

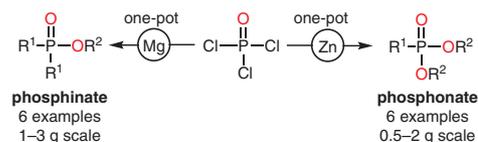
Selective Substitution of POCl₃ with Organometallic Reagents: Synthesis of Phosphinates and Phosphonates

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Abstract The selectivity of the substitution reaction of phosphoryl chloride with organometallic reagents was investigated using NMR spectroscopy. This led to the discovery that the selectivity of the substitution reaction can be tuned by choosing a proper organometallic reagent. A phosphinate could be obtained by using a Grignard reagent whereas an organozinc reagent provided a phosphonate. Based on these results, one-pot synthetic methods for the preparation of phosphinates and phosphonates using commercially available starting materials were developed. Both methods allow the synthesis of a broad range of either phosphinate or phosphonate derivatives in a straightforward and general procedure. Moreover, using these one-pot procedures, mixed systems substituted with different alkyl/aryl groups can be prepared.

Key words selectivity, substitution, phosphoryl chloride, phosphinate, phosphonate, Grignard reagent, organozinc reagent

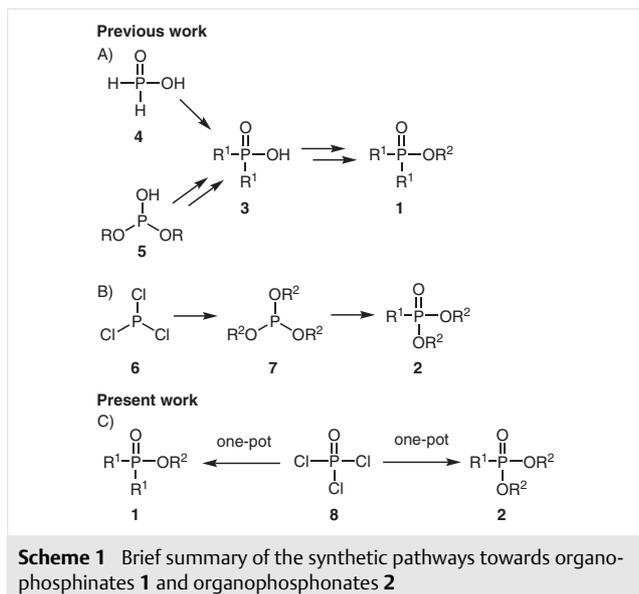
Organophosphinates **1** and organophosphonates **2**, the ester derivatives of organophosphinic **3** and organophosphonic acids, can be seen as intermediate compounds between the corresponding phosphates and phosphine oxides. Hence, the chemical, physical, and biological properties of phosphinates **1** and phosphonates **2** are in between these two extremes.¹ The synthesis of phosphinate **1** and phosphonate **2** derivatives is therefore an attractive approach to fine-tune the characteristics of organophosphorus(V) compounds. The attractiveness of these two classes of molecules is illustrated by their many applications. For example, they are used as halogen-free flame retardants in plastics,² as extractants for liquid-liquid extraction in hydrometallurgy,³ and solvometallurgy,⁴ as grafting agents to modify metal oxide surfaces,⁵ and as reagents for olefination reactions.⁶ Moreover, phosphinates **1** and phosphonates **2** are important in the treatment of several diseases,

typically as prodrugs for their corresponding acid derivatives.⁷ Noteworthy examples are nucleoside phosphonates applied in the treatment of various DNA virus and retrovirus infections, such as hepatitis B and HIV.⁸

However, the utility of organophosphinates **1** is limited by their tedious multistep synthesis. The corresponding phosphinic acids **3** are the key intermediates in this synthesis and they form, after activation to phosphinic halides, the desired phosphinates **1** via a nucleophilic substitution reaction (Scheme 1, path A).⁹ Of course, first the organophosphinic acids **3** need to be prepared using, for example, a hydrophosphonation reaction of alkenes with hypophosphorous acid **4**,¹⁰ a reaction between dialkyl hydrogen phosphites **5** and organometallic reagents followed by oxidation,¹⁰ etc.^{11,12} A generic strategy towards phosphinates **1** is not available yet.^{10,13} The used synthetic pathway is therefore dependent on the structure of the desired phosphinate **1**.

A more generic strategy is known for organophosphonates **2**. Phosphorus trichloride (**6**) can be substituted with an excess of alcohol in the presence of base and the resulting phosphite ester **7** can be subjected to an Michaelis-Arbuzov reaction with a haloalkane to form a phosphonate **2** (Scheme 1, path B).^{1,10,13} However, the latter reaction requires high temperatures and only primary haloalkanes react readily. Under certain conditions, secondary haloalkanes might also react, but tertiary haloalkanes and haloarenes are unreactive in the Michaelis-Arbuzov reaction.¹⁴ Moreover, when the alkyl group of the alcohol and the haloalkane are different, a mixture of phosphonates **2** might be formed. Besides this strategy, other less general synthetic pathways towards phosphonates **2** have also been described.^{1b,11,15}

A more straightforward and general strategy to synthesize both phosphinates **1** and phosphonates **2** could be envisioned as the reaction between phosphoryl chloride (**8**)



and, respectively, two or one equivalents of Grignard reagent, followed by quenching with an excess of alcohol (Scheme 1, path C). This one-pot procedure would be shorter than the conventional synthetic strategies, would use milder reaction conditions (i.e., heating is not required) and would allow different substituents on the phosphorus (R^1) and oxygen (R^2) atoms. However, this one-pot protocol is currently not used for the synthesis of either phosphinates **1** or phosphonates **2**. A poorly selective substitution of phosphoryl chloride (**8**) with Grignard reagents is often cited as the reason why this one-pot procedure is unsuitable for the synthesis of phosphinates **1** and phosphonates **2**.^{1a,13} According to the literature, Grignard reagents have a tendency to completely substitute phosphoryl chloride (**8**), but a detailed study of the extent of the side reactions has not been reported yet.¹³ It should also be noted that many examples that resulted in over-substitution used an unfavorable addition order of the reagents, namely phosphoryl chloride (**8**) was added to the Grignard reagent. Adding the Grignard reagent to phosphoryl chloride (**8**) can be expected to give better yields.¹⁶ Moreover, reported examples of the reaction between phosphoryl chloride (**8**) and organometallic reagents were typically limited to aryl Grignard reagents,^{16a} whereas alkyl groups and other organometallic reagents have been much less studied. Furthermore, most of these reports involved quenching the reaction with water, forming a phosphinic or phosphonic acid. Preparing esters by quenching the reaction with different alcohols is less common.

