Experimental Section

General methods and Materials: All experiments were performed under an inert atmosphere unless otherwise indicated. NMR spectra were collected at 23 °C. ^{1}H and ^{13}C NMR chemical shifts are reported in δ, ppm, and referenced to internal CD_3Cl at 7.26 or D_2O at 4.8. ^{13}C NMR spectra for compounds **2** and **6** were referenced to external methanol (10%) at 49.15. ^{31}P NMR spectra are reported as δ, ppm, and referenced to external phosphoric acid (5%) in D_2O. Compound for gas chromatography-mass spectrometry was separated on a DB-5 capillary column. Fast-atom bombardment (FAB) and electronic impact (EI) mass spectroscopy were used to obtain high-resolution mass spectra. Silica flash chromatography was performed with Merk silica gel (200-245 mesh).[1] Thin layer chromatography was on Merk Silica Gel 60 A° F_{254} TLC plates. Silica gel was visualized with phosphomolybdic acid. Cellulose for flash chromatography was purchased from Whatman and used according to method of Woodside.[2] Cellulose TLC plates were developed with a sulfosalicylic acid-ferric chloride spray.[3] All chemical reagents were purchased from Aldrich, and all solvents were distilled over calcium hydride prior to use.

Tetra-*n*-butylammonium dimethylphosphate (2)
To neat trimethylphosphate (6 mL, 51.3 mmol) was added 33.6 mL (51.3 mmol) of 40% (w/w) tetra-*n*-butylammonium hydroxide. The mixture was heated at reflux at 100 °C for 24 h. Methanol was removed by rotatory evaporation, and the residue was lyophilized for 24 h. Traces of water were removed by the addition of benzene, followed by its removal at reduced pressure, to give 18 g (95%) of a white solid; ^{1}H NMR (300 MHz, D_2O): 1.02 (12H, t, CH_3), 1.44 (8H, m, CH_2), 1.74 (8H, m, CH_2), 3.25 (8H, m, CH_2), 3.54 (6H, d, CH_3); ^{13}C NMR (D_2O) 12.73 (s, CH_3), 18.93 (s, CH_2), 22.88 (s, CH_2), 52 (d, CH_3), 57.78 (s, CH_2); ^{31}P NMR (D_2O) 2.83 (s); high resolution (FAB^-) mass spectrum $[M-1]^-$ calculated for $C_2H_7PO_4$ 125.00090, found 125.00037.

Tetramethyl thiodiphosphate (3)
tetra-n-Butylammonium dimethylphosphate (**2**) (9.8 g, 26.7 mmol) was dissolved in 7 mL of acetonitrile. The mixture was chilled to –35 °C before dropwise addition of dimethyl chlorothiophosphate (3 mL, 24.7 mmol). The mixture was allowed to stir at –35 °C for 30 min, immediately poured into a packed silica gel column (250 mL), and eluted with CH_2Cl_2. Solvent was removed in vacuo to give 1.85 g (30%) of a yellow oil; ^{1}H NMR 3.86 (d, 6 H, $J_{H,P}$ = 0.73), 3.9 (d, 6H, $J_{H,P}$ = 0.9); ^{13}C NMR δ 55.1 (d, CH_3), δ 55.4 (d, CH_3); ^{31}P NMR δ -13.8 (d, $J_{P,P}$ = 20, P(O)), δ 55.6 (d, $J_{P,P}$ = 20, P(S)); high resolution (EI) mass spectrum $[M]^+$ calculated for $C_{10}H_{12}SP_2O_6$ 249.9830, found 249.9841.

***Tris*-(tetra-*n*-butylammonium)thiodiphosphate (5)**
Iodotrimethyl silane (3.41 g, 33.84 mmol) was added dropwise to neat tetramethyl thiodiphosphate (1.5 g, 6 mmol) at –35 °C, and the mixture was slowly allowed to warm to room temperature over 6 h. The solvent was removed in vacuo to give *tris*-(trimethylsilane) thiodiphosphate (**4**) as a brown semi-solid; ^{31}P NMR (CD_3CN in 1M

