A new route to α-fluoroalkylphosphonates

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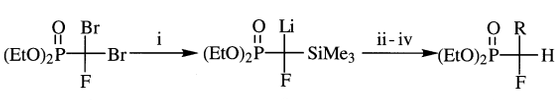
Several alkylated α-fluorophosphonates have been synthesized by the reaction of an alkyl iodide, bromide (or activated chloride) with a monofluorosilyllithium phosphonate species produced either from the reaction of butyllithium, phenyllithium or other alkyllithium reagent as base and trimethylsilyl chloride with a diethyl monofluoromethylphosphonate. A study of the reaction conditions with respect to the metallating agent, silylating agent and starting monofluorophosphonate has also been undertaken.

Phosphonates are becoming, slowly but certainly, complementary to phosphates in terms of biological activity.[1] One feature of phosphonates responsible for their success which has been largely exploited is the stability to hydrolysis of the P–C phosphonate linkage by chemical agents or by esterases. Further modification of the α-component of the phosphonate by the addition of an electronegative element such as fluorine can enable the closer mimicking of a phosphate in terms of the pK_a value of the second deprotonation of the phosphonate group. This pK_a value (6.4 for phosphate)[2] is thought to be important in the enzymatic binding of phosphate analogues. Furthermore, it has been shown that the pK_a value is closest to the parent phosphate for the monofluoromethylene phosphonate derivatives (pK_a = 6.5).[3] This modification should enhance the activity of phosphonates as phosphate mimics, as shown in a recent theoretical study,[4] and turn the synthesis of α-monofluorophosphonates into an important area of research[5] useful, for example, in the study of the glycolytic pathway.[6]

Following our previous work on the synthesis of α-fluorinated alkylphosphonates *via* the silylated lithio species **2**,[7] we investigated in further detail the nature and scope of this reaction with regard to the metallating species, silylating group, electrophilic species and starting fluoromethylphosphonate. We expected that these studies would give us an insight into the reactivity of our starting material (dibromofluoromethylphosphonate **1**) and provide a means of cleanly obtaining various α-fluorophosphonates **3**, with the minimum of preparation of reagents and laborious work-up procedures, and in high yield.

Results and discussion

Our previous work described the formation of the carbanion **2**, from the readily accessible (on a laboratory scale) diethyl 1,1-dibromo-1-fluoromethylphosphonate[8] **1** and butyllithium in the presence of trimethylsilyl chloride (TMSCl) used as a protecting group, and its subsequent reaction with an alkyl iodide to give monofluoroalkylphosphonates **3a–i** (Scheme 1).[7] The

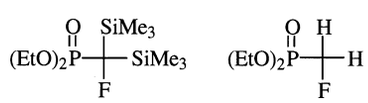


1 **2** **3a-i, 5**

Scheme 1 *Reagents and conditions:* i, BuLi (2 equiv.), TMSCl (1 equiv.), −78 °C, 10 min; for R ≠ H; ii, RI, −78 °C, 30 min; iii, LiOEt–EtOH, 0 °C, 10–30 min; iv, 2 M HCl, 0 °C (**3a–i**); for R = H ii, EtOH, −78–0 °C; iii, 2 M HCl, 0 °C **5**

preparation of the starting material **1** was again re-investigated with the aim of shortening the 12–15 day reaction time by accelerating the reaction. Diethyl dibromofluoromethylphosphonate **1** was synthesised by the reaction of triethyl phosphite and fluorotribromomethane in hexane, in sunlight at room temperature for 12–15 days. However, heating of the reaction mixture only resulted in many side-products being formed. Although for a reaction carried out in a quartz apparatus with a high-pressure mercury vapour lamp the reaction time was shorter (*ca.* 6 h), many side-products were still observed [δ ^{31}P (hexane) +11.7 (d), 6.1 (d), −1.1 (s), −8.5 (s)] and a large phosphate signal [δ ^{31}P (hexane) −0.5 (s)] appeared. A change in the wavelength of the light (use of a tungsten–halogen lamp) achieved slightly better results in that the reaction time was shorter (*ca.* 2 days), although again a large phosphate signal was observed; there were, however, few side-product signals. The use of azoisobutyronitrile (AIBN) as a radical initiator gave similar results to those obtained with the tungsten–halogen lamp. Thus, although the reaction time is long for the sunlight reaction we consider this to be the best method of synthesising **1** since there is little side-product or phosphate formation and essentially pure $(EtO)_2P(O)CFBr_2$ **1** is obtained on evaporation of the crude reaction mixture.

