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Controlled Monohalogenation of Phosphonates, Part II: Preparation of Pure Diethyl α -Monohalogenated Alkylphosphonates¹

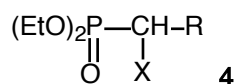
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Abstract : The reaction of diethyl alkylphosphonates with chlorotrimethylsilane in the presence of LDA leads to the corresponding diethyl 1-lithio(trimethylsilyl)alkylphosphonates which are cleanly halogenated (X=F, Cl, Br, I) with electrophilic reagents then deprotected to give pure diethyl α -monohalogenoalkylphosphonates. The reaction has been extended by the one pot conversion of triethyl phosphate into diethyl α -monohalogenobutylphosphonates in 85-97% overall yields.

Key words : diethyl alkylphosphonates, electrophilic halogenating agents, LDA, triethyl phosphate, diethyl α -monohalogenoalkylphosphonates.

Over the years, a number of methods have been described for the preparation of α -monohalogenated methyl^{2,3} or alkylphosphonates. In the majority of cases each halide is introduced in the α -position to phosphonates either by a specific method or with an appropriate reagent through oxidative or reductive processes (F,^{4,5} Cl,⁶⁻¹⁰ Br,^{6,11,12} I^{6,10}). There are no known methods for the conversion of alkylphosphonates to α -monohalogenated alkylphosphonates by a common route to the four halides. The importance of α -halogenated alkylphosphonates as precursors of more elaborated compounds or as reagents in organic synthesis has been well recognized in recent years.^{2,3,13} For example, they play an evergrowing role in the preparation of phosphonates bearing different functional groups.^{3,14} Our continuing interest in the use of α -monohalogenated alkylphosphonates **4** (Figure 1) prompted us to explore the possibility to develop a general method giving access to these compounds in mild conditions. At the same time we should like to demonstrate how easily and selectively any single chosen halogen can be introduced in the α -position to alkylphosphonates.



X = F, Cl, Br, I

R = Me, *n*-Pr, *i*-Pr, *n*-Pent

Figure 1.

Recently, we reported a new and efficient method for the conversion of diethyl benzylphosphonates to α -monohalogenated diethyl benzylphosphonates based on the electrophilic halogenation of α -phosphorylated- α -silylated carbanions.¹ This mild and versatile one-pot procedure, which results in overall yields of 68-97% of pure α -monohalogenobenzylphosphonates has now been further developed into a new one converting diethyl alkylphosphonates **1** into α -monofluoro-, monochloro-, monobromo- and monoiodoalkylphosphonates **4**. These two procedures are complementary with respect to the reactivity of phosphorylated carbanions toward TMSCl. Furthermore, the extension of this approach give us the possibility once more to promote electrophilic halogenating reagents such as hexachloroethane, dibromotetrachloroethane and dibromotetrafluoroethane which combine availability, cost, efficiency and ready elimination of byproducts.

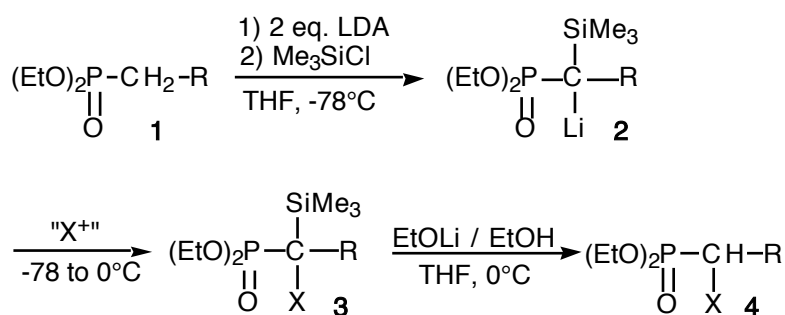
A variety of starting diethyl alkylphosphonates **1**, with short or long carbon chain, substituted or unsubstituted, are involved in the reaction sequence. They are easily available in high yields either by thermal reaction between triethyl phosphite and the corresponding alkylhalides (Michaelis-Arbuzov reaction)¹⁵⁻¹⁸ or by anionic reaction at low temperature between triethyl phosphate and the corresponding alkyllithiums (phosphate-phosphonate conversion)¹⁹. Once these starting materials in hands, the entire electrophilic halogenation procedure is performed in one reaction vessel without the isolation or purification of intermediates (Scheme 1).

In the first step, the diethyl 1-lithio-1-(trimethylsilyl)alkylphosphonates **2**, the key intermediates in the synthesis of α -monohalogenated phosphonates, are very selectively formed from diethyl alkylphosphonates **1** and TMSCl by using LDA (2 eq.) as metallating agent. The method gives optimum results by generating the diethyl 1-lithioalkylphosphonates at low temperature then by reacting the TMSCl at -78°C. In these conditions, the TMSCl is completely consumed, thus avoiding the competing reaction between TMSCl and *i*-Pr₂NH which generally appears on warming and provides an internal proton source.

The second deprotonation generating the stable carbanions **2** was monitored by ³¹P-NMR ($\delta^{31}\text{P}(\text{THF})=+54$). It appears that it is closely depending on the steric hindrance around the α -carbon. We observed a facile deprotonation at low temperature with silylated alkylphosphonates containing short (R= Me) or long (R= *n*-Pr, *n*-Pent) alkyl chain, while the

deprotonation of the corresponding silylated alkylphosphonates containing ramified alkyl chain (R= *i*-Pr) was more difficult. In that case an excess of LDA (3 eq.) has to be used to obtain a complete metallation of α -substituted silylated alkylphosphonates (R= *i*-Pr).

