49 (dt, *J* = 1.4, 7.4 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.34 (s, 3H); ¹³C NMR (CDCl₃, ppm) 200.9, 144.3, 138.8, 133.6, 129.0, 128.4, 111.5, 55.9, 41.5, 31.6, 16.3; Anal. calcd. for C₁₃H₁₆O₃S: C, 61.88; H, 6.39. Found: C, 61.80; H, 6.38.

6-(Ethylenedioxy)-1-(benzenesulfonyl)-3-methyl-(2E)-hexene (19): A mixture of **18** (3.0 g, 11.9 mmol), (CH₂OH)₂ (1.49 g, 24 mmol), and *p*-toluenesulfonic acid (50 mg) in toluene (50 mL) was refluxed for 4 h under nitrogen atmosphere using a Dean-Stark trap to remove the water. Saturated NaHCO₃ (30 mL) was added to the cold mixture and the organic phase was separated. The aqueous phase was extracted with ether (3 x 30 mL). Standard work-up followed by chromatography using ethyl acetate:hexane (6:4) as the eluant gave

acetal **19** (3.25 g, 92%) as an oil: IR and ^1H NMR spectra of **19** are in agreement of those reported in reference 16.

1-(Ethylenedioxy)-6-(benzenesulfonyl)-4,9,13,17-tetramethyl-(4E),(8E),(12E),16-octadecatetraene (20): This was prepared in 91% yield according to the procedure described in reference 16.

1-(Ethylenedioxy)-4,9,13,17-tetramethyl-(4E),(8E),(12E),16-octadecatetraene (21): This was prepared in 88% yield according to the procedure described in reference 16.

4,9,13,17-Tetramethyl-(4E),(8E),(12E),16-octadecatetraenal (22): This was prepared in 92% yield according to the procedure described in reference 16.

Diphenylphosphinoyl ethane-1-thiol (23): This was prepared in 80% yield according to the procedure described by Mikolajczyk¹⁷ for the synthesis of diethylphosphonate ethane-1-thiol. **23**: mp 138-141 °C; IR (KBr) 3053, 1618, 1182, 1119, 1071, 1027, 740 and 697 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 263 (M^++1 , 100); ^1H NMR (CDCl_3 , ppm) 7.90 (m, 4H), 7.50 (m, 6H), 3.45 (m, 1H), 2.07 (dd, $J_{\text{H-H}} = 7.0$ Hz; $J_{\text{P-H}} = 10.0$ Hz, 1H), 1.50 (dd, $J_{\text{H-H}} = 7.5$ Hz; $J_{\text{P-H}} = 15.0$ Hz, 3H), ^{13}C NMR (CDCl_3 , ppm) 128.5-131.9 (12C, m), 31.2, 18.7.

Diphenylphosphinoyl-1-(3-methyl-2,3-oxido-butylthio)ethane (26): To a solution of **24** (1.82 g, 21.1 mmol) in CH_2Cl_2 (60 mL) at -40 °C was added *m*-chloroperbenzoic acid (4.88 g, 85% weight, 24 mmol). The reaction mixture was stirred at -40 °C for 1 h and warmed to -20 °C for an additional 1 h. Excess *m*-CPBA was destroyed by addition of saturated $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and the organic phase was washed with saturated NaHCO_3 (2 x 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layer was washed with ice-cold 1N NaOH. Standard work-up gave the epoxy alcohol (1.41 g, ~65%): GC purity: 100%; IR (film) 3429, 1119 and 1064 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 103 (M^++1 , 100), 97 (2.3), 95 (2.2), 93 (2.9), 91 (4.2); ^1H NMR (CDCl_3 , ppm) 3.76 (m, 2H), 3.0 (dd, $J = 5.1, 6.4$ Hz, 1H), 2.6 (m, 1H), 1.36 (s, 3H), 1.31 (s, 3H). The epoxy alcohol was converted to the mesylate (**25**) by reaction with MeSO_2Cl in the presence of Et_3N at -50 °C (96%) as described in ref 11. Mesylate **25** was sufficiently pure (GC purity >98%) for use in the subsequent reaction. For **25**: CIMS m/z (isobutane, rel intensity) 181 (M^++1 , 100); ^1H NMR (CDCl_3 , ppm) 4.43 (dd, $J = 11.7, 4.2$ Hz, 1H), 4.23 (dd, $J = 11.7, 4.2$ Hz, 1H), 3.08 (s, 3H), 3.07 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H).