Next, we successively investigated the conditions for introduction of the protecting silyl group and the nature of the metallating agent in the alkylation shown in Scheme 1. Initially, we used trimethylsilyl chloride (TMSCl) in the reaction and found that 2 equiv. could be added without difficulty at low temperature to the carbanion resulting from a double lithium–bromine exchange to give an inert disilylated species **4** [δ ^{31}P



4 **5**

(THF) +24.5, J_{PF} 60.1]. On hydrolysis in THF using LiOEt–EtOH, **4** easily regenerates diethyl fluoromethylphosphonate **5** [δ ^{31}P (THF) +18.3]. The easy formation of **4** at low temperature demonstrates the enhanced nucleophilicity of the carbanion **2** compared to the analogous α-phosphorylated α-lithiated carbanion bearing H instead of F which slowly undergoes disilylation around 0 °C in the presence of an excess of TMSCl. By contrast, the steric hindrance with either a CH_3 or a Cl atom in the α position of an α-phosphorylated α-lithiated carbanion is a limiting factor and in these cases the unambiguous formation of a monosilylated compound is observed.[9]

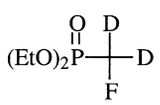
Thus, we realised that to avoid a decrease in yield due to the presence of unwanted fluoromethylphosphonate **5** (from ethanolysis of the simultaneously formed disilylated phosphorus species **4**), exactly 1 equiv. of TMSCl was required. We attempted to find a silyl reagent which would react only once with the carbanion resulting from the double lithium–bromine

Table 1 The reaction of alkyl iodides with **2** formed from BuLi, TMSCl and **1** (general procedure A)

Compound	R	Deprotection time/min	Yield (%)	Bp/°C (at 20 mmHg)
3a	Me	10	96	135–140
3b	Et	10	93	140–145
3c	Pr	10	96	145–150
3d	Bu	15	95	160–165
3e	CH_2=$CHCH_2$	10	91	165–170
3f	MeCH=$CHCH_2$	15	92	160–165
3g	C_5H_{11}	20	93	175–180
3h	$Cl(CH_2)_3$	20	87	195–200
3i	$C_{12}H_{25}$	30	88	195–200

exchange and could also be easily removed on hydrolysis under mild conditions. We found that *tert*-butyldimethylsilyl chloride (TBDMSCl) and triisopropylsilyl chloride (TIPSCl) added only once to the carbanion under the low-temperature conditions used. However, after alkylation of the two carbanions [δ ^{31}P (THF) +54.2, J_{PF} 100.8 for TBDMS carbanion and δ ^{31}P (THF) +53.4, J_{PF} 70.1 for TIPS carbanion] with propyl iodide we were unable to remove the silyl groups using either LiOEt–EtOH or LiOMe–MeOH in THF even at a higher reaction temperature. Furthermore, in the case of TBDMSCl, the monosilylated carbanion when heated added slowly a second equivalent of TBDMSCl to give an inert species [δ ^{31}P (THF) +21.7]. In conclusion, the advantages of TMSCl (economy, ease of introduction and ease of removal) outweighed the sole disadvantage of its high reactivity; it was, therefore, chosen as the best protecting group.

Direct quenching of the lithiated anion **2** with anhydrous EtOH gave **5** in 93% yield (see Scheme 1),[10] whereas quenching with EtO^2H gave the α,α-dideuteriated fluoromethylphosphonate **6** in 92% yield.



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The use of an alkyl iodide in Scheme 1 was necessary to avoid competing reactions between the lithiated carbanion **2** and the bromobutane (2 equiv.) formed as a co-product. This reaction at low temperature shows no competing side reactions which confirms the excellent nucleophilicity of **2**. These conditions enabled the synthesis of a range of alkylated monofluorophosphonates **3a**–**i** in high yields (see Table 1).

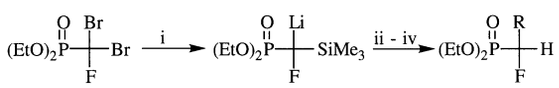
The conditions of removal of the TMS protecting group are important and failure to follow the procedure described here resulted in low yields or loss of product as a result of polymer formation. The TMS group was removed by adding a freshly prepared solution of LiOEt in EtOH (formed by the addition of lithium metal to anhydrous ethanol) to the reaction mixture at 0 °C. The reaction can be followed by ^{31}P NMR spectroscopy to ensure complete removal of the silicon group. The deprotection time was studied as a function of steric bulk of the alkyl group (R). We found that the length of time required for deprotection roughly correlated with the size of the alkyl group (see Table 1). The LiOEt was usually added in excess although we found that 1 equiv. of the reagent was sufficient to deprotect the silyl group; however, in each case the reaction was slightly slower due to higher dilution. After the deprotection was deemed to be complete the reaction mixture was poured into 2 M hydrochloric acid and stirred before extraction and distillation. We found that the reverse procedure, *i.e.* addition of acid to the reaction mixture, produced polymers after work-up and distillation. The halogen–metal exchange conditions, when modified by the use of phenyllithium instead of butyllithium, allowed use of alkyl bromides and activated alkyl chlorides as electrophilic reagents. Moreover, under these conditions it was possible to