Given the current poor understanding of the extent of the selectivity for the substitution reaction of phosphoryl chloride (**8**) with organometallic reagents, we set out to investigate this selectivity using NMR spectroscopy and to examine the possibility of using this substitution reaction in

the synthesis of phosphinates **1** and phosphonates **2**. Based on the results, practical one-pot syntheses of phosphinates **1** and phosphonates **2** using commercially available starting materials were developed (Scheme 1, path C).

The first step of this work was to study the selectivity of the substitution reaction of phosphoryl chloride (**8**) with one or two equivalents of Grignard reagent. In order to limit over-substitution, the Grignard reagent was slowly added to an anhydrous diethyl ether solution of phosphoryl chloride (**8**) while the solution was being cooled using an ice-salt mixture. Diethyl ether was chosen as the reaction solvent because all the Grignard reagents used in this study are commercially available as diethyl ether solutions. After addition of the Grignard reagent, the reaction was stirred at room temperature to achieve complete conversion. Samples were then taken and analyzed by ³¹P NMR spectroscopy to estimate the relative amounts of the formed products. Preliminary experiments with phenylmagnesium bromide showed that the formed phenylphosphonic dichloride and diphenylphosphinic chloride were too poorly soluble in diethyl ether^{16a} to allow analysis of the reaction mixture by ³¹P NMR spectroscopy. Because octylphosphonic dichloride and dioctylphosphinic chloride are more soluble, the selectivity of the substitution reaction was determined by using octylmagnesium bromide as the Grignard reagent.

Reacting one equivalent of octylmagnesium bromide with phosphoryl chloride (**8**) resulted in less than 10% of the desired octylphosphonic dichloride compound **9a** (Table 1, entry 1). Instead, about half of the reaction mixture was doubly reacted dioctylphosphinic chloride (**10a**) and the other half unreacted phosphoryl chloride (**8**). Thus, the added octylmagnesium bromide reacted twice with phosphoryl chloride (**8**), which is in agreement with the reported tendency of Grignard reagents to completely substitute phosphoryl chloride (**8**).^{1a,13} This lack of selectivity for monofunctionalization might be explained by considering the magnesium salt that is formed as a side product during the reaction. This Lewis acid will probably coordinate stronger to the more electron-rich octylphosphonic dichloride (**9a**) than to phosphoryl chloride (**8**), making the resulting octylphosphonic dichloride complex more electrophilic and hence more reactive toward the Grignard reagent.

In contrast to using one equivalent, reacting two equivalents of octylmagnesium bromide with phosphoryl chloride (**8**) did result in a selective reaction (Table 1, entry 4). Almost 75% of the reaction mixture consisted of the desired dioctylphosphinic chloride (**10a**), whereas only approximately 15% octylphosphonic dichloride (**9a**) and a trace of trioctylphosphine oxide were formed. This shows that, contrary to what is typically assumed in the literature, selective disubstitution of phosphoryl chloride (**8**) with two equivalents of a Grignard reagent is possible. This selectivity might be explained by considering the steric hindrance of

Table 1 Percentage of Phosphorus Compounds in the Reaction Mixture after P(O)Cl₃ has Reacted with 1 or 2 Equiv of an Octylorgano-metallic Reagent

Entry	RM ^a	Composition of reaction mixture (%) ^b			
		P(O)Cl ₃	RP(O)Cl ₂	R ₂ P(O)Cl	R ₃ P(O)
1	RMgX (1 equiv)	43	9	43	1
2	R ₂ Cd (0.5 equiv)	43	48	– ^c	– ^c
3	R ₂ Zn (0.5 equiv)	22	73	– ^c	– ^c
4	RMgX (2 equiv)	– ^c	15	73	2

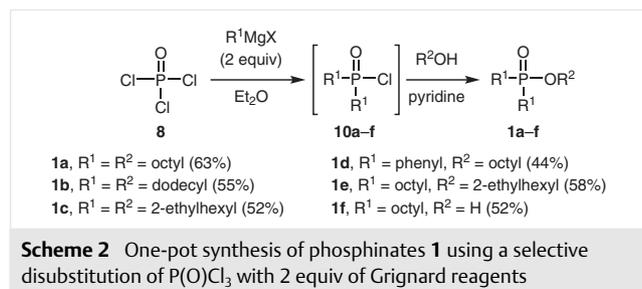
^a R = n-C₈H₁₇.

^b Percentage of phosphorus compounds in the reaction mixture as estimated by ³¹P NMR analysis.

^c Compound was not detected.

the reaction between dioctylphosphinic chloride (**10a**) and the Grignard reagent. Hence, this side reaction with dioctylphosphinic chloride (**10a**) will be less favorable than the less sterically hindered reaction with octylphosphonic dichloride (**9a**).

Given that the above-mentioned reaction mixture consisted mostly of dioctylphosphinic chloride, it should be possible to synthesize octyl dioctylphosphinate (**1a**) by quenching the reaction with an excess of 1-octanol. After addition of 1-octanol at a temperature below 0 °C, the reaction was stirred at room temperature until ³¹P NMR analysis showed complete consumption of the dioctylphosphinic chloride intermediate. It was found that pyridine needed to be added together with 1-octanol. In this way, the formed side product HCl could be neutralized and complete conversion could be achieved. This resulted in a reaction mixture that consisted mostly of the desired octyl dioctylphosphinate (**1a**) together with a small amount of dioctyl octylphosphonate (**2a**). After extractive workup and purification by column chromatography, octyl dioctylphosphinate (**1a**) was isolated in a good yield of 63% (Scheme 2).



