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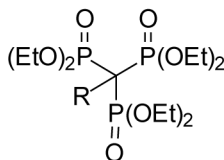
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Synthesis and Reactivity of Alkyl-1,1,1-trisphosphonate Esters

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Abstract


 R = allyl, propyl, benzyl,
prenyl, etc.

The α -trisphosphonic acid esters provide a unique spatial arrangement of three phosphonate groups, and may represent an attractive motif for inhibitors of enzymes that utilize di- or triphosphate substrates. To advance studies of this unique functionality, a general route to alkyl derivatives of the parent system (R = H) has been developed. A set of new α -alkyl-1,1,1-trisphosphonate esters has been prepared through phosphinylation and subsequent oxidation of tetraethyl alkylbisphosphonates, and the reactivity of these new compounds has been studied in representative reactions that afford additional examples of this functionality.

Introduction

The geminal bisphosphonate moiety is found in a number of drugs that are in widespread clinical use, including alendronate (**1**, Fosamax®), risedronate (**2**, Actonel®), and zoledronate (**3**, Zometa®).¹ The clinical applications of these compounds in treatment of various diseases of the bone,¹ together with the prevalence of di- and triphosphate intermediates in metabolism, have encouraged studies of many other bisphosphonates, and there are numerous reports on their chemical synthesis² and biological activity.³ In sharp contrast to the extensive work with geminal bisphosphonates, there are very few reported studies of aryl- or alkyl-1,1,1-trisphosphonate esters (**4**). Phosphonate esters often are prepared through reaction of a trialkyl phosphite with an alkyl halide, but simple alkyl halides are not very reactive in this classical Michaelis-Arbuzov synthesis and chloroform does not react with triethyl phosphite even under forcing conditions.⁴ However, trichloromethylamine is known to react with triethyl phosphite to afford the aminotrisphosphonate **5**⁵ through a reaction sequence now assumed to be based on elimination-addition reactions.⁶ A similar strategy with a quinone methide was used to prepare the aryl trisphosphonate **6**,⁷ and ultimately the parent compound **7** was prepared through addition to tetraethyl diazo-bisphosphonate.⁶ The parent trisphosphonate **7** also has been prepared via C-P bond formation. In this case, the anionic bisphosphonate proved unreactive with diethyl chlorophosphate but phosphinylation of the bisphosphonate anion

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 Supporting Information. The ¹H and ¹³C NMR spectra for compounds **10–16**, and **19–24**, and the titration curve for compound **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

followed by oxidation to the phosphonate was successful,⁶ a strategy which already had been applied to preparation of β -keto phosphonates from ketone and ester enolates.⁸ However, apart from some intriguing studies by Blackburn *et al.*, who prepared adenosine esters derived from compound **7** and its halogenated analogues,⁹ little has been done with trisphosphonates for some time. The limited information available on trisphosphonate esters and our longstanding interest in C-P bond formation¹⁰ led us to investigate the synthesis and reactivity of this functionality.

Results and Discussion

One might reasonably assume that the shortest route from tetraethyl methylenebisphosphonate (**8**) to a family of alkyl trisphosphonates would involve preparation of the parent trisphosphonate **7** followed by alkylation. To explore this possibility, compound **7** was prepared starting with the literature approach that employed phosphinylation of tetraethyl methylenebisphosphonate, but followed by oxidation of the presumed phosphinate intermediate with hydrogen peroxide^{8b,10b} rather than air (Scheme 1).⁶ This modified procedure gave an improved yield (48% vs. the 32% in the original report⁶) when the methylenebisphosphonate is thoroughly dried (*vide infra*), and the ¹H, ¹³C and ³¹P spectra of the material prepared this way matched literature data.⁶ Attempted reaction of the methylenebisphosphonate anion with diethyl chlorophosphate was not successful under the same reaction conditions.

Upon treatment of compound **7** with NaH, formation of the anion was strongly suggested by a downfield shift in the ³¹P NMR spectrum (from 14 to 32 ppm). However, addition of benzyl bromide did not induce any further change in the ³¹P NMR resonance, nor did addition of the less sterically encumbered alkylating agent allyl bromide. Presumably the limited reactivity of the anion under these conditions is a consequence of the fact that the carbanionic center is both well stabilized and considerably hindered. Several experiments were conducted to determine the approximate acidity of compound **7**. For example, the ³¹P NMR resonance observed for the anion at 32 ppm persisted even after addition of water or saturated NH₄Cl to the NMR sample. Only after addition of acetic acid was a resonance representing the neutral compound **7** again observed at 14 ppm. Titration of the trisphosphonate ester **7** with NaOH gave a pK_a of ~6.5, suggesting that the negative charge is highly delocalized and that this ester should be viewed as a strong carbon acid.

To explore alternate approaches to these compounds, tetraethyl benzylbisphosphonate **9** was prepared by alkylation of bisphosphonate **8**.^{2c, 2d} No evidence for C-P bond formation could be detected by ³¹P NMR upon treatment of compound **9** with NaH and diethyl chlorophosphate, but reactions that employed diethyl chlorophosphite as the electrophile^{6,8} were more encouraging. After treatment of bisphosphonate **9** with NaH and diethyl chlorophosphite, exposure to air under standard conditions afforded just trace amounts of the desired trisphosphonate. However, when reaction of the bisphosphonate **9** with NaHMDS and diethyl chlorophosphite at 0 °C was followed by treatment with H₂O₂, an exothermic reaction ensued. A new product was detected by TLC analysis, and analysis of the reaction mixture by ³¹P NMR revealed a new resonance at 18 ppm. After isolation of this product via column chromatography, the ¹H NMR spectrum displayed a notable phosphorus coupling to the benzylic hydrogens (q, *J* = 15.8 Hz). The ¹³C NMR spectrum was even more striking, with observable couplings to ³¹P throughout the spectrum and a resonance for the quaternary carbon that appeared as a clear quartet (*J*_{CP} = 118 Hz). Based on these data, as well as a consistent elemental analysis, the product was assigned the structure of trisphosphonate **10**.

