Squalene Synthetase Inhibitors: Synthesis of Sulfonium Ion Mimics of the Carbocationic Intermediates

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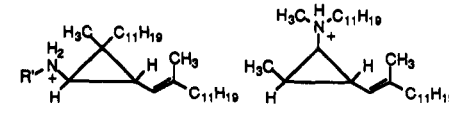
Synthesis of sulfonium ion mimics **15** and **16** of the carbocationic intermediates **3** and **7**, respectively, presumed to be involved in the squalene synthetase catalyzed rearrangement of farnesyl pyrophosphate (**1**), is reported. Synthesis of **15** involved combination of homogeranyl sulfide with ethyl α-bromoacetate through use of the thallium salt or via the combination of the copper enolate of ethyl acetate and homogeranyl thiosulfonate. Alkylation of the resulting thioester with farnesyl bromide followed by reduction of the ester moiety provided the required alcohol. The sulfur was methylated with iodomethane in a solution of CH_3CN and THF to yield **15**. Dialkylation of acetylene with farnesyl bromide and homogeranyl thiosulfonate followed by reduction of the triple bond gave vinyl sulfides, which were methylated with iodomethane in the presence of silver perchlorate to give **16**.

Introduction

Squalene synthetase (EC 2.5.1.21; SS) plays an important role in sterol biosynthesis by catalyzing the head-to-head condensation of two molecules of farnesyl pyrophosphate (FPP, **1**). The enzyme is a single 47 000 Da polypeptide that is bound to the subcellular membranes of the endoplasmic reticulum in yeast and mammalian liver.[1-4] The overall reaction occurs through two distinct steps and involves an isolated chiral intermediate, presqualene pyrophosphate (PPP, **2**).[1]

Several mechanisms have been proposed for the formation of presqualene pyrophosphate (PPP) from farnesyl pyrophosphate (FPP).[5] All involve the nonsymmetrical combination of two molecules of FPP. Initial velocity studies of the formation of PPP point to a ping-pong reaction that involves a farnesyl–enzyme intermediate.[6] In the first reaction an S_N2 displacement of the pyrophosphate moiety of one FPP by a nucleophilic group of SS yields a farnesyl–enzyme intermediate. Polarization of the C-2, C-3 double bond of a second molecule of FPP by a second nucleophilic group of SS is followed by attack at C-1′ of the farnesyl–enzyme. This results in formation of a bond between C-2 of second and C-1′ of the farnesyl–enzyme. If ionization of the C-1′, enzyme bond in a farnesyl–enzyme intermediate precedes attack by the double bond, then it is easy to envision that cationic intermediate **3** would be involved in the generation of PPP. In a second process, PPP is proposed to ionize to **4** and thence via C-1′, C-2 or C-1′, C-3 bond migration to a cyclobutyl (**5**) or a cyclopropylcarbinyl (**6**) cation. The latter or a subsequent squalene cation (**7**) is finally reduced by NADPH to squalene (**8**). Recent work by Rilling using solubilized SS revealed that when NADPH is present, activity for the formation of PPP was greater than that of its conversion to squalene.[4] Poulter has proposed that SS exerts its primary control on the conversion of PPP to squalene by directing the rearrangement of **4** to **5** or **6**.[7] The preference for conversion of **4** to these intermediates by SS is considered to be due to the ability of the enzyme to orient the departing pyrophosphate in such a way that it is antiparallel to the migrating C-1′, C-2 or C-1′, C-3 bond. According to Coates and Robinson in the case of C-1′, C-2 bond migration to give **5**, this conformational preference must be accompanied by orientation of the C-2′, C-3′ π-bond so that stabilization of any developing charge at C-1′ is minimized; otherwise, cleavage of **4** to **9** would be expected.[8] Solvolysis of analogues of **2** reveals that in solution **4** preferentially (>98%) rearranges by cleavage of the C-1′, C-2 bond to give the ring-opened allylic cation **9** (and thence **10**) or migration of the C-2, C-3 bond to give **11** (and thence **12**).[7] Poulter has pointed out that rearrangement of **4** to both **5** and **6** requires much less charge separation between the pyrophosphate anion and the paired carbocation than rearrangement to **9**.[7] Furthermore, the process involving conversion of **2** to squalene requires a maximum movement in any direction of only 1.5 Å to accommodate the entire reaction sequence.[7]

Mimics of reaction intermediates have been used to probe the involvement of the carbocationic intermediates proposed in Scheme I, as well as the number of active sites in SS. Since the overall reaction is composed of two steps, it is possible that one active site is involved in synthesis of **2** and another in its conversion to squalene. Alternatively, one active site could catalyze the formation of both **2** and squalene. The approach taken has been to administer inhibitors that are mimics of the presumptive intermediates and determine if one or both of the steps are blocked. The ammonium ion analogues **13a** and **14** of intermediates **4** and **6** were shown to be efficient inhibitors of SS only if inorganic pyrophosphate was added. A



13a, R′=H **14**

13b, R′= -$(CH_2)_3OPO_2PO_3^-$

phosphonophosphate tethered by a two-carbon fragment to an ammonium ion analogue (**13b**) of the intermediate **4** exhibited efficient inhibition at very low levels and in the absence of added inorganic pyrophosphate.[9,10] This

