Published in final edited form as:

Synth Commun. 2004 January 1; 34(2): 331–344. doi:10.1081/SCC-120027271.

SYNTHESIS OF SYMMETRICAL METHYLENEBIS(ALKYL HYDROGEN PHOSPHONATES) BY SELECTIVE CLEAVAGE OF METHYLENEBIS(DIALKYL PHOSPHONATES) WITH MORPHOLINE

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Abstract

The preparation of partial esters of methylenebisphosphonic acids has been of recent interest due to their potential therapeutic applications. This paper describes a convenient method to prepare symmetrical methylenebis(alkyl hydrogen phosphonates) by the selective cleavage of the corresponding methylenebis(dialkyl phosphonate) with refluxing morpholine. The effects of structural variations on the amine as well as the substrate have been investigated to understand the scope and limitations of this reaction. A superior approach to hindered bisphosphonic acid esters involves the cleavage of their dimethyl esters, **4**, using morpholine. This method is also useful to access a number of C-alkyl dialkyl methylenebisphosphonic acids such as **6**. This study clearly shows that cleavage with morpholine is convenient, inexpensive, and allows for the preparation of a variety of P,P'-disubstituted partial esters in good yields and high purity.

Keywords

bisphosphonic acids; metal ion extractants; bone disease

In recent years, there has been considerable interest in the synthesis of a variety of methylenebisphosphonic acid derivatives.¹ Bisphosphonate compounds are non-hydrolyzable P-C-P analogs of pyrophosphates with potential applications in the field of medicinal chemistry. A variety of tetraesters and partial esters of methylenebisphosphonic acid possessing different types of substitution on the central carbon, for example, have been studied for their activity against osteoporosis and various bone diseases.² Also, several clinical trials examining the effectiveness of bisphosphonates in delaying or preventing bone metastases in breast cancer treatment are underway.³ There has been much recent interest in developing prodrugs of bisphosphonates that may exhibit improved bioavailability.⁴ Further, the preparation of dialkyl-substituted derivatives of bisphosphonic acids is an important synthetic strategy that can be used to improve the lipophilicity of a bisphosphonic acid drug.

Our interest in symmetrical P,P'-disubstituted partial esters of methylenebisphosphonic acid arises from the potential application of these ligands as solvent extraction reagents for actinide ions.⁵ Bisphosphonate compounds comprise an important class of chelating ligands, capable of strongly coordinating to actinides, lanthanides, and ferric ion in preference to

other metal ions under highly acidic conditions.⁶ Unlike the parent bisphosphonic acid, the symmetrical dialkyl partial esters may be soluble in non-aqueous media and suitable for use in solvent extraction applications since the remaining acidic hydrogen atoms are readily available for exchange with a metal ion.⁷ This exchange may produce an easily extractable charge-neutral coordination complex. Bisphosphonic acids and their ester derivatives find applications in metal ion separations from aqueous solutions,⁸ either as holdback reagents or by incorporation into ion exchange resins⁹ or extraction chromatographic sorbents.¹⁰

A selective method that has been used to prepare the P,P'-dialkyl partial esters is the dicyclohexylcarbodiimide-promoted coupling of an alkylenebisphosphonic acid with two equivalents of an appropriate alcohol.^{7b-e, 11} The most serious shortcomings associated with this method are the long reaction time required at elevated temperature and the tedious acid-base extractive work up required for product isolation and purification. An alternative synthesis that was recently developed for preparing symmetrical di- and tetra- esters of methylenebisphosphonic acid in high yield uses 1 *H*-tetrazole to catalyze the coupling of methylenebis(phosphonic dichloride) with two or four equivalents of the desired alcohol, respectively.¹² The procedure is applicable for the preparation of many P,P'-disubstituted partial esters as well as homoleptic and symmetric mixed tetraesters. The method, however, is not applicable for the preparation of fluoroalkyl partial esters, nor does it work well with highly hindered alcohols.

