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Copper-mediated displacements of allylic THP ethers on a bisphosphonate template

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Abstract

The copper-mediated displacement of allylic THP ethers by Grignard reagents has been examined in a system that contains a geminal bisphosphonate ester. With Grignard reagents derived from several aromatic halides or benzyl bromide the displacement proceeds in attractive yields, but more mixed results were obtained from reactions with alkyl halides. In addition to its role as a nucleophile, the Grignard reagent also appears to deprotonate the bisphosphonate to generate an anionic intermediate. Formation of this anion appears to limit competitive nucleophilic attack at the phosphonate group and provides an intermediate that can be trapped by reaction with an electrophilic reagent such as methyl iodide to access a more substituted system.

Keywords: Bisphosphonate; Phosphonate; Grignard reagent; Displacement; THP ether

1. Introduction

The structural similarity of geminal bisphosphonic acids (**1**) to inorganic pyrophosphate (**2**) is widely recognized, and this relationship has served as the inspiration for synthesis of many derivatives of the parent methylenebisphosphonate. Several substituted bisphosphonates have clinical applications (Fig. 1), especially in treatment of bone diseases such as osteoporosis, Paget's disease of the bone, myeloma, and bone metastases [1]. As a result, a number of methods have been developed for their synthesis, including reaction of a carboxylic acid with phosphorous acid and phosphorus trichloride [2], by alkylation of tetraalkyl methylenebisphosphonate [3], by reaction of lactams or amides with trialkylphosphites [4], by Michael-type addition to ethylidene bisphosphonate esters [5], by nucleophilic addition of a dialkyl phosphite to an acyl phosphonate [6], and very recently through treatment of a carbonyl compound with an excess of strong base and diethyl phosphorochloridite followed by oxidation with hydrogen peroxide [7]. Structure–activity studies on geminal bisphosphonates have indicated that their activity is highly dependent upon the non-phosphorus substituents of the central carbon [8], but many of these synthetic methods involve carbon–phosphorus bond formation which can require that structural diversity be incorporated early in the synthetic sequence. Synthetic strategies that can be used to elaborate a carbon skeleton in the presence of the bisphosphonate motif might offer more efficient access to a variety of structures from a common intermediate.

Recently, we have reported a copper-mediated displacement of allylic tetrahydropyranyl (THP) ethers by various Grignard reagents [9]. While the THP ether is generally viewed as stable to Grignard reactions [10], displacement occurs readily in simple allylic systems upon exposure to Grignard reagents in the presence of Cu(I). Application of this reaction to substrates that

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1 (α,α-bisphosphonic acid) **2** (pyrophosphoric acid)

R = OH, R' = CH_3 (etidronate)
R = R' = Cl (clodronate)
R = OH, R' = $CH_2CH_2NH_2$ (pamidronate)
R = OH, R' = $(CH_2)_3NH_2$ (alendronate)
R = OH, R' = CH_2(*m*-C_5H_4N) (risedronate)

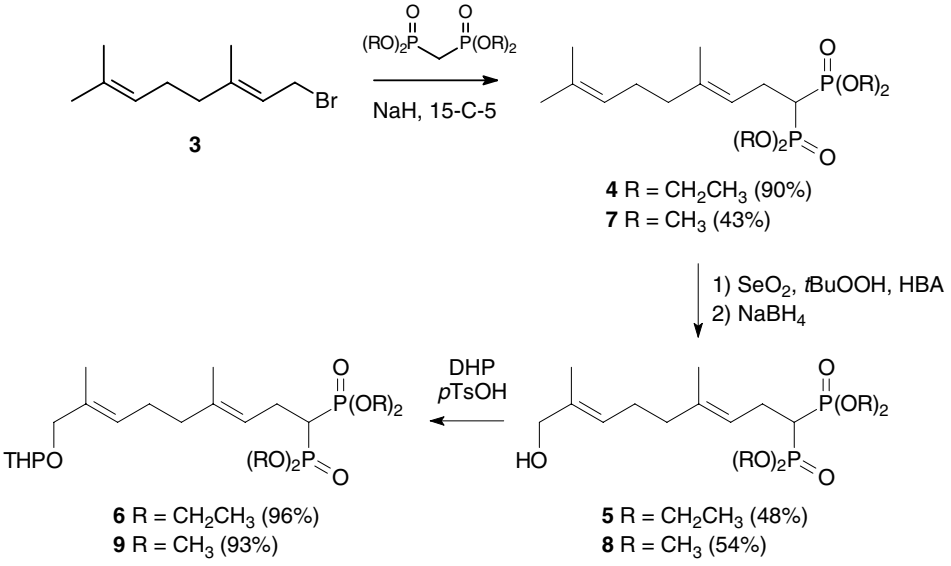
Fig. 1. General structure of an α,α-bisphosphonic acid (**1**) and some clinically useful examples.

include a bisphosphonate motif might be limited by Grignard attack at phosphorus itself or at the alkyl groups esterified to phosphorus [11]. However, some organometallic reagents add to the carbonyl group of β-keto phosphonates without significant attack at the phosphorus or its esters [12], and so this strategy appeared to be worthy of further exploration. In this paper, we report an investigation into the copper-mediated displacement of allylic THP ethers in the presence of the bisphosphonate functionality.

2. Results and discussion

Synthesis of the first substrates for this reaction proceeded as shown in Scheme 1. Commercially available geranyl bromide (**3**) was allowed to react with the anion of tetraethyl methylenebisphosphonate to afford the geranylated 1,1-bisphosphonate ester **4** along with a small amount of the dialkyl bisphosphonate [13]. Allylic hydroxylation of linear isoprenoids by reaction with selenium dioxide in the presence of 4-hydroxybenzoic acid (HBA) affords *E*-specific hydroxylation of the terminal prenyl unit [14]. When the bisphosphonate **4** was treated with selenium dioxide, a mixture of the allylic alcohol and the corresponding aldehyde resulted. This mixture, after work-up and concentration, was treated with sodium borohydride to afford the alcohol **5**. The reaction sequence allowed installation of an hydroxyl group at the *E* terminal position but, despite numerous attempts to optimize the reaction conditions, only modest yields were obtained. Reaction of the alcohol **5** with dihydropyran (DHP) under standard conditions gave the desired allylic THP ether **6** in good yield. A parallel series of reactions was used to prepare the tetramethyl ester **9** from tetramethyl methylenebisphosphonate. Yields for the later steps in this sequence closely matched those for the tetraethyl series, but the initial alkylation only proceeds in modest yield perhaps because the diminished steric hindrance of the methyl esters allows more facile dialkylation.