The three-step protocol of alkylation, phosphinylation, and oxidation proved to be successful with several other alkyl halides but the isolated yields initially were modest (<20%). Addition of excess base did not result in increased yields. Elemental analyses of alkylbisphosphonates have consistently revealed the presence of water, suggesting that hydroxide generated in situ might complicate formation of the desired intermediate in this case. Thorough drying of the alkylated bisphosphonates via azeotropic distillation with either benzene or toluene prior to deprotonation and phosphinylation resulted in a dramatic increase in reaction yields. Ultimately this strategy resulted in conversions ranging from 64 to 86% by ^{31}P NMR, with isolated yields typically just slightly lower. This methodology was then applied to the synthesis of a variety of alkyl trisphosphonates with good isolated yields (Table 1). Furthermore, there is at least the potential to recover the alkylbisphosphonate in the cases of lower conversion, and that decision can be based on inspection of the ^{31}P NMR spectrum of the reaction mixture (~18 ppm for trisphosphonate **10** versus ~23 ppm for the bisphosphonate **9**).

Because so few alkyl-1,1,1-trisphosphonates are known, it was unclear whether it would be possible to carry out various functional group transformations in the presence of this group. Some reactions proved to be routine while others were not. For example, treatment of allyl trisphosphonate **11** with hydrogen over Pd/C resulted in selective reduction of the olefin to afford the saturated compound **15** in good yield (Scheme 2). However, some oxidative transformations proved to be more problematic. After treatment of the allyl trisphosphonate **11** with ozone under typical conditions¹¹ some evidence for formation of the desired aldehyde **17** was obtained, including a resonance appropriate for the aldehyde hydrogen in the ^1H NMR spectrum. However, this material was obtained in low yield and there was detectable dephosphorylation to a bisphosphonate. Attempts to avoid decomposition by treatment with a limited amount of ozone under Rubin conditions¹² also resulted in decomposition of the allyl trisphosphonate. Similar observations were found upon attempted epoxidation. Treatment of allyl trisphosphonate **11** with *m*-CPBA resulted in the disappearance of the resonances for the olefinic hydrogens, but again only low amounts of material that appeared to be the epoxide **18** were obtained and decomposition to a bisphosphonate may be competitive.

As one might expect, the trisphosphonate functionality is of considerable size, and several attempted reactions appeared to be difficult due to steric hindrance. For example, the allyl trisphosphonate **11** did not undergo hydroboration readily upon treatment with 9-BBN, but treatment with borane in THF resulted in conversion to the primary alcohol **19** in reasonable yield. The trisphosphonate group was not significantly impacted by this oxidative work-up with H_2O_2 , as might be expected given that hydrogen peroxide was used during the trisphosphonate synthesis. Cross metathesis reactions of trisphosphonate **11** also may be affected by the size and proximity of the trisphosphonate moiety. Attempted cross metathesis with 2-methyl-2-butene and the Grubbs second generation catalyst gave the unexpected *cis* and *trans* 1,2-disubstituted olefins **20** as the major product, and only a small amount of the expected trisubstituted alkene **12**.¹³ The identity of the olefins **20** was established unequivocally when the cross metathesis reaction of trisphosphonate **11** with 2-butene also gave a mixture of the same *cis* and *trans* olefins **20**.

The importance of steric factors in the reactivity of compound **11** may be clarified by consideration of the reactivity of trisphosphonate **14**, which can be viewed as a less sterically congested analogue where the number of methylene carbons between the double bond and the trisphosphonate group has been increased. In this case, attempted cross metathesis of compound **14** with 2-methyl-2-butene proceeded smoothly and gave the expected trisubstituted olefin **21** in high yield (87%, Scheme 3). In a similar sense, treatment

of olefin **14** with 9-BBN followed by standard oxidative work-up gave the primary alcohol **22** in reasonable yield (57%).

While metathesis reactions of the trisphosphonate **11** may be limited in their ability to afford a diverse array of new trisphosphonates, this is clearly a promising approach with more distal olefins such as compound **14**. Another approach to facile preparation of compound libraries is based on the 1,3-dipolar cycloaddition of azides with acetylenes (or click chemistry).¹⁴ Somewhat to our surprise given the results with the metathesis reaction, the copper-catalyzed reaction of the acetylene trisphosphonate **16** with benzyl azide proceeded smoothly to give the triazole **23** in 85% yield (Scheme 4). This reaction clearly demonstrates that the trisphosphonate group will tolerate standard conditions for this cycloaddition, and strongly suggests that more distal acetylenes would react at least as well.

Hydrolysis of these trisphosphonate esters could provide a variety of salts depending upon the extent of ester hydrolysis. Initial attempts to bring about complete hydrolysis of benzyl trisphosphonate **10** by treatment with HCl under reflux resulted in decomposition.¹⁵ Even though the corresponding benzylbisphosphonate **9** undergoes complete hydrolysis under parallel conditions,^{2d} the more relevant comparison may be with the parent trisphosphonate **7** which also was reported to undergo decomposition when subjected to acid hydrolysis.⁶ Treatment of trisphosphonate **11** with TMSBr and collidine (Scheme 5)¹⁶ resulted in the formation of the TMS esters, as monitored by ³¹P NMR spectroscopy. Addition of 1N NaOH to a solution of the TMS ester led to complete hydrolysis and formation of the mixed sodium and collidinium salt¹⁷ (**24**) which could be isolated by standard work-up.

In conclusion, these studies have led to a synthesis of hexaethyl methanetrakisphosphonate more efficient than the original report,⁶ and determined that this compound should be viewed as a strong carbon acid. They also have established a general strategy for preparation of alkyl-1,1,1-trisphosphonates from the corresponding alkyl-1,1-bisphosphonates through phosphinylation and oxidation with hydrogen peroxide. As long as steric factors from the bulky trisphosphonate group are considered, alkyl-1,1,1-trisphosphonates can undergo a variety of functional group transformations although they are sensitive to some oxidative conditions. In particular, steric factors already have led to an interesting variation on the Grubbs metathesis where a disubstituted olefin was observed as the major product from metathesis with 2-methyl-2-butene rather than the expected trisubstituted alkene. Furthermore, the ability of an acetylene trisphosphonate to undergo click chemistry suggests that libraries of trisphosphonates should be readily available. Thus it appears likely that further studies of alkyl-1,1,1-trisphosphonates will unveil other new chemistry, and that screening of trisphosphonate libraries could be used to identify biologically active compounds of this general structure. Investigations along these lines are continuing, and will be reported in due course.