Table 2 The reaction of alkyl bromides, iodides and activated chlorides with **2** formed from PhLi, TMSCl and **1** (general procedure B)

Compound	R	Deprotection time/min	Yield (%)
3a*	Me	10	80
3g	C_5H_{11}	20	79
3j	$Me_2CHCH_2CH_2$	20	65
3k	$C_{10}H_{21}$	30	69
3l	$PhCH_2$	10	78
3l†	$PhCH_2$	10	70

* From RI. † from RCl.

observe the carbanion **2**, which is stable at 0 °C, by ^{31}P NMR spectroscopy [δ ^{31}P (THF) +52.8, J_{PF} 67.2]. These reaction conditions become possible since the phenyl bromide side-product is unable to engage in an S_N2 type reaction with the carbanion **2**. We synthesized a variety of analogues **3a**,**g**,**j**–**l**, by this method in reasonable yield using simple work-up methodology involving a combination of filtration through silica with hexane which removes most of the PhBr, excess of RBr starting material and a small amount of biphenyl (formed from reaction of an excess of PhLi with PhBr) followed by distillation (Scheme 2). However, the use of phenyllithium was rather

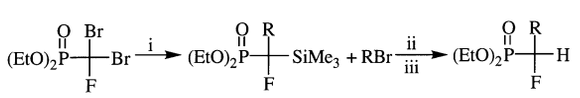


1 **2** **3a**,**g**,**j**-**l**

Scheme 2 *Reagents and conditions:* i, PhLi (2 equiv.), TMSCl (1 equiv.), −78 °C, 10 min; ii, RBr (RCl for **3l**, RI for **3a**), −78 °C, 30 min; iii, LiOEt–EtOH, 0 °C, 10–30 min; iv, 2 M HCl

disappointing because the elimination of phenyl bromide was always difficult and the yields suffered from the resulting purification problems (see Table 2).

Next we used an alkyllithium (RLi), prepared in Et_2O from an alkyl bromide and lithium metal, in place of BuLi or PhLi. This deliberately releases, in the reaction medium, 2 equiv. of alkyl bromide as side product on formation of the carbanion **2**. We can thus form the alkylated species **3a**,**d**,**g**,**j** relating to the alkyllithium (Scheme 3) by reaction of **2** with the liberated alkyl



1 **3a**,**d**,**g**,**j**

Scheme 3 *Reagents and conditions:* i, RLi (2 equiv.), TMSCl (1 equiv.), −78 °C, 30 min; ii, LiOEt–EtOH, −50 °C, 10–30 min; iii, 2 M HCl

bromide. Thus, methyllithium on reaction with dibromofluoromethylphosphonate **1** gives 1-fluoroethylphosphonate **3a** by condensation of the methyl bromide side product with **2**. To optimise the formation of the alkylated compound **3** it is important for the reaction to be carried out at <−50 °C. In this

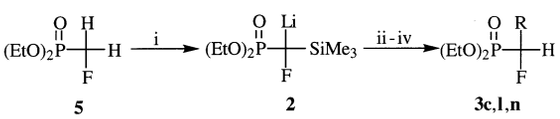
Table 3 The reaction of alkyllithiums with **1** and TMSCl (general procedure C)

Compound	R	Deprotection time/min	Yield (%)
3a	Me	10	64
3d	Bu	15	76
3g	C_5H_{11}	20	73
3j	iso-C_5H_{11}	20	68

Table 4 The reaction of alkyl bromides with **2** formed from LDA, TMSCl and **5** (general procedure D)

Compound	R	Deprotection time/min	Yield (%)
3c	Pr	10	85
3l	$PhCH_2$	10	87
3n	$Cl(CH_2)_3$	20	81

way, the products formed were essentially pure after work-up and were obtained in modest yield after distillation (64–76%). We also varied the starting phosphonate from dibromofluoromethylphosphonate **1** to fluoromethylphosphonate **5** to compare the behaviour of this reagent towards different bases and electrophiles. Compound **5** was obtained from reaction of the

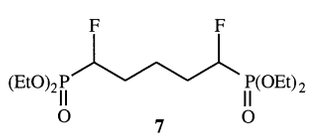


5 **2** **3c**,**l**,**n**

Scheme 4 *Reagents and conditions:* i, LDA (2 equiv.), TMSCl (1 equiv.), THF, −78 °C, 10 min; ii, RBr, −78 °C, 30 min; iii, LiOEt–EtOH, 0 °C, 10–30 min; iv, 2 M hydrochloric acid, 0 °C

carbanion **2** on treatment with LiOEt–EtOH as described before (see Table 1).

