Tetrahedron Vol. 46, No. 19, pp. 6645-6658, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

THE SYNTHESIS OF ISOPRENOID (PHOSPHINYLMETHYL)PHOSPHONATES

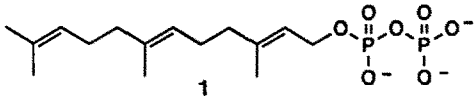
Scott A. Biller* and Cornelia Forster

The Squibb Institute for Medical Research
P.O. Box 4000, Princeton, New Jersey 08543-4000

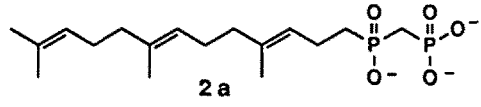
(*Received in USA* 18 *June* 1990)

Abstract: A synthetic route to isoprenoid (phosphinylmethyl)phosphonates (PMPs), stable analogues of the biologically important diphosphates, is described. This method involves the reaction of an α-phosphonate carbanion with an isoprenoid phosphonochloridate to provide the PMP triesters, followed by ester cleavage with TMSBr or TMSI. ^{13}C NMR, ^{31}P NMR, ^{19}F NMR and FAB-MS data were employed for the characterization of PMP salts and triesters.

The (phosphinylmethyl)phosphonate (PMP) function has received attention of late as a mimic of biologically important intermediates and transition states.[1-3] We have demonstrated[1] that the PMP moiety can serve as a stable surrogate for the reactive allylic diphosphate subunit of farnesyl diphosphate **1** in the design of inhibitors of squalene synthetase.[4] This class of enzyme inhibitors is represented by the prototype **2a**. Related studies by McClard and coworkers reveal that the PMP can replace the diphosphate in the creation of inhibitors and novel substrates for prenyl transferase.[2]



1



2a

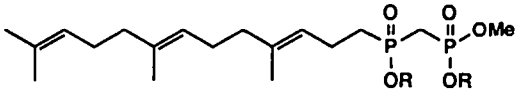
At the outset of our work, very few examples of PMPs had been reported,[3,5] and a versatile synthesis of PMPs did not exist. In this paper, we describe a general route for the synthesis of isoprenoid PMPs from phosphonic diesters (Scheme I). We expect that this method will have broad applicability to other substances containing the PMP moiety.

Results. Our route to PMPs utilizes the reaction of phosphonochloridates **5** with phosphonate stabilized carbanions (*eg*. **6** and **7**) to form PMP triesters **8** and **9** in the key coupling step[6] (Scheme I). Phosphonate diesters **4a-d** were converted to phosphonochloridates **5a-d** by base hydrolysis to the monoacids followed by acid chloride formation. In our early studies, acid chlorides **5** were prepared from the monoacid intermediates via reaction with oxalyl chloride in benzene catalyzed by DMF at RT (Method A). We later found that treatment of the monoacid with excess *N,N*-diethyltrimethylsilylamine in CH_2Cl_2 prior to acid chloride formation with oxalyl

chloride (catalytic DMF, CH_2Cl_2, 0°C to RT, Method B) resulted in a faster reaction and a cleaner ultimate transformation to **8** and **9**. This sequence is presumed to occur via the corresponding trimethylsilyl ester,[7] which liberates chlorotrimethylsilane upon reaction with oxalyl chloride, thereby minimizing contact of the substrate with HCl.

The C-P coupling reaction was performed by the dropwise addition of a THF solution of the acid chloride **5** to a solution of the anion **6** or **7** at -78°C. When **6** was employed as the nucleophile, 2-2.2 equiv of the anion was required in order to deprotonate the acidic triester **8**. Anion **6** was generated[8] via the deprotonation of dimethyl methylphosphonate with *n*-butyllithium in THF at -78°C, whereas anion **7** was formed[9] by the action of LDA on diethyl difluoromethylphosphonate.[10] The three-step transformation of phosphonate diesters **4a-d** to PCH_2P triesters **8a-d** proceeded in good overall yield, whereas the PCF_2P triesters **9a,b** were formed less efficiently. This route to PMP triesters should readily accommodate variation in the structure of R^1 and substitution on the P-C-P carbon,[11] and therefore may have advantages over the alternative methods (*vide infra*).[2,3,5]

The esters of **8a-d** were cleaved with TMSBr[12] (4-4.5 equiv) in the presence of 2,4,6-collidine (1.5-2 equiv) as an acid scavenger in CH_2Cl_2 at RT, followed by salt formation (> 3 equiv of KOH or NaOH) to provide **2a-d.** For the less reactive fluorinated esters **9a,b**, TMSI[13] (4 equiv, CH_2Cl_2, 0°C) in the presence of an acid scavenger (2 equiv BSTFA for **9a**, 2 equiv of 2,4,6-collidine for **9b**) was required to effect deprotection to **3a,b**. Triester **8a** could also be converted selectively to the monomethyl ester, disodium salt **10**, by treatment with NaOH at 50°C (eq 1).

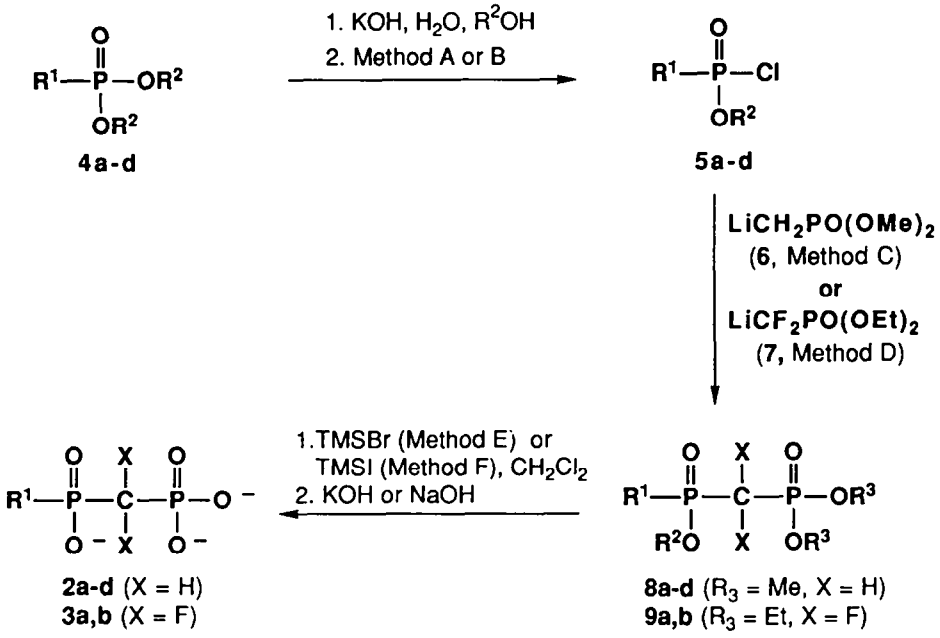


8a (R = Me) —1 M NaOH, 50°C→ **10 (R = Na)** (eq 1)

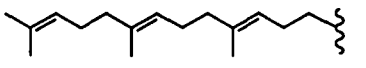
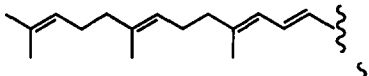
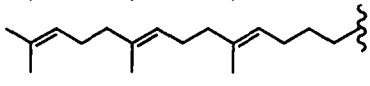
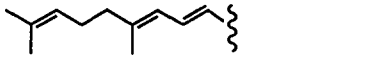
The crude salts were purified by reverse-phase MPLC on CHP20P gel in order to separate the desired product from inorganic salts and other minor impurities. In the case of **2a**, the corresponding dipotassium salt form (12%) eluted separately from the major, tripotassium salt form (65%), at higher acetonitrile concentrations. The two salt forms have very similar ^1H NMR, ^{31}P NMR and mass spectral properties, and when each was neutralized to the triacid with the appropriate equivalents of HCl, the resulting solutions gave nearly identical pH curves on potentiometric titration with 0.1 M KOH. We determined a pK_a value of 8.2 for the third OH group of the triacid. PMP **2b** was isolated as an unseparated mixture of tri- and di-potassium salts (ratio = 1 : 1.5). The more acidic PCF_2P compounds **3a** and **3b** were each obtained as a single, tri-potassium salt in high yield. In addition, the tri-sodium salts of PCH_2P compounds **2c** and **2d** were isolated without complication. It appears that sodium is preferable to potassium with respect to isolation of a single salt form on CHP20P chromatography. The trisodium salts also tend to be less hygroscopic, and hence we consider sodium to

be the counterion of choice.