Similar results could be obtained with other alkyl groups (Scheme 2). Reaction of phosphoryl chloride (**8**) with two equivalents of dodecylmagnesium bromide, followed by quenching with an excess of 1-dodecanol provided dodecyl didodecylphosphinate (**1b**) in an isolated yield of 55%. Furthermore, the more sterically hindered 2-ethylhexyl bis(2-ethylhexyl)phosphinate (**1c**) could be synthe-

sized in a similar yield by starting from the correspondingly branched Grignard reagent and alcohol. Besides alkyl Grignard reagents, phenylmagnesium bromide also allowed selective disubstitution of phosphoryl chloride (**8**). However, phenol was not reactive enough to substitute the resulting diphenylphosphinic chloride intermediate. Nonetheless, 1-octanol could react with diphenylphosphinic chloride and octyl diphenylphosphinate (**1d**) was isolated in a slightly lower yield than the other synthesized phosphinates **1**.

The last example illustrates another advantage of this one-pot procedure, namely that the substituents on the phosphorus (R¹) and oxygen (R²) atoms of the resulting phosphinate **1** do not need to be the same. Mixed phosphinates **1d–f** can be easily made using the same procedure and in similar yields. For example, reaction of phosphoryl chloride (**8**) with two equivalents of octylmagnesium bromide followed by quenching with an excess of 2-ethylhexanol resulted in 2-ethylhexyl dioctylphosphinate (**1e**) in a good yield of 58%. In a similar way, a phosphinic acid could be synthesized if the dioctylphosphinic chloride intermediate was quenched with water. After extraction and recrystallization, dioctylphosphinic acid (**1f**) was isolated in an acceptable yield.

This one-pot procedure is, compared to the different traditional multistep synthesis routes of phosphinates **1**, much more straightforward and general. Moreover, the overall yield of this process is, due to its shorter synthetic pathway, as good as or even better than those obtained via the traditional synthesis routes (Scheme 1, path A).^{9,10,11,13}

Given the success of disubstitution of phosphoryl chloride (**8**), selective monofunctionalization was further investigated using organometallic reagents other than Grignard reagents. Similar to phosphoryl chloride (**8**), reaction of phosphorus trichloride (**6**) with Grignard reagents is known to result in over-substitution.^{1a,17} However, it has been reported that reaction of phosphorus trichloride (**6**) with milder alkylating reagents, such as organomercury,¹⁸ organolead¹⁹ and organocadmium²⁰ reagents, did allow selective monoalkylation. Therefore, it was tested whether an organocadmium reagent could result in a similar selective monofunctionalization reaction with phosphoryl chloride (**8**). Organomercury and organolead compounds were not investigated due to their very high toxicity.²¹ It should be mentioned that also organocadmium compounds are toxic; however, they are less toxic than organomercury compounds and they are more commonly used as reagents in organic synthesis than organolead compounds.²²

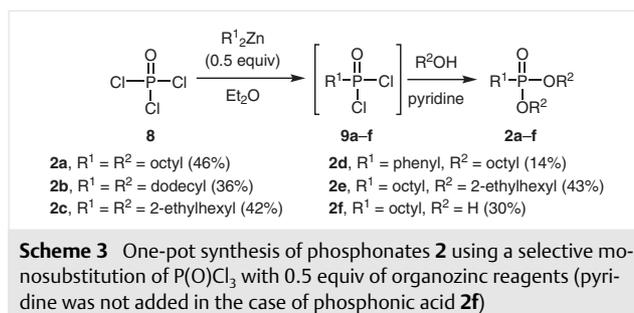
Dioctylcadmium was synthesized in situ by the reaction of octylmagnesium bromide with anhydrous CdCl₂ in diethyl ether at room temperature. After addition of one equivalent (relative to the initial amount of octylmagnesium bromide) of phosphoryl chloride (**8**) at a temperature below 0 °C, the reaction mixture was stirred at room temperature. Unfortunately, no reaction was observed at this temperature. Nevertheless, a slow reaction did occur when the reac-

tion mixture was heated at reflux. Over-substitution to dioctylphosphinic chloride (**10a**) was not detected and the major product was the desired octylphosphonic dichloride (**9a**) (Table 1, entry 2). Hence, with this less strongly alkylating organocadmium reagent, selective monofunctionalization of phosphoryl chloride (**8**) was indeed possible. After 45 hours, almost half of the reaction mixture consisted of the monoalkylated product, the rest was mostly unreacted phosphoryl chloride (**8**).

As dioctylcadmium was not reactive enough to allow complete conversion, even after 45 hours of reflux, dioctylzinc was used as a more reactive and less toxic alternative. Dioctylzinc was synthesized and used in a similar manner as dioctylcadmium. However, due to its higher reactivity, dioctylzinc did react with phosphoryl chloride (**8**) at room temperature. After 20 hours, almost 75% of the reaction mixture consisted of the desired octylphosphonic dichloride (**9a**) (Table 1, entry 3). Dioctylzinc reacted, just like dioctylcadmium, selectively with phosphoryl chloride (**8**) and over-substitution to dioctylphosphinic chloride (**10a**) was not detected. The amount of mono-octyl product in the reaction mixture after reaction with 0.5 equivalent of dioctylzinc (Table 1, entry 3) was similar to the amount of dioctyl product after reaction with 2 equivalents of Grignard reagent (Table 1, entry 4). Therefore, it is possible to tune the selectivity of the substitution reaction of phosphoryl chloride (**8**) by choosing a proper organometallic reagent.

Selective monoalkylation of phosphoryl chloride (**8**) to octylphosphonic dichloride was used next to develop a one-pot procedure for the synthesis of the corresponding phosphonate **2a**. Hence, the reaction of dioctylzinc with phosphoryl chloride (**8**) was quenched with an excess of 1-octanol in the presence of pyridine. The reaction mixture was cooled below 0 °C during the addition of these two reagents and was afterwards stirred at room temperature until ³¹P NMR analysis showed complete consumption of the octylphosphonic dichloride intermediate. The resulting mixture consisted mostly of dioctyl octylphosphonate (**2a**) together with a smaller amount of trioctyl phosphate. This trioctyl phosphate was formed from the reaction between 1-octanol and the remaining phosphoryl chloride (**8**). Unfortunately, the desired dioctyl octylphosphonate (**2a**) was found to be less stable than the corresponding phosphinate **1a**. Therefore, more product was lost during purification and dioctyl octylphosphonate (**2a**) was isolated in a lower yield of 46% (Scheme 3).