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Scheme I

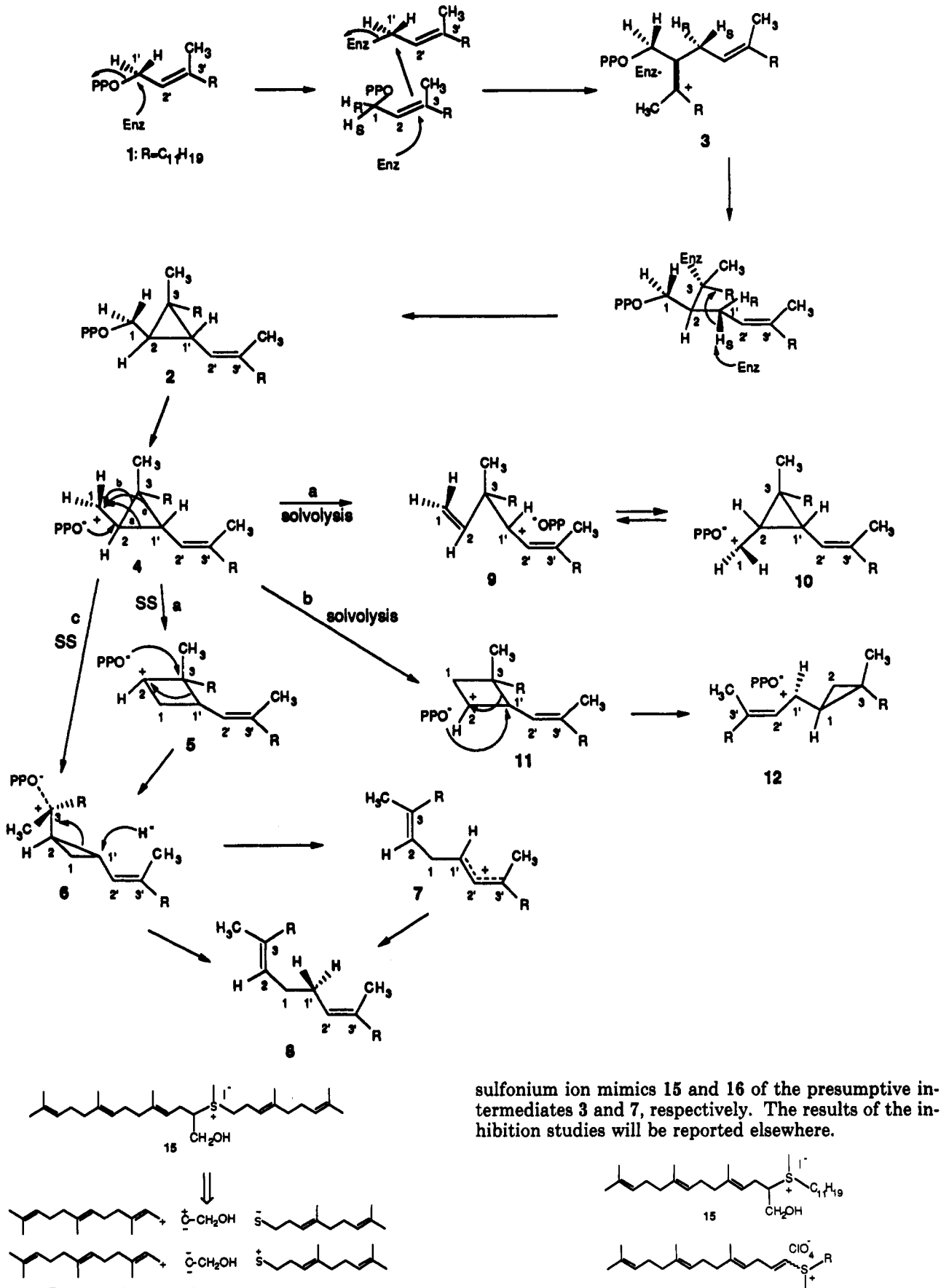
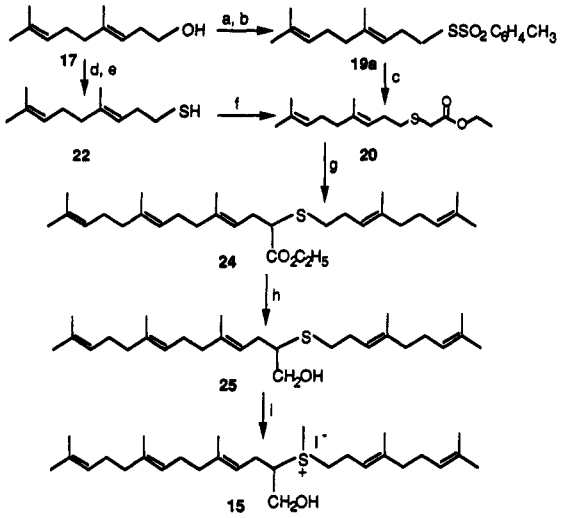


Figure 1. Retrosynthetic analysis of 15.

is good evidence for both the involvement of these cationic intermediates and the existence of a tight ion pair in which pyrophosphate is the anion. We here report syntheses of sulfonium ion mimics 15 and 16 of the presumptive intermediates 3 and 7, respectively. The results of the inhibition studies will be reported elsewhere.

a: E-$C_{11}H_{19}$
b: Z-$C_{11}H_{19}$
c: E-C_6H_{13}
d: Z-C_6H_{13}

Scheme II[a]



[a] (a) PPh_3, Br_2, pyridine, CH_2Cl_2; (b) $NaSSO_2C_6H_4CH_3$, DMF; (c) LDA, $CH_3CO_2C_2H_5$, CuI, THF; (d) PPh_3, *i*-$PrO_2CN{=}NCO_2Pr$-*i*, CH_3COSH; (e) $LiAlH_4$, ether; (f) $TlOC_2H_5$, $BrCH_2CO_2C_2H_5$, ether, *n*-hexane; (g) LDA, farnesyl bromide, THF; (h) $LiAlH_4$, ether; (i) CH_3I, CH_3CN, THF.

Results and Discussion

Synthesis of the Inhibitor 15. Retrosynthetic analysis of **15** reveals that the carbon skeleton of the inhibitor can be assembled from farnesyl and homogeranyl residues (Figure 1). Homogeraniol (**17**) was prepared from geraniol by the method of Leopold.[11] Alternate strategies for preparation of homogeraniol via geranyl cyanide were less satisfactory. The direct conversion of geraniol to geranyl cyanide failed in our hands,[12] although preparation of geranyl cyanide from geranyl bromide[13] was successful.[14] Hydrolysis of the former gave appreciable amounts of the *Z* isomer. Thiosulfonate **19a** was prepared from homogeraniol in two steps. Thus, treatment of homogeraniol with bromine and triphenylphosphine gave homogeranyl bromide (**18**) in 80% yield, which on treatment with sodium 4-methylbenzenethiosulfonate[15] in DMF provided **19a** in excellent yield.[16] Alkylation of homogeranyl thiosulfonate **19a** with the lithium enolate of ethyl acetate at −78 °C gave thioester **20** in poor yield due to the formation of the aldol product. This problem was circumvented through use of the much softer copper enolate to provide 48% of the desired product (Scheme II).[17]