Scheme I *



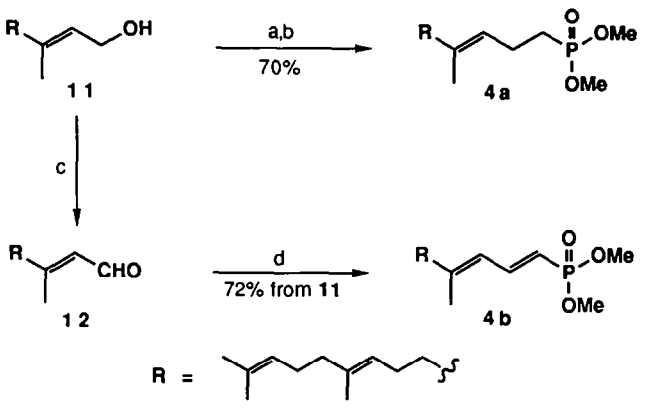
(* R^2 = Me, except for series c, where R^2 = Et)

R^1		% Yield from 4		% Yield from 8 or 9	
		8	9	2	3
	a	73%	42%	65%	82%
	b	71%	30%	81%	74%
	c	65%	___	71%	___
	d	59%	___	73%	___

The diesters **4a-d** were readily prepared starting from commercially available *(E,E)*-farnesol **11** or *(E)*-geraniol **13** (Schemes II and III). *(E,E)*-Farnesol was converted to the corresponding bromide, which was reacted with anion **6** to provide phosphonate **4a,** following the reported procedure.[16] *(E,E)*-Farnesaldehyde **12** was prepared from **11** via the Swern oxidation,[17] which proceeded with clean retention of

the 2-*(E)*-stereochemistry. The reaction of **12** with the sodium salt of tetramethyl methylenediphosphonate[18] provided the *(1E, 3E)*-dienyl phosphonate **4b** in 72% yield from **11**. Similarly, *(E)*-geraniol was converted to the lower prenylogue **4d** in 53% overall yield.

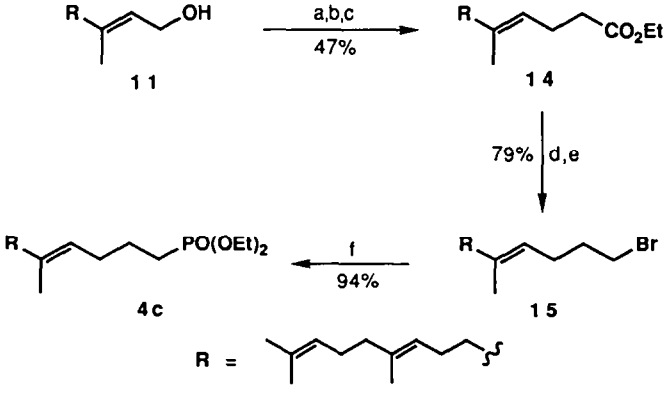
Scheme II



(a) PBr_3, Et_2O, 0°C. (b) **6**, THF, -78°C. (c) Oxalyl Chloride, DMSO, -60°C; Et_3N.
(d) $CH_2(PO(OMe)_2)_2$, NaH, THF, RT.

For the synthesis of phosphonate **4c** (Scheme III), **11** was subjected to a standard two-carbon homologation to ester **14**, followed by ester reduction and conversion of the resulting alcohol to bromide **15**. The Arbuzov reaction[19] of **15** with excess triethyl phosphite delivered the required diester **4c** in high yield.

Scheme III



(a) PBr_3, Et_2O, 0°C. (b) $CH_2(CO_2Et)_2$, NaH, THF. (c) LiCl, DMSO, H_2O, 160°C.
(d) LAH, Et_2O. (e) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; LiBr, THF. (f) $P(OEt)_3$, 150°C.

Spectral Characterization of PMP Triesters and Salts. A variety of spectral studies were employed to confirm the structures assigned to the new PMP triesters and salts. The ^{1}H-decoupled ^{31}P and ^{19}F NMR spectral data for the salts are presented in Table I. For PCH_2P compounds **2a-d** and **10**, the ^{31}P spectra contains two doublets for the phosphinic (P_i) and phosphonic (P_o) acids, due to P-P coupling (J(P-P) = 5.8-6.6 Hz). The doublet for P_i occurs at 36-39 ppm for **2a**, **2c** and **10**, which bear saturated C_α's, whereas the vinyl phosphinic acids of **2b** and **2d** occur upfield at 26-28 ppm. The P_o doublet of **2a-d** and **10** is found at 13-20 ppm. For the PCF_2P compounds **3a** and **3b**, both P_o and P_i are found upfield relative to the corresponding PCH_2P analogues **2a** and **2b** ($\Delta\delta$ = 5-6 ppm for P_i and 10-11 ppm for P_o).[14] Each phosphorus signal appears as a triplet of doublets due to the large doublet P-P coupling (46-47 Hz) as well as the triplet coupling to the adjacent CF_2 (74-82 Hz). In the ^{1}H-decoupled ^{19}F NMR spectra of **3a** and **3b**, the CF_2 signal at 120 ppm shows the expected P-F couplings complementary to that observed in the ^{31}P spectra.

Table I. ^{31}P- and ^{19}F-NMR Spectral Data for PMP Salts: C_α-$P_i(O_2)$-C-$P_o(O_3)$

	P_i				P_o				F		
PMP Salt	mult	δ (ppm)	J_{PP}	J_{PF}	mult	δ (ppm)	J_{PP}	J_{PF}	mult	δ (ppm)	J_{PF}
2a	d	38.9	5.9	___	d	14.2	5.9	___	___	___	___
2b	d	26.2	6.6	___	d	14.8	6.6	___	___	___	___
2c	d	38.8	5.9	___	d	15.5	5.9	___	___	___	___
2d	d	27.7	5.8	___	d	13.0	5.8	___	___	___	___
10	d	36.6	6.6	___	d	19.5	5.9	___	___	___	___
3a	td	32.7	46	77	td	4.0	46	74	t	120.4	76
3b	td	20.9	47	82	td	4.1	47	74	dd	119.9	74,81

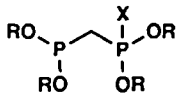
The PCH_2P resonance in the ^{13}C NMR spectra of triesters **8** appears at 26-28 ppm as a doublet of doublets, due to coupling to P_i (76-77 Hz for **8a** and **8c** with saturated C_α, 91-93 Hz for **8b** and **8d** with vinyl C_α) and P_o (134-136 Hz). For the corresponding salts, this resonance is shifted downfield (dd, 31-35 ppm, $J(P_o)$ = 117-118 Hz, $J(P_i)$ = 76-87 Hz). Unfortunately, the additional F-C coupling to the PCF_2P carbon made this signal too highly split to be clearly observed. In the ^{1}H NMR spectra of **8a-d**, the PCH_2P signal occurs at 2.3-2.5 ppm. For the vinyl PMPs **8b** and **8d**, this signal is a very complicated pattern, a result of the diastereotopic nonequivalence of this methylene, whereas for **8a** and **8c**, this resonance is a simple dd (J(P-H) = 16 and

21 Hz) due to coincidental equivalence. The PCH_2P signals for the corresponding salts are obscured by the allylic CH_2 signals (around 2 ppm), except in the case of **8d**, where it stands alone as a triplet at 1.95 ppm (J(P-H) = 18.5 Hz).

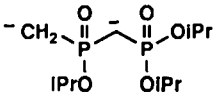
The coupling constants between P_i and its neighboring carbons in the isoprene chain (C_γ-C_β-C_α-P_i) are useful for assigning the ^{13}C NMR spectra of the triesters (**8**, **9**) and salts (**2**, **3**).[28] Large P-C coupling is observed to C_α (94-99 Hz for saturated C_α, 130-144 Hz for vinyl C_α), small coupling to C_β (3.8-5.7 Hz for triesters, typically 0 Hz for salts) and intermediate coupling to C_γ (15-25 Hz).

In a recent study, Poulter and coworkers reported the utility of FAB-MS in the structure confirmation of isoprenoid diphosphates.[15] We have also found the FAB technique to be extremely useful for the molecular weight determination of our PMP salts **2a-d**, **3a,b** and **10**. Strong molecular ions were found in both the negative and positive ion spectra. In the positive ion spectra, a series of ions were observed corresponding to M + K(Na), M + H, and M - K(Na) + 2H, where M represents the molecular weight of the isolated tri-K(Na) salt. A similar series is usually seen in the negative ion spectra: M - K, M - 2K + H, M - 3K +2H.