The scope of the one-pot synthesis of phosphonates **2** (Scheme 3) is the same as the scope of the one-pot synthesis of phosphinates **1** (Scheme 2). Unfortunately, all the synthesized phosphonates **2** were less stable than their phosphinate analogues **1** and were isolated in a lower yield. Nonetheless, phosphonates **2** with other alkyl groups, such as dodecyl (in compound **2b**) and the branched 2-ethylhexyl (in compounds **2c** and **2e**) could be synthesized in



moderate yields. In contrast, reaction of phosphoryl chloride (**8**) with diphenylzinc followed by quenching with an excess of 1-octanol gave the corresponding dioctyl phenylphosphonate (**2d**) in a low yield. The major product was actually trioctyl phosphate and a significant amount of octyl diphenylphosphinate (**1d**) was also present, indicating that 0.5 equivalent of diphenylzinc did not react selectively with phosphoryl chloride (**8**).

Mixed phosphonates, with different substituents on the phosphorus (R¹) and oxygen (R²) atoms, can be easily prepared using this one-pot procedure. For example, bis(2-ethylhexyl) octylphosphonate (**2e**) was obtained in a similar yield as its trioctyl derivative **2a** by reacting dioctylzinc with phosphoryl chloride (**8**) followed by quenching with an excess of 2-ethylhexanol. Moreover, octylphosphonic acid (**2f**) can be synthesized by quenching the reaction of dioctylzinc with water. Anhydride formation limited the yield of the desired acid **2f** but this can be reduced by not adding pyridine to the reaction mixture. In this way, octylphosphonic acid (**2f**) was isolated in a moderate yield.

The yields of the one-pot synthesis of phosphonates **2** are in general lower than those obtained for the traditional synthesis of phosphonates **2** based on the Michaelis–Arbuzov reaction (Scheme 1, path B).^{1,10,13} Nevertheless, this new procedure is a viable alternative for those cases where the Michaelis–Arbuzov reaction does not work.¹⁴ Moreover, this one-pot synthesis requires only one purification step, compared to the two purification steps required in the traditional strategy, uses milder reaction conditions than the Michaelis–Arbuzov reaction and is well suited for the synthesis of mixed phosphonates.

In conclusion, the selectivity of the substitution reaction of phosphoryl chloride (**8**) with organometallic reagents was investigated using NMR spectroscopy. It was found that 2 equivalents of octylmagnesium bromide reacted selectively to dioctylphosphinic chloride and that 0.5 equivalent of dioctylzinc reacted selectively to octylphosphonic dichloride. Hence, it is possible to tune the selectivity of the substitution reaction of phosphoryl chloride (**8**) by choosing a proper organometallic reagent. These results were used to develop one-pot synthetic methods for the preparation of phosphinates **1** and phosphonates **2** using commercially available Grignard reagents and alcohols. In this way,

phosphinates **1** were synthesized in good yields and phosphonates **2**, due to their lower stability, in moderate yields. Both procedures allow the synthesis of compounds with different substituents, of mixed systems and of their phosphinic and phosphonic acid derivatives. Compared to the traditional strategies to synthesize phosphinates **1** and phosphonates **2**, these one-pot procedures are shorter, more straightforward and more general.

All reactions were carried out in oven-dried glassware under a N₂ atmosphere. POCl₃ (99%), octylmagnesium bromide (2.0 M in Et₂O), (2-ethylhexyl)magnesium bromide (1.0 M in Et₂O), anhyd CdCl₂ (99%), 1-octanol (99%), and 1-dodecanol (98%) were purchased from Acros Organics. Dodecylmagnesium bromide (1.0 M in Et₂O) and phenylmagnesium bromide (3.0 M in Et₂O) were purchased from Sigma-Aldrich. 2-Ethyl-1-hexanol (99%) was purchased from Alfa Aesar, pyridine (99.7%) was purchased from VWR and anhyd ZnCl₂ (98–100%) was purchased from Chem-Lab. Anhyd Et₂O was obtained using a MBRAUN SPS-800 system. For column chromatography, 0.060–0.200 mm (60 Å) silica gel from Acros Organics was used as the stationary phase. All chemicals were used as received without further purification.

¹H and ¹³C NMR spectra were recorded at r.t. in CDCl₃ on a Bruker Ascend 400 MHz instrument operating at a frequency of 400 MHz for ¹H, 100 MHz for ¹³C and 162 MHz for ³¹P. ¹H chemical shifts were referenced to TMS (0.00 ppm), ¹³C chemical shifts were referenced to the CDCl₃ solvent signal (77.16 ppm) and ³¹P chemical shifts were referenced to aq 85% H₃PO₄ (0.00 ppm). Melting points were determined on a Mettler-Toledo DSC882e instrument under a He atmosphere using a heating rate of 5 °C min⁻¹. IR spectra were recorded on a Bruker Vertex 70 ATR-FTIR spectrophotometer. Low-resolution mass spectra were recorded on a Thermo Finnigan LCQ Advantage instrument (ESI mode). CHN elemental analysis was performed on a Thermo Scientific Flash 2000 Organic Elemental Analyzer.

Phosphinates **1**; General Procedure

To an oven-dried 100 mL two-necked flask, fitted with a reflux condenser were added anhyd Et₂O (amount depending on the concentration of the used Grignard reagent solution) and POCl₃ (0.93 mL, 10 mmol, 1 equiv). The solution was cooled in an ice-salt mixture and a Grignard reagent (20 mmol, 2 equiv) solution in Et₂O was slowly added. After stirring with cooling for 30 min, the reaction mixture was brought to r.t. and stirred for the indicated time. The mixture was then cooled again in an ice-salt mixture and the alcohol (20 mmol, 2 equiv) and pyridine (1.8 mL, 22 mmol, 2.2 equiv) were slowly added. Stirring with cooling for 5 min was followed by reaction at r.t. The reaction was quenched after the indicated time by cooling in an ice-salt mixture and adding sat. aq NH₄Cl (5 mL). The crude mixture was then poured into CH₂Cl₂ (100 mL), washed three times with dil HCl (1–2%, 100 mL in total), dried (MgSO₄), filtered, and evaporated to dryness. The excess of alcohol was removed using a short-path vacuum distillation apparatus and the resulting crude product was purified by column chromatography.