An alternate strategy for preparation of **20** from **17** was more successful. Homogeraniol was first converted to thiol **22** in two steps (Scheme II). The Mitsunobu reaction of **17** with thiolacetic acid gave thiolacetate **21**.[18] Preformation of the adduct of triphenylphosphine and diisopropyl azodicarboxylate is essential for the success of this reaction. Reduction of **21** with lithium tetrahydroaluminate provided the required thiol **22** in 53% overall yield. This was treated with thallium(I) ethoxide[19] and ethyl α-bromoacetate according to the procedure of Detty[20] to quantitatively produce **20**. Use of the thallium(I) salt of thiol **22** (a soft base) avoided 1,2-addition, which is characteristic of the harder sodium and lithium thiolates. Introduction of the farnesyl residue into **20** was accomplished by treatment with lithium diisopropylamide followed by addition of farnesyl bromide (**23**) to give **24** in excellent yield whose ^1H NMR spectrum gave a doublet of doublets between 3.23 and 3.27 ppm (J = 9, 6.5 Hz) for the hydrogen on the chiral methine carbon. One of the diastereotopic hydrogens of the methylene adjacent to this methine gave a doublet of triplets between 2.32 and 2.39 ppm (J = 15, 6.5 Hz) while the other gave a multiplet between 2.53 and 2.66 ppm (overlapping with methylene adjacent to sulfur). Reduction of **24** with lithium tetrahydridoaluminate gave alcohol **25** in 88% yield. The ^1H NMR spectrum of **25** revealed signals due to the diastereotopic hydrogens of the methylene carbon adjacent to hydroxy group between 3.44 and 3.5 ppm (J = 10.6, 6.5, 5.5 Hz) and between 3.63 and 3.69 ppm (J = 10.6, 7, 4.5 Hz). Methylation of **25** with iodomethane in CH_3CN/THF gave a 1:1 mixture of diastereoisomers of **15** in 96% yield. The NMR spectrum of this mixture exhibited a triplet at 3.77 ppm (J = 6 Hz) for the methylene hydrogens adjacent to sulfur for the one diastereoisomer while those in the other diastereoisomer gave a set of doublets of triplets between 3.55 and 3.62 ppm (J = 13, 7.5 Hz) and between 3.81 and 3.89 ppm (J = 13, 6.5 Hz). Irradiation of the methylene hydrogens at C-2′ (2.49 and 2.69 ppm) resulted in simplication of multiplets for the diastereotopic hydrogens adjacent to sulfur. The hydrogens of methyl on the sulfur gave two singlets at 3.15 and 3.17 ppm for both

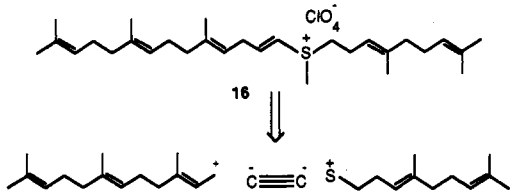
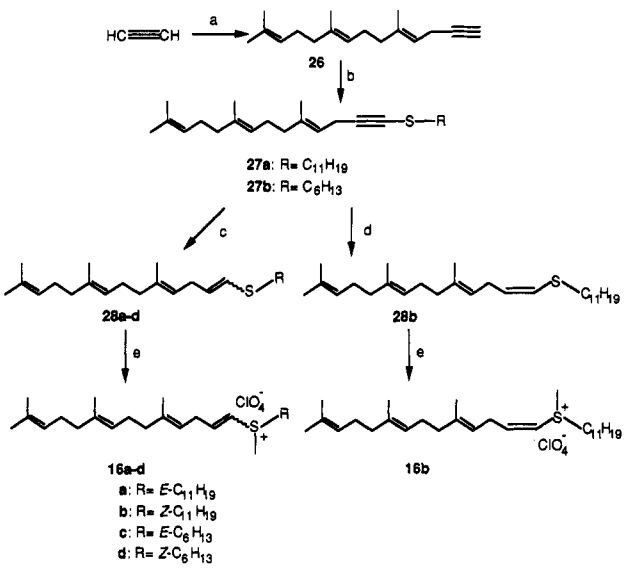


Figure 2. Retrosynthetic analysis of **16**.

Scheme III[a]



[a] *n*-BuLi, CuCN, farnesyl bromide, THF; (b) *n*-BuLi, $RSSO_2C_6H_5CH_3$, THF; (c) $LiAlH_4$, THF; (d) $LiAl(OMe)_3H$, $CuBr{\cdot}Me_2S$, THF, HMPA; (e) CH_3I, $AgClO_4$, CH_3CN.

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diastereoisomers. Signals at 4.24 and 4.37 ppm were attributed to the methine hydrogen of the diastereoisomers.

Synthesis of Inhibitors 16a–d. Synthesis of **16a–d** involved attachment of two isoprenoid units to acetylene followed by reduction of the triple bond to (*E*)- or (*Z*)-vinyl sulfides. Retrosynthetic analysis (Figure 2) revealed that the required isoprenoid units were the same as those used in the preparation of **15** and could be derived from farnseyl and geranyl residues. Thus, reaction of farnesyl bromide with monolithioacetylide in the presence of CuCN gave **26** in excellent yield (Scheme III). Coupling the anion of **26** with thiosulfonate **19a** yielded the alkynyl sulfide **27a**, which upon reduction with lithium tetrahydridoaluminate in THF gave a 65:35 mixture of (*E*)- and (*Z*)-vinyl sulfides **28a** and **28b**.[21] Likewise coupling of **26** with **19b** followed by reduction with lithium tetrahydroaluminate gave **28c** and **28d**. The structures of these vinyl sulfides, **28a** and **28b**, were confirmed by ^{1}H NMR spectroscopy. Thus, the vinyl hydrogen adjacent to sulfur in the *Z* isomer **28b** gave a doublet of triplets (J = 9.5, 7 Hz) between 5.48 and 5.54 ppm, whereas the signals between 5.56 and 5.63 ppm (J = 15, 7 Hz) were assigned to the analogous hydrogen in the *E* isomer **28a**. Hydrogens at C-2 in the *Z* and *E* isomers of **28** gave two sets of doublets of triplets at 5.920 ppm (J = 15, 1.5 Hz) and 5.923 ppm (J = 9.5, 1.5 Hz), respectively. Methylation of **28a** and **28b** with CH_3I with or without solvents failed to give the required product. However, when iodomethane was activated with silver perchlorate and treated with **28a** and **28b** in CH_3CN, sulfonium ions **16a** and **16b** were obtained in 59% yield. The NMR spectrum of the mixture of **16a** and **16b** gave signals at 638 ppm (J = 9, 1 Hz), and 6.58 ppm (J = 15, 1.5 Hz) for *Z* and *E* vinylic hydrogens C-1, respectively. The signals between 6.83 and 6.89 ppm and between 7.0 and 7.07 ppm (J = 15, 5.5 Hz) were assigned to *Z* and *E* vinylic hydrogens at C-2, respectively. Similarly, a mixture of *E* and *Z* isomers of the hexyl derivative (**16c** and **16d**, respectively) was synthesized by using the above strategy.

The *Z* isomer **16b** was obtained by the reduction of **27a** with copper hydride. Thus, reduction of **27a** with LiAl(OMe)$_3$H and CuBr·Me$_2$S provided **28b** in 80% yield[21] whose ^{1}H NMR spectrum gave two sets of signals, one between 5.48 and 5.55 ppm (J = 9.5, 7 Hz) and one between 5.91 and 5.94 ppm (J = 9.5, 1.5 Hz) for the vinyl hydrogens at C-2 and C-1, respectively. Methylation of **28b** with iodomethane in the presence of silver perchlorate gave sulfonium ion **16b** in 93% yield.