To a solution of NaOH (5.0 g, 125 mmol) in H_2O (10 mL) and toluene (10 mL) was added tetraoctylammonium bromide (0.05 g), **23** (0.472 g, 1.8 mmol) and **25** (0.413 g, 2.3 mmol) at room temperature. This reaction mixture was stirred for 12 h, then extracted with ether (3 x 30 mL). Standard

work-up followed by chromatography using ethyl acetate:hexane (7:3) as the eluant gave **26** (0.45 g, 72%) as an oil: IR (film) 3055, 1630, 1183, 1118, 1072, 723 and 695 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 347 ($M^{+}+1$, 100), 346 (M^{+} , 9.0), 331 (1.3), 329 (7.5), 275 (1.4), 261 (12); ^1H NMR (CDCl_3 , ppm) 7.96-7.75 (m, 4H), 7.60-7.40 (m, 6H), 3.59 (dq, $J_{\text{H-H}} = 7.4$ Hz, $J_{\text{P-H}} = 16.0$ Hz, 1H), 2.90 (m, 2H), 2.77 (m, 1H), 1.56 (dd, $J_{\text{H-H}} = 7.5$ Hz, $J_{\text{P-H}} = 15.0$ Hz, 1H), 1.28 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (CDCl_3 , ppm) 131.9-128.5 (12C, m), 63.5, 58.4, 37.3, 36.8, 24.4, 18.7, 16.2; Anal. calcd. for $\text{C}_{19}\text{H}_{23}\text{PO}_2\text{S}$: C, 65.88; H, 6.69. Found: C, 65.60; H, 6.56.

(6E)-5-Thia-2,3-oxidosqualene (2): A solution of phosphine oxide **26** (0.173 g, 0.5 mmol) in THF (10 mL) was added dropwise a solution of LDA [0.5 mmol, prepared from diisopropyl amine (0.07 mL, 0.5 mmol) and *n*-BuLi (0.2 mL, 0.5 mmol, 2.5 M in hexanes at -78 °C] in THF (5 mL) under argon, at -100 °C. After 20 min, aldehyde **22** (0.159 g, 0.5 mmol) in THF (5.0, mL) was added dropwise to the orange-colour solution. The resulting light yellow solution was stirred for 30 min and treated with acetic acid (100 mg) and H_2O (100 mg). The solvent was removed *in vacuo* and the resulting slurry filtered through a small column of silica gel using ethyl acetate:hexanes (7:3) as the eluant to give **27** and **28** (~6:4) (0.225 g, 68%). Thin layer chromatographic analysis on silica gel revealed two overlapping components. The major faster eluting isomer **27** (*syn*) was purified by column chromatography on silica gel in two cycles using ethyl acetate:hexanes (2:8 to 1:1) as the eluant. This gave pure **27** (0.103 g, 31%) and a mixture of **27** and **28**. Major isomer **27** (*syn*): IR (film) 3322, 2960, 2924, 2854, 1725, 1665, 1590, 1437, 1377, 1319, 1249, 1159, 1111, 1072, 850, 746 and 696 cm^{-1} ; ^1H NMR (CDCl_3 , ppm) 8.35 (m, 2H), 8.07 (m, 2H), 7.50 (m, 6H), 5.53 (bm, 1H), 5.17 (m, 1H), 5.10 (m, 3H), 4.07 (t, $J = 8.8$ Hz, 1H), 2.68 (m, 2H), 2.43 (dd, $J = 11.0, 6.6$ Hz, 1H), 2.28 (m, 1H), 2.10-1.90 (m, 15H), 1.67 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H), 1.56 (s, 3H), 1.40 (d, $J_{\text{P-H}} = 16.0$ Hz, 3H), 1.27 (s, 3H), 1.24 (s, 3H); Anal. calcd. for $\text{C}_{41}\text{H}_{59}\text{O}_3\text{PS}$: C, 74.28; H, 8.97. Found: C, 74.56; H, 9.06.

