at a given temperature was determined by averaging the rate constants from at least nine (typically over fifteen) injections. When the setting of the constant-temperature bath was changed, the system was allowed to equilibrate for 5-10 min before further data were collected.

**Curve Fitting and Rate Constant Extrapolation.** For all hydrides other than $HCr(CO)_3Cp$ the change in absorbance was a linear function of the extent of reaction and $k_{obs}$ was obtained by a direct exponential fit to the data. However, for $HCr(CO)_3Cp$ the change in absorbance was not a linear function of the extent of reaction (vide supra) and it was necessary to obtain $k_{obs}$ by fitting[78] eq 20 to the data. $R_0$ and $k$ were the adjustable parameters, while $K_{eq}$, $\epsilon_R$, and $\epsilon_D$ were set as constants. For all hydrides, the second-order rate constant, $k_H$, was obtained from the relation $k_H = k_{obs}/[MH]$ at each temperature. The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained from a linear fit of $\Delta G^{\ddagger}$ (calculated from the Eyring equation) versus $T$; the covariance of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ was then equal to the covariance of the intercept and slope of the fitted line. These values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were used to calculate $k_H$ at 25 °C (Table II). The standard error of $k_H$ at 25 °C was calculated from the standard errors and covariance of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

**Products from Reaction 9.** Outside the stopped-flow, solutions of each metal hydride and **1** were mixed and the organometallic products characterized by IR and UV-vis spectroscopy. For all hydrides other than $HCr(CO)_3Cp$ (where an equilibrium mixture of the monomer **3Cr** and the dimer **4Cr**[45] was formed) and $HRe(CO)_5$[42] the corresponding metal-metal dimers were the only organometallic products seen: $Mn_2(CO)_{10}$,[79] $H_2Os_2(CO)_8$,[23b] $Mn_2(CO)_8(PEtPh_2)_2$,[80] $W_2(CO)_6Cp_2$,[81] $Mo_2(CO)_6Cp_2$,[82] $Mo_2(CO)_6Cp^*_2$,[83] $Fe_2(CO)_4Cp_2$,[84] $Fe_2(CO)_4Cp^*_2$,[84] and $Ru_2(CO)_4Cp_2$.[85] For the reaction between **1** and $HMo(CO)_3Cp$, tris-(*p-tert*-butylphenyl)methane[27] and $Mo_2(CO)_6Cp_2$[82] were identified as the only products by $^1H$ NMR.

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# Solvolysis of Allylic Isoprene Phosphorothioate Esters. A Mechanistic Study of the Thiono → Thiolo Rearrangement

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**Abstract:** The reactions of *O,O*-dimethyl *O*-geranyl phosphorothionate (**1**-$OPS(OMe)_2$), *O,O*-dimethyl *S*-geranyl phosphorothiolate (**1**-$SPO(OMe)_2$), and *O,O*-dimethyl *S*-linalyl phosphorothiolate (**2**-$SPO(OMe)_2$) were studied in 65:35 TFE/water. Solvolysis of **1**-$OPS(OMe)_2$ at 20 °C gave substantial amounts of thiolo isomers **1**-$SPO(OMe)_2$ and **2**-$SPO(OMe)_2$, along with smaller quantities of solvent addition products. At 40-65 °C, rearrangement of linalyl phosphorothiolate **2**-SPO(OMe) to geranyl phosphorothiolate **1**-$SPO(OMe)_2$ and neryl phosphorothiolate **3**-$SPO(OMe)_2$ was also accompanied by solvolysis. Phosphorothiolate **1**-$SPO(OMe)_2$ reacted at 90-120 °C to give substitution products and **1**-$SPO_2(OMe)^-$, formed by hydrolysis of a methyl. The relative reactivities of **1**-$OPS(OMe)_2$, **1**-$SPO(OMe)_2$, and **2**-$SPO(OMe)_2$ are $1:(3 \times 10^{-7}):(6 \times 10^{-3})$, respectively. From a combination of kinetic and trapping experiments, we estimate that **1**-$OPS(OMe)_2$ is 11 kcal/mol less stable than its thiolo isomer. A dissociative mechanism with ion-paired intermediates is proposed for the thiono → thiolo rearrangements, and the utility of the phosphorothioate moiety as a tool for studying reactions involving ion pairs is discussed.

Phosphate esters and anhydrides fulfill a variety of biological roles in structure, binding, and reactivity that are indispensible. The mono-, di-, and triphosphate units found in numerous intermediary metabolites are excellent leaving groups, imparting the reactivity necessary for enzyme-catalyzed hydrolysis, esterification, nucleophilic displacement, condensation, fragmentation, and elimination reactions of biosynthesis and degradation.[1] At physiological pH, these moieties are negatively charged and, consequently, are relatively benign until sequestered within the catalytic site of an enzyme, where selective neutralization of negative charge can unleash their full reactivity. In contrast, the reactivities of leaving groups commonly encountered in organic chemistry, such as halides and sulfonate esters, cannot be attenuated in a comparable manner.

Substrates for enzyme-catalyzed electrophilic condensation, rearrangement, and cyclization reactions in the central part of the isoprene biosynthetic pathway are simple diphosphate esters.[2] The pathway contains numerous branch points, and at each, different enzymes transform a common substrate into a variety of products. Some prominent examples are the rearrangement of presqualene diphosphate to squalene or botryococcene[3] and the biosynthesis of numerous cyclic mono-,[4] sesqui-,[5] and diterpenes.[6] These reactions are thought to occur within enzyme-bound ion pairs consisting of the isoprene moiety of the substrate and inorganic pyrophosphate. In some cases, for example, the rearrangements of presqualene diphosphate, the precise structure of the ion pair is thought to play a critical role in the regiochemical

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outcome of the reaction.[3] In others, for example, all monoterpene and many sesquiterpene cyclizations, an allylic 1,3-rearrangement of geranyl or farnesyl diphosphate to their tertiary allylic isomers by internal return provides a low-energy pathway for isomerization of the trans C(2)–C(3) double bond before ring closure.[7-13] Direct evidence for ion pairs is difficult to obtain because the tertiary allylic intermediates are more reactive than the primary allylic substrates and are not released from the surface of the enzyme. An important exception is the isomerization of geranyl diphosphate to bornyl diphosphate, where the ultimate stable product of rearrangement and cyclization is formed by ion pair recombination.[8-10]

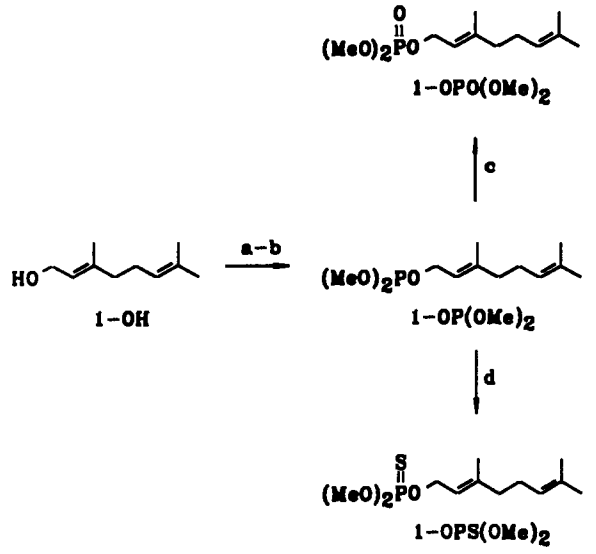
Substitution of an oxygen by sulfur perturbs both the structure and reactivity of phosphate groups. Recent NMR[14,15] and theoretical[16] studies show substantial differences in delocalization of charge for phosphate and phosphorothioate anions, with increasing localization of negative charge on sulfur as the degree of ionization increases. The sulfur atom in ambident phosphorothioates is much more nucleophilic than oxygen, and phosphorothiolates are typically the exclusive products of $S_N2$ displacements.[17,18] In addition, phosphorothionate esters undergo an O → S migration of alkyl groups. Studies of thermal[19] and acid-catalyzed[20,21] versions of this reaction indicate the thiolo (*S*-alkyl) isomers are considerably more stable than their thiono (*O*-alkyl) counterparts. Although the mechanisms are complex, depending on the nature of the migrating alkyl moiety, the environment at phosphorus, and the solvent, all of the results were explained by dissociative mechanisms with ion-paired intermediates.

The involvement of phosphate and pyrophosphate leaving groups in biological $S_N1$, $S_N2$, elimination, and fragmentation reactions presents exciting opportunities for using sulfur analogues as mechanistic probes.[22-24] In this paper, we address questions concerning the reactivity of phosphorothioate leaving groups and reactions of carbocation–phosphorothioate ion pairs in a study of $S_N1$ reactions of allylic thiono and thiolo phosphorothioates. Although the primary motivation for these studies was their biochemical applications, reactions of these compounds are of general interest, and our experiments provide a quantitative analysis of phosphorothioates as leaving groups in solvolysis reactions.

## Results and Discussion

**Synthesis of Phosphate and Phosphorothioate Esters.** It is sometimes difficult to prepare phosphate esters of allylic isoprene alcohols. The compounds are unstable when the phosphate moieties are not negatively charged, and procedures normally used for other classes of compounds commonly fail. We discovered that a simple $S_N2$ displacement of chloride or tosylate derivatives using tetrabutylammonium salts of $P_i$[25] or $PP_i$ gave excellent yields of the corresponding monoesters.[26] However, this reaction was not suitable for the synthesis of uncharged phosphate or phosphorothionate triesters for reasons mentioned above.

**Scheme I.** Synthesis of 1-OPO(OMe)$_2$ and 1-OPS(OMe)$_2$[a]




[a] Key: a, $MeOPCl_2$; b, MeOH; c, *t*-BuOOH; d, $S_8$.