We found that **5** did not react cleanly with butyllithium and gave products resulting from P–C bond fragmentation. However, **5** reacted well with lithium diisopropylamide (LDA), LiHMDS and phenyllithium, and we chose to perform the reaction with LDA. The silylated carbanion **2** was formed from reaction between **5**, 1 equiv. of TMSCl and 2 equiv. of LDA in THF at −78 °C. The process was similar to that described above with the dibromofluoromethylphosphonate starting material **1**. The carbanion **2** reacted at low temperature with a range of alkyl bromides to give a series of alkylated monofluorophosphonates, **3c**,**l**,**n**, as shown in Table 4. The carbanion **2** on reaction with 1 equiv. of 1,3-dibromopropane gave a mixture of mono- **3** and bis-phosphonate **7**. For this reason, the reaction was then conducted with 0.5 equiv. of 1,3-dibromopropane in order to orientate the alkylation towards the formation of the tetraalkyl 1,5-difluoropentane-1,5-diylbis(phosphonate) **7** (67%).



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Conclusions

The above reactions illustrate the ease with which many varied alkyl substituted α-fluoroalkylphosphonates can be prepared by several different, high-yielding methods; indeed, since our last publication[7] one of the above methods has been used to synthesise several biologically important phosphonates.[11] The careful choice of method should enable the synthesis of more elaborate monofluorophosphonates in high yield and with simple work-up procedures. As outlined above, care must be taken with the silyl reagent used to ensure that no more than 1 equiv. of reagent is used to give the maximum yield of product. Moreover, deprotection of the silyl group has also been shown to be a delicate procedure and must be performed with care in order not to affect the yields.

Experimental

NMR Spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for ^{1}H, 50.3 MHz for ^{13}C and 81.01 MHz for ^{31}P; ^{31}P downfield shifts (δ) are expressed with a positive sign, in ppm, relative to external 85% H_3PO_4 in water. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to $CDCl_3$ as internal standard. Coupling constants (J) are given in Hz. The following abbreviations are used: s, d, t, q, p, m for singlet, doublet, triplet, quartet, pentet and multiplet, respectively. Gas chromatography was performed on a Hewlett-Packard 5890 gas spectrometer with an SGE BPX (25M × 0.22 mm) column using splitless injection and a helium gas vector at 1 ml min^{-1}. Low-resolution mass spectra were recorded on a Hewlett-Packard 5898 B mass spectrometer. High-resolution mass spectra were recorded on VG ZAB-HSQ or Bruker CMS 47X ICR FT mass spectrometers. 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 were carried out under dry nitrogen.

Diethyl 1-fluoro-1-alkylmethylphosphonates

General procedure A. To a solution of BuLi (1.6 M solution in hexane; 13.75 ml, 22 mmol, 2.2 equiv.) in THF (30 ml) cooled to −78 °C was added a mixture of diethyl 1,1-dibromo-1-fluoromethylphosphonate (3.28 g, 10 mmol) and TMSCl (1.08 g, 10 mmol) in THF (10 ml) *via* a dropping funnel, the temperature being maintained at −78 °C. The reaction mixture was stirred at this temperature for 10 min after which the alkyl iodide (15 mmol) in THF (10 ml) was slowly added *via* a dropping funnel. The reaction mixture was then stirred at −78 °C for 30 min before it was allowed to warm to 0 °C by removal of the cooling bath. A freshly prepared solution of lithium ethoxide obtained by adding lithium metal (15–20 mmol) to anhydrous ethanol (15 ml) was then added to the reaction mixture after which it was stirred for 10–30 min at 0 °C; it was then poured into a beaker of 2 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to yield an oil which on distillation (bulb-to-bulb apparatus) gave the title compounds as mobile oils.

General procedure B. The procedure was similar to that described above except that instead of BuLi, phenyllithium (1.5 M solution in cyclohexane–ether; 14.7 ml, 22 mmol, 2.2 equiv.) was used and, instead of an alkyl iodide, an alkyl bromide (or activated alkyl chloride) was added after carbanion formation (15 mmol); the resulting oil was filtered through a silica plug (hexane–CH_2Cl_2–MeOH) before distillation.