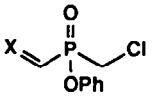
Summary. We have developed a general method for the preparation and purification of isoprenoid (phosphinylmethyl)phosphonates (PMPs). These substances are stable analogues of the corresponding diphosphates[1,2] (*eg.* **1**), which are intermediates in isoprene biosynthesis. In addition to the above mentioned studies on the isoprene pathway, Rosenthal and coworkers have incorporated the PMP as a diphosphate surrogate in analogues of phospholipids and nucleoside diphosphate diacylglycerols.[3b] The PMP subunit has also been elegantly utilized by Wedler[3a] and coworkers in the design of an inhibitor of glutamine synthetase. In this example, the PMP serves as a transition state analogue for nucleophilic attack at the carbonyl group of an acyl phosphate. Since phosphates are ubiquitous in biochemistry, we anticipate that the PMP function, as well as the synthetic route reported herein, will find utility in the synthesis of mimics of other biochemical intermediates and transition states.



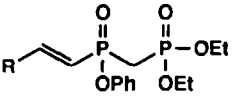
16 X = O or lone pair



17



18a X = Ph_3P
18b X = CHR



19

Several other processes have been utilized to synthesize PMPs. A route suggested by the work of Novikova[5] and exploited by McClard[2] and Wedler[3a] involves the Arbuzov reaction of a phosphorus(III) intermediate such as **16** with alkyl halides. McClard[20] has recently reported the chain extension of dianion **17** upon reaction with alkyl halides and sulphonates. These procedures have the advantage of brevity, but are limited with respect to the structure of the electrophile (it must be reactive in the S_n2 sense) and to substitution on the P-C-P carbon. In addition, the diphosphorus

intermediates represented by **16** are somewhat difficult to prepare. The methodology utilized by Rosenthal[3b] involves the Wittig reaction of **18a** with an aldehyde to form **18b**, followed by an Arbuzov reaction with triethyl phosphite to yield triester **19**. This procedure is limited to the preparation of PCH_2P compounds that can be derived from the adjacent olefin. In addition, the high temperatures required for the Arbuzov reaction (150°C, 48 h) suggests that this method will be restricted to thermally robust substrates.

Our method is versatile with respect to the structure of the phosphonate diester starting material **4** and substitution on the P-C-P carbon.[11] The main limitation is that the intermediates must be stable to the basic conditions for the hydrolysis of the diester **4** to the monoacid, as well those employed for the P-C-P coupling. The former should not be a major concern, since several dealkylative methods can be employed to arrive at the monoacids under milder conditions (for example: NaI/DMF, refluxing t-butylamine,[21] thiolate dealkylation[22] or TMSBr followed by monoesterification[23]).

Experimental Section

Methods and Materials. IR spectra were obtained on a Mattson Sirius 100 FT-IR spectrophotometer. Routine ^1H and ^{13}C NMR spectra were recorded on a JEOL JMN-FX270 NMR spectrometer at 270 MHz and 67.8 MHz, respectively. 400 MHz ^1H NMR spectra were obtained for salts **2**, **3**, and **10** on a JEOL JMN-GX400 instrument. ^{31}P and ^{19}F NMR spectra were measured on a JEOL FX90Q FT-NMR spectrometer, at 36.2 MHz and 84.3 MHz, respectively, utilizing the ^1H decoupled mode. The ^{31}P data were obtained using 85% H_3PO_4 as an external reference ($\delta = 0$); the ^{19}F data were obtained using $CFCl_3$ as an external reference ($\delta = 0$). Chemical ionization mass spectra (CI-MS) were determined with a Finnigan TSQ-4600 instrument equipped with a direct exposure probe using the indicated reagent gases. Fast atom bombardment mass spectra (FAB-MS) were recorded on a VG Analytical ZAB-2F spectrometer. Ions were generated by sputtering (8 keV Xe) from a matrix containing dithiothreitol, dithioerythritol, DMSO, glycerol and water. Unless otherwise indicated, the value utilized for M in the analysis of FAB spectra is the molecular weight of the isolated salt form. Microanalytical samples of salts **2**, **3** and **10** were dried to a constant weight at 50°C, except for **2a**, which was run in its isolated, hydrated form. Potentiometric titrations were carried out on a Metrohm Titroprocessor model 636, with 0.1 N KOH as the titrant.

All reactions were carried out under an atmosphere of dry argon or nitrogen. The following reagents and solvents were distilled prior to use from the indicated drying agents, where applicable: CH_2Cl_2, 2,4,6-collidine, and diisopropylamine (CaH_2); THF and diethyl ether (K, benzophenone); *N,N*-diethyltrimethylsilylamine and oxalyl chloride. Benzene was passed through neutral alumina (activity I) and stored over 4A-molecular sieves. Lithium bromide was dried at 100°C over P_2O_5. *(E,E)*-Farnesol (98%) was purchased from Aldrich Chemical Company, and was usually purified further by flash chromatography[24] on silica gel.

TLC was performed on E. Merck Silica Gel 60 F-254 plates (0.25 mm) or E. Merck Cellulose F plates (0.1 mm). Flash chromatography[24] was carried out using E. Merck Kieselgel 60 (230-400 mesh).

Reverse-phase chromatographic purification of PMP salts was carried out on CHP20P gel (75-150 μ), a highly porous, polystyrene-divinyl benzene copolymer available from Mitsubishi Chemical Industries, utilizing the following general procedure: To activate the CHP20P gel, approximately 1.5 L of CHP20P was stirred in 3 L of acetone, and after settling, the acetone was decanted to remove the fines. The support was transferred to a 3 L coarse fritted filter and was washed successively with CH_3OH (2 L), water (2 L), 30% w/v KOH (2 L), water (6 L), 10% HCl (2 L), water (until effluent is neutral), acetone (4 L), CH_3OH (4 L), and water (12 L). The gel can be recycled almost indefinitely using this process. An FMI Model RP-SY pump was utilized for solvent delivery. A column of CHP20P (2.5 cm diameter, 12-22 cm height) was slurry packed and washed with water (500-1000 mL), and a basic, aqueous solution of the crude salt was applied to the top of

the column. Typically, the column was eluted with water, followed by a gradient composed of increasing concentrations of acetonitrile or methanol in water. The gradient was created by placing the tip of a tightly stoppered separatory funnel containing 300-500 mL of the organic solvent, or an aqueous-organic mixture, just beneath the surface of a reservoir containing 300-500 mL of pure water. To start the gradient, the stopcock of the separatory funnel was opened, so that as the solvent was withdrawn by the pump from the reservoir, it was replaced with the solvent from the separatory funnel. Due to the low lipophilicity of **2d**, water alone was needed to elute the desired product. HPLC-grade solvents and Lectrostill steam distilled water were employed. Fractions were collected (10-15 mL each) at a flow rate of 5-10 mL per minute. Those fractions that contained pure product as judged by TLC were pooled, the organic solvents were evaporated and the aqueous residue was lyophilized to dryness.

***(E,E)*-[[Hydroxy(4,8,12-trimethyl)-3,7,11-tridecatrienyl)phosphinyl]methyl]-phosphonic acid, trimethyl ester (8a, Methods A and C).** A stirred solution of 2.22 g (6.76 mmol) of **4a** in 10 mL of 1:1 CH_3OH/water containing 4.4 g (68.2 mmol) of KOH was heated to 65-75°C for 5.5 h. The CH_3OH was evaporated and the residue was stirred with CH_2Cl_2/water and acidified by adding 10.0 g of solid $KHSO_4$. The mixture was stirred until the phases were homogeneous. The aqueous layer was washed with CH_2Cl_2 and the combined organic extracts were washed with 1:1 brine/water, dried ($MgSO_4$) and evaporated to provide 2.13 g (100%) of the monoacid as a pale yellow oil.

To a stirred solution of 2.05 g (6.50 mmol) of the monoacid in 20 mL of benzene containing 2 drops of DMF under nitrogen was added 1.7 mL (19.50 mmol) of oxalyl chloride over 10 min at RT. After 2.5 h, the solution was evaporated and the residue was twice dissolved in benzene and evaporated, and pumped under vacuum to provide the acid chloride **5a** as an orange oil.