Since phosphite leaving groups are less reactive than their phosphate counterparts and can be oxidized to phosphates or phosphorothionates under mild conditions,[27,28] we decided to use the approach shown in Scheme I to prepare dimethyl geranyl phosphate (1-OPO(OMe)$_2$) and *O,O*-dimethyl *O*-geranyl phosphorothionate (1-OPS(OMe)$_2$). Dimethyl geranyl phosphite (1-OP(OMe)$_2$) was synthesized by treatment of geraniol with methyl phosphorodichloridite followed by addition of methanol. The phosphite was oxidized with *tert*-butyl hydroperoxide or sulfur to yield 1-OPO(OMe)$_2$ or 1-OPS(OMe)$_2$, respectively. The triesters were reactive, but both could be purified by rapid chromatography on silica gel. The phosphite approach appears to be generally applicable for allylic alcohols. Shadid and coworkers also employed related reactions to synthesize a series of allylic phosphates,[27] and we recently used the phosphite procedure to prepare *O*-geranyl phosphorothioate,[28] which was subsequently converted to a thiodiphosphate.

*O,O*-Dimethyl *S*-geranyl phosphorothiolate (1-SPO(OMe)$_2$) was the sole regioisomer obtained when geranyl chloride was treated with the tetra-*n*-butylammonium salt of *O,O*-dimethyl phosphorothioate,[26] as anticipated for the relative differences in nucleophilicity of the oxygen and sulfur atoms.[17,18] *O,O*-Dimethyl *S*-linalyl phosphorothiolate (2-SPO(OMe)$_2$) was obtained by solvolysis of 1-OPS(OMe)$_2$ in 2,2,2-trifluoroethanol (TFE).

**Product Studies.** Upon solvolysis in 65:35 TFE/water containing 10 equiv of 2,6-lutidine, phosphorothioates 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$ each gave a complex mixture of phosphorothiolates, alcohols, and TFE ethers (see Scheme II). The monoterpene alcohols and ethers were readily identified by coinjection with authentic samples on capillary GLPC. Geraniol (1-OH), linalool (2-OH), and α-terpineol (4-OH) were available from previous mechanistic studies in our laboratory.[29,30] The

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**Scheme II.** Products from Solvolysis of 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$ in 65:35 TFE/H$_2$O

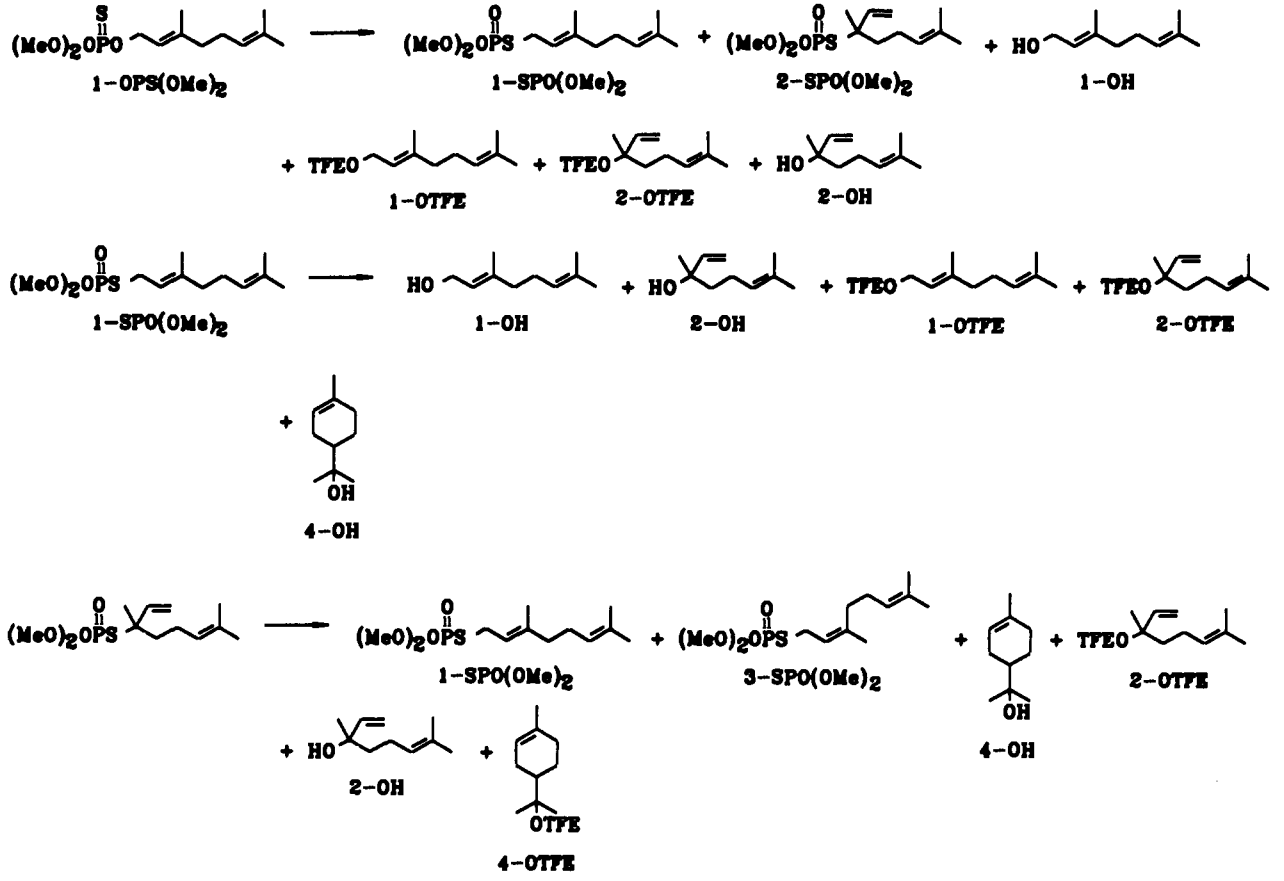



**Table I.** Products from Solvolysis of Phosphorothioates **4**–**6** in 65:35 TFE/D$_2$O[a]

| | | Phosphorothioates, % | | | | |
|---|---|---|---|---|---|---|
| reactant | *T*, °C | 1-SPO(OMe)$_2$ | 1-SPO$_2$(OMe)$^-$ | 2-SPO(OMe)$_2$ | 3-SPO(OMe)$_2$ | **5**[b] |
| 1-OPS(OMe)$_2$ | 20 | 39 | | 30 | | 31 |
| 1-SPO(OMe)$_2$ | 90 | | 76 | | | 24[c] |
| | 105 | | 67 | | | 33[c] |
| | 120 | | 61 | | | 39[c] |
| 2-SPO(OMe)$_2$ | 40 | 16 | | | 16 | 68 |
| | 50 | 20 | | | 14 | 66 |
| | 65 | 21 | | | 17 | 62 |

| | | Alcohols, %[d] | | |
|---|---|---|---|---|
| reactant | *T*, °C | 1-OH | 2-OH | 4-OH |
| 1-OPS(OMe)$_2$ | 20 | 3 | 19 | |
| 1-SPO(OMe)$_2$ | 90 | 4 | 15 | 2 |
| | 105 | 5 | 21 | 3 |
| | 120 | 7 | 24 | 3 |
| 2-SPO(OMe)$_2$ | 40 | | 18 | 33 |
| | 50 | | 18 | 32 |
| | 65 | | 17 | 31 |

| | | TFE Ethers, %[d] | | |
|---|---|---|---|---|
| reactant | *T*, °C | 1-OTFE | 2-OTFE | 4-OTFE |
| 1-OPS(OMe)$_2$ | 20 | 2 | 7 | |
| 1-SPO(OMe)$_2$ | 90 | 1 | 2 | |
| | 105 | 1 | 3 | |
| | 120 | 2 | 3 | |
| 2-SPO(OMe)$_2$ | 40 | | 3 | 14 |
| | 50 | | 3 | 13 |
| | 65 | | 2 | 12 |

[a] Limits of detection, 1%. [b] 2,6-Lutidinium salt. [c] Sum of **5**–**7**. [d] Percentages of sum of alcohols and TFE ethers normalized to the fraction of **5** in phosphorus-containing products. Less than 1% of 3-OH and 3-OTFE was seen.

corresponding TFE ethers were obtained by solvolysis of geranyl chloride in TFE. The distribution of phosphorus-containing products was determined by analyzing reaction mixtures by $^{31}$P NMR (see Table I). The resonance for phosphorothionate 1-OPS(OMe)$_2$ at 72.3 ppm was far removed from other peaks. $^{31}$P peaks for phosphorothiolates were also well-resolved at 30.7 ppm for 1-SPO(OMe)$_2$, 23.5 ppm for 1-SPO$_2$(OMe)$^-$, 26.5 ppm for

(30) Poulter, C. D.; King, C. H. R. *J. Am. Chem. Soc.* **1982**, *104*, 1422–1424.

2-SPO(OMe)$_2$, and 28.0 ppm for 3-SPO(OMe)$_2$, as were *O,O*-dimethyl phosphorothioate (**5**) at 60.5 ppm, *O,O,S*-trimethyl phosphorothiolate (**6**) at 31.0 ppm, and *O,S*-dimethyl phosphorothiolate (**7**) at 24.5 ppm.[31]

The products from solvent addition to 1-OPS(OMe)$_2$ and 1-SPO(OMe)$_2$ are typical of those reported for solvolysis of other geranyl derivatives.[29,30,32,33] The predominance of linalyl derivatives 2-OH and 2-OTFE over geranyl products 1-OH and 1-OTFE reflects the preference for addition of solvent to the more substituted carbon of the allylic geranyl cation. However, substitution only accounts for 31% of the products from 1-OPS(OMe)$_2$. The major products are thiolo isomers 1-SPO(OMe)$_2$ and 2-SPO(OMe)$_2$. Formation of linalyl phosphorothiolate 2-SPO(OMe)$_2$ demonstrates that the thiono → thiolo rearrangement is also accompanied by allylic 1,3-rearrangement. The simplest mechanism to account for these observations is formation of a geranyl cation–thiophosphate ion pair with internal return to sulfur. Bruzik and Stec proposed a similar ion pair mechanism for the acid-catalyzed thiono → thiolo rearrangement of 2-butenyl phosphorothionates, where they found allylic rearrangement, racemization, and solvolysis concomitant with O → S migration of the 2-butenyl moiety.[21]

In addition to geranyl and linalyl derivatives, *S*-geranyl phosphorothioate 1-SPO(OMe)$_2$ gave small amounts of α-terpineol (4-OH) and the corresponding ether 4-OTFE. These products cannot arise directly from a geranyl cation because its trans C(2)–C(3) double bond would generate a highly strained cyclic structure. It is commonly assumed that the α-terpinyl products detected during solvolysis of geranyl derivatives are formed from transient linalyl intermediates produced by an allylic 1,3-rearrangement of the leaving group.[29,30,32,33] Rotation about the C(2)–C(3) single bond in the linalyl system to an s-cis conformer then affords a low-energy pathway for isomerization prior to cyclization. Our results strongly support this mechanism. No α-terpinyl products were seen upon solvolysis of the thiono geranyl isomer 1-OPS(OMe)$_2$, where internal return gave almost exclusively phosphorothiolates 1-SPO(OMe)$_2$ and 2-SPO(OMe)$_2$ (see below), both of which did not react further at 20 °C. However, the thiolo isomer 1-SPO(OMe)$_2$ was much less reactive, and temperatures required for its reaction were also sufficient to solvolyze any 2-SPO(OMe)$_2$ formed by ion pair recombination. In this case, small amounts of 4-OH and 4-OTFE were detected among the products for 1-SPO(OMe)$_2$, presumably arising from 2-SPO(OMe)$_2$ formed by internal return.

