Pergamon

TETRAHEDRON

Tetrahedron 57 (2001) 8637–8645

Facile high yielding synthesis of symmetric esters of methylenebisphosphonic acid

Dominique C. Stepinski, Derek W. Nelson, Peter R. Zalupski and Albert W. Herlinger*

Department of Chemistry, Loyola University Chicago, 6525 N. Sheridan Road, Chicago, IL 60626, USA

Received 9 July 2001; revised 15 July 2001; accepted 16 July 2001

Abstract—The 1*H*-tetrazole catalyzed coupling of methylenebis(phosphonic dichloride), $CH_2(POCl_2)_2$, with primary alkyl, cyclic secondary alkyl, aromatic, and silicon- and fluorine-containing alcohols selectively affords symmetric *P*,*P*′-dialkyl partial esters as well as homoleptic and mixed tetraesters. Two partial ester intermediates, methylenebis(2-ethylhexyl phosphonic chloride) and 2-ethylhexyl methylenebisphosphonic trichloride, were observed by ^1H- and ^{31}P NMR spectroscopy in the esterification of $CH_2(POCl_2)_2$ with 2-ethyl-1-hexanol. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Bisphosphonic acids and their ester derivatives are among the most important of the organophosphorus compounds.[1,2] These molecules form very stable complexes with a wide variety of metal ions,[3,4] and many applications rely on their strong metal ion complexing ability.[1,5,6] In our laboratory, the design and functionalization of bisphosphonates is motivated by their ability to extract actinides under highly acidic conditions and their potential for use in transuranic mixed waste treatment. Partial esterification of a bisphosphonic acid can enhance its solubility in non-aqueous solvents and modify its aggregation or solvent extraction properties, while leaving the remaining acidic hydrogen atoms available for charge neutralization.[3–6]

Bisphosphonates are also widely used for the treatment of diseases of the skeletal system as well as bone formation and resorption disorders.[2,7] Chelation of a metal ion by a bisphosphonate may increase its toxicological acceptability, facilitate its transport and ensure its selective concentration in target organs.[2] Partial ester derivatives are particularly good candidates as drugs for the treatment of bone diseases since their lower polarity and acidity should lead to better binding to bone, improved bio-availability and superior therapeutic behavior.[8]

Utilization of partial esters has been limited to some extent by the lack of efficient synthetic methods for their preparation. The main difficulty in preparing partial esters is the selectivity of the reactions used to obtain a product with the desired number and location of ester substituents. One selective method that has been used for the preparation of *P*,*P*′-dialkyl partial esters is the carbodiimide-promoted coupling of an alkylenebisphosphonic acid with a primary alcohol.[6,9] The procedure, however, requires long reaction times at elevated temperature and it is not applicable for water soluble, phenyl, fluoroalkyl or some silicon-containing esters.[10] Separation of the desired product also requires a series of tedious acid–base extractions that generate large volumes of waste and render a large-scale synthesis laborious and costly.

Methods for the deprotection of tetraesters to the corresponding partial esters of dichloromethylenebisphosphonic acid using tertiary and secondary amines as dealkylating reagents have been developed. The deprotection, however, requires the presence of an activating group to instigate the reaction.[11,12] Dealkylation of methylenebisphosphonate tetraesters may be achieved with acids, bases and silylating reagents, but these methods generally are not selective, producing a mixture of products that require chromatography or efficient fractional crystallization for separation.[13]

Recently, we reported a highly efficient method for selectively coupling methylenebis(phosphonic dichloride), **1**, with two equivalents of alcohol under mild, anhydrous conditions to form water-immiscible *P*,*P*′-dialkyl partial esters of methylenebisphosphonic acid (**2a**–**2f**).[14] The method, which draws upon earlier work describing the formation of mixed dialkyl phosphonates[15] and nucleoside 5′-methylenebisphosphonates,[16] uses 1*H*-tetrazole to catalyze the coupling reaction. The procedure does not require chromatographic or acid–base extractive purification and offers substantial advantages over the carbodiimide-promoted coupling route.[14] This method has been expanded here to include water-soluble *P*,*P*′-disubstituted

---

Keywords: phosphonic acids and derivatives; esterification; tetrazoles; aggregation.

* Corresponding author. Tel.: +1-773-508-3127; fax: +1-773-508-3086; e-mail: aherlin@luc.edu

PII: S0040-4020(01)00846-8

partial esters as well as symmetric mixed and homoleptic methylenebisphosphonate tetraesters which are viable precursors to the symmetric partial esters.

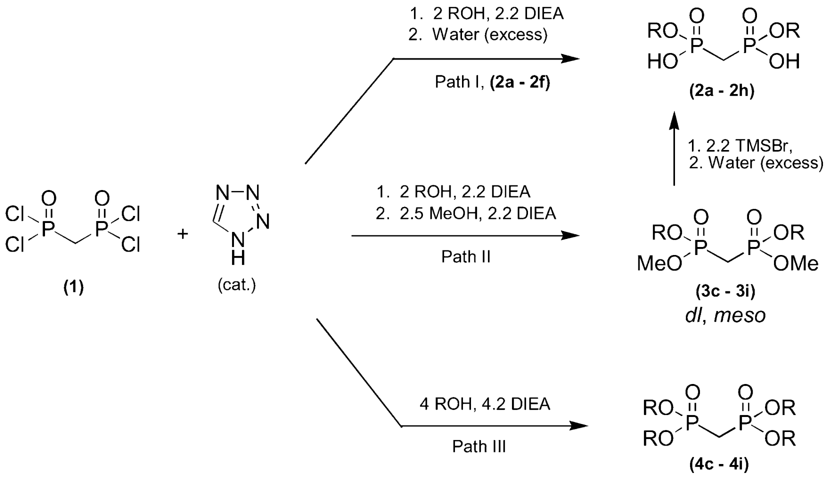
2. Results and discussion

A facile, high yielding synthesis of symmetric esters of methylenebisphosphonic acid from the corresponding acid chloride has been developed. The method has general synthetic applicability for the preparation of *P*,*P*′-disubstituted partial esters (**2a**–**2h**) as well as symmetric mixed dimethyl (**3c**–**3i**) and homoleptic (**4c**–**4i**) tetraesters (Scheme 1). Primary alkyl, cyclic secondary alkyl, aromatic, and fluoro- and silicon-containing alcohols were utilized in this method. The procedures afford the best yields with primary and cyclic secondary alcohols; typical yields of purified esters range from 85–98%. Lower yields (~25%) are obtained with highly hindered secondary alcohols, e.g. *sec*-butyl alcohol, as well as for the mixed aryl and fluoroalkyl tetraesters. No esterification products were obtained in the reaction of $CH_2(POCl_2)_2$ with *tert*-butyl alcohol. The product, if formed, presumably undergoes rapid hydrolysis.[13,15]

Reaction Paths I–III shown in Scheme 1 use 1*H*-tetrazole to catalyze the regioselective coupling of methylenebis(phosphonic dichloride) with two equivalents of alcohol under mild, anhydrous conditions to initially form a *P*,*P*′-disubstituted bisphosphonate partial ester acid chloride (vide infra). The resulting diester acid chloride is subsequently reacted with an excess of a hydroxylated compound that can be water, methanol or the same alcohol to form the corresponding partial ester, mixed methyl or homoleptic tetraester, respectively.

