Phosphorylation of Isoprenoid Alcohols

V. Jo Davisson, Andrew B. Woodside, Timothy R. Neal, Kay E. Stremler, Manfred Muehlbacher, and C. Dale Poulter*

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

Received August 7, 1986

Procedures for the synthesis and purification of 20 isoprenoid diphosphates and methanediphosphonate analogues from the corresponding alcohols are described. The alcohols are activated for phosphorylation by conversion of homoallylic systems to tosylates and allylic systems to halides. The activated intermediates are treated with tris(tetra-*n*-butylammonium) salts of pyrophosphoric, methanediphosphonic, or difluoromethanediphosphonic acid to obtain the corresponding esters in yields of 34–80%. Chromatography on cellulose is a general method for purification of isoprenoid diphosphates, and procedures are described for compounds with C_5 to C_{20} hydrocarbon moieties. The displacement by pyrophosphate occurs with inversion of configuration, and the procedure can be used to prepare isoprenoid diphosphates with chiral C1 methylene groups in high optical purity from the corresponding alcohols.

The isoprenoid biosynthetic pathway produces a vast array of metabolites, including such important classes of compounds as sterols,[1] carotenoids,[2] respiratory quinones,[3] dolichols,[4] sesquiterpenes,[5] and zeatins.[6] Diphosphate esters are ubiquitious intermediates in the early and middle stages of the pathway. These compounds are ultimately derived from mevalonic acid, and the diphosphate moiety is introduced by ATP-driven phosphorylations of the primary hydroxyl group in mevalonic acid early in the pathway.[7] Beyond this point, there are no known kinases capable of converting isoprenoid alcohols to diphosphates. Thus, biologically based syntheses of isoprenoid diphosphates use mevalonic acid as a substrate in cell-free or multienzyme systems and are only useful for preparing small amounts of a limited selection of compounds.[8]

Since isoprenoid diphosphates were first discovered over 25 years ago, few procedures for the chemical synthesis of these compounds have been reported.[9-11] The only reaction used routinely to prepare the highly reactive allylic systems,[12-16] which form the backbone of the pathway, was first published by Cramer and Bohm in 1959 and has not been altered substantially since then.[17-19] This procedure involves treatment of an alcohol with inorganic phosphate and trichloroacetonitrile; whereupon, the desired product is then isolated from a complex mixture of organic and inorganic mono-, di-, and triphosphates by ion-exchange chromatography or paper electrophoresis.[20-28] Yields are occasionally as high as 30% but are typically less than 10%. In addition, the procedure is difficult to manage if more than ca. 50 mg of product is desired. It occurred to us that many of the problems inherent in the synthesis of reactive allylic diphosphates could be circumvented if the diphosphate moieties were introduced in a final step by utilizing a salt of inorganic pyrophosphate in a direct displacement reaction. In a preliminary paper, we reported a new procedure based on this idea for the synthesis of allylic isoprenoid diphosphate esters using tris(tetra-*n*-butylammonium) hydrogen pyrophosphate.[29] The salt has since proved to be an excellent nucleophilic source of inorganic pyrophosphate for displacements on a wide variety of appropriately activated allylic and nonallylic primary alcohols.[30] In addition, we developed a simple, efficient purification procedure that gives excellent recoveries of pure materials. The displacement reaction has been used to prepare natural substrates, carbon chain analogues, and pyrophosphate analogues of isoprenoid disphosphates. We now present a detailed account of our synthetic work based on this methodology.

Results and Discussion

Tris(tetra-*n*-butylammonium) Hydrogen Pyrophosphate. The pyrophosphate salt is the key reagent in the synthesis of organic diphosphate esters. Isoprenoid

(1) Gaylor, J. L. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L., Eds. Wiley: New York, 1981; Vol. 1, pp 481–544.

(2) Spurgeon, S. L.; Porter, J. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L., Eds.; Wiley: New York, 1983; Vol. 2, pp 1–122.

(3) Hemming, F. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L., Eds.; Wiley: New York, 1983; Vol. 2, pp 305–354.

(4) Pennock, J. F.; Threlfall, D. R. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L.; Eds.; Wiley: New York, 1983; Vol. 2, pp 191–304.

(5) Cane, D. E. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L. Eds.; Wiley, New York, 1981; Vol. 1, pp 283–374.

(6) Akiyorkis, D. E.; Klee, H.; Amasino, R. M.; Nester, E. W.; Gordon, M. P. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 5994–5998.

(7) Qureshi, N.; Porter, J. W. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W.; Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, pp. 47–94.

(8) Cornforth, J. W. *Angew Chem., Int. Ed. Engl.* **1968**, *7*, 903–964.

(9) Lynen, F.; Eggerer, H.; Henning, U.; Kessel, I. *Angew Chem.* **1958**, *70*, 738–742.

(10) Lynen, F.; Agranoff, B. W.; Eggerer, H.; Henning, U.; Moselein, E. M. *Angew. Chem.* **1959**, *71*, 657–662.

(11) Chaykin, S.; Law, S.; Phillips, A. H.; Tohen, T. T.; Bloch, K. *Proc. Natl. Acad. Sci. U.S.A.* **1958**, *44*, 998.

(12) Tidd, B. K. *J. Chem. Soc. B* **1971**, 1168–1176.

(13) Astin, K. B.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1157–1160.

(14) Logan, D. M. *J. Lipid Res.* **1972**, *13*, 137–138.

(15) Vial, M. V.; Rojas, C.; Portilla, G.; Chayet, L.; Perez, L. M.; Cori, O.; Bunton, C. A. *Tetrahedron* **1981**, *37*, 2351–2359.

(16) Bunton, C. A.; Cori, O.; Hachey, D.; Leresche, J.-P. *J. Org. Chem.* **1979**, *44*, 3238–3244.

(17) Cramer, F.; Böhm, W. *Angew Chem.* **1959**, *71*, 775.

(18) Cramer, F.; Rittersdorf, W.; Böhm, W. *Justus Liebigs Ann. Chem.* **1962**, *654*, 180–188.

(19) Cornforth, R. H.; Popjak, G. *Methods Enzymol.* **1969**, *15*, 359–390.

(20) Dugan, R. E.; Rasson, E.; Porter, J. W. *Anal. Biochem.* **1968**, *22*, 249–259.

(21) Oster, M. O.; West, C. A. *Arch. Biochem. Biophys.* **1968**, *127*, 112–123.

(22) Holloway, P. W.; Popjak, G. *Biochem. J.* **1967**, *104*, 57–70.

(23) Mackie, H.; Overton, K. H. *Eur. J. Biochem.* **1977**, *77*, 101–106.

(24) Banthorpe, D. V.; Poonam, S.; Gutowski, J. A. *Phytochemistry* **1977**, *16*, 85.

(25) Banthorpe, D. V.; Christou, P. N.; Pink, C. R.; Watson, D. G. *Phytochemistry* **1983**, *22*, 2465–2468.

(26) Croteau, R.; Karp, F. *Arch. Biochem. Biophys.* **1976**, *176*, 734–746.

(27) Cane, D. E.; Iyengar, R.; Shiao, M.-S. *J. Am. Chem. Soc.* **1981**, *103*, 914–931.

(28) Cane, D. E.; Ha, H.-J.; Pargellis, C.; Waldmeier, F.; Swanson, S.; Murthy, P. P. N. *Bioorg. Chem.* **1985**, *13*, 246–265.

(29) Dixit, V. M.; Laskovics, F. M.; Noall, W. I.; Poulter, C. D. *J. Org. Chem.* **1981**, *46*, 1967–1969.

(30) Davisson, V. J.; Woodside, A. B.; Poulter, C. D. *Methods Enzymol.* **1984**, *110*, 130–144.

0022-3263/86/1951-4768$01.50/0

Table I

alcohol	activated precursor	phosphorylated derivative	yields, % activation	yields, % phosphorylation
C_5				
3-methyl-3-butan-1-ol	tosylate **7**	P_2O_7 **21**	95	80
	tosylate **7**	$PO_3CF_2PO_3$ **22**	95	68
3-methyl-2-buten-1-ol	bromide **16**	P_2O_7 **23**	70	80
	bromide **16**	$PO_3CF_2PO_3$ **24**	70	74
3-methyl-1-butanol	bromide[a]	P_2O_7 **25**	*a*	58
4-fluoro-3-methyl-1-butanol	tosylate **8**	P_2O_7 **26**	75	74
3-(fluoromethyl)-3-buten-1-ol	tosylate **9**	P_2O_7 **27**	85	67
(*Z*)-4-fluoro-3-methyl-2-buten-1-ol	bromide **17**	P_2O_7 **28**	62	34
(*E*)-4-fluoro-3-methyl-2-buten-1-ol	bromide **18**	P_2O_7 **29**	75	35
(*Z*)-4,4-difluoro-3-methyl-2-buten-1-ol	bromide **19**	P_2O_7 **30**	70	75
(*E*)-4,4-difluoro-3-methyl-2-buten-1-ol	bromide **20**	P_2O_7 **31**	73	64
(*N*,*N*-dimethylamino)ethanol	chloride[b]	P_2O_7 **32**	*b*	64
C_{10}				
(*E*)-3,7-dimethyl-2,6-octadien-1-ol	chloride **11**	P_2O_7 **33**	95	78
	chloride **11**	$PO_3CH_2PO_3$ **35**	95	60
	chloride **11**	$PO_3CF_2PO_3$ **36**	95	64
(*Z*)-3,7-dimethyl-2,6-octadien-1-ol	chloride **13**	P_2O_7 **37**	99	77
C_{15}				
(*E*,*E*)-3,7,11-trimethyl-2,6,10-octatrien-1-ol	chloride **14**	P_2O_7 **38**	98	72
	chloride **14**	$PO_3CF_2PO_3$ **39**	98	75
C_{20}				
3,7,11,15-tetramethylhexadecan-1-ol	tosylate **10**	P_2O_7 **40**	96	58
(*E*,*E*,*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-ol	chloride **15**	$PO_3CF_2PO_3$ **41**	98	35

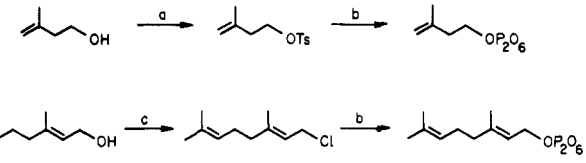
[a] Purchased from Aldrich Chemical Co. [b] Prepared from the hydrochloride salt (ref 68).

alcohols must first be converted to intermediates capable of undergoing displacement. However, suitably activated allylic intermediates are prone to decomposition via carbocationic intermediates.[12,13] Thus, the reaction requires an aprotic solvent which will not support solvolysis. Several different procedures for obtaining a soluble form of inorganic pyrophosphate were investigated in the early phase of the project.[31] Crown ethers in catalytic or stoichiometric amounts did not generate a species from potassium pyrophosphate capable of phosphorylating activated isoprenoids at room temperature. At temperatures above 30–40 °C, the starting materials decomposed, mainly by elimination. Pyridinium and lutidinium salts of pyrophosphoric acid were also ineffective. The principle products were from elimination or displacement by nitrogen, presumably from free amine in equilibrium with the ammonium salt. Trialkylammonium pyrophosphates of triethylamine, tributylamine, and trioctylamine were also ineffective. The salts were unstable under high vacuum, and displacement reactions with the trialkylammonium salts were significantly slower than their tetralkylammonium counterparts (vide infra) perhaps because the nucleophilicity of the pyrophosphate moiety is reduced by hydrogen bonding to the cation.

The phosphorylating reagent we prefer is tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (**1**). The salt is easily obtained by passing a solution of sodium dihydrogen pyrophosphate through a cation-exchange resin and titrating the eluant to pH 7.3 with tetra-*n*-butylammonium hydroxide. Lyophilization of the aqueous solution produces a white, hygroscopic solid which has a shelf life of several months when stored in a desiccator over calcium sulfate at −20 °C.

The tris(tetra-*n*-butylammonium) salt contains water of hydration. The total water content varies depending on the lyophilization step and the length of storage over a dehydrating agent. The amount of water in the reagent is easily measured by ^1H NMR. Attempts to remove additional water under vacuum with heating results in decomposition. The hydrate can, however, be partially dehydrated immediately before use by repeatedly dissolving the material in anhydrous acetonitrile and removing the solvent under vacuum at room temperature. Alternatively, a species with three waters of hydration can be obtained by crystallization of **1** from ethyl acetate. This hygroscopic, crystalline material is highly soluble in chloroform, dichloromethane, tetrahydrofuran, benzene, and acetonitrile. Nonaqueous solutions of the salt are basic as indicated by the complete exchange of hydrogen for deuterium within minutes of mixing tris(tetra-*n*-butylammonium) hydrogen pyrophosphate and chloroform-d_1 at room temperature.

Scheme I. Synthesis of Isoprenoid Diphosphates[a]



[a] (a) Tosyl chloride, (dimethylamino)pyridine; (b) tris(tetra-*n*-butylammonium) hydrogen pyrophosphate; (c) *N*-chlorosuccinimide, dimethyl sulfide.

Synthesis of Diphosphates and Methanediphosphonates. Isoprenoid diphosphates are prepared from the corresponding alcohols in two steps. The first step is an activation of the carbinyl carbon, and the second is a direct displacement at the activated position by the phosphorylating reagent, as illustrated in Scheme I for isopentenyl diphosphate (**21**) and geranyl diphosphate (**33**). A list of substrates and analogues we have prepared and representative yields are presented in Table I.

The choice of which activated derivative to use in the displacement reaction is important. In preliminary studies with allylic systems, we used bromides for displacement reactions.[29] Subsequently we have used bromides and chlorides. Generally, bromide is now used as the leaving group for C_5 systems to reduce problems associated with loss of material because of the volatility of halogenated intermediates. However, for more bulky systems where volatility is not a problem, chlorides are preferred because they are less prone to decomposition during preparation

(31) Neal, T. R. Ph.D. Dissertation, University of Utah, Salt Lake City, UT, 1981.

and purification. Attempts to phosphorylate isopentenyl chloride or bromide by direct displacement failed because of competing elimination to give isoprene. This undesirable side reaction was suppressed when the displacement was carried out on homoallylic tosylate **7**. Saturated primary systems can be phosphorylated as halides or tosylates. It is also possible to prepare fluorinated analogues (compounds **8** and **17–20**) where the fluorine is allylic to a double bond by selective displacement at homoallylic tosylate or allylic bromide centers. Previous syntheses of fluorinated isoprenoid diphosphates from the corresponding alcohols by the Cramer procedure gave yields of less than 5%.[32] We did not detect any rearranged products from allylic starting materials that could have come from competing S_n2' or S_n1 reactions.