Octyl Diocylphosphinate (**1a**)

[CAS Reg. No. 7065-29-4]

Prepared according to the general phosphinate synthesis procedure using anhyd Et₂O (20 mL), octylmagnesium bromide (10 mL, 20 mmol, 2 equiv), and 1-octanol (3.2 mL, 20 mmol, 2 equiv). The reac-

tion with the Grignard reagent was stirred at r.t. for 5 h and the reaction with the alcohol was stirred at r.t. for 21 h. After extractive workup, the excess of 1-octanol was removed using a short-path vacuum distillation apparatus at 250 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 8:2 v/v), providing the pure compound as a slightly yellowish liquid; yield: 2.52 g (63%).

IR (ATR): 2923, 2854, 1465, 1207, 1018, 721 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 3.95 (q, *J* = 6.6 Hz, 2 H), 1.72–1.64 (m, 6 H), 1.61–1.52 (m, 4 H), 1.41–1.22 (m, 30 H), 0.88 (t, *J* = 6.3 Hz, 9 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 64.1, 64.1, 32.0, 31.2, 31.0, 30.9, 29.4, 29.3, 29.3, 29.2, 28.6, 27.7, 25.8, 22.8, 22.1, 22.1, 14.2.

³¹P NMR (CDCl₃, 162 MHz): δ = 57.8.

MS (ESI): *m/z* = 403 [M + H]⁺, 425 [M + Na]⁺, 805 [2 M + H]⁺, 827 [2 M + Na]⁺.

Anal. Calcd for C₂₄H₅₁O₂P: C, 71.59; H, 12.77. Found: C, 71.40; H, 12.66.

Dodecyl Didodecylphosphinate (**1b**)

Prepared according to the general phosphinate synthesis procedure using anhyd Et₂O (10 mL), dodecylmagnesium bromide (20 mL, 20 mmol, 2 equiv), and 1-dodecanol (4.5 mL, 20 mmol, 2 equiv). The reaction with the Grignard reagent was stirred at r.t. for 24 h and the reaction with the alcohol was stirred at r.t. for 24 h. After extractive workup, the excess of 1-dodecanol was removed using a short-path vacuum distillation apparatus at 300 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 9:1 v/v), providing the pure compound as a white solid; yield: 3.16 g (55%); mp 39–41 °C.

IR (ATR): 2916, 2848, 1463, 1184, 966, 773 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 3.95 (q, *J* = 6.6 Hz, 2 H), 1.75–1.61 (m, 6 H), 1.61–1.50 (m, 4 H), 1.40–1.22 (m, 54 H), 0.88 (t, *J* = 6.6 Hz, 9 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 64.1, 64.1, 32.1, 31.1, 31.0, 30.9, 29.8, 29.7, 29.7, 29.5, 29.5, 29.4, 29.3, 28.6, 27.7, 25.8, 22.8, 22.1, 22.1, 14.3.

³¹P NMR (CDCl₃, 162 MHz): δ = 57.8.

MS (ESI): *m/z* = 571 [M + H]⁺, 593 [M + Na]⁺, 1142 [2 M + H]⁺, 1164 [2 M + Na]⁺, 1734 [3 M + Na].

Anal. Calcd for C₃₆H₇₅O₂P: C, 75.73; H, 13.24. Found: C, 76.43; H, 13.17.

2-Ethylhexyl Bis(2-ethylhexyl)phosphinate (**1c**)

[CAS Reg. No. 36333-32-1]

Prepared according to the general phosphinate synthesis procedure using anhyd Et₂O (10 mL), (2-ethylhexyl)magnesium bromide (20 mL, 20 mmol, 2 equiv), and 2-ethyl-1-hexanol (3.1 mL, 20 mmol, 2 equiv). The reaction with the Grignard reagent was stirred at r.t. for 18.5 h and the reaction with the alcohol was stirred at r.t. for 3 days. After extractive workup, the excess of 2-ethyl-1-hexanol was removed using a short-path vacuum distillation apparatus at 150 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 95:5 v/v), providing the pure compound as a colorless liquid; yield: 2.08 g (52%).

IR (ATR): 2957, 2927, 1460, 1224, 1017, 820 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 3.92–3.79 (m, 2 H), 1.81–1.71 (m, 2 H), 1.66–1.60 (m, 4 H), 1.58–1.34 (m, 11 H), 1.34–1.16 (m, 14 H), 1.07–0.69 (m, 18 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 66.0, 40.6, 40.5, 34.0, 33.9, 33.7, 32.8, 30.2, 29.1, 28.8, 28.7, 27.2, 27.1, 27.0, 23.6, 23.2, 23.1, 14.3, 14.2, 11.1, 10.5, 10.5$.

^{31}P NMR (CDCl_3 , 162 MHz): $\delta = 57.6$ (t, $J = 9.9$ Hz).

MS (ESI): $m/z = 403$ [M + H] $^+$, 425 [M + Na] $^+$, 805 [2 M + H] $^+$, 827 [2 M + Na] $^+$.

Anal. Calcd for $\text{C}_{24}\text{H}_{51}\text{O}_2\text{P}$: C, 71.59; H, 12.77. Found: C, 71.81; H, 12.62.

Octyl Diphenylphosphinate (1d)

[CAS Reg. No. 3389-73-9]

Prepared according to the general phosphinate synthesis procedure using anhyd Et_2O (40 mL), phenylmagnesium bromide (6.7 mL, 20 mmol, 2 equiv), and 1-octanol (3.2 mL, 20 mmol, 2 equiv). The reaction with the Grignard reagent was stirred at r.t. for 21.5 h and the reaction with the alcohol was stirred at r.t. for 25.5 h. After extractive workup, the excess of 1-octanol was removed using a short-path vacuum distillation apparatus at 250 °C. The resulting crude product was purified by column chromatography (silica gel; $\text{CH}_2\text{Cl}_2/\text{EtOAc}$; 9:1 v/v), providing the pure compound as a slightly yellowish liquid; yield: 1.45 g (44%).