To test the viability of the THP displacement in the presence of a bisphosphonate, the ether **6** was treated with an excess of commercial phenylmagnesium bromide (**10a**, ~10 eq) in the presence of copper iodide (1.5 eq). Displacement took place in high yield to afford the bisphosphonate **11a** with no evidence of attack at phosphorus based on TLC analysis. Several other aromatic Grignard reagents were examined, including the *m*-tolyl, *m*-trifluoromethylphenyl, *m*-methoxyphenyl, and *p*-biphenyl reagents (**10b–e**, respectively). In each case, the displacement proceeded smoothly to afford the substituted bisphosphonates **11b–e**. Results were more mixed with the Grignard reagents derived from alkyl bromides. Benzyl magnesium bromide (**10f**)



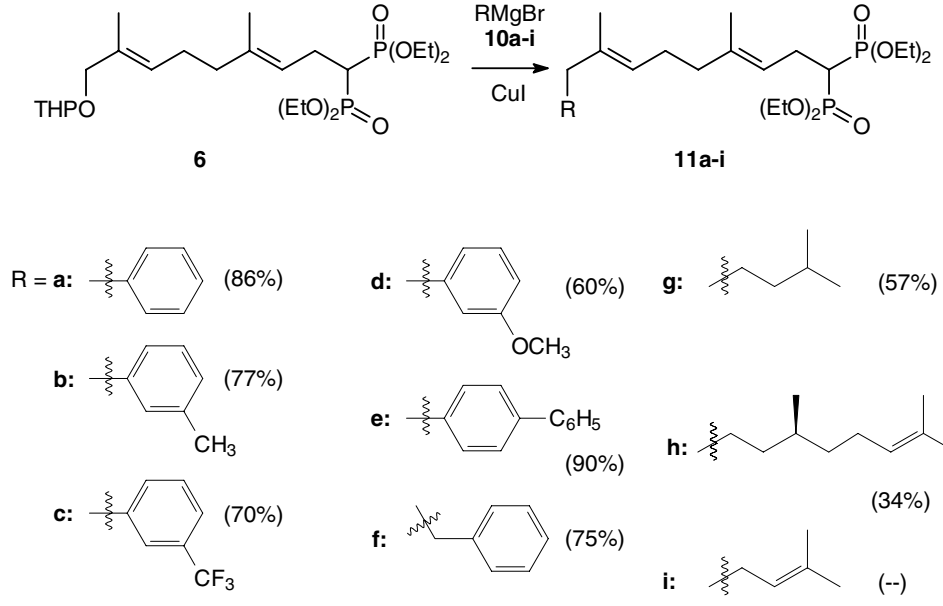
Scheme 1. Synthesis of allylic THP ethers incorporating a bisphosphonate moiety.

reacted smoothly to afford the expected bisphosphonate **11f** in 75% yield. Under the same reaction conditions, the Grignard reagents derived from isoamyl bromide (**10g**) or citronellyl bromide (**10h**) reacted in more moderate yields (57% and 34%, respectively), and no products were obtained from attempted reactions with 1-bromo-3-methyl-2-butene (**10i**). This could be a result of lower stability of the organometallic intermediates derived from these alkyl bromides or from their dimerization under the reaction conditions (Scheme 2).

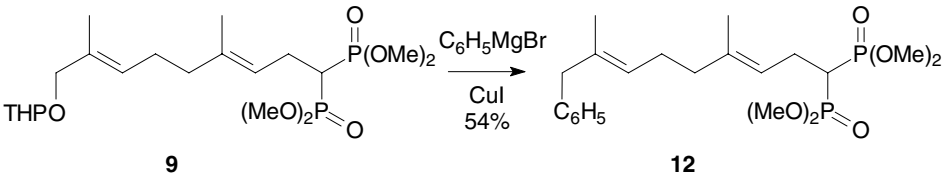
Reaction of the tetramethyl ester **9** with phenylmagnesium bromide (**10a**) also was examined (Scheme 3). In this case, the desired displacement was observed, but the yield was significantly lower than that observed with the tetraethyl ester **6** under parallel reaction conditions (54% vs 86%). The ^{31}P NMR spectrum of the reaction mixture did not reveal the presence of products resulting from attack at phosphorus (i.e., a phosphinate or phosphine oxide), but it is possible that Grignard attack at the methyl groups results in formation of toluene [11].

To gain access to more substituted bisphosphonates, and to secure more information about the processes involved in this reaction, the bisphosphonate **6** was treated with base and methyl iodide to obtain the methylated product **13** (Scheme 4). When bisphosphonate **13** was treated with phenylmagnesium bromide (**10a**), the desired bisphosphonate **14** was not observed. Instead, a complex mixture of polar products was obtained. The dialkyl bisphosphonate **14** could be obtained from compound **6** through a modified reaction sequence where displacement precedes alkylation. Because an excess of the Grignard reagent is employed in the THP displacements, it is likely that some is quenched through abstraction of a proton from the α position of the bisphosphonate. Generation of an intermediate bisphosphonate anion may limit attack at phosphorus itself or at the phosphonate esters while allowing a THP displacement at the remote allylic carbon. If this is the case, then the initial product of the displacement would be the anion **15**, and this anion might be available for further reaction. In the experiment, after treatment of bisphosphonate **6** with excess phenyl magnesium bromide, addition of methyl iodide prior to an acidic work-up did result in methylation and after work-up gave approximately a 1:1 mixture of the methylated product **14** and compound **11a**. While this mixture was difficult to separate, treatment with additional base and methyl iodide resulted in complete conversion to the desired product, compound **14**. These experiments do support the view that a bisphosphonate anion is formed during this reaction sequence, but also suggest that better yields of a dialkyl bisphosphonate might be obtained through a two-step procedure.

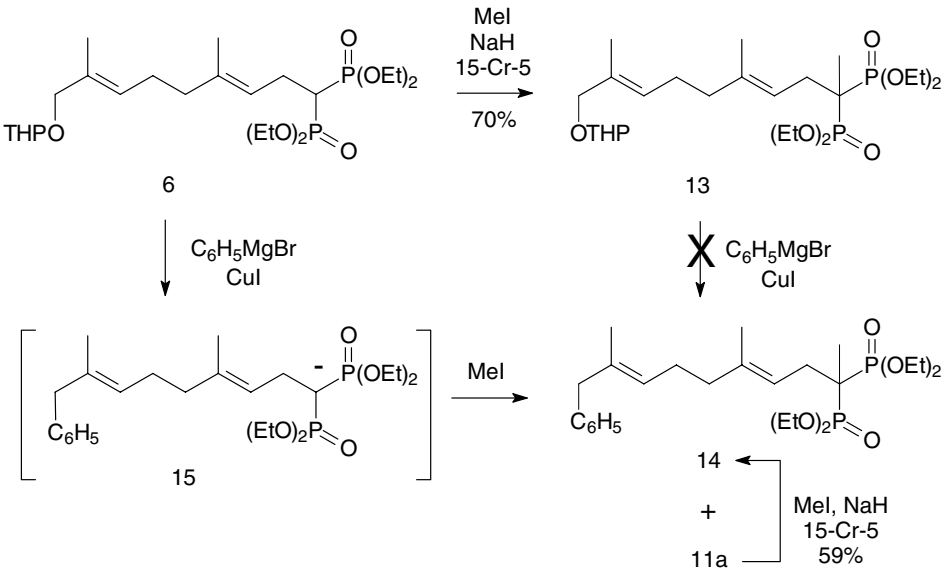
If the reaction sequence from the THP ether **6** to the substitution products **11a–i** does involve formation of an intermediate bisphosphonate-stabilized anion, the significant base strength of a typical Grignard reagent suggests that this process might be applicable in systems less acidic than a bisphosphonate. To begin exploration of this concept, the monophosphonate **16** was prepared (Scheme 5) by alkylation of an anion derived from diethyl methylphosphonate with geranyl bromide (**3**). Oxidation of phosphonate **16** with SeO_2 and ^{t}BuOOH, followed by reduction of the resulting mixture of aldehyde and alcohol with $NaBH_4$, gave the desired alcohol **17** in modest yield. After conversion of alcohol **17** to the THP ether **18**, treatment with