Conceptually, partial dialkyl esters of a bisphosphonic acid may be prepared by partial esterification of the parent acid or by selective cleavage of the corresponding bisphosphonate tetraester. Only a few methods for partial cleavage of identically-substituted phosphonate esters have been reported.¹³ Krawczyk and coworkers have reported that methylenebis-(diethyl phosphonate) can be cleaved to the lithium salt of P,P'-diethyl methylenebis-phosphonic acid, also named methylenebis(ethyl hydrogen phosphonate), by heating the tetraester with lithium bromide in 2-hexanone.¹⁴ Vepsäläinen and co-workers have developed a synthetic strategy to make symmetrical P,P'-disubstituted and asymmetrical P,P-disubstituted methylenebisphosphonates that are halogenated at the central carbon. They reported that secondary amines such as piperidine and morpholine selectively cleave tetraalkyl methylenebisphosphonates to methylenebis(alkyl hydrogen phosphonates), but only when the bridging methylene group bears electron-withdrawing dichloro or dibromo substituents.¹⁵ In addition, they reported only partial conversion with no selectivity for monohalogenated bisphosphonate esters and no reaction for methylenebisphosphonates that lack an electron-withdrawing group at the methylene bridging position.

As part of an ongoing program to develop novel bisphosphonic acid-based chelating agents for selective extraction of actinides, we required an efficient preparative method for the large-scale synthesis of high-purity symmetrical partial esters of bisphosphonic acids. We have found that a variety of methylenebisphosphonate tetraesters undergo selective cleavage in refluxing morpholine to give the methylenebis(alkyl hydrogen phosphonate) in high yield after acidification of the isolated morpholinium salt. Herein, we discuss the scope and practical application of this reaction.

RESULTS AND DISCUSSION

In our initial experiments, commercially available methylenebis(diethyl phosphonate), **1a**, was refluxed in a large excess of morpholine (15-20 equiv., bp 129°C) for 6 h (Scheme 1). The excess morpholine was removed *in vacuo* and the crude product washed with ether to remove residual traces of solvent and other impurities. Treatment of the morpholinium salt, **2a**, with an ion exchange resin (Dowex H⁺) in methanol gave the corresponding P,P'-diethyl methylenebisphosphonic acid, **3a**, in high yield after filtration and removal of the solvent.

The high selectivity of the cleavage step was supported by ^1H , ^{13}C and ^{31}P NMR analyses. The single peak in the ^{31}P NMR spectrum, for example, indicated the absence of phosphorus-containing impurities in the product. This promising result led us to explore the application of this cleavage reaction in the preparation of other symmetrical P,P'-disubstituted esters of methylenebisphosphonic acid.

A number of identically substituted tetraesters (**1a-j**) of methylenebisphosphonic acid were prepared by the 1-*H*-tetrazole catalyzed coupling of methylenebis(phosphonic dichloride) with four equivalents of the desired alcohol as previously described.^{12, 16} The phosphonate groups of the tetraester were selectively mono-O-dealkylated upon reflux with morpholine to furnish the symmetrical methylenebis(alkyl hydrogen phosphonate) (**3a-j**) as the morpholinium salt (**2a-j**). The salt was thoroughly washed with ether or a mixture of ether/hexane and converted to the corresponding acid using a Dowex ion exchange resin. The results obtained for the cleavage of the bisphosphonates **1a-j** are summarized in Table 1. All reaction products were characterized by elemental analysis and spectroscopic data, which are in full agreement with the assigned structures. In almost all cases, as detailed above for the dealkylation of methylenebis(diethyl phosphonate) (**1a**) with morpholine, a single resonance was observed in the ^{31}P NMR spectrum of the partial ester product. This indicates that within detection limits, the selectivity of the morpholine cleavage is >95% and the exclusive bisphosphonate product is the symmetrical P,P'-disubstituted partial ester (**3a-i**).

As shown in Table 1, the dealkylation of methylenebisphosphonate tetraesters with morpholine is generally quite facile, with most reactions typically reaching completion in 6 h. These results reveal some interesting electronic and steric effects in this cleavage reaction. For example, the reaction of morpholine with the tetraheptyl ester **1e**, although selective, was somewhat sluggish, requiring 18 h to reach completion. On the other hand, the di-3-(perfluorooctyl)propyl ester **1f** was selectively cleaved to the desired disubstituted partial ester **2f** in 6 h. We ascribe the greater reactivity of **1f** to the inductive effect of the electron withdrawing fluoroalkyl group on the alkoxy carbon of the ester during the $\text{S}_{\text{N}}2$ -type cleavage by morpholine. Cleavage of the 2-(trimethylsilyl)ethyl ester **1h** with morpholine was selective; that is, a single resonance was observed in the ^{31}P NMR spectrum at δ 15.2. However, the morpholinium salt **2h** was predictably unstable to acidic ion exchange conditions and the desired partial ester product **3h** was not isolated.