The desired *P*,*P*′-dialkyl partial ester (**2a**–**2f**) is formed directly when the unreacted P–Cl groups of the diester acid chloride are quenched with excess water by Path I. If the partial ester formed is water immiscible, it remains in the organic phase while the tetrazole and diisopropylethylamine partition into the aqueous phase as their respective salts.[15] Features of the process which are critical to obtaining a high purity product are careful control of reagent stoichiometry, use of anhydrous solvents, and slow simultaneous addition of alcohol and hindered base to the acid chloride. Pyridine has been used as an HCl binder in a very high yielding preparation of tetraalkyl methylenebisphosphonates,[7] but under the conditions reported here, it is not effective in catalyzing the selective formation of symmetric partial esters from **1**. Further, it has been reported that pyridine does not catalyze the direct formation of mixed diesters from phosphonic dichlorides.[15] Advantages of Path I over existing methods for preparing symmetric bisphosphonate partial esters include: higher yields, shorter reaction times, milder conditions, less expensive and less toxic starting reagents, smaller secondary waste streams and simpler isolation and purification procedures.

An excess of methanol or the first alcohol is used in Path II or III in place of water to form a mixed *P*,*P*′-dimethyl (**3c**–**3i**) or homoleptic tetraester (**4c**–**4i**), respectively. The tetraesters, which are amenable to separation and purification by flash chromatography, are viable precursors to water-soluble symmetric *P*,*P*′-disubstituted partial esters. This modified version of the procedure provides an attractive alternate route to partial esters when the first alcohol reacts vigorously with the acid chloride to produce a mixture of all possible bisphosphonate esters. A variety of mineral acid (HCl), lithium halide[17] and trimethylsilyl halide[18] reagents were investigated in attempts to deprotect the bisphosphonate precursors to the partial esters. Selective dealkylation of the mixed dimethyl esters to the corresponding partial esters was achieved using bromotrimethylsilane (TMSBr) as the deprotecting agent as reported by McKenna and coworkers.[18] The selective deprotection achieved using TMSBr exploits the greater reactivity of the methyl ester to silylation and the significantly higher hydrolysis rate of the resulting silyl ester compared to that of a primary, secondary or aryl ester.[13,18] The bromotrimethylsilane dealkylation is milder than most other deprotection procedures and provides an added advantage of simplicity of workup. Under the conditions described below, dealkylation of the mixed dimethyl esters **3c**–**3h** is highly selective. The yield of high purity partial ester achieved using this method is



Scheme 1. **a**, R=octyl; **b**, R=2,4,4-trimethylpentyl; **c**, R=hexyl; **d**, R=cyclohexyl; **e**, R=2-ethylhexyl; **f**, R=3-(trimethylsilyl)propyl; **g**, R=butyl; **h**, R=phenyl; **i**, R=2,2,3,3,4,4,4-heptafluorobutyl; DIEA=diisopropylethylamine, TMSBr=bromotrimethylsilane.

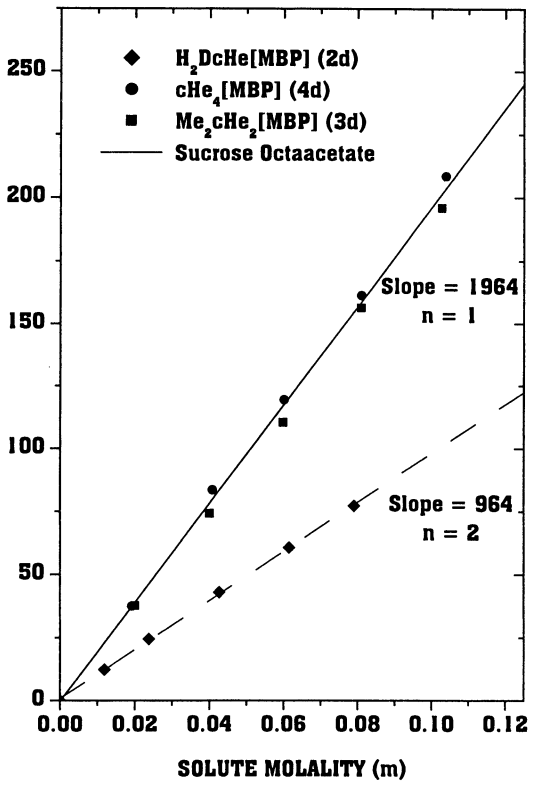


Figure 1. Vapor pressure osmometry measurements (microvolts, μV, versus molality, *m*) for $H_2DcHe[MBP]$ (**2d**), $Me_2cHe_2[MBP]$ (**3d**), and $cHe_4[MBP]$ (**4d**) relative to the monomeric standard sucrose octaacetate in toluene at 25°C. The average aggregation number, *n*, for the bisphosphonate was determined from the ratio of the slope of the best fit straight line for the sucrose octaacetate data to the slope of the best fit straight line for the bisphosphonate data, i.e. $n=(\mu V/m)_{\mathrm{standard}}/(\mu V/m)_{\mathrm{bisphosphonate}}$.

higher than that previously obtained using carbodiimide-promoted coupling procedures.[6,9] Dealkylation of the fluoroalkyl ester $Me_2(C_4H_2F_7)_2[MBP]$ (**3i**) using TMSBr was not selective. Consequently, isolation of the corresponding fluoroalkyl partial ester, $H_2(C_4H_2F_7)_2[MBP]$, was not attempted.

The tetrazole catalyzed esterification of **1** was investigated in a variety of aprotic aromatic (benzene and toluene) and chlorinated hydrocarbon (CH_2Cl_2 and $CHCl_3$) solvents. Aromatic solvents afford the highest yields and best purity. Toluene with its lower vapor pressure and toxicity appears to be the solvent of choice. Yields are generally 20–25% lower with chlorinated hydrocarbon solvents and product purity is lowered by the presence of non-phosphorus containing hydrocarbon byproducts.

Fig. 1 compares the results of the vapor pressure osmometry (VPO) measurements for a symmetric partial ester, $H_2DcHe[MBP]$ (**2d**), with those for the corresponding mixed methyl and homoleptic tetraesters, $Me_2cHe_2[MBP]$ (**3d**) and $cHe_4[MBP]$ (**4d**). As previously observed for $H_2DEH[MBP]$ (**2e**)[19,20] and $H_2DTMSP[MBP]$ (**2f**),[9] the VPO data indicates that the partial esters are dimeric in toluene at 25°C in the 0.01–0.12 m concentration range. The linearity of the data indicates that the aggregation constants are sufficiently large that the aggregation of the partial esters remains essentially unchanged over the concentration range studied. The VPO data for the tetraesters in contrast to that for the partial esters indicates that the tetraesters are monomeric.

The ^{31}P NMR spectra of the $H_2R_2[MBP]$ partial esters (**2a**–**2h**) and the $R_4[MBP]$ homoleptic tetraesters (**4c**–**4i**) consist of a single sharp resonance. The position of this resonance at ~19 and ~20 ppm for the $H_2R_2[MBP]$ and $R_4[MBP]$ esters, respectively, is influenced by the nature of the ester-substituent. The resonance occurs at slightly higher δ values in the fluoroalkyl esters and considerably lower δ values in the aryl esters. The ^1H NMR spectra of these esters exhibit resonances of the expected intensity and splitting patterns in the appropriate spectral regions. There is no evidence of unreacted alcohol in the samples.