Sulfonium ions **15** and **16a–d** are inhibitors of squalene synthetase.[22] The details of inhibition studies will be reported elsewhere.

Experimental Section

Mass spectra were obtained for the sulfonium ion salts (thioglycerol matrix) by using fast atom bombardment (FAB). Gas chromatographic analysis was carried out on a J and W fused silica DB-1 column (7 m or 15 m × 0.25 mm i.d.). Thin layer chromatography was conducted on aluminum sheets precoated with silica gel 60F$_{254}$ (E Merck, Darmstadt). All flash column chromatography was performed on silica gel 60 (230–400 mesh, E Merck, Darmstadt).

Tetrahydrofuran was freshly distilled from potassium benzophenone–ketyl. Dimethyl sulfoxide, hexamethylphosphorus triamide, diisopropylamine, triethylamine, and dimethylformamide were distilled from CaH_2 and stored over molecular sieves (3A). Dichloromethane was distilled from P_2O_5 and stored over molecular sieves (4A). Farnesyl bromide and geraniol were purchased from Aldrich Chemical Co. Unless otherwise stated all reactions were conducted under argon in flame-dried glassware. A nitrogen glovebag was used to weigh all the moisture-sensitive compounds. Syringe and canula were used to transfer reagents.

Sodium 4-methylbenzenethiosulfonate was prepared according to the method of Mintel et al.:[15] ^{1}H NMR (D_2O) δ 2.39 (s, 3 H, phenyl-CH_3), 7.35–7.78 (AA'BB', 4 H, phenyl H); IR (KBr) 1330, 1200, 1090, 980, 800 (b) cm^{-1}.

4,8-Dimethyl-3(*E*),7-nonadien-1-ol (17) was prepared by the method of Leopold.[11]

1-Bromo-4,8-dimethyl-3(*E*),7-nonadiene (18). Bromine was added dropwise to an efficiently stirred ice-cooled solution of triphenylphosphine (1.5 g, 5.5 mmol) in 10 mL of CH_2Cl_2 until a permanent yellow color appeared. A few milligrams of triphenylphosphine were added to consume excess Br_2. At this point (0.8 mL, 10 mmol) of pyridine was added and the reaction stirred for 10 min. Homogeraniol (**17**) (0.85 g, 5 mmol) in 5 mL of CH_2Cl_2 was added dropwise and the reaction was stirred for 1.5 h. Solvents were removed, the precipitate was washed with pentane (4 × 40 mL), and the combined pentane extracts were washed with 1 N HCl (20 mL) and brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Distillation gave **18** (0.92 g, 80%): bp 90 °C (1 mm) lit.[23] bp 98 °C (5 mm); ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 6 H, vinyl methyl), 1.69 (s, 3 H, vinyl methyl), 1.96–2.13 (m, 4 H, C_5, C_6-CH_2), 2.39–2.74 (q, 2 H, C_2-CH_2, J = 6.67 Hz), 3.27–3.52 (t, 2 H, C_1-CH_2, J = 6.66 Hz), 5.03–5.27 (m, 2 H, vinyl H); MS, m/e (rel intensity), 232 (10.5), 230 (11.7), 217 (5.8), 215 (8.2), 189 (28.2), 187 (30.5), 123 (18.8), 69 (100).

4,8-Dimethyl-3(*E*),7-nonadienyl 4'-Methylbenzenethiosulfonate (19a). General Method. To a solution of sodium 4-methylbenzenethiosulfonate (1.57 g, 7.5 mmol) in 15 mL of DMF was added homogeranyl bromide (**18**) (1.5 g, 6.6 mmol) in 5 mL of DMF. After being stirred for 48 h at room temperature, the solution was poured into water (100 mL). The aqueous layer was extracted with ether (6 × 40 mL). The combined etheral solution was washed with 30 mL of $NaHCO_3$ and with brine (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give the product. Flash column chromatography using hexane/ethyl acetate (9/1) as an eluant gave 1.9 g (85%) of **19a**: IR (film) 2965.8, 2922.2, 2855.3, 1665.6, 1594.5, 1447.1, 1327.9, 1143.5, 1078.1, 812.9, 703.3, 654.7 588.5, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3 H, vinyl methyl), 1.58 (s, 3 H, vinyl methyl), 1.66 (s, 3 H, vinyl methyl), 1.92–2.06 (m, 4 H, C_5, C_6-CH_2), 2.28–2.35 (q, 2 H, C_2-CH_2, J = 6.7 Hz), 2.46 (s, 3 H, phenyl-CH_3), 2.96–2.99 (t, 2 H, C_1-CH_2, J = 6.7 Hz), 4.99–5.04 (m, 2 H, vinyl H), 7.32–7.84 (AA'BB', 4 H, phenyl H); MS, m/e (rel intensity), 338 (19), 255 (100), 183 (38), 135 (21.4), 113 (30.9), 100 (26), 91 (61.9), 69 (35.7). Anal. Calcd for $C_{18}H_{26}O_2S_2$: C, 63.88; H, 7.75. Found: C, 63.60; H, 7.57.

Hexyl 4'-Methylbenzenethiosulfonate (19b). This compound was prepared in 84% yield: IR (film) 2956, 2928.5, 2857.2, 1594.3, 1459.6, 1327.4, 1143.3, 1077.8, 813, 703, 655, 588, 521.1 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3 H, CH_3, J = 7 Hz), 1.15–1.32 (m, 6 H, CH_2), 1.52–1.62 (m, 2 H, C_2-CH_2), 2.45 (s, 3 H, Ph-CH_3), 2.8 (t, 2 H, SCH_2, J = 7 Hz), 7.31–7.84 (AA'BB', 4 H, phenyl); MS (CI, isobutane) m/e (rel intensity) 273 (100), 157 (18.3), 117 (20.4). Anal. Calcd for $C_{13}H_{20}O_2S_2$: C, 57.33; H, 7.41. Found: C, 57.31; H, 7.26.