General procedure C. The procedure was similar to that described above except that an alkyllithium (such as methyl-, butyl-, pentyl- or hexyl-lithium) (2.2 equiv.) was used without addition of an alkyl halide. The reaction was initially carried out at −78 °C and the mixture stirred at this temperature for 40 min before being allowed to warm to −50 °C prior to treatment with LiOEt–EtOH; subsequent work-up was as described above.

General procedure D. To a solution of BuLi (1.6 M solution in hexane; 13.75 ml, 22 mmol, 2.2 equiv.) was added, at −20 °C, diisopropylamine (2.42 g, 24 mmol) in THF (30 ml). To the thus formed LDA, cooled to −78 °C, was added a mixture of diethyl 1-fluoromethylphosphonate (1.70 g, 10 mmol) and TMSCl (1.08 g, 10 mmol) in THF (10 ml) *via* a dropping funnel, the temperature being maintained at −78 °C. The reaction mixture

was stirred at this temperature for 10 min after which the alkyl bromide (15 mmol) in THF (10 ml) was slowly added *via* a dropping funnel. The reaction mixture was then stirred at −78 °C for 30 min before being allowed to warm to 0 °C by removal of the cooling bath. A freshly prepared solution of lithium ethoxide obtained by adding lithium metal (15–20 mmol) to anhydrous ethanol (15 ml) was then added to the reaction mixture, after which it was stirred for 10–30 min at 0 °C before being poured into a beaker of 2 M hydrochloric acid. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to yield an oil which was dissolved in diethyl ether and filtered before distillation (bulb-to-bulb apparatus) to give the title compounds as mobile oils.

Diethyl 1-fluoroethylphosphonate 3a. NMR ($CDCl_3$) ^{31}P 19.3 (d, *J* 73.8); ^{1}H 1.38 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 1.6 (ddd, 3 H, *J* 17, 6, 25, $PCCH_3$), 4.07–4.32 (m, 4 H, OCH_2) and 4.87 (ddq, 1 H, *J* 3, 6, 47, PCHF); ^{13}C (JMOD) 15.68–16.51 (m, $PCCH_3$, OCH_2CH_3), 62.69–63.24 (m, OCH_2) and 85.19 (t, *J* 189, PCHF); *m*/*z* (EI) 184 (M^+, 2%), 157 (27), 137 (28) and 129 (21) (Found: C, 39.08; H, 7.65. Calc. for $C_6H_{14}FO_3P$: C, 39.14; H, 7.66%).

Diethyl 1-fluoropropylphosphonate 3b. NMR ($CDCl_3$) ^{31}P 18.6 (d, *J* 76.0); ^{1}H 1.00 (t, 3 H, *J* 7, CH_2CH_3), 1.26 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 1.7–2.0 (m, 2 H, CH_2), 4.10 (m, 4 H, 2 × OCH_2) and 4.55 (m, 1 H, PCHF); ^{13}C 9.1 (dd, *J* 12.4, 4.8, CH_2CH_3), 15.8 (d, *J* 4.9, CH_3CH_2O), 23.1 (d, *J* 20.8, CH_2CH_3), 62.2 (dd, *J* 19.3, 6.6, OCH_2) and 89.4 (dd, *J* 179.6, 169.9, PCHF); *m*/*z* (EI) 199 (M^+ + 1, 57%), 183 (73), 171 (79) and 170 (100) (Found: C, 42.34; H, 8.12. Calc. for $C_7H_{16}FO_3P$: C, 42.43; H, 8.14%).

Diethyl 1-fluorobutylphosphonate 3c. NMR ($CDCl_3$) ^{31}P 19.0 (d, *J* 75.5); ^{1}H 0.92 (t, 3 H, *J* 7, CH_2CH_3), 1.2–1.5 (m, 8 H, 2 × OCH_2CH_3, CH_2CH_3), 1.7–2.0 (m, 2 H, $PCCH_2$), 4.05–4.32 (m, 4 H, 2 × OCH_2) and 4.7–5.05 (m, 1 H, PCHF); ^{13}C 13.57 (CH_3), 16.21 (CH_3CH_2O), 18.45 (d, *J* 13.49, CH_2), 31.80 (d, *J* 20.09, CH_2), 62.35–63.27 (m, OCH_2) and 88.3 (dd, *J* 179.8, 170.4, PCHF); *m*/*z* (EI) 213 (M^+ + 1, 6%), 185 (10), 183 (19) and 170 (100) (Found: C, 45.10; H, 8.53. Calc. for $C_8H_{18}FO_3P$: C, 45.28; H, 8.55%).