The ^{31}P NMR spectra of the mixed tetraesters $Me_2R_2[MBP]$ (**3a**–**3i**) consist of two singlets (δ~21) of approximately equal intensity suggesting that diastereomers, a *dl* enantiomeric pair and a *meso* form, are present. This product distribution is further confirmed by the ^1H NMR behavior of the $P–CH_2–P$, OCH_3 and OCH_2 functionalities. These groups show additional resonances of expected intensities for the

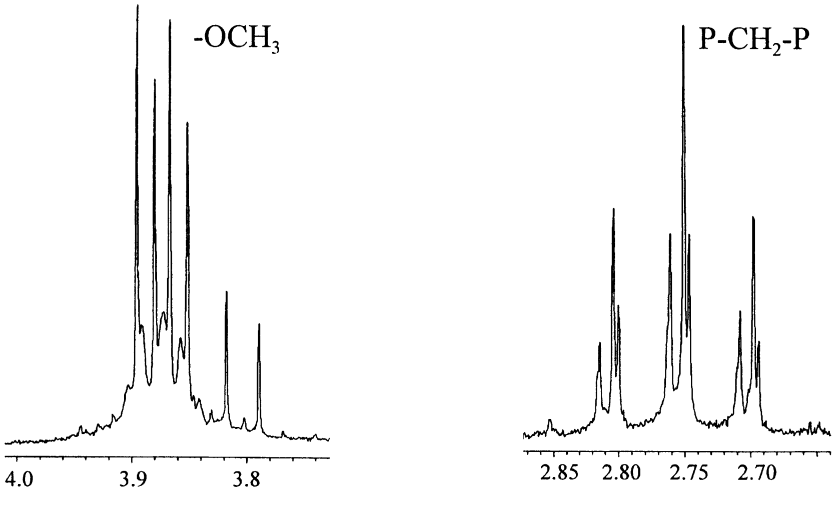


Figure 2. The 400 MHz ^1H NMR spectrum of $Me_2Ph_2[MBP]$ (**3h**) in CD_2Cl_2.

presence of two diastereomers in approximately equal amounts. The ^{31}P- and ^{1}H NMR spectra of the methylenebisphosphonic acids (**2a**–**2h**) do not contain additional resonances due to the presence of diastereomers because their acidic hydrogen atoms undergo rapid exchange on the NMR time scale. The position of the ^{31}P resonance in the mixed methyl esters is also influenced by the nature of the substituent as described above for the partial and homoleptic esters.

The ^{31}P NMR spectrum of methylenebis(phenyl methyl phosphonate) Me$_2$Ph$_2$[MBP] (**3h**) shows the two singlets indicative of diastereomers, consistent with the behavior discussed for the other mixed tetraesters. The ^{1}H NMR spectrum shows three resonances as expected for the bridging methylene (P–CH$_2$–P), however, additional resonances rather than the two expected for the methoxy (–OCH$_3$) groups are observed (Fig. 2). This behavior may arise from the diamagnetic anisotropy of the phenyl ring. Because of the anisotropy of the magnetic field exerted by an aromatic ring, protons of groups close to the ring may resonate at different values of the applied magnetic field. This phenomenon was previously observed by Siddall and Prohaska for certain phosphinyl chlorides, phosphinates, phosphonates, phosphates and phosphonites which contained a phenyl ring.[21,22] The ^{1}H NMR spectrum of the diphenyl methylenebisphosphonic acid H$_2$DPh[MBP] (**2h**) does not show the additional resonances. This is consistent with the observations previously made by Siddall and Prohaska,[21,22] and it is due to rapid exchange of the acidic hydrogen atoms.

The infrared spectra of the symmetric partial esters have three broad bands of medium intensity, characteristic of the P(O)(OH) group, which appear at approximately 2715, 2325, and 1675 cm^{-1}. The presence of these bands is indicative of a strongly hydrogen-bonded alkylenebisphosphonic acid.[23] These characteristic features have been previously discussed in detail for H$_2$DEH[MBP] (**2e**)[19,20] and H$_2$DTMSP[MBP] (**2f**).[9] The P(O)(OH) bands are not present in the spectra of the tetraesters and, as expected, the phosphoryl (P=O) band in the partial esters (∽1240 cm^{-1}) is lower in energy than in the tetraesters (∽1260 cm^{-1}). While the P=O band position generally is not strongly influenced by the nature of the alkyl-substituent, the band appears ~15 cm^{-1} higher in the aryl compounds and ~30 cm^{-1} lower in the fluoroalkyl compounds as previously reported for related organophosphorus extractants.[24] The fluoroalkyl and aryl compounds show stretching and bending vibrations in the characteristic C–F and aromatic regions, respectively.[25]

The selective esterification of **1** with 2-ethyl-1-hexanol was carried out under anhydrous conditions in a NMR tube using benzene-d$_6$ as the solvent and tetrazole as the catalyst and base. The reaction was followed by ^{31}P- and ^{1}H NMR spectroscopy. Two principal reaction intermediates were observed and identified on the basis of chemical shifts and splitting patterns as methylenebis(2-ethylhexyl phosphonic chloride), Cl$_2$EH$_2$[MBP] (**5**) and 2-ethylhexyl methylenebisphosphonic trichloride, Cl$_3$EH[MBP] (**6**). As the reaction proceeded, the ^{31}P NMR spectrum, Fig. 3, showed the disappearance of the singlet at δ 22.1 due to **1**, as well as the appearance of two doublets of equal intensity at δ 25.4 and 21.3 (J=39.4 Hz) that are assigned to the ester triacid chloride **6**. During the early stages of the reaction, the CH$_2$(POCl$_2$)$_2$ singlet disappeared at approximately the same rate as the Cl$_3$EH[MBP] doublets appeared. Throughout the latter stages of the reaction, the doublets disappear at