Experimental

General Procedures

Both THF and Et₂O were distilled from sodium and benzophenone immediately prior to use. All non-aqueous reactions were performed with either oven-dried or flame-dried glassware under an argon atmosphere. Flash chromatography was performed on silica gel with an average particle size of 40-63 μm. The ¹H NMR spectra were recorded at 300 MHz (75 MHz for ¹³C) with CDCl₃ as solvent and (CH₃)₄Si as internal standard unless otherwise noted. The ¹H NMR spectra recorded in D₂O used residual H₂O (4.80 ppm) as a reference, while 1,4-dioxane (67.0 ppm) was used as a reference for these ¹³C NMR spectra. Chemical shifts of ³¹P NMR spectra are reported in ppm relative to H₃PO₄ as an external standard. Elemental analyses were performed at a commercial facility. High resolution mass spectral

analysis was performed with a quadrupole time of flight hybrid mass spectrometer with the capacity for positive and negative ionization modes. Electrospray ionization was employed with acetonitrile or aqueous (**24**) solutions.

Methyldynetrtrisphosphonic acid, hexaethyl ester (**7**)

Tetraethyl methylenebisphosphonate (251 mg, 0.87 mmol) was dissolved in benzene (5 mL) and then concentrated *in vacuo* to remove traces of water. After three such cycles, the residue was dissolved in THF (10 mL) and cooled to 0 °C in an ice bath. A solution of NaHMDS in THF (1.0 M, 1.3 mL, 1.3 mmol) was added, and the mixture was allowed to stir at 0 °C for 30 min after which CIP(OEt)₂ (340 mg, 2.17 mmol) was added. After an additional 30 min, H₂O₂ (2.0 mL, 17.6 mmol) was very slowly added dropwise to the vessel. The reaction mixture was allowed to stir for one h, then diluted with brine, and extracted with CH₂Cl₂. The organic portions were combined, dried (MgSO₄), and filtered, and the filtrate was concentrated *in vacuo*. Final purification via flash chromatography (silica gel, 0 to 50% EtOH in EtOAc) gave the desired trisphosphonate **7** as a light yellow oil (176 mg, 48%). Both ³¹P and ¹H NMR data were consistent with previously reported values.^{5b,6}

2-Phenylethylidynetrisphosphonic acid, hexaethyl ester (**10**)

General procedure for the synthesis of alkyl trisphosphonates. A sample of tetraethyl benzylbisphosphonate (**9**)^{18, 19} (518 mg, 1.37 mmol) was dissolved in benzene (5 mL) and then concentrated *in vacuo*. After three such cycles, the residue was dissolved in THF (6.4 mL) and cooled to 0 °C in an ice bath. A solution of NaHMDS in THF (1.0 M, 2.1 mL, 2.1 mmol) was added, and the mixture was allowed to stir at 0 °C for 30 min, after which CIP(OEt)₂ (437 mg, 2.74 mmol) was added. After an additional 30 min, excess H₂O₂ (2.0 mL, ~30% by titration) was slowly added dropwise (5 – 10 min) to the vessel. The reaction mixture was allowed to stir for one h, then diluted with brine, and extracted with CH₂Cl₂. The organic portions were combined, dried (MgSO₄), and filtered, and the filtrate was concentrated *in vacuo*. Final purification via flash chromatography (silica gel, 0 to 30% EtOH in EtOAc) gave the desired trisphosphonate **10** as a clear oil (432 mg, 61%): ¹H NMR δ 7.60–7.57 (m, 2H), 7.23–7.20 (m, 3H), 4.24–4.13 (m, 12H), 3.59 (q, *J*_{PH} = 15.8 Hz, 2H), 1.27 (t, *J* = 8.9 Hz, 18H); ¹³C NMR (100 MHz) δ 136.3 (q, *J*_{PC} = 5.9 Hz), 132.5 (2C), 126.9 (2C), 126.6, 63.4 (m, 6C), 52.8 (q, *J*_{PC} = 117.8 Hz), 36.1 (q, *J*_{PC} = 5.1 Hz), 16.3 (m, 6C); ³¹P NMR (121 MHz, CDCl₃) +17.7 ppm; HRMS calcd for C₂₀H₃₇O₉NaP₃ (M+Na)⁺ 537.1548, found 537.1553. Anal. Calcd for C₂₀H₃₇O₉P₃·H₂O: C, 45.12; H, 7.38. Found: C, 45.26; H, 7.57.

3-Butenylidynetrisphosphonic acid, hexaethyl ester (**11**)

According to the general procedure for synthesis of alkylated trisphosphonates, allylbisphosphonate²⁰ (985 mg, 3.0 mmol) was treated with NaHMDS (4.5 mL, 4.5 mmol) and CIP(OEt)₂ (1.29 g, 8.2 mmol), and then after 30 min H₂O₂ (3.50 mL, 31 mmol) was added to the reaction mixture. After standard workup the product was purified via column chromatography on silica gel (0 to 40% EtOH in EtOAc) and compound **11** was isolated as a clear oil (987 mg, 71%): ¹H NMR δ 6.32–6.18 (m, 1H), 5.15–5.05 (m, 2H), 4.34–4.14 (m, 12H), 2.92 (qd, *J*_{PH} = 9.0 Hz, *J* = 6.6 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 18H); ¹³C NMR δ 134.4 (q, *J*_{PC} = 6.3 Hz), 117.1, 63.4 (m, 6C), 50.5 (q, *J*_{PC} = 119.8 Hz), 35.0 (q, *J*_{PC} = 5.5 Hz), 16.5 (m, 6C); ³¹P NMR +18.0 ppm; HRMS calcd for C₁₆H₃₅O₉NaP₃ (M+Na)⁺, 487.1392, found 487.1407. Anal. Calcd for C₁₆H₃₅O₉P₃·H₂O: C, 39.84; H, 7.73. Found: C, 40.19; H, 7.83.