IR (ATR): 2925, 1438, 1227, 1129, 991, 727, 694, 560, 537 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 7.81$ (ddd, $J = 12.2, 8.2, 1.3$ Hz, 4 H), 7.56–7.48 (m, 2 H), 7.49–7.40 (m, 4 H), 4.02 (q, $J = 6.7$ Hz, 2 H), 1.76–1.68 (m, 2 H), 1.43–1.34 (m, 2 H), 1.33–1.22 (m, 8 H), 0.87 (t, $J = 6.9$ Hz, 3 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 132.6, 132.2, 132.2, 131.9, 131.8, 131.2, 128.7, 128.6, 65.2, 65.2, 31.9, 30.7, 30.7, 29.3, 29.3, 25.8, 22.8, 14.2$.

^{31}P NMR (CDCl_3 , 162 MHz): $\delta = 31.3$.

MS (ESI): $m/z = 331$ [M + H] $^+$, 353 [M + Na] $^+$, 661 [2 M + H] $^+$, 683 [2 M + Na] $^+$.

Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{O}_2\text{P}$: C, 72.70; H, 8.24. Found: C, 73.23; H, 8.36.

2-Ethylhexyl Dioctylphosphinate (1e)

[CAS Reg. No. 1400694-65-6]

Prepared according to the general phosphinate synthesis procedure using anhyd Et_2O (20 mL), octylmagnesium bromide (10 mL, 20 mmol, 2 equiv), and 2-ethyl-1-hexanol (3.1 mL, 20 mmol, 2 equiv). The reaction with the Grignard reagent was stirred at r.t. for 20 h and the reaction with the alcohol was stirred at r.t. for 24 h. After extractive workup, the excess of 2-ethyl-1-hexanol was removed using a short-path vacuum distillation apparatus at 150 °C. The resulting crude product was purified by column chromatography (silica gel; $\text{CH}_2\text{Cl}_2/\text{EtOAc}$; 8:2 v/v), providing the pure compound as a slightly yellowish liquid; yield: 2.35 g (58%).

IR (ATR): 2924, 2855, 1461, 1208, 1016, 811 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 3.90$ –3.81 (m, 2 H), 1.75–1.62 (m, 4 H), 1.61–1.50 (m, 5 H), 1.42–1.34 (m, 6 H), 1.33–1.22 (m, 22 H), 0.96–0.83 (m, 12 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 66.2, 66.1, 40.5, 40.5, 31.9, 31.1, 31.0, 30.2, 29.2, 29.2, 29.1, 28.5, 27.6, 23.6, 23.1, 22.8, 22.2, 22.1, 14.2, 14.2, 11.1$.

^{31}P NMR (CDCl_3 , 162 MHz): $\delta = 57.6$.

MS (ESI): $m/z = 403$ [M + H] $^+$, 425 [M + Na] $^+$, 805 [2 M + H] $^+$, 827 [2 M + Na] $^+$.

Anal. Calcd for $\text{C}_{24}\text{H}_{51}\text{O}_2\text{P}$: C, 71.59; H, 12.77. Found: C, 72.18; H, 12.78.

Dioctylphosphinic Acid (1f)

[CAS Reg. No. 683-19-2]

To an oven-dried 100 mL two-neck flask, fitted with a reflux condenser were added anhyd Et_2O (20 mL) and POCl_3 (0.93 mL, 10 mmol, 1 equiv). The solution was cooled in an ice-salt mixture and octylmagnesium bromide (10 mL, 20 mmol, 2 equiv) was slowly added. After stirring with cooling for 30 min, the reaction mixture was brought to r.t. and stirred for 19.5 h. The mixture was then cooled again in an ice-salt mixture, and H_2O (5 mL) and pyridine (1.8 mL, 22 mmol, 2.2 equiv) were slowly added. Stirring with cooling for 5 min was followed by reaction at r.t. for 7 h. The crude mixture was then poured into CH_2Cl_2 (100 mL), washed three times with dil HCl (1–2%, 100 mL in total), dried (MgSO_4), filtered, and evaporated to dryness. The resulting crude product was purified by recrystallization from hot heptane (50 mL), filtered, and washed with pentane, providing the pure compound as a white solid; yield: 1.52 g (52%); mp 83–84 °C.

IR (ATR): 2915, 2846, 1463, 967, 779 cm^{-1} .

^1H NMR (CDCl_3 , 400 MHz): $\delta = 10.52$ (s, 1 H), 1.71–1.52 (m, 8 H), 1.43–1.33 (m, 4 H), 1.33–1.20 (m, 16 H), 0.87 (t, $J = 6.8$ Hz, 6 H).

^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 32.0, 31.1, 31.0, 29.6, 29.3, 29.3, 28.7, 22.8, 21.7, 21.7, 14.2$.

^{31}P NMR (CDCl_3 , 162 MHz): $\delta = 60.4$.

MS (ESI): $m/z = 289$ [M – H] $^-$, 579 [2 M – H] $^-$, 601 [2 M – 2 H + Na] $^-$.

Anal. Calcd for $\text{C}_{16}\text{H}_{35}\text{O}_2\text{P}$: C, 66.17; H, 12.15. Found: C, 66.67; H, 12.07.