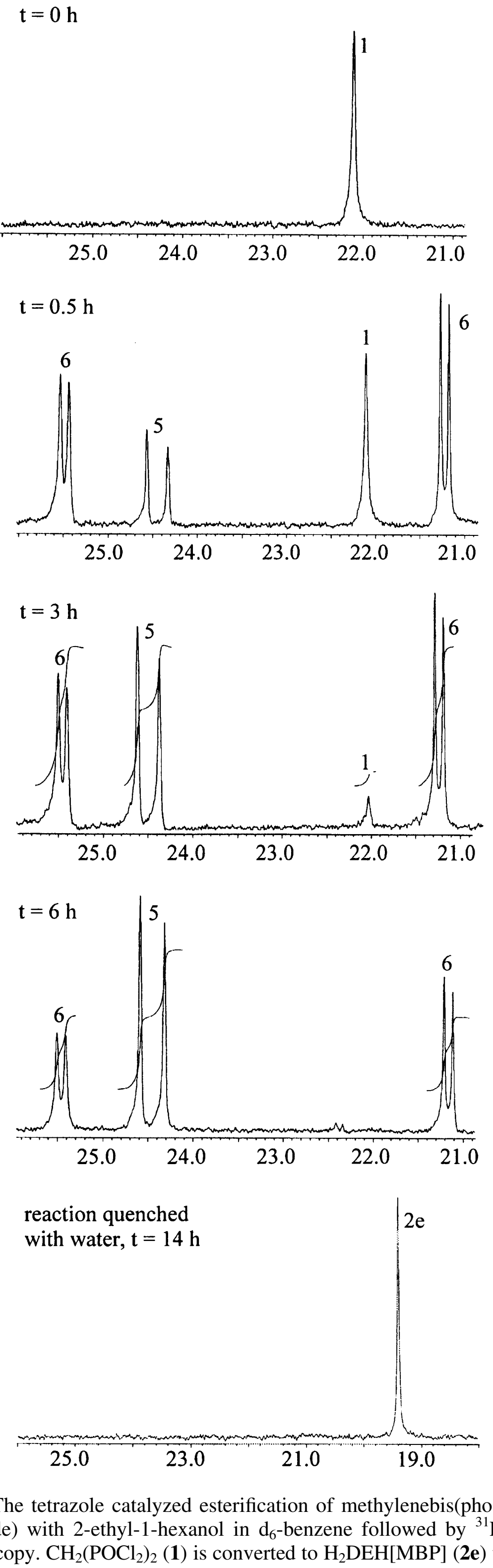


Fig. 3. The tetrazole catalyzed esterification of methylenebis(phosphonic dichloride) with 2-ethyl-1-hexanol in d$_6$-benzene followed by ^{31}P NMR spectroscopy. CH$_2$(POCl$_2$)$_2$ (**1**) is converted to H$_2$DEH[MBP] (**2e**) through the partial ester acid chloride intermediates Cl$_2$EH$_2$[MBP] (**5**) and Cl$_3$EH[MBP] (**6**).

about the same rate as two singlets of nearly equal intensity appear at δ 24.6 and 24.4. The singlets are attributed to the formation of the ester diacid chloride **5** that exists in solution as a mixture of diastereomers.

The ^{1}H NMR spectrum is less informative because of its complexity, but the presence of 2-ethyl-1-hexanol as well as several phosphorus-containing partial esters is evident. The signals in the P–CH$_2$–P and O–CH$_2$ chemical shift regions change in intensity as the reaction proceeds. The ^{1}H resonances associated with the P–CH$_2$–P groups of the phosphorus-containing intermediates appear ~0.3 ppm downfield from the corresponding signal in the symmetric partial ester. This downfield shift is consistent with the presence of electron-withdrawing chloro groups on the phosphorus atoms of the bisphosphonate intermediates.

In this work, no attempt was made to isolate the acid chloride intermediates. A report in the literature describes the isolation of ethylenebis(cyclohexyl phosphonic chloride) prepared by reacting ethylenebis(dicyclohexyl phosphonate) with phosphorus pentachloride.[26] Attempts to purify this diester acid chloride precursor resulted in decomposition, but the impure product was successfully converted to *P*,*P*′-dicyclohexyl ethylenebisphosphonic acid by hydrolysis with water. Attempts to prepare the methylenebis(cyclohexyl phosphonic chloride) homologue by this method, however, were unsuccessful.[26]

The mechanism for the tetrazole catalyzed coupling of methylenebis(phosphonic dichloride) with alcohol has not been established, but it has been postulated that tetrazole functions as a nucleophilic catalyst.[15] In this role, tetrazole adds to **1** forming a trigonal bipyramidal pentacovalent intermediate that subsequently ejects the leaving group in the microscopic reverse of the nucleophilic addition reaction.[27,28] The pentacovalent intermediate is short lived and not observed in the ^{31}P NMR spectrum.[27] Tetrazole is also a good leaving group that enhances the susceptibility of phosphorus to alcoholysis.[29]

An investigation of the solvent extraction of metal ions by the bisphosphonate ligands reported here is currently underway in our laboratory. Initial results indicate that the extraction performance of H$_2$DEH[MBP] (**2e**) and H$_2$DTMSP[MBP] (**2f**) formed by the 1*H*-tetrazole catalyzed esterification of methylenebis(phosphonic dichloride) is as good if not better than the performance of these extractants formed by carbodiimide-promoted coupling procedures.[30]

3. Conclusion

A facile, high yielding synthesis of symmetric esters of methylenebisphosphonic acid by the 1*H*-tetrazole catalyzed coupling of methylenebis(phosphonic dichloride) with a variety of alcohols has been developed. The procedures, which are carried out under mild conditions, have general synthetic applicability for the preparation of *P*,*P*′-disubstituted partial esters as well as homoleptic and symmetric mixed tetraesters. The catalyzed coupling works best when employed with primary and cyclic secondary alcohols. The procedures are not applicable for the preparation of fluoroalkyl partial esters of methylenebisphosphonic acid, nor do they work well with highly hindered alcohols. The symmetric partial esters are dimeric in toluene at 25°C whereas the mixed methyl esters and the homoleptic tetraesters are monomeric. Two partial ester acid chloride reaction intermediates Cl$_2$EH$_2$[MBP] (**5**) and Cl$_3$EH[MBP] (**6**) were observed in the esterification of CH$_2$(POCl$_2$)$_2$ (**1**) with 2-ethyl-1-hexanol. The diester acid chloride Cl$_2$EH$_2$[MBP] (**5**) and the Me$_2$R$_2$[MBP] mixed tetraesters (**3c**–**3i**) exist in solution as a mixture of diastereomers, a *dl* enantiomeric pair and a *meso* form.

4. Experimental

4.1. General methods

All reagents were supplied by Aldrich and used as received without further purification. Methylenebis(phosphonic dichloride) was handled under anhydrous conditions. Anhydrous solvents were dispensed from Aldrich Sure-Seal bottles and all glassware was oven dried at 120°C. Flash column chromatography was performed using silica gel (32–63 μm, Selecto, Fisher Scientific). The purity of the compounds was established by ^{1}H- and ^{31}P NMR spectroscopy, potentiometric titration, elemental analysis and infrared spectroscopy.

The ^{1}H- and ^{31}P NMR spectra were recorded on a VXR 400 MHz spectrometer using CDCl$_3$ as the solvent (unless stated otherwise). The δ values in parts per million (ppm) are relative to internal CHCl$_3$ (unless stated otherwise) and external 85% H$_3$PO$_4$, respectively. Infrared spectra were obtained on a Mattson Genesis series FTIR spectrometer operating in the 4000–600 cm^{-1} region using a liquid IR cell with NaCl windows. Spectra were recorded for 0.10 M solutions of the esters in CCl$_4$ using 64 scans at 4 cm^{-1} resolution with solvent as the background.

The aggregation properties of the partial and tetraesters were measured in toluene at 25°C by vapor pressure osmometry as previously described.[19] The instrument was calibrated using standard toluene solutions of sucrose octaacetate. A plot of the measured voltage (μV) versus sucrose octaacetate molality (*m*) gave a slope of 1964 μV m^{-1} for the instrument calibration constant.