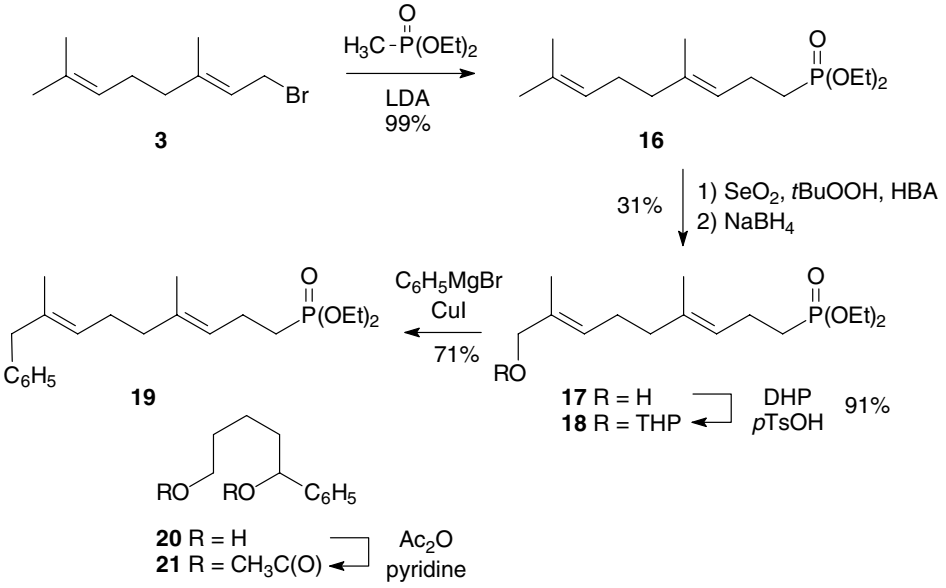
Scheme 2. Cu-mediated displacements of allylic THP ethers.



Scheme 3. Cu-mediated displacement of an allylic THP ether.



Scheme 4. Synthesis of a dialkyl biphosphonate.



Scheme 5. Displacement of an allylic THP ether on a phosphonate substrate.

C_6H_5MgBr under standard conditions gave the displacement product **19**. Isolation of compound **19** was complicated by chromatographic behavior that was very similar to that of the by-product produced from the THP group, the diol **20**. However, after treatment of the mixture with acetic anhydride and pyridine, the diacetate **21** was readily separated and phosphonate **19** was isolated in 71% yield.

In conclusion, these studies have shown that displacement of allylic THP ethers can be accomplished through a copper-mediated displacement reaction in the presence of a geminal bisphosphonate ester. While excess Grignard reagent is required for an efficient reaction, the initial product of the displacement is an anion which, in some cases, can be trapped by reaction with methyl iodide. A parallel displacement also has been demonstrated on a phosphonate ester rather than a bisphosphonate, suggesting that this strategy can be applied to the preparation of some variety of phosphorus containing compounds. Other applications of this approach, as well as some studies on the biological activity of the resulting phosphorus compounds, will be reported in due course.

3. Experimental section

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone directly before use, while dichloromethane was distilled over calcium hydride. CuI (98%) was purchased from Aldrich and used without further purification. All nonaqueous reactions were performed in oven-dried glassware and beneath an atmosphere of argon. Flash chromatography was performed using silica gel with 40 μm average particle diameter. NMR spectra were recorded on a 300 MHz instrument for ^1H (75 MHz for ^{13}C) with $CDCl_3$ as the solvent and $(CH_3)_4Si$ as an internal standard, unless otherwise stated. Chemical shifts of ^{31}P NMR are reported in ppm relative to 85% H_3PO_4 (external standard). High resolution and electron-spray mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

3.1. Tetraethyl 4,8-dimethyl-3,7-nonadienyl-1,1-bisphosphonate (4)

To a stirred suspension of NaH (1.97 g, 49.3 mmol, washed with hexanes and dried in vacuo) in THF (10 mL), 15-crown-5 (0.90 mL, 4.41 mmol) was added via syringe at 0 °C over 15 min. Tetraethyl methylenebisphosphonate (12.3 mL, 48.3 mmol) was added as a neat liquid to the suspension over 10 min and the reaction mixture was allowed to stir for 30 min. The mixture was then transferred via cannula to a stirred solution of geranyl bromide (**3**, 10.0 g, 46.1 mmol) in THF (20 mL) at 0 °C. The resulting solution was stirred for 2 h, filtered through celite, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (gradient, 0–5% methanol in Et_2O) to give the desired product **4** (13.9 g, 84%) with ^1H, ^{13}C, and ^{31}P spectra identical to literature data [13,15].

3.2. Tetraethyl 4,8-dimethyl-3,7-nonadienyl-9-ol-1,1-bisphosphonate (5)

To a stirred suspension of SeO_2 (1.34 g, 11.9 mmol) and *p*-hydroxybenzoic acid (0.33 g, 2.36 mmol) in CH_2Cl_2 (50 mL), geranyl bisphosphonate (**4**, 9.98 g, 23.5 mmol) in CH_2Cl_2 (20 mL) was added via cannula at 0 °C. After the reaction was stirred for 5 min, *tert*-butyl hydroperoxide (13.0 mL, 93.9 mmol) was added as a neat liquid via syringe. The reaction mixture was allowed to warm to rt and stir for 18 h. The mixture was quenched by addition of $NaHCO_3$(sat) and extracted with Et_2O. The organic portions were combined, dried ($MgSO_4$), and concentrated in vacuo. The resulting yellow oil was dissolved in methanol (200 mL) and $NaBH_4$ (0.89 g, 23.5 mmol) was added very slowly over 10 min at 0 °C. After 2 h, the reaction was quenched with NH_4Cl(sat) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. A white solid (NH_4Cl) emerged in the yellow oil, which was dissolved in minimum amount of water and extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. After concentration of the aqueous layer by a stream of air, the solid was dissolved in a minimum amount of water and extracted with Et_2O, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (gradient, 0–10% methanol in Et_2O) producing a pale yellow oil **5** (4.54 g, 44%): ^1H NMR δ 5.40–5.30 (m, 2H), 4.22–4.11 (m, 8H), 3.96 (s, 2H), 3.06 (br s, 1H), 2.61 (tt, $J = 17.4$, 6.5 Hz, 2H), 2.36 (tt, $J = 17.8$, 6.2 Hz, 1H), 2.20–2.07 (m, 4H), 1.63 (s, 6H), 1.35 (t, $J = 7.1$ Hz, 12H); ^{13}C NMR δ 136.1, 135.1, 124.5, 122.2 (t, $J_{CP} = 7.1$ Hz), 68.4, 62.6 (t, $J_{CP} = 6.2$ Hz, 4C), 39.2, 37.5 (t, $J_{CP} = 133.5$ Hz), 25.4, 24.2 (t, $J_{CP} = 5.0$ Hz), 16.5 (d, $J_{CP} = 1.5$ Hz, 2C), 16.4 (d, $J_{CP} = 1.5$ Hz, 2C), 16.0, 15.3; ^{31}P NMR +23.1 ppm. Anal. Calc. for $C_{19}H_{38}O_7P_2$: C, 51.81; H, 8.70. Found: C, 51.47; H, 8.85%.