To a stirred solution of 1.80 g (14.50 mmol) of dimethyl methylphosphonate in 30 mL of THF at -78°C was added 8.7 mL (14.0 mmol) of 1.6 M butyllithium in hexane over 5 min under argon to provide a white suspension. After stirring for 15 min at -78°C, the acid chloride **5a** described above was added in 13 mL of THF over 5 min. After 1 h at -78°C, the reaction was allowed to warm to 0°C for 1 h and was diluted with ether and quenched with 10% HCl. The ether solution was separated, washed with water, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give 1.57 g of crude **8a**. The combined aqueous layers were back extracted with CH_2Cl_2 and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to provide an additional 1.10 g of crude **8a**. Flash chromatography on silica gel packed in 2:98 and eluted with 4:96 CH_3OH/CH_2Cl_2 gave 2.01 g (73%) of pure **8a** as a colorless oil. TLC Silica gel (5:95 CH_3OH/CH_2Cl_2) R_f = 0.22. IR (CCl_4) 2955, 2917, 2853, 1450, 1259, 1240, 1184, 1166, 1064, 1039, 845, 822, 781 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.14 (m, 3 H), 3.81 (d, 6 H, J = 11 Hz), 3.77 (d, 3 H, J = 10.5 Hz), 2.40 (dd, 2 H, J = 21.1 and 16.3 Hz), 2.30 (m, 2 H), 2.01 (m, 10 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 136.8, 135.0, 131.1, 124.2, 123.8, 122.5 (d, J = 15.1 Hz), 52.9 (d, J = 3.8 Hz), 51.3 (d, J = 7.6 Hz), 39.6, 39.5, 29.3 (d, J = 96.5 Hz), 26.6, 26.4, 26.3 (dd, J = 76 and 136 Hz), 25.5, 20.1 (d, J = 3.8 Hz), 17.5, 15.9, 15.8 ppm. MS (CI-H_2O, + ions) m/z 421 (M + H).

***(E,E,E)*-[Difluoro[methoxy(4,8,12-trimethyl-1,3,7,11-tridecatetraenyl)phosphinyl]methyl]phosphonic acid, diethyl ester (9b, Methods B and D).** A solution of 2.43 g (7.44 mmol) of diester **4b** in 40 mL of CH_3OH was treated with 30 mL of 1 M KOH and heated to 65°C for 5 h. The pH was adjusted to 7.5 and the CH_3OH was evaporated. The aqueous solution was acidified with 10% HCl and extracted with two portions of EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to provide 2.33 g (100%) of the monoacid as a pale yellow liquid.

To a stirred solution of 1.09 g (3.48 mmol) of the monoacid in 6 mL of CH_2Cl_2 under argon was added 1.3 mL (7.0 mmol) of *N,N*-diethyltrimethylsilylamine. The mixture was allowed to stir for 2 h at RT, the solvent was evaporated, the residue was dissolved in benzene, evaporated, and pumped under vacuum for 30 min. The residue was dissolved in 8 mL of CH_2Cl_2 containing 2 drops of DMF at 0°C under nitrogen, and 0.5 mL (5.73 mmol) of oxalyl chloride was added over 10 min. The solution was allowed to stir at 0°C for 75 min and RT for 45 min followed by solvent evaporation. The residue was dissolved in benzene, evaporated, and pumped at high vacuum to give acid chloride **5b** as an orange oil with some suspended solid.

To a solution of 0.59 mL (4.18 mmol) of distilled diisopropylamine in 7 mL of THF at -78°C under argon was added dropwise 2.4 mL (3.84 mmol) of 1.6 M butyllithium in hexane over 5 min. The reaction was allowed to warm to 0°C for 15 min, followed by cooling to -78°C. A solution of 691 mg (3.67 mmol) of diethyl difluoromethylphosphonate[10] in 4 mL of THF was added over 10 min. The pale yellow solution was allowed to stir for 30 min at -78°C and the acid chloride **5b** described

above was added in 4 mL of THF over 10 min. The solution was maintained at -78°C for 1.5 h and then placed in a -85°C freezer for 15 h. The reaction was quenched with 0.3 mL of acetic acid in 4 mL of ether and allowed to warm to RT. The mixture was partitioned between ether and 10% HCl, and the ether layer was washed with water and saturated $NaHCO_3$. The combined aqueous layers were extracted with two portions of CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and evaporated to provide 1.62 g of an orange oil. The crude product was flash chromatographed twice on silica gel, eluting with 45:55 EtOAc/pet ether in the first column and 10:90 THF/toluene in the second column, to provide 511.1 mg (30%) of **9b** as a pale yellow liquid. TLC Silica gel (35:65 THF/toluene) R_f = 0.39. ^1H NMR ($CDCl_3$, 270 MHz) δ 7.56 (ddd, 1 H, J = 20, 17, and 11 Hz), 6.06 (d, 1 H, J = 11 Hz), 5.72 (dd, 1 H, J = 25 and 17 Hz), 4.35 (m, 4 H), 3.93 (d, 3 H, J = 10 Hz), 1.9-2.3 (m, 8 H), 1.92 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 151.7, 149.2 (d, J = 3.8 Hz), 135.8, 131.1, 124.2 (d, J = 24.6 Hz), 124.0, 123.1, 110.7 (d, J = 143.8 Hz), 65.0 (d, J = 8.6 Hz), 53.0 (d, J = 7.6 Hz), 40.1, 39.5, 26.5, 26.0, 25.5, 17.4, 16.2, 16.1, 15.8 ppm.[25] MS (CI-CH_4, + ions) m/z 483 (M + H).

***(E,E,E)*-[[Hydroxy(4,8,12-trimethyl-1,3,7,11-tridecatetraenyl)phosphinyl]-methyl]phosphonic acid, trimethyl ester (8b, Methods A and C)** was obtained from **4b** in 76% yield as a pale yellow oil. TLC Silica gel (5:95 CH_3OH/CH_2Cl_2) R_f = 0.15. IR (film) 2958, 2924, 2855, 1638, 1450, 1384, 1241, 1186, 1121, 1108, 1033, 845, 819 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 7.47 (ddd, 1 H, J = 20, 17 and 11 Hz), 6.02 (d, 1 H, J = 11 Hz), 5.78 (dd, 1 H, J = 25 and 17 Hz), 5.09 (m, 2 H), 3.81 (d, 3 H, J = 9.5 Hz), 3.77 (d, 3 H, J = 9 Hz), 3.75 (d, 3 H, J = 9 Hz), 2.48 (m, 2 H), 2.15 (m, 4 H), 2.02 (m, 4 H), 1.90 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 149.6, 146.0 (d, J = 5.7 Hz), 135.6, 131.0, 124.0 (d, J = 22.7 Hz), 123.9, 123.0, 116.1 (d, J = 138 Hz), 52.8 (d, J = 7.6 Hz), 52.5 (d, J = 7.6 Hz), 51.0 (d, J = 5.7 Hz), 39.9, 39.4, 27.7 (dd, J = 91 and 134 Hz), 26.4, 25.9, 25.4, 17.4, 17.2, 15.8 ppm. MS (CI-CH_4/N_2O, + ions) m/z 447 (M + C_2H_5), 419 (M + H).

***(E,E)*-[[Ethoxy(5,9,13-trimethyl-4,8,12-tetradecatrienyl)phosphinyl]methyl]-phosphonic acid, dimethyl ester (8c, Methods B and C)** was obtained from **4c** in 65% yield as a pale yellow oil. TLC Silica gel (7:93 CH_3OH/CH_2Cl_2) R_f = 0.21. IR (CCl_4) 2955, 2929, 2854, 1449, 1384, 1368, 1259, 1234, 1184, 1164, 1063, 1037, 955, 843, 821, 780, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.20 (m, 3 H), 4.13 (m, 2 H), 3.80 (d, 6 H, J = 10.5 Hz), 2.29 (dd, 2 H, J = 16 and 21 Hz), 1.8 - 2.1 (m, 12 H), 1.68 (s, 3 H), 1.60 (s, 9 H), 1.34 (t, 3 H, J = 7 Hz) ppm.[26] ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 136.4, 134.8, 131.0, 124.2, 123.9, 122.7, 60.8 (d, J = 7.5 Hz), 52.8 (d, J = 6 Hz), 39.6, 29.3 (d, J = 98.4 Hz), 28.7, 26.6, 26.5, 26.4 (dd, J = 76.5 and 135 Hz), 25.5, 21.7, 17.5, 16.4 (d, J = 6 Hz), 16.0, 15.8 ppm. MS (CI-CH_4, + ions) m/z 477 (M + C_2H_5), 449 (M + H), 417 (M + H - CH_3OH).