The equivalent weight of the partial esters was determined by titration with 0.1 M NaOH in an isopropanol–toluene mixture using an Orion EA 940 pH meter. Combustion analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. High-resolution fast atom bombardment (HRFAB) mass spectrometry was performed by the Washington University Resource for Biomedical and Bioorganic Mass Spectrometry, St. Louis, MO. Melting points were measured using an Arthur H. Thomas, Hoover capillary melting point apparatus with a calibrated thermometer.

4.2. A representative synthetic procedure for the preparation of water-immiscible *P*,*P*′-partial esters of methylenebisphosphonic acid (2a–2f), Path I

Methylenebis(phosphonic dichloride) (4.00 mmol) and

1*H*-tetrazole (0.6 mmol) were placed in a 100 mL Schlenk flask under a nitrogen atmosphere and dissolved with vigorous stirring in 50 mL of toluene. When the dissolution was complete, a solution of the alcohol (7.92 mmol) and diisopropylethylamine (8.80 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2 h period. After stirring overnight at room temperature, the reaction was quenched with water (30 mL) and the stirring was continued for 15 min. The reaction mixture was transferred to a separatory funnel and the organic phase washed with two 30 mL portions of 0.1 M HCl. The tetrazole and diisopropylethylamine partitioned into the aqueous phase as the salts and the partial ester remained in the organic phase. The final product was obtained by removing the solvent under reduced pressure at 60°C on a rotary evaporator equipped with a water aspirator.

4.3. A representative synthetic procedure for the preparation of *P*,*P*′-dialkyl dimethyl methylenebisphosphonates (3c–3i) and *P*,*P*′-dialkyl methylenebisphosphonic acids (2c–2h), Path II

Methylenebis(phosphonic dichloride) (4.00 mmol) and 1*H*-tetrazole (0.6 mmol) were placed in a 100 mL Schlenk flask and dissolved in 50 mL of toluene with vigorous stirring under a nitrogen atmosphere. When the dissolution was complete, a solution of the alcohol (8.00 mmol) and diisopropylethylamine (8.80 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2 h period. After stirring overnight at room temperature under an atmosphere of nitrogen, a solution of methanol (10.0 mmol) and diisopropylethylamine (8.80 mmol) in 20 mL of toluene was added over a 20 min period. After stirring for an additional 15 min, the diisopropylethylammonium and tetrazonium salts were removed by filtration and the crude product was purified by flash chromatography. The mixed tetraester product was obtained by removing the solvent under reduced pressure at 60°C on a rotary evaporator equipped with a water aspirator.

Bromotrimethylsilane (7.50 mmol) was added at room temperature to a stirred solution of the methylenebisphosphonate (3.00 mmol) in 5 mL of CH_2Cl_2. After stirring for 30 min, the alkyl bromide byproducts and excess bromosilane were removed in vacuo and the reaction was quenched with water (5 mL). The partial ester was obtained by removing the water under reduced pressure at 60°C on a rotary evaporator equipped with a water aspirator.

4.3.1. Methylenebis(butyl methyl phosphonate) monohydrate, Me_2Bu_2[MBP]·H_2O (3g). This mixed tetraester, obtained as a colorless oil in 85% yield after purification by flash chromatography (5:95 v/v CH_3OH/CH_2Cl_2; R_f=0.9), is monomeric in toluene (slope 1803 $\mu V\ m^{-1}$). ^1H NMR ($CDCl_3$) δ 4.11 (dt, 4H, $J_{P,H}=J=6.8$ Hz, OCH_2),[31] 3.81 (d, 6H, $J_{P,H}=11.2$ Hz, OCH_3),[31] 2.46 (t, 2H, $J_{P,H}=21.2$ Hz, P–CH_2–P), 1.67 (tt, 4H, $J=6.8$ Hz, OCH_2CH_2), 1.46–1.36 (m, 4H CH_2CH_3), 0.94 (t, 6H, $J=7.4$ Hz, CH_2CH_3); ^{31}P NMR ($CDCl_3$) δ 21.40 (s), 21.38 (s). IR (CCl_4) ν (cm^{-1}) 3462, 2962, 2935, 2875, 1466, 1369, 1261, 1180, 1028, 987, 901, 818, 781, 756. Anal. calcd for $C_{11}H_{26}O_6P_2 \cdot H_2O$: C, 39.52; H, 8.44, found: C, 39.77; H, 8.09. HRMS-FAB (*m/z*): $[M+H]^+$ calcd 317.1284, found 317.1276.

4.3.2. *P*,*P*′-Dibutyl methylenebisphosphonic acid, H_2DBu[MBP] (2g). This water-soluble partial ester, obtained as a colorless oil in 96% yield, is dimeric in toluene (slope 950 $\mu V\ m^{-1}$). ^1H NMR ($CDCl_3$) δ 8.81 (s, 2H, OH), 4.11 (dt, 4H, $J_{P,H}=J=6.8$ Hz, OCH_2), 2.45 (t, 2H, $J_{P,H}=21.6$ Hz, P–CH_2–P), 1.68 (tt, 4H, $J=6.8$ Hz, OCH_2CH_2), 1.46–1.36 (m, 4H, CH_2CH_3), 0.95 (t, 6H, $J=7.2$ Hz, CH_2CH_3); ^{31}P NMR ($CDCl_3$) δ 19.4 (s). IR (CCl_4) ν (cm^{-1}) 2962, 2933, 2902, 2875, 2615, 2318, 1674, 1466, 1369, 1240, 1190, 1063, 1032, 1001, 895, 816, 777, 739. Equiv. wt.: calcd 144 $g\ mol^{-1}$, found 139 $g\ mol^{-1}$.

4.3.3. Methylenebis(hexyl methyl phosphonate) monohydrate, Me_2He_2[MBP]·H_2O (3c) and *P*,*P*′-dihexyl methylenebisphosphonic acid, H_2DHe[MBP] (2c). The mixed ester, obtained as a colorless oil in 85% yield after purification by flash chromatography (5:95 v/v CH_3OH/ethyl acetate; R_f=0.8), is monomeric in toluene (slope 1905 $\mu V\ m^{-1}$). ^1H NMR ($CDCl_3$) δ 4.10 (dt, 4H, $J_{P,H}=J=7.0$ Hz, OCH_2),[31] 3.81 (d, 6H, $J_{P,H}=11.2$ Hz, OCH_3),[31] 2.45 (t, 2H, $J_{P,H}=21.0$ Hz, P–CH_2–P), 1.87 (br s, 2H, H_2O), 1.68 (tt, 4H, $J=6.9$ Hz, OCH_2CH_2), 1.41–1.24 (m, 12H, CH_2), 0.89 (t, 6H, $J=7.0$ Hz, CH_2CH_3); ^{31}P NMR ($CDCl_3$) δ 21.40 (s), 21.38 (s). IR (CCl_4) ν (cm^{-1}) 3473, 2958, 2931, 2860, 1741, 1468,1379, 1259, 1178, 1043, 1018, 962, 835, 779. Anal. calcd for $C_{15}H_{34}O_6P_2 \cdot H_2O$: C, 46.15; H, 9.29, found: C, 46.31; H, 8.88. The yield of the hydrolysis of the mixed ester to the partial ester[32] was 90%. Equiv. wt.: calcd 172 $g\ mol^{-1}$, found 181 $g\ mol^{-1}$. The H_2DHe[MBP] partial ester is dimeric in toluene (slope 949 $\mu V\ m^{-1}$). IR (CCl_4) ν (cm^{-1}) 2960, 2931, 2860, 2603, 2326, 1672, 1468, 1368, 1241, 1189, 1042, 1003, 855, 811.