Linalyl phosphorothiolate 2-SPO(OMe)$_2$ underwent internal return to produce substantial amounts of geranyl (1-SPO(OMe)$_2$) and neryl (3-SPO(OMe)$_2$) phosphorothiolates. In contrast, the substitution products were exclusively linalyl (2-OH and 2-OTFE) or α-terpinyl (4-OH and 4-OTFE) derivatives. Since the rotational barriers in allylic cations are high with respect to those for reaction with solvent, the trans C(2)–C(3) double bond in 1-SPO(OMe)$_2$ must result from collapse of a geranyl cation–phosphorothioate ion pair (1$^+$ $^-$SPO(OMe)$_2$), as depicted in Scheme III, while the cis double bond in 3-SPO(OMe)$_2$ arises from internal return of the neryl ion pair (3$^+$ $^-$SPO(OMe)$_2$). In addition, formation of α-terpinyl products 4-OH and 4-OTFE places an additional constraint on 3$^+$ $^-$SPO(OMe)$_2$, since the C(6)–C(7) double bond must be in a conformation suitable for cyclization.[34] In this regard, it is interesting to note that α-terpinyl products from internal return were not detected. The least hindered "anti" conformation of 2-SPO(OMe)$_2$, which leads directly to the α-terpinyl skeleton,[29,35] places the phosphorothioate and the C-

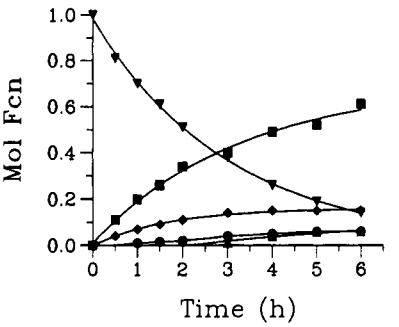
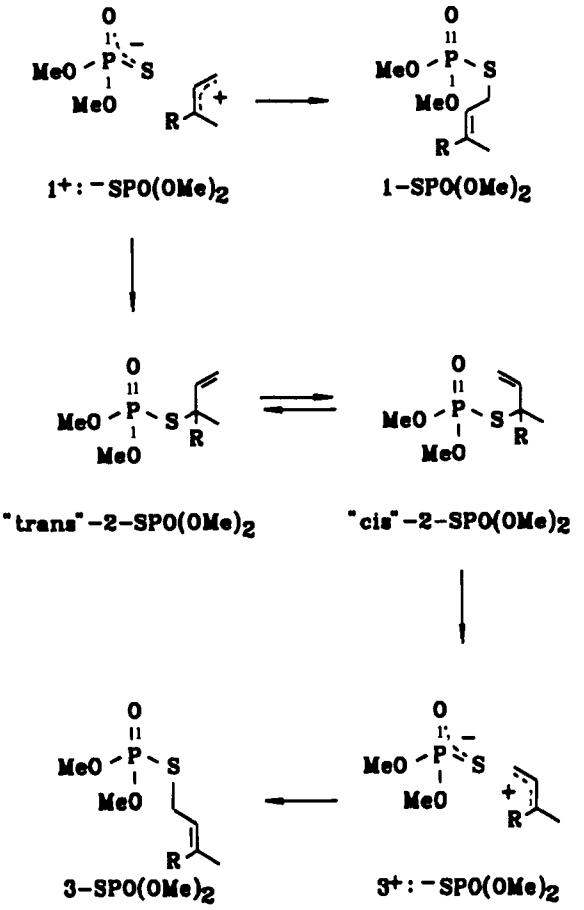
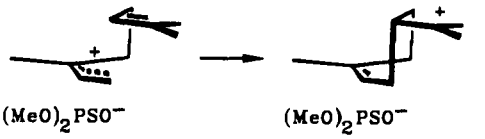



**Figure 1.** Time course for reaction of 1-SPO(OMe)$_2$ in 65:35 TFE/$H_2O$ at 105 °C: ▼, 1-SPO(OMe)$_2$; ■, 1-SPO$_2$(OMe)$^-$; ◆, 5; ●, 6; ▲, 7.

**Scheme III.** Mechanism for Formation of 1-SPO(OMe)$_2$ and 3-SPO(OMe)$_2$ from 2-SPO(OMe)$_2$




(7)–C(8) double bond on opposite faces of the allylic moiety and requires separation of charge upon formation of the cationic center at C(7) during cyclization. Our results suggest that cyclization




and reaction with solvent are faster than reorientation of the phosphorothioate ion pair to a structure that allows internal return to C(7). In contrast, Winstein et al.[32] reported that solvolysis of linalyl *p*-nitrobenzoate (2-OPNB) in 70% aqueous acetone at 50 °C gave 7% rearrangement to 4-OPNB. Whether the differences seen for phosphorothioate and *p*-nitrobenzoate leaving groups result from different lifetimes or different conformations of the ion pairs cannot be answered at this time.

Thiolo geranyl isomer 1-SPO(OMe)$_2$ is considerably less reactive than 1-OPS(OMe)$_2$. Although the thioester bond is sus-

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(34) We cannot distinguish between mechanisms involving two conformers of 3$^+$ $^-$SPO(OMe)$_2$, one that cyclizes to yield 4-OH and 4-OTFE and another that gives 3-SPO(OMe)$_2$, or a single conformer that collapses to all three. With regard to the latter possibility, we have presented evidence of discrete neryl and α-terpinyl cations during the solvolysis/cyclization of neryl derivatives.[29,30]
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**Table II.** Kinetics Constants for Solvolysis[a] of 1-OPO(OMe)$_2$, 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$

| reactant | $T$, °C | $k$, s$^{-1}$ | $k_{rel}$ |
|---|---|---|---|
| 1-OPO(OMe)$_2$[b] | 20 | $9.2 \pm 0.02 \times 10^{-4}$ | 0.8 |
| 1-OPS(OMe)$_2$[b] | 20 | $1.1 \pm 0.05 \times 10^{-3}$ | 1 |
| 1-SPO(OMe)$_2$ | 20 | $3.2 \times 10^{-10}$[c] | $3 \times 10^{-7}$ |
| | 90 | $6.0 \pm 0.5 \times 10^{-6}$ | |
| | 105 | $3.1 \pm 0.4 \times 10^{-5}$ | |
| | 120 | $1.4 \pm 0.2 \times 10^{-4}$ | |
| 2-SPO(OMe)$_2$[b] | 20 | $6.1 \times 10^{-6}$[d] | $6 \times 10^{-3}$ |
| | 40 | $9.9 \pm 0.01 \times 10^{-5}$ | |
| | 50 | $3.2 \pm 0.2 \times 10^{-4}$ | |
| | 65 | $1.6 \pm 0.2 \times 10^{-3}$ | |

[a] 65:35 (v/v) TFE/$D_2O$ containing 40 mM 2,6-lutidine. [b] With 70 mM 4-amino-2,2,6,6-tetramethylpiperidinooxy. [c] Extrapolated from higher temperatures; $\Delta H^{\ddagger} = 29 \pm 2$ kcal/mol, $\Delta S^{\ddagger} = 2 \pm 6$ eu. [d] Extrapolated from higher temperatures; $\Delta H^{\ddagger} = 24 \pm 1$ kcal/mol, $\Delta S^{\ddagger} = 0.3 \pm 4$ eu. Maximum errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated according to Wiberg: Wiberg, K. B. *Physical Organic Chemistry*; John Wiley & Sons: New York, 1964; pp 377–379.

ceptible to solvolysis, as indicated by formation of monoterpene alcohols and ethers, the major product was 1-SPO$_2$(OMe)$^-$, generated by hydrolysis of a methyl group. The time course for reaction of 1-SPO(OMe)$_2$ at 105 °C was followed by $^{31}$P NMR, and the results are summarized in Figure 1. The initial phosphorus-containing products were **5**, from solvolytic cleavage of the *S*-geranyl bond, and *O*-methyl *S*-geranyl phosphorothiolate 1-SPO$_2$(OMe)$^-$. Subsequently, triester 1-SPO(OMe)$_2$ and diester **5** disproportionated to generate **6** and additional 1-SPO$_2$(OMe)$^-$. Finally, **6** disproportionated or hydrolyzed to give **7**. Similar disproportionations have been reported by Chabrier et al. in acetonitrile at 100 °C.[36]

**Kinetic Measurements.** First-order rate constants for solvolysis of phosphate 1-OPO(OMe)$_2$ and phosphorothioates 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$ were measured in TFE/$D_2O$ by monitoring the decrease in intensities of $^{31}$P signals for the reactants relative to the intensity for the $^{31}$P resonance of a benzene solution of trimethyl phosphate in a coaxial tube. $T_1$ values for the $^{31}$P resonances in 1-OPO(OMe)$_2$, 1-OPS(OMe)$_2$, and 2-SPO(OMe)$_2$ were reduced to less than 1 s by including 4-amino-2,2,6,6-tetramethylpiperidinooxy, a hindered nitroxide radical,[37] in the samples. This permitted us to acquire FID's rapidly without saturating the $^{31}$P signals.

