ELSEVIER

Journal of Organometallic Chemistry 529 (1997) 267–278

Journal of Organometallic Chemistry

A useful magnesium reagent for the preparation of 1,1-difluoro-2-hydroxyphosphonates from diethyl bromodifluoromethylphosphonate via a metal–halogen exchange reaction

Rachel Waschbüsch, Mohammad Samadi, Philippe Savignac *

Hétéroéléments et Coordination, URA CNRS 1499, DCPH, Ecole Polytechnique, 91128 Palaiseau Cedex, France

Received 11 March 1996; revised 20 May 1996

Abstract

When $(EtO)_2P(O)CF_2Br$ (**1**) is treated with isopropylmagnesium chloride in THF at low temperature it gives a magnesium species (**2**) which undergoes reactions with strong electrophiles (HCl, TMSCl, halogens, aldehydes and ketones). The formation of products depends strongly on the reaction conditions. With 1.5 equivalents of **2** between −78 and 0 °C, a conversion of more than 90% of aldehydes and ketones into 2-hydroxyphosphonates (**7** and **8**) can be achieved. These compounds (**7** and **8**) in the presence of base (NaH, LDA) are rearranged into 2,2-difluoroethylphosphates without concomitant formation of 1,1-difluoroolefines.

Keywords: Isopropylmagnesium chloride; Metal–halogen exchange; Bromodifluorophosphonate; 1,1-Difluoro-2-hydroxyphosphonate; Halogen; Phosphoric acid

1. Introduction

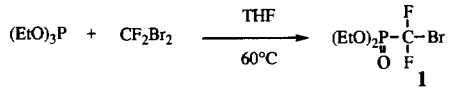
The metal–halogen exchange reaction is a valuable tool in organic synthesis, since it can be performed under mild conditions and usually with great efficiency [1]. In the chemistry of phosphonates we started to make use of the metal–halogen reaction with diethyl trichloromethylphosphonate, which has been tested as a representative compound [2–12]. The successive exchange reactions of the three chlorine atoms by treatment with butyllithium and an appropriate electrophile in THF was used for the synthesis of functionalized phosphonates without any complications. With the use of isopropylmagnesium chloride the same trichloromethyl phosphonate can undergo the exchange reaction of only one chlorine atom to give the desired diethyl dichloromethylphosphonate [13]. To our knowledge it is still the best method for obtaining pure dichloromethylphosphonate in high yield. As we were developing the metal–halogen reaction as a synthetic tool, we became interested in the extension of the reductive dehalogenation reaction to diethyl bromodifluoromethylphosphonate (**1**) as well as in exploiting the synthetic potential of the magnesium species. Such a metal–bromine exchange reaction had already been performed on this reagent with Li, Zn and Cd as metal [14–27], we chose to perform it with Mg under mild conditions.

2. Results

Our study anticipated an easy access to diethyl bromodifluoromethylphosphonate (**1**). This reagent was first prepared by Burton and Flynn [28] via a Michaelis–Arbuzov type reaction from dibromodifluoromethane (CF_2Br_2) and triethylphosphite ($(EtO)_3P$) in refluxing Et_2O; a long reaction time was required (24 h). Later the same reaction was reported as "a violent reaction which blew out the addition funnel, nitrogen inlet and stopper. This explosion could be controlled by running the reaction in a steel bomb" [29].

* Corresponding author.

PII S0022-328X(96)06541-2

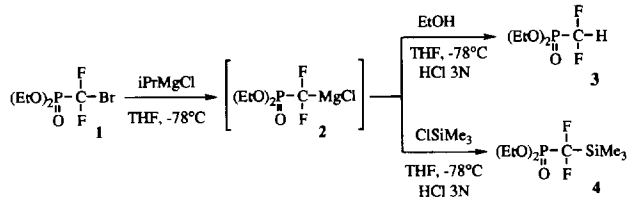


Scheme 1.

For our part we found that the synthesis of **1** could be achieved on a molar scale and in safe conditions by slow addition of pure $(EtO)_3P$ to a solution of CF_2Br_2 in refluxing THF. Under these conditions CF_2Br_2 reacts readily, cleanly and quantitatively with $(EtO)_3P$. A ^{31}P NMR spectroscopic investigation of the reaction mixture revealed that half an hour after the end of the addition $(EtO)_3P$ was no longer detected and the only phosphorus species observed in the reaction mixture was diethyl bromodifluoromethylphosphonate (**1**) (δ ^{31}P (THF) −0.4). A number of 1,1,1-trihalogenated phosphonates have been conveniently prepared according to this process, which can be connected unambiguously to the Michaelis–Arbuzov reaction [30–39]. However, among all the mechanistic pathways which are believed to be involved (ionic, radical and mono-electronic transfer), only the halophylic substitution (S_NCl^+) has been retained as the major contribution [40] (Scheme 1).