***(E,E)*-[[(4,8-Dimethyl-1,3,7-nonatrienyl)hydroxyphosphinyl]methyl]phosphonic acid, trimethyl ester (8d, Methods B and C)** was obtained from **4d** in 59% yield as a pale yellow oil. TLC Silica gel (5:95 CH_3OH/CH_2Cl_2) R_f = 0.17. IR (CCl_4) 2954, 1258, 1241, 1184, 1064, 1037, 849, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 7.47 (ddd, 1 H, J = 20, 17 and 11 Hz), 6.02 (d, 1 H, J = 11 Hz), 5.79 (dd, 1 H, J = 17 and 25 Hz), 5.07 (br, 1 H), 3.80 (d, 3 H, J = 11.5 Hz), 3.77 (d, 3 H, J = 11.5 Hz), 3.72 (d, 3 H, J = 11.5 Hz), 2.48 (m, 2 H), 2.15 (m, 4 H), 1.89 (s, 3 H), 1.68 (s, 3 H), 1.61 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 149.6, 146.1 (d, J = 3.8 Hz), 132.0, 124.0, 123.1, 116.0 (d, J = 138.2 Hz), 52.9 (d, J = 5.7 Hz), 52.6 (d, J = 7.6 Hz), 51.1 (d, J = 5.7 Hz), 39.9, 27.8 (dd, J = 93 and 136 Hz), 26.0, 25.4, 17.5, 17.2 ppm. MS (CI-CH_4/N_2O, + ions) m/z 391 (M + C_3H_5), 379 (M + C_2H_5), 351 (M + H), 319 (M + H - CH_3OH).

***(E,E)*-[Difluoro[methoxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)phosphinyl]-methyl]phosphonic acid, diethyl ester (9a, Methods A and D)** was obtained from **4a** as a yellow oil, contaminated with 0.17 mol equiv of diethyl difluoromethylphosphonate, in 42% yield, corrected for the contaminant. TLC Silica gel (EtOAc) R_f = 0.34. IR (CCl_4) 2983, 2963, 2931, 2918, 2857, 1444, 1272, 1254, 1049, 985 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.10 (m, 3 H), 4.36 (m, 4 H), 3.92 (d, 3 H, J = 10.6 Hz), 2.36 (m, 2 H), 2.03 (m, 10 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.60 (s, 6 H), 1.41 (t, J = 7 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 136.9, 134.9, 130.9, 124.2, 123.8, 122.2 (d, J = 17 Hz), 65.2 (d, J = 5.7 Hz), 65.1 (d, J = 7.5 Hz), 53.4 (d, J = 7.5 Hz), 39.5, 39.4, 26.6, 26.3, 25.4, 25.3 (d, J = 94.6 Hz), 18.7, 17.4, 16.1 (d, J = 5.7 Hz), 15.8 ppm.[25] MS (CI-CH_4/N_2O, + ions) m/z 514 (M + C_2H_5), 485 (M + H).

***(E,E)*-[[Hydroxy(5,9,13-trimethyl-4,8,12-tetradecatrienyl)phosphinyl]methyl]phosphonic acid, trisodium salt (2c, Method E).** A solution of 196.4 mg (0.44 mmol) of triester **8c** and 87 μL (0.66 mmol) of 2,4,6-collidine in 1.0 mL of dry CH_2Cl_2 under nitrogen at RT was treated with 260 μL (1.98 mmol) of bromotrimethylsilane and stirred for 6 h. After evaporating the solvent, the residue was stirred with 2.0 mL (2.0 mmol) of 1 M NaOH for 15 min and the solution was lyophilized. The crude product was dissolved in water and loaded onto a column of

CHP20P gel (2.5 cm diameter x 12 cm height) packed in water. The column was eluted with water (fractions 1-20), followed by a gradient created by the addition of 400 mL of acetonitrile to a reservoir of 400 mL of water, collecting approximately 10 mL fractions every two minutes. Fractions 36 through 39 were combined, the acetonitrile was evaporated and the aqueous remainder was lyophilized. The white, amorphous solid was further dried under vacuum to obtain 143.0 mg (71%) of **2c**. TLC Cellulose (7:2:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.56. IR (KBr) 3500, 2966, 2926, 2858, 1449, 1380, 1155, 1094, 1062, 976, 896, 829, 795 cm^{-1}. ^1H NMR (D_2O/CD_3OD 1:1, 400 MHz) δ 5.19 (t, 1 H, *J* = 6.5 Hz), 5.09 (m, 2 H), 1.9-2.2 (m, 12 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.58 (s, 6 H) ppm.[27] ^{13}C NMR (D_2O/CD_3OD 1:1, 67.8 MHz) δ 137.2, 136.4, 133.3, 125.4, 125.2, 40.2, 40.1, 32.1 (d, *J* = 96.5 Hz), 31.6 (dd, *J* = 75.7 and 119 Hz), 30.0 (d, *J* = 17 Hz), 27.1, 27.0, 25.8, 23.4, 17.9, 16.3, 16.1 ppm. MS (FAB, + ions) m/z 481 (M + Na), 459 (M + H), 437 (M + 2H - Na), 419. Anal. Calcd for $C_{18}H_{31}Na_3O_5P_2$: C, 47.17; H, 6.82; P, 13.52. Found: C, 47.57; H, 7.14; P, 13.67.

***(E,E,E)*-[Difluoro[hydroxy(4,8,12-trimethyl-1,3,7,11-tridecatetraenyl)phosphinyl]methyl]phosphonic acid, tripotassium salt (3b, Method F).** To 434.7 mg (0.901 mmol) of **9b** in 6 mL of dry CH_2Cl_2 under argon at 0°C was added 0.24 mL (1.82 mmol) of 2,4,6-collidine followed by 0.50 mL (3.81 mmol) of iodotrimethylsilane, dropwise over 5 min. The reaction was allowed to stir at 0°C for 2.5 h, the solvent was evaporated and the residue was pumped under vacuum. Aqueous 1 M KOH (3.2 mL) was added and the solution was freeze-dried. The tan powder was chromatographed on a column of CHP20P gel (2.5 cm diameter x 22 cm height) packed in water. The column was eluted with a gradient created by the addition of 800 mL of 75:25 CH_3OH/water to 600 mL of water, collecting 10-15 mL fractions. Fractions 42-61 were combined, and the CH_3OH was evaporated. The aqueous residue was lyophilized and further dried under high vacuum to provide 349.3 mg (74%) of **3b** as a white, amorphous powder. TLC Silica gel (6:3:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.31. IR (KBr) 3300, 2972, 2924, 2854, 1640, 1218, 1199, 1118, 1045, 997 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 7.22 (td, 1 H, *J* = 17 and 11 Hz), 6.07 (d, 1 H, *J* = 11 Hz), 5.93 (dd, 1 H, *J* = 17 and 22 Hz), 5.17 (m, 2 H), 2.17 (s, 4 H), 2.10 (q, 2 H, *J* = 7 Hz), 2.02 (t, 2 H, *J* = 7 Hz), 1.87 (s, 3 H), 1.68 (s, 3 H), 1.61,1.62 (two s, 3 H each) ppm. ^{13}C NMR (D_2O, 67.8 MHz) δ 148.0, 142.2, 137.0, 133.7, 124.8 (d, *J* = 23 Hz), 124.6, 124.3, 121.3 (d, *J* = 134.3 Hz), 39.5, 39.0, 26.0, 25.9, 25.1, 17.2, 16.6, 15.5 ppm.[25] MS (FAB, + ions) m/z 565 (M + K), 527 (M + H), 489 (M - K + 2H), 309, 271, 246, 217, 208, 157. Anal. Calcd for $C_{17}H_{25}F_2K_3O_5P_2$: C, 38.77; H, 4.79; F, 7.22; P, 11.76. Found: C, 38.87, H, 4.82; F, 7.32; P, 11.87.