4-Methyl-3-pentenylidynetrisphosphonic acid, hexaethyl ester (**12**)

According to the general procedure for synthesis of alkylated trisphosphonates, prenylbisphosphonate^{2e} (494 mg, 1.39 mmol) was treated with NaHMDS (2.10 mL, 2.1

mmol) and CIP(OEt)₂ (472 mg, 2.77 mmol). After 30 min H₂O₂ (2.00 mL, 17.6 mmol) was added to the reaction mixture. The product **12** was purified by column chromatography on silica gel (0 to 30% EtOH in EtOAc) and was isolated as a faint yellow oil (461 mg, 68%): ¹H NMR δ 5.67 (t, *J* = 6.6 Hz, 1H), 4.29–4.17 (m, 12H), 2.86 (qd, *J*_{PH} = 15.9 Hz, *J* = 6.6 Hz, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.36–1.30 (m, 18H); ¹³C NMR δ 132.5, 120.2 (q, *J*_{PC} = 6.1 Hz), 63.4–63.3 (m, 6C), 50.4 (q, *J*_{PC} = 117.6 Hz), 29.5, (q, *J*_{PC} = 5.4 Hz), 26.0, 17.9, 16.5–16.3 (m, 6C); ³¹P NMR (121 MHz, CDCl₃) +18.6 ppm; HRMS calcd for C₁₈H₄₀O₉P₃ (M+H)⁺, 493.1885, found 493.1883.

(3E)-4,9-Dimethyl-3-nonadienyldynetrisphosphonic acid, hexaethyl ester (**13**)

According to the general procedure for synthesis of alkylated trisphosphonates, geranylbisphosphonate^{3e} (249 mg, 0.6 mmol) was treated with NaHMDS (1.00 mL, 1.0 mmol) and CIP(OEt)₂ (125 mg, 0.8 mmol) and then after 30 min H₂O₂ (1.00 mL, 8.8 mmol) was added to the reaction mixture. After standard workup, the product **13** was purified by column chromatography on silica gel (0 to 30% EtOH in EtOAc) and was isolated as a faintly yellow oil (208 mg, 63%): ¹H NMR δ 5.72 (t, *J* = 6.3 Hz, 1H), 5.13 (t, *J* = 6.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 12H), 2.87 (qd, *J*_{PH} = 16.2, *J* = 7.1 Hz, 2H), 2.09–2.03 (m, 4H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.33 (t, *J* = 6.6 Hz, 18H); ¹³C NMR δ 135.8, 131.1, 124.1, 119.8 (q, *J*_{PC} = 6.2 Hz), 63.1 (m, 6C), 50.2 (q, *J*_{PC} = 119.6 Hz), 39.9, 29.2 (q, *J*_{PC} = 5.6 Hz), 26.5, 25.5, 17.4, 16.3–16.2 (m, 6C), 16.1; ³¹P NMR +18.6 ppm; HRMS calcd for C₂₃H₄₈O₉P₃ (M+H)⁺, 561.2511, found 561.2529. Anal. Calcd for C₂₃H₄₇O₉P₃·H₂O: C, 47.75; H, 8.54. Found: C, 47.98; H, 8.44.

Tetraethyl 6-hepten-1,1-bisphosphonate

Tetraethyl methylenebisphosphonate (5.31 g, 18.4 mmol) was added dropwise to a stirring suspension of NaH (810 mg, 20.2 mmol) in THF (10 mL). After 30 min, 6-bromo-1-hexene (3.00 g, 18.4 mmol) was added and the mixture was heated at reflux overnight. After the reaction mixture had cooled to room temperature, saturated NH₄Cl was added and the organic and aqueous portions were separated. The aqueous portion was extracted with Et₂O and the organic layers were combined, dried (MgSO₄), and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, 10% EtOH in hexanes) and the desired bisphosphonate was isolated in 46% yield (3.10 g): ¹H NMR δ 5.84–5.73 (m, 1H), 5.03–4.92 (m, 2H), 4.23–4.12 (m, 8H), 2.27 (tt, *J*_{PH} = 24.3 Hz, *J* = 6.3 Hz, 1H), 2.01–1.83 (m, 4H) 1.64–1.54 (m, 2H), 1.45–1.32 (m, 14H); ¹³C NMR δ 138.6, 114.3, 62.4–62.1 (m, 4C) 36.6 (t, *J*_{PC} = 132.5 Hz), 28.5 (2C), 25.3, 16.3–16.2 (m, 4C); ³¹P NMR +23.9 ppm; HRMS calcd for C₁₅H₃₃O₆P₂ (M+H)⁺, 371.1752, found 371.1745.

6-Heptenyldynetrisphosphonic acid, hexaethyl ester (**14**)

According to the general procedure for synthesis of alkylated trisphosphonates, tetraethyl 6-hepten-1,1-bisphosphonate (508 mg, 1.37 mmol) was treated with NaHMDS (2.06 mL, 2.06 mmol) and CIP(OEt)₂ (438 mg, 2.75 mmol), and then H₂O₂ (2.00 mL, 17.6 mmol) was added. After standard workup the product **14** was purified by column chromatography on silica gel (0 to 30% EtOH in EtOAc) and was isolated as a faintly yellow oil (435 mg, 78%): ¹H NMR (CDCl₃) δ 5.89–5.75 (m, 1H), 5.04–4.92 (m, 2H), 4.29–4.19 (m, 12H), 2.11–2.00 (m, 4H; 2 exchange with D₂O) 1.91–1.80, (m, 2H) 1.43–1.13 (m, 22H); ¹³C NMR (CDCl₃) δ 138.8, 114.2, 63.4–63.1 (m, 6C), 50.6 (q, *J*_{PC} = 119.3 Hz), 33.4, 30.8 (q, *J*_{PC} = 5.3 Hz), 29.3, 25.2 (q, *J*_{PC} = 5.0 Hz), 16.5–16.2 (m, 6C); ³¹P NMR (121 MHz, CDCl₃) +18.7 ppm; HRMS calcd for C₁₉H₄₁O₉NaP₃ (M+Na)⁺, 529.1861, found 529.1867.