Satisfied with the preparation of **1**, which was repeated with equal success several times, we decided to examine its reactivity. Diethyl bromodifluoromethylphosphonate (**1**) was treated at low temperature in THF with 1.1 equivalents of ^{i}PrMgCl. The magnesium–bromine exchange reaction was complete and the resultant magnesium compound **2** was obtained as a colorless, clear solution which could be stored at low temperature without any change. It is well known that diethyl lithiodifluoromethylphosphonate has to be kept at low temperature to prevent the thermal dissociation of the anion [27,41] when by contrast the organocadmium and organozinc reagents are remarkably stable at room temperature [14,21]. The organomagnesium has an intermediate thermal stability. Effectively, when a cold solution of **2** in THF was slowly heated, the solution remained colorless until −40 °C and then turned progressively brown. This transformation was monitored by following the change in the ^{31}P NMR spectra of samples taken at various temperatures from −40 °C and hydrolysed in acidic medium. They revealed a decreasing intensity of the triplet corresponding to **3**, indicating a slow decomposition of the magnesium species **2**.

The reactions of **2** were necessarily conducted at low temperature in order to prevent the anticipated decomposition. **2** reacts only with strong electrophiles such as aldehydes, ketones, halogens, chlorosilanes and mineral acid. This restricted reactivity is due to the poor nucleophilicity of the highly stabilized anion, which moreover is thermally unstable above −40 °C. Therefore, it seemed necessary to find out how the reaction conditions influenced yields and reactivities. Firstly we decided to examine two good electrophiles, the proton and chlorotrimethylsilane.

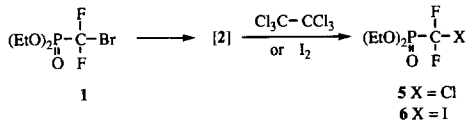


Scheme 2.

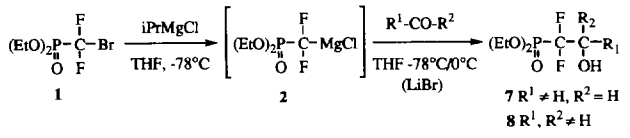
The production of diethyl difluoromethylphosphonate (**3**) depended strongly on the proton source. H_2O protonated the magnesium species **2** with only a reasonable yield (75%). It was clear that the strongly electron-withdrawing difluoro group activated considerably the phosphoryl group, which is very sensitive to nucleophilic attack [41]. A fast reaction with the electrophile at low temperature was required, and thus the use of a dilute hydrochloric acid solution was preferred.

The complete conversion of **2** to **3** on a preparative scale was achieved by pouring at low temperature a solution of **2** into a cold, stirred biphasic mixture of 3 M hydrochloric acid and CH_2Cl_2; under these conditions **3** could be isolated in a pure form and in good yield (85%). With chlorotrimethylsilane, the magnesium reagent **2** also underwent complete conversion into a silylated compound, to give **4** in excellent yield (90%) after treatment in acidic medium (Scheme 2).

To obtain a further insight into the synthetic potential of the magnesium species **2**, we also examined the reactivity of **2** with halogens (I_2) and halogenating agents (C_2Cl_6). With iodine in THF at low temperature iodination remained the main reaction (δ ^{31}P (THF) −1.4) (80%), but two by-products could be detected; we assumed that these compounds were **3** (δ ^{31}P 4.9) and the difluoromethyl bis(diethylphosphonate) (δ ^{31}P (THF) 3.4). After acidic work-up at low temperature, iododifluoromethylphosphonate (**6**) was isolated and purified by distillation (48%). With hexachloroethane at low temperature, formation of chlorodifluoromethylphosphonate was the main reaction, and the synthesis of **5** could be achieved with reasonable yield (60%). This method of preparation of **5** and **6** is the most practical, because attempts to prepare the compounds by reaction of Cl^- or I^- with **1** would give only dealkylation products by attack of the nucleophile on the phosphonate esters (Scheme 3).



