Synthesis of (6*E*)-8-Thia- and (14*E*)-13-Thia-2,3-oxidosqualene: Inhibitors of 2,3-Oxidosqualene-Lanosterol Cyclase

Yi Feng Zheng and Allan C. Oehlschlager*

Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, Canada V5A 1S6

Peter G. Hartman

F. Hoffmann-La Roche Ltd., CH-4002 Basel, Switzerland

Received March 11, 1994[⊗]

Synthesis of (6*E*)-8-thia-2,3-oxidosqualene (**22**) and (14*E*)-13-thia-2,3-oxidosqualene (**34**) as inhibitors of 2,3-oxidosqualene-lanosterol cyclase are reported. Synthesis of **22** required the stereospecific generation of a vinyl sulfide. This was achieved by a new coupling of a benzenethiosulfonate (**15**) and a lithiated vinyl iodide (**18**). Synthesis of **34** involved similar coupling of benzenethiosulfonate **29** with lithium reagent obtained from vinyl iodide **33**. The required (*E*)-vinyl iodides **18** and **33** were prepared by zirconium-catalyzed carboalumination of 4-pentyn-1-ol, (**16**) and 2,6-dimethyl-2(*E*),6(*E*)-dien-10-yne (**32**) respectively. Both **22** and **34** inhibited 2,3-oxidosqualene-lanosterol cyclase from *Candida albicans* with IC_{50} values of 0.68 and 45 μM, respectively.

Introduction

2,3-Oxidosqualene-lanosterol cyclases (OSCs) play important roles in terpenoid biosynthesis through catalysis of the cyclization of (3*S*)-2,3-oxidosqualene (**1**) to a number of tetracyclic triterpenes.[1,2] OSC's are considered to initially bind (3*S*)-2,3-oxidosqualene (**1**) in a chair-boat-chair conformation and then mediate the sequential formation of four new C–C bonds leading to tetracyclic protosterol (**2**). Backbone rearrangement of **2** by OSC leads to lanosterol **3**. There is direct[3] and indirect evidence[4–9] to suggest that the cyclization of **1** to **2** proceeds through conformationally rigid and enzyme-stabilized intermediates **4**, **5**, and **6** (Figure 1). One strategy to gain further insight into the involvement of cabocationic intermediates is the study of the inhibition of OSC by mimicks of the presumptive intermediates. This has been well developed by our laboratory[9] and other groups.[5d,6,8,10] In the present study we prepared oxidosqualene analogs (6*E*)-8-thia-2,3-oxidosqualene (**22**) and (14*E*)-13-thia-2,3-oxidosqualene (**34**). These contain sulfur in skeletal positions β or α, respectively, to carbons considered to be cationic during OSC mediated cyclization of **1** (Figure 2). The underlying assumption is that these strategically placed heteroatoms will halt the cyclization through intra- or intermolecular stabilization of the carbocation intermediates.[5d,6a,b,9]

Results and Discussion

Synthesis of oxidosqualene analogs **22** and **34** in which either C-8 or C-13 were replaced by sulfur required construction of trisubstituted (*E*) vinyl sulfides. Retrosynthetic analysis reveals that both can be assembled from allylic sulfonium equivalents and vinyl anion synthons (Figure 3). Previous methodologies for preparation of (*E*)-vinyl sulfides have usually produced mixtures of *E* and *Z* stereoisomers.[11,12,13a] Stereospecific methodologies such as catalytic hydroboration-coupling[13b] or metal-catalyzed sulfenylation of alkenyl halides[13c,d] are not applicable to the present synthesis because of the highly unsaturated backbone of the target molecule. A stereospecific method to prepare (*Z*)-divinyl sulfides involves cross-coupling of cuprous thiolates with alkenyl halides but requires high temperature and gives relatively low yields.[13e,f] Although all of the above could be applied to the synthesis of the (*E*)-vinyl sulfides required, we expected problems to be associated with each route. To circumvent anticipated problems, we developed a new and convenient method to couple trisubstituted *E*-vinylic anions and arylthiosulfonates.[14]

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1994.

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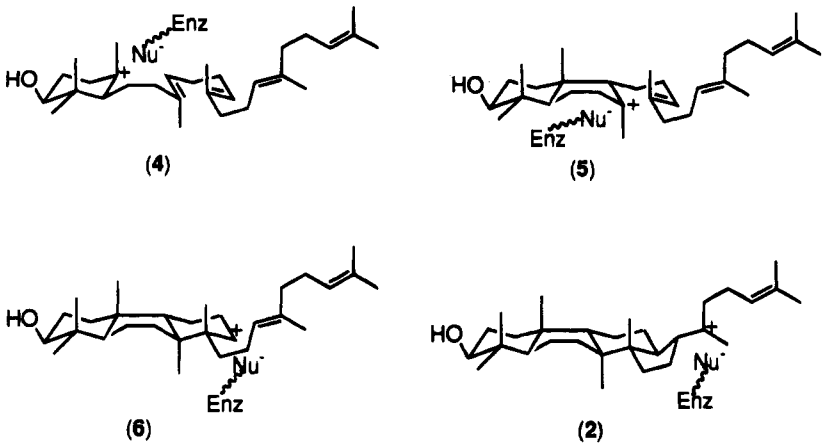

Figure 1.

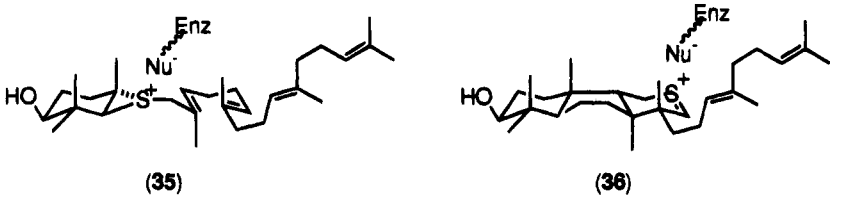

Figure 2.