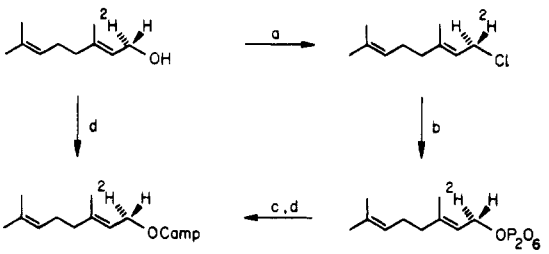
It is possible to follow the progress of the phosphorylation reaction by measuring the decrease in intensity for the ^1H NMR signal of the carbinyl protons in the halogenated intermediates or the AA'XX' spin system in the tosylates. Under typical conditions described in the Experimental Section, the reaction was 70% complete in 5 min for a solution 0.26 M in geranyl chloride (**11**) and 0.55 M in ammonium salt **1** and complete (>95%) after 30 min at 20 °C. A similar reaction 0.26 M in **1** was only 60% complete in 10 min and 90% complete after 9 h. Homoallylic tosylates are slightly less reactive than allylic chlorides. A solution 0.26 M in isopentenyl tosylate **7** and 0.79 M in **1** had gone to 50% completion after 10 min and required over an hour to reach completion (>95%).

A potential side reaction in the displacement procedure is competition between newly formed isoprenoid diphosphate monoester and inorganic salt for unreacted halide or tosylate. Only during formation of isopentenyl pyrophosphate (**21**) did we obtain conclusive evidence for formation of a diester. Treatment of **7** with 1 equiv of pyrophosphate salt **1** gave a side product whose ^1H and ^{31}P NMR spectra and mobility on thin-layer chromatography were consistent with the symmetrical *P*1, *P*2 diester. When the molar ratio of salt was raised from 1:1 to 2:1, the amount of side product decreased from 14.2% to 3.4%. At a 3:1 ratio, only monoester was obtained. For allylic reactants, a 2:1 molar ratio of salt to halide is sufficient to ensure a clean conversion to monoester. It is important not to use a large excess of salt because of subsequent problems during the purification steps.

The displacement procedure lends itself to the synthesis of isoprenoid analogues in the pyrophosphate moiety that were previously unavailable. For example, we prepared methanediphosphonate analogues of geranyl pyrophosphate from tris(tetra-*n*-butylammonium) salts of methanediphosphonic acid (**2**) and difluoromethanediphosphonic acid (**6**)[33–37] using the displacement reaction. Diphosphonic acid salts **2** and **6** are prepared by the same procedure used for tris(tetra-*n*-butylammonium) hydrogen pyrophosphate, have similar properties, and are stored in the same manner.

The only failure we experienced with the displacement procedure was for primary cyclopropylcarbinyl systems. Several attempts to convert chrysanthemol to chrysanthemyl diphosphate were unsuccessful.[38] For example,

Scheme II. Stereochemistry of Phosphorylation[a]



[a] (a) *N*-Chlorosuccinimide, dimethyl sulfide; (b) tris(tetra-*n*-butylammonium) hydrogen pyrophosphate; (c) *E. coli* alkaline phosphatase; (d) (−)-camphanoyl chloride, (dimethylamino)pyridine.

chrysanthemyl tosylate was prepared by deprotonation of the alcohol at −78 °C with butyllithium and treatment of the resulting alkoxide with an equivalent of tosyl chloride at −20 °C. However, addition of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate followed by slow warming to room temperature gave none of the desired diphosphate. Instead a mixture consisting of at least three pyrophosphorylated materials, presumably formed by rearrangement of the cyclopropylcarbinyl skeleton, was obtained. Attempts to use less reactive leaving groups were also unsuccessful. *N*-Methyl-4-alkoxypyridinium iodides[39] and sulfates[40] or phenylphosphinates[41] failed to react at room temperature for periods of up to a week, and the materials decomposed upon warming the reactions to 40 °C without formation of chrysanthemyl diphosphates. By analogy, we anticipate that the displacement reaction is not suitable for synthesis of presqualene[42,43] and prephytoene[44,45] diphosphates.

Stereochemistry of the Phosphorylation. Substrates stereospecifically labeled with deuterium or tritium at normally prochiral centers are valuable tools for stereochemical and mechanistic studies of enzyme-catalyzed reactions.[28,46–48] One would anticipate that the displacement reaction would be suitable for synthesis of these materials as well. If the reaction is an S_n2 process, the pyrophosphorylation step should proceed with inversion of configuration. Thus, one would expect net inversion at C1 for diphosphates obtained from isoprenoid alcohols activated as tosylates and net retention for diphosphates activated as halides as a result of inversions in both the activation and the phosphorylation steps.

The latter proposal was verified by the synthesis of (*S*)-[1-^{2}H]geranyl diphosphate (**34**). (*S*)-[1-^{2}H]Geraniol (**46**) was prepared by reduction of ethyl geranate (**43**)[49,50] with lithium aluminum deuteride,[51] oxidation of [1-$^2H_2$]-

(32) Wiggins, P. L. Ph.D. Dissertation, University of Utah, Salt Lake City, UT, 1980.
(33) Burton, D. J.; Flynn, R. M. *J. Fluorine Chem.* **1977**, *10*, 329–332.
(34) Flynn, R. M. Ph.D. Dissertation, University of Iowa, Iowa City, IA, 1979.
(35) Burton, D. J.; Shihara, T.; Flynn, R. M. *J. Fluorine Chem.* **1982**, *20*, 121–126.
(36) Burton, D. J.; Flynn, R. M. U.S. Patent 4 330 486, 1982.
(37) McKenna, C. E.; Shen, P. *J. Org. Chem.* **1981**, *46*, 4573–4576.
(38) Crombie, L.; Firth, P. A.; Houghton, R. P.; Whitney, D. A.; Woods, D. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 642–652.
(39) Poulter, C. D.; Hughes, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 3824–3829.
(40) Poulter, C. D.; King, C.-H. R. *J. Am. Chem. Soc.* **1982**, *104*, 1420–1422.
(41) Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643–2647.
(42) Epstein, W. W.; Rilling, H. C. *J. Biol. Chem.* **1970**, *245*, 4597–4605.
(43) Altman, L. J.; Kowerski, R. C.; Laungani, P. R. *J. Am. Chem. Soc.* **1978**, *100*, 6174–6182.
(44) Popjak, G.; Edmond, J.; Wong, S.-W. *J. Am. Chem. Soc.* **1973**, *95*, 2713–2714.
(45) Altman, L. J.; Ash, L.; Kowerski, R. C.; Epstein, W. W.; Larsen, B. R.; Rilling, H. C.; Muscio, D. E.; Gregonis, D. E. *J. Am. Chem. Soc.* **1972**, *94*, 3257–3259.
(46) Cane, D. E. *Tetrahedron* **1980**, *36*, 1109–1159.
(47) Coates, R. M.; Cavender, P. L. *J. Am. Chem. Soc.* **180**, *102*, 6358–6359.
(48) Croteau, R.; Felton, N. M.; Wheeler, C. J. *J. Biol. Chem.* **1985**, *260*, 5956–5962.
(49) Machleidt, H.; Hartman, V.; Bünger, H. *Leibigs Ann. Chem.* **1973**, *667*, 35–47.
(50) Katzenellenbogen, J. A.; Utawanit, T. *J. Am. Chem. Soc.* **1974**, *96*, 6153–6158.

geraniol with manganese dioxide,[52] and reduction of the resulting aldehyde with horse liver alcohol dehydrogenase[28] as outlined in Scheme II. A portion of the resulting alcohol was converted to geranyl diphosphate by the standard displacement procedure, and the product from the phosphorylation was hydrolyzed with *E. coli* alkaline phosphatase. Samples of unlabeled geraniol and deuterium-labeled geraniol from the alcohol dehydrogenase reduction and the phosphorylation–hydrolysis sequence were converted to (–)-camphanate esters and analyzed by ^{1}H NMR spectroscopy.[53] In the presence 0.5 molar equiv of Eu(thd)$_3$, the diastereotopic C1 protons in the geranyl chain of unlabeled ester appeared as well-resolved signals at 6.30 and 6.65 ppm (Figure 1a). The (–)-camphanate ester of (*S*)-[1-^{2}H]geraniol from the dehydrogenase reduction had an intense resonance at 6.35 ppm and a barely visible signal at 6.75 ppm (Figure 1b). The (–)-camphanate esters of [1-^{2}H]geraniol recovered after hydrolysis by alkaline phosphatase also had an intense peak for the high-field C1 methylene proton and a small, but more pronounced, resonance at lower field. Since alkaline phosphatase hydrolyzes pyrophosphate esters to alcohols with retention of configuration,[54] it is evident that the chlorination–phosphorylation sequence proceeds with overall retention at C1 to yield (*S*)-[1-^{2}H]geranyl pyrophosphate.

A comparison of ^{1}H NMR spectra of (–)-camphanate esters of (*S*)-[1-^{2}H]geraniol from the alcohol dehydrogenase reduction and from phosphatase hydrolysis shows that a small amount of racemization occurred during the phosphorylation sequence. The intensity of the small methylene peaks at lower field increased from ca. 4% of the higher field resonance in the original material to 10% for labeled geraniol recovered after phosphorylation. Although racemization could have occurred during either step of the phosphorylation procedure, we believe that the chlorination reaction is the more likely possibility.[55] In general, halogenations of 3,3-dialkylallylic alcohols are sensitive reactions that must be carefully controlled in order to prevent decomposition or rearrangement.[56–58] As a general rule, we do not attempt to store allylic chlorides or bromides but use the materials immediately in the phosphorylation reaction once we have verified by ^{1}H NMR spectroscopy that the reactive intermediates were indeed prepared. In any event, it is clear that the displacement reaction is useful for the synthesis of stereospecifically labeled substrates.

Purification of Isoprenoid Diphosphates. As optimal conditions were being developed for the displacement reaction, it became apparent from NMR spectra of the reaction mixtures that pyrophosphorylation of activated precursors was usually a very efficient process. Although yields after purification using published procedures were occassionally as high as 60%, recoveries were usually substantially lower. Several chromatographic systems, including DOWEX AG1-X8,[12,19] DEAE Sephadex A-25,[15,20,21] silica gel,[19,59,60] and Amberlite,[19,22,23] were investigated. In our hands, no single support was satisfactory for all of the diphosphates listed in Table I. In addition, the recovery of materials was not reproducible and substantial losses were often encountered during chromatography. Finally, it was sometimes difficult to detect products because large volumes were often required for elution and components in the buffers often interfered with detection of the diphosphates.

We discovered that the ammonium salts of the diphosphates had much better chromatographic properties than their tetra-*n*-butylammonium counterparts. Ion exchange was most efficiently achieved with a 10-fold excess

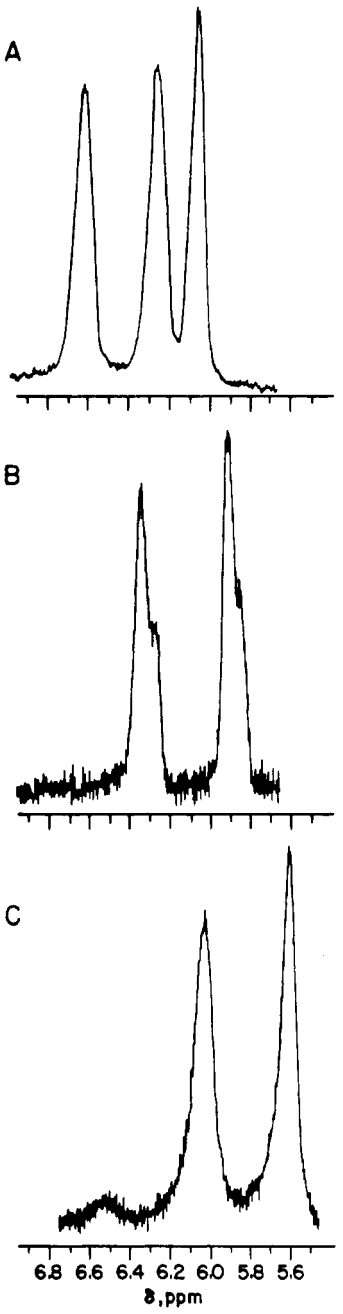


Figure 1. ^{1}H NMR spectra at 300 MHz of the (–)-camphanate esters of geraniol (A), (*S*)-[1-^{2}H]geraniol (B), and [1-^{2}H]geraniol recovered upon hydrolysis of [1-^{2}H]geranyl diphosphate by *E. coli* alkaline phosphatase (C). Spectra were run in carbon tetrachloride at 24 °C in solutions containing 0.5 molar equiv of Eu(thd)$_3$. The region between 5.5 and 6.8 ppm contains resonances for the vinyl proton at C2 and the diastereotopic methylene protons at C1 of the geranyl moiety.

(51) Friedman, L.; Jurewicz, A. T. *J. Org. Chem.* **1968**, *33*, 1254–1255.
(52) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. H.; Hems, R. A.; Jansen, B. H.; Walker, T. *J. Chem. Soc.* **1952**, 1094.
(53) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274–275.
(54) Fernley, H. N. *The Enzymes*, 3rd ed.; Boyer, P. O., Ed.; Academic: New York, 1971; Vol. 4, pp 417–447.
(55) Corey, E. J.; Kim, C. V.; Taheeda, M. *Tetrahedron Lett.* **1972**, 4339–4341.
(56) Collington, E. N.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044–3045.
(57) Calzada, J. G.; Hooz, J. *Org. Synth.* **1974**, *54*, 63–67.
(58) Stork, G.; Grieco, P. A.; Gregson, M. *Org. Synth.* **1974**, *54*, 68–70.
(59) Plieninger, H.; Immel, H. *Chem. Ber.* **1965**, *98*, 414–418.
(60) Gafni, V.; Shechter, I. *Anal. Biochem.* **1979**, *92*, 248–252.

of DOWEX AG50-X8 cation-exchange resin (ammonium form) by using dilute buffered solutions containing small amounts of isopropyl alcohol. Materials recovered after lyophilization were routinely checked by ^1H NMR spectroscopy for residual tetra-*n*-butylammonium cation. Typically less than 5% was found; however, larger amounts of the tetraalkylammonium counterion resulted in excessive tailing and poor yields in the subsequent chromatography. Therefore, it is imperative to reduce the amount of tetra-*n*-butylammonium before continuing the purification, and this, on occasion, required a second pass through a fresh cation-exchange column.

After ion exchange and lyophilization the residue consists of a mixture of ammonium salts of organic diphosphate, inorganic pyrophosphate, and the displaced leaving group. A simple extraction procedure removes the isoprenoid diphosphates from inorganic ammonium salts. This step significantly enhances the amount of material that can be loaded and the resolution in the following chromatography.