Both the boiling point of the amine and its nature (secondary or tertiary) were expected to play a role in the selectivity and kinetics of the cleavage reaction. To investigate the effect of these parameters, methylenebis(diethyl phosphonate) (**1a**) was reacted with various amine bases such as N-methylmorpholine (bp 117°C), piperidine (bp 106 °C), N-methylpiperazine (bp 138°C) and N-ethylpiperazine (bp 157°C). The dealkylation with N-methylmorpholine was very slow and did not yield the desired product **3a**. After refluxing for five days, the triethyl ester of methylenebisphosphonic acid was isolated in 85% yield after acidification of the resulting morpholinium salt. Selective cleavage to the symmetrical bisphosphonate **3a** was realized with piperidine, N-methylpiperazine and N-ethylpiperazine, giving the desired product in ~95% isomeric purity based on ^{31}P NMR data. In practice, morpholine appears to be the optimal reagent for selectively cleaving a sterically unhindered methylenebis(dialkyl phosphonate) to the corresponding symmetrical P,P'-disubstituted partial ester. Further, the results suggest that secondary amines are superior to tertiary amines in effecting this dealkylation reaction.

Examination of hindered esters such as methylenebis(diisopropyl phosphonate) (**1i**) and methylenebis(di-2-ethylhexyl phosphonate) (**1j**) clearly revealed the steric limitations of the morpholine cleavage reaction. Dealkylation with morpholine under typical conditions was found to be very slow for both substrates, the reaction failing to reach completion even after

several days. Reaction of the isopropyl ester with morpholine in a sealed tube at 150°C for 5 days, however, led to the formation of the desired partial ester **3i** with ~95% selectivity. Under similar conditions, the reaction of morpholine with the 2-ethylhexyl ester was still very slow and after five days yielded a mixture of partial ester products. In an effort to access more sterically hindered P,P'-disubstituted esters, the cleavage of **1i** and **1j** with N-methylpiperazine and N-ethylpiperazine was examined. The 2-ethylhexyl ester **1j** was cleaved with good selectivity by refluxing with N-methylpiperazine (92%) or N-ethylpiperazine (94%) for 4 days. However, only N-methylpiperazine was found effective for cleavage of the isopropyl ester (95% selectivity). The reaction of **1i** with N-ethylpiperazine was not selective.

To obtain hindered symmetrical P,P'-disubstituted methylenebisphosphonic acids, we have examined an alternate approach involving the selective cleavage of the symmetrical methylenebis(alkyl methyl phosphonates) **4**. Selective cleavage of the methyl esters in these substrates with morpholine was found to proceed smoothly to give the corresponding symmetrical P,P'-disubstituted esters **3j** and **3k** in high yield and selectivity (eqn 1). This approach is particularly useful when the ester substituent is very hindered, the starting alcohol is expensive or difficult to obtain, or hydrolysis with other reagents is not selective.¹²

eqn 1

The selective cleavage of C-alkyl substituted tetraethyl esters of methylenebisphosphonic acid with morpholine was also investigated. The C-alkylated tetraethyl esters **5a** and **5b** were prepared by alkylation of methylenebis(diethyl phosphonate) (**1a**) by treatment with potassium *tert*-butoxide and the corresponding alkyl triflate/iodide in toluene (Scheme 2). The morpholine cleavage of **5a** and **5b** proceeded smoothly to give the corresponding symmetrical P,P'-disubstituted methylenebisphosphonic acids **6a** and **6b** in good yield and purity.