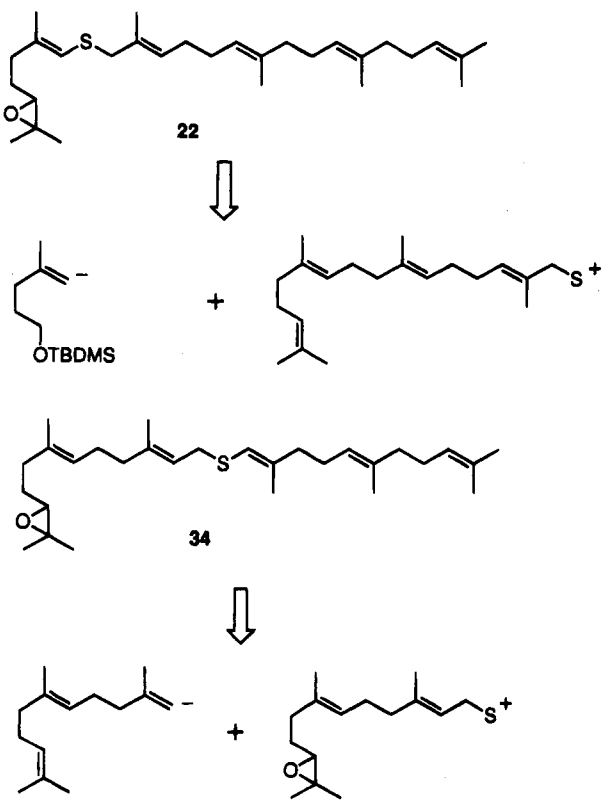

Figure 3.

Synthesis of 22 and 34. The synthesis of **22** commenced with conversion of commercially available (*E,E*)-farnesol to farnesyl bromide (**8**) in 91% yield.[15] Alkylation of **8** with the lithium enolate of ethyl acetate in the presence of CuI at −100 °C gave **9** in 91% yield according to the procedure described by Coates.[16] Reduction of **9** with $LiAlH_4$ followed by Swern oxidation[17] gave **11**[16] in 86% yield over two steps (Scheme 1). Aldehyde **11** was then treated with (carbethoxyethylidene)triphenylphosphorane in refluxing methylene chloride to generate the desired (*E*)-α,β-unsaturated ester **12** in 90% yield (*E*-isomer > 97%). The *E*-geometry of **12** was confirmed by ^1H NMR, which revealed a triplet of quartets at δ 6.76 (J = 7.3, 1.4 Hz) for one hydrogen attached to C-3. Reduction of **12** with DIBAL-H gave an allylic alcohol which was converted with NCS−DMS[18] to allylic chloride **14** in 74% yield over two steps. The latter was converted to **15** in excellent yield by reaction with potassium 4-methylbenzenethiosulfonate in DMF.[14a] The required vinyl anion synthon **17** was prepared by zirconium-catalyzed carboalumination of 4-pentyn-1-ol (**16**) followed by iodine trapping (82%).[19] Capillary GC analysis of **17** revealed a single product. This reaction allowed introduction of the desired *E*-geometry. Reaction of **17** with *tert*-butyldimethysilyl chloride and Et_3N gave **18** in 95% yield (Scheme 2). Analysis of **18** by GC/MS revealed two components with an *E*:*Z* ratio of 96:4. Conversion of **18** to **19** (91%) was effected *via* the vinylic lithium (*n*-BuLi in THF at −78 °C) followed by addition of **15**. This new coupling reaction is the key step in the generation of the *E*-vinylic sulfide of **22**. The structure of **19** was confirmed by ^1H NMR, which revealed a quartet at δ 5.58 (J = 1.0 Hz) for the vinyl sulfide hydrogen (C-5) and a singlet at δ 3.19 for the two hydrogens on the methylene carbon (C-7) adjacent to sulfur. Assignments were confirmed by decoupling experiments. Deprotection of **19** with Bu_4NF in methylene chloride followed by Swern oxidation[17] gave **21** in 85% over the two steps. The NOE difference

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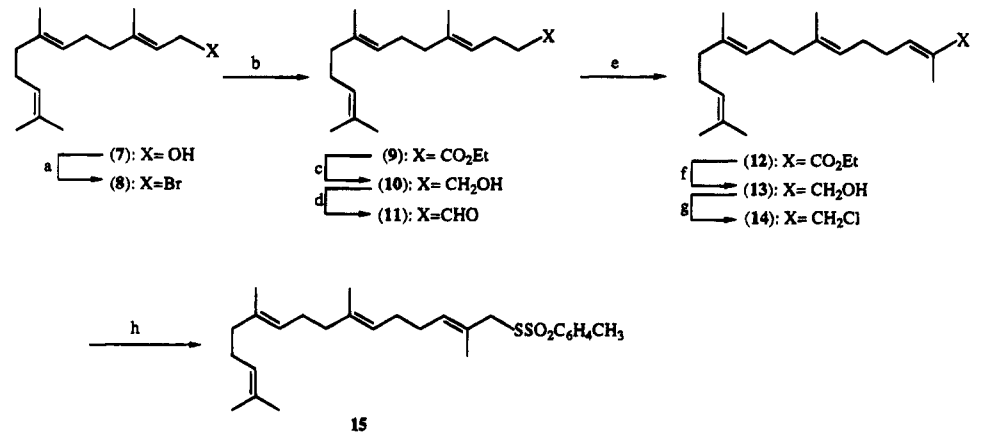
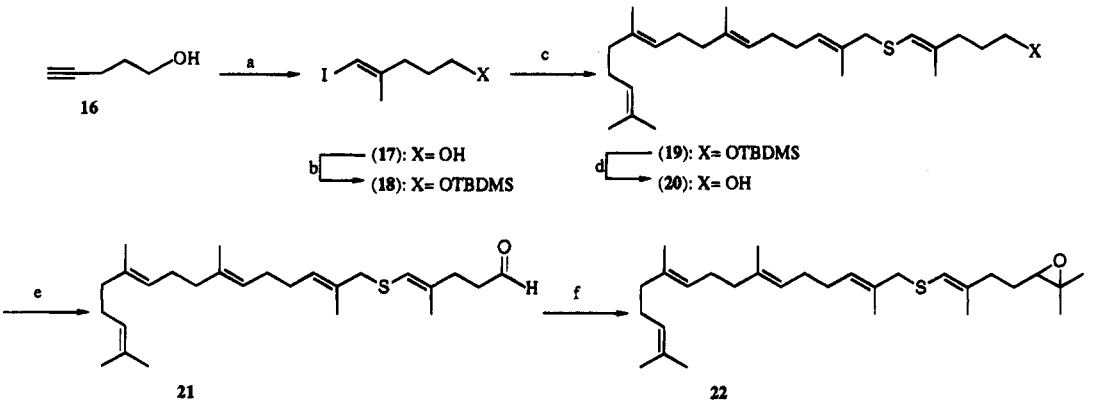
Scheme 1

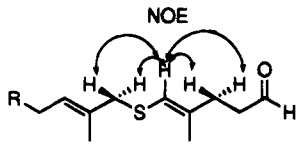


[a] (a) PBr_3, Et_2O; (b) CH_3CO_2Et, CuI, LDA, THF, −100 °C; (c) LAH, Et_2O; (d) Swern oxidation; (e) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2; (f) DIBAL-H, Et_2O; (g) NCS, DMS, CH_2Cl_2; (h) $KSSO_2C_6H_4CH_3$, DMF.