Cellulose is the support of choice for the final chromatography. Elution of the diphosphates as pure materials can be achieved rapidly from packed columns of fibrous cellulose under isocratic conditions using aqueous mixtures of organic solvents buffered with ammonium bicarbonate. Optimal conditions for elutions were developed by cellulose thin-layer chromatography and used without further modification for separations with the packed column. Cellulose TLC is also an excellent analytical method for detecting which fractions contain isoprenoid diphosphate following column chromatography. The conditions for elution of the diphosphates from cellulose are mild and selective for a broad range of phosphorylated materials. The solvent is buffered with low concentrations of ammonium bicarbonate, and this amount of salt is easily removed under vacuum at room temperature. It is important to control the pH at all stages of the purification. ^1H and ^{31}P NMR spectra indicate that the diphosphates hydrolyze to monophosphates and inorganic phosphate at pH >9 and decompose to isoprenoid alcohols and inorganic pyrophosphate at pH <6.5.

Following chromatography, fractions containing the diphosphate esters are pooled, and the material is recovered as a white powder by lyophilization. Occasionally the samples are contaminated by ammonium carbonate. In these cases, the material is dissolved in a minimal amount of 10 mM ammonium bicarbonate and carbon dioxide is bubbled through the solution until the pH drops to 7.2. The material is then lyophilized again. While it is important to remove all of the ammonium bicarbonate, one should avoid leaving the ammonium salts under high vacuum for prolonged periods. It is possible to decompose ammonium salts of allylic diphosphates under vacuum, presumably by removal of ammonia, which converts the tris(ammonium) salt to a more reactive bis(salt). We have prepared sodium salts of dimethylallyl diphosphate (**23**), geranyl diphosphate (**33**), farnesyl diphosphate (**38**), and phytanyl diphosphate (**40**) from the corresponding ammonium salts by cation exchange on DOWEX AG50-X8 (sodium form) and found that these materials were stable under vacuum at room temperature. The yields for all of the diphosphates listed in Table I were based on materials that were homogeneous by thin-layer chromatography and by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The salts were stored as powders over calcium sulfate at −78 °C for periods of up to 2 years without significant decomposition.

The procedures we developed to purify diphosphates from the displacement reaction can also be used to obtain pure materials from the more complex mixtures obtained during the Cramer phosphorylation. Linalyl diphosphate[26] and presqualene diphosphate,[42] both of which were prepared by the Banthorpe modification[25] of the Cramer reaction, were purified by the extraction–chromatography sequence. Although the yields were low (4% and 22%, respectively), the losses were a result of the syntheses, and the compounds were homogeneous following chromatography.

Summary. Synthesis of isoprenoid diphosphates from the corresponding alcohols by direct displacement of activated intermediates is an excellent route to this class of compounds. With few exceptions the yields for unhindered primary and primary allylic systems are high and in all instances are superior to other published syntheses. The displacement proceeds with inversion at the activated carbon, and the reaction can be used to prepare diphosphates with isotopically labeled chiral C1 methylene groups in high optical purity. In addition, this method has been adapted to the synthesis of radiolabeled isoprenoid diphosphates.[61] Cellulose chromatography using mixed organic–aqueous solvents buffered by low concentrations of ammonium bicarbonate provides a rapid, general procedure for purification of the diphosphates. The chromatography is also useful for isolating isoprenoid diphosphates from the more complex mixtures obtained from the Cramer phosphorylation. Twenty isoprenoid metabolites and analogues with hydrocarbon chains containing from 5 to 30 carbons have now been purified in this manner by simply adjusting the composition of the elution buffer. In addition the displacement reaction will convert nucleosides activated at the 5′-position to diphosphates and methanediphosphonates.[62] The only primary substrate that has thus far proved to be intractable is the unstable, sterically congested chrysanthemyl system.

Experimental Section

General Methods. Proton and carbon NMR spectra are reported in parts per million downfield from either internal Me_4Si or DDS, fluorine spectra in parts per million upfield from external trichlorofluoromethane, and phosphorous spectra in parts per million downfield from external phosphoric acid. NMR spectra were obtained in either deuteriochloroform or deuterium oxide (Aldrich Chemical Co.). Infrared spectra were calibrated to the 1602 cm^{-1} absorption of polystyrene. All absorptions are reported in wave numbers (cm^{-1}). Gas chromatographic analyses were performed on 12.5-m OV-1 WCOT and 25-m SE-54 capillary columns. Silica gel flash chromatography was performed on grade 60, 235–400 mesh silica gel (Aldrich Chemical Co.), and TLC was performed on silica gel 60 F-254 glass plates (American Scientific Products). Silica TLC plates were visualized under UV light, by iodine, or by dipping in a 10% solution of phosphomolybdic acid in ethanol followed by heating. Cellulose flash chromatography was performed on Whatman CF-11 fibrous cellulose, and TLC was performed on cellulose 0.1-mm glass plates (American Scientific Products). Cellulose TLC plates were visualized by iodine or sulfosalicylic acid–ferric chloride[30] stain.

Materials. Dowex AG 50W-X8 cation-exchange resin (100–200 mesh) was purchased from Bio-Rad. Reagent grade hexanes were purified by washing with acid and base, filtration through neutral alumina, and distillation from glass. Reagent grade anhydrous diethyl ether, tetrahydrofuran, and purified hexanes were dried over lithium aluminum hydride and distilled from sodium metal/benzophenone ketal. Reagent grade acetonitrile and dichloromethane were distilled from anhydrous phosphorus pen-

(61) Davisson, V. J.; Zabriskie, T. M.; Poulter, C. D. *Bioorg. Chem.* **1986**, *14*, 46–54.
(62) Dixit, V. M.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 4055–4058.
(63) Coates, R. M.; Ley, D. A.; Cavender, D. L. *J. Org. Chem.* **1978**, *43*, 4915–4922.

toxide. All solvents for chromatography were of reagent grade and glass distilled prior to use except for acetonitrile and isopropyl alcohol used for cellulose flash chromatography. These were used without purification. Disodium dihydrogen pyrophosphate, horse liver alcohol dehydrogenase (EC 1.1.1.1), *E. coli* alkaline phosphatase (EC 3.1.3.1), nicotinamide adenine dinucleotide, lysine, ammonium bicarbonate, magnesium chloride, and Tween-80 were purchased from Sigma Chemical Co. Lithium aluminum deuteride, triethyl phosphonoacetate, *N*-chlorosuccinimide, dimethyl sulfide, (-)-camphanic acid, (*N,N*-dimethylamino)pyridine, 2-(dimethylamino)ethyl chloride hydrochloride, triethyl phosphite, dibutyl phosphite, sodium metal, 1-bromo-3-methylbutane bromotrimethylsilane, geraniol, nerol, and tetra-*n*-butylammonium hydroxide were purchased from Aldrich Chemical Co. Methanediphosphonic acid and dibromodifluoromethane were purchased from Alfa Chemical Co. *p*-Toluenesulfonyl chloride was purchased from J.T. Baker Chemical Co. and recrystallized from cold hexanes and diethyl ether.

Tris(tetra-*n*-butylammonium) Hydrogen Pyrophosphate (1). A solution of 3.33 g (15.0 mmol) of disodium dihydrogen pyrophosphate in 15 mL of 10% (v/v) aqueous ammonium hydroxide was passed through a 2.5 × 7.0 cm, (58 mequiv) column of Dowex AG 50W-X8 cation-exchange resin (100–200 mesh, hydrogen form). The free acid was eluted with 110 mL of deionized water, and the resulting solution (pH 1.2) was immediately titrated to pH 7.3 with 40% (w/w) aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 150 mL total volume) was dried by lyophilization to yield 13.1 g of a hygroscopic white solid (97%): ^{1}H NMR (90 MHz, D_2O) δ 0.83–1.01 (36 H, m, CH_3), 1.14–1.73 (48 H, m, CH_2), 3.03–3.19 (24 H, m, CH_2), 4.65 (s, OH); ^{31}P NMR (32 MHz, D_2O) δ -1.60 (s).

The initially recovered hydrate from above can be purified by recrystallization. A 2.5-g portion of the white solid was partially dried by twice treating with 75 mL of acetonitrile and azeotropic removal of solvent by rotary evaporation to yield a tacky solid. This material was warmed (40 °C) in 50 mL of ethyl acetate before gravity filtration. The clear, colorless filtrate was concentrated to one-half the volume by rotary evaporation and cooled to -20 °C. The short, white needles were recovered on sintered glass and washed with diethyl ether. Typical recoveries were 40–55%. The water content of the hygroscopic solid was determined by ^{1}H NMR in benzene-d_6.

Tris(tetra-*n*-butylammonium) Hydrogen Methanediphosphonate (2). A solution of 1.0 g (5.68 mmol) of methanediphosphonic acid in 20 mL of deionized water (pH 1.0) was titrated to pH 10.0 with 40% (w/w) aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 32 mL total volume) was dried by lyophilization to yield 4.97 g of a hygroscopic, oily solid (97%): ^{1}H NMR (300 MHz, D_2O) δ 0.87 (36 H, m, CH_3), 1.27 (24 H, m, CH_2), 1.84 (2 H, t, $J_{H,P}$ = 20.6 Hz), 3.10 (24 H, m, CH_2), 4.83 (s, OH); ^{13}C NMR (75 MHz, D_2O)[64] δ 15.2 (q), 21.3 (t), 25.2 (t), 31.0 (dt, $J_{C,P}$ = 112.7 Hz), 60.2 (t); ^{31}P NMR (32 MHz, D_2O) δ 16.07 (s).

Diethyl (Bromodifluoromethyl)phosphonate (3). According to the procedure of Burton and Flynn,[33] a solution of 23.26 g (0.14 mol) of triethyl phosphite in 75 mL of diethyl ether was cooled, under a nitrogen atmosphere, to 4 °C before addition of 33.6 g (0.16 mol) of dibromofluoromethane. The mixture was allowed to warm to room temperature and then heated at reflux for 24 h. Ether was removed by rotary evaporation, and the resultant liquid was distilled to afford 33.59 g (90%) of a clear colorless liquid: bp 97–98 °C (19 mmHg) [lit.[33] bp 99–102 °C (16 mmHg)]; IR (neat) 2990, 2940, 2920, 1475, 1445, 1395, 1370, 1290, 1020, 880 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (3 H, t, $J_{H,H}$ = 6.8 Hz), 4.37 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 16.4 (q), 16.5 (q), 66.6 (t), 66.7 (t), 117.6 (td, $J_{C,F}$ = 330.0 Hz, $J_{C,P}$ = 238.0 Hz); ^{31}P NMR (32 MHz, $CDCl_3$) δ -1.10 (1 P, t, $J_{F,P}$ = 92.0 Hz); ^{19}F NMR (85 MHz, $CDCl_3$) δ 61.8 (d, $J_{F,P}$ = 92.0 Hz).

Butyl and Ethyl Difluoromethanediphosphonates. Following the procedure of Burton and Flynn,[34-36] 7.09 g (36.5 mmol) of dibutyl phosphite was added to a suspension of 0.84 g (36.5 mmol) of sodium metal in 30 mL of hexanes under a nitrogen atmosphere. The resulting mixture was allowed to stir at room temperature for 18 h, during which time the metallic sodium was consumed. The resulting solution was then added dropwise to a solution of 9.74 g (36.5 mmol) of phosphonate **3** in 20 mL of hexanes at 4 °C. The reaction was followed by monitoring the disappearance of the doublet at 61.8 ppm for fluorine in the bromodifluoromethyl group of the phosphonate by ^{19}F NMR spectroscopy. After 4 h, 50 mL of 0.5 M aqueous sodium carbonate was added to the reaction mixture. After an additional 10 min, the aqueous and organic phases were separated. The organic phase was washed with four 15-mL portions of water and dried over anhydrous magnesium sulfate. Solvent was removed by rotary evaporation, and the resulting yellow liquid was distilled to afford 5.63 g (41%) of a clear colorless oil: bp 130–170 °C (1 mmHg) [lit.[36] bp 126–153 °C (0.2 mmHg)]; IR (neat) 2965, 2940, 2920, 2890, 1470, 1390, 1370, 1270, 1035, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95–1.40 (m), 1.42–1.78 (m), 4.05–4.38 (m); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 13.6 (q), 13.7 (q), 16.5 (q), 18.7 (t), 18.9 (t), 19.0 (t), 32.5 (t), 32.6 (t), 32.7 (t), 65.5 (t), 67.5 (t), 67.6 (t), 69.1 (t), 116.5 (tt, $J_{C,P}$ = 186.5 Hz, $J_{C,F}$ = 280.4 Hz), 116.5 (tt, $J_{C,P}$ = 186.5 Hz, $J_{C,F}$ = 280.7 Hz), 116.7 (tt, $J_{C,P}$ = 186.2 Hz, $J_{C,F}$ = 278.9 Hz); ^{31}P NMR (32 MHz, $CDCl_3$) δ 3.82 (t, $J_{F,P}$ = 86.0 Hz), 3.86 (t, $J_{F,P}$ = 86.0 Hz), 3.90 (t, $J_{F,P}$ = 85.9 Hz); ^{19}F NMR (85 MHz, $CDCl_3$) δ 122.4 (t, $J_{F,P}$ = 86.0 Hz), 122.5 (t, $J_{F,P}$ = 86.0 Hz), 122.6 (t, $J_{F,P}$ = 85.9 Hz).

Tetrakis(trimethylsilyl) Difluoromethanediphosphonate (5). Following the procedure of McKenna and Shen,[37] bromotrimethylsilane (1.0 g, 95.0 mmol) was added dropwise to a neat solution of 3.6 g (11 mmol) of mixed difluoromethanediphosphonate esters at room temperature. After the mixture was heated at reflux for 18 h, excess bromotrimethylsilane was removed by vacuum distillation [40 °C (2 mmHg)]. The residue was distilled to afford 4.5 g (95%) of a clear liquid: bp 97–107 °C (1.5 mmHg) [lit.[37] bp 93–95 °C (0.2 mmHg)]; IR (neat) 2960, 2910, 1460, 1412, 1286, 1255, 1060, 850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.37 (36 H, s); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 15.5 (q), 114.9 (tt, $J_{C,P}$ = 154.7 Hz, $J_{C,F}$ = 276.6 Hz); ^{31}P NMR (32 MHz, $CDCl_3$) δ -15.0 (2 P, t, $J_{F,P}$ = 89.0 Hz); ^{19}F NMR (85 MHz, $CDCl_3$) δ 124.1 (t, $J_{F,P}$ = 89.0 Hz).