4.3.4. Methylenebis(cyclohexyl methyl phosphonate) monohydrate, Me_2cHe_2[MBP]·H_2O (3d) and *P*,*P*′-dicyclohexyl methylenebisphosphonic acid, H_2DcHe[MBP] (2d). The mixed methyl ester, obtained as a colorless oil in 85% yield after purification by flash chromatography (25:75 v/v hexane/acetone; R_f=0.7), is monomeric in toluene (slope 1931 $\mu V\ m^{-1}$). ^1H NMR ($CDCl_3$) δ 4.54–4.44 (m, 2H, CH), 3.78 (d, 6H, $J_{P,H}=11.4$ Hz, OCH_3),[31] 2.43 (t, 2H, $J_{P,H}=21.0$ Hz, P–CH_2–P), 2.06–1.17 (m, 20H); ^{31}P NMR ($CDCl_3$) δ 19.97 (s), 19.91(s). IR (CCl_4) ν (cm^{-1}) 3454, 2939, 2860, 1450, 1371, 1255, 1178, 1047, 1009, 895, 825, 766. Anal. calcd for $C_{15}H_{30}O_6P_2 \cdot H_2O$: C, 46.63; H, 8.35, found: C, 46.98; H, 8.19. The yield of the hydrolysis of the mixed methyl ester to the H_2DcHe[MBP] partial ester[32] was 94%. Equiv. wt.: calcd 184 $g\ mol^{-1}$, found 174 $g\ mol^{-1}$. The H_2DcHe[MBP] partial ester is dimeric in toluene (slope 964 $\mu V\ m^{-1}$). IR (CCl_4) ν (cm^{-1}) 2939, 2861, 2659, 2322, 1674, 1451, 1371, 1235, 1188, 1124, 1081, 1012, 892, 872.

4.3.5. Methylenebis(2-ethylhexyl methyl phosphonate) half-hydrate, Me_2EH_2[MBP]·1/2 H_2O (3e) and *P*,*P*′-di(2-ethylhexyl) methylenebisphosphonic acid, H_2DEH[MBP] (2e). The mixed methyl ester, isolated as a colorless oil in 82% yield after purification by flash chromatography (25:75 v/v hexane/acetone; R_f=0.8), is monomeric in toluene (slope 1960 $\mu V\ m^{-1}$). ^1H NMR ($CDCl_3$) δ 4.06–3.95 (m, 4H, OCH_2), 3.82 (d, 6H,

$J_{P,H}$=11.2 Hz, OCH_3),[31] 2.45 (t, 2H, $J_{P,H}$=21.2 Hz, P–CH_2–P),[31] 1.70 (br s, ~1H, H_2O), 1.61–1.54 (m, 2H, CH), 1.47–1.23 (m, 16H, CH_2), 0.92–0.88 (m, 12H, CH_3); ^{31}P NMR ($CDCl_3$) δ 21.01 (s), 20.97 (s). IR (CCl_4) ν (cm^{-1}) 3473, 2960, 2931, 2860, 1464, 1381, 1259, 1178, 1026, 868, 818, 787. Anal. calcd for $C_{19}H_{42}O_6P_2\cdot1/2\ H_2O$: C, 52.16; H, 9.91, found: C, 52.29; H, 9.70. The yield of the hydrolysis of the mixed methyl ester to the H_2DEH[MBP] partial ester[32] was 92%. Equiv. wt.: calcd 200 g mol^{-1}, found 203 g mol^{-1}.

4.3.6. Methylenebis(3-(trimethylsilyl)propyl methyl phosphonate) monohydrate, Me_2TMSP_2[MBP]·H_2O (3f) and *P*,*P*′-di(3-(trimethylsilyl)propyl) methylenebisphosphonic acid, H_2DTMSP[MBP] (2f). The silyl-containing mixed methyl ester, obtained as a colorless oil in 65% yield after purification by flash chromatography (20:80 v/v CH_2Cl_2/acetone; R_f=0.8), is monomeric in toluene (slope 1980 μV m^{-1}). ^{1}H NMR ($CDCl_3$) δ 4.06 (dt, 4H, $J_{P,H}$=*J*=7.2 Hz, OCH_2),[31] 3.82 (d, 6H $J_{P,H}$=11.2 Hz, OCH_3),[31] 2.46 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH_2–P),[31] 1.72–1.64 (m, 4H, OCH_2CH_2), 0.52–0.48 (m, 4H, CH_2Si), −0.02 (s, 18H Si(CH_3)$_3$); ^{31}P NMR ($CDCl_3$) δ 20.93 (s), 20.91 (s). IR (CCl_4) ν (cm^{-1}) 3444, 2954, 2896, 2853, 1467, 1369, 1252, 1183, 1045, 1007, 933, 841, 694. HRMS-FAB (*m*/*z*): [M+H]$^+$ calcd 433.1716, found 433.1745. Anal. calcd for $C_{15}H_{38}O_6P_2Si_2\cdot H_2O$: C, 39.98; H, 8.95, found: C, 40.11; H, 9.09. The yield of the hydrolysis of the mixed ester to the silyl-containing H_2DTMSP[MBP] partial ester[32] was 95%. Equiv. wt.: calcd 202 g mol^{-1}, found 194 g mol^{-1}.

4.3.7. Methylenebis(methyl phenyl phosphonate) monohydrate, Me_2Ph_2[MBP]·H_2O (3h). The preparation of Me_2Ph_2[MBP] was carried out as described above with the reaction mixture at −78°C. This mixed aryl ester, obtained as a colorless oil in 25% yield after purification by flash chromatography (30:70 v/v acetone/ethyl acetate; R_f=0.5), is monomeric in toluene (slope 1654 μV m^{-1}). ^{1}H NMR (CD_2Cl_2) δ 7.44–7.16 (m, 10H, Ar), 3.88 (d, 6H, $J_{P,H}$=11.6 Hz, OCH_3),[33] 2.75 (t, 2H, $J_{P,H}$=21.2 Hz, P–CH_2–P)[33]; ^{31}P NMR (CD_2Cl_2) δ 16.7 (s), 16.6 (s). IR (CCl_4) ν (cm^{-1}) 3072, 2958, 2927, 2856, 1593, 1491, 1367, 1275, 1205, 1180, 1165, 1056, 933, 903, 843, 688. Anal. calcd for $C_{15}H_{18}O_6P_2\cdot H_2O$: C, 48.14; H, 5.39, found: C, 48.01; H, 5.41.

4.3.8. *P*,*P*′-Diphenyl methylenediphosphonic acid, H_2DPh[MBP] (2h). This partial aryl ester was obtained as a white solid in 85% yield from the mixed tetraester after recrystallization from water. Mp 181–183°C (lit. 177–179°C).[34] ^{1}H NMR (CD_3OD) δ 7.28–7.06 (m, 10H, Ar), 2.65 (t, 2H, $J_{P,H}$=21.4 Hz, P–CH_2–P); ^{31}P NMR (CD_3OD) δ 15.4 (s). IR (CCl_4) ν (cm^{-1}) 2983, 2927, 2854, 2633, 2327, 1714, 1491, 1460, 1392, 1228, 1167, 1095, 1051, 1034, 991, 966, 730. Equiv. wt.: calcd 164 g mol^{-1}, found 167 g mol^{-1}. The toluene solubility of H_2DPh[MBP] is too low to permit measurement of its aggregation properties by vapor pressure osmometry.