Diethyl 1-fluoropentylphosphonate 3d. NMR ($CDCl_3$) ^{31}P 18.8 (d, *J* 75.7); ^{1}H 0.89 [t, 3 H, *J* 6.8, $(CH_2)_3CH_3$], 1.2–1.6 [m, 10 H, 2 × OCH_2CH_3, $(CH_2)_2CH_3$], 1.7–2.0 (m, 2 H, $PCCH_2$), 4.05–4.28 (m, 4 H, 2 × OCH_2) and 4.5–4.9 (m, 1 H, PCHF); ^{13}C (JMOD) 14.85 [$(CH_2)_3CH_3$], 17.58 (OCH_2CH_3), 23.34 (CH_2), 23.34 (CH_2), 26.46 (d, *J* 12, CH_2), 30.76 (d, *J* 20, CH_2), 63.62–64.66 (m, OCH_2) and 89.90 (t, *J* 189, PCHF); *m*/*z* (EI) 227 (M^+ + 1, 3%), 211 (9), 183 (22) and 170 (100) (Found: C, 47.72; H, 8.89. Calc. for $C_9H_{20}FO_3P$: C, 47.78; H, 8.91%).

Diethyl 1-fluorobut-3-enylphosphonate 3e. NMR ($CDCl_3$) ^{31}P 18.0 (d, *J* 74.2); ^{1}H 1.35 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 2.5–2.8 (m, 2 H, $CFCH_2$), 4.21 (m, 4 H, 2 × OCH_2), 4.72 (m, 1 H, PCHF), 5.18 (m, 2 H, $=CH_2$) and 5.84 (m, 1 H, =CH); ^{13}C (JMOD) 15.61 (OCH_2CH_3), 33.98 (d, *J* 20, CH_2CH), 62.01–62.90 (m, OCH_2), 67.20 (dd, *J* 180, 171, PCHF), 112.28 ($=CH_2$) and 131.55 (d, *J* 13.4, =CH); *m*/*z* (EI) 210 (M^+, 6%), 183 (28), 166 (33) and 138 (75) (Found: C, 45.70; H, 7.66. Calc. for $C_8H_{16}FO_3P$: C, 45.72; H, 7.67%).

Diethyl 1-fluoropent-3-enylphosphonate 3f. NMR ($CDCl_3$) ^{31}P 18.3 (d, *J* 75.9); ^{1}H 1.35 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 1.67 (t, 3 H, *J* 7, CH_3), 2.25–2.75 (m, 2 H, $CFCH_2$), 4.19 (m, 4 H, 2 × OCH_2), 4.7 (m, 1 H, PCHF) and 5.43–5.72 (m, 2 H, 2 × =CH); ^{13}C (JMOD) 16.12 (OCH_2CH_3), 17.55 ($CHCH_3$), 33.03, 33.43 (d, *J* 20, CH_2CH), 62.29–63.26 (m, OCH_2), 67.90 (dd, *J* 180, 171, PCHF), 127.35 (CH=) and 128.91 (CH=); *m*/*z* (EI) 224 (M^+, 25%), 204 (18), 170 (30) and 138 (59) (Found: C, 48.10; H, 8.06. Calc. for $C_9H_{18}FO_3P$: C, 48.21; H, 8.09%).

Diethyl 1-fluorohexylphosphonate 3g. NMR ($CDCl_3$) ^{31}P 19.0 (d, *J* 74.9); ^{1}H 0.9 (t, 3 H, *J* 6, CH_2CH_3), 1.1–2.2 [m, 8 H, $(CH_2)_4$], 1.35 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 4.1–4.32 (m, 4 H, 2 × OCH_2) and 4.52–4.91 (m, 1 H, PCHF); ^{13}C (JMOD) 13.69 (CH_3), 16.15 (OCH_2CH_3), 22.23 (CH_2), 24.89 (m, CH_2), 29.89 (d, *J* 20, CH_2), 31.09 (CH_2), 62.36–63.4 (m, OCH_2) and 66.54 (dd, *J* 181, 169, PCHF); *m*/*z* (EI) 241 (M^+ + 1, 3%), 211 (37), 183 (26) and 170 (100) (Found: C, 49.81; H, 9.20. Calc. for $C_{10}H_{22}FO_3P$: C, 49.99; H, 9.23%).