Scheme 3.



Scheme 4.

With aldehydes [42–44], the reaction parameters that we chose to study were stoichiometry, temperature, reaction time and effect of lithium salts. The metallation time was 5 min at −78 °C in THF. The variation in stoichiometry **2**:aldehydes was tested for 1:1.1 and 1.5:1, the temperatures were −78 to 0 °C for 1 h and 0 °C to room temperature for an additional hour; in addition some of the experiments were run under the influence of electrophilic assistance by lithium bromide in order to facilitate the condensation. The composition of the crude reaction mixture was determined by ^{31}P and ^{1}H NMR spectroscopy (Scheme 4).

The addition of an aldehyde to **2** in stoichiometric ratio led to two phosphorus products, **7** and **3**, and unreacted aldehyde detected by ^{1}H NMR. For example, the 1,1-difluoro-2-hydroxyethylphosphonates **7e** and **7g** (Table 1) were isolated after treatment in acidic medium with 70% and 60% yields respectively. The amount of 1,1-difluoro-2-hydroxyphosphonate (**7**) was strongly dependent on the quantity of magnesium species **2**. The increase in amount of **2** (1.5 equiv.) led to a mixture of 1,1-difluoro-2-hydroxyethylphosphonate (**7**) with **3**, the ratios of which are dependent on the reaction conditions, but without any trace of aldehyde. With these new conditions the previously prepared 1,1-difluoro-2-hydroxyethylphosphonates **7e** and **7g** were isolated with 85% and 96% yields respectively (Table 1). With regard to these results, there is an increase in the yield of **7** with increasing number of equivalents of **2**. These conditions were extended to a large class of aldehydes, aliphatic, aromatic and heteroaromatic, and the results of these experiments are summarised in Table 2.

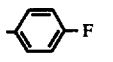
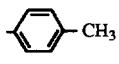
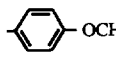
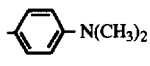
Increasing the time of reaction between **2** and aldehydes led to a cleaner reaction, but omitting the heating step between 0 °C and room temperature had a negative effect, since formation of a third compound (**13**) took place. This was detected by ^{31}P NMR spectroscopy (δ ^{31}P (THF) +3.4) and isolated by hydrolysing the reaction mixture at an early stage. After column chromatography, a mixture of **7** and **13** with **13** as the minor product was obtained. Trituration with hexane allowed **13**, contaminated with a small amount of **7**, to be obtained. Thus **13** was attributed to difluoromethyl bis-(diethylphosphonate) in accordance with ^{19}F NMR spectroscopy (δ ^{19}F ($CDCl_3$) 122.0 (t, ^{2}J(P–F) = 87.6)) and mass spectrum (m/z (IE) 324).

Performing the reaction between **2** and aldehydes in the presence of LiBr, in stoichiometric ratio, had a beneficial effect since the amount of 1,1-difluoro-2-hydroxyphosphonates (**7**) did not decrease by running the reaction at −40 °C instead of −78 °C. This is particularly obvious in the case of 4-methoxybenzaldehyde (Table 1 and Fig. 1), where the presence of LiBr made the formation of product **7g** easier, whereas decomposition mainly took place at the same temperature (−40 °C) in the absence of LiBr.

Table 1
Effect of LiBr on the reaction of **2** with 4-methoxybenzaldehyde

Reaction temperature (°C)	Yield	
	Without LiBr	With LiBr
−78	96%	95%
−40	partial decomposition	95%
−20	major decomposition	major decomposition

Table 2
$(EtO)_2P(O)CF_2CH(OH)R^1$ (**7**)

Compound	R^1–	Yield (%)
a	$-(CH_2)_6CH_3$	85(b)
b	$-CH(CH_3)CH_2CH_3$	70(a) *
c	$-C(CH_3)_3$	84(a)
d	$-CH=CHCH_3$(E)	89(b)
e		85(b)
f		95(b)
g		96(b)
h		92(b)
i		94(b)
j		96(b)
k		82(b)

Products are purified by (a) distillation or (b) chromatography.
* One diastereomer partially distilled with **3**.