Further attempts to obtain **2** with bases such as LiHMDS or *n*-BuLi have not been successful. For example, LiHMDS, which has been selectively used in the metallation of diethyl benzylphosphonates,¹ was not strong enough to abstract a proton from either diethyl alkylphosphonates or diethyl trimethylsilylalkylphosphonates. The use of *n*-BuLi under internal quench conditions was also disappointing. The addition at low temperature of a stoichiometric mixture of diethyl alkylphosphonate **1** and TMSCl to *n*-BuLi (2 eq.) gave an exothermic reaction resulting in the formation of three compounds, the expected diethyl 1-lithio-1-(trimethylsilyl)phosphonate **2** (70%), and two side products in approximately equal amount, the diethyl trimethylsilylalkylphosphonate and the starting phosphonate **1**. Presumably with these conditions, the *n*-BuLi is consumed as a nucleophile towards TMSCl to undergo a silylation reaction and as a base towards **1** to give an hydrogen-metal exchange reaction. The competition between these two reactions prevents the selective formation of **2**.



R = Me, *n*-Pr, *i*-Pr, *n*-Pent

X = F, Cl, Br, I

"X⁺" = (PhSO₂)₂NF, C₂Cl₆, C₂Cl₄Br₂, I₂

Scheme 1.

The halogenation step of **2** takes place at low temperature using a slight excess of halogenating agent "X⁺" (1.1 eq.). We used commercial halogenating agents, *N*-fluorobenzenesulfonimide (NFBS) for fluorination, hexachloroethane for chlorination, dibromotetrachloroethane or dibromotetrafluoroethane for bromination and iodine for iodination. However, availability of dibromotetrafluoroethane may be affected by regulations. These reagents, which liberate inert byproducts after reaction, are particularly appreciated.

With alkylphosphonates containing short or long carbon chain the halogenation reaction results in rapid, clean and quantitative formation of the halogenated derivatives **3**. However, with alkylphosphonates sterically hindered in α position, the halogenation reaction gives

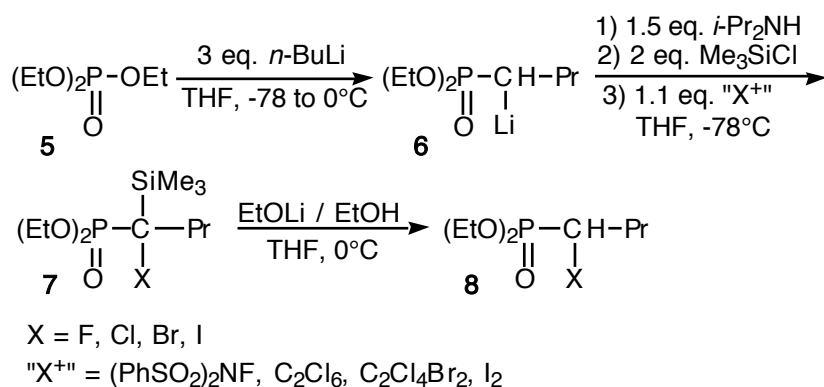
satisfactory results only for the chloro **3e**, the bromo **3h** and the fluoro **3b** derivatives. Unfortunately, the 1-iodo-1-(trimethylsilyl)isopropylphosphonate ($\delta^{31}\text{P}(\text{THF})=27.5$) is unstable and decomposes by losing iodine to give the 1-(trimethylsilyl)isopropylphosphonate ($\delta^{31}\text{P}(\text{THF})=35.2$). By contrast, the 1-fluoro-1-(trimethylsilyl)isopropylphosphonate **3b** is produced in 90% only, the complement being the 1-(trimethylsilyl)isopropylphosphonate. In that case, the fluorination is slowed down by the steric hindrance in the approach of the NFBS to the carbanion and the *i*-Pr₂NH is competitively fluorinated to give *i*-Pr₂N-F, ($\delta^{19}\text{F}(\text{THF})=-87$).²⁰

The TMS group is removed in the third step. After warming, lithium ethylate in ethanol was added at 0°C to slowly remove the TMS group. It was established that no deprotection occurs in the THF solution until the proton source is introduced by quenching the reaction mixture with ethanol. The complete deprotection of compounds **3** proceeds readily with short as well as with long chain alkylphosphonates and requires only few minutes for all halogenoalkylphosphonates. We chose to accomplish deprotection of compounds **3** under similar conditions for 30 min.. After acid hydrolysis of the reaction mixture with 3 M HCl and extraction, the crude diethyl α -monohalogenoalkylphosphonates **4** were isolated in practically pure form. The crude products can be passed through a silica plug with AcOEt/Hexane (30/70) as eluent or distilled using a bulb to bulb apparatus. All the structures are confirmed by the analytical and spectral data and by comparison with known compounds.