***(E,E)*-[[Hydroxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)phosphinyl]methyl]phosphonic acid, tripotassium salt (2a, Method E)** was obtained from **8a** as a white, amorphous solid in 65% yield. TLC Cellulose (7:2:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.54. IR (KBr) 3415, 2968, 2928, 2858, 1660, 1449, 1383, 1161, 1107, 1077, 1043, 973, 799 cm^{-1}. ^1H NMR (CD_3OD/D_2O 1:1, 400 MHz) δ 5.20, 5.08, 5.06 (three t, 1 H each, *J* = 7 Hz), 2.22 (m, 2 H), 1.9-2.1 (m, 10 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.56 (s, 6 H) ppm.[26] ^{13}C NMR (CD_3OD/D_2O 1:1, 67.8 MHz) δ 136.0, 135.9, 132.6, 126.3 (d, *J* = 7 Hz), 125.3, 125.1, 40.5, 40.4, 33.5 (dd, *J* = 81.4 and 117.3 Hz), 33.3 (d, *J* = 92.7 Hz), 27.5, 27.3, 25.9, 22.0, 17.8, 16.2, 16.1 ppm. MS (FAB, + ions) m/z 531 (M + K), 493 (M + H), 455 (M + 2H - K). Anal. Calcd for $C_{17}H_{29}K_3O_5P_2$ x 2.8 mol equiv H_2O: C, 37.60; H, 6.42; P, 11.42. Found: C, 37.58; H, 6.19; P, 11.47.

***(E,E,E)*-[Hydroxy(4,8,12-trimethyl-1,3,7,11-tridecatetraenyl)phosphinyl]methyl]phosphonic acid, di- and tripotassium salts (2b, Method E)** was obtained from **8b** in 81% yield as an amorphous, white solid. This material is a 1.5:1 mixture of di- and tripotassium salts. TLC Cellulose (7:2:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.54. IR (KBr) 3400, 2968, 2924, 2854, 1641, 1449, 1383, 1236, 1174, 1154, 1127, 1109, 1079, 969, 886, 792 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 7.04 (td, 1 H, *J* = 18 and 11 Hz), 5.97 (d, 1 H, *J* = 11 Hz), 5.95 (dd, 1 H, *J* = 22 and 18 Hz), 5.11 (m, 2 H), 2.11 (s, 4 H), 1.9-2.1 (m, 6 H), 1.81 (s, 3 H), 1.63 (s, 3 H), 1.57 (s, 3 H), 1.56 (s, 3 H) ppm. ^{13}C NMR (D_2O, 67.8 MHz) δ 146.2, 138.3, 136.6, 133.2, 124.9 (d, *J* = 138 Hz), 124.8 (d, *J* = 20.8 Hz), 124.5, 124.2, 39.5, 39.0, 33.7 (dd, *J* = 118 and 85 Hz), 26.0, 25.1, 17.2, 16.5, 15.4 ppm. MS (FAB, + ions) m/z 529 (M + K), 491 (M + H), 453 (M + 2H - K), where M = 490 (molecular weight of tripotassium salt). Anal. Calcd for $C_{17}H_{27.6}K_{2.4}O_5P_2$: C, 43.65; H, 5.95; P, 13.24. Found: C, 43.78; H, 6.47; P, 13.36.

***(E,E)*-[[(4,8-Dimethyl-1,3,7-nonatrienyl)hydroxyphosphinyl]methyl]phosphonic acid, trisodium salt (2d, Method E)** was obtained from **8d** in 73% yield as a faintly pink, flocculent lyophilate. TLC Cellulose (7:2:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.42. IR (KBr) 3390, 2969, 2925, 2858, 1640, 1380, 1236, 1152, 1088, 976, 885, 862, 790, 722 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 7.03 (td, 1 H, *J* = 17 and 11 Hz), 6.03 (dd, 1 H, *J* = 17 and 22 Hz), 6.01 (d, 1 H, *J* = 11 Hz), 5.16 (m, 1 H), 2.13 (br, 4 H), 1.95 (t, 2 H, *J* = 18.5 Hz), 1.82 (s, 3 H), 1.65 (s, 3 H), 1.60 (s, 3 H) ppm. ^{13}C NMR (D_2O, 67.8 MHz) δ 146.1, 138.1 (d, *J* = 3.8 Hz), 134.1, 126.5 (d, *J* = 130.6 Hz), 125.1 (d, *J* = 20.8 Hz), 124.2, 39.5, 34.6 (dd, *J* = 117 and 87 Hz), 25.9, 25.1, 17.2, 16.5 ppm. MS (FAB, + ions) m/z 397 (M + Na), 375 (M + H), 353

(M + 2H - Na), 331 (M + 3H - 2Na). Anal. Calcd for $C_{12}H_{19}Na_3O_5P_2$: C, 38.52; H, 5.12; P, 16.55. Found: C, 38.96, H, 5.45; P, 17.11.

***(E,E)*-[Difluoro[hydroxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)phosphinyl]-methyl]phosphonic acid, tripotassium salt (3a, Method F)** was obtained from **9a** in 82% yield as a white, amorphous lyophilate. In this example, bis(trimethylsilyl)trifluoroacetamide (2 equiv) was utilized as an acid scavenger in place of 2,4,6-collidine. TLC Silica gel (6:3:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.31. IR (KBr) 3500, 3200, 2968, 2924, 1215, 1132, 1102, 1051, 999, 954 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 5.24 (t, 1 H, *J* = 6.6 Hz), 5.16 and 5.18 (two overlapping t, *J* = 7 Hz, 2 H total), 2.22 (m, 2 H), 1.98 and 2.06 (two m, 8 H total), 1.77 (m, 2 H), 1.64 (s, 3 H), 1.61 (s, 3 H), 1.57 (s, 6 H) ppm. ^{13}C NMR (D_2O, 67.8 MHz) δ 136.7, 136.5, 133.4, 124.8 (d, *J* = 17 Hz), 124.6, 124.5, 39.0, 38.9, 27.7 (d, *J* = 94.6 Hz), 26.1, 26.0, 25.0, 19.5, 17.1, 15.4 ppm. MS (FAB, + ions) m/z 567 (M + K), 529 (M + H), 429 (M + 2H - K). Anal. Calcd for $C_{17}H_{27}F_2K_3O_5P_2$: C, 38.62; H, 5.15; F, 7.19; P, 11.72. Found: C, 38.70; H, 5.49; F, 7.19; P, 11.50.

***(E,E)*-[[Hydroxy(4,8,12-trimethyl-3,7,11-tridecatrienyl)phosphinyl]methyl]-phosphonic acid, monomethyl ester, disodium salt (10).** An emulsion of 333.2 mg (0.79 mmol) of **8a** in 3.95 mL (3.95 mmol) of 1 M NaOH was stirred at 50°C under nitrogen for 16 h, then cooled to RT. The amber solution was loaded onto a 2.5 cm diameter x 16 cm height column of CHP20P gel packed with water. The column was eluted with a gradient created by the gradual addition of 450 mL of acetonitrile to 450 mL of water. Approximately 10 mL fractions were collected every two minutes. Fractions 24-28 were combined and lyophilized to afford 206.4 mg (60%) of **10** as an amorphous, white solid. TLC Silica gel (7:2:1 *n*-C_3H_7OH/con NH_3/H_2O) R_f = 0.30. IR (KBr) 3427, 3282, 2966, 2924, 2854, 1218, 1172, 1146, 1102, 1064, 790, 747 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 5.24 (m, 1 H), 5.16 (m, 2 H), 3.55 (d, 3 H, *J* = 11 Hz), 2.20 (m, 2 H), 2.0-2.2 (m, 10 H), 1.67 (s, 3 H), 1.65 (s, 3 H), 1.60 (s, 6 H) ppm.[26] ^{13}C NMR (D_2O, 67.8 MHz) δ 136.8, 136.5, 133.3, 125.2 (d, *J* = 19 Hz), 124.9, 51.7 (d, *J* = 5.7 Hz), 39.4, 31.7 (d, *J* = 98.5 Hz), 29.4 (dd, J = 75.7 and 114.9 Hz), 26.4, 25.4, 21.1, 17.5, 15.7 ppm. MS (FAB, + ions) m/z 437 (M + H), 415 (M + 2H - Na). Anal. Calcd for $C_{18}H_{32}Na_2O_5P_2$: C, 49.54; H, 7.39; P, 14.20. Found: C, 49.78; H, 7.62; P, 14.49.