Although the rates of disappearance of 1-OPO(OMe)$_2$, 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$), and 2-SPO(OMe)$_2$ all followed first-order kinetics, as noted above, product studies indicated two competing pathways for 1-SPO(OMe)$_2$. A decrease in the intensity of the $^{31}$P resonance at 34.3 ppm was accompanied by appearance of signals at 59.0 ppm for *O,O*-dimethyl phosphorothioate (**5**) and at 23.3 ppm for *S*-geranyl *O*-methyl phosphorothioate 1-SPO(OMe)$^-$. At low conversions, **5** and 1-SPO$_2$(OMe)$^-$ were the principle $^{31}$P-containing products. At longer reaction times, 1-SPO(OMe)$_2$ and **5** disproportionated to 1-SPO$_2$(OMe)$^-$ and **6**, and **6** then hydrolyzed to **7**. The disproportionation reaction is a second-order process that did not contribute substantially to formation of 1-SPO$_2$(OMe)$^-$ during the first half-life of the reaction. Even at 90% completion, **6** and **7** comprised less than 10% of the products from 1-SPO(OMe)$_2$. Thus, the rate constant for solvolysis of the thiogeranyl bond in 1-SPO(OMe)$_2$ ($k_s$) is given by eq 1 during the early stages of the reaction, where $k_{obs}$ and $k_H$ are rate constants for disappearance and hydrolysis, respectively. Our kinetic data are summarized in Table II.

$$k_s = k_{obs} - k_H \quad (1)$$

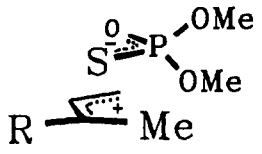
The most striking observation is the substantial difference in the reactivities of the thiono and thiolo esters. In contrast, the first-order rate constants for dimethyl geranyl phosphate (1-OPO(OMe)$_2$) and 1-OPS(OMe)$_2$ are almost identical. Enthalpies and entropies of activation were calculated for 1-SPO(OMe)$_2$ and 2-SPO(OMe)$_2$ from kinetic data taken at elevated temperatures and used to estimate rate constants for both isomers at 20 °C. A comparison between 1-OPS(OMe)$_2$ and 1-SPO(OMe)$_2$ indicates that the *O*-geranyl phosphorothionate is approximately 3-million-fold more reactive than its *S*-geranyl isomer. Thus, the ambident thiophosphate moiety is an excellent leaving group for detecting ion pair recombination. Not only is internal return to sulfur highly favored over oxygen, the phosphorothiolates formed by this reaction are much less reactive than their thiono counterparts. Even the tertiary *S*-linalyl isomer is 160 times less reactive than 1-OPS(OMe)$_2$. If the 20000-fold difference in reactivity between 1-SPO(OMe)$_2$ and 2-SPO(OMe)$_2$ is indicative of the relative reactivities of the primary and tertiary allylic systems bearing other phosphate leaving groups, it clearly would not be possible to directly detect internal return to C(3) of the allylic cation upon solvolysis of geranyl phosphate or diphosphate[33] without resorting to a leaving group that generates an ambident nucleophile such as **5**.

**Trapping Experiments.** The thiono → thiolo rearrangement of 1-OPS(OMe)$_2$, accompanied by allylic 1,3-rearrangement under neutral solvolytic conditions, suggests an ion pair mechanism for both reactions. We could not directly measure competition between oxygen and sulfur during internal return because recombination to oxygen at C(1) regenerated starting material and recombination at C(3) gave a transient product that was considerably more reactive than starting material. We were, however, able to detect ion pair return to oxygen via external return in a trapping experiment. A solution of geranyl tosylate (1-OTs) in 65:35 TFE/water containing 250 mM **5** was shaken at 20 °C for 1 min and immediately extracted with 1:1 pentane/ether. A $^{31}$P NMR spectrum of the extract had resonances for 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$, along with a small amount of **5**. The three triesters were formed in a relative ratio of 1:50:5.

Typically, solvolysis of geranyl derivatives gives a larger proportion of linalyl than geranyl products, as reflected in the relative ratios of tertiary and primary allylic alcohols and TFE ethers formed from 1-OPS(OMe)$_2$. The product distribution is thought to reflect the relative charge densities at the primary and tertiary centers in the allylic cation. In contrast, the trapping experiment gave mostly 1-SPO(OMe)$_2$. It is unlikely that the low proportion of 2-SPO(OMe)$_2$ is due to its instability to the trapping conditions. During our product studies, we found that 2-SPO(OMe)$_2$ gave substantial amounts of neryl phosphorothioate 3-SPO(OMe)$_2$. This compound is stable during trapping and was not detected among the phosphorothioate products. We conclude that the change in product ratios to favor the primary isomer reflects increased steric interactions during ion pair return for the rather bulky *O,O*-dimethyl phosphorothioate moiety.

It is interesting to note that the relative ratios of 1-SPO(OMe)$_2$:2-SPO(OMe)$_2$ increased from 1.3:1 for internal return from the ion pair generated from 1-OPS(OMe)$_2$ to 10:1 for external return in the trapping experiment. We suggest that the different product ratios reflect different structures for the ion pairs, which collapse to covalent products. In an elegant set of stereochemical experiments, Rotto and Coates found evidence for an enhanced rate of solvolysis for a rigid tethered allylic phosphate locked in a conformation that positioned the *P*-oxide moiety over the carbon–carbon double bond.[38] Preferential solvolysis of 1-OPS(OMe)$_2$ from a similar conformation places the thiono sulfur over C(3). This orientation takes advantage of the simultaneous development of positive charge in the allylic fragment and negative charge in the thiophosphate moiety to maximize charge–charge interactions during approach to the transition state. As a consequence, sulfur is positioned to recombine with C(3) as shown below for $1^+$ $^-$OPS(OMe)$_2$. The large proportion of 2-SPO(OMe)$_2$ seen during solvolysis of 1-OPS(OMe)$_2$ may well reflect successful competition of this conformation during internal return. It follows that the predominant structure of the ion pair

(36) Chabrier, P. M.; Thanh, T. N.; Chabrier, J. P. *C. R. Acad. Sci.* **1966**, *263C*, 1168–1169.
(37) Stanislawski, D. A.; Van Wazer, J. R. *Anal. Chem.* **1980**, *52*, 96–101.
(38) Rotto, N. T.; Coates, R. M. *J. Am. Chem. Soc.* **1989**, *111*, 8941–8943.



generated by external return, which then collapses to phosphorothiolate products, is different from that generated directly from 1-OPS(OMe)$_2$.[39]

**Free Energy Diagrams for 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$.** The free energy diagram shown in Figure 2 was constructed from kinetic data and trapping experiments at 20 °C in 65:35 TFE/water. Free energies of activation were calculated from rate constants at 20 °C with use of the Eyring equation. Although the relative free energies of the ion pairs involved in the thiono → thiolo rearrangements cannot be determined, it is possible to estimate *differences* in the transition states leading from $1^+$-SPO(OMe)$_2$ to 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$ from the product distributions of trapping experiments.[40] Where three pseudo-first-order reactions compete for a single species to form products A, B, and C

$$d[A]/d[B] = k_A/k_B \qquad d[A]/d[C] = k_A/k_C \tag{2}$$

and the differences in activation barriers leading to A and B ($\Delta\Delta G_{AB}^{\ddagger}$) or A and C ($\Delta\Delta G_{AC}^{\ddagger}$) are

$$\Delta\Delta G_{AB}^{\ddagger} = -RT \ln ([A]/[B])$$
$$\Delta\Delta G_{AC}^{\ddagger} = -RT \ln ([A]/[C]) \tag{3}$$

The [A]/[B] and [A]/[C] ratios are easily calculated from product distributions.

From the data summarized in Figure 2, we estimate thiono 1-OPS(OMe)$_2$ is 11 kcal/mol less stable than thiolo isomer 1-SPO(OMe)$_2$. Although accurate dissociation energies are not available for all of the bonding pairs that change during the thiono → thiolo rearrangement, it is safe to assume that the major driving force for the reaction is the formation of a stable phosphoryl bond. Comparisons of combustion data for triethyl phosphate and triethyl phosphorothionate indicate that P=O is ~60 kcal/mol more stable than P=S.[41] This difference is not canceled by concomitant PO → PS (~30 kcal/mol less stable) and CO → CS (~20 kcal/mol less stable) rearrangements.[42,43] Since the transition state leading to 1-SPO(OMe)$_2$ is only 2.2 kcal/mol below that for 1-OPS(OMe)$_2$, the difference in ground-state energies between the thiolo and thiono isomers is principally responsible for their 3.3-million-fold difference in reactivities.

Tertiary phosphorothiolate 2-SPO(OMe)$_2$ is 7 kcal/mol less stable than 1-SPO(OMe)$_2$, and again differences in ground-state energies are responsible for the 20000-fold difference in the relative reactivities of the allylic isomers. In contrast, the corresponding tertiary *p*-nitrobenzoate (2-OPNB) is only 64-fold more reactive than 1-OPNB.[32] We suggest that the large difference between 1-SPO(OMe)$_2$ and 2-SPO(OMe)$_2$ is mostly due to steric interactions between the primary and tertiary hydrocarbon chains and the bulky dimethyl phosphorothioate moiety. As discussed previously, there appears to be a small steric contribution at the transition states that inverts the regioselectivity normally observed for nucleophilic substitution at the primary and tertiary carbons in the geranyl cation. These interactions should be magnified in the covalent primary and tertiary thiolo isomers.