Scheme 2



(a) $Zr(Cp)_2Cl_2$, $AlMe_3$, then I_2, CH_2Cl_2; (b) TBDMSCl, DMAP, Et_3N, CH_2Cl_2; (c) *n*-BuLi, −78 °C, then **15**, THF; (d) Bu_4NF, H_2O, THF; (e) Swern oxidation; (f) $Ph_2S(i\text{-}Pr)BF_4$, *t*-BuLi, THF.



R= (*E*),(*E*)-Farnesyl chain

(**21**)

Figure 4.

spectrum of ^1H NMR of **21** confirmed the stereochemistry of the vinyl sulfide. When the C-5 vinyl hydrogen (δ 5.62, J = 1.0 Hz) was irradiated, no enhancement of the methyl attached to C-4 (δ 1.72, J = 1.0 Hz) was observed. In this experiment enhancement of the signal attributed to the C-3 hydrogens (δ 2.37, J = 7.4 Hz) was observed (Figure 4). These results indicate that the methyl attached to C-4 and the C-5 vinyl hydrogen are *trans* to each other while the C-5 vinyl hydrogen and the C-3 hydrogens are *cis*.[20] Generation of the sulfonium ylide of $Ph_2S(i\text{-}Pr)BF_4$ by treatment with *t*-BuLi in THF at −78 °C under argon followed by reaction with **21** gave **22** in 90% yield.[21] The generation of **22** from **7** in 12 steps proceeded with an overall yield of 27.7%.

The synthesis of **34** commenced with conversion of **7** to **24** in 95% yield. Reaction of the latter with NBS in THF−H_2O followed by treatment with K_2CO_3 in methanol gave **26** in 37% yield over two steps (Scheme 3). Deprotection of **26** with Bu_4NF in THF gave **27**, which was converted to the allylic chloride **28** by reaction with NCS−DMS complex[18] (72% over two steps). Reaction of **28** with potassium 4-methylbenzenethiosulfonate in DMF gave epoxy thiosulfonate **29** in 85%.[14a] Reaction of geraniol (**30**) with NCS−DMS complex [18] gave geranyl chloride (**31**)[22] in 80%. The latter was then converted to **32** in 78% yield according to the procedure of Hooz.[23] Treatment of **32** with $AlMe_3$ in the presence of $Zr(Cp)_2Cl_2$ followed by treatment with iodine gave **33** in 81%[19] (Scheme 4). Reaction of **33** with *n*-BuLi in THF at −78 °C under argon followed by addition of **29** gave **34** in 28% yield ((7) steps from **7**, overall yield, 6.1%). We believe that the lower yield in this coupling reaction is due to epoxide cleavage by the vinyl anion. The *E*-geometry of vinyl sulfide of **34** was again confirmed by an NOE difference experiment. Irradiation of the C-14 vinyl hydrogen (δ 5.64) enhanced the signal of the hydrogens attached C-16 hydrogens (δ 2.07) while no enhancement of the signal due to the methyl attached to C-15 (δ 1.73) was observed[20] (Figure 5).

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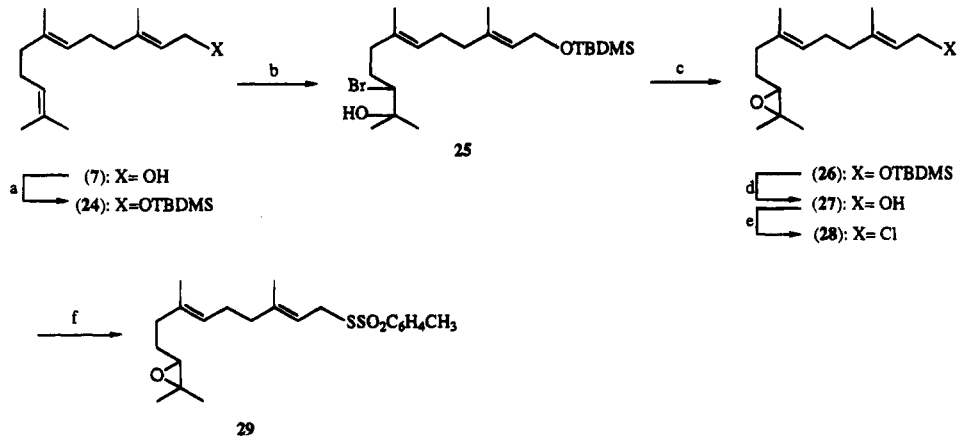
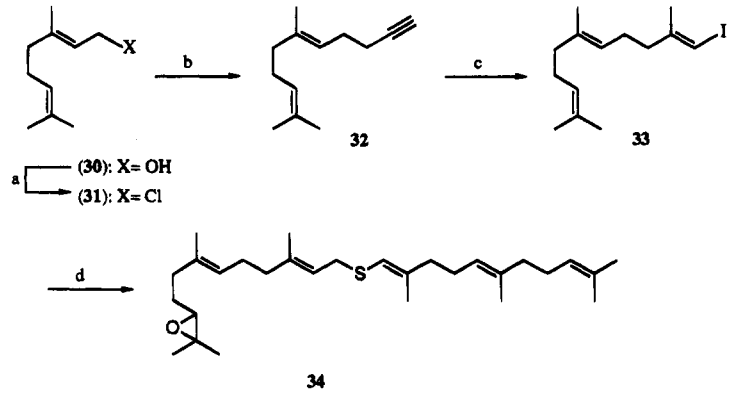
Scheme 3



(a) TBDMSCl, DAMP, Et_3N, CH_2Cl_2; (b) NBS, H_2O, THF, 0 °C; (c) K_2CO_3, CH_3OH; (d) Bu_4NF, H_2O, THF; (e) NCS, DMS, CH_2Cl_2, −20 °C; (f) $KSSO_2C_6H_4CH_3$, DMF.