Tris(tetra-*n*-butylammonium) Hydrogen Difluoromethanediphosphonate (6). To 25 mL of deionized water was added 4.5 g (10.5 mmol) of **5**, and the resulting suspension was allowed to stir for 45 min. The phases were separated, and the aqueous phase was washed with two 15-mL portions of diethyl ether. The aqueous solution (pH 1.0) was titrated to pH 7.3 with 40% (w/w) aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 75 mL total volume) was dried by lyophilization to yield 8.92 g (91%) of a hygroscopic white solid: ^{1}H NMR (300 MHz, D_2O) δ 0.93 (36 H, m, CH_3), 1.35 (24 H, m, CH_2), 1.63 (24 H, m, CH_2), 3.18 (24 H, m, CH_2), 4.83 (s, OH); ^{13}C NMR (75 MHz, D_2O)[64] δ 15.1 (q), 21.2 (t), 25.2 (t), 60.0 (t), 122.7 (tt, $J_{C,P}$ = 231.0 Hz, $J_{C,F}$ = 272.7 Hz); ^{31}P NMR (32 MHz, D_2O) δ 5.4 (t, $J_{F,P}$ = 79.1 Hz); ^{19}F NMR (85 MHz, D_2O) δ 121.1 (t, $J_{F,P}$ = 80.4 Hz).

General Procedure for Preparation of Tosylates. In a flame-dried flask under a nitrogen atmosphere were combined 1 equiv of *p*-toluenesulfonyl chloride and 1.2 equiv of 4-(*N,N*-dimethylamino)pyridine with magnetic stirring in dichloromethane (0.2 M in *p*-toluenesulfonyl chloride). To this solution was added 1.0 equiv of the desired alcohol. After 2–2.5 h, the mixture was poured into a 100 volume excess of hexanes, and the resulting precipitate was removed by filtration. The filtrate was concentrated by rotary evaporation, diluted with diethyl ether, and filtered again. After removal of solvent at reduced pressure, the remaining oil could be used directly in the phosphorylation step. If samples are to be stored for extended periods, residual 4-(*N,N*-dimethylamino)pyridine was removed by passing the materials through a short column of silica gel 60 with hexanes/diethyl ether as the eluent.

3-Methyl-3-buten-1-yl *p*-Toluenesulfonate (Isopentenyl Tosylate, 7). 3-Methyl-3-buten-1-ol (0.043 g, 0.5 mmol) was treated with *p*-toluenesulfonyl chloride (0.105 g, 0.55 mmol) and 4-(*N,N*-dimethylamino)pyridine (0.073 g, 0.6 mmol) in 2.5 mL of methylene chloride. Following workup, 0.118 g (95%) of **7** was obtained as colorless oil. ^{1}H and ^{13}C spectra for **7** were identical with those reported by Trost and co-workers.[65]

(64) Off-resonance pattern included in ^{13}C multiplicity.

4-Fluoro-3-methyl-1-butyl *p*-Toluenesulfonate (8). 4-Fluoro-3-methyl-1-butanol (0.100 g, 0.942 mmol) was treated with *p*-toluenesulfonyl chloride (0.197 g, 1.04 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.139 g, 1.14 mmol) in 2 mL of methylene chloride for 8 h. Following workup and flash chromatography (2:1 hexene/ethyl acetate), 0.18 g (75%) of **8** was obtained as a colorless oil: R_f 0.41; IR (CCl_4) 3080, 3030, 2955, 2895, 1595, 1490, 1466, 1454, 1429, 1363, 1302, 1287, 1206, 1183, 1175, 1091, 1033, 1016, 968, 941, 870, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3 H, d, $J_{H,H}$ = 6.9 Hz, CH_3 at C3′), 1.43–1.80 (2 H, m, H at C2) 1.80–2.27 (1 H, m, H at C3), 2.43 (3 H, s, tosyl CH_3), 4.07 (2 H, t, $J_{H,H}$ = 6.6 Hz, H at C2), 4.18 (2 H, dd, $J_{H,F}$ = 4.8 Hz, $J_{H,F}$ = 48.0 Hz, H at C4), 7.31 (2 H, d, $J_{H,H}$ = 8.4 Hz, phenyl H), 7.75 (2 H, d, $J_{H,H}$ = 8.4 Hz, phenyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (d, $J_{C,F}$ = 5.5 Hz), 21.6 (s), 30.6 (d, $J_{C,F}$ = 27.1 Hz), 31.7 (d, $J_{C,F}$ = 5.1 Hz), 68.3 (s), 87.4 (d, $J_{C,F}$ = 170.2 Hz), 127.7 (s), 127.8 (s), 129.7 (s), 144.6 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ 223.96 (1 F, dt, $J_{H,F}$ = 21.4 Hz, $J_{H,F}$ = 47.1 Hz).

Anal. Calcd for $C_{12}H_{17}FO_3S$: C, 55.37; H, 6.58. Found: C, 55.57; H, 6.82.

3-(Fluoromethyl)-3-buten-1-yl *p*-Toluenesulfonate (9). 3-(Fluoromethyl)-3-buten-1-ol (0.100 g, 0.960 mmol) was treated with *p*-toluenesulfonyl chloride (0.201 g, 1.06 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.141 g, 1.15 mmol) in 2 mL of methylene chloride for 8 h. Following workup and flash chromatography (3:1 hexane/ethyl acetate), 0.211 g (85%) of **9** was obtained as a colorless oil: R_f = 0.35; IR (CCl_4) 3080, 3060, 3035, 2960, 2920, 2890, 1735, 1647, 1593, 1489, 1360, 1184, 1172, 1092, 970, 902, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (3 H, s, tosyl CH_3) 2.46 (2 H, t, $J_{H,H}$ = 6.9 Hz, H at C2), 4.16 (2 H, t, $J_{H,H}$ = 6.7 Hz, H at C1), 4.75 (2 H, d, $J_{H,F}$ = 47.2 Hz, H at C3′), 5.02 (1 H, d, $J_{H,H}$ = 0.6 Hz, H at C4), 5 17 (1 H, d, $J_{H,H}$ = 3.3 Hz, H at C4), 7.35 (2 H, d, $J_{H,H}$ = 8.' Hz, phenyl H), 7.80 (2 H, d, $J_{H,H}$ = 8.2 Hz, phenyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7 (s), 31.9 (s), 68.4 (s), 85.4 (d, $J_{C,F}$ = 166.9 Hz), 116.7 (d, $J_{C,F}$ = 9.5 Hz), 128.3 (s), 130.3 (s), 133.4 (s), 139.8 (d, $J_{C,F}$ = 14.8 Hz), 145.3 (s); ^{19}F NMR (282 MHz, $CDCl_3$) δ 215.9 (1 F, dt, $J_{H,F}$ = 3.5 Hz, $J_{H,F}$ = 47.0 Hz).

Anal. Calcd for $C_{12}H_{15}FO_3S$: C, 55.80; H, 5.85. Found: C, 55.99; H, 6.06.

3,7,11,15-Tetramethylhexadecan-1-yl *p*-Toluenesulfonate (Dihydrophytyl Tosylate, 10). 3,7,11,15-Tetramethylhexadecan-1-ol (90 mg, 0.30 mmol) was treated with *p*-toluenesulfonyl chloride (63 mg, 0.33 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (44 mg, 0.36 mmol) in 1.5 mL of methylene chloride for 12 h. Following workup, 130 mg (96%) of **10** was obtained: IR (neat) 2960, 2930, 2870, 1600, 1462, 1365, 1190, 1177, 1098, 943, 888, 812, 760, 663 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.85 (15 H, d, $J_{H,H}$ = 6.6 Hz, CH_3 at C3′, C7′, C11′, C15′, C16′), 0.50–1.73 (24 H, m), 2.40 (3 H, s, tosyl CH_3), 4.03 (2 H, t, $J_{H,H}$ = 6.6 Hz, H at C1), 7.28 (2 H, d, $J_{H,H}$ = 7.5 Hz, phenyl H), 7.75 (2 H, $J_{H,H}$ = 7.5 Hz, phenyl H).

General Procedure for Preparation of Chlorides. The procedure is based upon the Corey–Kim reaction[55] for the synthesis of allylic chlorides and bromides from the corresponding alcohols. A flame-dried, three-necked, 100-mL, round-bottomed flask equipped with a rubber septum, a low-temperature thermometer, and a magnetic stirrer was used. The reaction was run under a blanket of nitrogen. *N*-chlorosuccinimide (1.1 equiv) was dissolved in 45 mL of dry methylene chloride. The contents of the flask were cooled to −30 °C in an acetonitrile/dry ice bath. Dimethyl sulfide (1.2 equiv) was added dropwise by syringe to the cold, well-stirred, heterogeneous reaction mixture. The contents of the flask were briefly allowed to warm to 0 °C before the temperature was lowered to −40 °C. A solution of 1 equiv of the alcohol in 5 mL of dry methylene chloride was added by syringe to the milky white suspension over 3 min. The reaction was slowly allowed to warm to 0 °C (1 h) and maintained at that temperature for an additional hour. During this period, the mixture becomes a clear, colorless solution. The ice bath was then removed, and the reaction was allowed to stir at room temperature for 15 min before the mixture was poured into a 250-mL separatory funnel that contained 25 mL of cold saturated sodium chloride. The aqueous layer was extracted with two 20-mL portions of pentane. The organic layers were combined with an additional 20 mL of pentane and washed with two 10-mL portions of cold saturated sodium chloride. The organic layer was then dried over magnesium sulfate for 15 min and filtered by gravity. Solvent was removed by rotary evaporation at aspirator vacuum. Traces of volatile impurities could be removed from the less volatile chlorides under vacuum (1.0 mmHg) at room temperature. The chlorides are colorless oils which can be stored at −20 °C in an inert atmoephere for up to 2 months.

(*E*)-1-Chloro-3,7-dimethyl-2,6-octadiene (Geranyl Chloride, 11). Geranyl chloride[55] was prepared as described previously: IR (neat) 2985, 2920, 2855, 1665, 1450, 1380, 1255, 1155, 1115, 985, 840, 790, 675 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.61 (3 H, s, CH_3), 1.70 (3 H, CH_3), 1.75 (3 H, s, CH_3), 2.10 (4 H, br m, H at C4 and C5), 4.09 (2 H, d, $J_{H,H}$ = 8.9 Hz, H at C1), 5.1 (1 H, br m, H at C6), 5.47 (1 H, t, $J_{H,H}$ = 8.9 Hz H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 15.6 (q), 17.2 (q), 25.3 (q), 26.0 (t), 39.2 (t), 40.5 (t), 120.5 (d), 123.6 (d), 131.6 (s), 142.3 (s).

(*R*)-(*E*)-[1-^{2}H]-1-Chloro-3,7-dimethyl-2,6-octadiene [(*R*)-[1-^{2}H]Geranyl Chloride, 12]. (*S*)-1-Deuteriogeraniol (**46**) (100 mg, 0.65 mmol) was treated with *N*-chlorosuccinimide (130 mg, 0.97 mmol) and dimethyl sulfide (60 mg, 1.3 mmol) in 4 mL of methylene chloride. Following workup, 0.89 g (93%) of **12** was obtained as a colorless oil: R_f 0.65 (1:2 ethyl acetate/hexanes); IR (neat) 2985, 2920, 2855, 2150, 1665, 1450, 1380, 1255, 1155, 1115 (w), 985 (w), 840, 790 (w), 675 cm^{-1}.

(*Z*)-1-Chloro-3,7-dimethyl-2,6-octadiene (Neryl Chloride, 13). Nerol (0.17 mL, 0.15 g, 1.0 mmol) was treated with *N*-chlorosuccinimide (1.5 g, 1.1 mmol) and dimethyl sulfide (0.08 mL, 70 mg, 1.2 mmol) in 5 mL of methylene chloride. Following workup, 0.17 g (99%) of **13**[66] was obtained as a colorless oil: R_f 0.65 (1:2 ethyl acetate/hexanes); IR (neat) 2960, 2920, 2860, 1660, 1445, 1375, 1280, 1155, 1030, 980, 835, 670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 2.11 (4 H, m, H at C4 and C5), 4.04 (2 H, d, $J_{H,H}$ = 8.5 Hz, H at C1), 5.10 (1 H, m, H at C6), 5.42 (1 H, t, $J_{H,H}$ = 8.5 Hz, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 17.6 (q), 23.4 (q), 25.6 (q), 26.5 (t), 31.9 (t), 40.7 (t), 121.2 (d), 123.4 (d), 131.9 (s), 142.1 (s).

(*E*,*E*)-1-Chloro-3,7,11-trimethyl-2,6,10-dodecatriene (Farnesyl Chloride, 14). (*E*,*E*)-Farnesyl chloride[30] was prepared as described previously: IR (neat) 2960, 2920, 2855, 1660, 1455, 1380, 1250, 1110, 980, 835, 740, 665 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.63 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.72 (6 H, s, CH_3s), 2.02 (8 H, br m, H at C4, C5, C8, and C9), 4.11 (2 H, d, $J_{H,H}$ = 8.9 Hz, H at C1), 5.14 (2 H, br m, H at C6 and C10), 5.48 (1 H, t, $J_{H,H}$ = 8.9 Hz, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 14.0 (q), 15.8 (q), 22.7 (q), 25.5 (q), 26.1 (t), 26.7 (t), 31.7 (t), 39.4 (t), 39.7 (t), 120.5 (d), 123.3 (d), 124.2 (d), 135.2 (s), 141.8 (s), 141.9 (s).

(*E*,*E*,*E*)-1-Chloro-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraene (Geranylgeranyl Chloride, 15). (*E*,*E*,*E*)-Geranylgeraniol (50 mg, 0.172 mmol) was treated with *N*-chlorosuccinimide (24.9 mg, 0.187 mmol) and dimethyl sulfide (13 mg, 0.204 mmol) in 2.8 mL of methylene chloride. Following workup, 51 mg (98%) of **15**[67] was obtained as a colorless oil: IR (neat) 2988, 2918, 2868, 1668, 1450, 1380, 1255, 838 (br), 675 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.54 (9 H, s, CH_3s), 1.66 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 2.02 (12 H, m, H at C4, C5, C8, C9, C12, and C13), 4.08 (2 H, d, $J_{H,H}$ = 8.9 Hz, H at C1), 5.09 (3 H, m, H at C6, C10, C14), 5.40 (1 H, t, $J_{H,H}$ = 8.9 Hz, H at C2).

General Procedure for Preparation of Bromides. This procedure was patterned after that reported by Coates, Ley, and Cavender.[63] A flame-dried, two-necked, round-bottomed flask equipped with a rubber septum and a magnetic stirrer was used. All of the glassware was oven-dried at 100 °C, and the reaction was run under a blanket of nitrogen. Typically 0.8–4 mmol of alcohol was used. A solution of the allylic alcohol (1 equiv) in 3 mL of pentane was cooled to 4 °C in an ice bath. Phosphorus tribromide (1.1 equiv) was added dropwise via syringe to the well-stirred solution. The reaction was allowed to proceed for 10–25 min before addition of 3.3 equiv of methanol. After the

(65) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.