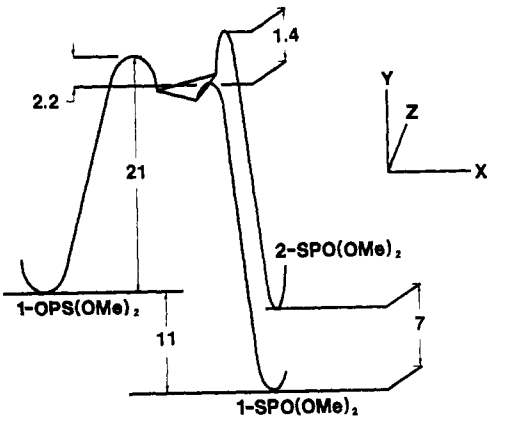
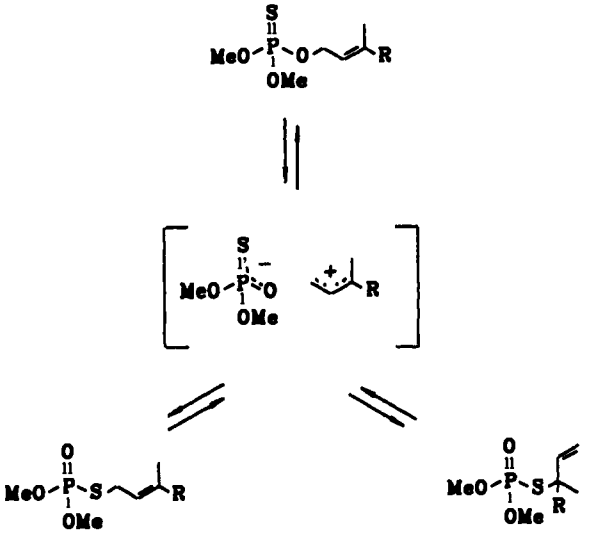



**Figure 2.** Free energy diagram for 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$.

**Scheme IV.** Mechanism for Thiono → Thiolo Rearrangement



## Conclusions

The phosphorothioate leaving group is an excellent tool for studying ion pairs. It is particularly useful in cases where rearrangement of the carbon skeleton accompanies ion pair return to generate a species more reactive than the original substrate, as illustrated by the isomerization of 1-OPS(OMe)$_2$ to 2-SPO(OMe)$_2$ (see Scheme IV). With other leaving groups, the products of simultaneous internal return and primary → tertiary allylic isomerization cannot be detected because they are unstable to the reaction conditions, which then leads to uncertainties in the origin of the stable products. The much higher reactivity of sulfur in the ambident phosphorothioate nucleophile and the stability of the thiolo isomers toward subsequent solvolysis allowed us to detect internal return to the linalyl isomer and unambiguously identify substitution products arising from the geranyl substrate.

Product studies of phosphorothiolates formed by recombination of ion pairs with internally generated or externally supplied nucleophile indicate that there are at least two different arrangements of counterions within the geranyl cation–phosphorothioate ion pair. The ion pair generated from 1-OPS(OMe)$_2$ gave a much higher proportion of 2-SPO(OMe)$_2$ upon rearrangement than did the ion pair(s) formed during external return in trapping experiments. We suggest that the transition states to 1-OPS(OMe)$_2$ and 2-SPO(OMe)$_2$ are selectively lowered by charge–charge interactions for folded structures where the sulfur is near the tertiary allylic carbon, as recently proposed for allylic phosphates.[38]

(39) While we cannot rigorously exclude the possibility that the increase in the 1-SPO(OMe)$_2$:2-SPO(OMe)$_2$ ratio in the trapping experiment results from a competing $S_N2$ pathway, work with the related dimethylallyl cation indicates that there is no $S_N2$ component during the solvolysis of dimethylallyl 4-methoxybenzene sulfonate in the presence of azide. The lifetime of the dimethylallyl cation in water was estimated to be $3 \times 10^{-9}$ s. Rodriguez, C. L. Ph.D. Dissertation, University of Utah, 1990.

(40) This analysis is somewhat oversimplified because it does not take into account different orientations that might exist for the two partners of the intimate ion pair, which in turn could give different distributions of isomers from internal return. As noted above, the ratio of 1-SPO(OMe)$_2$ to 2-SPO(OMe)$_2$ varied depending on how the ion pair was generated. However, the difference in relative barrier heights for ion pair recombination by internal or external return at 20 °C was ~1 kcal/mol or less.

(41) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic Press: New York, 1970; pp 482–485.

(42) Hartley, S. B.; Holmes, W. S.; Jacques, J. K.; Mole, M. F.; McCoubrey, J. C. *Q. Rev.* **1963**, *17*, 204–223.

(43) Steudel, R. In *Chemistry of the Non-Metals English ed.*; Nachod, F. C., Zuckerman, J. J., Eds.; Gruyter: Berlin, 1977; p 130.

Procedures are now available to synthesize a variety of thiophosphates, including isoprene derivatives.[28] These compounds may prove useful for detecting ion pairs in enzyme-catalyzed reactions where positional isotope exchange experiments fail because substrates and intermediates are not released before formation of products.

## Experimental Section

**General Methods.** $^1H$ and $^{13}C$ NMR chemical shifts are referenced to TMS. $^{31}P$ NMR spectra are reported as positive values downfield from external 1 M phosphoric acid in a coaxial tube. Analytical gas chromatography was performed on a 20 m × 0.25 mm DB-5 capillary column. Preparative gas chromatography was on a 2 m × 3 mm Carbowax 20 M column. Silica gel flash chromatography was performed on 40 μM silica gel (J. T. Baker Chemical Co.). $R_f$ values are reported for TLC on silica gel 60 F-254 glass plates (American Scientific Products). Silica TLC plates were visualized by UV light and then by dipping the plate into a 10% solution of phosphomolybdic acid in ethanol followed by heating. Extracts were dried over magnesium sulfate before solvent was removed.

**Materials.** Gold Label 4-amino-2,2,6,6-tetramethylpiperidinooxy, tetrabutylammonium phosphate trihydrate, dimethyl hydrogen phosphonate, sublimed sulfur, methyl phosphorodichloridite, methyl iodide, and $D_2O$ were used without additional purification. $CH_2Cl_2$ was distilled from phosphorus pentoxide. Reagent grade hexanes were acid and base washed, passed through activated alumina, and distilled. Ethyl acetate and geraniol were distilled prior to use. Diisopropylethylamine, 2,6-lutidine, chlorotrimethylsilane, and dimethyl sulfide were distilled from $CaH_2$. Methanol was distilled from Mg and a catalytic amount of $I_2$. Diethyl ether and tetrahydrofuran (THF) were distilled from 3-Å molecular sieves and then sodium metal. TFE was distilled from activated 4-Å molecular sieves. *N*-Chlorosuccinimide and tosyl chloride were recrystallized from benzene prior to use. Hexanes, ethyl acetate, diethyl ether, $CH_2Cl_2$, methyl iodide, $PCl_3$, and THF were purchased from EM Science. $D_2O$ was purchased from Cambridge Isotope Laboratories. All other reagents were purchased from Aldrich Chemical Co.

***O,O*-Dimethyl *O*-((*E*)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphorothioate (1-OPS(OMe)$_2$).** A solution of 2.58 g of methyl phosphorodichloridite (19 mmol) in 120 mL of anhydrous diethyl ether was chilled to −35 °C in an acetonitrile/dry ice bath before 2.49 g (16 mmol) of geraniol and 5.53 g (0.43 mol) of diisopropylethylamine in 50 mL of diethyl ether were added dropwise. After 15 min, methanol (1.04 g, 0.32 mol) was added rapidly and the solution was allowed to stir for 10 min at −35 °C. The cold bath was removed, and the suspension was allowed to warm to room temperature. The sample was filtered, and ether was removed with a stream of nitrogen. The residue was dissolved in $CH_2Cl_2$, and 1.03 g of sublimed sulfur (32 mmol) was added. After 1 h, solvent was removed with a stream of nitrogen, the residue was dissolved in hexanes, and the suspension was filtered through a plug of glass wool. Solvent was removed at reduced pressure and the residue purified by flash chromatography to yield 2.05 g (46%) of a light yellow oil: $R_f$ 0.8 (hexanes); IR (neat) 2950, 2850, 1670, 1450, 1370, 1260, 1180, 1020, 880, 820 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.46 (3 H, s, H at geranyl methyl), 1.49 (3 H, s, H at geranyl methyl), 1.57 (3 H, s, H at geranyl methyl), 1.95 (4 H, br m, H at C(4) and C(5)), 3.43 (6 H, d, $J_{P,H}$ = 13.7 Hz, phosphate methyl), 4.50 (2 H, dd, $J_{H,H}$ = 7.2 Hz, $J_{P,H}$ = 10.4, H at C(1)), 5.02 (1 H, br m, H at C(6)), and 5.31 (1 H, t, $J_{H,H}$ = 7.2 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 16.6 (q), 17.9 (q), 25.9 (q), 26.7 (t), 39.7 (t), 54.2 (t), 65.1 (t), 119.6 (d), 124.2 (d), 131.6 (s), and 142.4 (s); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 72.3 (9 lines, $J_{P,H}$ = 12.7 Hz); high-resolution (+) FAB mass spectrum calcd for $C_{12}H_{23}O_3PS$ (M + 1) 279.1184, found 279.1163.

***O,O*-Dimethyl *S*-((*E*)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphorothioate (1-SPO(OMe)$_2$).** A solution of 2.94 g (16 mmol) of geranyl chloride[44] in 15 mL of $CH_2Cl_2$ was cooled to 0 °C, and 9.34 g (18 mmol) of **5** (tetrabutylammonium salt) in 10 mL of chilled $CH_2Cl_2$ was added. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The solution was washed with saturated NaCl solution, and the aqueous layer was extracted with $CH_2Cl_2$. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography to yield 3.85 g (82%) of a colorless oil: $R_f$ 0.25 (3:2 hexanes/ethyl acetate); IR (neat) 2950, 2910, 2870, 1660, 1440, 1370, 1260, 1180, 1020, 820, 790, and 760 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.50 (6 H, s, H at geranyl methyls), 1.63 (3 H, s, H at geranyl methyl), 2.02 (4 H, br m, H at C(4) and C(5)), 3.40 (6 H, d, $J_{P,H}$ = 12.6 Hz, $POCH_3$). 3.46 (2 H, m, H at C(1)), 5.10 (1 H, br m, H at C(6)), and 5.30 (1 H, t, $J_{H,H}$ = 8.0 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 16.0 (q), 17.7 (q), 25.8 (q), 26.6 (t), 28.9 (dt, $J_{P,C}$ = 3.1 Hz), 39.7 (t), 53.1 (dq, $J_{P,C}$ = 5.6 Hz), 120.1 (d), 124.3 (d), 131.5 (s), and 140.5 (s); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 30.7 (9 lines, $J_{P,H}$ = 12.7 Hz); high-resolution (+) FAB mass spectrum calcd for $C_{12}H_{23}O_3PS$ (M + 1) 279.1184, found 279.1187.