To a solution of **27** (90 mg, 0.136 mmol) in THF (10 mL) was added NaH (pre-washed in the hexanes, 15 mg, 0.625 mmol). This mixture was stirred for 3 h under argon and the reaction was quenched by addition of water (0.1 mL). The solvent was removed *in vacuo* and column chromatography using ethyl acetate:hexanes (5:95) as the eluant gave pure **2** (52 mg, 86%) as an oil: IR (film) 2963, 2921, 2854, 1717, 1666, 1630, 1449, 1377, 1249, 1124 and 838 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 445 ($M^{+}+1$, 6.4), 359 (11.9), 327 (3.1), 295 (3.0), 217 (2.8), 191 (5.0), 189 (5.4), 177 (11), 171 (100) 163 (7.5), 161 (5.9); ^1H NMR (CDCl_3 , ppm) 5.55 (tq, $J = 7.1, 1.20$ Hz, 1H), 5.12 (m, 4H), 2.92 (m, 2H), 2.67 (dd, $J = 2.2, 8.8$ Hz, 1H), 2.18 (dt, $J = 7.3, 7.4$ Hz, 2H), 2.0 (14 H, bm), 1.92 (d, $J = 1.20$ Hz, 3H), 1.68 (s, 3H), 1.60 (s, 12H), 1.32 (s, 3H),

1.29 (s, 3H); ^{13}C NMR (CDCl_3 , ppm) 138.6, 135.3, 134.5, 132.9, 131.2, 129.5, 125.0, 124.9, 124.5, 124.4, 63.2, 59.0, 39.8, 39.2, 39.2, 30.9, 30.3, 28.5, 27.9, 26.9, 26.8, 25.6, 24.6, 24.2, 18.8, 18.2, 17.7, 16.1, 16.0; Anal. calcd. for $\text{C}_{29}\text{H}_{48}\text{OS}$: C, 78.32; H, 10.89. Found: C, 78.23; H, 10.95.

1-(Ethylenedioxy)-4,9,13,17-tetramethyl-16-bromo-17-hydroxy-(4E),(8E),(12E)-octadecatriene (29): To a vigorously stirred solution of **21** (2.15 g, 6.0 mmol) in THF (100 mL) and water (30 mL) at 0 °C was added dropwise a solution of N-bromosuccinimide (1.07 g, 6.0 mmol) in THF (15 mL) and water (5.0 mL) over 30 min. The mixture was stirred for 1 h at 0 °C, then the THF was removed *in vacuo* and the aqueous layer was extracted with ether (4 x 30 mL). Standard work-up followed by flash column chromatography of the concentrate using ethyl acetate:hexane (65:35) as the eluant gave pure **29** (1.04 g, 38%) as an oil: IR (film) 3477, 1667, 1630, 1446, 1384, 1141 and 1037 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 459/457 (M^++1 , 42.7/45.5), 441/439 ($\text{M}^++1-\text{H}_2\text{O}$, 17.4/18.2), 397/395 (100/97.9) 379/377 (52.2/92.7), 359 (51.5), 315 (97.1), 297 (77.3), 243 (18.3), 205 (22.6); ^1H NMR (CDCl_3 , ppm) 5.22-5.10 (m, 3H), 4.85 (t, $J = 4.82$ Hz, 1H), 3.98 (dd, $J = 1.8, 11.3$ Hz, 1H), 3.96 (m, 2H), 3.85 (m, 2H), 2.38-2.25 (m, 1H), 2.22-1.92 (m, 12H), 1.82-1.72 (m, 3H), 1.60 (s, 3H), 1.59 (s, 6H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (CDCl_3 , ppm) 134.9, 134.3, 133.0, 126.0, 124.5, 124.4, 104.4, 72.4, 70.9, 64.8, 39.6, 38.2, 33.9, 32.5, 32.2, 28.2, 28.1, 26.6, 25.8, 16.0, 15.8; Anal. calcd. for $\text{C}_{24}\text{H}_{41}\text{BrO}_3$: C, 63.13; H, 9.06. Found: C, 63.30; H, 9.09.

4,9,13,17-Tetramethyl-16-bromo-17-hydroxy-(4E),(8E),(12E)-octadecatrien-1-ol (30): This was prepared in 42% yield by the procedure described for **22** in ref 16. ^1H -NMR and IR spectra of **30** are in agreement with those reported in reference 14.