(66) Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097–4104.

(67) Spectral data are similar to that reported for geranylgeranyl bromide.[66]

mixture was stirred an additional 5 min at 4 °C, the aqueous layer was removed. The organic layer was filtered through a plug of 200 mg each of Celite and magnesium sulfate. Solvent was removed by rotary evaporation at 4 °C by using an ice bath to cool the flask.

1-Bromo-3-methyl-2-butene (Dimethylallyl Bromide, 16). Dimethylallyl alcohol (300 mg, 3.5 mmol) was treated with phosphorus tribromide (409 mg, 1.51 mmol) in 5 mL of pentane. Following workup, 0.443 g (85%) of **16**[30] was obtained as a colorless oil: IR (neat) 2970, 2910, 2855, 1665, 1445, 1375, 1150, 980, 845, 765, 665 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.77 (3 H, s, CH_3), 1.80 (3 H, s, CH_3), 4.00 (2 H, d, $J_{H,H}$ = 18.4 Hz, H at C1), 5.33 (1 H, t, $J_{H,H}$ = 8.4 Hz, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 25.9 (q), 28.8 (q), 34.3 (t), 120.7 (d), 139.9 (s).

(*Z*)-1-Bromo-3-(fluoromethyl)-2-butene (17). (*Z*)-3-(Fluoromethyl)-2-buten-1-ol (110 mg, 1.1 mmol) was treated with phosphorus tribromide (115 mg, 0.42 mmol) in 5 mL of pentane. Following workup, 0.110 g (62%) of **7** was obtained as a colorless oil: IR (neat) 2978, 2941, 2919, 1665, 1443, 1377, 1250, 1199, 982, 906, 784, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.87 (3 H, s, CH_3), 4.01 (2 H, d, $J_{H,H}$ = 8.5 Hz, H at C1), 4.97 (2 H, d, $J_{H,F}$ = 47.1 Hz, fluoromethyl), 5.74 (1 H, t, $J_{H,H}$ = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 20.5 (dq, $J_{C,F}$ = 3.2 Hz), 26.7 (t), 80.4 (dt, $J_{C,F}$ = 164.8 Hz), 125.4 (dd, $J_{C,F}$ = 7.3 Hz), 137.0 (d, $J_{C,F}$ = 15.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 219.0 (t, $J_{H,F}$ = 47.1 Hz); mass spectrum, *m/z* (relative intensity) 40.9 (23.1), 59.0 (28.0), 67.1 (19.6), 69.0 (19.0), 87.1 (100), 147.0 (10.0), 149.0 (13.6), 166.0 (1.6), 168.0 (1.2).

(*E*)-1-Bromo-3-(fluoromethyl)-2-butene (18). (*E*)-3-(Fluoromethyl)-2-buten-1-ol (150 mg, 1.4 mmol) was treated with phosphorus tribromide (156 mg, 1.4 mmol) in 5 mL of pentane. Following workup, 0.180 g (75%) of **18** was obtained as a colorless oil: IR (neat) 2950, 2920, 2878, 1667, 1446, 1368, 1229, 1201, 1123, 1038, 1008, 975, 858, 771 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.78 (3 H, s, CH_3), 3.98 (2 H, d, $J_{H,H}$ = 7.5 Hz, H at C1), 4.75 (2 H, d, $J_{F,H}$ = 48.0 Hz, fluoromethyl), 5.83 (1 H, t, $J_{H,H}$ = 7.5 Hz, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 12.6 (dq, $J_{C,F}$ = 3.0 Hz), 27.0 (t), 86.4 (dt, $J_{C,F}$ = 169.7 Hz), 123.4 (dd, $J_{C,F}$ = 11.8 Hz), 137.2 (t, $J_{C,F}$ = 13.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 218.1 (t, $J_{H,F}$ = 48.0 Hz); mass spectrum, *m/z* (relative intensity) 39.0 (14.2), 39.8 (14.5), 41.0 (39.6), 59.0 (44.8), 87.1 (100.0), 166.0 (3.9), 168.0 (3.8).

(*Z*)-1-Bromo-3-(difluoromethyl)-2-butene (19). (*Z*)-3-(Difluoromethyl)-2-buten-1-ol (240 mg, 2.0 mmol) was treated with phosphorus tribromide (231 mg, 0.185 mmol) in 5 mL of pentane. Following workup, 0.251 g (70%) of **19** was obtained as a colorless oil: IR (neat) 2982, 2955, 2923, 2860, 1672, 1449, 1395, 1329, 1240, 1200, 1137, 1093, 1070, 1020, 924, 873, 797, 738 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.85 (3 H, s, CH_3), 3.97 (2 H, d, $J_{H,H}$ = 7.5 Hz, H at C1), 5.88 (1 H, t, $J_{H,H}$ = 7.5 Hz, H at C2), 6.43 (1 H, t, $J_{H,F}$ = 55.0 Hz, difluoromethyl); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 16.0 (tq, $J_{C,F}$ = 3.2 Hz), 24.6 (t), 111.1 (td, $J_{C,F}$ = 235.7 Hz), 129.0 (td, $J_{C,F}$ = 9.2 Hz), 133.8 (t, $J_{C,F}$ = 23.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 117.9 (d, $J_{H,F}$ = 55.0 Hz); mass spectrum, *m/z* (relative intensity) 32.0 (46.6), 39.0 (22.6), 41.0 (17.3), 51.0 (14.0), 53.1 (19.5), 59.0 (33.9), 65.1 (20.5), 77.1 (51.7), 85.1 (15.8), 105.1 (100.0), 184.0 (3.6), 186.0 (3.3).

(*E*)-1-Bromo-3-(difluoromethyl)-2-butene (20). (*E*)-3-(Difluoromethyl)-2-buten-1-ol (180 mg, 1.5 mmol) was treated with phosphorus tribromide (160 mg, 0.59 mmol) in 5 mL of pentane. Following workup, 0.200 g (73%) of **20** was obtained as a clear colorless oil: IR (neat) 2960, 2930, 2878, 1670, 1450, 1398, 1370, 1351, 1245, 1202, 1146, 1099, 1005, 879, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (3 H, s, CH_3), 3.99 (2 H, d, $J_{H,H}$ = 8.4 Hz, H at C1), 5.95 (1 H, t, $J_{H,F}$ = 55.5 Hz, difluoromethyl), 6.03 (1 H, t, $J_{H,H}$ = 8.4 Hz, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 9.1 (tq, $J_{C,F}$ = 2.5 Hz), 25.1 (t), 116.5 (td, $J_{C,F}$ = 237.2 Hz), 128.0 (td, $J_{C,F}$ = 11.3 Hz), 134.4 (t, $J_{C,F}$ = 21.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ 116.1 (d, $J_{H,F}$ = 55.5 Hz); mass spectrum, *m/z* (relative intensity) 29.0 (35.0), 41.0 (60.9), 57.1 (91.6), 83.0 (100.0), 96.0 (33.1), 105.0 (29.0), 184.0 (9.8), 186.0 (9.6).

General Procedure for Preparation of Diphosphates. The reactions were run under a blanket of nitrogen in a flame-dried, round-bottomed flask equipped for magnetic stirring. Typically, 1–2 mmol of halide or tosylate were used in this reaction. To a stirred solution of 2 equiv of inorganic diphosphate in acetonitrile (0.5–1.0 M) was added by syringe a solution of 1 equiv of tosylate or halide in a minimum amount of acetonitrile (0.25–0.5 M). The resulting mixture was allowed to stir for 2 h at room temperature. For homoallylic tosylates, 3 equiv of inorganic pyrophosphate was used. Solvent was then removed by rotary evaporation, and the resulting opaque residue was dissolved in 1:49 (v/v) isopropyl alcohol and 25 mM ammonium bicarbonate (ion-exchanger buffer). The clear colorless solution was slowly passed through a column containing 30 equiv of DOWEX AG 50W-X8 (100–200 mesh) cation-exchange resin (ammonium form) that had been equilibrated with two column volumes of ion-exchange buffer. The column was eluted with two column volumes of the same buffer at a flow rate of one column volume/15 min. The clear colorless eluent was lyophilized to dryness to yield a fluffy white solid. It is important that the ion exchange be complete or the subsequent chromatography on cellulose will not be successful. If a ^1H NMR spectrum of the solid shows more than 10% of residual tetra-*n*-butyl-ammonium salt, the material must be passed through a second column of fresh ion-exchange resin. The residue was then dissolved in 0.1 M ammonium bicarbonate, and the clear solution was transferred to a centrifuge tube. A mixture of acetonitrile and isopropyl alcohol was added, and the contents were mixed thoroughly on a vortex mixer, during which time a white precipitate formed. The suspension was cleared by centrifugation for 5 min at 2000 rpm. The supernatant was removed with a pipet, and the process was repeated two to three times. The combined supernatants were concentrated by rotary evaporation at 40 °C and then freeze-dried. The resulting solid was dissolved in a minimum amount of chromatography buffer and loaded onto a cellulose flash column. Fractions were analyzed on cellulose TLC plates, developed with iodine or sulfosalicylic acid–ferric chloride spray,[30] pooled, and concentrated by rotary evaporation at 40 °C. The material was transferred to a freeze-drying flask and lyophilized. The resulting white solid was collected and stored at −78 °C.

3-Methyl-3-buten-1-yl Diphosphate (Isopentenyl Diphosphate, 21). To 3-methyl-3-buten-1-yl tosylate (288 mg, 1.20 mmol) was added 3.25 g (3.6 mmol) of **1** in 3.5 mL of acetonitrile, and the resulting solution was allowed to stir for 2 h. The resulting material was converted to the ammonium form with 108 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate extracted twice with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm cellulose column (4.5:2.5:3 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.24 g (80%) of a white solid: R_f 0.35; ^1H NMR (300 MHz, D_2O/ND_4OD) δ 1.77 (3 H, s, CH_3 at C3), 2.39 (2 H, t, $J_{H,H}$ = 6.6 Hz, H at C2), 4.05 (2 H, dt, $J_{H,H}$ = 6.6 Hz, $J_{H,P}$ = 3.3 Hz, H at C1), 4.86 (2 H, s, H at C4); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 24.5, 40.7 (d, $J_{C,P}$ = 7.2 Hz), 67.0 (d, $J_{C,P}$ = 4 Hz), 114.6, 147.4; ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ −11.03 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), −7.23 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2).

3-Methyl-3-buten-1-yl Difluoromethanediphosphonate (Isopentenyl Difluoromethanediphosphonate, 22). 3-Methyl-3-buten-1-yl tosylate (288 mg, 1.20 mmol) was treated with 3.36 g (3.6 mmol) of **6** in 3.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 120 mequiv of resin, and after lyophilization the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted three times with 10 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 16 cm cellulose column (4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.270 g (68%) of a white solid: R_f 0.34; ^1H NMR (300 MHz, D_2O/ND_4OD) δ 1.77 (3 H, s, CH_3), 2.36 (2 H, t, J = 6.8 Hz, H at C2), 4.12 (2 H, dt, $J_{H,H}$ = 6.8 Hz, $J_{H,P}$ = 3.4 Hz, H at C1), 4.86 (2 H, m, H at C4); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 24.3 (q), 41.1 (dd, $J_{C,P}$ = 4.9 Hz), 67.5 (dd, $J_{C,P}$ = 5.5 Hz), 114.2 (d), 123.7 (tdd, $J_{C,F}$ = 260.1 Hz, $J_{C,P}$ = 157.4 Hz, $J_{C,P}$ = 167.3 Hz), 146.0 (s); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ 1.28 (1 P, dt, $J_{F,P}$ = 86.4, $J_{P,P}$ = 50.8 Hz), 3.76 (1 P, dt, $J_{F,P}$ = 86.4 Hz, $J_{P,P}$ = 50.8 Hz); ^{19}F NMR (85 MHz, D_2O/ND_4OD) δ 126.6 (dd, $J_{F,P}$ = 73.3 Hz, $J_{F,P}$ = 86.4 Hz).

3-Methyl-2-buten-1-yl Diphosphate (Dimethylallyl Diphosphate, 23). 3-Methyl-2-buten-1-yl bromide (179 mg, 1.20 mmol) was treated with 2.27 g (2.52 mmol) of **1** in 5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 108 mequiv of resin, and after lyophilization

the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted three times with 10 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm cellulose column (4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.24 g (80%) of a white solid: R_f 0.35; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.72 (3 H, s, CH_3), 1.76 (3 H, s, CH_3), 4.45 (2 H, dd, $J_{H,H}$ = 7.0 Hz, $J_{H,P}$ = 7.0 Hz, H at C1), 5.46 (1 H, t, $J_{H,H}$ = 7.0 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 20.0, 27.8, 65.4 (d, $J_{C,P}$ = 4.0 Hz), 123.0 (d, $J_{C,P}$ = 7.2 Hz), 143.3; ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ −11.03 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), −9.02 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2).

3-Methyl-2-buten-1-yl Difluoromethanediphosphonate (Dimethylallyl Difluoromethanediphosphonate, 24). 3-Methyl-2-buten-1-yl bromide (179 mg, 1.2 mmol) was treated with 2.35 g (2.5 mmol) of **6** in 4 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 110 mequiv of resin, and after lyophilization the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted three times with 10 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 17 cm cellulose column (4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.294 g (74%) of a white solid: R_f 0.35; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.72 (3 H, s, CH_3), 1.76 (3 H, s, CH_3), 4.28 (dd, 2 H, $J_{H,H}$ = 6.1 Hz, $J_{H,P}$ = 6.1 Hz, H at C1), 5.17 (t, 1 H, $J_{H,H}$ = 6.1 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 19.8 (q), 27.5 (q), 65.7 (td, $J_{C,P}$ = 5.9 Hz), 122.5 (dd, $J_{C,P}$ = 6.0 Hz), 123.6 (tdd, $J_{C,F}$ = 272.5 Hz, $J_{C,P}$ = 157.1, $J_{C,P}$ = 166.8 Hz), 142.2 (s); ^{31}P NMR (121 MHz, D_2O/ND_4OD) δ 0.96 (td, $J_{F,P}$ = 73.3 Hz, $J_{P,P}$ = 50.3 Hz), 3.58 (td, $J_{F,P}$ = 86.0 Hz, $J_{P,P}$ = 50.3 Hz); ^{19}F NMR (85 MHz, D_2O/ND_4OD) δ 129.8 (dd, $J_{F,P}$ = 73.3 Hz, $J_{F,P}$ = 86.0 Hz).