EDTA), -32.64 (d, $J_{P,P}$ = 16.5, P(O)), 29.94 (d, $J_{P,P}$ = 16.5, P(S)). The TMS derivative **(4)** was dissolved in 20 mL of acetonitrile. The solution was titrated with 40% (w/w) tetra-n-butylammonium hydroxide to pH 7.2, followed by removal of acetonitrile at reduce pressure. The mixture was diluted with 10 mL of benzene to give a heterogeneous mixture composed of three layers. The bottom layer was separated, concentrated in vacuo, and lyophilized to give 5.36 g (96%) as a yellow gelatinous substance, which was used directly in next step; ^{31}P NMR (CD_3Cl), -7.68 (d, $J_{P,P}$ = 30, P(O)), 36.88 (d, $J_{P,P}$ = 30, P(S)); ^{1}H NMR (CD_3Cl), 1.02 (12H, t, CH_3), 1.44 (8H, m, CH_2), 1.74 (8H, m, CH_2), 3.25 (8H, m, CH_2); high resolution (FAB^-) mass spectrum $[M-1]^-$ calculated for $H_4SP_2O_6$ 192.91256, found 192.91181.

***(E)*-3,7-Dimethyl-2,6-octadien-1-yl- S-thiolodiphosphate (6) (Geranyl –S-thiolodiphosphate)**

Geranyl bromide (0.438 g, 2 mmol) was added dropwise to a cold solution of *tris*-(tetra-*n*-butylammonium)thiodiphosphate (4.30g, 4.62 mmol) in 20 mL of acetonitrile. The reaction mixture was allowed to stir for 30 min, and solvent was removed at reduced pressure. The residue was passed through a column containing 40 mequiv of DOWEX AG 50W-X8 (100-200 mesh) cation-exchange resin (NH_4^+ form). The column was eluted with two volumes of ion-exchange buffer (25 mM NH_4HCO_3 and 2% (v/v) of isopropanol in water), and the eluent was lyophilized. The resulting powder was dissolved in a limited amount of water and purified by chromatography on cellulose with a 50 mM in 1:2:1 (v/v/v) acetonitrile/isopropanol/water buffer. Fractions containing product were pooled, concentrated by rotatory evaporation, and lyophilized to yield 0.61g (80%) of a white-yellowish solid: : R_f 0.38; H^1 NMR (D_2O) 5.4 (t, 1H, $J_{H,H}$ = 9Hz), 5.15 (b, 1H), 3.5 (t, 2H, $J_{H,P}$ = 8.79Hz), 2.1 (m, 4H), 1.7 (d, 6H, $J_{H,H}$ = 5.13Hz), 1.6 (s, 3H); ^{13}C NMR (D_2O) 15.74 (s), 17.49 (s), 25.34 (s), 26.11(s), 28.27(s), 39.20 (s), 120.30 (d), 124.50 (s), 133.55 (s), 141 (s); P^{31} NMR (D_2O) 7.97 (d, P(S), $J_{P,P}$=29 Hz), -7.43 (d, P(O), $J_{P,P}$ = 29 Hz); high resolution (FAB^-) mass spectrum $[M-1]^-$ calculated for $C_5H_{11}SP_2O_6$ 329.03776, found 329.03612.

Acid-lability assay

The radioactivity of acid-labile products from the coupling of [^{14}C] isopentenyl diphosphate with **6** or **7** was measured by the protocol of Rilling *et. al.*[4] Each assay mixture contained 40 mM BHDA (bicyclo[2.2.1] hept-5-ene-2,3-dicarboxylic acid) at pH 7.3, 20mM BME (2-mercaptoethanol), 2 mM $MgCl_2$, 2 mg/mL BSA (crystalized albumin), with 70 ng of purified enzyme in a total volume of 200 µL. The assay mixtures were incubated at 37 °C for 10 min. Substrate concentrations for standard assays were as follows: 20 µM [^{14}C]IPP (10 µCi/µmol) and 50 µM **6** or **7**. IC_{50} were measured with 4.5 µM GPP, 10 µM [^{14}C]IPP (10 µCi/µmol), and varied concentrations of inhibitor **6** (0.5, 1, 5, 10, 50, 100 µM). The assays were quenched with 200 µL of methanol/HCl (4:1, v/v), incubated for an addition of 10 minutes, and extracted with 1 mL of ligroine. The radioactivity in a 0.5 mL sample of the organic layer was measured by liquid scintillation spectrometry.

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3. Davisson, V. J.; Woodside, A. B.; Poulter, C. D. *Methods Enzymol.* ***1984***, 110, 130-144.
4. Rilling, H. C. *Method Enzymol.* **1985**, 110, 145-152.