4,8-Dimethyl-3(*E*),7-nonadienyl Thioacetate (21). To an efficiently stirred solution of triphenylphosphine (21 g, 80 mmol) in THF (200 mL) was added diisopropyl azodicarboxylate (16.7 g, 80 mmol) at 0 °C. The reaction was stirred for 0.5 h, after which time a thick white precipitate was obtained. A mixture of thiolacetic acid (6.1 g, 80 mmol) and **17** (6.72 g, 40 mmol) in 100 mL of THF was added dropwise while the temperature was maintained below 0 °C. The reaction was stirred for 1.5 h at 0 °C and then overnight at room temperature. Solvent was removed in vacuo and the residue purified by flash chromatography using hexane/CH_2Cl_2 (3:1) as an eluant. Distillation gave 7.54 g (83%) of **21**: bp 65–67 °C (0.01 mm); GC purity (99%); IR (film) 3350, 2910, 1690, 1435, 1350, 1130, 1100, 950, 830 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H, vinyl methyl), 1.60 (s, 3 H, vinyl methyl), 1.67 (s, 3 H, C_4-vinyl methyl), 1.95–2.06 (m, 4 H, CH_2), 2.22–2.27 (q, 2 H, C_2-CH_2, J = 7.3 Hz), 2.31 (s, 3 H, $COCH_3$), 2.84–2.87 (t,

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2 H, C_1-CH_2, J = 7.3 Hz), 5.05–5.12 (m, 2 H, C_3, C_7-vinyl H); MS, m/e (rel intensity), 226.2 (0.1), 186.2 (0.1), 185.1 (0.6), 184.2 (1.5), 81.1 (59.5), 69.0 (100), 43.1 (42.5), 41.1 (45.3). Anal. Calcd for $C_{13}H_{22}SO$: C, 69.02; H, 9.73. Found: C, 69.22; H, 9.75.

4,8-Dimethyl-3(*E*),7-nonadiene-1-thiol (22). To a stirred solution of lithium tetrahydridoaluminate (1.22 g, 8.0 equiv) in anhydrous ether (30 mL) was added dropwise a solution of **21** (7.26 g, 32.1 mmol) in 15 mL of anhydrous ether at 0 °C. After 0.5 h excess hydride was destroyed by careful addition of ice-cold 1 N HCl. Precipitated salts were removed by filtration through Celite. The organic layer was washed with brine (2 × 30 mL) and dried ($MgSO_4$) and the solvent was removed to give the crude product (7.5 g). Distillation gave 5.42 g (92%) of **22**: bp 46 °C (0.01 mm); GC purity (96%); IR (film) 2920, 2560, 1735, 1660, 1440, 1285, 1110, 980 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.44 (t, 1 H, SH, J = 7.6 Hz), 1.59 (s, 3 H, vinyl methyl), 1.61 (s, 3 H, vinyl methyl), 1.67 (s, 3 H, C_4-vinyl methyl), 1.98–2.02 (m, 2 H, C_6-CH_2), 2.04–2.08 (m, 2 H, C_5-CH_2), 2.28–2.33 (q, 2 H, C_2-CH_2, J = 7.1 Hz), 2.49–2.54 (dt, 2 H, C_1-CH_2, J = 7.1, 7.5 Hz), 5.07–5.11 (m, 2 H, C_3, C_7-vinyl H) [Irradiation of the triplet at δ 1.40–1.44 resulted in the simplification of the signal at 2.49–2.54 (C_1-CH_2), confirming the signal at 1.40–1.44 to be that of the SH]; MS, m/e (rel intensity), 186.2 (0.1), 185.2 (0.2), 141.1 (96.9), 81.1 (36.5), 69.2 (100) and 41.1 (41.0); CI (isobutane), m/e (rel intensity), 186.0 (12.48), 185.0 (100), 151.0 (20.8), 95.0 (16.64).

Ethyl [(4,8-Dimethyl-3(*E*),7-nonadienyl)thio]acetate (20). Method 1. To a Schlenk tube, connected via a two-way stopcock to an argon inlet and a vacuum line, was added **22** (4.05 g, 22 mmol) in 20 mL of ether/hexane (1/1). To this stirred solution was added thallium(I) ethoxide (5 g, 20 mmol) via a syringe. Immediate yellow coloration was observed. The reaction was stirred for 5 min and then the solvent was removed under vacuum. The oily residue was washed with ether (2 × 10 mL), the solvent was removed under vacuum, and the residue was redissolved in 50 mL of anhydrous ether. Ethyl bromoacetate (3.32 g, 20 mmol) was added dropwise, whereupon a white precipitate of thallous bromide was formed. After 1 h at room temperature the suspension was filtered through Celite. The solvent was removed to give a crude product, which was purified by flash chromatography using hexane/dichloromethane (2/1) to give **20** as a single product, 5.3 g (97%): GC purity (96%); IR (film) 2980, 2960, 1735, 1450, 1380, 1275, 1130, 1030 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, OCH_2CH_3, J = 6.7 Hz), 1.59 (s, 6 H, vinyl methyl), 1.66 (s, 3 H, vinyl methyl), 1.96–2.1 (m, 4 H, CH_2), 2.3 (q, 2 H, C_2-CH_2, J = 7.1 Hz), 2.61 (t, 2 H, C_1-CH_2, J = 7.1 Hz), 3.25 (s, 2 H, SCH_2CO), 4.2 (q, 2 H, OCH_2CH_3, J = 6.6 Hz), 5.06–5.16 (m, 2 H, C_3, C_7-vinyl H); MS, m/e (rel intensity), 272 (2.0), 270.6 (10.0), 201 (30), 183 (9.0), 150 (22), 107 (29), 81 (58.5), 69 (100), and 41 (41.5). Anal. Calcd for $C_{15}H_{26}O_2S$: C, 66.66; H, 9.63. Found: C, 66.46 H, 9.90.

Method 2. LDA in 5 mL of THF [(2 mmol, prepared from diisopropylamine (0.277 mL, 2 mmol) and *n*-butyllithium (0.8 mL, 2 mmol at −78 °C)] was added to a mixture of ethyl acetate (0.2 mL, 2 mmol) and CuI (0.76 g, 4 mmol) in 10 mL of THF at −110 °C. The mixture was stirred for 2.5 h until the temperature reached −30 °C. Sulfonate **19a** (0.338 g, 1 mmol) in THF (5 mL) was added to the above mixture at −30 °C. The reaction mixture was warmed to 5 °C over a period of 1.5 h, at which point it was quenched with aqueous NH_4Cl and extracted with ether (5 × 20 mL). The combined etheral solution was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvent was removed to yield the product. Flash column chromatography using *n*-hexane/ethyl acetate (19/1) as eluent gave **20** (0.13 g, 48%).

1-Bromo-3,7,11-trimethyl-2(*E*),6(*E*),10-dodecatriene (23) was prepared by the method of Osbond.[13a] Alternatively, it can now be purchased from Aldrich Chemical Co.