Table 1. Diethyl α -monohalogenoalkylphosphonates **4**

4	X	R	³¹ P-NMR (CDCl ₃): δ	¹⁹ F-NMR (CDCl ₃): δ	Yield (%)
a ⁵	F	Me	18.6 (d, ² J _{PF} =76.2)	-200.0 (d, ² J _{PF} =75.0)	89
b	F	<i>i</i> -Pr	18.2 (d, ² J _{PF} =79.3)	-210.8 (d, ² J _{PF} =78.5)	74
c ⁵	F	<i>n</i> -Pent	18.8 (d, ² J _{PF} =76.6)	-207.2 (d, ² J _{PF} =77.0)	82
d ⁶	Cl	Me	21.8 (s)	-	99
e	Cl	<i>i</i> -Pr	20.3 (s)	-	91
f	Cl	<i>n</i> -Pent	21.2 (s)	-	99
g ⁶	Br	Me	21.5 (s)	-	98
h	Br	<i>i</i> -Pr	20.0 (s)	-	98
i	Br	<i>n</i> -Pent	20.8 (s)	-	93
j ⁶	I	Me	23.3 (s)	-	83
k	I	<i>n</i> -Pent	22.6 (s)	-	89

Once the diethyl α -halogenoalkylphosphonates **4** were in hands, it appeared interesting to combine the selective electrophilic halogenation reaction with the phosphate-phosphonate conversion¹⁹ to prepare directly the α -halogenoalkylphosphonates **6** from triethyl phosphate **5**. This approach was exemplified by the conversion of triethyl phosphate **5** into diethyl α -halogenobutylphosphonates **6**. Thus, we have synthesised the four diethyl α -halogenobutylphosphonates **6** from triethyl phosphate **5** and *n*-BuLi in a sequential one-pot procedure with the same halogenating agents "X⁺" as previously, with an overall yield of 85-97% (Scheme 2). The sequential procedure consists in the addition at low temperature of triethyl phosphate **5** to a solution of *n*-BuLi (3 eq.) in THF which produces quantitatively the intermediate diethyl 1-lithiobutylphosphonate **6** ($\delta^{31}\text{P}(\text{THF})=+54.1$). Once the formation of **6** established, *i*-Pr₂NH (1.5 eq.), TMSCl (2.1 eq.) and the halogenating agent (1.1 eq.) are successively added at low temperature to cleanly produce **7**. The removal of TMS from **7** is achieved as previously described to give **8** (Table 2). The interest of this route is the simplicity and the efficiency with which the four diethyl α -halogenobutylphosphonates **8** are elaborated selectively and in high yields from the common starting material **5**.



Scheme 2.

Table 2. Diethyl α -monohalogenobutylphosphonates **8**

8	X	³¹ P-NMR (CDCl ₃): δ	¹⁹ F-NMR (CDCl ₃): δ	Yield (%)
a ⁵	F	18.8 (d, ² J _{PF} =76.2)	-207.5 (d, ² J _{PF} =76.2)	85
b ⁶	Cl	21.3 (s)	-	97
c ⁶	Br	20.8 (s)	-	90
d ⁶	I	22.5 (s)	-	92

In conclusion, the present procedure, combined with the phosphate-phosphonate conversion,¹⁹ appears as the method of choice for the synthesis of diethyl α -monohalogenoalkylphosphonates **4** and **8**. The entire procedure is performed in a single reaction vessel without the isolation or purification of intermediates and requires commercial or readily available starting materials. The overall yields of the pure α -monohalogenoalkylphosphonates **4** or **8** are in the range of 82-99% in repeated runs.

NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon, 81.01 MHz for phosphorus and 235 MHz for fluor. ³¹P downfield shifts (δ) are expressed with a positive sign, in ppm, relative to external 85% H₃PO₄ in H₂O. ¹H and ¹³C chemical shifts (δ) are reported in ppm relative to CDCl₃ as internal standard. ¹⁹F chemical shifts (δ) are reported in ppm relative to CFC₃ as external standard. Coupling constants (*J*) are given in Hz. The following abbreviations are used: s, d, t, q, p, h, m for singlet, doublet, triplet, quadruplet, pentuplet, heptuplet and multiplet respectively. Low resolution mass spectra were recorded on a Hewlett-Packard 5989 B GC-MS spectrometer (BPX5 column, positive chemical ionisation NH₃). Organic solvents were purified by standard procedures. THF was distilled under an inert atmosphere from purple solutions of sodium-benzophenone ketyl. The synthesis of all compounds was carried out under dry nitrogen.

Synthesis of diethyl 1-halogenoalkylphosphonates 4; General procedure:

n-BuLi (14.4 mL of 1.6 M solution in hexane; 23 mmol) is added to THF (20 mL) and cooled to -78 °C. A solution of *i*-Pr₂NH (2.42 g; 24 mmol) in THF (20 mL) is then slowly added at this temperature *via* a dropping funnel. After 15 min., the diethyl alkylphosphonate (10 mmol) in THF (20 mL) is added to the reaction mixture maintaining the temperature at -78°C. Stirring is continued for 10 min. at this temperature and then TMSCl (1.2 g; 11 mmol) in THF (20 mL) is added. The reaction mixture is allowed to warm slowly to 0°C then cooled again to -78°C. The halogenating agent (11 mmol) in THF (20 mL) is slowly added. The resulting pale-yellow mixture is then left to warm to 0°C over a period of 15 min. At this temperature, 20 mL of a EtOLi/EtOH solution (1 M) is added and after 30 min. the deprotection is complete. The reaction mixture is then poured with rapid stirring into a mixture of 2 M HCl (15 mL), CH₂Cl₂ (15 mL) and crushed ice, then extracted with CH₂Cl₂ (2 x 20 mL) and the organic layers dried (MgSO₄). Filtration and evaporation yield the crude title compounds **4**. In the case of fluoro compounds, the crude is diluted with hexane (200 mL) to precipitate the benzenesulfonimide. All products can be purified further by distillation, according to previously described procedures.