3.3. Tetraethyl 4,8-dimethyl-9-(tetrahydro-pyran-2-yloxy)-nona-3,7-dienyl-1,1-bisphosphonate (6)

To a stirred solution of bisphosphonate **5** (2.28 g, 5.17 mmol) in CH_2Cl_2(20 mL), DHP (1.25 mL, 13.3 mmol) was added as a neat liquid at 0 °C. After 5 min, a catalytic amount of *p*-TsOH (0.02 g, 0.10 mmol) was added neat and the mixture was allowed to warm to rt over 3.5 h. The reaction was quenched by addition of $NaHCO_3$(sat) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. This oil was purified by flash chromatography (3% methanol in Et_2O) to afford a pale yellow oil **6** (2.61 g, 96%): ^1H NMR δ 5.42 (t, $J = 6.9$ Hz, 1H), 5.33 (t, $J = 7.0$ Hz, 1H), 4.60 (t, $J = 3.9$ Hz, 1H), 4.17 (p, $J = 7.2$ Hz, 8H), 4.10 (d,

J = 11.8 Hz, 1H), 3.92–3.82 (m, 2H), 3.54–3.46 (m, 1H), 2.64 (tt, J = 17.2, 6.6 Hz, 2H), 2.32 (tt, J = 23.7, 6.1 Hz, 1H), 2.18–2.01 (m, 4H), 1.89–1.51 (m, 12H), 1.34 (t, J = 7.0 Hz, 12H); ^{13}C NMR δ 136.6, 132.1, 127.7, 122.1 (t, J_{CP} = 7.2 Hz), 97.5, 73.0, 62.6–62.4 (m, 4C), 62.2, 39.4, 37.6 (t, J_{CP} = 132.8 Hz), 30.7, 26.3, 25.6, 24.1 (t, J_{CP} = 4.8 Hz), 19.6, 16.6–16.4 (m, 4C), 16.2, 14.1; ^{31}P NMR +23.4 ppm. Anal. Calc. for $C_{24}H_{46}O_8P_2 \cdot 0.5H_2O$: C, 54.02; H, 8.88. Found: C, 54.36; H, 8.89%.

3.4. Tetramethyl 4,8-dimethyl-3,7-nonadienyl-1,1-bisphosphonate (7)

To a stirred suspension of NaH (373.9 mg, 9.35 mmol, washed with hexanes and dried in vacuo) in THF (30 mL), 15-crown-5 (0.17 mL, 0.84 mmol) was added via syringe at 0 °C over 15 min. Tetramethyl methylenebisphosphonate (2.04 g, 8.78 mmol) was added as a neat liquid to the suspension over 10 min, and the reaction mixture was allowed to stir for 1 h. Geranyl bromide (**3**, 1.8 mL, 9.45 mmol) was added as a neat liquid at 0 °C over 10 min. The resulting solution was stirred for 1 h, quenched by addition of NH_4Cl(sat), and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (gradient, 5–9% methanol in Et_2O) to give the desired product **7** (1.43 g, 45%): ^{1}H NMR δ 5.27 (t, J = 6.8 Hz, 1H), 5.09 (t, J = 5.5 Hz, 1H), 3.83 (d, J = 1.7 Hz, 6H), 3.80 (d, J = 1.7 Hz, 6H), 2.64 (tt, J = 17.2, 6.6 Hz, 2H), 2.38 (tt, J = 24.0, 6.6 Hz, 1H), 2.09–2.01 (m, 4H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H); ^{13}C NMR δ 137.1, 131.2, 123.9, 121.2 (t, J_{CP} = 7.2 Hz), 53.1–52.9 (m, 4C), 39.5, 36.5 (t, J_{CP} = 133.1 Hz), 26.4, 25.5, 23.8 (t, J_{CP} = 5.0 Hz), 17.5, 15.9; ^{31}P NMR +25.7 ppm. Anal. Calc. for $C_{15}H_{30}O_6P_2$: C, 48.91; H, 8.21. Found: C, 48.74; H, 8.31%.

3.5. Tetramethyl 4,8-dimethyl-3,7-nonadienyl-9-ol-1,1-bisphosphonate (8)

Under conditions parallel to those used for preparation of the tetraethyl ester **5**, the bisphosphonate **7** (2.38 g, 6.47 mmol) was treated with SeO_2 (373.3 mg, 3.30 mmol), *p*-hydroxybenzoic acid (96.7 mg, 0.69 mmol), and *tert*-butyl hydroperoxide (70% in water, 3.6 mL, 26.0 mmol). After standard work-up and treatment with $NaBH_4$ (352.4 mg, 9.32 mmol), the reaction was quenched with NH_4Cl(sat), concentrated under a stream of air, dissolved in a minimum amount of water, and placed in a continuous liquid–liquid extractor (Et_2O) for 3 h. The organic layer was concentrated in vacuo to a yellow oil that was purified by flash chromatography (8% methanol in Et_2O) to produce compound **8** as a pale yellow oil (1.34 g, 54%): ^{1}H NMR δ 5.40–5.36 (m, 1H), 5.28 (t, J = 6.9 Hz, 1H), 3.95 (br s, 2H), 3.82 (d, J = 2.7 Hz, 6H), 3.79 (d, J = 2.7 Hz, 6H), 3.53 (br s, 1H), 2.63 (tt, J = 17.4, 6.6 Hz, 2H), 2.40 (tt, J = 24.1, 5.4 Hz, 2H), 2.19–2.04 (m, 4H), 1.64 (s, 6H); ^{13}C NMR δ 136.7, 135.0, 124.3, 121.4 (t, J_{CP} = 7.1 Hz), 68.4, 53.2–53.0 (m, 4C), 39.0, 36.4 (t, J_{CP} = 133.7 Hz), 25.4, 23.9 (t, J_{CP} = 5.1 Hz), 15.8, 13.6; ^{31}P NMR +25.5 ppm. Anal. Calc. for $C_{15}H_{30}O_7P_2 \cdot 0.5\ H_2O$: C, 45.80; H: 7.94. Found: C, 45.38; H, 7.89%.