Diethyl 1-fluoro-4-chlorobutylphosphonate 3h. NMR ($CDCl_3$) ^{31}P 18.0 (d, *J* 76.7); ^{1}H 1.36 (t, 6 H, *J* 6.5, 2 × OCH_2CH_3), 1.83–2.35 (m, 4 H, 2 × CH_2), 3.60 (t, 2 H, *J* 7, CH_2Cl), 4.22 (m, 4 H, 2 × OCH_2) and 4.71 (m, 1 H, PCHF); ^{13}C 16.5 (d, *J* 5.0, CH_3CH_2O), 27.6 (d, *J* 20.2, $PCHFCH_2CH_2$), 28.4 (dd, *J* 13.0, 3.7, $PCHFCH_2$), 44.2 (s, CH_2Cl), 63.0 (dd, *J* 17.4, 6.8, OCH_2) and 88.2 (dd, *J* 180.1, 170.9, PCHF); *m*/*z* (EI) 247 (M^+ + 1, ^{35}Cl, 2%), 211 (93), 183 (40) and 173 (^{35}Cl, 23) (Found: C, 39.01; H, 6.96. Calc. for $C_8H_{17}FClO_3P$: C, 38.96; H, 6.95%).

Diethyl 1-fluorotridecylphosphonate 3i. NMR ($CDCl_3$) ^{31}P 18.2 (d, *J* 76.7); ^{1}H 0.7–0.9 (m, 3 H, CH_3), 1.1–1.35 (m, 26 H, 2 × OCH_2CH_3, 10 × CH_2), 1.6–2.0 (m, 2 H, CH_2), 4.0–4.28 (m, 4 H, 2 × OCH_2) and 4.45–4.7 (m, 1 H, PCHF); ^{13}C (JMOD) 13.97 (CH_3), 16.28 (OCH_2CH_3), 22.64 (CH_2), 25.13 (CH_2), 25.37 (CH_2), 29.07 (CH_2), 29.35 (CH_2), 29.53 (CH_2), 29.62 (CH_2), 29.82 (CH_2), 30.22 (CH_2), 31.90 (CH_2), 62.45–62.99 (m, OCH_2) and 88.65 (dd, *J* 180, 170, PCHF); *m*/*z* (EI) 339 (M^+ + 1, 5%), 309 (2), 211 (14) and 170 (41) (Found: C, 60.10; H, 10.71. Calc. for $C_{17}H_{36}FO_3P$: C, 60.33; H, 10.72%).

Diethyl 1-fluoro-4-methylpentylphosphonate 3j. NMR ($CDCl_3$) ^{31}P 16.4 (d, *J* 63.7); ^{1}H 0.7–0.92 [d, 6 H, *J* 6, $CH(CH_3)_2$], 1.09–1.6 [m, 3 H, CH_2, $CH(CH_3)_2$], 1.35 (t, 6 H, *J* 6, 2 × OCH_2CH_3), 1.7–2.0 (m, 2 H, $PCCH_2$), 4.05–4.28 (m, 4 H, 2 × OCH_2) and 4.5–4.9 (m, 1 H, PCHF); ^{13}C (JMOD) 16.54 (OCH_2CH_3), 22.42 (CH_3), 22.57 (CH_3), 27.66 (CH), 28.2 (d, *J* 20, CH_2), 34.9 (d, *J* 12, CH_2), 62.61–63.35 (m, OCH_2) and 89.2 (dd, *J* 180, 170, PCHF); *m*/*z* (EI) 241 (M^+ + 1, 8%), 225 (20), 197 (13) and 170 (100) (Found: C, 49.95; H, 9.22. Calc. for $C_{10}H_{22}FO_3P$: C, 49.99; H, 9.23%).

Diethyl 1-fluoroundecylphosphonate 3k. NMR($CDCl_3$) ^{31}P 18.7 (d, *J* 76); ^{1}H 0.9 (t, 3 H, *J* 7, CH_2CH_3), 1.14–1.56 [m, 22 H, 2 × OCH_2CH_3, $(CH_2)_8CH_3$], 1.77–2.04 (m, 2 H, $PCCH_2$), 4.13–4.36 (m, 4 H, 2 × OCH_2) and 4.36–4.55 (m, 1 H, PCHF); ^{13}C (JMOD) 14.17 (CH_3), 16.49 (OCH_2CH_3), 22.61 (CH_2), 25.29 (CH_2), 22.55 (CH_2), 29.23 (CH_2), 29.50 (CH_2), 29.70 (CH_2), 30.01 (CH_2), 30.41 (CH_2), 32.06 (CH_2), 62.70–63.25 (m, OCH_2) and 88.86 (dd, *J* 180, 170, PCHF); *m*/*z* (EI) 311 (M^+ + 1, 4%), 281 (3), 211 (10) and 170 (45) (Found: C, 57.82; H, 10.35. Calc. for $C_{15}H_{32}FO_3P$: C, 58.04; H, 10.39%).