3-Methyl-1-butyl Diphosphate (25). 1-Bromo-3-methylbutane (100 mg, 0.662 mmol) was treated with 1.19 g (1.32 mmol) of **1** for 24 h. The resulting material was converted to the ammonium form with 40 mequiv of resin, and after lyophilization the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted four times with 4 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3 cm × 20 cm cellulose column (3.5:3.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.11 g (58%) of a white solid: R_f 0.28; ^{1}H NMR (300 MHz, D_2O) δ 0.90 (6 H, d, $J_{H,H}$ = 6.6 Hz, CH_3s), 1.50 (2 H, q, $J_{H,H}$ = 6.7 Hz, H at C2), 1.67–1.70 (1 H, m, H at C3), 3.69 (2 H, q, J = 6.8 Hz, H at C1); ^{13}C NMR (75 MHz, D_2O) δ 24.8, 27.1, 41.7 (d, $J_{C,P}$ = 7.2 Hz), 67.8 (d, $J_{C,P}$ = 3.6 Hz); ^{31}P NMR 32 MHz (D_2O/ND_4OD) δ −10.0 (1 P, d, $J_{P,P}$ = 22.0 Hz, P1), −6.0 (1 P, d, $J_{P,P}$ = 22.0 Hz, P2).

4-Fluoro-3-methyl-1-butyl Diphosphate (26). 4-Fluoro-3-methyl-1-butyl *p*-toluenesulfonate (100 mg, 0.383 mmol) was treated with 1.04 g (1.15 mmol) of **1** in 0.3 mL of acetonitrile for 16 h. The resulting material was dissolved in 4 mL of ion-exchange buffer and converted to the ammonium form with 35 mequiv of resin. After lyophilization the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted four times with 4 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3 cm × 20 cm cellulose column (3.5:3.5:3 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 81 mg (67%) of a white solid: R_f 0.29; ^{1}H NMR (300 MHz, D_2O) δ 0.93 (3 H, d, $J_{H,H}$ = 6.8 Hz, CH_3), 1.44–1.53 (1 H, m, H at C2), 1.68–1.79 (1 H, m, H at C2), 1.88–2.06 (1 H, m, H at C3), 3.92–3.98 (2 H, m, H at C1), 4.35 (2 H, dd, $J_{H,F}$ = 47.7 Hz, $J_{H,H}$ = 5.6 Hz, H at C4); ^{13}C NMR (75 MHz, D_2O) δ 17.5 (d, $J_{C,F}$ = 7.7 Hz, C3′), 32.9 (d, $J_{C,F}$ = 19.4 Hz, C3), 35.0 (t, J = 6.8 Hz, C2), 66.6 (d, $J_{C,P}$ = 6.8 Hz, C1), 91.8 (d, $J_{C,F}$ = 162.2 Hz, C4); ^{31}P NMR (32 MHz, D_2O) δ −7.18 (1 P, d, $J_{P,P}$ = 22.9 Hz), −9.83 (1 P, d, $J_{P,P}$ = 21.2 Hz); ^{19}F NMR (85 MHz, (D_2O) δ 221.6 (dt, $J_{H,F}$ = 20.6 Hz, $J_{H,F}$ = 47.3 Hz).

3-(Fluoromethyl)-3-buten-1-yl Diphosphate (27). 3-(Fluoromethyl)-3-buten-1-yl *p*-toluenesulfonate (100 mg, 0.387 mmol) was treated with 1.05 g (1.16 mmol) of **1** for 3 h. The resulting material was dissolved in 4 mL of ion-exchange buffer converted to the ammonium form with 35 mequiv of resin, and after lyophilization the resulting powder was dissolved in 4 mL of 0.1 M ammonium bicarbonate and extracted four times with 4 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3 cm × 20 cm cellulose column (3.5:3.5:3 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 90.3 mg (74%) of a white solid: R_f 0.23; ^{1}H NMR (300 MHz, D_2O) δ 2.47 (2 H, dt, J = 1.0 Hz, J = 6.6 Hz, H at C2), 4.07 (2 H, q, $J_{H,H}$ = 6.6 Hz, H at C1), 4.93 (2 H, d, $J_{F,H}$ = 46.9 Hz, H at C3′), 5.19 (1 H, d, J = 0.6 Hz, H at C4), 5.24 (1 H, d, J = 3.6 Hz, H at C4); ^{13}C NMR (75 MHz, D_2O) δ 35.5 (d, $J_{P,C}$ = 7.3 Hz), 66.9 (d, $J_{P,C}$ = 3.7 Hz), 89.2 (d, $J_{F,C}$ = 162.7 Hz), 117.8 (d, $J_{F,C}$ = 11.0 Hz), 144.5 (d, $J_{F,C}$ = 14.6 Hz); ^{31}P NMR (32 MHz, D_2O) δ −10.3 (1 P, d, $J_{P,P}$ = 22.0 Hz, P1), −5.9 (1 P, d, $J_{P,P}$ = 22.0 Hz, P2); ^{19}F NMR (75 MHz, D_2O) δ 217.7 (dt, $J_{H,F}$ = 3.7 Hz, $J_{H,F}$ = 47.2 Hz).

(*Z*)-3-(Fluoromethyl)-2-buten-1-yl Diphosphate (28). (*Z*)-3-(Fluoromethyl)-2-buten-1-yl bromide (109 mg, 0.65 mmol) was treated with 1.47 g (1.63 mmol) of **1** in 5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 83 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm cellulose column (4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 110 mg (34%) of a white solid: R_f 0.35; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.84 (3 H, s, CH_3), 4.51 (2 H, m, H at C1), 5.04 (2 H, d, $J_{H,F}$ = 46.0 Hz, fluoromethyl), 5.73 (1 H, t, $J_{H,H}$ = 6.0 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 22.1 (d, $J_{C,F}$ = 3.3 Hz), 63.8 (d, $J_{C,F}$ = 4.5 Hz), 84.3 (d, $J_{C,F}$ = 155.2 Hz), 129.21 (dd, $J_{C,F}$ = 8.0 Hz, $J_{C,P}$ = 4.0 Hz), 138.1 (d, $J_{C,F}$ = 10.4 Hz); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ −11.32 (1 P, d, $J_{P,P}$ = 20.6 Hz, P1), −7.68 (1 P, d, $J_{P,P}$ = 20.6 Hz, P2); ^{19}F NMR (282 MHz, D_2O/ND_4OD) δ 214.88 (t, $J_{H,F}$ = 46.0 Hz).

(*E*)-3-(Fluoromethyl)-2-buten-1-yl Diphosphate (29). (*E*)-3-(Fluoromethyl)-2-buten-1-yl bromide (109 mg, 0.65 mmol) was treated with 2.44 g (2.70 mmol) of **1** in 5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 83 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm cellulose column (4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 120 mg (35%) of a white solid: R_f 0.35; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.75 (3 H, s, CH_3), 4.54 (2 H, m, H at C1), 4.85 (2 H, d, $J_{H,F}$ = 46.6 Hz, fluoromethyl at C3), 5.78 (1 H, m, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 15.4 (d, $J_{C,F}$ = 2.6 Hz), 64.7 (d, $J_{C,F}$ = 5.0 Hz), 90.7 (d, $J_{C,F}$ = 160.3 Hz), 127.3 (dd, $J_{C,F}$ = 7.6 Hz, $J_{C,P}$ = 3.4 Hz), 139.3 (d, $J_{C,F}$ = 13.4 Hz); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ −9.02 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), −4.84 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2); ^{19}F NMR (282 MHz, D_2O/ND_4OD) δ 212.54 (t, $J_{H,F}$ = 46.6 Hz).

(*Z*)-3-(Difluoromethyl)-2-buten-1-yl Diphosphate (30). (*Z*)-3-(Difluoromethyl)-2-buten-1-yl bromide (130 mg, 1.90 mmol) was treated with 1.80 g (2.0 mmol) of **1** in 5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 63 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm cellulose column (4.5:2.5:2.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 250 mg (75%) of a white solid: R_f 0.40; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.82 (3 H, s, CH_3), 4.6 (2 H, m, H at C1), 5.91 (1 H, t, $J_{H,H}$ = 7.0 Hz, H at C2), 6.70 (1 H, t, $J_{H,F}$ = 55 Hz, fluoromethyl at C3); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 17.4 (t, $J_{C,F}$ = 3.0 Hz), 63.2 (d, $J_{C,P}$ = 5.0 Hz), 115.2 (t, $J_{C,F}$ = 232.0 Hz), 132.7 (dt, $J_{C,F}$ = 9.0 Hz, $J_{C,P}$ = 4.5 Hz), 134.9 (t, $J_{C,F}$ = 22.0 Hz); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ −12.69 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), −8.01 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2); ^{19}F NMR (282 MHz, D_2O/ND_4OD) δ 117.22 (d, $J_{H,F}$ = 55 Hz).

(*E*)-3-(Difluoromethyl)-2-buten-1-yl Diphosphate (31). (*E*)-3-(Difluoromethyl)-2-buten-1-yl bromide (200 mg, 1.08 mmol) was treated with 2.44 g (2.70 mmol) of **1** in 5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 83 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 15 cm

cellulose column 4.5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 230 mg (64%) of a white solid: R_f 0.40; ^{1}H NMR (90 MHz, D_2O/ND_4OD) δ 1.71 (3 H, s, CH_3), 4.5 (2 H, m, H at C1), 5.96 (1 H, m, H at C2), 6.08 (1 H, t, $J_{H,F}$ = 54.6 Hz, difluoromethyl); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 11.41 (t, $J_{C,F}$ = 2.2 Hz), 64.1 (d, $J_{C,P}$ = 4.8 Hz), 119.9 (t, $J_{C,F}$ = 234 Hz), 132.1 (dt, $J_{C,F}$ = 10.4 Hz, $J_{C,P}$ = 5.2 Hz), 134.6 (t, $J_{C,F}$ = 22.0 Hz); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ -11.14 (1 P, d, J = 21.7 Hz, P1), -7.57 (1 P, d, J = 21.7 Hz, P2); ^{19}F NMR (282 MHz, D_2O/ND_4OD) δ 115.6 (d, $J_{H,F}$ = 54.6 Hz).

2-(Dimethylamino)ethyl Diphosphate (32). 2-(Dimethylamino)ethyl chloride[68] (100 mg, 0.929 mmol) was treated with 1.68 g (1.86 mmol) of **1** for 24 h. The resulting material was dissolved in 4 mL of ion-exchange buffer, converted to the ammonium form with 56 mequiv of resin, and lyophilized. Flash chromatography on a 3 cm × 20 cm cellulose column (57:43 (v/v) isopropyl alcohol/0.1 M ammonium bicarbonate) yielded 0.170 g (64%) of a white solid: R_f 0.42; ^{1}H NMR (300 MHz, D_2O) δ 2.89 (6 H, s, CH_3s at N), 3.4 (2 H, br t, J = 5.1 Hz, H at C2), 4.22 (2 H, br, dt, $J_{H,P}$ = 8.0 Hz, J = 5.1 Hz, H at C1); ^{13}C NMR (75 MHz, D_2O) δ 45.5, 60.4, (d, $J_{C,P}$ = 5.4 Hz), 62.5; ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ -10.4 (1 P, d, J = 22.0 Hz, P1), -5.5 (1 P, d, J = 22.4 Hz, P2).

(*E*)-3,7-Dimethyl-2,6-octadien-1-yl Diphosphate (Geranyl Diphosphate, 33). (*E*)-3,7-Dimethyl-2,6-octadien-1-yl chloride (206 mg, 1.20 mmol) was treated with 2.27 g (2.52 mmol) of **1** in 3.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 76 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 10 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 11 cm cellulose column (5:2.5:2.5 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 0.30 g (78%) of a white solid: R_f 0.30; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.62 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 2.11 (4 H, m, H at C4 and C5), 4.47 (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz, H at C1), 5.22 (1 H, t, J = 6.5 Hz, H at C6), 5.47 (1 H, t, J = 6.5 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 18.3, 19.7, 27.6, 28.3, 41.6, 65.4, (d, $J_{C,P}$ = 4.0 Hz), 122.9 (d, $J_{C,P}$ = 7.5 Hz), 127.1, 136.7, 145.8; ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ -11.23 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), -9.10 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2).

(*S*)-(*E*)-[1-^{2}H]-3,7-Dimethyl-2,6-octadien-1-yl Diphosphate (34). Following a procedure similar to that described for **33**, 1.27 g (1.1 mmol) of **1** was treated with 89 mg (0.51 mmol) of (*R*)-(*E*)-1-deuteriogeranyl chloride (**12**). Ion exchange, extraction, and purification were performed as described for **33** by using the same elution buffer for the cellulose flash chromatography to yield 56 mg (30%) of a white solid; R_f 0.30; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.62 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 2.11 (4 H, m, H at C4 and C5), 4.45 (1 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz, H at C1), 5.22 (1 H, s, H at C6), 5.44 (1 H, d, J = 6.5 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 18.5 (q), 19.9 (q), 27.8 (q), 28.5 (t), 41.7 (t), 64.5 (dt, $J_{^2H,C}$ = 18.3 Hz, $J_{C,P}$ = 2.8 Hz), 122.4 (dd, $J_{C,P}$ = 7.3 Hz), 126.9 (d), 136.5 (s), 145.8 (s); ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ -10.43 (1 P, d, $J_{P,P}$ = 20.5 Hz, P1), -9.10 (1 P, d, $J_{P,P}$ = 20.5 Hz, P2).

(*E*)-3,7-Dimethyl-2,6-octadien-1-yl Methanediphosphonate (Geranyl Methanediphosphonate, 35). (*E*)-3,7-Dimethyl-2,6-octadien-1-yl chloride (210 mg, 1.2 mmol) was treated with 2.16 g (2.4 mmol) of **2** in 3.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 108 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 12 cm cellulose column (5:2.5:2.5 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 240 mg (60%) of a white solid: R_f 0.42; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.62 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 2.13 (6 H, m, H at C4 and C5 and at phosphonate C), 4.43 (2 H, dd, J = 7.3 Hz, $J_{H,P}$ = 7.3 Hz, H at C1), 5.20 (1 H, m, H at C6), 5.43 (1 H, t, J = 7.3 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 18.2 (q), 19.6 (q), 27.6 (q), 28.5 (t), 30.2 (dt, $J_{C,P}$ = 123.5 Hz), 41.6 (t), 63.9 (dt, $J_{C,P}$ = 6.4 Hz), 122.9 (dd, $J_{C,P}$ = 7.3 Hz), 127.0 (d), 135.0 (s), 144.4 (s); ^{31}P NMR (121 MHz, D_2O/ND_4OD) δ 16.73 (1 P, d, $J_{P,P}$ = 8.8 Hz, P2), 18.85 (1 P, d, $J_{P,P}$ = 8.8 Hz, P1).