Ethyl 2-(4′,8′-Dimethyl-3′(*E*),7′-nonadienyl)thio]-5,9,13-trimethyl-4(*E*),8(*E*),12-tetradecatrienoate (24). To diisopropylamine (0.8 mL, 5 mmol) in 20 mL of THF was added *n*-BuLi (2 mL, 5 mmol) dropwise at −10 °C. After 20 min the reaction was cooled to −78 °C, and **20** (0.8 g, 3 mmol) in 5 mL of THF was added. After 1 h farnesyl bromide (1.5 mL, 5 mmol) was added and the resulting mixture was warmed to room temperature over a period of 3.5 h, whereupon it was quenched with ice-cold aqueous NH_4Cl. The aqueous solution was extracted with ether (5 × 30 mL). The organic phase was washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give a crude product. Flash column chromatography using *n*-hexane/ethyl acetate (19/1) gave 1.1 g (77.5%) of **24**: IR (film), 2930, 1735, 1450, 1380, 1150, 1110 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H, $COOCH_2CH_3$, J = 7.1 Hz), 1.59 (s, 15 H, vinyl methyl), 1.67 (s, 6 H, vinyl methyl), 1.91–2.1 (m, 12 H, $C_{5'}$, $C_{6'}$, C_6, C_7, C_{10}, C_{11}-CH_2), 2.2–2.3 (m, 2 H, C_2-CH_2), 2.32–2.39 (dt, 1 H, C_3-CH_b, J = 15, 6.5 Hz), 2.53–2.66 (m, 3 H, C_3-CH_a, SCH_2), 3.23–3.27 (dd, 1 H, -SCH-, J = 9, 6.5 Hz), 4.14–4.21 (m, 2 H, OCH_2CH_3), 5.06–5.13 (m, 5 H, $C_{3'}$, $C_{7'}$, C_4, C_8, C_{12} vinyl H); MS, m/e (rel intensity), 474 (0.6), 405 (4.8), 183 (3), 95 (14.8), 81 (25.9), 69 (100), 41 (57). Anal. Calcd for $C_{30}H_{50}O_2S$: C, 75.90; H, 10.55. Found: C, 75.64; H, 10.74.

2-[(4′,8′-Dimethyl-3(*E*),7′-nonadienyl)thio]-5,9,13-trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-ol (25). To a suspension of $LiAlH_4$ (0.056 g, 1.4 mmol) in 5 mL of ether was added thioacetate **24** (0.48 g, 1 mmol) at 0 °C. After 1 h the mixture was quenched by careful addition of ice-cold 1 N HCl. The salts were removed by filtration through Celite, the filtrate was washed with brine (2 × 30 mL) and dried ($MgSO_4$), and the solvents were removed to afford the crude product. Purication by flash column chromatography using *n*-hexane/ethyl acetate (9/1) gave 0.38 g (88%) of **25**: IR (film), 3440, 2920, 2860, 1450, 1380, 1030 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59–1.62 (3 s, 15 H, vinyl methyl), 1.67 (s, 6 H, vinyl methyl), 1.95–2.1 (m, 12 H, $C_{5'}$, $C_{6'}$, C_6, C_7, C_{10}, C_{11}-CH_2), 2.22–2.31 (m, 4 H, $C_{2'}$, C_3-CH_2), 2.48–2.57 (m, 2 H, SCH_2), 2.75–2.81 (m, 1 H, -SCH-), 3.44–3.50 (ddd, 1 H, HCH_aOH, J = 10.65, 6.5, 5.5 Hz), 3.63–3.69 (ddd, 1 H, HCH_bOH, J = 10.65, 7, 4.5 Hz), 5.06–5.24 (m, 5 H, vinyl H); MS, m/e (rel intensity) 432 (6.5), 363 (80.54), 213 (6.5), 183 (4.4), 81 (15.2), 69 (100), and 41 (17.4). Anal. Calcd for $C_{28}H_{48}OS$: C, 77.78; H, 11.11. Found: C, 77.53; H, 11.36.

Synthesis of 15. Iodomethane (0.02 mL, 0.092 mmol) was added to alcohol **25** (0.04 g, 0.092 mmol) in a solution of CH_3CN (1 mL) and THF (0.2 mL). The mixture was stored at room temperature for a week in the dark. Solvents were removed in vacuo and the paste was washed with pentane (5 × 20 mL) to provide 0.05 g (96%) of **15**: ^1H NMR ($CDCl_3$) δ 1.55–1.63 (s, 15 H, vinyl methyl), 1.68 (s, 6 H, vinyl methyl), 2.02–2.13 (m, 12 H, methylene), 2.49–2.69 (m, 4 H, $C_{2'}$, C_3-CH_2), 3.15 (s, SCH_3 of one diastereoisomer), 3.17 (s, SCH_3 of other diastereoisomer), 3.55–3.62 (dt, SCH_2 of one diastereoisomer, J = 13, 7.5 Hz), 3.77 (t, SCH_2 of other diastereoisomer, J = 6 Hz), 3.81–3.89 (dt, SCH_2 of one diastereoisomer, J = 13, 6.5 Hz), 3.98–4.08 (ddd, OCH_2 of a diastereoisomer, J = 13, 6.5, 6 Hz), 4.24–4.37 (m, OCH_2, methine of both diastereoisomers), 5.02–5.18 (m, 5 H, vinyl H); MS, FAB (Xenon/thioglycerol) m/e 447 (M^+, 100).

5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-yne (26). A stream of dry acetylene was bubbled through 50 mL of THF for 2 min at −50 °C. *n*-BuLi (2.56 mL, 6.4 mmol) was added dropwise at −78 °C. After 30 min CuCN (0.286 g, 3.2 mmol) was added in one portion. The tan suspension was stirred for 30 min at −78 °C followed by 1 h at 0 °C. After recooling the bath to −78 °C farnesyl bromide (**23**) (0.8 mL, 2.5 mmol) was added and the reaction was warmed to 0 °C over 3 h. Usual workup and flash column chromatography (using hexane as an eluant) gave 0.47 g (82%) of **26**: IR (film) 3290, 2950, 2910, 2840, 2100, 1660, 1440, 1370, 1100, 920 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 6 H, vinyl methyl), 1.62 (s, 3 H, vinyl methyl), 1.67 (s, 3 H, vinyl methyl), 1.95–2.10 (m, 9 H, C_6, C_7, C_{10}, C_{11}-CH_2, CH), 2.88–2.91 (m, 2 H, C_3-CH_2), 5.08–5.15 (m, 2 H, C_8, C_{12}-vinyl H), 5.17–5.2 (tq, 1 H, C_4-vinyl H, J = 1.5, 7 Hz); MS, m/e (rel intensity), 230 (3.3), 215 (20), 187 (26.6), 136 (26.6), 105 (20), 91 (33.3), 81 (46.6), 69 (100). Anal. Calcd for $C_{17}H_{26}$: C, 88.69; H, 11.30. Found: C, 88.65; H, 11.31.