Scheme 4



(a) NDS, DMS, CH_2Cl_2, −20 °C; (b) CH_2CCH_2, *n*-BuLi, Et_2O; (c) $Zr(Cp)_2Cl_2$, $AlMe_3$, then I_2, CH_2Cl_2; (d) *n*-BuLi, −78 °C, then **29**, THF.

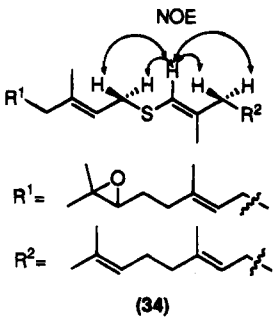


Figure 5.

In summary , we achieved the total synthesis of (6*E*)-8-thia and (14*E*)-13-thia-2,3-oxidosqualenes. The key to the syntheses was a new methodology for generation of (*E*)-vinyl sulfides involving stereospecific coupling of trisubstituted vinyl anions with alkyl 4-methylbenzenethiosulfonates. The commercial availability of potassium 4-methylbenzenethiosulfonate and the convenient generation of vinyl anions by reaction of vinyl iodides with alkyllithiums make this a useful method.

Biological Results. Both **22** and **34** inhibited cell-free OSC of *C. albicans* with IC_{50} values of 0.68 and 45 μM, respectively. The comparison IC_{50} values of these two compounds reveals that **34** is ~60-fold less effective than **22**. The inhibition and the kinetic behavior of related sulfur-substituted 2,3-oxidosqualene analogues[24] lead us suggest that **22** and **34** most likely act as competitive inhibitors of fungal OSC. The IC_{50} value of **22** (IC_{50} = 0.68 μM) is comparable with 4-{[6-(*N*,*N*-dimethylamino)-hexyl]oxy}-2′,4′-dichlorobenzophenone[25] (IC_{50} = 0.66 μM, *C. albicans*), a good inhibitor of 2,3-oxidosqualene-lanosterol cyclase.

Experimental Section

A. General Chemical Procedures. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Triethylamine (Et_3N) and dichloromethane (CH_2Cl_2) were freshly distilled from CaH_2 prior to use. *N*,*N*-Dimethylformamide (DMF) was dried over 4A molecular sieves. *N*-Bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) were recrystallized from glacial acetic acid, washed with ice−water, and dried under high vacuum before use. Iodine was purified by sublimation. 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 air-sensitive reagents.

(24) Related sulfur-substituted 2,3-oxidosqualene anlogues have been tested on purified pig liver 2,3-oxidosqualene cyclase in collaboration with Professor G. Prestwich at State University of New York at Stony Brook, Stony Brook, NY. The inhibition results along with the kinetic analysis will be reported elsewhere. Stack, D.; Zheng, Y. F.; Perez, A. L.; Oehlshlager, A. C.; Abe, I.; Prestwich, G. D. Unpublished results.

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Unless otherwise stated, standard workup refers the combination of organic extracts, washing with ice-cold brine, drying over anhydrous $MgSO_4$, and concentration *in vacuo*.

B. Assay of Enzyme Inhibition. As described in ref 26, 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 of cell mass were used 1 mg of zymolase, 12.5 μL of 2-mercaptoethanol, and 5 mL of 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 at pH 6.9. After centrifugation at 15 000*g*, the supernatant is a 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 metabolism 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}.

Ethyl 5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrienoate (9). This was prepared according to the procedure of Coates *et al.*[16] in 91% yield. IR and ^{1}H NMR spectra are in agreement with those reported in ref 16.

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-ol (10). This was prepared according to the procedure of Coates *et al.*[16] in 92% yield. IR and ^{1}H NMR spectra are in agreement with those reported in ref 16.

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-al (11). This was prepared by Swern oxidation [17] of **10** in 93% yield. IR and ^{1}H NMR spectra are in agreement with those reported in ref 16.

Ethyl 2,7,11,15-Tetramethyl-2(*E*),6(*E*),10(*E*),14-hexadecatetraenoate (12). To powdered (carbethoxyethylidene)-triphenylphosphorane (3.90 g, 10.1 mmol) under argon was added a solution of **11** (2.49 g, 10 mmol) in CH_2Cl_2 (100 mL), and the mixture was refluxed under argon for 12 h. Water (40 mL) was added to the cooled mixture and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (5/95) as eluant gave geometrically pure **12** (2.90 g, 90% yield): IR (film) 1711, 1649 cm^{-1}; CIMS *m*/*z* (isobutane, rel intensity) 333 (M^+ + 1, 100), 287 (24.3), 259 (43.1), 251 (53.5), 237 (21.9), 223 (30), 209 (38.3), 205 (23.8), 197 (37.0), 193 (20.6), 183 (31.7), 177 (24.2), 149 (31.8), 137 (73.0), 123 (41.1); ^{1}H NMR ($CDCl_3$, ppm) 6.76 (tq, J = 7.3, 1.4 Hz, 1H), 5.16–5.05 (m, 3H), 4.18 (q, J = 7.1 Hz, 2H), 2.25–1.91 (m, 12H), 1.81 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.58 (s, 6H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm) 168.14, 141.76, 136.16, 134.93, 131.11, 127.87, 124.36, 124.08, 123.13, 60.25, 39.66, 28.96, 26.92, 26.73, 25.60, 17.58, 15.97, 15.91, 14.23, 12.23. Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.59; H, 10.68.