3.6. Tetramethyl 4,8-dimethyl-9-(tetrahydro-pyran-2-yloxy)-nona-3,7-dienyl-1,1-bisphosphonate (9)

To a stirred solution of bisphosphonate **8** (628.8 mg, 1.64 mmol) in CH_2Cl_2, DHP (0.40 ml, 4.25 mmol) was added as a neat liquid at 0 °C. After 5 min, a catalytic amount of *p*-TsOH (0.02 g, 0.09 mmol) was added and the mixture was allowed to warm to rt and stirred for 2 d. The reaction was quenched by addition of $NaHCO_3$(sat) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. Final purification of this oil by flash chromatography (10% methanol in Et_2O) afforded compound **9** as a pale yellow oil (712 mg, 93%): ^{1}H NMR δ 5.41 (t, J = 5.6 Hz, 1H), 5.28 (t, J = 6.9 Hz, 1H), 4.60–4.58 (m, 1H), 4.10 (d, J = 11.4 Hz, 1H), 3.91–3.79 (m, 2H), 3.83 (d, J = 1.8 Hz, 6H), 3.80 (d, J = 1.8 Hz, 6H), 3.58–3.46 (m, 1H), 2.63 (tt, J = 17.2, 6.5 Hz, 2H), 2.38 (tt, J = 24.0, 5.6 Hz, 1H), 2.19–2.02 (m, 4H), 1.89–1.79 (m, 1H), 1.76–1.54 (m, 11H); ^{13}C NMR δ 137.1, 132.1, 127.5, 121.6 (t, J_{CP} = 7.2 Hz), 97.4, 72.9, 62.1, 53.3–53.1 (m, 4C), 39.3, 36.6 (t, J_{CP} = 133.2 Hz), 30.7, 26.3, 25.5, 24.0 (t, J_{CP} = 5.1 Hz), 19.6, 16.1, 14.1; ^{31}P NMR +25.7 ppm. Anal. Calc. for $C_{20}H_{38}O_8P_2 \cdot 0.5H_2O$: C, 50.31; H, 8.23. Found: C, 50.30; H, 8.21%.

3.7. General procedure for copper-mediated Grignard displacement of allylic THP ethers

3.7.1. Aryl Grignard reagents

Magnesium metal (10 eq) was ground in a mortar and pestle and then placed in a round bottom flask with a Teflon stirbar and flame dried. After the flask had cooled to rt, the magnesium was covered in a minimum amount of ether and the bromide (10 eq) and a crystal of I_2 were added. After the solution ceased to boil, the reaction mixture was heated to reflux for approximately 30 min and allowed to cool to rt. In a separate flask, the THP ether (1.0 eq) was dissolved in a THF (usually ~10 mL) and CuI (1.5 eq) was added. The copper-THP solution was warmed to 35 °C and the Grignard reagent was transferred via cannula. The reaction mixture was heated to 50–55 °C for 1–3 h. The reaction was quenched by the addition of 10 mL of 10% NH_4OH in

NH_4Cl, extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Final purification was conducted by column chromatography on silica gel with gradient elution (2–6% CH_3OH in ether).

3.7.2. Alkyl Grignard reagents

After preparation of the reagents as described above, the copper-THP solution was cooled to −35 °C and the solution of the Grignard reagent was transferred via cannula over 1 h. The reaction mixture was allowed to warm to −10 °C for 2 d. The reaction was allowed to warm to rt, quenched, and the product was purified as described above.

*3.8. Tetraethyl 4,8-dimethyl-9-phenyl-nona-3,7-dienyl-1,1-bisphosphonate (**11a**)*

263 mg, 86%; ^{1}H NMR δ 7.30–7.14 (m, 5H), 5.34 (t, J = 6.9 Hz, 1H), 5.24 (t, J = 5.6 Hz, 1H), 4.22–4.12 (m, 8H), 3.27 (s, 2H), 2.65 (tt, J = 17.1, 6.6 Hz, 2H), 2.32 (tt, J = 23.8, 5.9 Hz, 1H), 2.17–2.02 (m, 4H), 1.65 (s, 3H), 1.52 (s, 3H), 1.34 (dt, J = 7.0, 0.7 Hz, 12H); ^{13}C NMR δ 140.4, 136.6, 134.5, 128.8 (2C), 128.2 (2C), 126.2, 125.9, 122.1 (t, J_{CP} = 7.2 Hz), 62.6–62.4 (m, 4C), 46.3, 39.7, 37.6 (t, J_{CP} = 132.9 Hz), 26.6, 24.1 (t, J_{CP} = 4.9 Hz), 16.5 (d, J_{CP} = 5.9 Hz, 4C), 16.1, 15.8; ^{31}P NMR +23.6 ppm. Anal. Calc. for $C_{25}H_{42}O_6P_2$: C, 59.99; H, 8.46. Found: C, 59.69; H, 8.52%.

*3.9. Tetraethyl 4,8-dimethyl-9-m-tolyl-nona-3,7-dienyl-1,1-bisphosphonate (**11b**)*

236 mg, 77%; ^{1}H NMR δ 7.19–7.13 (m, 1H), 7.01–6.94 (m, 3H), 5.34 (t, J = 6.9 Hz, 1H), 5.24 (t, J = 5.8 Hz, 1H), 4.22–4.12 (m, 8H), 3.23 (br s, 2H), 2.65 (tt, J = 17.2, 6.1 Hz, 2H), 2.42–2.22 (m, 4H), 2.17–2.02 (m, 4H), 1.66 (s, 3H), 1.54 (s, 3H), 1.34 (dt, J = 7.0, 0.6 Hz, 12H); ^{13}C NMR δ 140.4, 137.7, 136.8, 134.6, 129.7, 128.2, 126.7, 129.1, 125.9, 122.1 (t, J_{CP} = 7.2 Hz), 62.6–62.4 (m, 4C), 46.3, 39.7, 37.7 (t, J_{CP} = 132.8 Hz), 26.7, 24.2 (t, J_{CP} = 4.9 Hz), 21.5, 16.5 (d, J_{CP} = 6.4 Hz, 4C), 16.2, 15.9; ^{31}P NMR +23.6 ppm. Anal. Calc. for $C_{26}H_{44}O_6P_2 \cdot 0.5H_2O$: C, 59.64; H, 8.66. Found: C, 59.39; H, 8.70%.

*3.10. Tetraethyl 4,8-dimethyl-9-(m-trifluoromethyl-phenyl)-nona-3,7-dienyl-1,1-bisphosphonate (**11c**)*

234 mg, 70%; ^{1}H NMR δ 7.46–7.33 (m, 4H), 5.34 (t, J = 6.7 Hz, 1H), 5.26 (t, J = 6.8 Hz, 1H), 4.22–4.12 (m, 8H), 3.32 (s, 2H), 2.65 (tt, J = 17.0, 7.0 Hz, 2H), 2.31 (tt, J = 23.8, 6.0 Hz, 1H), 2.18–2.02 (m, 4H), 1.65 (s, 6H), 1.33 (t, J = 7.1 Hz, 12H); ^{13}C NMR δ 141.6, 136.7, 133.8, 132.4 (d, J_{CP} = 1.4 Hz), 128.8, 127.4, 125.6 (q, J_{CF} = 3.8 Hz), 124.5 (q, J_{CF} = 270.5 Hz), 123.0 (q, J_{CF} = 3.8 Hz), 122.3 (t, J_{CP} = 7.1 Hz), 62.7 (t, J_{CP} = 7.4 Hz, 4C), 46.1, 39.8, 37.8 (t, J_{CP} = 31.9 Hz), 26.8, 24.3 (t, J_{CP} = 4.8 Hz), 16.6 (d, J_{CP} = 6.5 Hz, 4C), 16.3, 16.0; ^{31}P NMR +23.5 ppm.