***(E,E)*-Farnesal (12).** To a stirred solution of 2.5 mL (28.7 mmol) of distilled oxalyl chloride in 50 mL of dry CH_2Cl_2 at -60°C was added 4.2 mL (58.5 mmol) of DMSO in 10 mL of CH_2Cl_2 over 6 min between -60 and -55°C, with much gas evolution. After 7 min at -60°C, a solution of 5.0 g (22.5 mmol) of **11** in 14 mL of CH_2Cl_2 was added over 15 min to give a thick white suspension. After 20 min at -65°C, 19 mL (136 mmol) of triethylamine was added over 7 min, and 5 min later the cold bath was removed and the reaction was allowed to warm to RT over 50 min. The mixture was diluted with 400 mL of ether, washed with two 50 mL portions each of water and brine, dried over $MgSO_4$, and evaporated. The residue was taken up in ether, filtered to remove some insoluble solid, and evaporated to provide 5.06 g (100%) of crude *(E,E)*-farnesal, contaminated with a trace of the *2Z*-isomer. This material was used in crude form in general, but could be further purified by flash chromatography on silica gel. TLC Silica gel (20:80 EtOAc/hexane) R_f = 0.38. ^1H NMR ($CDCl_3$, 270 MHz) δ 10.00 (d, 1 H, *J* = 8 Hz), 5.88 (d, 1 H, *J* = 8 Hz), 5.09 (m, 2 H), 2.24 (m, 4 H), 2.17 (s, 3 H), 2.01 (m, 4 H), 1.68 (s, 3 H), 1.61 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 190.9, 163.5, 136.3, 131.2, 127.3, 123.9, 122.3, 40.5, 39.5, 26.5, 25.5, 17.5, 17.4, 15.9 ppm.

***(E,E,E)*-(4,8,12-Trimethyl-1,3,7,11-tridecatetraenyl)phosphonic acid, dimethyl ester (4b).** A 1.0 g (25.0 mmol) sample of 60% sodium hydride in mineral oil was washed with two 20 mL portions of pentane, and suspended in 50 mL of THF. A solution of 5.80 g (25.0 mmol) of tetramethyl methylenebisphosphonate in 12 mL of THF was added dropwise over 15 min at 0°C. The reaction was allowed to warm to RT for 20 min to give a clear solution. Aldehyde **12** (4.97 g, 22.5 mmol) in 14 mL of THF was added over 10 min and the reaction was allowed to stir for 1.5 h at RT. Upon dilution with ether, the solution was washed twice with water and once with brine, dried over $MgSO_4$, and evaporated to provide 7.05 g of a yellow oil. The crude product was purified by flash chromatography on silica gel, eluted with 25:75 followed by 75:25 EtOAc/hexane to provide 0.946 g (13%) of the *(1E, 3Z)*-isomer and 5.29 g (72%) of the desired *(1E, 3E)*-isomer **4b**. TLC Silica gel (EtOAc) R_f = 0.28 [*(1E, 3Z)*-isomer: R_f = 0.39]. IR (CCl_4) 2968, 2951, 2928, 2919, 2851, 1640, 1589, 1448, 1385, 1254, 1237, 1185, 1062, 1036, 987, 867, 832, 792, 774 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39 (ddd, 1 H, *J* = 21, 17 and 11 Hz), 5.97 (d, 1 H, *J* = 11 Hz), 5.51 (dd, 1 H, *J* = 20 and 17 Hz), 5.08 (m, 2 H), 3.72 (d, 6 H, *J* = 11 Hz), 2.15 (m, 4 H), 2.00 (m, 4 H), 1.88 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 149.2, 146.0 (d, *J* = 7.6 Hz), 135.8, 131.3, 124.3 (d, *J* = 26.5 Hz), 124.2, 123.1, 112.4 (d, *J* = 193 Hz), 52.1 (d, *J* = 5.6 Hz), 40.1, 39.6, 26.7, 26.1, 25.6, 17.6, 17.4, 16.0 ppm. MS (CI-CH_4/N_2O, + ions) m/z 367 (M + C_3H_5), 355 (M + C_2H_5), 327 (M + H).

***(E,E)*-(4,8-Dimethyl-1,3,7-nonatrienyl)phosphonic acid, dimethyl ester (4d).** *(E)*-Geranial was prepared identically to *(E,E)*-farnesal.[17] A 1.53 g (38.2 mmol) sample of 60% sodium hydride in mineral oil was washed with three 20 mL portions of pentane and suspended in 80 mL of THF. A solution of 8.32 g (38.2 mmol) of tetramethyl methylenebisphosphonate in 15 mL of THF was added dropwise over 20 min at RT under argon to give a clear solution. *(E)*-Geranial (5.41 g, 35.5 mmol) in 20 mL of THF was added dropwise over 15 min, and the reaction was allowed to stir for 1.5 h at RT before quenching with water. Upon dilution with 350 mL of ether, the solution was washed with two 75 mL portions of water and 75 mL of brine, dried over $MgSO_4$ and evaporated to yield 8.24 g of a yellow oil. Purification by flash chromatography on 800 g of silica gel, eluted with 1:1 EtOAc/pet ether provided 4.75 g (53%) of the desired *(1E, 3E)*-isomer of **4d**, as well as 217.7 mg (3%) of the *(1Z, 3E)*-isomer. TLC Silica gel (EtOAc) R_f = 0.36 [*(1Z, 3E)*-isomer: R_f = 0.44]. IR (CCl_4) 2970, 2950, 2931, 2917, 2851, 1640, 1588, 1448, 1383, 1253, 1238, 1185, 1104, 1061, 1036, 986, 869, 831 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 7.39 (ddd, 1 H, *J* = 21.0, 17.0 and 11.5 Hz), 5.97 (d, 1 H, *J* = 11.5 Hz), 5.52 (dd, 1 H, *J* = 20.0 and 17.0 Hz), 5.07 (br, 1 H), 3.72 (d, 6 H, *J* = 11 Hz), 2.14 (m, 4 H), 1.88 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 3 H) ppm. MS (CI-CH_4/N_2O, + ions) m/z 299 (M + C_3H_5), 287 (M + C_2H_5), 259 (M + H), 227 (M + H - CH_3OH).

***(E,E)*-5,9,13-Trimethyl-4,8,12-tetradecatrienoic acid, ethyl ester (14).** To a solution of 3.0 g (13.5 mmol) of *(E,E)*-farnesol in 25 mL of ether at 0°C was added 0.58 mL (6.08 mmol) of PBr_3 in 6 mL of ether over 10 min and the reaction was allowed to stir for 1 h. The mixture was quenched with water, diluted with pet ether and washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated to provide 3.83 g (99%) of *(E,E)*-farnesyl bromide as a pale yellow liquid.

To a suspension of 1.62 g (40.5 mmol) of 60% NaH in mineral oil (washed three times with pentane) in 150 mL of THF at RT under argon was slowly added 6.15 mL (40.5 mmol) of diethyl malonate. The resulting solution was stirred for 0.5 h, then treated with a solution of 3.83 g (13.5 mmol) of *(E,E)*-farnesyl bromide in 10 mL of THF. After stirring for 6 h, the reaction was quenched with saturated NH_4Cl and diluted with 300 mL of ether. The organic layer was washed with two 100 mL portions of water and 100 mL of brine, dried over $MgSO_4$, evaporated and the bulk of the diethyl malonate removed by spinning under high vacuum to afford 4.29 g (87%) of crude product. TLC Silica gel (1:9 EtOAc/hexane) R_f = 0.37.

A mixture of 4.10 g (11.2 mmol) of diester, 0.20 mL (11.2 mmol) of water, and 950 mg (22.4 mmol, 2 equiv) of LiCl in 20 mL of DMSO was heated at reflux for four hours. After cooling, the reaction mixture was diluted with 180 mL of a 1:1 mixture of ether/pet ether and washed with five 50 mL portions of water and 50 mL of brine, dried over $MgSO_4$, and evaporated to yield 3.6 g of crude product as a yellow-orange oil. Flash chromatography on 180 g of silica gel, eluted with 3:97 EtOAc/pet ether provided 1.84 g (56%) of ester **14** as a pale yellow oil. TLC Silica gel (5:95 EtOAc/hexane) R_f = 0.27. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.08 (br, 3 H), 4.12 (q, 2 H, *J* = 6.7 Hz), 2.31 (m, 4 H), 1.9-2.1 (m, 8 H), 1.67 (s, 3 H), 1.62 (s, 3 H), 1.59 (s, 6 H), 1.25 (t, 3 H, *J* = 6.7 Hz) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 173.3, 136.5, 134.9, 131.2, 124.3, 124.0, 122.3, 60.1, 39.7, 39.6, 34.5, 26.7, 26.5, 25.6, 23.5, 17.6, 15.9, 14.2 ppm.