2,7,11,15-Tetramethyl-2(*E*),6(*E*),10(*E*),14-hexadecatetraen-1-ol (13). To a solution of **12** (2.50 g, 7.53 mmol) in anhydrous diethyl ether (80 mL) at −78 °C under argon was added DIBALH (19 mL, 19 mmol, 1 M solution in THF). The mixture was allowed to warm to 0 °C and stirred for 2 h. Excess DIBALH was destroyed by addition of distilled water (2 mL) and the mixture was poured into ice-cold 5% aqueous solution of tartaric acid (20 mL). The mixture was extracted with ether (3 × 40 mL), and the combined organic phase was washed with $NaHCO_3$ solution. Standard workup followed by flash column chromatography using ethyl acetate/hexane (2/8) gave **13** (1.98 g, 91% yield): CIMS *m*/*z* (isobutane, rel intensity) 291 (M^+ + 1, 8.7), 290 (M^+, 4.3), 273 (8.7), 217 (19), 205 (41), 191 (36), 177 (26.2), 163 (35.5), 149 (71.1), 137 (100), 123 (76); ^{1}H NMR ($CDCl_3$, ppm) 5.45–5.37 (m, 1H), 5.18–5.06 (m, 3H), 3.98 (s, 2H), 2.12–1.92 (m, 12H), 1.68 (s, 3H), 1.66 (s, 3H), 1.60 (s, 9H), 1.35 (br, 1H); ^{13}C NMR ($CDCl_3$, ppm) 135.50, 134.95, 134.91, 131.20, 126.15, 124.44, 124.24, 123.95, 69.03, 39.72, 27.95, 27.88, 26.80, 26.66, 25.61, 17.62, 16.03, 15.99, 13.64. Anal. Calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.47; H, 11.69.

1-Chloro-2,7,11,15-tetramethyl-2(*E*),6(*E*),10(*E*),14-hexadecatetraene (14). To a solution of *N*-chlorosuccinimide (NCS) (0.735 g, 5.5 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C under argon was added dropwise dimethyl sulfide (DMS) (0.45 mL, 6.0 mmol). This mixture was cooled to −20 °C, and **13** (1.39 g, 4.79 mmol) in CH_2Cl_2 (3 mL) was added to the mixture over 5 min. The mixture was allowed to warm to 0 °C, stirred for 1 h, and then poured into ice-cold brine. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (1/9) gave pure **14** (1.19 g, 81% yield): IR (film) 1667, 1264, and 685 cm^{-1}; CIMS *m*/*z* (isobutane, rel intensity) 309 (M^+ + 1, 10.3), 308 (M^+, 3.1), 273 (35.2), 217 (14.2), 205 (34.3), 191 (29.0), 177 (18.1), 163 (23.6), 149 (53.0), 137 (100), 123 (72.8); ^{1}H NMR ($CDCl_3$, ppm) 5.57–5.50 (m, 1H), 5.16–5.04 (m, 3H), 4.02 (s, 2H), 2.24–1.92 (m, 12H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$, ppm) 135.84, 134.99, 131.82, 131.21, 130.68, 124.45, 124.23, 123.57, 52.48, 39.74, 28.36, 27.53, 26.83, 26.65, 25.63, 17.65, 16.06, 16.00, 14.12. Anal. Calcd for $C_{20}H_{33}Cl$: C, 77.76; H, 10.77. Found: C, 77.48; H, 10.69.

2,7,11,15-Tetramethyl-2(*E*),6(*E*),10(*E*),14-hexadecatetraenyl 4-Methylbenzenethiosulfonate (15). To a solution of potassium 4-methylbenzenethiosulfonate (0.90 g, 3.8 mmol) in DMF (20.0 mL) was added a solution of **14** (1.11 g, 3.6 mmol) in DMF (5 mL). This mixture was stirred at room temperature for 24 h and then poured into ice-cold water (30 mL). The mixture was extracted with diethyl ether (4 × 30 mL), and the ethereal solution was washed with saturated $NaHCO_3$ solution (20 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (15/85) gave pure **15** (1.42 g, 86% yield): IR (film) 1666, 1595, 1329, 1142, and 812 cm^{-1}; CIMS *m*/*z* (isobutane, rel intensity) 461 (M^+ + 1, 2.2), 305 (14.0), 295 (8.7), 279 (18.0), 273 (17.2), 157 (100), 156 (2.9), 139 (16.2), 123 (4.5); ^{1}H NMR ($CDCl_3$, ppm) 7.78–7.32 (AA'BB', 4H), 5.38–5.30 (m, 1H), 5.12–5.00 (m, 3H), 3.65 (s, 2H), 2.44 (s, 3H), 2.10–1.88 (m, 12H), 1.67 (s, 3H), 1.59 (s, 6H), 1.57 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 144.40, 142.62, 135.81, 135.00, 131.42, 131.21, 129.63 (2C), 127.71, 127.06 (2C), 124.42, 124.19, 123.50, 45.69, 39.73, 28.48, 27.50, 26.81, 26.65, 25.64, 21.57, 17.66, 16.06, 16.00, 15.00. Anal. Calcd for $C_{27}H_{40}O_2S_2$: C, 70.39; H, 8.76. Found: C, 70.11; H, 8.88.

5-Iodo-4-methyl-4(*E*)-penten-1-ol (17). To a slurry of $ZrCp_2Cl_2$ (2.54 g, 8.75 mmol) in dry CH_2Cl_2 (100 mL) at −20 °C under argon was added $AlMe_3$ (10.38 mL, 105 mmol) dropwise over 5 min. 4-Pentyn-1-ol (**16**) (3.01 g, 35 mmol) in CH_2Cl_2 (5 mL) was then added dropwise. The mixture was warmed to room temperature and stirred for 15 h. The mixture was then cooled to −30 °C, and iodine (10.15 g, 40 mmol) in THF (50 mL) was added slowly. Twenty minutes after addition of iodine, excess $AlMe_3$ was destroyed (caution!!) by the addition of 5 mL of distilled water under argon at 0 °C. The slurry was diluted with 100 mL of hexane and the precipitated salt was filtered through a pad of Celite. The pad was rinsed thoroughly with 50 mL of hexane. Standard workup of the filtrate followed by flash chromatography using ethyl acetate/hexane (3/7) as the eluant gave pure **17** (6.49 g, 82% yield): IR (film) 3347, 1617, 1062, and 769 cm^{-1}; ^{1}H NMR ($CDCl_3$, ppm) 5.91 (s, 1H), 3.61 (t, J = 6.4 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.83 (s, 3H),1.80–1.60 (m, 3H); ^{13}C NMR ($CDCl_3$, ppm) 147.46, 74.90, 62.04, 35.78, 30.61, 23.84. Anal. Calcd for $C_6H_{11}IO$: C, 31.86; H, 4.91. Found : C, 32.13; H, 5.04.