4,9,13,17-Tetramethyl-16,17-oxido-(4E),(8E),(12E)-octadecatrien-1-ol (31) This was prepared in 87% by ring closure of bromohydrin, **30**, in a procedure similar to that described in ref 13 for synthesis of 10,11-Epoxy-,3,7,11-trimethyl-(2E),(6E)-dodecadienyl *tert*-butyldimethylsilyl ether. ^1H -NMR and IR spectra of **31** are in agreement with those reported in reference 15.

Diphenylphosphinoyl-1-(3-methyl-2-butenylthio)ethane (33): This was prepared in 73% yield by coupling **23** and 1-chloro-3-methyl-2-butene, **32**, under phase-transfer conditions as described for preparation of **26**. **33**: IR (film) 3055, 1667, 1186, 1118, 1072, 722 and 697 cm^{-1} ; CIMS m/z (isobutane, rel intensity) 333/331 (M^++1 , 7.8/100), 263 (2.0), 231 (5.8), 230 (11.7), 229 (4.6); ^1H NMR (CDCl_3 , ppm) 7.95-7.75 (m, 4H), 7.58-7.40 (m, 6H), 5.07 (t, $J = 7.7$ Hz, 1H), 3.27 (dq, $J_{\text{H-H}} = 7.4$ Hz, $J_{\text{P-H}} = 14.7$ Hz, 1H), 3.12 (dd, $J = 3.3, 7.7$ Hz, 2H), 1.71 (s, 3H), 1.58 (s, 3H), 1.55 (dd, $J_{\text{H-H}} = 7.4$ Hz, $J_{\text{P-H}} = 15.0$ Hz, 3H); ^{13}C NMR (CDCl_3 ,

ppm) 136.9, 132.6, 132.2, 131.9, 131.8, 131.6, 131.5, 130.6, 128.5, 128.4, 128.3, 119.5, 36.5, 30.0, 25.7, 17.7, 16.1; Anal. calcd. for C₁₉H₂₃POS: C, 69.07; H, 7.02. Found: C, 68.92; H, 6.89.

(18E)-20-Thia-2,3-oxidosqualene (5): This was prepared by the procedure described for 2. A mixture of *syn* and *anti* isomers (**34** and **35**, ~65:35) was obtained. Flash column chromatography partially separated this mixture to give pure *syn* isomer **34** in 33% yield: IR (film) 3315, 2960, 2927, 2854, 1730, 1666, 1590, 1438, 1377, 1319, 1156, 1112, 745 and 699 cm⁻¹; ¹H NMR (CDCl₃, ppm) 8.40 (m, 2H), 8.10 (m, 2H), 7.54 (m, 6H), 5.66 (bm, 1H), 5.51 (m, 3H), 4.96 (t, *J* = 8.0 Hz, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 2.84 (dd, *J* = 8.3, 10.9 Hz, 1H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.41 (dd, *J* = 8.0, 10.9 Hz, 1H), 2.34 (m, 1H), 2.20-1.90 (m, 15H), 1.67 (s, 3H), 1.61 (s, 3H), 1.59 (s, 6H), 1.54 (s, 3H), 1.42 (d, *J*_{P-H} = 16.2 Hz, 3H), 1.29 (s, 3H), 1.25 (s, 3H); Anal. calcd. for C₄₁H₅₉O₃PS: C, 74.28; H, 8.97. Found: C, 74.04; H, 9.02.

5: IR (film) 2960, 2923, 2858, 1663, 1630, 1448, 1376, 1247 and 1120 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 445 (M⁺+1, 90), 427 (28.5), 375 (44.4), 343 (100), 325 (32.3); ¹H NMR (CDCl₃, ppm) 5.35 (tq, *J* = 7.1, 1.20 Hz, 1H), 5.23 (brt, *J* = 7.4 Hz, 1H), 5.19-5.10 (m, 3H), 3.30 (d, *J* = 7.4 Hz, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.20-1.94 (bm, 16H), 1.87 (s, 3H), 1.72 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 6H), 1.30 (s, 3H), 1.26 (s, 3H); ¹³C NMR (CDCl₃, ppm) 138.2, 135.1, 134.6, 131.1, 129.6, 126.9, 125.0, 124.6, 124.4, 119.7, 64.2, 58.2, 39.7, 39.4, 36.4, 30.0, 29.3, 28.3, 27.7, 27.6, 26.8, 25.6, 24.9, 24.0, 18.8, 18.1, 17.8, 16.1, 16.0; Anal. calcd. for C₂₉H₄₈OS: C, 78.32; H, 10.89. Found: C, 78.41; H, 11.01.