4.3.9. Methylenebis(2,2,3,3,4,4,4-heptafluoro-1-butyl methyl phosphonate), $Me_2(C_4H_2F_7)_2$[MBP] (3i). This mixed fluoroalkyl ester, obtained as a colorless oil in 25% yield after purification by flash chromatography (40:60 v/v ethyl acetate/CH_2Cl_2, R_f=0.7), is monomeric in toluene (slope 1584 μV m^{-1}). ^{1}H NMR ($CDCl_3$) δ 4.71–4.54 (m, 4H, OCH_2), 3.85 (d, 6H, $J_{P,H}$=12.0 Hz, OCH_3),[31] 2.62 (t, 2H, $J_{P,H}$=21.6 Hz, P–CH_2–P);[31] ^{31}P NMR ($CDCl_3$) δ 21.8 (s), 21.6 (s). IR (CCl_4) ν (cm^{-1}) 2960, 2931, 2856, 1458, 1404, 1356, 1269, 1232, 1207, 1184, 1124, 1092, 1039, 1014, 966, 926, 868, 820, 800, 766, 706, 633. Anal. calcd for $C_{11}H_{12}F_{14}O_6P_2$: C, 23.26; H, 2.13, found: C, 23.14; H, 2.30. Dealkylation of **3i** was not selective and isolation of the fluoroalkyl partial ester was not attempted.

4.4. A representative synthetic procedure for the preparation of homoleptic tetraesters of methylenebisphosphonic acid (4c–4i), Path III

Methylenebis(phosphonic dichloride) (4.00 mmol) and 1*H*-tetrazole (0.6 mmol) were placed in a 100 mL Schlenk flask under a nitrogen atmosphere and dissolved in 50 mL of toluene with vigorous stirring. When the dissolution was complete, a solution of the alcohol (16.0 mmol) and diisopropylethylamine (17.6 mmol) in 20 mL of toluene was added dropwise through an addition funnel over a 2 h period. After stirring overnight at room temperature, the diisopropylethylammonium and tetrazonium salts were removed by filtration and the product was purified by flash chromatography. The homoleptic tetraester product was obtained by removing the solvent under reduced pressure at 60°C on a rotary evaporator equipped with a water aspirator.

4.4.1. Methylenebis(dibutyl phosphonate), Bu_4[MBP] (4g). This previously reported ester,[7] obtained as a colorless oil in 98% yield, is monomeric in toluene (slope 1897 μV m^{-1}). ^{1}H NMR ($CDCl_3$) δ 4.10 (dt, 8H, $J_{P,H}$=*J*=6.7 Hz, OCH_2), 2.44 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH_2–P), 1.67 (tt, 8H, *J*=6.8 Hz, OCH_2CH_2), 1.46–1.36 (m, 8H, CH_2CH_3), 0.93 (t, 12H, *J*=7.2 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ 19.7 (s). IR (CCl_4) ν (cm^{-1}) 2962, 2940, 2875, 1466, 1380, 1259, 1182, 1026, 906, 823, 746.

4.4.2. Methylenebis(dihexyl phosphonate), He_4[MBP] (4c). This previously reported compound,[7] isolated as a colorless oil in 85% yield, is monomeric in toluene (slope 1967 μV m^{-1}). ^{1}H NMR ($CDCl_3$) δ 4.09 (dt, 8H, $J_{P,H}$=*J*=6.9 Hz, OCH_2), 2.45 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH_2–P), 1.68 (tt, 8H, *J*=6.9 Hz, OCH_2CH_2), 1.41–1.20 (m, 24H, CH_2), 0.89 (t, 12H, *J*=7.0 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ 19.7 (s). IR (CCl_4) ν (cm^{-1}) 2958, 2931, 2860, 1467, 1379, 1259, 1176, 1039, 999, 815, 733.

4.4.3. Methylenebis(dicyclohexyl phosphonate) half-hydrate, cHe_4[MBP]·1/2 H_2O (4d). This compound,[26] obtained as a colorless oil in 85% yield after purification by flash chromatography (25:75 v/v acetone/hexane; R_f=0.9), is monomeric in toluene (slope 2003 μV m^{-1}). ^{1}H NMR ($CDCl_3$) δ 4.54–4.40 (m, 4H, OCH), 2.41 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH_2–P), 2.08–1.15 (m, 40H, CH_2); ^{31}P NMR ($CDCl_3$) δ 17.7 (s). IR (CCl_4) ν (cm^{-1}) 2937, 2860, 1452, 1371, 1253, 1176, 1039, 993, 895, 868, 829, 785, 758. Anal. calcd for $C_{25}H_{46}O_6P_2\cdot1/2\ H_2O$: C, 58.47; H, 9.23, found: C, 58.72; H, 9.43.

4.4.4. Methylenebis(di-2-ethylhexyl phosphonate), EH$_4$[MBP] (4e). This compound, obtained as a colorless oil in 85% yield after purification by flash chromatography (10:90 v/v acetone/hexane; R_f=0.85, first band), is monomeric in toluene (slope 2049 μV m^{-1}). ^{1}H NMR (CDCl$_3$) δ 4.05–3.94 (m, 8H, OCH$_2$), 2.44 (t, 2H, $J_{P,H}$=21.2 Hz, P–CH$_2$–P), 1.62–1.53 (m, 4H, CH), 1.49–1.22 (m, 32H, CH$_2$), 0.89 (t, 24H, J=7.6 Hz, CH$_3$); ^{31}P NMR (CDCl$_3$) δ 19.9 (s). IR (CCl$_4$) ν (cm^{-1}) 2961, 2931, 2861, 1464, 1380, 1259, 1176, 1013, 878, 842, 823, 779, 762, 742. Anal. calcd for $C_{33}H_{70}O_6P_2$: C, 63.43; H, 11.29, found: C, 63.41; H, 11.51. HRMS-FAB (*m/z*): [M+H]$^+$ calcd 625.4727, found 625.4702.

4.4.5. Methylenebis(di-3-(trimethylsilyl)propyl phosphonate), TMSP$_4$[MBP] (4f). This silyl ester, obtained as a colorless oil in 83% yield after purification by flash chromatography (50:50 v/v diethyl ether/ethyl acetate; R_f=0.8), is monomeric in toluene (slope 2093 μV m^{-1}). ^{1}H NMR (CDCl$_3$) δ 4.04 (dt, 8H, $J_{P,H}$=J=7.2 Hz, OCH$_2$), 2.45 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH$_2$–P), 1.72–1.64 (m, 8H, OCH$_2$CH_2), 0.52–0.48 (m, 8H, CH$_2$Si), 0.0 (s, 36H, Si(CH$_3$)$_3$); ^{31}P NMR (CDCl$_3$) δ 20.0 (s). IR (CCl$_4$) ν (cm^{-1}) 2954, 2894, 1469, 1414, 1387, 1245, 1178, 1063, 1024, 999, 935, 856, 789, 762, 694, 606. Anal. calcd for $C_{25}H_{62}O_6P_2Si_4$: C, 47.43; H, 9.87, found: C, 47.11; H, 9.85. HRMS-FAB (*m/z*): [M+H]$^+$ calcd 633.3178, found 633.3164.