Butylidynetrisphosphonic acid, hexaethyl ester (15)

According to the general procedure for synthesis of alkylated trisphosphonates, propylbisphosphonate^{19, 21} (292 mg, 0.9 mmol) was treated with NaHMDS (1.30 mL, 1.3 mmol) and CIP(OEt)₂ (346 mg, 2.2 mmol). After 30 min H₂O₂ (2.00 mL, 17.6 mmol) was added to the reaction mixture. Standard workup and purification via column chromatography on silica gel (0 to 35% EtOH in EtOAc) gave compound **15** as a clear oil (324 mg, 79%). Both the ³¹P and ¹H NMR spectra are consistent with material prepared via hydrogenation of compound **11** (*vide infra*).

3-Butyn-1-ylidynetrisphosphonic acid, hexaethyl ester (16)

According to the general procedure for synthesis of alkylated trisphosphonates, propargylbisphosphonate²² (291 mg, 0.9 mmol) was treated with NaHMDS (0.9 mL, 0.9 mmol) and CIP(OEt)₂ (280 mg, 1.8 mmol) and then after 30 min H₂O₂ (2.00 mL, 17.6 mmol) was added to the reaction mixture. After standard workup the product was purified via column chromatography on silica gel (0 to 30% EtOH in EtOAc) and compound **16** was isolated as a clear oil (243 mg, 59%): ¹H NMR δ 4.33–4.21 (m, 12H), 3.03 (qd, *J*_{PH} = 14.7 Hz, *J* = 3.3 Hz 2H), 2.09–2.07 (m, 1H), 1.34–1.32 (m, 18H); ¹³C NMR δ 79.9 (q, *J*_{PC} = 9.1 Hz), 70.5, 63.9–63.6 (m, 6C), 49.7 (q, *J*_{PC} = 120.0 Hz), 21.0 (q, *J*_{PC} = 5.6 Hz), 16.4–16.3 (m, 6C); ³¹P NMR +16.7 ppm; HRMS calcd for C₁₆H₃₄O₉P₃ (M+H)⁺, 463.1416, found 463.1420.

Trisphosphonate 15 via catalytic hydrogenation of compound 11

Trisphosphonate **11** (96 mg, 0.2 mmol) in EtOH (5 mL) was treated with Pd/C (23 mg, 0.2 mmol) under an H₂ atmosphere. After 12 h the reaction mixture was filtered through celite, and the filtrate was collected and concentrated *in vacuo*. The resulting oil was purified using flash chromatography (silica gel, 0 to 25% EtOH in EtOAc) to obtain compound **15** as a clear oil (81 mg, 84%): ¹H NMR δ 4.30–4.18 (m, 12H), 2.18–1.77 (m, 4H), 1.34 (t, *J* = 6.6 Hz, 18H), 0.91 (t, *J* = 6.9 Hz, 3H); ¹³C NMR δ 63.4 (m, 6C), 51.6 (q, *J*_{PC} = 119.8 Hz), 33.0 (q, *J*_{PC} = 5.5 Hz), 19.2 (q, *J*_{PC} = 5.2 Hz) 16.4 (m, 6C), 15.0; ³¹P NMR +18.8 ppm; HRMS calcd for C₁₆H₃₇O₉NaP₃ (M+Na)⁺, 489.1548, found 489.1564. Anal. Calcd for C₁₆H₃₇O₉P₃·H₂O: C, 39.67; H, 8.11. Found: C, 39.66; H, 8.02.

4-Hydroxybutylidynetrisphosphonic acid, hexaethyl ester (19)

Trisphosphonate **11** (102 mg, 0.22 mmol) was dried under vacuum in the presence of P₂O₅ overnight. The remaining oil was dissolved in THF (5 mL) and placed into an ice bath. To the reaction flask, BH₃·THF (1M in THF, 0.45 mL, 0.45 mmol) was added and the mixture was allowed to stir. After 1.5 h, MeOH (2 mL) was added to the flask, followed by NaOH (3M, 0.5 mL, 1.5 mmol) and then H₂O₂ (0.3 mL, 2.7 mmol), and the resulting mixture was heated at 50 °C for 1 h. The reaction mixture was washed with saturated NaCl and the aqueous portions were retained and extracted with CH₂Cl₂. The organic portions were combined, dried (MgSO₄), and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, 0 to 45% EtOH in EtOAc) to obtain compound **19** as a clear oil (66 mg, 62%): ¹H NMR δ 4.33–4.20 (m, 12H), 3.64 (t, *J* = 5.7 Hz, 2H), 2.30–2.05 (m, 7H; 2 exchange with D₂O) 1.35 (t, *J* = 6.6 Hz, 18H); ¹³C NMR δ 63.5–63.4 (m, 6C), 63.0, 51.6 (q, *J*_{PC} = 119.8 Hz), 33.0 (q, *J*_{PC} = 5.5 Hz), 19.2 (q, *J*_{PC} = 5.2 Hz) 16.4 (m, 6C); ³¹P NMR +18.8 ppm; HRMS calcd for C₁₆H₃₇O₁₀NaP₃ (M+Na)⁺, 505.1497, found 505.1503.

3-Pentenylidynetrisphosphonic acid, hexaethyl ester (20) and compound 12

Grubbs second generation catalyst (4.9 mg, 3 mol %) was dissolved in 2-methyl-2-butene (1 mL) and placed in a 1-dram vile. The trisphosphonate **11** (88.3 mg, 0.2 mmol) was added to

this mixture, along with an additional 1 mL of 2-methyl 2-butene. The vile was sealed and the reaction was allowed to stir at 40 °C overnight. After the solvent was removed *in vacuo*, the resulting oil was purified via flash chromatography (silica gel, 0 to 30% EtOH in EtOAc). The reaction products (76 mg, 83% total) were isolated as an inseparable mixture of cis and trans isomers of compound **20** (68%, 1.2:4.3 isomer ratio) and prenyl trisphosphonate **12** (15%, 1:5.5 ratio with respect to olefins **20**). The ³¹P, ¹H and ¹³C NMR spectra were consistent with a mixture of compounds **20** and **12**, both of which had been prepared independently.