*Diethyl α -fluoroethylphosphonate (4a)*⁵ C₆H₁₄O₃FP (M=184) : ³¹P-NMR +18.6 (d, ²J_{PF}=76.2). / ¹⁹F-NMR -200.0 (d, ²J_{PF}=75.0). / ¹H-NMR 1.15 (t, ³J_{HH}=7.0, 6H, CH₃CH₂O), 1.39 (ddd, ³J_{PH}=16.7, ³J_{HH}=7.1, ³J_{FH}=25.6, 3H, CHFCH₃), 4.20-4.33 (m, 4H,

CH₃CH₂O), 4.94 (ddq, ²J_{PH}=2.2, ³J_{HH}=7.1, ²J_{FH}=46.1, 1H, CHF). / ¹³C-NMR 16.5 (d, ²J_{FC}=21.3, CHFCH₃), 17.1 (d, ³J_{PC}=5.3, CH₃CH₂O), 63.9 (d, ²J_{PC}=6.6, (CH₃CH₂O)_A), 64.2 (d, ²J_{PC}=7.1, (CH₃CH₂O)_B), 85.9 (dd, ¹J_{PC}=172.6, ¹J_{FC}=177.2, CHF). / m/z (CI): 185 (M+1, 100), 202 (M+18, 39).

Diethyl α-fluoroisobutylphosphonate (4b) C₈H₁₈O₃FP (M=212) : ³¹P-NMR +18.2 (d, ²J_{PF}=79.3). / ¹⁹F-NMR -210.8 (d, ²J_{PF}=78.5). / ¹H-NMR 1.10 (dt, ³J_{HH}=6.7, ⁴J_{PH}=⁴J_{FH}=1.6, 6H, CH(CH₃)₂), 1.35 (t, ³J_{HH}=7.1, 6H, CH₃CH₂O), 2.26 (ddh, ³J_{HH}=6.7, ³J_{PH}=6.7, ³J_{FH}=9.0, 1H, CH(CH₃)₂), 4.20-4.33 (m, 4H, CH₃CH₂O), 4.94 (ddd, ²J_{PH}=6.4, ³J_{HH}=3.3, ²J_{FH}=45.7, 1H, CHF). / ¹³C-NMR 16.7 (d, ³J_{PC}=5.5, CH₃CH₂O), 17.9 (dd, ³J_{PC}=7.7, ³J_{FC}=8.3, (CH(CH₃)₂)_A), 19.2 (dd, ³J_{PC}=5.4, ³J_{FC}=7.3, (CH(CH₃)₂)_B), 29.8 (d, ²J_{FC}=19.1, CH(CH₃)₂), 62.9 (d, ²J_{PC}=6.5, (CH₃CH₂O)_A), 63.4 (d, ²J_{PC}=7.0, (CH₃CH₂O)_B), 93.4 (dd, ¹J_{PC}=167.7, ¹J_{FC}=182.8, CHF). / m/z (CI): 213 (M+1, 100), 230 (M+18, 32).

Diethyl α-fluorohexylphosphonate (4c)⁵ C₁₀H₂₂O₃FP (M=240) : ³¹P-NMR +18.8 (d, ²J_{PF}=76.6). / ¹⁹F-NMR -207.2 (d, ²J_{PF}=77.0). / ¹H-NMR 0.84-0.95 (m, 3H, CH₂CH₂CH₃), 1.37 (t, ³J_{HH}=7.1, 6H, CH₃CH₂O), 1.17-2.01 (m, 8H, CH₂CH₂CH₂CH₂), 4.14-4.30 (m, 4H, CH₃CH₂O), 4.72 (ddt, ²J_{PH}=10.1, ³J_{HH}=3.1, ²J_{FH}=46.9, 1H, CHF). / ¹³C-NMR 14.6 (s, CH₂CH₂CH₃), 17.1 (d, ³J_{PC}=5.6, CH₃CH₂O), 23.0 (s, CH₂CH₂CH₃), 25.6 (dd, ³J_{PC}=2.7, ³J_{FC}=12.5, CHFCH₂CH₂), 30.6 (d, ²J_{FC}=30.1, CHFCH₂CH₂), 31.9 (s, CH₂CH₂CH₃), 63.5 (d, ²J_{PC}=6.9, (CH₃CH₂O)_A), 63.8 (d, ²J_{PC}=7.0, (CH₃CH₂O)_B), 89.5 (dd, ¹J_{PC}=169.7, ¹J_{FC}=179.9, CHF). / m/z (CI): 241 (M+1, 100), 258 (M+18, 17).