Diethyl 1-fluoroethyl-2-phenylphosphonate 3l. NMR ($CDCl_3$) ^{31}P 15.5 (d, *J* 76); ^{1}H 1.35–1.48 (m, 6 H, 2 × OCH_2CH_3), 3.02–3.32 (m, 2 H, $PhCH_2$), 4.05–4.32 (m, 4 H, 2 × OCH_2) and 4.7–5.05 (m, 1 H, PCHF); ^{13}C 16.53–16.66 (m, OCH_2CH_3), 36.61 (d, *J* 2.8, $PhCH_2$), 62.91–63.66 (m, OCH_2), 89.2 (dd, *J* 169, 183, PCHF), 127.15 (Ph), 128.7 (Ph), 129.4 (Ph) and 136.5 (Ph); *m*/*z* (EI) 261 (M^+ + 1, 1%), 240 (18), 187 (12) and 138 (38) (Found: C, 55.43; H, 6.99. Calc. for $C_{12}H_{18}FO_3P$: C, 55.38; H, 6.97%).

Diethyl 1-fluoro-1,1-bis(trimethylsilyl)methylphosphonate 4. NMR ($CDCl_3$) ^{31}P 22.2 (d, *J* 60); ^{1}H 0.22 [2s, 18 H, 2 × $Si(CH_3)_3$], 1.32 (t, 6 H, *J* 7.1, 2 × OCH_2CH_3) and 4.14 (p, 4 H, *J* 7.1, 2 × OCH_2); ^{13}C −0.7 [3s, $Si(CH_3)_3$], 16.9 (d, *J* 6.3, OCH_2CH_3) and 62.5 (d, *J* 7.3, OCH_2); *m*/*z* (EI) 314 (M^+, 0.5%), 257 (18), 219 (20) and 153 (56).

Diethyl 1-fluoromethylphosphonate 5. NMR ($CDCl_3$) ^{31}P 17.0 (d, *J* 63.5); ^{1}H 1.20 (t, 6 H, *J* 7.1, 2 × OCH_2CH_3), 4.04 (qd, 4 H, 8.1, 7.1, 2 × OCH_2) and 6.08 (dd, 2 H, *J* 46.9, 4.7, $PCFH_2$); ^{13}C 16.0 (d, *J* 4.8, OCH_2CH_3), 22.1 (d, *J* 6.1, OCH_2), 76.2 (dd, *J* 179.9 and 169.2, $PCFH_2$); *m*/*z* (EI) 171 (M^+ + 1, 2%), 155 (6), 143 (71) and 137 (28).

Diethyl 1,1-dideuterio-1-fluoromethylphosphonate 6. NMR ($CDCl_3$) ^{31}P 17.6 (d, *J* 63.8); ^{1}H 1.1–1.45 (m, 6 H, 2 × OCH_2CH_3) and 3.9–4.2 (m, 4 H, 2 × OCH_2); ^{13}C 16.12–16.21, (m, OCH_2CH_3) and 62.66–62.78 (m, OCH_2); $PCFD_2$ not

apparent (weak signal); *m*/*z* (EI) 173 ($M^+ + 1$, 2%), 157 (6), 145 (70) and 137 (26) [HRMS: Found ($M^+ - 1$), 171.0577. Calc. for $C_5H_{10}D_2FO_3P$ ($M - 1$), 171.0550].

Tetraethyl 1,5-difluoropentane-1,5-diylbis(phosphonate) 7. NMR ($CDCl_3$) ^{31}P 17.90 (d, *J* 75.5); ^{1}H 1.34 (t, 12 H, *J* 7.1, 4 × OCH_2CH_3), 1.7–2.1 (m, 6 H, 3 × CH_2), 4.18 (pd, 8 H, *J* 7.1, 3.7, 4 × OCH_2) and 4.7 (dm, 2 H, 2 × PCHF); ^{13}C 16.6 (d, *J* 5.1, OCH_2CH_3), 21.5 (tm, *J* 13.3, PCHF−CH_2CH_2), 29.7 (dd, *J* 20.0, 3.0, PCHF−CH_2), 63.2 (dd, *J* 18.2, 6.5, OCH_2) and 88.6 (dd, *J* 180.4, 170.4, PCHF); *m*/*z* (EI) 381 ($M^+ + 1$, 2%), 307 (5), 279 (7) and 243 (100) (Found: C, 40.96; H, 7.40. Calc. for $C_{13}H_{28}F_2O_6P_2$: C, 41.06; H, 7.42%).

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