It is important to note that fluorinated methylenebisphosphonates such as **1f** and **5b**, which are readily attainable by the routes described herein, are selectively cleaved with morpholine to the symmetrical fluoroalkyl-substituted partial esters **3f** and **6b**. These novel fluorinated esters are not attainable using carbodiimide-promoted coupling methodology. Further, the 1*H*-tetrazole catalyzed synthesis of methylenebis(fluoroalkyl methyl phosphonates) from the acid chloride proceeds in low yields and dealkylation of the resulting mixed fluoroalkyl esters with bromotrimethylsilane is not selective.¹²

In summary, symmetrical methylenebis(alkyl hydrogen phosphonates) may be prepared by selective cleavage of the corresponding methylenebis(dialkyl phosphonate) with morpholine. In contrast to earlier reports, we find that the reaction does not require an

electronegative substituent on the bridging carbon of the methylenebisphosphonate to achieve the desired dealkylation. The cleavage with morpholine, which is convenient and inexpensive, allows a variety of P,P'-disubstituted partial ester products to be obtained in good yield and high purity.

EXPERIMENTAL

General

Melting points were obtained on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR 1720X spectrometer. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in CDCl_3 with signals recorded downfield from an internal tetramethylsilane reference unless otherwise noted. ^{31}P NMR were obtained at 162 MHz using 85% H_3PO_4 as an external standard. Column chromatography was done on silica gel (Merck 60-230 mesh). All amine reagents were obtained from Aldrich Chemical Company and used without purification. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Mass spectra were performed by the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry, St. Louis, MO.

Representative Experimental Procedure A

Preparation of Methylenebis(ethyl hydrogen phosphonate), 3a¹⁴—A solution of methylenebis(diethyl phosphonate), **1a**, (2.30 g, 8.00 mmol) in morpholine (12 mL, 138 mmol) was heated at reflux for 6 h. The reaction mixture was cooled to rt and excess unreacted morpholine was removed under vacuum. The residue was thoroughly washed with anhydrous ether (20 mL) and the resulting solid dried under vacuum to give morpholinium methylenebis(ethyl phosphonate) **2a** (3.20 g, 98%), as a pale yellow solid.: IR (KBr, cm^{-1}) 1217, 1112; ^1H NMR (CDCl_3) δ 1.25 (t, 6H, $J = 4.3$ Hz), 2.05 (t, 2H, $J_{\text{P,H}} = 19.6$ Hz), 3.18 (br s, 8H), 3.87 (m, 12H); ^{13}C NMR (CDCl_3) δ 16.5, 26.6 (t, $J_{\text{P,C}} = 121.4$ Hz), 42.9, 59.9, 64.0. Anal. calcd for $\text{C}_{13}\text{H}_{32}\text{N}_2\text{P}_2\text{O}_8$: C, 38.43; H, 7.94; N, 6.89, found: C, 38.28; H, 7.74; N, 6.74.

Dowex 50W-X8 (H^+) resin (3.136 g) was added to a solution of **2a** (3.20 g, 7.88 mmol) in methanol (20 mL) and the resulting mixture stirred at rt for 4 h. The solution was filtered and removal of the solvent under reduced pressure gave the symmetrical P,P'-diethyl methylenebisphosphonic acid, **3a**, (1.62 g, 89%) as a white crystalline solid.: mp 91-95 °C; IR (CDCl_3 , cm^{-1}) 1234, 1185, 1037, 1001; ^1H NMR (CDCl_3) δ 1.32 (t, 6H, $J = 7.2$ Hz), 2.42 (t, 2H, $J_{\text{P,H}} = 21.2$ Hz), 4.14 (dq, 4H, $J_{\text{P,H}} = 8.4$ Hz, $J = 7.2$ Hz), 11.05 (s, 2H); ^{13}C NMR (CDCl_3) δ 16.0, 25.9 (t, $J_{\text{P,C}} = 137.8$ Hz), 61.8; ^{31}P NMR (CDCl_3) δ 19.5 (s). Anal. calcd for $\text{C}_5\text{H}_{14}\text{P}_2\text{O}_6$: C, 25.87; H, 6.08, found: C, 26.10; H, 6.34.

Methylenebis(methyl hydrogen phosphonate), 3b^{7b}—Following procedure A, the partial ester **3b** was obtained from tetramethyl ester, **1b**, as a pale yellow oil in 97%. IR (neat, cm^{-1}) 1197, 1048; ^1H NMR (CDCl_3) δ 2.42 (t, 2H, $J_{\text{P,H}} = 22.0$ Hz), 3.74 (d, 6H, $J_{\text{P,H}} = 10.2$ Hz); ^{13}C NMR (CDCl_3) δ 25.1 (t, $J_{\text{P,C}} = 138.7$ Hz), 51.9; ^{31}P NMR (CDCl_3) δ 20.7 (s). Anal. calcd for $\text{C}_3\text{H}_{10}\text{P}_2\text{O}_6 \cdot 0.25\text{CH}_3\text{OH}$: C, 18.33; H, 5.20, found: C, 18.58; H, 4.86.