Diethyl α-chloroethylphosphonate (4d)⁶ C₆H₁₄O₃CIP (M=200.5) : ³¹P-NMR +21.8 (s). / ¹H-NMR 1.24 (t, ³J_{HH}=7.0, 6H, CH₃CH₂O), 1.57 (dd, ³J_{HH}=7.2, ³J_{PH}=16.6, 3H, CHClCH₃), 3.86 (dq, ²J_{PH}=9.7, ³J_{HH}=7.2, 1H, CHCl), 4.1 (dq, ³J_{PH}=3.5, ³J_{HH}=7.0, 4H, CH₃CH₂O). / ¹³C-NMR 16.8 (d, ³J_{PC}=5.6, CH₃CH₂O), 19.7 (s, CHClCH₃), 47.3 (d, ¹J_{PC}=161.6, CHCl), 63.7 (d, ²J_{PC}=6.4, (CH₃CH₂O)_A), 64.0 (d, ²J_{PC}=6.6, (CH₃CH₂O)_B). / m/z (CI): 201 (M+1 ³⁵Cl, 100), 203 (M+1 ³⁷Cl, 38), 218 (M+18 ³⁵Cl, 40), 220 (M+18 ³⁷Cl, 14).

Diethyl α-chloroisobutylphosphonate (4e) C₈H₁₈O₃CIP (M=228.5) : ³¹P-NMR +20.3 (s). / ¹H-NMR 0.97 (d, ³J_{HH}=6.7, 6H, CH(CH₃)₂), 1.23 (t, ³J_{HH}=7.0, 6H, CH₃CH₂O), 2.30 (ddh, ³J_{PH}=6.7, ³J_{HH}=6.7, ³J_{HH}=3.3, 1H, CH(CH₃)₂), 3.73 (dd, ²J_{PH}=12.1, ³J_{HH}=3.3, 1H, CHCl), 4.06 (p, ³J_{PH}=³J_{HH}=7.2, 2H, (CH₃CH₂O)_A), 4.10 (p, ³J_{PH}=³J_{HH}=7.2, 2H, (CH₃CH₂O)_B). / ¹³C-NMR 16.8 (d, ³J_{PC}=5.6, CH₃CH₂O), 17.8 (d, ³J_{PC}=2.6, (CH(CH₃)₂)_A), 21.4 (d, ³J_{PC}=13.6, (CH(CH₃)₂)_B), 30.4 (s, CH(CH₃)₂), 59.5 (d, ¹J_{PC}=157.5, CHCl), 63.3 (d,

$^2J_{\text{PC}}=7.1$, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 63.9 (d, $^2J_{\text{PC}}=6.8$, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **m/z** (CI): 229 (M+1 ^{35}Cl , 100), 231 (M+1 ^{37}Cl , 40), 246 (M+18 ^{35}Cl , 19), 248 (M+18 ^{37}Cl , 7).

Diethyl α -chlorohexylphosphonate (4f) $\text{C}_{10}\text{H}_{22}\text{O}_3\text{ClP}$ (M=256.5) : **$^{31}\text{P-NMR}$** +21.2 (s). / **$^1\text{H-NMR}$** 0.78 (t, $^3J_{\text{HH}}=6.3$, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.24 (t, $^3J_{\text{HH}}=7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 1.20-2.10 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 3.86 (dt, $^2J_{\text{PH}}=10.5$, $^3J_{\text{HH}}=3.3$, 1H, CHCl), 4.08 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.2$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 4.11 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.2$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **$^{13}\text{C-NMR}$** 14.3 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 16.8 (d, $^3J_{\text{PC}}=5.3$, $\text{CH}_3\text{CH}_2\text{O}$), 22.7 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 26.4 (d, $^2J_{\text{PC}}=12.2$, $\text{CHClCH}_2\text{CH}_2$), 31.2 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 32.4 (s, $\text{CHClCH}_2\text{CH}_2$), 54.2 (d, $^1J_{\text{PC}}=160.0$, CHCl), 63.5 (d, $^2J_{\text{PC}}=6.8$, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 63.9 (d, $^2J_{\text{PC}}=7.3$, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **m/z** (CI): 257 (M+1 ^{35}Cl , 100), 259 (M+1 ^{37}Cl , 29), 274 (M+18 ^{35}Cl , 10), 276 (M+18 ^{37}Cl , 3).

*Diethyl α -bromoethylphosphonate (4g)*⁶ $\text{C}_6\text{H}_{14}\text{O}_3\text{BrP}$ (M=245) : **$^{31}\text{P-NMR}$** +21.5 (s). / **$^1\text{H-NMR}$** 1.27 (t, $^3J_{\text{HH}}=7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 1.74 (dd, $^3J_{\text{HH}}=7.3$, $^3J_{\text{PH}}=16.7$, 3H, CHBrCH_3), 3.81 (dq, $^2J_{\text{PH}}=7.7$, $^3J_{\text{HH}}=7.3$, 1H, CHBr), 4.07-4.19 (m, 4H, $\text{CH}_3\text{CH}_2\text{O}$). / **$^{13}\text{C-NMR}$** 16.8 (d, $^3J_{\text{PC}}=5.7$, $\text{CH}_3\text{CH}_2\text{O}$), 20.4 (d, $^2J_{\text{PC}}=1.7$, CHBrCH_3), 35.4 (d, $^1J_{\text{PC}}=159.8$, CHBr), 63.8 (d, $^2J_{\text{PC}}=7.3$, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 64.1 (d, $^2J_{\text{PC}}=7.4$, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **m/z** (CI): 245 (M+1 ^{79}Br , 100), 247 (M+1 ^{81}Br , 100), 262 (M+18 ^{79}Br , 27), 264 (M+18 ^{81}Br , 27).