5,9,13-Trimethyl-(4E),(8E),12-tetradecatrien-1-ol (36): This was prepared according to the procedure of Coates.²⁰

5,9,13-Trimethyl-(4E),(8E),12-tetradecatrien-1-al (37): This was prepared according to the procedure of Coates.²⁰

3,7-Dimethyl-6,7-oxido-(2E)-hexen-1-ol (39): To a stirred solution of 6,7-oxido geraniol acetate (**38**) (10.6 g, 50 mmol) in MeOH (200 mL) was added K₂CO₃ (2.0 g, excess). After 5 h, most MeOH was removed *in vacuo* and the slurry diluted with H₂O (50 mL) and extracted with ether (4 x 30 mL). Standard work-up followed by chromatography using ethyl acetate:hexanes (3:7) as the eluant gave **39** (7.6 g, 90%) as a clear oil. IR (film) 3406, 1668, 1451, 1379, 1323, 1250, 1117, 1003 and 871 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 171 (M⁺+1, 1), 153 (100), 135 (20), 123 (4), 109 (trace); ¹H NMR (CDCl₃, ppm) 5.43 (tq, *J* = 7.0, 1.2 Hz, 1H), 4.13 (d, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 1H), 2.15 (m, 2H), 1.68 (s, 3H), 1.64-1.60 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃, ppm) 137.9, 124.2, 64.0, 59.0, 58.3, 36.2, 27.0, 24.7, 18.6, 16.11.

1-Chloro-3-methyl-6,7-oxido-(2E)-hexene (40): To a stirred solution of *N*-chlorosuccinimide (6.0 g, 45 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added DMS (5.51 mL, 75 mmol). The resulting slurry was cooled to -20 °C and to this was added dropwise **39** (5.0 g, 30 mmol) in CH₂Cl₂ (25 mL). After 5 h at 0 °C, the clear mixture was diluted with ice-cold H₂O (100 mL), the organic layer separated and the aqueous layer extracted with CH₂Cl₂ (2 x 50 mL). Standard work-up followed by chromatography using ethyl acetate:hexanes (1:9) as the eluant gave **40** (4.5 g, 80 %) as an oil: IR (film) 1662, 1451, 1378, 1253, 1121 and 875 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 189 (M⁺+1, 51), 171 (40), 153 (100), 135 (25), 125 (5); ¹H NMR (CDCl₃, ppm) 5.54 (tq, *J* = 8.0, 1.20 Hz, 1H), 4.09 (d, *J* = 8.0 Hz, 2H), 2.69 (t, *J* = 6.5 Hz, 1H), 2.20 (m, 2H), 1.74 (s, 3H), 1.65 (t, *J* = 7.0 Hz, 2H), 1.30 (s, 3H), 1.25 (s, 3H); ¹³C NMR (CDCl₃, ppm) 141.6, 120.9, 63.7, 58.2, 40.7, 36.1, 27.0, 24.7, 18.7, 16.0. Anal. calcd. for C₁₀H₁₇OCl: C, 63.65; H, 9.08. Found: C, 63.83; H, 9.18.