4.4.6. Methylenebis(diphenyl phosphonate), Ph$_4$[MBP] (4h). This aryl ester, a white solid, was obtained in 85% yield after recrystallization from diethyl ether, mp 81–83°C (lit. 82–83°C).[34] ^{1}H NMR (CD$_2$Cl$_2$) δ 7.40–7.20 (m, 20H, Ar), 3.12 (t, 2H, $J_{P,H}$=21.0 Hz, P–CH$_2$–P); ^{31}P NMR (CD$_2$Cl$_2$) δ 10.7 (s).

4.4.7. Methylenebis(2,2,3,3,4,4,4-heptafluoro-1-butyl phosphonate), (C$_4$H$_2$F$_7$)$_4$[MBP] (4i). This fluoroalkyl tetraester was obtained as a yellow oil in 82% yield after purification by flash chromatography (50:50 v/v diethyl ether/ethyl acetate; R_f=0.85). The solubility of this ester in toluene is too low to permit aggregation measurements by vapor pressure osmometry. ^{1}H NMR (CDCl$_3$) δ 4.71–4.54 (m, 8H, OCH$_2$), 2.84 (t, 2H, $J_{P,H}$=22.0 Hz, P–CH$_2$–P); ^{31}P NMR (CDCl$_3$) δ 21.3 (s). IR (CCl$_4$) ν (cm^{-1}) 2972, 2931, 1456, 1406, 1356, 1279, 1232, 1186, 1132, 1072, 1014, 966, 926, 881, 835, 766, 727, 633. Anal. calcd for $C_{17}H_{10}F_{28}O_6P_2$: C, 22.58; H, 1.11, found: C, 22.25; H, 1.10.

Acknowledgements

The authors thank Julie A. Dzielawa and Daniel R. McAlister for helpful discussions and suggestions. This work was supported by the PG Research Foundation, Inc., Darien, IL 60561.

References

1. Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: New York, 2000; pp 12–15.
2. Zolotukhina, M. M.; Krutikov, V. I.; Lavrent'ev, A. N. *Russ. Chem. Rev. (Engl. Transl.)* **1993**, *62*, 647–659.
3. Rizkalla, E. N. *Rev. Inorg. Chem.* **1983**, *5*, 223–304.
4. Nash, K. L. *J. Alloys Compd.* **1994**, *213/214*, 300–304.
5. Chiarizia, R.; Horwitz, E. P.; Alexandratos, S. D.; Gula, M. J. *Sep. Sci. Technol.* **1997**, *32*, 1–35.
6. Chiarizia, R.; Horwitz, E. P.; Rickert, P. G.; Herlinger, A. W. *Solvent Extr. Ion Exch.* **1996**, *14*, 773–792.
7. Vepsäläinen, J.; Nupponen, H.; Pohjala, E.; Ahlgrén, M.; Vainiotalo, P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 835–842.
8. Hannuniemi, R.; Laurén, L.; Puolijoki, H. *Drugs Today* **1991**, *27*, 375–390.
9. Griffith-Dzielawa, J. A.; Barrans, Jr., R. E.; McAlister, D. R.; Dietz, M. L.; Herlinger, A. W. *Synth. Commun.* **2000**, *30*, 2121–2132.
10. Dzielawa, J. A. Ph.D. Dissertation, Loyola University Chicago, Chicago, 2001.
11. Vepsäläinen, J. J.; Kivikoski, J.; Ahlgrén, M.; Nupponen, H. E.; Pohjala, E. K. *Tetrahedron* **1995**, *51*, 6805–6818.
12. Vepsäläinen, J.; Nupponen, H.; Pohjala, E. *Tetrahedron Lett.* **1996**, *37*, 3533–3536.
13. Vepsäläinen, J.; Nupponen, H.; Pohjala, E. *Tetrahedron Lett.* **1993**, *34*, 4551–4554.
14. Stepinski, D. C.; Herlinger, A. W. *Synth. Commun.*, submitted for publication.
15. Zhao, K.; Landry, D. W. *Tetrahedron* **1993**, *49*, 363–368.
16. Lesiak, K.; Watanabe, K. A.; George, J.; Pankiewicz, K. W. *J. Org. Chem.* **1998**, *63*, 1906–1909.
17. Krawczyk, H. *Synth. Commun.* **1997**, *27*, 3151–3161.
18. McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M. *Tetrahedron Lett.* **1977**, *2*, 155–158. McKenna, C. E.; Schmidhauser, J. *Chem. Commun.* **1979**, 739.
19. Herlinger, A. W.; Ferraro, J. R.; Chiarizia, R.; Horwitz, E. P. *Polyhedron* **1997**, *16*, 1843–1854.
20. Barrans, Jr., R. E.; McAlister, D. R.; Herlinger, A. W.; Chiarizia, R.; Ferraro, J. R. *Solvent Extr. Ion Exch.* **1999**, *17*, 1195–1217.
21. Siddall III, T. H.; Prohaska, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 2502–2506.
22. Siddall III, T. H.; Prohaska, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 3467–3473.
23. Thomas, L. C. The Identification of Functional Groups in Organophosphorus Compounds. *Analysis of Organic Materials, An International Series of Monographs*; Belcher, R., Anderson, D. M. W., Eds.; Academic: London, UK, 1974; Vol. 7, pp. 23–48.
24. Ferraro, J. R.; Peppard, D. F. *Nucl. Sci. Eng.* **1963**, *16*, 389–400.
25. Bellamy, L. J. *The Infrared Spectra of Complex Molecules*; Wiley: New York, 1954; pp 260–261 and 270–271.
26. Petrov, K. A.; Raksha, M. A.; Korotkova, V. P. *J. Gen. Chem. USSR* **1969**, *39*, 809–811.
27. Scudder, P. H. *The Electron Flow Pathways: Electron Flow in Organic Chemistry*; Wiley: New York, 1992; p 123.
28. Thatcher, G. R. J.; Kluger, R. Mechanism and Catalysis of Nucleophilic Substitution in Phosphate Esters. *Advances in Physical Organic Chemistry*; Bethell, D., Ed.; Academic: New York, 1989; VOL. 25, pp. 99–266.
29. Nurminen, E. J.; Mattinen, J. K.; Lönnberg, H. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1621–1628.
30. McAlister, D. R.; Herlinger, A. W. Unpublished results.
31. A distinct additional resonance with the expected splitting

pattern is observed for the other diastereomer at a δ value that is nearly identical to the reported chemical shift.

32. The complete characterization of this partial ester, which was previously prepared by Path I quenching the reaction with water as shown in Scheme 1, is reported in Ref. 14.
33. Additional resonances are observed at δ 3.90–3.79 (m, OCH_3) and 2.754 (td, $J_{P,H}$=21.2 Hz, J=5.6 Hz, P–CH_2–P) for the other diastereomer.
34. Lang, G.; Herrmann, E. *Z. Anorg. Allg. Chem.* **1986**, *536*, 187–196.