Diethyl α -bromoisobutylphosphonate (4h) $\text{C}_8\text{H}_{18}\text{O}_3\text{BrP}$ (M=273) : **$^{31}\text{P-NMR}$** +20.0 (s). / **$^1\text{H-NMR}$** 0.91 (d, $^3J_{\text{HH}}=6.6$, 3H, ($\text{CH}(\text{CH}_3)_2$)_A), 1.08 (dd, $^3J_{\text{HH}}=6.7$, $^4J_{\text{PH}}=6.7$, 3H, ($\text{CH}(\text{CH}_3)_2$)_B), 1.35 (t, $^3J_{\text{HH}}=7.0$, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 2.26 (ddh, $^3J_{\text{PH}}=6.7$, $^3J_{\text{HH}}=6.7$, $^3J_{\text{HH}}=2.9$, 1H, $\text{CH}(\text{CH}_3)_2$), 3.86 (dd, $^2J_{\text{PH}}=11.6$, $^3J_{\text{HH}}=2.9$, 1H, CHBr), 4.19 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.2$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 4.23 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.2$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **$^{13}\text{C-NMR}$** 17.0 (d, $^3J_{\text{PC}}=5.8$, $\text{CH}_3\text{CH}_2\text{O}$), 19.2 (d, $^3J_{\text{PC}}=2.3$, ($\text{CH}(\text{CH}_3)_2$)_A), 22.7 (d, $^3J_{\text{PC}}=14.5$, ($\text{CH}(\text{CH}_3)_2$)_B), 30.2 (s, $\text{CH}(\text{CH}_3)_2$), 51.7 (d, $^1J_{\text{PC}}=154.7$, CHBr), 63.8 (d, $^2J_{\text{PC}}=7.1$, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 64.2 (d, $^2J_{\text{PC}}=7.2$, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **m/z** (CI): 273 (M+1 ^{79}Br , 100), 275 (M+1 ^{81}Br , 100), 290 (M+18 ^{79}Br , 23), 292 (M+18 ^{81}Br , 23).

Diethyl α -bromohexylphosphonate (4i) $\text{C}_{10}\text{H}_{22}\text{O}_3\text{BrP}$ (M=301) : **$^{31}\text{P-NMR}$** +20.8 (s). / **$^1\text{H-NMR}$** 0.73 (t, $^3J_{\text{HH}}=6.4$, 3H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.18 (t, $^3J_{\text{HH}}=7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$), 1.30-2.10 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 3.62 (dt, $^2J_{\text{PH}}=9.9$, $^3J_{\text{HH}}=3.5$, 1H, CHBr), 4.01 (dq, $^3J_{\text{PH}}=4.5$, $^3J_{\text{HH}}=7.1$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_A), 4.07 (dq, $^3J_{\text{PH}}=4.5$, $^3J_{\text{HH}}=7.1$, 2H, ($\text{CH}_3\text{CH}_2\text{O}$)_B). / **$^{13}\text{C-NMR}$** 14.1 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 16.6 (d, $^3J_{\text{PC}}=5.5$, $\text{CH}_3\text{CH}_2\text{O}$), 22.6 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 27.5 (d, $^2J_{\text{PC}}=12.3$, $\text{CHBrCH}_2\text{CH}_2$), 31.0 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 32.5 (s, $\text{CHBrCH}_2\text{CH}_2$), 42.5 (d,

$^1J_{\text{PC}}=158.2$, $\underline{\text{CHBr}}$), 63.5 (d, $^2J_{\text{PC}}=7.2$, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{A}$), 63.8 (d, $^2J_{\text{PC}}=7.2$, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{B}$). / **m/z** (CI): 301 (M+1 ^{79}Br , 100), 303 (M+1 ^{81}Br , 100), 318 (M+18 ^{79}Br , 15), 320 (M+18 ^{81}Br , 15).

*Diethyl α -iodoethylphosphonate (4j)*⁶ $\text{C}_6\text{H}_{14}\text{O}_3\text{IP}$ (M=292) : **$^{31}\text{P-NMR}$** +23.3 (s). / **$^1\text{H-NMR}$** 1.19 (t, $^3J_{\text{HH}}=7.0$, 6H, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 1.84 (dd, $^3J_{\text{HH}}=7.4$, $^3J_{\text{PH}}=17.1$, 3H, CHICH_3), 3.72 (dq, $^2J_{\text{PH}}=9.8$, $^3J_{\text{HH}}=7.4$, 1H, $\underline{\text{CHI}}$), 4.03 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.2$, 4H, $\text{CH}_3\underline{\text{CH}_2\text{O}}$). / **$^{13}\text{C-NMR}$** 7.7 (d, $^1J_{\text{PC}}=155.9$, $\underline{\text{CHI}}$), 16.7 (d, $^3J_{\text{PC}}=5.4$, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 22.1 (s, CHICH_3), 63.8 (d, $^2J_{\text{PC}}=6.9$, $\text{CH}_3\underline{\text{CH}_2\text{O}}$). / **m/z** (CI): 293 (M+1, 100), 310 (M+18, 29).