***(E,E)*-5,9,13-Trimethyl-4,8,12-tetradecatrienyl bromide (15).** A solution of 7.05 g (24 mmol) of monoester **14** in 65 mL of dry ether at 0°C was treated portionwise with 915 mg (24 mmol) of LAH and stirred at RT for 3 h. After cooling to 0°C, the reaction was quenched with 7 mL of water, 7 mL of 15% NaOH, and stirred for 15 min. An additional 21 mL of water was added, and the reaction was stirred 30 min and anhydrous Na_2SO_4 was added. The mixture was filtered through Celite, the solids were washed with diethyl ether, and the filtrate was evaporated to give 5.66 g of a colorless oil. Purification by flash chromatography on silica gel eluted with 15:85 EtOAc/pet ether provided 5.23 g (87%) of the alcohol as a colorless oil. TLC Silica gel (20:80 EtOAc/hexane) R_f = 0.21. IR (neat) 3330, 2964, 2926, 2873, 2858, 1448, 1384, 1107, 1059 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.10 (m, 3 H), 3.63 (t, 2 H, *J* = 6.5 Hz), 1.9-2.2 (m, 10 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 6 H) ppm.[26] MS (CI-CH_4/N_2O, + ions) m/z 251 (M + H), 249 (M + H - H_2), 137, 123, 109, 69.

To a stirred solution of 2.02 g (8.07 mmol) of the alcohol in 20 mL of CH_2Cl_2 at 0°C was added 2.2 mL (16.1 mmol) of triethylamine followed by 0.69 mL (8.90 mmol) of methanesulfonyl chloride, dropwise over 15 min. After stirring for 1.5 h at 0°C, the reaction was diluted with CH_2Cl_2, washed with 20 mL each of 10% HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give 2.71 g of the crude mesylate as a colorless oil. TLC Silica gel (CH_2Cl_2) R_f = 0.46. To a solution of 2.56 g (7.79 mmol) of the mesylate in 15 mL of THF at RT was added 2.02 g (23.37 mmol) of anhydrous lithium bromide, resulting in a mild exotherm. The suspension was allowed to stir for 23 h at RT,

when it was diluted with ether, washed with water (two portions) and brine, dried ($MgSO_4$) and evaporated to provide 2.29 g of a pale yellow liquid. Flash chromatography on 65 g of silica gel eluted with pet ether gave 2.22 g (91%) of bromide **15** as a colorless liquid. TLC Silica gel (hexane) R_f = 0.35. IR (neat) 2965, 2926, 2856, 1666, 1440, 1383, 1249, 1109 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 5.10 (br, 3 H), 3.39 (t, 2 H, J = 6.5 Hz), 1.8-2.3 (m, 12 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 136.7, 135.0, 131.1, 124.4, 124.1, 122.4, 39.7, 33.3, 32.9, 26.8, 26.5, 26.3, 25.6, 17.6, 16.1, 16.0 ppm. MS (CI-CH_4/N_2O, + ions) m/z 315, 313 (M + H), 313, 311 (M + H - H_2).

***(E,E)*-(5,9,13-Trimethyl-4,8,12-tetradecatrienyl)phosphonic acid, diethyl ester** (4c). A mixture of 1.12 g (3.57 mmol) of bromide **15** and 12.3 mL (71.5 mmol) of triethyl phosphite under argon was stirred at 140-150°C for 20 h. After cooling, the triethyl phosphite was removed under high vacuum. The crude product was combined with that from a previous reaction on 1.11 mmol of bromide **15** and purified by flash chromatography on 180 g silica gel, eluted with 1:1 EtOAc/pet ether to obtain 1.63 g (94%) of **4c** as a colorless oil. TLC Silica gel (EtOAc) R_f = 0.36. IR (CCl_4) 2980, 2930, 2914, 2874, 2857, 1444, 1390, 1241, 1164, 1098, 1061, 1034, 959, 778, 746 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 4.99 (m, 3 H), 4.00 (m, 4 H), 1.8-2.1 (m, 10 H), 1.57 (s, 3 H), 1.50 (s, 9 H), 1.4-1.6 (m, 4 H), 1.22 (t, 6 H, J = 7 Hz) ppm. ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 136.2, 134.8, 130.9, 124.2, 123.9, 122.9, 61.1 (d, J = 6 Hz), 39.5, 28.4 (d, J = 17 Hz), 26.6, 26.4, 25.5, 25.0 (d, J = 140 Hz), 22.5 (d, J = 4 Hz), 17.5, 16.3 (d, J = 6 Hz), 16.2, 15.9 ppm. MS (CI-*i*-butane/N_2O, + ions) m/z 371 (M + H).

Acknowledgement. We would like to thank the Squibb Analytical Chemistry Department for obtaining elemental analyses, mass spectra, ir spectra, potentiometric titrations, and certain NMR spectra.

References and Notes

(1) Biller, S. A.; Forster, C.; Gordon, E. M.; Harrity, T.; Scott, W. A.; Ciosek, C. P., Jr. *J. Med. Chem.* **1988**, *31*, 1869-1871.

(2) McClard, R. W.; Fujita, T. S.; Stremler, K. E.; Poulter, C. D. *J. Am Chem. Soc.* **1987**, *109*, 5544-5545.

(3) (a) Farrington, G. K.; Kumar, A.; Wedler, F. C. *J. Med. Chem.* **1987**, *30*, 2062-2067. (b) Vargas, L. A.; Miao, L. X.; Rosenthal, A. F. *Biochim. Biophys. Acta* **1984**, *796*, 123-128.

(4) Poulter, C. D.; Rilling, H. C. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, Chapter 8.

(5) Novikova, Z. S.; Prishchenko, A. A.; Skorobogatova, S. Ya.; Martynov, V. I.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1980**, *50*, 787-790.

(6) Related chemistry has been employed to prepare diphosphonate Horner-Emmons reagents,[6a] and photoaffinity reagents[6b]: (a) Teulade, M.-P.; Savignac, P.; Aboujaoude, E. E.; Liétge, S.; Collignon, N. *J. Organomet. Chem.* **1986**, *304*, 283-300. (b) Bartlett, P. A.; Carruthers, N. I.; Winter, B. M.; Long, K. P. *J. Org. Chem.* **1982**, *47*, 1284-1291.

(7) Bhongle, N. N.; Notter, R. H.; Turcotte, J. G. *Synth. Commun.* **1987**, *17*, 1071-1076. Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972-3974.

(8) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654-5656.

(9) Obayashi, M.; Ito, E.; Matsui, K.; Kondo, K. *Tetrahedron Lett.* **1982**, *23*, 2323-2326.

(10) Gryszkiewicz-Trochimowski, E. *Bull. Soc. Chim. Fr.* **1967**, 4289-4290.

(11) Other examples of this reaction sequence will be reported in due course.

(12) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C.*Tetrahedron Lett.* **1977**, 155-158.

(13) Blackburn, G. M.; Ingleson, D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1150-1153.

(14) McKenna, C. E.; Khawli, L. A.; Ahmad, W-Y.; Pham, P.; Bongartz, J-P. *Phosphorus and Sulfur* **1988**, *37*, 1-12.

(15) Davisson, V. J.; Sharp, T. R.; Poulter, C. D. *Bioorganic Chem.* **1988**, *16*, 111-123.

(16) Corey, E. J.; Volante, R. P. *J. Am. Chem. Soc.* **1976**, *98*, 1291-1293.

(17) (a) Mancuso, A. J.; Huang, S-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482. (b) Leopold, E. J. *Org. Syn.* **1985**, *64*, 164-174

(18) (a) Hullar, T. L. *J. Med. Chem.* **1969**, *12*, 58-63. (b) Meyer, R. B., Jr.; Stone, T. E.; Jesthi, P. K. *J. Med. Chem.* **1984**, *27*, 1095-1098.

(19) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

(20) Stowell, M. H. B.; Witte, J. F.; McClard, R. W. *Tetrahedron Lett.* **1989**, *30*, 411-414.

(21) Gray, M. D. M.; Smith, D. J. H. *Tetrahedron Lett.* **1980**, *21*, 859-860.

(22) (a) Andrus, A.; Beaucage, S. L. *Tetrahedron Lett.* **1988**, *29*, 5479-5482. (b) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603-1609.

(23) Gilmore, W. F.; McBride, H. A. *J. Pharm. Sci.* **1974**, *63*, 965-966. Jones, G. H.; Albrecht, H. P.; Damodaran, N. P.; Moffat, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 5510-5511.

(24) Clark, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

(25) The PCF_2P carbon signal is too highly split by P and F to be clearly observed.

(26) An additional CH_2 multiplet is hidden under the vinyl CH_3's.

(27) Two additional CH_2 multiplets are hidden under the vinyl CH_3's.

(28) Gorenstein, D. G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *16 (1)*, 1-98.