***O,O*-Dimethyl *O*-((*E*)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphate (1-OPO(OMe)$_2$).** A solution of 0.61 g of methyl phosphorodichloridite (4.6 mmol) in 50 mL of anhydrous diethyl ether was chilled to −35 °C in an acetonitrile/dry ice bath before 0.71 g (4.6 mmol) of geraniol and 1.39 g (13.7 mmol) of triethylamine in 75 mL of diethyl ether were added dropwise. Methanol (0.15 g, 4.6 mmol) was added rapidly, and the solution was allowed to stir for 10 min at −35 °C. The cold bath was removed, and the suspension was allowed to warm to 0 °C. A 5.3-mL portion of toluene containing *tert*-butyl hydroperoxide (2.6 M) was added, and stirring was continued 1 h. The mixture was washed with water. Solvent was removed from the organic layer by rotary evaporation to afford 1.47 g of crude oil. A 103-mg portion of the residue was purified by flash chromatography on silica gel to yield 66 mg (78%) of a colorless oil: $R_f$ 0.3 (3:2 hexanes/ethyl acetate); IR (neat) 2960, 2940, 2850, 1670, 1640, 1450, 1380, 1270, 1190, 1030, 840 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.46 (3 H, s, H at geranyl methyl), 1.48 (3 H, s, H at geranyl methyl), 1.62 (3 H, s, H at geranyl methyl), 1.95 (4 H, br m, H at C(4) and C(5)), 3.39 (6 H, d, $J_{P,H}$ = 10.9 Hz, phosphate methyl), 4.54 (2 H, dd, $J_{H,H}$ = 7.1 Hz, $J_{P,H}$ = 8.9 Hz, H at C(1)), 5.07 (1 H, br m, H at C(6)), and 5.43 (1 H, t, $J_{H,H}$ = 7.1 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 16.4 (q), 17.8 (q), 25.9 (q), 26.7 (t), 39.9 (t), 53.4 (dq, $J_{P,C}$ = 5.9 Hz), 64.3 (dt, $J_{P,C}$ = 5.4 Hz), 119.7 (dd, $J_{P,C}$ = 6.0 Hz), 124.2 (d), 131.6 (s), and 142.4 (s); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 0.7.

***O,O*-Dimethyl *S*-(3,7-Dimethyl-1,6-octadien-3-yl) Phosphorothioate (2-OPS(OMe)$_2$).** A solution of 1.2 g (4.3 mmol) of 1-OPS(OMe)$_2$ and 4.82 g (45 mmol) of 2,6-lutidine in 100 mL of TFE was allowed to stir for 2.5 h at 10 °C. Saturated NaCl was added, and the mixture was extracted twice with $CH_2Cl_2$. Volatile components were removed by rotary evaporation and high vacuum (0.5 mmHg). The residue was purified by flash chromatography to yield 219 mg (18%) of a light yellow oil: $R_f$ 0.29 (3:2 hexanes/ethyl acetate); IR (neat) 2950, 2850, 1640, 1450, 1410, 1370, 1260, 1180, 1020, 920, 830, and 760 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.53 (3 H, s, H at linalyl methyl), 1.61 (3 H, s, H at linalyl methyl), 1.63 (3 H, s, H at linalyl methyl), 2.05 (4 H, br m, H at C(4) and C(5)), 3.39 (6 H, d, $J_{P,H}$ = 12.6 Hz, phosphate methyl), 4.95 (1 H, d, $J_{H,H}$ = 10.6 Hz, H at C(1)), 5.02 (1 H, d, $J_{H,H}$ = 17.6 Hz, H at C(1)), 5.13 (1 H, br m, H at C(6)), and 6.13 (1 H, dd, $J_{H,H}$ = 10.6 Hz, $J_{H,H}$ = 17.6 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 17.8 (q), 24.2 (t), 25.4 (q), 25.9 (q), 42.6 (t), 53.5 (q), 56.3 (s), 113.4 (t), 124.1 (d), 131.8 (s), and 143.3 (d); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 26.5 (septet, $J_{P,H}$ = 12.6 Hz); high-resolution (+) FAB mass spectrum calcd for $C_{12}H_{23}O_3PS$ (M + 1) 279.1184, found 279.1188.

**2,6-Lutidinium *O,O*-Dimethyl Phosphorothioate (5).** A solution of 5.76 g (52 mmol) of dimethyl hydrogen phosphonate in 50 mL of $CH_2Cl_2$ was chilled to −20 °C. Triethylamine (13.5 g, 0.130 mol) in 20 mL of $CH_2Cl_2$ was added at a rate such that the reaction temperature did not exceed −10 °C. Chlorotrimethylsilane (14.2 g, 0.130 mol) was added, and the cloudy white suspension was allowed to warm to 8 °C before 3.4 g (0.104 mol) of sublimed sulfur was added. The temperature of the mixture increased to 30 °C briefly and then cooled to room temperature. The solution was filtered, and solvent was removed by rotary evaporation. The residue was dissolved in benzene and filtered. Solvent was removed by rotary evaporation, and 40 mL of THF was added, followed by 19.7 g (62 mmol) of crystalline tetrabutylammonium fluoride. The mixture was allowed to stir for 2 h. Volatile components were removed by rotary evaporation, followed by high vacuum (0.5 mmHg), to yield 21.88 g of a viscous brown oil.

A 5.3-g portion of the residue was passed through 20 mequiv of AG 50W-X8 cation exchange resin (hydrogen form), neutralized with aqueous 2,6-lutidine, and lyophilized to give 2.3 g of a waxy white solid: $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.71 (6 H, s, methyls at C(2) and C(6) of lutidine), 3.51 (6 H, d, $J_{P,H}$ = 12.7 Hz, phosphorothioate methyls), 7.29 (1 H, t, $J_{H,H}$ = 7.9 Hz, H at C(4) of lutidine), and 7.29 (2 H, d, $J_{H,H}$ = 7.9 Hz, H at C(3) and C(5) of lutidine); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 19.3 (q), 52.6 (dq, $J_{P,C}$ = 5.9 Hz), 123.8 (d), and 153.6 (s); $^{31}P$ NMR (121 MHz, $CDCl_3$) δ 60.5 (septet, $J_{P,H}$ = 12.7 Hz).

***O,O,S*-Trimethyl Phosphorothioate (6).** To a solution containing 1.07 g (0.4 mmol) of the 2,6-lutidinium salt of **5** in 30 mL of $CH_2Cl_2$ was added 2.38 g (17 mmol) of methyl iodide. After 0.5 h, the mixture was washed with saturated NaCl. Solvent was removed by rotary evaporation, and the residue was purified by distillation to yield 423 mg (63%) of a colorless oil: bp 34–35 °C (1 mmHg); IR (neat) 2964, 2855, 1646, 1450, 1265, 1195, 1020, 830, 800, and 783 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.81 (3 H, d, $J_{P,H}$ = 14.6 Hz, *S*-methyl), and 3.33 (6 H. d, $J_{P,H}$

(44) Davisson, V. J.; Woodside, A. B.; Poulter, C. D. *Methods Enzymol.* **1985**, *110*, 130–144.

= 12.4 Hz, O-methyls); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 12.2 (dq, $J_{P,C}$ = 4.4 Hz), and 53.3 (dq, $J_{P,C}$ = 6.0 Hz); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 31.0 (10 lines, $J_{P,H}$ = 13.5 Hz); high-resolution EI mass spectrum (17 eV) calcd for $C_3H_9O_3PS$ 156.0010, found 156.0003.

**O,O-Dimethyl S-((Z)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphorothioate (3-SPO(OMe)$_2$).** A solution of 0.13 g (0.72 mmol) of neryl chloride in 15 mL of $CH_2Cl_2$ was cooled to 0 °C, and 0.36 g (1.44 mmol) of **5** (lutidinium form) in 10 mL of chilled $CH_2Cl_2$ was added. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The solution was washed with saturated NaCl solution, and the aqueous layer was extracted with $CH_2Cl_2$. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography to yield 120 mg (60%) of a colorless oil: $R_f$ 0.25 (3:2 hexanes/ethyl acetate); IR (neat) 2920, 2850, 1660, 1445, 1375, 1260, 1180, 1015, 825, 790, and 765 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.51 (3 H, s, H at neryl methyl), 1.53 (3 H, s, H at neryl methyl), 1.63 (3 H, s, H at neryl methyl), 2.02 (4 H, br m, H at C(4) and C(5)), 3.40 (6 H, d, $J_{P,H}$ = 12.9 Hz, phosphate methyls), 3.46 (2 H, dd, $J_{H,H}$ = 8.1 Hz, $J_{P,H}$ = 12.9 Hz, H at C(1)), 5.10 (1 H, br m, H at C(6)), and 5.30 (1 H, t, $J_{H,H}$ = 8.1 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 17.8 (q), 23.5 (q), 26.0 (q), 26.9 (t), 29.9 (dt, $J_{P,C}$ = 4.0 Hz), 32.2 (t), 53.2 (dq, $J_{P,C}$ = 5.9 Hz), 121.6 (dd, $J_{P,C}$ = 6.1 Hz), 124.3 (d), 131.9 (s), and 140.4 (s); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 28.0 (9 lines, $J_{P,H}$ = 12.9 Hz); high-resolution (+) FAB mass spectrum calcd for $C_{12}H_{23}O_3PS$ (M + 1) 279.1184, found 279.1194.