5-Iodo-4-methyl-4(*E*)-pentenyl *tert*-Butyldimethylsilyl Ether (18). To a solution of *tert*-butyldimethylsilyl chloride (4.04 g, 26 mmol) in CH_2Cl_2 (80 mL) and Et_3N (27.3 g, 27 mmol) at 0 °C were added **17** (5.65 g, 25 mmol) and 4,6-(dimethy-

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

lamino)pyridine (0.05 g). This was stirred at room temperature for 6 h and the mixture was poured into water (20 mL). The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (5/95) as eluant gave **18** (8.08 g, 95% yield) as colorless liquid: IR (film) 1618, 1105, 836, and 775 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 341 (M^+ + 1, 28.0), 283 (27.6), 251 (3.6), 210 (7.2), 209 (100), 123 (10.4); ^1H NMR ($CDCl_3$, ppm) 5.88 (q, *J* = 1.10 Hz, 1H), 3.58 (t, *J* = 6.27 Hz, 2H), 2.26 (t, *J* = 7.65 Hz, 2H), 1.83 (d, *J* = 1.10 Hz, 3H), 1.68–1.60 (m, 2H), 0.89 (s,9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 147.79, 74.60, 62.15, 35.85, 30.84, 25.93, 23.87, 18.33, −5.32.

6-Thia-4,8,13,17,21-pentamethyl-4(*E*),8(*E*),12(*E*),16(*E*),-20-docosapentaenyl *tert*-Butyldimethylsilyl Ether (19). To a stirred solution of **18** (0.558 g, 1.64 mmol) in dry THF (40 mL) at −78 °C under argon was added dropwise *n*-BuLi (0.66 mL, 1.65 mmol, 2.5 M solution in hexane), and the mixture was stirred for 20 min. To this mixture, at −78 °C under argon, was added dropwise a solution of **15** (0.75 g, 1.63 mmol) in THF (3 mL) over 3 min. The mixture was stirred at −78 °C for 15 min, and water (10 mL) was added. The mixture was warmed to room temperature and extracted with diethyl ether (4 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (5/95) as eluant gave pure **19** (0.767 g, 91% yield): IR (film) 1668, 1104, and 836 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 519 (M^+ + 1, 100), 518 (M^+, 7.0), 461 (2.1), 387 (3.8), 305 (11.1), 303 (51.8), 273 (42.3), 247 (18.0), 231 (20.0), 191 (16.2), 149 (15.0), 137 (33.0), 123 (23); ^1H NMR ($CDCl_3$, ppm) 5.58 (q, *J* = 1.0 Hz, 1H), 5.35–5.28 (m, 1H), 5.17–5.06 (m, 3H), 3.57 (t, *J* = 6.5 Hz, 2H), 3.19 (s, 2H), 2.12–1.94 (m, 14H), 1.72 (d, *J* = 1.0 Hz, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.64–1.56 (m, 2H), 1.60 (s, 9H), 0.89 (s, 9H), 0.042 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.38, 135.40, 134.88, 131.43, 131.10, 128.22, 124.46, 124.27, 123.96, 117.75, 62.59, 43.33, 39.75, 35.53, 31.12, 28.47, 28.06, 26.69, 26.59, 26.04, 25.87, 25.84, 18.29, 18.05, 17.64, 16.05, 15.99, 14.90, −5.27. Anal. Calcd for $C_{32}H_{58}SiOS$: C, 74.07; H, 11.28. Found: C, 74.25; H, 11.49.

6-Thia-4,8,13,17,21-pentamethyl-4(*E*),8(*E*),12(*E*),16(*E*),-20-docosapentaen-1-ol (20). To a solution of **19** (0.67 g, 1.29 mmol) in THF (15.0 mL) at room temperature was added tetrabutylammonium fluoride (5 mL, 5 mmol, 1 M solution in THF). The mixture was stirred at room temperature for 10 h and then poured into ice-cold water (5 mL). The mixture was extracted with diethyl ether (3 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (3/7) as eluant gave pure **20** (0.49 g, 94% yield): IR (film) 3348, 1666, and 1063 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 405 (M^+ + 1, 100), 404 (M^+, 6.3), 307 (14.4), 273 (38.3), 205 (6.7), 191 (12.1), 173 (16.5), 149 (12.2), 137 (19.9), 123 (12.9); ^1H NMR ($CDCl_3$, ppm) 5.61 (q, *J* = 1.0 Hz, 1H), 5.35–5.28 (m, 1H), 5.18–5.06 (m, 3H), 3.61 (t, *J* = 6.5 Hz, 2H), 3.20 (s, 2H), 2.15–1.93 (m, 14H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.70–1.63 (m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.59 (s, 9H), 1.42 (br, 1H); ^{13}C NMR ($CDCl_3$, ppm) 136.09, 135.45, 134.91, 131.40, 131.11, 128.25, 124.41, 124.22, 123.88, 118.19, 62.45, 43.30, 39.69, 35.53, 30.79, 28.40, 27.99, 26.78, 26.65, 25.56, 17.90, 17.57, 15.99, 14.84. Anal. Calcd for $C_{26}H_{44}OS$: C, 77.17; H, 10.97. Found: C, 77.48; H, 11.20.

6-Thia-4,8,13,17,21-pentamethyl-4(*E*),8(*E*),12(*E*),16(*E*),-20-docosapentaen-1-al (21). To a vigorously stirred solution of oxalyl chloride (0.10 mL, 1.15 mmol) in CH_2Cl_2 (15 mL) at −60 °C under argon was added dimethyl sulfoxide (0.16 mL, 2.25 mmol). The mixture was stirred for 5 min at −60 °C; then a solution of **20** (0.37 g, 0.91 mmol) in CH_2Cl_2 (2 mL) was added. After the solution was stirred for 30 min, triethylamine (0.84 mL, 6.0 mmol) was added over 2 min, and the mixture was allowed to warm to room temperature. Water (10 mL) was added and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 20 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (1/9) as eluant gave **21** (0.33 g, 90% yield): IR (film) 1727, 1667, and 1069 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 403 (M^+ + 1, 100), 402 (M^+, 5.1), 273 (47.7), 205 (6.4), 191 (11.0), 171 (12.2), 149 (12.3), 137 (12.0); ^1H NMR ($CDCl_3$, ppm) 9.74 (t, *J* = 1.7 Hz, 1H), 5.62 (q, *J* = 1.0 Hz, 1H), 5.35–5.27 (m, 1H), 5.17–5.05 (m, 3H), 3.20 (s, 2H), 2.55–2.49 (m, 2H), 2.37 (t, *J* = 7.4, Hz, 2H), 2.10–1.92 (m, 12H), 1.72 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$, ppm) 201.66, 135.53, 134.96, 133.71, 131.22, 128.54, 124.41, 124.20, 123.84, 119.31, 43.21, 42.04, 39.72, 31.48, 28.42, 28.01, 26.79, 26.65, 25.64, 18.07, 17.64, 16.05, 15.98, 14.84. Anal. Calcd for $C_{26}H_{42}OS$: C, 77.55; H, 10.51. Found: C, 77.28; H, 10.74.