Diphenylphosphinoyl 1-[3,7-dimethyl-6,7-oxido-(2E)-hexenylthio]ethane (41): This was prepared in 66% by coupling **23** and **40** under phase-transfer conditions as described for **26**. **41**: IR (film) 3024, 1661, 1591, 1437, 1378, 1322, 1248, 1190, 1118, 1072, 1027, 998, 873, 741 and 699 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 417 (M⁺+2, 27), 416 (M⁺+1, 100), 263 (30), 231 (21), 230 (32), 229 (18), 153 (22), 135 (10); ¹H NMR (CDCl₃, ppm) 7.85 (m, 4H), 7.50 (m, 6H), 5.15 (m, 1H), 3.27 (dq, *J*_{H-H} = 7.5 Hz; *J*_{P-H} = 11.0 Hz, 1H), 3.15 (m, 2H), 2.66 (brt, *J* = 6.0 Hz, 1H), 2.15 (m, 2H), 1.60-1.50 (m, 8H), 1.28 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃, ppm) 139.6, 132.6-128.3 (12C, m), 119.9, 63.9, 58.2, 36.7, 29.7, 27.3, 24.8, 18.8, 16.1. Anal. calcd. for C₂₄H₃₁O₂SP: C, 69.54; H, 7.54. Found: C, 69.80; H, 7.44.

(10E)-9-Thia-2,3-oxidosqualene (3): This was prepared by the procedure described for **2**. ¹H NMR analysis of the mixture showed the ratio of **42:43** to be ~65:35. Flash column chromatography partially separated this mixture to give pure *syn* isomer **42** in 27% yield: IR (film) 3314, 2923, 1690, 1437, 1378, 1324, 1566, 1112, 910, 856, 723 and 697 cm⁻¹; ¹H NMR (CDCl₃, ppm) 8.40 (m, 2H), 8.10 (m, 2H), 7.58 (m, 6H), 5.67 (bs, 1H), 5.09 (bm, 3H), 5.00 (t, *J* = 8.5 Hz, 1H), 4.07 (t, *J* = 8.5 Hz, 1H), 2.87 (brt, *J* = 8.5 Hz, 1H), 2.65 (t, *J* = 6.0 Hz, 1H), 2.30 (bm, 2H), 2.20-1.90 (bm, 14H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H), 1.57 (s, 3H), 1.55 (s, 3H), 1.40 (d, *J*_{P-H} = 16.0 Hz, 3H), 1.30 (d, *J* = 2.0 Hz, 3H), 1.25 (s, 3H).

3: IR (film) 2921, 1665, 1630, 1444, 1377, 1248, 1118 and 838 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 445 (M⁺+1, trace), 427 (trace), 277 (9), 259 (15), 187 (5), 177 (7), 169 (16), 167 (5), 155 (12), 154 (15), 153 (100), 137 (15), 135 (28); ¹H NMR (CDCl₃, ppm) 5.38 (tq, *J* = 6.70, 1.19 Hz, 1H), 5.30 (tq, *J* = 7.5, 1.20 Hz, 1H), 5.10 (s, 3H), 3.32 (d, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 1H), 2.20-1.94 (bm, 16H), 1.87 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.60 (bs, 9H), 1.30 (s, 3H), 1.26 (s, 3H); ¹³C NMR (CDCl₃, ppm) 138.2, 135.7,

135.0, 131.2, 129.7, 127.0, 124.4, 124.2, 123.7, 120.2, 63.9, 58.2, 39.7, 36.2, 29.7, 29.2, 27.9, 27.4, 26.8, 26.7, 25.6, 24.8, 18.7, 18.1, 17.6, 16.1, 16.0, 15.9. Anal. calcd. for C₂₉H₄₈OS: C, 78.32; H, 10.88. Found: C, 78.50; H, 11.14.

1-[(*tert*-Butyldimethylsilyloxy)-5,9,13-trimethyl-(4*E*),(8*E*),12-tetradecatriene (44): To a solution of alcohol **36** (1.0 g, 4.0 mmol) in CH₂Cl₂ (25 mL), was added Et₃N (0.83 mL, 6.0 mmol) and *tert*-butyldimethylsilyl chloride (0.670 g, 4.8 mmol) and *N,N*-dimethylaminopyridine (50 mg). The mixture was stirred for 10 h, diluted with water and extracted with ether (3 x 35 mL). Standard work-up followed by chromatography using ethyl acetate:hexanes (5:95) as the eluant gave silyl ether, **44** (1.4 g, 96%). IR (film) 2928, 2851, 1444, 1383, 1255, 1099, 836 and 775 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 365 (M⁺+1), 307 (6), 234 (18), 233 (100), 231 (24); ¹H NMR (CDCl₃, ppm) 5.12 (m, 3H), 3.60 (t, *J* = 6.0 Hz, 2H), 2.10-1.95 (bm, 10H), 1.68 (s, 3H), 1.60 (s, 9H), 1.55 (bm, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃, ppm) 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.