Phosphonates 2; General Procedure

To an oven-dried 100 mL two-necked flask, fitted with a reflux condenser were added anhyd ZnCl_2 (0.75 g, 5.5 mmol, 0.55 equiv) and anhyd Et_2O (amount depending on the concentration of the used Grignard reagent solution). The mixture was cooled in an ice-bath and a Grignard reagent (10 mmol, 1 equiv) solution in Et_2O was slowly added. The reaction mixture was stirred 10 more min at 0 °C followed by stirring at r.t. for the indicated time. The solution was then cooled in an ice-salt mixture and POCl_3 (0.93 mL, 10 mmol, 1 equiv) was added. After stirring with cooling for 5 min, the mixture was brought to r.t. and stirred for the indicated time. The mixture was cooled again in an ice-salt mixture and the alcohol (30 mmol, 3 equiv) and pyridine (2.7 mL, 33 mmol, 3.3 equiv) were slowly added. Stirring with cooling for 5 min was followed by reaction at r.t. The reaction was quenched after the indicated time by cooling in an ice-salt mixture and adding dil HCl (1–2%, 5 mL). The crude mixture was then poured into CH_2Cl_2 (100 mL), washed three times with dil HCl (1–2%, 100 mL in total), dried (MgSO_4), filtered, and evaporated to dryness. The excess of alcohol was removed using a short-path vacuum distillation apparatus and the resulting crude product was purified by column chromatography.

Dioctyl Octylphosphonate (2a)

[CAS Reg. No. 7098-33-1]

Prepared according to the general phosphonate synthesis procedure using anhyd Et_2O (20 mL), octylmagnesium bromide (5 mL, 10 mmol, 1 equiv), and 1-octanol (4.7 mL, 30 mmol, 3 equiv). The corresponding organozinc reagent was synthesized by stirring 2 h at r.t. The reaction with the formed organozinc reagent was stirred at r.t. for 51 h and the reaction with the alcohol was stirred at r.t. for 17 h. After ex-

tractive workup, the excess of 1-octanol was removed using a short-path vacuum distillation apparatus at 200 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 95:5 v/v), providing the pure compound as a slightly yellowish liquid; yield: 1.92 g (46%).

IR (ATR): 2923, 2854, 1465, 1248, 996, 722 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 4.06–3.94 (m, 4 H), 1.77–1.53 (m, 10 H), 1.39–1.25 (m, 28 H), 0.88 (t, *J* = 6.4 Hz, 9 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 65.7, 65.6, 32.0, 31.9, 30.9, 30.8, 30.7, 30.7, 29.4, 29.3, 29.2, 26.4, 25.7, 25.0, 22.8, 22.6, 22.6, 14.2.

³¹P NMR (CDCl₃, 162 MHz): δ = 32.8.

MS (ESI): *m/z* = 419 [M + H]⁺, 441 [M + Na]⁺, 837 [2 M + H]⁺, 859 [2 M + Na]⁺.

Anal. Calcd for C₂₄H₅₁O₃P: C, 68.86; H, 12.28. Found: C, 69.31; H, 12.24.

Didodecyl Dodecylphosphonate (2b)

Prepared according to the general phosphonate synthesis procedure using anhyd Et₂O (15 mL), dodecylmagnesium bromide (10 mL, 10 mmol, 1 equiv), and 1-dodecanol (6.7 mL, 30 mmol, 3 equiv). The corresponding organozinc reagent was synthesized by stirring 3 h at r.t. The reaction with the formed organozinc reagent was stirred at r.t. for 46 h and the reaction with the alcohol was stirred at r.t. for 5 h. After extractive workup, the excess of 1-dodecanol was removed using a short-path vacuum distillation apparatus at 300 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 95:5 v/v), providing the pure compound as a white solid; yield: 2.12 g (36%); mp 34–36 °C.

IR (ATR): 2913, 2847, 1469, 1233, 992, 837, 718 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 4.08–3.91 (m, 4 H), 1.76–1.68 (m, 2 H), 1.67–1.62 (m, 4 H), 1.62–1.55 (m, 2 H), 1.42–1.16 (m, 54 H), 0.88 (t, *J* = 6.8 Hz, 9 H).

¹³C NMR (CDCl₃, 150 MHz): δ = 65.6, 65.6, 32.1, 30.8, 30.8, 30.7, 30.7, 29.8, 29.8, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 26.2, 25.7, 25.2, 22.8, 22.6, 22.6, 14.3.

³¹P NMR (CDCl₃, 162 MHz): δ = 32.8.

MS (ESI): *m/z* = 558 [M + H]⁺, 610 [M + Na]⁺.

Anal. Calcd for C₃₆H₇₅O₃P: C, 73.67; H, 12.88. Found: C, 74.30; H, 12.82.

Bis(2-ethylhexyl) (2-Ethylhexyl)phosphonate (2c)

[CAS Reg. No. 126-63-6]

Prepared according to the general phosphonate synthesis procedure using anhyd Et₂O (15 mL), (2-ethylhexyl)magnesium bromide (10 mL, 10 mmol, 1 equiv), and 2-ethyl-1-hexanol (4.7 mL, 30 mmol, 3 equiv). The corresponding organozinc reagent was synthesized by stirring 2.5 h at r.t. The reaction with the formed organozinc reagent was stirred at r.t. for 46.5 h and the reaction with the alcohol was stirred at r.t. for 21.5 h. After extractive workup, the excess of 2-ethyl-1-hexanol was removed using a short-path vacuum distillation apparatus at 150 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 8:2 v/v), providing the pure compound as a slightly yellowish liquid; yield: 1.77 g (42%).

IR (ATR): 2958, 2928, 1461, 1246, 1011, 869 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 3.98–3.85 (m, 4 H), 1.81–1.65 (m, 3 H), 1.55–1.50 (m, 2 H), 1.50–1.35 (m, 8 H), 1.35–1.17 (m, 16 H), 1.05–0.73 (m, 18 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 67.5, 67.4, 40.5, 40.4, 34.3, 34.3, 33.8, 33.7, 30.3, 30.2, 30.2, 29.1, 28.9, 28.7, 26.9, 26.8, 23.5, 23.5, 23.2, 23.1, 14.3, 14.2, 11.1, 10.5.

³¹P NMR (CDCl₃, 162 MHz): δ = 32.9.

MS (ESI): *m/z* = 419 [M + H]⁺, 441 [M + Na]⁺, 837 [2 M + H]⁺, 859 [2 M + Na]⁺.

Anal. Calcd for C₂₄H₅₁O₃P: C, 68.86; H, 12.28. Found: C, 69.30; H, 12.22.