Diethyl α -iodohexylphosphonate (4k) $\text{C}_{10}\text{H}_{22}\text{O}_3\text{IP}$ (M=348) : **$^{31}\text{P-NMR}$** +22.6 (s). / **$^1\text{H-NMR}$** 0.72 (t, $^3J_{\text{HH}}=5.9$, 3H, $\text{CH}_2\text{CH}_2\underline{\text{CH}_3}$), 1.13 (t, $^3J_{\text{HH}}=7.1$, 3H, $(\underline{\text{CH}_3\text{CH}_2\text{O}})_\text{A}$), 1.16 (t, $^3J_{\text{HH}}=7.1$, 3H, $(\underline{\text{CH}_3\text{CH}_2\text{O}})_\text{B}$), 1.30-2.40 (m, 8H, $\underline{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$), 3.30-3.65 (m, 1H, $\underline{\text{CHI}}$), 4.00 (dq, $^3J_{\text{PH}}=1.8$, $^3J_{\text{HH}}=7.1$, 2H, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{A}$), 4.03 (dq, $^3J_{\text{PH}}=1.8$, $^3J_{\text{HH}}=7.1$, 2H, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{B}$). / **$^{13}\text{C-NMR}$** 14.0 (s, $\text{CH}_2\text{CH}_2\underline{\text{CH}_3}$), 16.6 (d, $^3J_{\text{PC}}=5.9$, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 18.3 (d, $^1J_{\text{PC}}=154.1$, $\underline{\text{CHI}}$), 22.5 (s, $\text{CH}_2\underline{\text{CH}_2\text{CH}_3}$), 29.8 (d, $^2J_{\text{PC}}=12.7$, $\text{CHICH}_2\text{CH}_2$), 30.8 (s, $\underline{\text{CH}_2\text{CH}_2\text{CH}_3}$), 33.2 (s, $\text{CHICH}_2\underline{\text{CH}_2}$), 63.6 (d, $^2J_{\text{PC}}=8.2$, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{A}$), 63.8 (d, $^2J_{\text{PC}}=7.9$, $(\text{CH}_3\underline{\text{CH}_2\text{O}})_\text{B}$). / **m/z** (CI): 349 (M+1, 100).

Synthesis of diethyl 1-halogenobutylphosphonates 8 ; General procedure:

n-BuLi (20.6 mL of 1.6 M solution in hexane; 33 mmol) is added to THF (20 mL) and cooled to -78 °C. A solution of triethyl phosphate (1.82 g; 10 mmol) in THF (20 mL) is slowly added with return to 0°C. After 15 min. at 0°C, the reaction mixture is cooled to -78°C and a solution of *i*-Pr₂NH (1.21 g; 12 mmol) in THF (20 mL) is added *via* a dropping funnel. A solution of TMSCl (2.4 g; 22 mmol) in THF (20 mL) is slowly added. The resulting mixture is allowed to warm slowly to 0°C and cooled again to -78°C. The halogenating agent (11 mmol) in THF (20 mL) is slowly added. The resulting pale-yellow mixture is then left to warm to 0°C over a period of 15 min. At this temperature, 20 mL of a EtOLi/EtOH solution (1 M) is added and after 30 min. the deprotection is complete. The reaction mixture is then poured with rapid stirring into a mixture of 2 M HCl (15 mL), CH₂Cl₂ (15 mL) and crushed ice, then extracted with CH₂Cl₂ (2 x 20 mL) and the organic layers dried (MgSO₄). Filtration and evaporation yield the crude title compounds **8**. In the case of fluoro compounds, the crude is diluted with hexane (200 mL) to precipitate the benzenesulfonimide. All products can be purified further by distillation, according to previously described procedures.

*Diethyl α -fluorobutylphosphonate (8a)*⁵ $\text{C}_8\text{H}_{18}\text{O}_3\text{FP}$ (M=212) : **$^{31}\text{P-NMR}$** +18.8 (d, $^2J_{\text{PF}}=76.2$). / **$^{19}\text{F-NMR}$** -207.5 (d, $^2J_{\text{PF}}=76.2$). / **$^1\text{H-NMR}$** 0.92 (t, $^3J_{\text{HH}}=7.2$, $\text{CH}_2\text{CH}_2\underline{\text{CH}_3}$), 1.31 (t, $^3J_{\text{HH}}=7.1$, 6H, $\underline{\text{CH}_3\text{CH}_2\text{O}}$), 1.10-1.96 (m, 4H, $\underline{\text{CH}_2\text{CH}_2\text{CH}_3}$), 4.15 (p,

$^3J_{\text{PH}}=^3J_{\text{HH}}=7.1$, 2H, (CH₃CH₂O)_A), 4.17 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.1$, 2H, (CH₃CH₂O)_B), 4.69 (ddt, $^2J_{\text{PH}}=10.3$, $^3J_{\text{HH}}=3.1$, $^2J_{\text{FH}}=46.8$, 1H, CHF). / **¹³C-NMR** 13.9 (s, CH₂CH₂CH₃), 16.9 (d, $^3J_{\text{PC}}=5.4$, CH₃CH₂O), 19.0 (dd, $^3J_{\text{PC}}=3.7$, $^3J_{\text{FC}}=13.0$, CH₂CH₂CH₃), 32.4 (d, $^2J_{\text{FC}}=20.1$, CH₂CH₂CH₃), 63.4 (d, $^2J_{\text{PC}}=6.8$, (CH₃CH₂O)_A), 63.7 (d, $^2J_{\text{PC}}=6.7$, (CH₃CH₂O)_B), 89.0 (dd, $^1J_{\text{PC}}=169.9$, $^1J_{\text{FC}}=179.7$, CHF). / **m/z** (CI): 213 (M+1, 100), 230 (M+18, 26).