*3.11. Tetraethyl 4,8-dimethyl-9-(m-methoxy-phenyl)-nona-3,7-dienyl-1,1-bisphosphonate (**11d**)*

163 mg, 60%; ^{1}H NMR δ 7.19 (dt, J = 7.5, 0.9 Hz, 1H), 6.77–6.72 (m, 3H), 5.33 (t, J = 7.5 Hz, 1H), 5.25 (t, J = 7.5 Hz, 1H), 4.23–4.12 (m, 8H), 3.79 (s, 3H), 2.65 (tt, J = 17.2, 6.4 Hz, 2H), 2.32 (tt, J = 23.8, 6.0 Hz, 1H), 2.16–2.01 (m, 4H), 1.65 (s, 3H), 1.61 (s, 2H), 1.53 (s, 3H), 1.34 (dt, J = 6.7, 0.7 Hz, 12H); ^{31}P NMR +23.5 ppm. Anal. Calc. for $C_{26}H_{44}P_2O_7 \cdot 1H_2O$: C, 56.92; H, 8.45. Found: C, 56.94; H, 8.46%.

*3.12. Tetraethyl 9-biphenyl-4,8-dimethyl-nona-3,7-dienyl-1,1-bisphosphonate (**11e**)*

258 mg, 76%; ^{1}H NMR δ 7.60–7.57 (m, 2H), 7.53–7.50 (m, 2H), 7.44–7.39 (m, 2H), 7.34–7.28 (m, 1H), 7.24–7.22 (m, 2H), 5.35 (t, J = 7.0 Hz, 1H), 5.28 (dt, J = 6.8, 1.1 Hz, 1H), 4.22–4.11 (m, 8H), 3.31 (br s, 2H), 2.66 (tt, J = 17.1, 6.9 Hz, 2H), 2.33 (tt, J = 23.8, 5.9 Hz, 1H), 2.19–2.04 (m, 4H), 1.66 (s, 3H), 1.56 (s, 3H), 1.33 (dt, J = 7.0, 0.58 Hz, 12H); ^{13}C NMR δ 146.0, 139.7, 139.0, 136.8, 134.5, 129.4 (2C), 128.8 (2C), 127.2 (2C), 127.1 (2C), 127.1, 126.5, 122.2 (t, J_{CP} = 7.2 Hz), 62.7–62.5 (m, 4C), 46.0, 39.8, 37.8 (t, J_{CP} = 132.8 Hz), 26.8, 24.3 (t, J_{CP} = 5.0 Hz), 16.6 (d, J_{CP} = 5.8 Hz, 4C), 16.3, 16.0; ^{31}P NMR +23.7 ppm. Anal. Calc. for $C_{31}H_{46}O_6P_2$: C, 64.57; H, 8.04. Found: C, 64.40; H, 8.11%.

*3.13. Tetraethyl 4,8-dimethyl-10-phenyl-deca-3,7-dienyl-1,1-bisphosphonate (**11f**)*

149 mg, 75%; ^{1}H NMR δ 7.30–7.15 (m, 5H), 5.31 (t, J = 6.8 Hz, 1H), 5.12 (t, J = 6.8 Hz, 1H), 4.17 (p, J = 7.6 Hz, 8H), 2.72–2.56 (m, 4H), 2.41–2.21 (m, 3H), 2.10–1.95 (m, 4H), 1.64 (s, 6H), 1.33 (t, J = 7.0 Hz, 12H); ^{13}C NMR δ 142.3, 136.6, 134.4, 128.3 (2C), 128.1 (2C), 125.5, 124.5, 121.9 (t, J_{CP} = 7.1 Hz), 62.4–62.2 (m, 4C), 41.5, 39.5, 37.5 (t, J_{CP} = 132.8 Hz), 34.7, 26.4, 24.0 (t, J_{CP} = 4.9 Hz), 16.4 (d, J_{CP} = 6.4 Hz, 4C), 16.0 (2C); ^{31}P NMR δ +23.5 ppm. Anal. Calc. for $C_{21}H_{34}O_6P_2 \cdot 0.5H_2O$: C, 55.62; H, 7.78. Found: C, 55.69; H, 7.93%.

*3.14. Tetraethyl 4,8,12-trimethyl-trideca-3,7-dienyl-1,1-bisphosphonate (**11g**)*

114 mg, 57%; ^{1}H NMR δ 5.32 (t, J = 6.9 Hz, 1H), 5.09 (t, J = 6.2 Hz, 1H), 4.15 (p, J = 7.3 Hz, 8H), 2.64 (tt, J = 17.1, 6.7 Hz, 2H), 2.31 (tt, J = 23.8, 6.2 Hz, 1H), 2.07–1.90 (m, 6H), 1.65 (s, 3H), 1.58–1.48 (m,

4H), 1.39–1.30 (m, 14H), 1.16–1.09 (m, 2H), 0.87 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR δ 137.0, 135.6, 123.9, 122.0 (t, $J_{CP} = 7.1$ Hz), 62.7–62.5 (m, 4C), 40.1, 39.9, 38.7, 37.7 (t, $J_{CP} = 133.0$ Hz), 28.0, 26.7, 25.9, 24.2 (t, $J_{CP} = 5.0$ Hz), 22.8 (2C), 16.6 (d, $J_{CP} = 6.3$ Hz, 4C), 16.3, 16.0; ^{31}P NMR δ +23.5 ppm. Anal. Calc. for $C_{24}H_{48}O_6P_2 \cdot 0.5H_2O$: C, 57.24; H, 9.81. Found: C, 57.42; H, 9.97%.

3.15. Tetraethyl (12R)-4,8,12,16-tetramethyl-heptadeca-3,7,15-trienyl-1,1-bisphosphonate (**11h**)

14.8 mg, 19%; ^{1}H NMR δ 5.31 (t, $J = 6.9$ Hz, 1H), 5.10 (t, $J = 7.1$ Hz, 2H), 4.17 (p, $J = 7.2$ Hz, 8H), 2.64 (tt, $J = 18.2$, 5.9 Hz, 2H), 2.31 (tt, $J = 23.8$, 6.2 Hz, 1H), 2.10–1.90 (m, 8H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.48–1.00 (m, 17H), 1.18–1.05 (m, 2H), 0.86 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR δ 137.1, 135.7, 131.1, 125.2, 124.0, 121.9 ($J_{CP} = 7.2$ Hz), 62.8–62.6 (m, 4C), 40.2, 40.0, 37.7 (t, $J_{CP} = 132.9$ Hz), 37.3, 36.8, 32.5, 31.1, 26.7, 25.9, 25.8, 25.5, 24.2 (t, $J_{CP} = 5.0$ Hz), 19.8, 16.6 (d, $J_{CP} = 6.2$ Hz, 4C), 16.3, 16.0; ^{31}P NMR δ +23.5 ppm. Anal. Calc. for $C_{29}H_{56}O_6P_2 \cdot 0.5H_2O$: C, 60.90; H, 10.05. Found: C, 60.65; H, 9.99%.