Diocetyl Phenylphosphonate (2d)

[CAS Reg. No. 1754-47-8]

Prepared according to the general phosphonate synthesis procedure using anhyd Et₂O (40 mL), phenylmagnesium bromide (3.3 mL, 10 mmol, 1 equiv), and 1-octanol (4.7 mL, 30 mmol, 3 equiv). The corresponding organozinc reagent was synthesized by stirring 2 h at r.t. The reaction with the formed organozinc reagent was stirred at r.t. for 21.5 h and the reaction with the alcohol was stirred at r.t. for 29 h. After extractive workup, the excess of 1-octanol was removed using a short-path vacuum distillation apparatus at 250 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 95:5 v/v), providing the pure compound as a slightly yellowish liquid; yield: 0.55 g (14%).

IR (ATR): 2924, 2855, 1439, 1251, 1131, 977, 748, 695, 564 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 7.87–7.74 (m, 2 H), 7.58–7.51 (m, 1 H), 7.51–7.42 (m, 2 H), 4.11–3.95 (m, 4 H), 1.71–1.62 (m, 4 H), 1.39–1.31 (m, 4 H), 1.31–1.20 (m, 16 H), 0.87 (t, *J* = 6.9 Hz, 6 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 132.5, 132.4, 132.0, 131.9, 129.5, 128.6, 128.5, 127.7, 66.3, 66.2, 31.9, 30.6, 30.6, 29.3, 29.2, 25.7, 22.8, 14.2.

³¹P NMR (CDCl₃, 162 MHz): δ = 18.9.

MS (ESI): *m/z* = 383 [M + H]⁺, 405 [M + Na]⁺, 765 [2 M + H]⁺, 787 [2 M + Na]⁺.

Anal. Calcd for C₂₂H₃₉O₃P: C, 69.08; H, 10.28. Found: C, 69.94; H, 10.43.

Bis(2-ethylhexyl) Octylphosphonate (2e)

[CAS Reg. No. 52894-02-7]

Prepared according to the general phosphonate synthesis procedure using anhyd Et₂O (20 mL), octylmagnesium bromide (5 mL, 10 mmol, 1 equiv), and 2-ethyl-1-hexanol (4.7 mL, 30 mmol, 3 equiv). The corresponding organozinc reagent was synthesized by stirring 2 h at r.t. The reaction with the formed organozinc reagent was stirred at r.t. for 24 h and the reaction with the alcohol was stirred at r.t. for 25 h. After extractive workup, the excess of 2-ethyl-1-hexanol was removed using a short-path vacuum distillation apparatus at 150 °C. The resulting crude product was purified by column chromatography (silica gel; CH₂Cl₂/EtOAc; 95:5 v/v), providing the pure compound as a slightly yellowish liquid; yield: 1.82 g (43%).

IR (ATR): 2926, 2858, 1461, 1248, 1010, 863 cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ = 3.98–3.84 (m, 4 H), 1.77–1.67 (m, 2 H), 1.63–1.50 (m, 4 H), 1.45–1.34 (m, 6 H), 1.33–1.20 (m, 20 H), 0.97–0.82 (m, 15 H).

¹³C NMR (CDCl₃, 100 MHz): δ = 67.7, 67.6, 40.4, 40.4, 32.0, 30.8, 30.7, 30.1, 29.2, 29.2, 29.1, 26.2, 24.8, 23.5, 23.5, 23.1, 22.8, 22.7, 22.6, 14.2, 14.2, 11.1.

³¹P NMR (CDCl₃, 162 MHz): δ = 32.7.

MS (ESI): $m/z = 419 [M + H]^+$, $441 [M + Na]^+$, $837 [2 M + H]^+$, $859 [2 M + Na]^+$.

Anal. Calcd for $C_{24}H_{51}O_3P$: C, 68.86; H, 12.28. Found: C, 69.27; H, 12.14.

Octylphosphonic Acid (2f)

[CAS Reg. No. 4724-48-5]

To an oven-dried 100 mL two-neck flask, fitted with a reflux condenser were added anhyd $ZnCl_2$ (0.75 g, 5.5 mmol, 0.65 equiv) and anhyd Et_2O (20 mL). The mixture was cooled in an ice-bath and octylmagnesium bromide (4.2 mL, 8.4 mmol, 1 equiv) was slowly added. The reaction mixture was stirred 10 more min at $0^\circ C$ followed by 2 h at r.t. The solution was then cooled in an ice-salt mixture and $POCl_3$ (0.78 mL, 8.4 mmol, 1 equiv) was added. After stirring with cooling for 5 min, the mixture was brought to r.t. and stirred for 20 h. The mixture was cooled again in an ice-salt mixture and H_2O (5 mL) was slowly added. Stirring with cooling for 5 min was followed by reaction at r.t. for 25.5 h. The crude mixture was then poured into CH_2Cl_2 (100 mL), washed three times with dil HCl (1–2%, 100 mL in total), dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting crude product was purified by recrystallization from hot heptane (50 mL), filtered and washed with pentane, providing the pure compound as a white solid; yield: 0.49 g (30%); mp $100\text{--}102^\circ C$.

IR (ATR): 2918, 1468, 1106, 994, 943, 778, 715 cm^{-1} .

1H NMR ($CDCl_3$, 400 MHz): $\delta = 9.53$ (s, 2 H), 1.81–1.68 (m, 2 H), 1.68–1.55 (m, 2 H), 1.41–1.33 (m, 2 H), 1.33–1.22 (m, 8 H), 0.88 (t, $J = 6.8$ Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.9, 30.7, 30.5, 29.2, 29.2, 26.1, 24.7, 22.8, 22.2, 22.1, 14.2$.

^{31}P NMR ($CDCl_3$, 162 MHz): $\delta = 37.7$.

MS (ESI): $m/z = 193 [M - H]^-$, $387 [2 M - H]^-$, $581 [3 M - H]^-$, $603 [3 M - 2 H + Na]^-$, $797 [4 M - 2 H + Na]^-$.

Anal. Calcd for $C_8H_{19}O_3P$: C, 49.48; H, 9.86. Found: C, 49.19; H, 9.71.

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Supporting Information

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