4′,8′-Dimethyl-3′(*E*),7′-nonadienyl 5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-ynyl Sulfide (27a). General Method. To alkyne **26** (0.23 g, 1 mmol) in 4 mL of THF was added with stirring *n*-BuLi (0.5 mL, 1.2 mmol) at −10 °C. After 30 min **19a** (0.4 g, 1.2 mmol) was added to the reddish orange solution. The reaction was stirred for 2 h and quenched with aqueous NH_4Cl. Normal workup and flash column chromatography using hexanes/ethyl acetate (49/1) as eluant gave 0.41 g of **27a** (99% yield): IR (film) 2965.6, 2922.5, 2855.6, 2183.7, 2140, 1667.1, 1448, 1376.7, 1107.9, 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59–1.62 (3s, 15 H, vinyl methyl), 1.68 (s, 6 H, vinyl methyl), 1.97–2.12 (m,

12 H, $C_{5'}$, $C_{6'}$, C_6, C_7, C_{10}, C_{11}-CH_2), 2.45 (q, 2 H, C_2-CH_2, J = 7.1 Hz), 2.67 (t, 2 H, C_1-CH_2, J = 7.1 Hz), 3.01 (d, 1 H, C_3-CH_2, J = 7.1 Hz), 5.08-5.2 (m, 5 H, vinyl H); MS, m/e (rel intensity) 412 (5.0), 373 (7.5), 344 (12.5), 333 (15), 303 (27.5), 275 (25), 259 (20), 207 (30), 183 (70), 165 (45), 135 (15), 109 (20), 81 (52.5), 69 (100). Anal. Calcd for $C_{28}H_{44}S$: C, 81.55; H, 10.67. Found: C, 81.57; H, 10.61.

Hexyl 5,9,13-Trimethyl-4(*E*),8(*E*),12-tetradecatrien-1-ynyl Sulfide (27b). The title compound was obtained in 96% yield: IR (film) 2927.6, 2856.4, 2361.3, 2184, 1669.4, 1452.1, 11378.2, 1284, 834.4 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.5 Hz), 1.22-1.45 (m, 6 H, C_2, C_3, C_4, C_5-CH_2), 1.54 (s, 6 H, vinyl methyl), 1.59 (s, 3 H, vinyl methyl), 1.68 (s, 3 H, vinyl methyl), 1.95-2.12 (m, 8 H, $C_{6'}$, $C_{7'}$, $C_{10'}$, $C_{11'}$-CH_2), 2.66 (t, 2 H, -SCH_2, J = 6.5 Hz), 3.0 (d, 2 H, C_3-CH_2, J = 6.5 Hz), 5.04-5.21 (m, 2 H, vinyl H), 5.19 (t, 1 H, C_4-CH, J = 6.5 Hz); MS, m/e (rel intensity) 346 (2.3), 331 (4.7), 261 (38), 159 (30.9), 125 ((28.5), 105 (4.5), 91 (38), 81 (35.7), 69 (100); HRMS m/e calcd 346.2694, found 346.2703.

4',8'-Dimethyl-3'(*E*),7-nonadienyl 5,9,13-Trimethyl-1(*E*/*Z*),4(*E*),8(*E*),12-tetradecatraienyl Sulfides (28a,b). General Method. To a suspension of $LiAlH_4$ (0.08 g, 2 mmol) in 2 mL of dry THF was added **27a** (0.41 g, 1 mmol) in 3 mL of THF. The reaction was heated for 3 h at 40 °C to 60 °C and then cooled to 0 °C. Excess hydride was destroyed by careful addition of 1 N HCl. The aqueous solution was diluted with brine and extracted with ether (6 × 30 mL). The combined etheral solution was washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to give a crude product. Flash column chromatography using n-hexane gave 0.23 g (56%) of **28a,b**: IR (film) 2965.4, 2918, 2854.6, 2358.6, 1666.3, 1605.7, 1440.4, 1376.4, 1278.7, 1107.7, 834.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (s, 15 H, vinyl methyl), 1.67 (s, 6 H, vinyl methyl), 1.97-2.07 (m, 12 H, $C_{5'}$, $C_{6'}$, C_6, C_7, C_{10}, C_{11}-CH_2), 2.3-2.33 (m, 2 H, C_2-CH_2), 2.61-2.67 (m, 2 H, C_1-CH_2), 2.77 (t, 2 H_{trans}, C_3-CH_2, J = 6.8 Hz), 2.82 (t, 2 H_{cis}, C_3-CH_2, J = 6.8 Hz), 5.08-5.15 (m, 5 H, vinyl H), 5.48-5.54 (dt, 1 H_{cis}, C_2-vinyl H, J = 9.5, 7 Hz), 5.56-5.63 (dt, 1 H_{trans}, vinyl H, J = 15, 7 Hz), 5.92 (dt, 1 H_{trans}, C_1-vinyl H, J = 15, 1.5 Hz), 55.923 (dt, 1 H_{cis}, C_1-vinyl H, J = 9.5 1.5 Hz); MS, m/e (rel intensity) 414 (38.7), 345 (51.6), 277 (25.8), 263 (22.5), 205 (25.8), 135 (22.5), 109 (38.7), 81 (19.3), 69 (100). Anal. Calcd for $C_{28}H_{46}S$: C, 81.15; H, 11.11. Found: C, 81.17; H, 11.21.

Hexyl 5,9,13-Trimethyl-1(*E*/*Z*),4(*E*),8(*E*),12-tetradecatraienyl Sulfides (28c,d). The title compounds were obtained in 54% yield: IR (film) 2940, 2900, 2840, 1660, 1600, 1435, 1370, 1100, 935, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, CH_3, J = 7 Hz), 1.22-1.41 (m, C_2, C_3, C_4, C_5-CH_2), 1.6 (s, 9 H, vinyl methyl), 1.67 (m, 3 H, vinyl methyl), 1.95-2.15 (m, 8 H, $C_{6'}$, $C_{7'}$, $C_{10'}$, $C_{11'}$-CH_2), 2.61-2.66 (m, 2 H, -SCH_2), 2.76 (t, 2 H_{trans}, $C_{3'}$-CH_2, J = 7 Hz), 2.81 (t, 2 H_{cis}, $C_{3'}$-CH_2, J = 7 Hz), 5.05-5.25 (m, 3 H, vinyl H), 5.47-5.53 (dt, 1 H_{cis}, C_2-CH, J = 9.5, 7 Hz), 5.54-5.61 (dt, 1 H_{trans}, C_2-CH, J = 15, 7 Hz), 5.90 (d, 1 H, C_1-CH, J = 9.5 Hz), 9.1 (d, 1 H, C_1-CH, J = 15 Hz); MS, m/e (rel intensity) 348 (26.6), 279 (23.3), 263 (333.3), 191 (40), 157 (26.6), 135 (20), 105 (20), 93 (100), 69 (73.3). Anal. Calcd for $C_{23}H_{40}S$: C, 79.24; H, 11.56. Found: C, 79.24; H, 11.39.