Compound 20 via metathesis with 2-butene

Grubbs second generation catalyst (2.3 mg, 6 mol %) was dissolved in CH₂Cl₂ (0.5 mL) and placed in a 1-dram vile, and trisphosphonate **11** (24 mg, 0.1 mmol) was added to this mixture. After 2-butene was added to the vessel via balloon, the vessel was sealed and the reaction was allowed to stir at 40 °C overnight. The volatile materials were removed *in vacuo* and the resulting oil was purified via flash chromatography (silica gel, 0 to 30% EtOH in EtOAc). The olefins **20** were isolated as a mixture of trans and cis isomers (19 mg, 78%) in a 2.8:1 ratio. For the trans isomer: ¹H NMR (500 MHz, CDCl₃) δ 5.85 (dt, *J* = 14.0, 7.0 Hz, 1H), 5.57–5.50 (m, 1H), 4.29–4.18 (m, 12H), 2.89–2.84 (m, 2H), 1.67 (dd, *J* = 7.0, 1.5 Hz, 3H), 1.35–1.32 (m, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 128.0, 126.7 (q, *J*_{PC} = 6.3 Hz), 63.4–63.3 (6C), 50.7 (q, *J*_{PC} = 119.5 Hz), 33.9 (q, *J*_{PC} = 5.3 Hz), 17.9, 16.5–16.3 (6C); ³¹P NMR (121 MHz, CDCl₃), +18.4 ppm. For the cis isomer: ¹H NMR (500 MHz, CDCl₃) δ 5.94–5.92 (m, 1H), 5.57–5.50 (m, 1H), 4.29–4.18 (m, 12H), 2.89–2.84 (m, 2H), 1.64 (dd, *J* = 7.0, 1.0 Hz, 3H), 1.35–1.32 (m, 18H); ¹³C NMR (125 MHz, CDCl₃) 126.1 (q, *J*_{PC} = 6.0 Hz), 125.0, 63.5–63.4 (6C), 50.1 (q, *J*_{PC} = 119.6 Hz), 28.3 (q, *J*_{PC} = 8.0 Hz), 16.5–16.3 (6C), 12.9; ³¹P NMR (121 MHz, CDCl₃) +18.5 ppm; HRMS calcd for C₁₇H₃₇O₉NaP₃ (M+Na)⁺, 501.1548, found 501.1554. Anal. Calcd for C₁₇H₃₇O₉P₃·H₂O: C, 41.13; H, 7.92. Found: C, 41.35; H, 7.91.

7-Methyl-6-octenyldynetrtrisphosphonic acid, hexaethyl ester (21)

Grubbs second generation catalyst (3.1 mg, 3 mol %) was dissolved in 2-methyl-2-butene, placed in a 1-dram vile, and trisphosphonate **14** (62 mg, 0.12 mmol) was added along with an additional 1 mL of 2-methyl-2-butene. The vile was sealed and the reaction was allowed to stir at 40 °C overnight. After concentration *in vacuo*, the resulting oil was purified via flash chromatography (silica gel, 0 to 30% EtOH in EtOAc), and the desired product **21** was isolated as an oil (57 mg, 87%): ¹H NMR δ 5.12 (t, *J* = 6.0 Hz, 1H), 4.19–4.31 (m, 12H), 1.96–2.24 (m, 6H), 1.77–1.88 (m, 2H), 1.68 (3H), 1.57 (3H), 1.34 (t, *J* = 6.6 Hz, 18H); ¹³C NMR δ 131.2, 124.7, 63.5–63.2 (m, 6C), 50.7 (q, *J*_{PC} = 119.4 Hz), 31.0–30.9 (m), 30.9, 27.8, 25.7, 25.4 (q, *J*_{PC} = 5.2 Hz) 17.6, 16.4–16.2 (m, 6C); ³¹P NMR +18.8 ppm; HRMS calcd for C₂₁H₄₆O₉P₃ (M+H)⁺, 535.2355, found 535.2357.

7-Hydroxyheptyldynetrtrisphosphonic acid, hexaethyl ester (22)

Trisphosphonate **14** (109 mg, 0.2 mmol) was dried overnight under vacuum in the presence of P₂O₅. The remaining oil was dissolved in THF (5 mL) and placed into an ice bath. To the reaction flask, 9-BBN (0.5 M in THF, 1.0 mL, 0.5 mmol) was added and the mixture was allowed to stir. After 1.5 h, MeOH (2 mL) was added to the flask, followed by NaOH (3 M, 0.5 mL, 1.5 mmol) and then H₂O₂ (0.5 mL, 4.4 mmol), and the resulting mixture was heated at 50 °C for 1 h. The reaction mixture was washed with saturated NaCl and the aqueous portions were retained and extracted with CH₂Cl₂. The organic portions were combined, dried (MgSO₄), and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, 0 to 40% EtOH in EtOAc) to obtain compound **22** as a clear oil (64 mg, 57%): ¹H NMR δ 4.30–4.17 (m, 12H), 3.63 (t, *J* = 6.3 Hz, 2H), 2.18–2.03 (m, 3H),

1.90–1.82 (m, 2H), 1.60–1.53 (m, 2H), 1.44–1.28 (m, 22); ^{13}C NMR δ 63.5–63.2 (m, 6C), 62.8, 50.6 (q, $J_{\text{PC}} = 119.5$ Hz), 32.7, 30.8 (q, $J_{\text{PC}} = 5.3$ Hz), 30.3, 25.5 (q, $J_{\text{PC}} = 5.3$ Hz), 25.3, 16.5–16.2 (6C); ^{31}P NMR +18.8 ppm; HRMS calcd for $\text{C}_{19}\text{H}_{43}\text{O}_{10}\text{NaP}_3$ (M+Na) $^+$, 547.1967, found 547.1991.