3.16. Tetramethyl 4,8-dimethyl-9-phenyl-nona-3,7-dienyl-1,1-bisphosphonate (**12**)

193 mg, 52%; ^{1}H NMR δ 7.30–7.14 (m, 5H), 5.31–5.21 (m, 2H), 3.82 (d, $J = 1.7$ Hz, 6H), 3.79 (d, $J = 1.7$ Hz, 6H), 3.27 (s, 2H), 2.64 (tt, $J = 17.2$, 6.7 Hz, 2H), 2.37 (tt, $J = 24.0$, 5.8 Hz, 1H), 2.20–2.03 (m, 4H), 1.65 (s, 3H), 1.53 (s, 3H); ^{13}C NMR δ 140.5, 137.4, 134.7, 129.0 (2C), 128.3 (2C), 126.2, 126.1, 121.7 (t, $J_{CP} = 7.2$ Hz), 53.3 (t, $J_{CP} = 6.2$ Hz, 4C), 46.4, 39.8, 36.8 (t, $J_{CP} = 133.2$ Hz), 26.7, 24.1 (t, $J_{CP} = 5.0$ Hz), 16.2, 15.9; ^{31}P NMR +25.9 ppm. Anal. Calc. for $C_{21}H_{34}O_6P_2 \cdot 0.5H_2O$: C, 55.62; H, 7.78. Found: C, 55.69; H, 7.93%.

3.17. Tetraethyl 1,4,8-trimethyl-9-(tetrahydro-pyran-2-yloxy)-nona-3,7-dienyl-1,1-bisphosphonate (**13**)

To a stirred solution of THP ether **6** (601 mg, 1.15 mmol) in THF (20 mL), 15-crown-5 (0.01 mL, 0.05 mmol) and NaH (63 mg, 1.56 mmol) were added at 0 °C. After 30 min, CH_3I (0.08 mL, 1.28 mmol) was added as a neat liquid and the reaction mixture was stirred for 1 h. The reaction mixture was then quenched by addition of NH_4Cl(sat), extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (2% methanol in Et_2O) afforded compound **13** (430 mg, 70%): ^{1}H NMR δ 5.44–5.37 (m, 2H), 4.61–4.58 (m, 1H), 4.23 (p, $J = 7.1$ Hz, 8H), 4.10 (d, $J = 11.5$ Hz, 1H), 3.92–3.82 (m, 2H), 3.54–3.47 (m, 1H), 2.61 (dt, $J = 15.6$, 7.5 Hz, 2H), 2.20–2.04 (m, 4H), 1.86–1.50 (m, 12H), 1.33 (dt, $J = 7.1$, 1.5 Hz, 15H); ^{13}C NMR δ 137.7, 132.1, 127.9, 119.4 (t, $J_{CP} = 7.3$ Hz), 97.6, 73.1, 62.8–62.6 (m, 4C), 62.3, 41.2 (t, $J_{CP} = 134.0$ Hz), 39.8, 31.1 (t, $J_{CP} = 4.4$ Hz), 30.8, 26.5, 25.7, 19.7, 16.7–16.6 (m, 4C), 16.4, 16.3 (t, $J_{CP} = 6.8$ Hz), 14.2; ^{31}P NMR +27.1 ppm. Anal. Calc. for $C_{25}H_{48}O_8P_2 \cdot 0.5H_2O$: C, 54.83; H, 9.02. Found: C, 54.43; H, 8.93%.

3.18. Tetraethyl 1,4,8-trimethyl-9-phenyl-nona-3,7-dienyl-1,1-bisphosphonate (**14**)

Solid CuI (360 mg, 1.85 mmol) was added to a stirred solution of THP ether **6** (644 mg, 1.23 mmol) in THF (20 mL) at 35 °C. Phenylmagnesium bromide (12.5 mL, 0.98 M), was added via syringe to the suspension at 50 °C. After 1.5 h, the reaction appeared to be complete by TLC and CH_3I (2.0 mL, 32.0 mmol) was added as a neat liquid. The resulting solution was allowed to stir for 10 min until a color change occurred. A solution of 10% NH_4OH in NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic layers were then dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (1% methanol in ethyl acetate) resulted in a 1:1 mixture of non-methylated and methylated products, **11a** and **14**, respectively. This mixture was dissolved in THF (20 mL) and treated with NaH (48 mg, 1.21 mmol) and CH_3I (0.15 mL, 2.40 mmol), and then quenched by addition of NH_4Cl (sat). The reaction mixture was then extracted with Et_2O, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash column chromatography (1% methanol in ethyl acetate) afforded compound **14** (368 mg, 58%): ^{1}H NMR δ 7.29–7.14 (m, 5H), 5.42 (t, $J = 7.2$ Hz, 1H), 5.25 (t, $J = 5.6$ Hz, 1H), 4.19 (p, $J = 7.1$ Hz, 8H), 3.26 (s, 2H), 2.63 (dt, $J = 15.6$, 7.5 Hz, 2H), 2.17–2.02 (m, 4H), 1.64 (s, 3H), 1.52 (s, 3H), 1.40 (t, $J = 16.6$ Hz, 3H), 1.33 (dt, $J = 7.1$, 1.4 Hz, 12H); ^{13}C NMR δ 140.2, 137.4, 134.2, 128.6 (2C), 128.0 (2C), 126.1, 125.7, 119.1 (t, $J_{CP} = 7.1$ Hz), 62.4–62.3 (m, 4C), 46.1, 40.9 (t, $J_{CP} = 133.9$ Hz), 39.8, 30.9 (t, $J_{CP} = 4.3$ Hz), 26.5, 16.4–16.3 (m, 4C), 16.1, 16.1 (t, $J_{CP} = 6.0$ Hz), 15.6; ^{31}P NMR +27.0 ppm. Anal. Calc. for $C_{26}H_{44}O_6P_2 \cdot 0.5H_2O$: C, 59.64; H, 8.66. Found: C, 59.34; H, 8.66%.

3.19. Diethyl 4,8-dimethyl-3,7-nonadienyl-1-phosphonate (**16**)

To a stirred suspension of LDA [27.91 mmol, prepared *in situ* from diisopropylamine (4.0 mL) and *n* BuLi (12.35 mL, 2.38 M in hexane)] in THF (20 mL) was added dimethyl methylphosphonate (4.0 mL, 26.6 mmol) via syringe at −78 °C over 1 h. The solution was permitted to warm to rt and geranyl bromide (**3**,

5.4 mL, 27.2 mmol) was added as a neat liquid at 0 °C. The resulting solution was stirred for 1 h, quenched by the addition of NH_4Cl (sat), and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (1% methanol in Et_2O) to afford phosphonate **16** [16] (7.58 g, 99%): ^1H NMR δ 5.15–5.06 (m, 2H), 4.19–4.01 (m, 4H), 2.35–2.23 (m, 2H), 2.08–1.98 (m, 4H), 1.81–1.70 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR δ 136.4, 131.5, 124.3, 123.2 (d, $J_{CP} = 17.3$ Hz), 61.5 (d, $J_{CP} = 6.5$ Hz, 2C), 39.7, 26.7, 25.8 (d, $J_{CP} = 162.1$ Hz), 25.2, 21.1 (d, $J_{CP} = 4.6$ Hz), 17.8, 16.6 (d, $J_{CP} = 6.0$ Hz, 2C), 16.1; ^{31}P NMR +31.6 ppm. Anal. Calc. for $C_{15}H_{29}O_3P \cdot 0.5H_2O$: C, 60.59; H, 10.17. Found: C, 60.75; H, 9.97%.