Methylenebis(benzyl hydrogen phosphonate), 3c—Following procedure A, **3c** was obtained from tetraester, **1c**, as a pale yellow oil in 83% yield.: IR (neat, cm^{-1}) 1213, 1009; ^1H NMR (CDCl_3) δ 2.45 (t, 2H, $J_{\text{P,H}} = 21.7$ Hz), 4.56-4.82 (br s, 2H), 5.08 (d, 4H, $J_{\text{P,H}} = 7.7$ Hz), 7.26-7.44 (m, 10H); ^{13}C NMR (CDCl_3) δ 26.4 (t, $J_{\text{P,C}} = 137.0$ Hz), 67.1 (d, $J_{\text{P,C}} = 4.6$ Hz), 127.8, 128.4, 135.5 (d, $J_{\text{P,C}} = 6.4$ Hz); ^{31}P NMR (CDCl_3) δ 19.9 (s). Spectral data indicated that the product was ~95% pure.

Methylenebis(allyl hydrogen phosphonate), 3d—Following procedure A, **3d** was obtained from tetraester, **1d**, as a colorless oil in 82% yield.: IR (neat, cm^{-1}) 1217, 1107, 1029; ^1H NMR (CDCl_3) δ 2.48 (t, 2H, $J_{\text{P,H}} = 21.6$ Hz), 4.57 (dd, 4H, $J_{\text{P,H}} = J = 6.9$ Hz), 5.23–5.39 (m, 4H), 5.83–6.00 (m, 2H), 9.80–10.10 (br s, 2H); ^{13}C NMR (CDCl_3) δ 25.9 (t, $J_{\text{P,C}} = 136.3$ Hz), 66.2 (d, $J_{\text{P,C}} = 5.5$ Hz), 117.9, 132.3 (d, $J_{\text{P,C}} = 6.1$ Hz); ^{31}P NMR (CDCl_3) δ 19.8 (s). Anal. calcd for $\text{C}_7\text{H}_{14}\text{P}_2\text{O}_6 \cdot 0.5\text{H}_2\text{O}$: C, 31.71; H, 5.70, found: C, 31.64; H, 5.54.

Methylenebis(heptyl hydrogen phosphonate), 3e—Following procedure A, **3e** was obtained from tetraheptyl ester, **1e**, as a pale yellow oil in 72% yield IR (neat, cm^{-1}) 1220, 1077, 1014; ^1H NMR (CDCl_3) δ 0.88 (t, 6H, $J = 6.8$ Hz), 1.15–1.45 (m, 16H), 1.55–1.75 (m, 4H), 2.42 (t, 2H, $J_{\text{P,H}} = 21.9$ Hz), 4.08 (dt, 4H, $J_{\text{P,H}} = J = 6.6$ Hz), 10.11 (s, 2H); ^{13}C NMR (CDCl_3) δ 13.9, 22.4, 25.2, 26.3, 28.6, 30.2, 31.5, 65.7; ^{31}P NMR (CDCl_3) δ 19.5 (s). Anal. calcd for $\text{C}_{15}\text{H}_{34}\text{P}_2\text{O}_6$: C, 48.38; H, 9.20, found: C, 48.43; H, 9.44.

Methylenebis(3-(perfluorooctyl)propyl hydrogen phosphonate), 3f—Following procedure A, **3f** was obtained from **1f** as a pale yellow solid in 71% yield.: mp 87–88°C; IR (KBr, cm^{-1}) 1204, 1142, 1043; ^1H NMR (CD_3OD) δ 2.00–2.15 (m, 4H), 2.30–2.55 (m, 4H), 2.64 (t, 2H, $J_{\text{P,H}} = 21.0$ Hz), 4.27 (dt, 4H, $J_{\text{P,H}} = J = 7.0$ Hz); ^{13}C NMR (CD_3OD) δ 20.6, 24.2, 26.3 (t, $J_{\text{P,C}} = 22.2$ Hz), 63.4, 105–120 (m); ^{31}P NMR (CDCl_3) δ 20.2 (s). Anal. calcd for $\text{C}_{23}\text{H}_{16}\text{P}_2\text{O}_6\text{F}_{34}$: C, 25.20; H, 1.47, found: C, 24.95; H, 1.34.