1-Benzyl-4-[2,2,2-tris(diethoxyphosphinyl)ethyl]-1H-1,2,3-triazole (23)

Benzyl bromide (182 mg, 1.1 mmol) was added to a suspension of sodium azide (83 mg, 1.3 mmol) in DMF (5 mL) and the resulting mixture was allowed to stir. After 10 min, trisphosphonate **16** (164 mg, 0.4 mmol) was added along with 0.1 mL CuSO_4 (5M), sodium ascorbate (43 mg, 0.2 mmol), and a solution of tBuOH in water (1:4 ratio, 5 mL), and the reaction mixture was allowed to stir at room temperature. After 24 h EDTA and 1M NH_4OH were added, the resulting solution was placed in a continuous liquid-liquid extractor and extracted for 4 h with EtOAc. The organic portion was retained and concentrated *in vacuo*. The resulting oil was purified via flash chromatography (silica gel, 0 to 50% EtOH in EtOAc) to provide the desired triazole **23** (179 mg, 85%): ^1H NMR δ 7.95 (s, 1H), 7.35–7.31 (m, 5H), 5.47 (s, 2H), 4.22–4.07 (m, 12H), 3.66 (q, $J_{\text{PH}} = 15.9$ Hz), 1.26–1.21 (m, 18H); ^{13}C NMR δ 143.3 (q, $J_{\text{PC}} = 7.4$ Hz), 135.2, 128.9 (2C), 128.4, 128.0 (2C), 124.7, 63.7–63.4 (m, 6C), 53.9, 50.6 (q, $J_{\text{PC}} = 119.2$ Hz), 27.9, (q, $J_{\text{PC}} = 5.5$ Hz), 16.4–16.1 (m, 6C); ^{31}P NMR +17.6 ppm; HRMS calcd for $\text{C}_{23}\text{H}_{40}\text{N}_3\text{O}_9\text{NaP}_3$ (M+Na) $^+$, 618.1875, found 618.1893.

3-Butenylidynetrisphosphonic acid, pentasodium, 2,4,6-trimethylpyridinium salt (24)

A solution of 2,4,6-collidine (524 mg, 4.3 mmol) and TMSBr (568 mg, 4.3 mmol) was allowed to stir in an ice bath. After 20 min, trisphosphonate **11** (75mg, 0.2 mmol) was added and the reaction was allowed to stir for 24 h with periodic monitoring by ^{31}P NMR spectroscopy. Once the reaction was complete, it was diluted by addition of toluene, the solvent was removed *in vacuo*, and aqueous sodium hydroxide (1.5 mmol, 9 eq) was added. The mixture was allowed to stir overnight and again was monitored by ^{31}P NMR. The reaction mixture then was lyophilized, the resulting solid was dissolved in a minimum amount of water, then slowly poured into cold acetone and kept at 40 °C overnight. The resulting precipitate was filtered and washed with cold acetone. The remaining residue was dissolved in water and lyophilized to afford compound **24** as a flocculent white residue (51 mg, 60%): ^1H NMR (D_2O) δ 7.43 (s, 2H), 6.19–6.10 (m, 1H), 5.23–5.05 (m, 2H), 2.92–2.85 (m, 2H), 2.93 (s, 6H), 2.50 (s, 3H); ^{13}C NMR (D_2O) δ 164.1 (2C), 155.8, 139.1–139.0 (m), 129.2, 121.6 (2C), 52.3 (q, $J_{\text{PC}} = 103.6$ Hz), 38.6, 25.3 (2C), 22.5; ^{31}P NMR (121 MHz, D_2O) +17.5 ppm; HRMS calcd for $\text{C}_4\text{H}_{10}\text{O}_9\text{P}_3$ (M–H) $^-$, 294.9538, found 294.9542.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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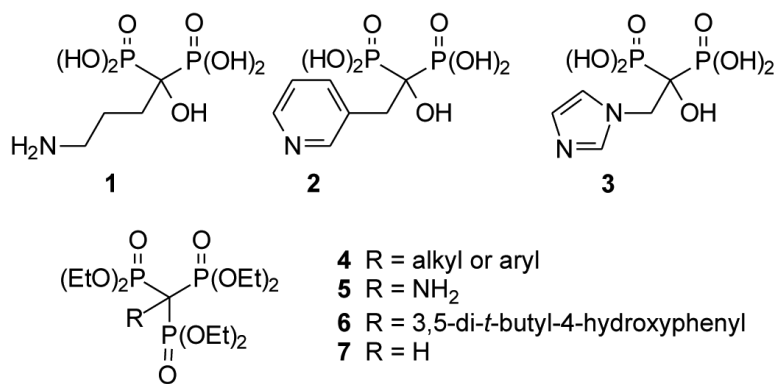
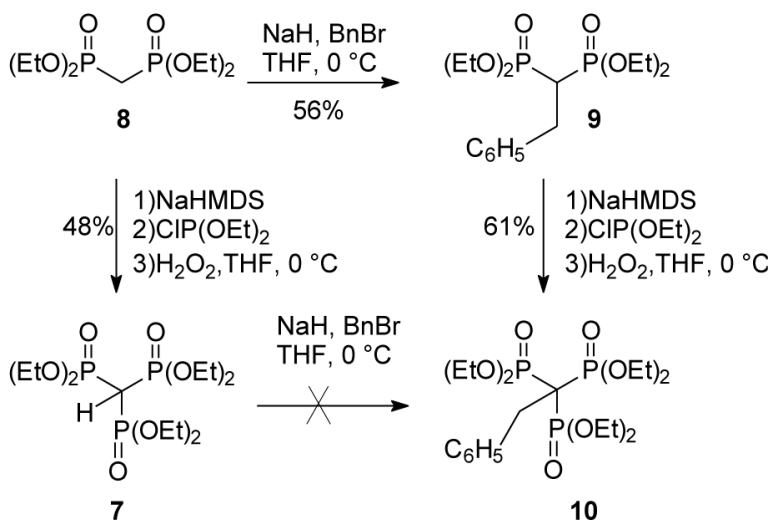
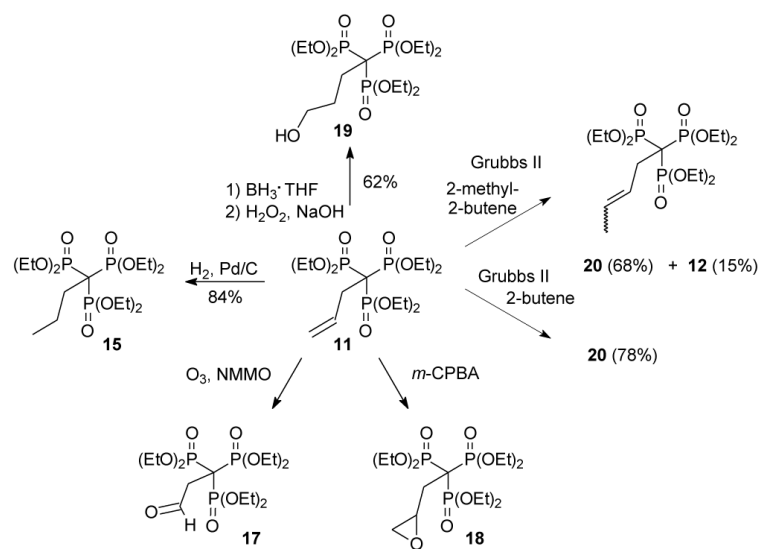