(6*E*)-8-Thia-2,3-oxidosqualene (22). To a stirred solution of diphenylisopropylsulfonium fluoborate (0.167 g, 0.53 mmol) in dry THF (15 mL) at −78 °C, under argon, was added dropwise *t*-BuLi (0.31 mL, 0.53 mmol, 1.7 M in hexane). This mixture was stirred at −78 °C under argon for 1 h, and then a solution of **21** (0.209 g, 0.52 mmol) in THF (3 mL) was added dropwise. The mixture was maintained at −70 °C for 1 h and between −70 and −50 °C for 1 h. The mixture was then treated with distilled water (10 mL) and extracted with diethyl ether (3 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (5/95) as eluant gave **22** (0.208 g, 90% yield): IR (film) 1669, 1247, and 1122 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 445 (M^+ + 1, 65.5), 444 (M^+, 3.9), 403 (35.1), 305 (19.5), 273 (45.2), 191 (12.3), 173 (12.5), 149 (11.7), 139 (100), 123 (12.0); ^1H NMR ($CDCl_3$, ppm) 5.63 (s, 1H), 5.35–5.27 (m, 1H), 5.16–5.03 (m, 3H), 3.20 (s, 2H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.28–2.11 (m, 2H), 2.10–1.92 (m, 12H), 1.73 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.66–1.61 (m, 2H), 1.60 (s, 9H), 1.30 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 135.51, 135.25, 134.97, 131.35, 128.38, 124.42, 124.23, 123.87, 118.53, 63.90, 58.29, 43.29, 39.74, 36.01, 28.45, 28.04, 27.49, 26.81, 26.68, 25.64, 24.84, 18.72, 18.07, 17.65, 16.00, 14.99. Anal. Calcd for $C_{29}H_{48}OS$: C, 78.32; H, 10.89. Found: C, 78.22; H, 11.02.

3,7,11-Trimethyl-2(*E*),6(*E*),10-dodecatrienyl *tert*-Butyldimethylsilyl Ether (24). This was prepared in 95% yield by same procedure as described for **18**. **24**: IR (film) 1669, 1110, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.31 (t, *J* = 6.2 Hz, 1H), 5.10 (t, *J* = 6.0 Hz, 2H), 4.19 (d, *J* = 6.5 Hz, 2H), 2.04 (m, 8H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.89, 135.16, 131.23, 124.47, 124.40, 124.01, 60.35, 39.72, 39.56, 26.78, 26.35, 26.03, 25.65, 18.41, 17.65, 16.35, 15.98, −5.04.

10-Bromo-11-hydroxy-3,7,11-trimethyl-2(*E*),6(*E*)-dodecadienyl *tert*-Butyldimethylsilyl Ether (25). To a vigorously stirred solution of **24** (3.14 g, 9.33 mmol) in THF (200 mL) and water (50 mL) at 0 °C was added dropwise a solution of *N*-bromosuccinimide (1.66 g, 9.33 mmol) in THF (30 mL) and H_2O (10 mL) over a period of 30 min. The mixture was stirred for 1 h at 0 °C, and then THF was removed *in vacuo*. The mixture was extracted with 10% ether/hexane mixture (4 × 30 mL). Standard workup followed by flash column chromatography using ethyl acetate/hexane (15/85) as eluant afforded unreacted TBS ether (**24**) (1.53 g) and **25** (1.58 g, 39% yield): IR (film) 3452, 1668, and 1064 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.30 (t, *J* = 6.1 Hz, 1H), 5.20 (t, *J* = 6.0 Hz, 1H), 4.19 (d, *J* = 6.5 Hz, 2H), 3.96 (dd, *J* = 10.0 Hz, 1.5 Hz, 1H), 2.03 (m, 8H),1.62 (s, 3H), 1.58 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 0.90 (s, 9H), 0.064 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.63, 133.29, 125.73, 124.63, 72.45, 70.79, 60.35, 39.41, 38.17, 32.17, 26.63, 26.30, 26.03, 25.89, 18.43, 16.35, 15.85, −5.03.

10,11-Epoxy-3,7,11-trimethyl-2(*E*),6(*E*)-dodecadienyl *tert*-Butyldimethylsilyl Ether (26). To a solution of **25** (1.09 g, 2.50 mmol) in methanol (30 mL) was added K_2CO_3 (0.693 g, 5.0 mmol). This mixture was stirred for 1 h after which time most methanol was removed *in vacuo*. The resulting slurry was then diluted with water (20 mL), and the mixture was extracted with diethyl ether (3 × 40 mL). Standard workup followed by chromatography using ethyl acetate/hexane (1/9) as eluant gave **26** (0.861 g, 97% yield): IR (film) 1668, 1253, 1110, 1065, and 835 cm^{-1}; ^1H NMR ($CDCl_3$, ppm) 5.30 (t, *J* = 6.0 Hz, 1H), 5.15 (t, *J* = 6.0 Hz, 1H), 4.13 (d, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.09 (m, 6H), 1.61 (m, 2H), 1.60 (s, 6H), 1.29 (s, 3H), 1,25 (s, 3H), 0.90 (s, 9H), 0.046 (s, 6H); ^{13}C NMR ($CDCl_3$, ppm) 136.70, 134.27, 124.64, 124.55, 64.16, 60.30, 58.23, 39.44, 36.30, 27.48, 26.31, 26.01, 24.86, 18.73, 18.40, 16.33, 15.97, −5.06.