Methylenebis(3-(trimethylsilyl)propyl hydrogen phosphonate), 3g ^{12a}—

Following procedure A, the silyl partial ester **3g** was obtained from the tetraester **1g** as a colorless oil in 47% yield.: IR (neat, cm^{-1}) 1249, 1067, 1013; ^1H NMR (CDCl_3) δ 0.01 (s, 18H), 0.45–0.58 (m, 4H), 1.55–1.80 (m, 4H), 2.44 (t, 2H, $J_{\text{P,H}} = 23.6$ Hz), 4.04 (dt, 4H, $J_{\text{P,H}} = J = 6.9$ Hz), 4.95 (br s, 2H); ^{13}C NMR (CDCl_3) δ –1.0, 11.8, 24.8, 25.9 (t, $J_{\text{P,C}} = 138.1$ Hz), 68.1; ^{31}P NMR (CDCl_3) δ 19.6 (s). Anal. calcd for $\text{C}_{13}\text{H}_{34}\text{P}_2\text{O}_6\text{Si}_2$: C, 38.60; H, 8.47, found: C, 38.90; H, 8.68.

Morpholinium methylenebis(2-(trimethylsilyl)ethyl phosphonate), 2h—

Following procedure A, the salt **2h** was obtained from tetraester **1h** as a pale yellow solid in 92% yield.: IR (KBr, cm^{-1}) 1201, 1099; ^1H NMR (CDCl_3) δ 0.00 (s, 18H), 1.01 (t, 4H, $J = 8.9$ Hz), 2.07 (t, 2H, $J_{\text{P,H}} = 19.6$ Hz), 3.13 (br s, 8H), 3.85–4.05 (m, 12H); ^{13}C NMR (CDCl_3) δ –1.6, 19.8, 27.1 (t, $J_{\text{P,C}} = 122.1$ Hz), 43.0, 61.8, 64.3; ^{31}P NMR (CDCl_3) δ 15.2. Spectral data indicated that the morpholinium salt was about 95% pure. The exchange reaction with Dowex H^+ in methanol led to decomposition of **2h** and the partial ester **3h** was not isolated.

Methylenebis(isopropyl hydrogen phosphonate), 3i^{8b}—Compound **3i**, isolated as a pale yellow solid, was prepared from the corresponding tetraester, **1i**, by cleavage with refluxing N-methylpiperazine (2 d) in 51% yield after acidification.: mp 69–72 °C; IR (KBr, cm^{-1}) 1179, 1106, 1014; ^1H NMR (CDCl_3) δ 1.33 (d, 12H, $J = 6.2$ Hz), 2.40 (t, 2H, $J_{\text{P,H}} = 20.6$ Hz), 4.70–4.90 (m, 2H), 9.60 (br s, 2H); ^{13}C NMR (CDCl_3) δ 23.6, 26.9 (t, $J_{\text{P,C}} = 138.5$ Hz), 70.9; ^{31}P NMR (CDCl_3) δ 18.5 (s). Anal. calcd for $\text{C}_7\text{H}_{18}\text{P}_2\text{O}_6 \cdot 0.5\text{H}_2\text{O}$: C, 31.24; H, 7.11, found: C, 31.00; H, 7.09.

Methylenebis(2-ethylhexyl hydrogen phosphonate), 3j^{7e}—This compound, isolated as a pale yellow oil, was prepared from the tetra(2-ethylhexyl) ester, **1j**,¹² by N-methylpiperazine cleavage in 78% yield and by morpholine cleavage of methylenebis(2-ethylhexyl methyl phosphonate), **4j**,¹² in 64% yield.: IR (neat, cm^{-1}): 1218, 1031; ^1H NMR (CDCl_3) 0.90 (m, 12H), 1.21–2.10 (m, 18H), 2.45 (t, 2H, $J_{\text{P,H}} = 21.2$ Hz), 4.00 (m, 4H), 10.46 (s, 2H); ^{13}C NMR (CDCl_3) δ 10.7, 13.8, 22.7, 23.1, 25.7 (t, $J_{\text{P,C}} = 138.1$ Hz), 28.7,

29.7, 39.8, 67.7; ^{31}P NMR (CDCl_3) δ 19.9 (s). Anal. calcd for $\text{C}_{17}\text{H}_{38}\text{P}_2\text{O}_6$: C, 50.99; H, 9.57, found: C, 50.95; H, 9.87.