3.20. Diethyl 4,8-dimethyl-3,7-nonadienyl-9-ol-1-phosphonate (*17*)

According to the procedure described for bisphosphonate **5**, the geranyl phosphonate **16** (2.61 g, 9.0 mmol) was treated with SeO_2 (518 mg, 4.67 mmol), *p*-hydroxybenzoic acid (129 mg, 0.93 mmol) and *tert*-butyl hydroperoxide (70% in water, 5.0 mL, 36.1 mmol). After standard work-up and treatment with $NaBH_4$ (352 mg, 9.3 mmol) in methanol, the resulting yellow oil was purified by flash chromatography (2 % methanol in Et_2O) to afford compound **17** as a pale yellow oil (854 mg, 31%): ^1H NMR δ 5.37 (t, $J = 6.5$ Hz, 1H), 5.15 (t, $J = 6.8$ Hz, 1H), 4.14–4.00 (m, 4H), 3.94 (s, 2H), 2.34–2.22 (m, 2H), 2.14–2.02 (m, 4H), 1.81–1.70 (m, 2H), 1.63 (s, 3H), 1.62 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR δ 135.9, 135.2, 124.4, 123.1 (d, $J_{CP} = 15.6$ Hz), 68.0, 61.4 (d, $J_{CP} = 6.5$ Hz, 2C), 39.2, 26.0, 25.7 (d, $J_{CP} = 139.2$ Hz), 20.9 (d, $J_{CP} = 4.7$ Hz), 16.4 (d, $J_{CP} = 6.0$ Hz, 2C), 15.9, 13.6; ^{31}P NMR +31.5 ppm. Anal. Calc. for $C_{15}H_{29}O_4P \cdot 0.33H_2O$: C, 58.06; H, 9.63. Found: C, 58.33; H, 9.55%.

3.21. Diethyl 4,8-dimethyl-9-(tetrahydro-pyran-2-yloxy)-nona-3,7-dienyl-1-phosphonate (*18*)

To a stirred solution of phosphonate **17** (2.26 g, 7.42 mmol) in CH_2Cl_2 (40 mL), DHP (1.75 mL, 18.6 mmol) was added as a neat liquid at 0 °C. After 5 min, a catalytic amount of *p*-TsOH (0.03 g, 0.16 mmol) was added as a neat solid and the mixture was allowed to warm to rt and stir for 2 d. The reaction was quenched by addition of $NaHCO_3$(sat) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. Final purification by flash chromatography (1% methanol in Et_2O) gave compound **18** as a pale yellow oil (2.58 g, 91%): ^1H NMR δ 5.42–5.38 (m, 1H), 5.16–5.12 (m, 1H), 4.61–4.58 (m, 1H), 4.18–4.01 (m, 5H), 3.91–3.82 (m, 2H), 3.54–3.45 (m, 1H), 2.35–2.23 (m, 2H), 2.18–2.00 (m, 4H), 1.89–1.70 (m, 4H), 1.65 (s, 3H), 1.62 (s, 3H), 1.61–1.48 (m, 3H), 1.33 (t, $J = 7.1$ Hz, 6H), 1.28–1.09 (m, 1H); ^{13}C NMR δ 136.1, 132.1, 127.6, 123.4 (d, $J_{CP} = 17.4$ Hz), 97.4, 72.9, 62.2, 61.5 (d, $J_{CP} = 6.5$, 2C), 39.2, 30.7, 26.3, 26.0 (d, $J_{CP} = 138.7$ Hz), 25.6, 21.1 (d, $J_{CP} = 4.6$ Hz), 19.6, 16.6 (d, $J_{CP} = 6.0$ Hz, 2C), 16.0, 14.1; ^{31}P NMR +31.5 ppm. Anal. Calc. for $C_{20}H_{37}O_5P$: C, 61.84; H, 9.60. Found: C, 61.74; H, 9.70%.

3.22. Diethyl 4,8-dimethyl-9-phenyl-nona-3,7-dienyl-1-phosphonate (*19*)

To a stirred solution of phosphonate **18** (402 mg, 1.04 mmol) in CH_2Cl_2(21 mL), copper iodide (310 mg, 1.60 mmol) was added at 35 °C. Once the temperature reached 50 °C, phenyl magnesium bromide (0.98 M in THF, 10.8 ml, 10.5 mmol) was added and the mixture stirred until the starting material had been consumed. The reaction mixture was allowed to cool to rt and quenched by the addition of 20 mL of 10% NH_4OH in NH_4Cl(sat). The mixture was extracted with ether, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography (Et_2O) to provide a pale yellow oil as a single spot by TLC. Analysis by ^1H NMR indicated the presence of both diol **20** and the desired product **19**. The mixture was dissolved in pyridine (10 mL) and acetic anhydride (3.0 mL) was added at rt. After stirring overnight, the reaction was quenched by addition of NH_4Cl (sat) and extracted with Et_2O. The combined organic layers were washed repeated with $NiCl_2$ (2.0 M) to remove pyridine, until the aqueous layer remained green. The resulting organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The mixture was purified by flash chromatography (gradient, 30% Et_2O in hexane to 1% methanol in Et_2O) to provide two oils, phosphonate **19** (246 mg, 71%) and the diacetate **21** (240 mg, 88%).

*For phosphonate **19***: ^1H NMR δ 7.29–7.14 (m, 5H), 5.23–5.19 (m, 1H), 5.16–5.11 (m, 1H), 4.16–4.03 (m, 4H), 2.35–2.23 (m, 2H), 2.16–2.00 (m, 4H), 1.80–1.69 (m, 2H), 1.62 (s, 3H), 1.52 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR δ 140.4, 136.2 (d, $J_{CP} = 1.8$ Hz), 134.5, 128.8 (2C), 128.2 (2C), 126.2, 125.9, 123.3 (d, $J_{CP} = 17.5$ Hz), 61.4 (d, $J_{CP} = 6.5$, 2C), 46.3, 39.5, 26.5, 26.0 (d, $J_{CP} = 138.7$ Hz), 21.1 (d, $J_{CP} = 4.6$ Hz), 16.5 (d, $J_{CP} = 6.0$ Hz, 2C), 16.0, 15.8; ^{31}P NMR +31.6 ppm. *For compound **21***: ^1H NMR δ 7.32–7.24 (m, 5H), 5.73 (dd, $J = 7.6$, 6.2 Hz, 1H), 4.01 (t, $J = 6.6$ Hz, 2H), 2.04 (s, 3H), 1.99 (s, 3H), 1.98–1.75 (m, 2H), 1.67–1.58 (m, 2H), 1.48–1.21 (m, 2H); ^{13}C NMR δ 170.9, 170.1, 140.5, 128.4 (2C), 127.9, 126.4 (2C), 75.7, 64.0, 35.8, 28.2, 21.9, 21.2, 20.9.

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