1-[(*tert*-Butyldimethylsilyloxy)-12,13-oxido-5,9,13-trimethyl-(4*E*),(8*E*)-tetradeca- triene (45): This was prepared from **44** in two steps in 51% yield by the procedure described for **29** and **31**. **45**: IR (film) 2928, 2856, 1462, 1378, 1253, 1100, 1006, 836 and 775 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 382/381 (M⁺+1, 12/41), 363 (15), 250 (10), 249 (53), 232 (17), 231 (100); ¹H NMR (CDCl₃, ppm) 5.15 (m, 2H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 1H), 2.15-1.96 (m, 10H), 1.60 (s, 3H), 1.59 (s, 3H), 1.54 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 0.95 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃, ppm) 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. Anal. calcd. for C₂₃H₄₄O₂Si: C, 72.57; H, 11.65. Found: C, 72.53; H, 11.53.

5,9,13-Trimethyl-12,13-oxido-(4*E*),(8*E*)-tetradecatrien-1-ol (46): Epoxy-silyl ether **45** (0.50 g, 1.32 mmol) was dissolved in a 1.0 M solution of tetrabutylammonium fluoride in THF (20 mL, 20 mmol) and stirred for 4 h. Ice and water were added and the aqueous phase was extracted with ether (4 x 25 mL). Standard work-up followed by chromatography using ethyl acetate:hexanes (3:7) as the eluant gave epoxy alcohol, **46** (0.330 g, 95 %) as an oil: IR (film) 3432, 1447, 1379, 1250, 1122, 1059 and 873 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 267 (M⁺+1, 100), 250 (17), 249 (95), 153 (30), 137 (11), 135 (27), 127 (16), 123 (15), 111 (16), 109 (27); ¹H NMR (CDCl₃, ppm) 5.13 (m, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.70 (t, *J* = 6.5 Hz, 1H), 2.18-1.98 (bm, 10H), 1.60 (m, 8H), 1.29 (s, 3H), 1.25 (s, 3H); ¹³C NMR (CDCl₃, ppm) 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. Anal. calcd. for C₁₇H₃₀O₂: C, 76.64; H, 11.35. Found: C, 76.36; H, 11.18.

5,9,13-Trimethyl-12,13-oxido-(4E),(8E)-tetradecatrien-1-ol (47): To a stirred solution of epoxy alcohol **46** (0.730 g, 2.74 mmol) and Et₃N (3.8 mL, 27.4 mmol) in DMSO (25 mL) under argon was added dropwise a solution of sulfur trioxide-pyridine complex (1.54 g, 9.7 mmol) in DMSO (10 mL). The mixture was stirred at room temperature for 3.5 h, diluted with ice-cold saturated aqueous NaCl (50 mL) and extracted with Et₂O (4 x 50 mL). The combined extracts were washed with ice-cold water (50 mL). Standard work-up followed by chromatography using ethyl acetate:hexanes (1:9) as the eluant gave **47** (0.70 g, 95 %) as an oil. IR (film) 1725, 1687, 1450, 1378, 1249, 1122, 1054 and 874 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 265 (M⁺+1, 79), 248 (17), 247 (100), 230 (8), 229 (48), 165 (9), 163 (9), 161 (29), 153 (43), 149 (11), 137 (13), 135 (32), 127 (10), 125 (15), 121 (11), 109 (16), 107 (30); ¹H NMR (CDCl₃, ppm) 9.75 (t, *J* = 1.8 Hz, 1H), 5.10 (m, 2H), 2.70 (t, *J* = 6.0 Hz, 1H), 2.45 (td, *J* = 7.0, 1.8 Hz, 2H), 2.32 (q, *J* = 7.0 Hz, 2H), 2.20-1.90 (m, 8H), 1.60 (m, 6H), 1.29 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃, ppm) 202.3, 136.7, 134.2, 124.6, 120.9, 64.1, 58.2, 43.9, 39.6, 36.3, 26.6, 26.4, 24.8, 20.9, 18.7, 16.0, 15.9. Anal. calcd. for C₁₇H₂₈O₂: C, 77.21; H, 10.68. Found: C, 77.40; H, 10.73.