Methylenebis(butyl hydrogen phosphonate), 3k^{12a}—Following procedure A, the dibutyl ester **3k** was obtained from the corresponding dibutyl dimethyl ester, **4k**,^{12a} as pale yellow oil in 70% yield. IR (neat, cm^{-1}) 1219, 1067, 1031; ^1H NMR (CDCl_3) δ 0.90 (t, 6H, $J = 6.7$ Hz), 1.30–1.50 (m, 4H), 1.55–1.75 (m, 4H), 2.42 (t, 2H, $J_{\text{P,H}} = 21.7$ Hz), 4.00–4.85 (m, 4H); ^{13}C NMR (CDCl_3) δ 13.2, 18.4, 25.7 (t, $J_{\text{P,H}} = 137.8$ Hz), 31.9, 65.3; ^{31}P NMR (CDCl_3) δ 19.4. Anal. calcd for $\text{C}_9\text{H}_{22}\text{P}_2\text{O}_6$: C, 37.51; H, 7.69, found: C, 37.77; H, 7.68.

Representative Experimental Procedure B

C-alkylation of methylene bis(diethyl phosphonate), 1a: Preparation of (C-perfluorooctylpropyl)methylenebis(diethyl phosphonate), 5b—A solution of methylenebis(diethyl phosphonate), **1a**, (2.88 g, 10 mmol) in dry toluene (20 mL) was slowly added under N_2 to a stirred suspension of potassium *tert*-butoxide (1.25 g, 11 mmol) in toluene (20 mL) at 0°C . After stirring for one hour, the freshly prepared triflate of (3-perfluorooctyl)-1-propanol (6.10 g, 10 mmol) was added to the reaction mixture and stirred overnight at rt. The reaction mixture was cooled to 0°C , quenched with saturated aqueous NH_4Cl (4 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by chromatography on silica gel (1:1 acetone-hexane) to give **5b** (3.12 g, 42%) as a pale yellow oil.: IR (neat, cm^{-1}) 1244, 1028; ^1H NMR (CDCl_3) δ 1.35 (t, 12H, $J = 6.7$ Hz), 1.85–2.20 (m, 7H), 4.20 (dq, 8H, $J_{\text{P,H}} = J = 6.7$ Hz); ^{13}C NMR (CDCl_3) δ 15.8, 19.3, 24.8, 30.2 (t, $J_{\text{F,C}} = 21.8$ Hz), 35.9 (t, $J_{\text{P,C}} = 131.8$ Hz), 62.6, 105–125 (m); HRMS (FAB) Calcd for $\text{C}_{20}\text{H}_{27}\text{P}_2\text{O}_6\text{F}_{17}$ ($\text{M} + \text{H}^+$): 749.1089. Found: 749.1101.

(C-allyl)methylenebis(diethyl phosphonate), 5a—Compound **5a** was prepared as a colorless oil in 40% yield by alkylation of methylenebis(diethyl phosphonate), **1a**, with allyl iodide using representative procedure B. IR (neat, cm^{-1}) 1250, 1165; ^1H NMR (CDCl_3) δ 1.30 (t, 12H, $J = 6.8$ Hz), 2.15–2.80 (m, 3H), 4.15 (dq, 8H, $J_{\text{P,H}} = J = 6.8$ Hz), 5.00–5.15 (m, 2H), 5.80–6.05 (m, 1H); ^{13}C NMR (CDCl_3) δ 16.1, 29.6, 36.9 (t, $J_{\text{P,C}} = 132.5$ Hz), 62.3, 116.3, 135.7. Anal. calcd for $\text{C}_{12}\text{H}_{26}\text{P}_2\text{O}_6 \cdot 0.33\text{H}_2\text{O}$: C, 43.12; H, 8.04, found: C, 43.09; H, 8.35.