(*E*)-3,7-Dimethyl-2,6-octadien-1-yl Difluoromethanediphosphonate (Geranyl Difluoromethanediphosphonate, 36). (*E*)-3,7-Dimethyl-2,6-octadien-1-yl chloride (**12**) (210 mg, 1.2 mmol) was treated with 2.20 g (2.4 mmol) of **6** in 3.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 108 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 12 cm cellulose column (5:2.5:2.5 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 280 mg (64%) of a white solid: R_f 0.36; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.62 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 2.10 (4 H, m, H at C4 and C5), 4.57 (2 H, dd, J = 6.7 Hz, $J_{H,P}$ = 6.7 Hz, H at C1), 5.18 (1 H, m, H at C6), 5.43 (1 H, t, J = 6.7 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 18.2 (q), 19.7 (q), 27.6 (q), 28.4 (t), 41.6 (t), 66.0 (dt, $J_{C,P}$ = 5.5 Hz), 123.1 (dd, $J_{C,P}$ = 5.5 Hz), 123.7 (tdd, $J_{C,F}$ = 263.7 $J_{C,P}$ = 158.9 Hz, $J_{C,P}$ = 166.7 Hz), 127.0 (d), 136.0 (s), 145.3 (s); ^{31}P NMR (121 MHz, D_2O/ND_4OD) δ 1.21 (1 P, dt, $J_{F,P}$ = 73.9 Hz, $J_{P,P}$ = 51.7 Hz), 3.38 (1 P, dt, $J_{F,P}$ = 86.0 Hz, $J_{P,P}$ = 51.7 Hz); ^{19}F NMR (85 MHz, D_2O/ND_4OD) δ 140.4 (dd, $J_{F,P}$ = 86.0 Hz, $J_{F,P}$ = 73.9 Hz).

(*Z*)-3,7-Dimethyl-2,6-octadien-1-yl Diphosphate (Neryl Diphosphate, 20). (*Z*)-3,7-Dimethyl-2,6-octadien-1-yl chloride (**13**) (170 mg, 1.0 mmol) was treated with 2.0 g (2.22 mmol) of **1** in 3.0 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 108 mequiv of resin, and after lyophilization the resulting powder was dissolved in 3 mL of 0.1 M ammonium bicarbonate and extracted three times with 7 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 3.5 cm × 12 cm cellulose column (5:2.5:2.5 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 280 mg (77%) of a white solid: R_f 0.38; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.62 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.76 (3 H, s, CH_3), 2.14 (4 H, m, H at C4 and C5), 4.45 (2 H, dd, J = 6.7 Hz, $J_{H,P}$ = 7.1 Hz, H at C1), 5.19 (1 H, m, H at C6), 5.45 (1 H, t, J = 6.7 Hz, H at C1); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 19.7 (q), 25.4 (q), 27.6 (q), 28.8 (t), 34.0 (t), 65.2 (dt, $J_{C,P}$ = 5.1 Hz), 123.8 (dd, $J_{C,P}$ = 7.4 Hz), 127.0 (d), 137.0 (s), 145.8 (s); ^{31}P NMR (121 MHz, D_2O/ND_4OD) δ -10.27 (1 P, d, $J_{P,P}$ = 21.0 Hz, P1), -7.34 (1 P, d, $J_{P,P}$ = 21.0 Hz, P2).

(*E,E*)-3,7,11-Trimethyl-2,6,10-dodecatrien-1-yl Diphosphate (Farnesyl Diphosphate, 38). (*E,E*)-3,7,11-Trimethyl-2,6,10-dodecatrien-1-yl chloride (**14**) (144 mg, 0.60 mmol) was treated with 1.1 g (1.20 mmol) of **1** in 3.0 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 48 mequiv of resin, and after lyophilization the resulting powder was dissolved in 5 mL of 0.1 M ammonium bicarbonate and extracted three times with 16 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 4.5 cm × 11 cm cellulose column (8.5:1.5 (v/v) tetrahydrofuran/0.1 M ammonium bicarbonate) yielded 190 mg (72%) of a white solid: R_f 0.28; ^{1}H NMR (300 MHz, D_2O/ND_4OD) δ 1.58 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 2.06 (8 H, m, H at C4, C5, C8, and C9), 4.46 (2 H, dd, J = 6.0 Hz, $J_{H,P}$ = 6.0 Hz, H at C1), 5.15 (2 H, m, H at C6 and C10), 5.46 (1 H, t, J = 6.4 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD) δ 18.2, 18.5, 19.9, 27.9, 28.9, 29.1, 42.0, 42.1, 65.2 (d, $J_{C,P}$ = 4.0 Hz), 122.9 (d, $J_{C,P}$ = 7.5 Hz), 127.1, 127.4, 134.4, 138.6, 145.3; ^{31}P NMR (32 MHz, D_2O/ND_4OD) δ -11.45 (1 P, d, $J_{P,P}$ = 20.0 Hz, P1), -10.53 (1 P, d, $J_{P,P}$ = 20.0 Hz, P2).

(*E,E*)-3,7,11-Trimethyl-2,6,10-dodecatrien-1-yl Difluoromethanediphosphonate (Farnesyl Difluoromethanediphosphonate, 39). (*E,E*)-3,7,11-Trimethyl-2,6,10-dodecatrien-1-yl chloride (**14**) (288 mg, 1.20 mmol) was treated with 2.24 g (2.4 mmol) of **6** in 4.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 44 mequiv of resin, and after lyophilization the resulting powder was dissolved in 20 mL of 0.1 M ammonium bicarbonate and extracted three times with 64 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Flash chromatography on a 4.5 cm × 18 cm cellulose column (8.5:1.5 (v/v) tetrahydrofuran/0.1 M ammonium bicarbonate) yielded 340 mg (75%) of a white solid: R_f 0.32; ^{1}H NMR (300 MHz, D_2O,

(68) Burtner, R. R. *J. Am. Chem. Soc.* **1949**, *71*, 2578.

ND_4OD) δ 1.68 (6 H, s, CH_3s), 1.74 (3 H, s, CH_3), 1.78 (3 H, s, CH_3), 2.16 (8 H, br m, H at C4, C5, C8, and C9), 4.63 (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz, H at C1), 5.25 (2 H, m, H at C6 and C10), 5.51 (1 H, t, J = 6.5 Hz, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 18.0 (q), 18.3 (q), 19.7 (q), 27.6 (q), 28.3 (t), 28.5 (t), 41.5 (t), 41.6 (t), 65.9 (td, $J_{C,P}$ = 6.0 Hz), 117.5 (tdd, $J_{C,F}$ = 331.1 Hz, $J_{C,P}$ = 218.1 Hz, $J_{C,P}$ = 236.9 Hz), 122.7 (dd, $J_{C,P}$ = 6.1 Hz), 126.8 (d), 127.0 (d), 135.9 (s), 139.1 (s), 145.1 (s); ^{31}P NMR (121 MHz, D_2O, ND_4OD) δ 1.07 (td, $J_{F,P}$ = 78.3, $J_{P,P}$ = 53.8 Hz) 2.74 (td, $J_{F,P}$ = 85.1 Hz, $J_{P,P}$ = 53.8 Hz); ^{19}F NMR (85 MHz, D_2O, ND_4OD) δ 140.4 (dd, $J_{F,P}$ = 85.1 Hz, $J_{F,P}$ = 78.3 Hz).

3,7,11,15-Tetramethylhexadecan-1-yl Diphosphate (Dihydrophytyl Diphosphate, 40). Dihydrophytyl tosylate (10) (117 mg, 0.259 mmol) was treated with 700 mg (0.78 mmol) of 1 in 2.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 15 mequiv of resin. After lyophilization the resulting powder was purified by flash chromatography on a cellulose column (8.8:1.2 (v/v) tetrahydrofuran/0.025 M ammonium bicarbonate) to yield 98 mg (70%) of a white powder. This material was converted to the sodium form with 5 mL of resin to yield 82 mg (58%) of a white solid: ^1H NMR (300 MHz, D_2O) δ 0.84 (15 H, br s, CH_3s), 1.28 (14 H, br m, CH_2s), 3.97 (2 H, s, H at C1); ^{31}P NMR (32 MHz, D_2O) δ −9.59 (1 P, d, $J_{P,P}$ = 17.6 Hz, P1), −7.80 (1 P, d, $J_{P,P}$ = 17.6 Hz, P2).

(*E*,*E*,*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraen-1-yl Difluoromethanediphosphonate (Geranylgeranyl Difluoromethanediphosphonate, 41). Geranylgeranyl chloride (15) (52 mg, 0.17 mmol) was treated with 0.40 g (0.43 mmol) of 6 in 1.5 mL of acetonitrile for 2 h. The resulting material was converted to the ammonium form with 17 mequiv of resin. After lyophilization the resulting powder was purified by flash chromatography on a cellulose column (8.8:1.2 (v/v) tetrahydrofuran/0.025 M ammonium bicarbonate) to yield 41 mg (45%) of a white solid. This material was converted to the sodium form with 6 mL of resin to afford 33 mg (35%) of a white solid: ^1H NMR (300 MHz, D_2O) δ 1.55 (6 H, s, CH_3s), 1.59 (3 H, s, CH_3), 1.62 (3 H, s, CH_3), 1.69 (3 H, s, CH_3), 2.02 (12 H, m, H at C4, C5, C8, C9, C12, and C13), 4.55 (2 H, m, H at C1), 5.09 (3 H, m, H at C6, C10, and C14), 5.41 (1 H, m, H at C2); ^{31}P NMR (32 MHz, D_2O) δ 5.22 (dt, $J_{F,P}$ = 73.3 Hz, $J_{P,P}$ = 60.8 Hz), 5.72 (dt, $J_{F,P}$ = 80.8 Hz, $J_{P,P}$ = 60.8 Hz).

3,7-Dimethyl-1,6-octadien-3-yl Diphosphate (Linalyl Diphosphate, 42). Linalyl diphosphate was prepared by the Banthorpe modification[25] of the Cramer phosphorylation from linalool (308 mg, 2 mmol). The resulting material was converted the ammonium form with 187 mequiv of resin, and after lyophilization the resulting powder was dissolved in 12 mL of 0.1 M ammonium bicarbonate and extracted three times with 48 mL of 1:1 (v/v) acetonitrile/isopropyl alcohol. Chromatography at a flow rate of 5–10 mL/min on a 6.0 cm × 18.8 cm cellulose column (5:2.5:3.0 (v/v/v) isopropyl alcohol/acetonitrile/0.1 M ammonium bicarbonate) yielded 29 mg (4%) of a white solid: R_f 0.27; ^1H NMR (300 MHz, D_2O/ND_4OD) δ 1.58 (3 H, s, CH_3), 1.64 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 1.78 (2 H, m, CH_2), 2.06 (2 H, m, CH_2), 5.22 (3 H, m, H at C1 and C6), 6.15 (1 H, m, H at C2); ^{13}C NMR (75 MHz, D_2O/ND_4OD)[64] δ 25.2 (t), 26.4 (q), 27.5 (q), 43.8 (q), 57.0 (t), 80.4 (d, $J_{C,P}$ = 8.5 Hz), 115.8 (t), 127.1 (d), 136.0 (s), 145.4 (dd, $J_{C,P}$ = 3.9 Hz); ^{31}P NMR (121 MHz, D_2O/ND_4OD) δ −8.75 (1 P, d, $J_{P,P}$ = 20.7 Hz, P1), −1.19 (1 P, d, $J_{P,P}$ = 20.7 Hz, P2).

Ethyl (*E*)- and (*Z*)-3,7-Dimethyl-2,6-octadienoate (Ethyl Geranoate, 43). Ethyl geranoate was prepared from 6-methyl-5-hepten-2-one (4.04 g, 32 mmol) and triethyl phosphonoacetate (1.38 g, 57.5 mmol).[49] Purification by flash chromatography on a 6.0 cm × 16.5 cm silica gel column gave 5.56 g (95%) of a clear colorless liquid. Gas chromatographic analysis of the liquid showed the isomeric ratio to be 79:21 *E*/*Z*: TLC, R_f 0.54 (1:5.6 ethyl acetate/hexanes); IR (neat) 2965, 2915, 1710, 1650, 1445, 1375, 1220, 1140, 1060, 1035, 860 cm^{-1};[50] ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3 H, t, J = 7.0 Hz), 1.50 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 2.06 (5 H, m, H at C4 and CH_3 at C3), 2.54 (2 H, m, H at C5), 4.04 (2 H, q, J = 7.0 Hz, CH_2 in ethyl group), 5.05 (1 H, s, H at C6), 5.56 (1 H, s, H at C2);[50] ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 13.9 (q), 17.1 (q), 18.1 (q), 25.1 (q), 25.8 (t), 40.6 (t), 58.7 (t), 115.3 (d), 122.7 (d), 131.5 (s), 158.6 (s), 165.6 (s).

(*E*)-[1,1-$^2H_2$]-3,7-Dimethyl-2,6-octadien-1-ol ([1,1-$^2H_2$]-Geraniol, 44). 1,1-Dideuteriogeraniol was prepared by reduction of 2.20 g (11.22 mmol) ethyl geranoate (42) with lithium aluminum deuteride (1.04 g, 24.7 mmol).[51] Purification by flash chromatography on a 5.0 cm × 16.5 cm silica gel column afforded 1.48 g (86%) of a colorless liquid. Gas chromatographic analysis of the product showed that isomeric ratio was 67% *E* and 33% *Z*. The isomers were separated by semipreparative HPLC (1.0 cm × 25.0 cm; 1:9 *tert*-butyl methyl ether/hexanes) to yield 0.95 g (55%) of the *E* isomer: TLC, R_f 0.32 (1:2 ethyl acetate/hexanes); IR (CCl_4) 3400, 2970, 2925, 2880, 2200, 2100, 1720, 1690, 1660, 1445, 1375, 1210, 1090, 1070, cm^{-1}; ^1H NMR[69] (300 MHz, $CDCl_3$) δ 1.61 (3 H, s, CH_3), 1.68 (6 H, s, CH_3s), 2.06 (4 H, m, H at C4 and C5), 5.10 (1 H, s, H at C6), 5.42 (1 H, s, H at C2), ^{13}C NMR (75 MHz, $CDCl_3$)[64,70] δ 16.0 (q), 17.5 (q), 25.5 (q), 26.2 (t), 39.4 (t), 123.4 (d), 124.0 (d), 131.9 (s), 140.0 (s); ^2H NMR (46 MHz, $CHCl_3$) δ 4.10 (s).