**2,6-Lutidinium O,S-Dimethyl Phosphorothioate (7).** In independent experiments, solutions of **5** (0.03 M) and **6** (0.1 M) in TFE/$D_2O$ containing 0.40 M 2,6-lutidine were heated at 120 °C for 6 h. Solvent was removed by lyophilization. The residue was suspended in ethyl acetate and applied to a plug of silica gel. The silica was washed with ethyl acetate and eluted with methanol. Methanol was removed from samples derived from **5** and **6** at reduced pressure, and each gave **7** as a waxy white solid: $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.22 (3 H, d, $J_{P,H}$ = 14.4 Hz, S-methyl), and 3.66 (3 H, d, $J_{P,H}$ = 12.8 Hz, O-methyl); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.4, 53.2; $^{31}P$ NMR (121 MHz, $CDCl_3$) δ 25.4 (7 lines, $J_{P,H}$ = 13.5 Hz).

**Trifluoroethyl Ethers 1-OTFE, 2-OTFE, and 4-OTFE.** To a solution of 3.3 g (1.9 mmol) of geranyl chloride[44] in 6 mL of $CH_2Cl_2$ at 0 °C was added 25 mL of TFE containing 1.8 M 2,6-lutidine chilled to 0 °C. After 3 h, 50 mL of pentane was added, and the mixture was washed with saturated brine. The aqueous layer was extracted with pentane. Solvent was removed by rotary evaporation to give 10.92 g of a rose-colored residue. A 1.8-g portion was chromatographed on silica. A fast-moving fraction ($R_f$ = 0.9, hexanes) was collected, and solvent was removed at reduced pressure to give 0.52 g of a colorless oil. A portion of the sample was chromatographed on a preparative (2 m × 3 mm) Carbowax 20M column at 135 °C. The first component to elute was **2**-OTFE. The second peak contained a mixture of **1**-OTFE and **4**-OTFE, which was then separated by chromatography on a 5-μ normal phase HPLC silica column eluted with isooctane.

**3,7-Dimethyl-2,6-octadien-1-yl 2,2,2-Trifluoroethyl Ether (1-OTFE):** $^1H$ NMR (300 MHz, $C_6D_6$) δ 1.38 (3 H, s, H at geranyl methyl), 1.50 (3 H, s, H at geranyl methyl), 1.64 (3 H, s, H at geranyl methyl), 1.95 (4 H, br m, H at C(4) and C(5)), 3.31 (2 H, q, $J_{H,F}$ = 9.0 Hz, H at ethyl C(1)), 3.80 (2 H, d, $J_{H,H}$ = 7.1 Hz, H at geranyl C(1)), 5.09 (1 H, br m, H at C(6)), and 5.25 (1 H, t, $J_{H,H}$ = 7.1 Hz, H at geranyl C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 16.3 (q), 17.8 (q), 25.9 (q), 26.7 (t), 39.5 (t), 66.6 (q, $J_{C,F}$ = 33.3 Hz), 68.3 (t), 120.1 (d), 124.2 (d), 124.9 (q, $J_{C,F}$ = 277.1 Hz), 131.6 (s), and 141.4 (s).

**3,7-Dimethyl-1,6-octadien-3-yl 2,2,2-Trifluoroethyl Ether (2-OTFE):** $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.92 (3 H, s, H at linalyl methyl), 1.52 (3 H, s, H at linalyl methyl), 1.64 (3 H, s, H at linalyl methyl), 2.05 (4 H, br m, H at C(4) and C(5)), 3.35 (2 H, dq, $J_{H,F}$ = 8.9 Hz, H at ethyl C(1)), 4.88 (1 H, d, $J_{H,H}$ = 17 Hz, H at C(1)), 4.92 (1 H, d, $J_{H,H}$ = 11 Hz, H at C(1)), 5.10 (1 H, t, $J_{H,H}$ = 7.1 Hz, H at C(6)), and 5.50 (1 H, dd, $J_{H,H}$ = 11 Hz, $J_{H,H}$ = 17.5 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 17.7 (q), 21.5 (q), 22.7 (q), 25.9 (t), 40.2 (t), 61.2 (tq, $J_{C,F}$ = 33.7 Hz), 78.1 (s), 115.8 (t), 124.6 (d), 125.0 (q, $J_{C,F}$ = 276.7 Hz), 131.4 (s), and 141.4 (d).

**α-Terpinyl 2,2,2-Trifluoroethyl Ether (4-OTFE):** $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.76 (3 H, s, H at terpinyl methyl), 0.78 (3 H, s, H at terpinyl methyl), 1.11 (1 H, m, H at terpinyl methine), 1.37 (2 H, m, H at terpinyl methylene), 1.61 (3 H, s, H at terpinyl methyl), 1.70 (2 H, m, H at terpinyl methylene), 1.81 (2 H, m, H at terpinyl methylene), 3.26 (2 H, q, $J_{H,F}$ = 8.9 Hz, H at ethyl C(1)), and 5.35 (1 H, m, H at terpinyl olefin); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 22.0 (q), 22.4 (q), 23.6 (q), 24.0 (t), 27.1 (t), 31.2 (t), 42.5 (d), 60.2 (tq, $J_{C,F}$ = 33.7 Hz), 78.5 (s), 121.0 (d), 125.0 (q, $J_{C,F}$ = 276 Hz), and 133.6 (s).

**O,O-Bis(2-(trimethylsilyl)ethan-1-yl) O-Methyl Phosphorothioate (8).** A solution of 1.00 g (7.5 mmol) of methyl phosphorodichloridite in 100 mL of anhydrous diethyl ether was chilled to −35 °C in an acetonitrile-/dry ice bath before 1.96 g (17 mmol) of 2-(trimethylsilyl)ethanol and 2.28 g (23 mmol) of triethylamine in 50 mL of diethyl ether were added dropwise. The bath was removed, and the suspension was allowed to warm to 0 °C before 0.48 g of sublimed sulfur (15 mmol) was added. After 1 h, pentane was added, and the suspension was extracted with saturated NaCl. The combined organic layers were dried over $MgSO_4$ and concentrated at reduced pressure. The residue was chromatographed on silica gel with hexanes/ethyl acetate (95:5, v/v) to yield 2.14 g (87%) of a colorless oil: $R_f$ 0.85 (hexanes/ethyl acetate (95:5, v/v)); IR (neat) 2950, 2900, 2850, 1460, 1420, 1375, 1250, 1175, 1040, 990, 930, 850, 820 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ −0.09 (18 H, s, silylmethyl), 1.00 (4 H, t, $J_{H,H}$ = 7.5 Hz, H at C(2)), 3.50 (3 H, d, $J_{P,H}$ = 12.4 Hz, phosphate methyl), and 4.27 (4 H, dt, $J_{H,H}$ = 7.5 Hz, $J_{P,H}$ = 9.9, H at C(1)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ −1.4 (q), 19.5 (dt, $J_{P,C}$ = 6.8 Hz), 54.0 (dq, $J_{P,C}$ = 5.8 Hz), and 66.8 (dt, $J_{P,C}$ = 5.8 Hz); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 67.5 (br m); high-resolution (+) FAB mass spectrum calcd for $C_{11}H_{29}O_3PS$ (M + 1) 329.1191, found 329.1183.

**O-Methyl O-(2-(Trimethylsilyl)ethan-1-yl) Phosphorothioate (9).** To a solution of **8** (0.20 g, 0.61 mmol) in 5 mL of THF was added 0.19 g (0.61 mmol) of crystalline tetrabutylammonium fluoride trihydrate. After 3 h, the solvent was removed by rotary evaporation to yield 319 mg (99%) of a viscous oil: IR (neat) 2980, 2920, 2885, 1885, 1650, 1465, 1380, 1250, 1180, 1050, 940 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ −0.01 (9 H, s, silyl methyls), 1.00 (18 H, br m, H at butyl C(4) and ethyl C(2)), 1.43 (12 H, br m, H at butyl C(3)), 1.65 (12 H, br m, H at butyl C(2)), 3.35 (12 H, br m, H at butyl C(1)), 3.58 (3 H, d, $J_{P,H}$ = 12.4 Hz, phosphate methyl), and 3.98 (2 H, m, H at ethyl C(1)); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ −2.1 (q), 13.0 (q), 18.9 (t), 19.0 (t), 23.3 (t), 51.2 (dq, $J_{P,C}$ = 6.0 Hz), 57.8 (t), and 61.6 (dt, $J_{P,C}$ = 6.9 Hz); $^{31}P$ NMR (121 MHz, $CDCl_3$) δ 52.4 (br m).

**O-Methyl O-(2-(Trimethylsilyl)ethan-1-yl) S-((E)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphorothioate (1-SPO(OMe)(OTMSE)).** A solution of 0.20 g (1.1 mmol) of geranyl chloride[44] in 5 mL of $CH_2Cl_2$ was cooled to 0 °C, and 367 mg (0.70 mmol) of **9** in 5 mL of chilled $CH_2Cl_2$ was added. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The solution was mixed with hexanes and washed with saturated NaCl. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography on silica gel to yield 199 mg (78%) of a colorless oil: $R_f$ 0.35 (3:2 hexanes/ethyl acetate); IR (neat) 3020, 2950, 2920, 2870, 1660, 1440, 1370, 1250, 1175, 1040, 980, 930, 850 cm$^{-1}$; $^1H$ NMR (300 MHz, $C_6D_6$) δ −0.12 (9 H, s, silyl methyls), 1.01 (2 H, t, $J_{H,H}$ = 8.3 Hz, H at ethyl C(2)), 1.50 (3 H, s, H at geranyl methyl), 1.55 (3 H, s, H at geranyl methyl), 1.64 (3 H, s, H at geranyl methyl), 2.02 (4 H, br m, H at C(4) and C(5)), 3.48 (3 H, d, $J_{P,H}$ = 12.8 Hz, phosphate methyls), 3.53 (2 H, dd, $J_{H,H}$ = 7.6 Hz, $J_{P,H}$ = 13.1 Hz, H at C(1)), 4.20 (2 H, br m, H at ethyl C(1)), 5.10 (1 H, br m, H at C6), and 5.38 (1 H, t, $J_{H,H}$ = 7.6 Hz, H at C(2)); $^{13}C$ NMR (75 MHz, $C_6D_6$) δ 1.4 (q), 16.2 (q), 17.9 (q), 19.7 (dt, $J_{P,C}$ = 6.2 Hz), 26.0 (q), 26.9 (t), 29.3 (dt, $J_{P,C}$ = 3.3 Hz), 39.9 (t), 53.1 (dq, $J_{P,C}$ = 5.9 Hz), 65.9 (dt, $J_{P,C}$ = 6.1 Hz), 120.3 (dd, $J_{P,C}$ = 5.8 Hz), 124.3 (d), 131.5 (s), and 140.3 (s); $^{31}P$ NMR (121 MHz, $C_6D_6$) δ 26.0 (br m).