10,11-Epoxy-3,7,11-trimethyl-2(*E*),6(*E*)-dodecadien-1-ol (27). This was prepared by the same procedure as described for **20**. Flash column chromatography using ethyl acetate/hexane (6/4) as eluant gave **27** in 91% yield as a colorless liquid: IR (film) 3424, 1642, 1249, 1120, and 836 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 239 ($M^+ + 1$, 1.6), 221 (100.0), 203 (59.3), 186 (18.0), 153 (45.9), 135 (35.1); ^1H NMR ($CDCl_3$, ppm) 5.40 (t, $J = 6.0$ Hz, 1H), 5.15 (t, $J = 6.0$ Hz, 1H), 4.13 (d, $J = 7.4$ Hz, 2H), 2.68 (t, $J = 6.2$ Hz, 1H), 2.08 (m, 6H), 1.66 (s, 3H), 1.62 (m, 2H), 1.60 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 139.17, 134.36, 124.55, 123.77, 64.15, 59.29, 58.30, 39.40, 36.33, 27.34, 26.20, 24.83, 18.75, 16.20, 15.96.

1-Chloro-10,11-epoxy-3,7,11-trimethyl-2(*E*),6(*E*)-dodecadiene (28). This was obtained by the same procedure as described for **14**. Flash column chromatography using ethyl acetate/hexane (15/85) as eluant gave **28** in 79% yield: IR (film) 1662, 1252, 874, and 678 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 257 ($M^+ + 1$, 88), 239 (53.2), 221 (100), 203 (47.3), 153 (43.2), 135 (36.9); ^1H NMR ($CDCl_3$, ppm) 5.43 (t, $J = 8.0$ Hz, 1H), 5.13 (t, $J = 6.1$ Hz, 1H), 4.08 (d, $J = 8.0$ Hz, 2H), 2.69 (t, $J = 6.2$ Hz, 1H), 2.10 (m, 6H), 1.71 s, 3H), 1.61 (s, 3H), 1.60 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 142.51, 134.76, 124.09, 120.52, 64.12, 58.20, 41.01, 39.34, 36.31, 27.49, 26.11, 24.88, 18.75, 16.04; HRMS *m/z* calcd for $C_{15}H_{25}ClO$ 256.1594, found 256.1598.

10,11-Epoxy-3,7,11-trimethyl-2(*E*),6(*E*)-dodecadienyl 4-Methylbenzenethiosulfonate (29). This was prepared in 85% yield by same procedure as described for **15**. For **29**: IR (film) 1659, 1594, 1326, 1142, and 813 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 409 ($M^+ + 1$, 3.5), 222 (6.7), 201 (3.1), 157 (100), 155 (6.1), 141 (15.8), 127 (10.5); ^1H NMR ($CDCl_3$, ppm) 7.32–7.84 (AA'BB', 4H), 5.07 (m, 2H), 3.67 (d, $J = 7.9$ Hz, 2H), 2.68 (t, $J = 6.2$ Hz, 1H), 2.44 (s, 3H), 2.03 (m, 6H), 1.61 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 144.51, 143.32, 142.44, 134.78, 129.73, 127.04, 124.00, 115.47, 64.10, 58.20, 39.34, 36.30, 34.22, 27.52, 26.07, 24.88, 21.57, 18.76, 16.24, 16.01; HRMS *m/z* calcd for $C_{22}H_{32}O_3S_2$ 408.1792, found: 408.1786. Anal. Calcd for $C_{22}H_{32}O_3S_2$: C, 64.67; H, 7.89. Found: C, 64.84; H, 7.78.

1-Iodo-2,6,10-trimethyl-1(*E*),5(*E*),9-undecatriene (33). This was prepared by the same procedure as described for **17** except $AlMe_3$ and **32** were used in a 2:1 molar ratio. Flash column chromatography using ethyl acetate/hexane (1/9) as eluant gave **33** in 81% yield: CIMS *m/z* (isobutane, rel intensity) 319 ($M^+ + 1$, 3.9), 263 (2.6), 249 (1.9), 235 (2.4), 192 (16.2), 191 (100), 178 (1.6), 163 (1.8); ^1H NMR ($CDCl_3$, ppm) 5.87 (s, 1H), 5.07 (m, 2H), 2.11 (m, 8H), 1.84 (s, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 147.81, 136.07, 131.37, 124.26, 123.00, 74.65, 39.68, 39.50, 26.73, 26.31, 25.66, 23.94, 17.68, 16.00.

(14*E*)-13-Thia-2,3-oxidosqualene (34). This was prepared in 28% yield by the same procedure as described for **19**. For **34**: IR (film) 1663, 1248, and 1122 cm^{-1}; CIMS *m/z* (isobutane, rel intensity) 445 ($M^+ + 1$, 48.4), 237 (11.5), 221 (100), 204 (10.3), 191 (44.6), 153 (28.5), 135 (22.6); ^1H NMR ($CDCl_3$, ppm) 5.64 (s, 1H), 5.28 (t, $J = 7.8$ Hz, 1H), 5.15 (t, $J = 6.8$ Hz, 1H), 5.09 (m, 2H), 3.27 (d, $J = 7.8$ Hz, 2H), 2.70 (t, $J = 6.2$ Hz, 1H), 2.07 (m, 14H), 1.73 (s, 3H), 1.68 (s, 6H), 1.61 (s, 3H), 1.60 (m, 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, ppm) 138.71, 137.38, 135.44, 134.42, 131.26, 124.52, 124.38, 123.77, 120.57, 117.62, 64.15, 58.20, 39.72, 39.56, 39.38, 36.33, 31.50, 27.53, 26.81, 26.54, 25.63, 24.88, 18.75, 18.07, 17.65, 16.17, 16.00; HRMS calcd for $C_{29}H_{48}OS$ 444.3426, found 444.3425. Anal. Calcd for $C_{29}H_{48}OS$: C, 78.32; H, 10.88. Found: C,78.28; H, 10.79.

Acknowledgment. Y. F. Zheng would like to thank Dr. Dharmpal S. Dodd for providing compound **32** and his invaluable discussions throughout this work. We thank the Natural Sciences and Engineering Research Council of Canada for support of this work through research and strategic grants to A.C.O.