Diphenylphosphinoyl-1-[3,6-dimethyl-(2E),(6E)-octadienylthio]ethane (48): This was prepared in 72% yield by the procedure described for **26**. **48**: IR (film) 3024, 1437, 1376, 1190, 1118, 1072, 741, 723 and 697 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 399 (M⁺+1, 100), 397(13), 230 (31), 229 (78), 137 (25); ¹H NMR (CDCl₃, ppm) 7.87 (m, 4H), 7.50 (m, 6H), 5.05 (m, 2H), 3.27 (dt, *J*_{P-H} = 11.0 Hz; *J*_{H-H} = 7.50 Hz, 1H), 3.12 (dd, *J* = 8.0 Hz, 3.5 Hz, 2H), 2.10-1.98 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.56 (s, 6H), 1.54 (dd, *J*_{P-H} = 15.0 Hz; *J*_{H-H} = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, ppm) 140.5, 132.2-128.2 (13C), 123.8, 119.3, 39.6, 36.5, 29.9, 26.5, 25.6, 17.7, 16.1, 16.0. Anal. calcd. for C₂₄H₃₁OSP: C, 72.33; H, 7.84. Found: C, 72.00; H, 7.67.

(14E)-16-Thia-2,3-oxidosqualene (4): This was prepared by the procedure described for **2**. A mixture of *syn* and *anti* isomers (**49** and **50**) was obtained in a ratio of ~65:35 (¹H-NMR analysis). Flash column chromatography partially separated this mixture to give pure *syn* isomer **49** in 36% yield: IR (film) 3314, 2925, 1739, 1664, 1590, 1437, 1377, 1323, 1245, 1166, 1111, 1087, 855, 748, 750 and 698 cm⁻¹; ¹H NMR (CDCl₃, ppm) 8.40 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 9.0 Hz, 2H), 7.50 (m, 6H), 5.54 (d, 3.5 Hz, 1H), 5.13 (m, 2H), 5.03 (t, *J* = 6.5 Hz, 1H), 4.94 (t, *J* = 8.0 Hz, 1H), 4.07 (bt, *J* = 8.0 Hz, 1H), 2.85 (dd, *J* = 11.0, 8.0 Hz, 1H), 2.68 (t, *J* = 6.0 Hz, 1H), 2.33 (m, 2H), 2.20-1.90 (m, 15H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.40 (d, *J*_{P-H} = 16.0 Hz, 3H), 1.29 (s, 3H), 1.24 (s, 3H).

4: IR (film) 2962, 2923, 2854, 1714, 1665, 1626, 1447, 1377, 1248, 1119 and 841 cm⁻¹; CIMS *m/z* (isobutane, rel intensity) 445 (M⁺+1, 10), 309 (15), 307 (7), 291 (14), 275 (31), 257 (11), 169 (10), 138 (18),

137 (100), 135 (14), 127 (11), 125 (10), 123 (10); ^1H NMR (CDCl_3 , ppm) 5.38 (tq, $J = 7.0, 1.20$ Hz, 1H), 5.25 (tq, $J = 7.5, 1.20$ Hz, 1H), 5.14 (m, 2H), 5.07 (brt, $J = 7.5$ Hz, 1H), 3.31 (d, $J = 7.5$ Hz, 2H), 2.70 (t, $J = 6.0$ Hz, 1H), 2.10-1.97 (bm, 16H), 1.87 (bs, 3H), 1.68 (s, 6H), 1.62 (s, 3H), 1.60 (bs, 6H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (CDCl_3 , ppm) 139.1, 135.5, 134.1, 131.6, 129.8, 126.9, 124.9, 124.0, 123.8, 119.5, 64.2, 58.2, 39.7, 39.6, 36.3, 29.9, 29.2, 28.0, 27.6, 26.7, 26.6, 25.6, 24.9, 18.7, 18.1, 17.7, 16.1, 16.0, 15.9. Anal. calcd. for $\text{C}_{29}\text{H}_{48}\text{OS}$: C, 78.32; H, 10.89. Found: C, 78.19; H, 10.68. HRMS calcd for $\text{C}_{29}\text{H}_{48}\text{OS}$, 444.3426. Found 444.3434.

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