(C-perfluorooctylpropyl)methylenebis(ethyl hydrogen phosphonate), 6b—Following procedure A, the partial ester **6b** was obtained from **5b**, as a brown colored oil in 81% yield.: IR (neat, cm^{-1}) 1245, 1162, 1033; ^1H NMR (CDCl_3) δ 1.34 (t, 6H, $J = 6.5$ Hz), 1.80–2.50 (m, 7H), 4.10–4.30 (m, 4H); ^{13}C NMR (CDCl_3) δ 16.6, 20.1, 25.4, 31.0 (t, $J_{\text{F,C}} = 23.4$ Hz), 37.2 (t, $J_{\text{P,C}} = 137.5$ Hz), 62.6, 105–125 (m); ^{31}P NMR (CDCl_3) δ 23.2 (s). Anal. calcd for $\text{C}_{16}\text{H}_{19}\text{P}_2\text{O}_6\text{F}_{17} \cdot 0.5\text{H}_2\text{O}$: C, 27.40; H, 2.87, found: C, 27.17; H, 2.51.

(C-allyl)methylenebis(ethyl hydrogen phosphonate), 6a—Following procedure A, the partial ester **6a** was obtained **5a**, as a pale yellow oil in 84% yield.: IR (neat, cm^{-1}) 1232, 1046, 1008; ^1H NMR (CDCl_3) δ 1.33 (t, 6H, $J = 6.8$ Hz), 2.20–2.50 (m, 1H), 2.60–2.85 (m, 2H), 4.05–4.25 (dq, 4H, $J_{\text{P,H}} = J = 6.8$ Hz), 4.95–5.15 (m, 2H), 5.80–6.00 (m, 1H); ^{13}C NMR (CDCl_3) δ 15.9, 29.3, 36.8 (t, $J_{\text{P,C}} = 134.4$ Hz), 61.5, 116.1, 135.5; ^{31}P NMR (CDCl_3) δ 23.0 (s). Anal. calcd for $\text{C}_8\text{H}_{18}\text{P}_2\text{O}_6$: C, 35.30; H, 6.67, found: C, 34.92; H, 6.75.

Acknowledgments

This work was funded by the Environmental Management Sciences Program of the Offices of Science and Environmental Management, U. S. Department of Energy, under grant numbers 991172402 (NMSU) and DE-FG07-98ER14928 (LUC) and contract number W-31-109-ENG-38 (ANL). We would also like to acknowledge

financial support from the National Institutes of Health under PHS Grant No. SO6 GM08136 (NMSU). We thank Mr. Dickie Romero (NMSU), Mr. James Allen (NMSU) and Mr. Peter R. Zalupski (LUC) for technical assistance.

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(i) ROH, tetrazole(cat.), iPr₂EtN, toluene; (ii) morpholine, reflux; (iii) Dowex 50W-X8 (H⁺), MeOH, rt

Scheme 1.

(i) KOtBu, allyl iodide or 3-(perfluorooctyl)-1-propanol triflate, toluene (ii) morpholine, reflux; then Dowex H⁺, MeOH, rt

Scheme 2.

Table 1

Selective Cleavage of Methylenebisphosphonate Tetraesters

Ester (1)	R	Amine	Time (h)	Salt (2) % yield	Acid (3) % yield
a	C ₂ H ₅	morpholine	6	98	89
		piperidine	6	72	88
		N-Me morpholine	5 days		^a
b	CH ₃	morpholine	6	98	99
		piperidine	6	100	89
		N-Me morpholine	18	100	85
c	PhCH ₂	morpholine	6	97	86
d	allyl	morpholine	6	97	85
e	C ₇ H ₁₅	morpholine	18	78	92
f	C ₈ F ₁₇ (CH ₂) ₃	morpholine	6	87	82
g	Me ₃ Si(CH ₂) ₃	morpholine	6	78	47
h	Me ₃ Si(CH ₂) ₂	morpholine	6	92	--
i	iPr	morpholine ^b	5 days	86	71
		morpholine	30 h	^c	
		N-Me piperazine	2 days	79	65
j	2-ethylhexyl	morpholine	54 h	^c	
		morpholine ^b	5 days	^c	
		N-Me piperazine	4 days	92	78

^a product isolated after acidification was the triethyl partial ester (85% yield two steps)^b sealed tube at 150°C^c mixture of starting material with various partial esters