4',8'-Dimethyl-3'(*E*),7'-nonadienyl 5,9,13-Trimethyl-1(*Z*),4(*E*),8(*E*),12-tetradecatraienyl Sulfide (28b). To a suspension of LAH (0.069 g, 1.8 mmol) in 5 mL of THF was added MeOH (0.02 mL, 0.5 mmol) at room temperature. The flask was cooled to -60 °C and CuBr·Me_2S (0.309 g, 1.5 mmol) was added. After 15 min, **27a** (0.25 g, 0.6 mmol) was added followed by 2 mL of HMPA at -60 °C. The reaction mixture was warmed to room temperature over 2.5 h and quenched with aqueous NH_4Cl. The precipitate was filtered through Celite and the filtrate washed with aqueous NH_4Cl (20 mL) and brine (2 × 20 mL). After drying ($MgSO_4$) and removal solvent, the product was flash chromatographed, using hexanes/ethyl acetate (49/1), to provide **28b** in (0.2 g) 80% yield: IR (film 2965.4, 2921.6, 2854.6, 2361.2, 1696.5, 1666.1, 1605.2, 1447.2, 1376.6, 1107.6, 834.2 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59-1.65 (3s, 15 H, vinyl methyl), 1.68 (s, 6 H, vinyl methyl), 1.95-2.12 (m, 12 H, CH_2), 2.31 (q, 2 H, $C_{2'}$-CH_2, J = 7 Hz), 2.65 (t, 2 H, -SCH_2, J = 7 Hz), 2.82 (t, 2 H, C_3-CH_2, J = 7 Hz), 5.05-5.25 (m, 5 H, vinyl H), 5.48-5.55 (dt, 1 H, C_2-CH, J = 9.5, 7 Hz), 5.91-5.94 (dt, C_1-CH, J = 9.5, 1.5 Hz); MS, m/e (rel intensity) 414 (6.6), 345 (60), 277 (13.3) 263 (20), 135 (13.3), 121 (33.3), 101 (33.3), 81 (20), 69 (100). Anal. Calcd for $C_{28}H_{46}S$: C, 81.09; H, 11.18. Found: C, 79.91; H, 10.69.

Synthesis of 16a,b. General Method. Silver perchlorate (0.062 g, 0.3 mmol) was added to a solution of a mixture of **28a,b** (0.12 g, 0.289 mmol) in CH_3CN (2 mL) followed by iodomethane (0.15 mL, 0.982 mmol) at 0 °C. The mixture was stirred for 3 h at 0 to 5 °C. Silver iodide was removed by filtration and the filtrate concentrated in vacuo. The paste was washed with pentane (8 × 30 mL) to remove unreacted **28a,b** and the crude product was purified by column chromatography on Celite with CH_2Cl_2 as eluant to give 90 mg (59%) of a mixture of **16a,b**: ^1H NMR ($CDCl_3$) δ 1.75-1.9 (s, 21 H, vinyl methyl), 3.1-2.45 (m, 12 H, methylene), 2.55 (q, 2 H, $C_{2'}$-CH_2, J = 6.5 Hz), 3.05 (s, 3 H, (*Z*)-*S*-methyl), 3.07 (s, 3 H, (*E*)-*S*-methyl), 3.19-3.61 (m, 4 H, -SCH_2, C_3-CH_2), 5.1-5.83 (m, 5 H, vinyl H), 6.38 (dt, 1 H, C_1-vinyl H, J = 9, 1 Hz), 6.58 (dt, 1 H, C_1-vinyl, H, J = 15, 1.5 Hz), 6.83-6.89 (m, 1 H, C_2-H), 7.0-7.07 (dt, 1 H, C_2-H, J = 15, 5.5 Hz); MS, FAB (xenon/thioglycerol) 429 (M^+, 100).

Synthesis of 16c,d. These compounds were prepared in 90% yield: ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, methyl, J = 7 Hz), 1.15-1.55 (m, 8 H, methylene), 1.85-1.95 (s, 12 H, vinyl methyl), 2.21-2.55 (m, 8 H, methylene), 3.05 (s, 3 H, (*Z*)-*S*-CH_3), 3.06 (s, 3 H, (*E*)-*S*-CH_3), 3.26-3.54 (m, 4 H, -SCH_2, C_3-CH_2), 5.45-5.7 (m, 2 H, vinyl H), 5.82 (t, 1 H, vinyl H, J = 6 Hz), 6.36 (d, 1 H, C_1-H, J = 9 Hz), 6.51 (d, 1 H, C_1-H, J = 16 Hz), 6.87-6.91 (m, 1 H, C_2-H), 7.03-7.09 (dt, 1 H, C_2-H, J = 16, 6.7 Hz); MS, FAB (xenon/thioglycerol) 363 (M^+, 100).

Synthesis of 16b. This was obtained in 93% yield: ^1H NMR ($CDCl_3$) δ 1.75-1.95 (s, 21 H, vinyl methyl), 2.11-2.48 (m, 12 H, methylene), 2.59 (q, 2 H, $C_{2'}$-CH_2, J = 6.5 Hz), 3.05 (s, 3 H, SCH_3), 3.25-3.51 (m, 4 H, SCH_2, C_3-CH_2), 5.38-5.60 (M, 4 H, vinyl H), 5.67-5.81 (m, 1 H, vinyl H), 6.36 (d, 1 H, C_1-H, J = 9.5 Hz), 6.83-6.89 (m, 1 H, C_2-H); MS FAB (xenon/thioglycerol) 429 (M^+, 100).

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Diastereomerically Pure R_P and S_P Dinucleoside H-Phosphonates: The Stereochemical Course of Their Conversion into *P*-Methylphosphonates, Phosphorothioates, and [^{18}O] Chiral Phosphates

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The dinucleoside H-phosphonates **7a,b-14a,b** were prepared by condensation of the phosphonates **1-4**[1] with the protected nucleosides **5** or **6** using pivaloyl chloride. The P-chiral dimers formed in about equal amounts were then separated. The fast-migrating dimers exhibited ^{31}P NMR chemical shifts located upfield compared to the slow

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