*Diethyl α-chlorobutylphosphonate (8b)*⁶ C₈H₁₈O₃ClP (M=228.5) : **³¹P-NMR** +21.3 (s). / **¹H-NMR** 0.76 (t, $^3J_{\text{HH}}=7.2$, 3H, CH₂CH₂CH₃), 1.17 (t, $^3J_{\text{HH}}=7.1$, 6H, CH₃CH₂O), 1.15-1.95 (m, 4H, CH₂CH₂CH₃), 3.67 (dt, $^2J_{\text{PH}}=10.6$, $^3J_{\text{HH}}=3.5$, 1H, CHCl), 4.01 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.4$, 2H, (CH₃CH₂O)_A), 4.04 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.4$, 2H, (CH₃CH₂O)_B). / **¹³C-NMR** 13.3 (s, CH₂CH₂CH₃), 16.6 (d, $^3J_{\text{PC}}=5.7$, CH₃CH₂O), 19.8 (d, $^3J_{\text{PC}}=12.3$, CH₂CH₂CH₃), 34.2 (s, CHClCH₂CH₂), 52.2 (d, $^1J_{\text{PC}}=160.2$, CHCl), 63.3 (d, $^2J_{\text{PC}}=6.4$, (CH₃CH₂O)_A), 63.7 (d, $^2J_{\text{PC}}=7.2$, (CH₃CH₂O)_B). / **m/z** (CI): 229 (M+1 ³⁵Cl, 100), 231 (M+1 ³⁷Cl, 40), 246 (M+18 ³⁵Cl, 43), 248 (M+18 ³⁷Cl, 13).

*Diethyl α-bromobutylphosphonate (8c)*⁶ C₈H₁₈O₃BrP (M=273) : **³¹P-NMR** +20.8 (s). / **¹H-NMR** 0.73 (t, $^3J_{\text{HH}}=7.4$, 3H, CH₂CH₂CH₃), 1.14 (t, $^3J_{\text{HH}}=7.1$, 6H, CH₃CH₂O), 1.08-2.00 (m, 4H, CH₂CH₂CH₃), 3.59 (dt, $^2J_{\text{PH}}=10.0$, $^3J_{\text{HH}}=3.6$, 1H, CHBr), 3.98 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.0$, 2H, (CH₃CH₂O)_A), 4.01 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.1$, 2H, (CH₃CH₂O)_B). / **¹³C-NMR** 13.2 (s, CH₂CH₂CH₃), 16.6 (d, $^3J_{\text{PC}}=5.5$, CH₃CH₂O), 21.0 (d, $^3J_{\text{PC}}=13.1$, CH₂CH₂CH₃), 34.4 (s, CHBrCH₂CH₂), 42.1 (d, $^1J_{\text{PC}}=158.0$, CHBr), 63.4 (d, $^2J_{\text{PC}}=6.6$, (CH₃CH₂O)_A), 63.7 (d, $^2J_{\text{PC}}=7.2$, (CH₃CH₂O)_B). / **m/z** (CI): 273 (M+1 ⁷⁹Br, 100), 275 (M+1 ⁸¹Br, 100), 290 (M+18 ⁷⁹Br, 18), 292 (M+18 ⁸¹Br, 18).

*Diethyl α-iodobutylphosphonate (8d)*⁶ C₈H₁₈O₃IP (M=320) : **³¹P-NMR** +22.5 (s). / **¹H-NMR** 0.75 (t, $^3J_{\text{HH}}=7.2$, 3H, CH₂CH₂CH₃), 1.17 (t, $^3J_{\text{HH}}=7.1$, 6H, CH₃CH₂O), 1.08-1.80 (m, 4H, CH₂CH₂CH₃), 3.59 (dt, $^2J_{\text{PH}}=10.9$, $^3J_{\text{HH}}=7.4$, 1H, CHI), 4.00 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.0$, 2H, (CH₃CH₂O)_A), 4.02 (p, $^3J_{\text{PH}}=^3J_{\text{HH}}=7.0$, 2H, (CH₃CH₂O)_B). / **¹³C-NMR** 13.1 (s, CH₂CH₂CH₃), 16.6 (d, $^3J_{\text{PC}}=5.5$, CH₃CH₂O), 18.0 (d, $^1J_{\text{PC}}=153.8$, CHI), 23.4 (d, $^3J_{\text{PC}}=13.4$, CH₂CH₂CH₃), 35.2 (s, CHICH₂CH₂), 63.5 (d, $^2J_{\text{PC}}=7.6$, (CH₃CH₂O)_A), 63.7 (d, $^2J_{\text{PC}}=6.6$, (CH₃CH₂O)_B). / **m/z** (CI): 321 (M+1, 100), 338 (M+18, 16).

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