**2,6-Lutidinium Methyl S-((E)-3,7-Dimethyl-2,6-octadien-1-yl) Phosphorothioate (1-SPO$_2$(OMe)$^-$).** To 50 mg (0.14 mmol) of **1**-SPO(OMe)(OTMSE) in 5 mL of THF was added 88 mg (0.28 mmol) of crystalline tetrabutylammonium fluoride trihydrate (0.28 mmol) with stirring. After 3 h, the solvent was removed by rotary evaporation, and the residue was dissolved in distilled water containing 2% (v/v) 2,6-lutidine. The solution was passed through 37 mequiv of Dowex AG 50W-X8 cation exchange resin (lutidinium form). Water was removed by lyophilization, and the residue extracted with $CH_2Cl_2$. Solvent was removed at reduced pressure to yield 48 mg (94%) of a white solid: IR (neat) 2960, 2930, 2860, 1660, 1450, 1380, 780, 715 cm$^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.48 (3 H, s, H at geranyl methyl), 1.56 (3 H, s, H at geranyl methyls), 1.95 (4 H, br m, H at C(4) and C(5)), 2.81 (6 H, s, methyls at lutidinium C(2) and C(6)), 3.34 (2 H, dd, $J_{H,H}$ = 7.9 Hz, $J_{P,H}$ = 10.7 Hz, H at C(1)), 3.56 (3 H, d, $J_{P,H}$ = 13.0 Hz, phosphate methyl), 4.96 (1 H, t, $J_{H,H}$ = 6.4 Hz, H at C(6)), 5.20 (1 H, t, $J_{H,H}$ = 7.9 Hz, H at C(2)), 7.42 (2 H, d, $J_{H,H}$ = 7.8 Hz, H at lutidinium C(3) and C(5)), and 8.08 (1 H, t, $J_{H,H}$ = 7.8 Hz, H at lutidinium C(2)); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 15.9 (q), 17.6 (q), 19.5 (q), 25.6 (q), 26.2 (t), 28.2 (dt, $J_{P,C}$ = 3.0 Hz), 39.4 (t), 52.8 (dq, $J_{P,C}$ = 3.0 Hz), 119.6 (d), 123.6 (d), 124.4 (d), 131.3 (s), 139.4 (s), 144.5 (d), and 153.5 (s); $^{31}P$ NMR (121 MHz, $CDCl_3$) δ 23.5 (6 lines, $J_{P,H}$ = 11.9 Hz).

**Kinetic Studies.** A stock solution of 65:35 (v/v) TFE/$D_2O$ containing 0.40 M 2,6-lutidine was prepared. For compounds **1**-OPO(OMe)$_2$, **1**-OPS(OMe)$_2$, and **2**-SPO(OMe)$_2$, the solutions contained 70 mM 4-amino-2,2,6,6-tetramethylpiperidinooxy to reduce phosphorus $T_1$ values to <1 s.

Compounds 1-OPO(OMe)$_2$ and 1-OPS(OMe)$_2$ (7 mg) were mixed separately with 0.6 mL of stock solution (40 mM). Spectra were recorded at 20 ± 1 °C. A solution of 2-SPO(OMe)$_2$ (60 mM) was divided into 500-μL portions and frozen at -20 °C. The samples were allowed to thaw in a water bath at the appropriate temperature and to equilibrate in the probe for 5 min before spectra were recorded. A 90 mM solution of 1-SPO(OMe)$_2$ was divided into glass ampules and flame-sealed. Samples were heated in an oil bath, removed periodically, placed in an ice water bath to quench the reaction, and stored at 4 °C until analysis. Upon completion of a kinetic run, $^{31}$P NMR spectra were recorded.

Reactions were monitored for at least 2 half-lives. Each kinetic point was the average of 10 aquisitions during a period of 20 s with a delay of at least 6 $T_1$'s between radio frequency pulses. Measurements of the points from sealed ampules used 100 acquisitions with a similar delay. $^{31}$P NMR signals were referenced to trimethyl phosphate in benzene contained in a coaxial tube.

**Product Studies.** NMR samples for each phosphorothioate were diluted with an equal volume of diethyl ether and water and mixed. The ether phase was dried, and solvent was removed by rotary evaporation. The residue was passed through a short bed of silica prior to GC analysis. Peaks for the products were identified by coinjection with known compounds. The volume of the aqueous phase was reduced by lyophilization, and components were analyzed by $^{31}$P NMR with addition of known samples to confirm peak assignments. Intensities of $^{31}$P NMR signals were compared to external solutions of trimethyl phosphate in benzene or 1 M phosphoric acid in $D_2O$ in a coaxial tube. Material balances of water-soluble (phosphorothioates) and extractable (alcohols and TFE ethers) compounds were greater than 85%.

**Solvolysis of Geranyl Tosylate (1-OTs) in 65:35 TFE/$D_2O$ Containing 5.** KH (0.12 g, 3.0 mmol) was rinsed twice with 4 mL of diethyl ether, and excess ether was removed by a gentle stream of nitrogen. THF (2 mL) was added, and 0.46 g (3.0 mmol) of geraniol was added in 1 mL of THF. The solution was stirred at room temperature for 0.5 h and then cooled to -78 °C in an acetone/dry ice bath. Tosyl chloride (0.57 g, 3.0 mmol) was added, and the solution was allowed to stir for 0.5 h. The volume of the solution was reduced to approximately 1 mL under high vacuum. The flask was removed from the bath, and 4 mL of a solution containing 65:35 (v/v) TFE/$D_2O$, 0.4 M 2,6-lutidine, and 1 mmol of 5 (lutidinium form) at 20 °C was added. The mixture was shaken vigorously for 1 min. Pentane/diethyl ether (1:1) and water were added. The layers were separated, and pentane/ether was removed by rotary evaporation to give 0.43 g of a mixture of phosphorothioates, alcohols, and TFE ethers. The residue was analyzed by $^{31}$P NMR; peaks were seen at δ 69.5, 29.4, and 25.4 with respective relative intensities of 1, 50, and 5 for 1-OPS(OMe)$_2$, 1-SPO(OMe)$_2$, and 2-SPO(OMe)$_2$.

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# Palladium-Catalyzed Oxyhexatriene Cyclization: A Novel Approach to Cyclohexenone Annulation[1]

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**Abstract:** Palladium(II) catalysts mediate the cyclization of [(trimethylsilyl)oxy]hexatrienes (SOHs) to afford cyclohexenones. This novel reaction represents the first general approach to the hexatriene cyclization of dienone enolates or their derivatives. Fully-conjugated dienones are readily converted to the kinetic enolates with LDA and trapped as the silyl enol ethers. Heating of these compounds in refluxing toluene or xylenes in the presence of 5 mol % Pd(PFu$_3$)$_2$Cl$_2$ gives the corresponding cyclohexenones in good yield. Substituents α to the carbonyl interfere with the cyclization. Treatment of cross-conjugated dienones with LDA causes formation of the *trans*-SOH. However, cis/trans isomerization occurs under the reaction conditions, and cyclization still proceeds, albeit in moderate yields. Attempts at thermal cyclization of the kinetic potassium or lithium enolates of 1-acetyl-2-vinylcyclohex-2-ene or the corresponding SOH in the absence of a palladium catalyst led to little or no cyclohexenone formation. This observation confirms that the cyclization is catalyzed by palladium and suggests that the concerted thermal electrocyclization of electron-rich hexatrienes may be a difficult process. Pd(PFu$_3$)$_2$Cl$_2$ is proposed to mediate SOH cyclization by causing palladium enolate formation, followed by addition across a distal carbon–carbon double bond and trapping of the annulated product as the silyl enol ether.

The synthesis of six-membered rings has traditionally been one of the most important endeavors of the synthetic organic chemist, leading to a number of methods for the formation of cyclohexenones.[2,3] The most utilized approach, the Robinson annulation, involves the Michael addition of an enolate to an alkyl vinyl ketone followed by aldol condensation of the resulting 1,4-dione (Scheme I).[3] Many modifications of the Michael/aldol scheme have been made, all of which lead to compounds of comparable regiochemistry.[3] Martin[4] and Fuchs[5] have developed conjugate addition/intramolecular Wittig approaches to cyclohexenone annulation that allow somewhat greater variation in the products available.

While studying a route for the total synthesis of corticosteroids, we required a facile conversion of a cyclohexanone into the corresponding Δ$^2$-bicyclo[4.4.0]decen-2-one. Unfortunately, none of the aforementioned methodology appeared suitable for our needs. In 1978 Magnus proposed a general approach to the annulation of cyclohexenones involving the thermal cyclization of enolates derived from acyclic dienones.[6] To date, this proposal, based on earlier findings of Scanio[7] and Yoshikoshi,[8] has not been tested. We observed that the thermal (110 °C) cyclization of a hexatrienolate proceeds very slowly to afford cyclohexenones in low yield.

Herein, we report the first general cyclization of hexatrienolate derivatives. Palladium complexes mediate the cyclization of [(trimethylsilyl)oxy]hexatrienes (SOHs) to afford cyclohexenones after deprotection. As shown in Scheme I, the SOH cyclization is complementary to both the Robinson and the Martin–Fuchs

(1) (a) Presented in part at the 197th National Meeting of the American Chemical Society, 9–14 April 1989, Dallas, TX; ORGN 151. (b) Presented in part at the Fifth IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis; 1–6 Oct 1989, Florence, Italy; Abstract No. OP-B33.

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