(*E*)-[1,1-^2H]-3,7-Dimethyl-2,6-octadienal ([1,1-^2H]Geranial, 45]. 1,1-Deuteriogeranial was prepared by oxidation of 309 mg (2.0 mmol) 1,1-dideuteriogeraniol 44 with activated manganese dioxide[52] to afford 0.3 g (98%) of a yellow oil. This material was used in the next step without further purification: IR (neat) 2970, 2920, 2880, 2735, 2100, 1655, 1440, 1375, 1185, 1105, 980, 820, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (3 H, s, CH_3), 1.69 (6 H, s, CH_3s), 2.20 (4 H, m, H at C4 and C5), 5.08 (1 H, s, H at C6), 5.87 (1 H, s, H at C2); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 17.2 (q), 17.4 (q), 25.3 (q), 25.4 (t), 40.1 (t), 122.1 (d), 126.8 (d), 132.3 (s), 163.4 (s), 190.4 (dt, $J_{^2H,C}$ = 26.5 Hz); ^2H NMR (46 MHz, $CHCl_3$) 9.92 (s).

(*S*)-(*E*)-[1-^2H]-3,7-Dimethyl-2,6-octadien-1-ol (46). Following a procedure similar to that described for (*S*)-[1-^3H]farnesol,[28] 200 mg (1.32 mmol) of deuterio aldehyde 45 was reduced with 250 mg (0.381 mmol) of NAD^+ and 20 drops of Tween-80 in 100 mL of pH 7 potassium phosphate buffer. This solution was treated with 35.7 mg (100 units) of horse liver alcohol dehydrogenase for 36 h at 30 °C. The solution was extracted with ethyl acetate and dried over magnesium sulfate. Solvent was removed by rotary evaporation, and the residue was purified by flash chromatography on a 2.0 cm × 15.0 cm silica gel column to yield 190 mg, 96% of a clear colorless oil. Gas chromatographic analysis of the product showed the isomeric ratio to be 88% *E* and 12% *Z*. The isomers were separated by semipreparative HPLC (1.0 cm × 25.0 cm; 1:9 *tert*-butyl methyl ether/hexanes) to yield 112 mg (62%) of 46; TLC, R_f 0.24 (1:2.5 ethyl acetate/hexanes); IR (CCl_4) 3400, 2965, 2920, 2880, 2160, 1720, 1690, 1660, 1440, 1370, 1175, 1090, 1030, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (3 H, s, CH_3), 1.68 (6 H, s, CH_3s), 2.05 (4 H, m, H at C4 and C5), 4.13 (1 H, d, J = 6.6 Hz, H at C1), 5.10 (1 H, s, H at C6), 5.41 (1 H, d, J = 6.6 Hz, H at C2); ^{13}C NMR (75 MHz $CDCl_3$)[64] δ 16.8 (q), 17.4 (q), 25.8 (q), 26.7 (t), 39.8 (t), 58.8 (dt, $J_{^2H,C}$ = 21 Hz), 123.4 (d), 124.1 (d), 131.9 (s), 139.9 (s); ^2H NMR (46 MHz, $CHCl_3$) δ 4.06 (s).

(*E*)-3,7-Dimethyl-2,6-octadien-1-yl Camphanate (Geranyl Camphanate, 47). To a solution of 28.7 mg (0.19 mmol) of gerianol and 25.6 mg (0.21 mmol) of 4-(*N*,*N*-dimethylamino)-pyridine in 0.4 mL of dichloromethane was added 101 mg (0.47 mmol) of (−)-camphanoyl chloride. The reaction was monitored by TLC, and after 45 min, all of the gerianol [TLC, R_f 0.14 (1:5.7 ethyl acetate/hexanes)] had been consumed. After the reaction was complete, 0.2 mL of water and 3.0 mL of 1:1 dichloromethane/diethyl ether were added. The mixture was transferred to a separatory funnel, and the phases were separated. The organic phase was washed with one 0.5-mL portion of water, one 0.5-mL portion of 2.0 N hydrochloric acid, and one 0.5-mL portion of saturated sodium bicarbonate. The solution was dried over anhydrous magnesium sulfate, and solvent was removed by rotary evaporation to afford a yellow oil. The material was purified by flash chromatography on a 2.0 cm × 16.5 cm silica gel column to yield 41 mg (66%) of a white crystalline solid: TLC, R_f 0.21 (1:5.7 ethyl acetate/hexanes); IR (CCl_4) 2960, 2920, 2880, 2860, 1790, 1735, 1665, 1445, 1375, 1165, 1095, 1055, 1005, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (3 H, s), 1.05 (3 H, s), 1.11 (3 H, s), 1.60 (3 H, s), 1.68 (3 H, s), 1.73 (3 H, s), 1.92 (2 H, m), 2.07 (4 H, m), 2.44 (2 H, m), 4.75 (2 H, d, J = 7.3 Hz), 5.08 (1 H, s), 5.38 (1 H,

(69) Kjosen, H.; Liaaen-Jensen, S. *Acta Chem. Scand.* **1971**, *25*, 85–93.
(70) The resonance for C1 was not observed.

d, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 9.7 (q), 16.6 (q), 16.7 (q), 16.8 (q), 17.7 (q), 25.7 (q), 26.2 (t), 29.0 (s), 30.6 (s), 39.5 (t), 54.1 (t), 54.7 (t), 62.3 (t), 91.1 (s), 117.5 (d), 123.4 (d), 131.7 (s), 143.2 (s), 167.2 (s), 178.0 (s).

(*S*)-(*E*)-[1-^{2}H]-3,7-Dimethyl-2,6-octadien-1-yl Camphanate ([1-^{2}H]Geranyl Camphanate, 48). In a fashion similar to that described for **47**, 141 mg (0.65 mmol) of camphanoyl chloride was added to a solution of 39 mg (0.26 mmol) of (*S*)-1-deuteriogeraniol **46** and 67 mg (0.55 mmol) of 4-(*N*,*N*-dimethylamino)pyridine in 0.45 mL of dichloromethane. The reaction was monitored and worked up as described for **45**. The resultant oily residue was purified by flash chromatography on a 1.0 cm × 16.5 cm silica gel flash column to yield 66.5 mg (78%) of a white crystalline solid: TLC, R_f 0.21 (1:5.7 ethyl acetate/hexanes); IR (CCl_4) 2970, 2930, 2870, 2150, 1795, 1755, 1725, 1445, 1375, 1160, 1095, 1055, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3 H, s), 1.03 (3 H, s), 1.15 (3 H, s), 1.61 (3 H, s), 1.69 (3 H, s), 1.74 (3 H, s), 1.96 (2 H, m), 2.08 (4 H, m), 2.48 (2 H, m), 4.76 (1 H, d, J = 7.3 Hz), 5.08 (1 H, s), 5.39 (1 H, d, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)[64] δ 9.8 (q), 16.6 (q), 16.7 (q), 16.8 (q), 17.7 (q), 25.7 (q), 26.3 (t), 29.0 (s), 30.7 (s), 39.5 (t), 54.5 (t), 55.1 (t), 62.3 (dt, $J_{^2H,C}$ = 22.7 Hz), 90.8 (s), 117.5 (d), 123.5 (d), 131.7 (s), 143.4 (s), 167.2 (s), 178.0 (s); ^{2}H NMR (46 MHz, $CHCl_3$) δ 4.71 (s).

Rate of Pyrophosphorylation of Isopentenyl Tosylate (7). Into a dry 5-mm NMR tube, was added a solution of 90 mg (0.1 mmol) of recrystallized tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (**1**) in 0.4 mL of dry acetonitrile by syringe. To this clear colorless solution was added, by syringe, 0.1 mL of a 0.5 M stock solution of 3-methyl-3-buten-1-yl *p*-toluenesulfonate in acetonitrile that was prepared by diluting 120 mg (0.5 mmol) of isopentenyl tosylate (**7**) into 1 mL of dry acetonitrile. The rate of the reaction was monitored by integration, at 15–20-min intervals, of the AA′XX′ resonances for starting material (AA′ at 7.44 ppm and XX′ at 7.78 ppm) and product AA′ at 7.56 ppm and XX′ at 7.13 ppm).

Rate of Pyrophosphorylation of Geranyl Chloride (11). A. Following a procedure that is similar for that described for **7**, 90 mg (0.1 mmol) of **1** was treated with 0.1 mL of a slightly turbid, 0.5 M solution of **11** in acetonitrile that was prepared by diluting 86 mg (0.5 mmol) of **11** into 1 mL of dry acetonitrile. The rate of the reaction was monitored by integration, at 15–20-min intervals, of the resonances for the protons at C1 of the starting material [4.05 ppm (2 H, d, J = 9.0 Hz)] and product [4.47 ppm (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz)].

B. Following a procedure similar for that described for **7**, 90 mg (0.1 mmol) of **1** in 0.30 mL of dry acetonitrile was treated with 0.20 mL of a slightly turbid, 0.5 M solution of **11** in acetonitrile that was prepared as above. The rate of chloride displacement was monitored by integration, at 15–20-min intervals, of the resonances for the protons at C1 of the starting material [4.05 ppm (2 H, d, J = 9.0 Hz)] and product [4.47 ppm (2 H, dd, J = 6.5 Hz, $J_{H,P}$ = 6.5 Hz)].

Enzymatic Hydrolysis of 49. To a solution of 0.46 mg (200 units) of *E. coli* alkaline phosphatase in 2.5 mL of 0.2 mL of 0.2 M lysine buffer, pH 10.4, containing 2.0 mM magnesium chloride was added 46 mg (0.13 mmol) of (*S*)-[1-^{2}H]geranyl diphosphate (**34**). This mixture was incubated at 37 °C for 7 h with addition of enzyme (0.23 mg, 10.1 units) and magnesium chloride (5 μL of a 1.0 M stock solution) at 2-h intervals. The reaction mixture was transferred to a separatory funnel and extracted with four 2-mL portions of dichloromethane. The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford 16.7 mg (86%) of the desired *S* alcohol. This material was converted to its camphanate ester as described for the authentic camphanate ester **47**.

Acknowledgment. We are grateful for support of this work by the Institute of General Medical Sciences (Grants GM-25521 and GM-21328). The 300-MHz NMR spectrometer utilized in this study was acquired with National Science Foundation and National Institutes of Health instrumentation grants. Mass spectrometry is supported by National Science Foundation (Grants CHE-8100424 and CHE-8310031) and the University of Utah Instrument Funds Committee.

Registry No. **1**, 76947-02-9; **3**, 65094-22-6; **5**, 78715-61-4; **6**, 104714-96-7, 781-03-3; **8**, 104714-97-8; **9**, 104714-98-9; **10**, 100566-23-2; **11**, 5389-87-7; **12**, 104714-99-0; **13**, 104759-81-1; **14**, 67023-84-1; **15**, 68799-82-6; **16**, 870-63-3; **17**, 104715-00-6; **18**, 104715-01-7; **19**, 104715-02-8; **20**, 104715-03-9; **21**, 3415-48-3; **22**, 104715-04-0; **23**, 22679-02-3; **24**, 104715-05-1; **25**, 104715-06-2; **26**, 104715-07-3; **27**, 104715-08-4; **28**, 104715-09-5; **29**, 104715-10-8; **30**, 104715-11-9; **31**, 104715-12-0; **32**, 104715-13-1; **33**, 104715-14-2; **34**, 104715-15-3; **35**, 104715-16-4; **36**, 104715-17-5; **37**, 104715-18-6; **38**, 104715-19-7; **39**, 104715-20-0; **40**, 104715-21-1; **41**, 104738-00-3; **42**, 104715-22-2; (*E*)-**43**, 32659-21-5; (*Z*)-**43**, 32659-20-4; (*E*)-**44**, 32637-86-8; (*Z*)-**44**, 32637-85-7; **45**, 141-27-5; **46**, 104715-23-3; **47**, 41809-74-9; **48**, 104715-24-4; CH_2=$C(CH_3)CH_2CH_2OH$, 763-32-6; $(CH_3)_2C$=$CHCH_2OH$, 556-82-1; $(CH_3)_2CHCH_2CH_2OH$, 123-51-3; $FCH_2CH(CH_3)CH_2CH_2OH$, 104715-25-5; CH_2=$C(CH_2F)CH_2CH_2OH$, 104715-26-6; (*Z*)-$FCH_2C(CH_3)$=$CHCH_2OH$, 5944-19-4; (*E*)-$FCH_2C(CH_3)$=$CHCH_2OH$, 5944-60-5; (*Z*)-$F_2CHC(CH_3)$=$CHCH_2OH$, 104715-27-7; (*E*)-$F_2CHC(CH_3)$=$CHCH_2OH$, 104715-28-8; $(CH_3)_2NCH_2CH_2OH$, 108-01-0; (*E*)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=$CHCH_2OH$, 106-24-1; (*Z*)-$(CH_3)_2C$=$CHCH_2CH_2C(CH_3)$=$CHCH_2OH$, 106-25-2; (*E*,*E*)-$(CH_3)_2C$=$CH(CH_2)_2(C(CH_3)$=$CH(CH_3)$=$CH(CH_2)_2)_2C(CH_3)$=$CHCH_2OH$, 106-28-5; $(CH_3)_2CH(CH_2)_3(CH(CH_3)(CH_2)_3)_2CH(CH_3)(CH_2)_2OH$, 645-72-7; $(CH_{32}C$=$CH(CH_2)_2(C(CH_3)$=$CHCH_2CH_2)_2C(CH_3)$=$CHCH_2OH$, 24034-73-9; $(CH_3)_2CHCH_2CH_iBr$, 107-82-4; $(CH3)_2NCH_2CH_2Cl$, 107-99-3; tris(tetra-*n*-butylammonium) hydrogen methanediphosphonate, 93978-76-8; butyl difluoromethanediphosphonate, 74860-86-9; ethyl difluoromethanediphosphonate, 78715-58-9; dibutyl phosphite sodium salt, 2244-27-1; triethyl phosphite, 122-52-1; dibromofluoromethane, 1868-53-7; bromotrimethylsilane, 2857-97-8; linalool, 78-70-6; 6-methyl-5-hepten-2-one, 110-93-0; triethyl phosphonoacetate, 867-13-0.

Auxiliary Structure and Asymmetric Induction in the Ene Reactions of Chiral Glyoxylates

James K. Whitesell,* Robert M. Lawrence, and Huang-Hsing Chen

Department of Chemistry, University of Texas at Austin, Austin, Texas 78712

Received November 15, 1985

A variety of chiral auxiliaries (**1a–13a**) were prepared and tested for levels of asymmetric induction control in the ene reaction of chiral glyoxylates. Structural features required for high levels of control were defined by systematic modification of the auxiliary, providing systems with induction levels that ranged from 1.2 to 1 to better than 99.9 to 0.1.

In 1982 we reported a new method for the control of absolute stereochemistry using the ene reactions of chiral glyoxylates (eq 1).[1] This method represents by far the most powerful method so far reported for the formation

0022-3263/86/1951-4779$01.50/0