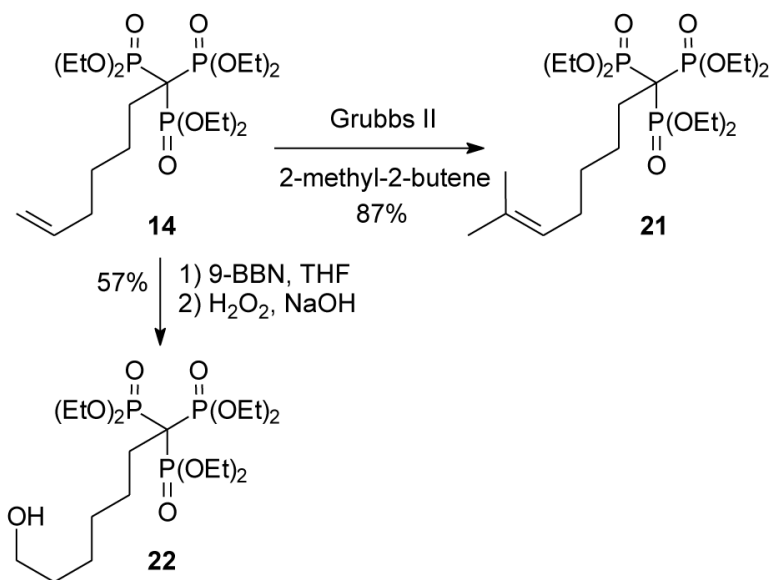
Figure 1.
Bis- and Trisphosphonates



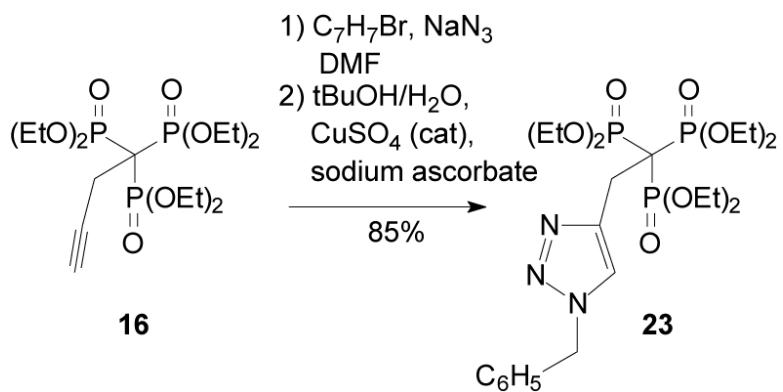
Scheme 1.
Strategies for trisphosphonate synthesis.



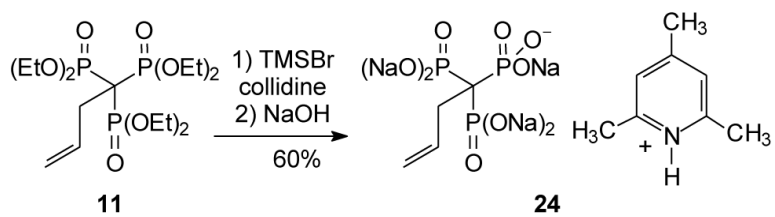
Scheme 2.
Reactions of trisphosphonate **11**.



Scheme 3.
Reactions of trisphosphonate **14**.



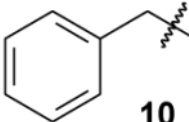

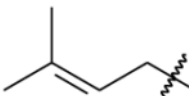
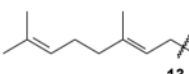
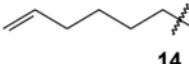


Scheme 4.
A click reaction with trisphosphonate **16**.



Scheme 5.
Hydrolysis of trisphosphonate **11**.

Table 1

Synthesis of α -alkyl-1,1,1- trisphosphonates

$ \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ (\text{EtO})_2\text{P} - \text{C} - \text{P}(\text{OEt})_2 \\ \quad \\ \text{R} \quad \text{H} \end{array} \xrightarrow[2) \text{H}_2\text{O}_2, \text{THF}, 0^\circ\text{C}]{1) \text{NaHMDS}, \text{ClP}(\text{OEt})_2} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ (\text{EtO})_2\text{P} - \text{C} - \text{P}(\text{OEt})_2 \\ \quad \\ \text{R} \quad \text{P}(\text{OEt})_2 \\ \quad \parallel \\ \quad \text{O} \end{array} $			
R =	Conversion (by ^{31}P NMR) (%)	Isolated Yield (%)	
 10	67%	61%	
 11	77%	71%	
 12	74%	68%	
 13	69%	63%	
 14	84%	78%	
 15	86%	79%	
 16^a	64%	59%	

^aIn this case, the bisphosphonate was prepared via conjugate addition of sodium acetylide to vinyl bisphosphonate.^{2a}