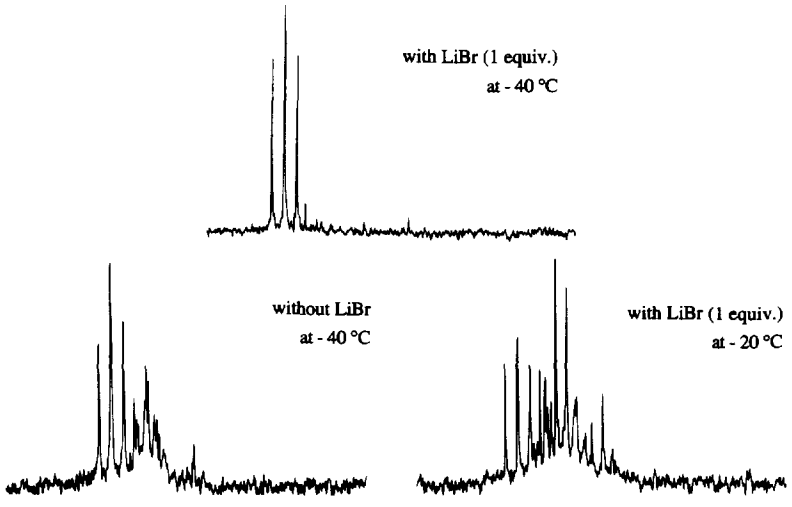


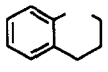
Fig. 1. ^{31}P NMR spectra of the condensation reaction of **2** with 4-methoxybenzaldehyde under various experimental conditions.

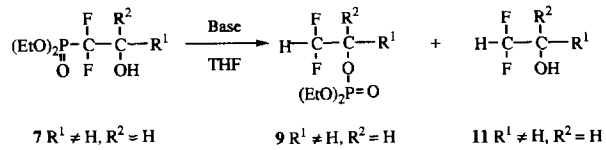
We also examined the reactivity of ketones (Table 3). The metallation reaction was performed at −78 °C, and the resulting magnesium species **2** was heated to −40 °C and reacted at this temperature with ketones in a stoichiometric ratio 1.5:1 in the presence of LiBr (1.5 equiv.). In spite of these conditions, the conversion to 1,1-difluoro-2-hydroxyethylphosphonate (**8**) was never complete, and the maximum yield of these reactions was 82%.

In addition, to obtain further information on the reactivity of the 1,1-difluoro-2-hydroxyethylphosphonates **7** and **8**, we explored their reactions with various bases (NaH, ^{t}BuOK, ^{n}BuLi and LDA). Our objective was to investigate the rearrangement reactions that they might undergo, and to obtain 1,1-difluoroolefines on a preparative scale. There has been some previous work in this area, and the initial observation of Obayashi et al. [16] that lithiodifluoromethylphosphonate reacts with carbonyl compounds to produce 1,1-difluoroolefines led us to examine the related chemistry of compounds **7** and **8**.

In THF at room temperature, 1,1-difluoro-2-hydroxyethylphosphonate (**7e**) (Table 2), on reaction with NaH, gave only diethyl 2,2-difluoro-1-(4′-fluoro)phenylethylphosphate (**9e**), which was isolated in pure form with 61% yield. With ^{t}BuOK, even with a large excess, formation of **9e** remained the main reaction, but other by-products could be detected. With LDA and ^{n}BuLi in refluxing THF, there was formation of one major product, 1,1-difluoromethyl-(4′-fluoro)benzylalcohol (**11e**), indicating that the prior rearrangement of **7e** into phosphate was followed by a loss of the phosphate moiety. By comparison the reaction was extended to **8a** (Table 3), and we observed that rearrangement to phosphate remained the main process. Rearrangement with NaH giving the best results, it has been extended to several 2-hydroxyphosphonates (**7a,b,c,e,f,g,h,k** (Table 2) and **8a,c** (Table 3)) in order to obtain the phosphates **9** and **10**, which have been isolated with the following yields: **9a** (68%), **9b** (51%), **9c** (47%), **9e** (61%), **9f** (64%), **9g** (80%), **9k** (54%), **10a** (72%). However, in all the reported experiments, the desired 1,1-difluoroolefine was never detected except for **7h** (15%) and **8c** (20%) (Scheme 5).

Table 3
$(EtO)_2P(O)CF_2C(OH)R^1R^2$ (**8**)

Compound	$-R^1,R^2-$	Yield (%)
a	$-(CH_2)_5-$	72
b	$-(CH_2)_2-CH(C(CH_3)_3)-(CH_2)_2-$	82
c		46
d	 -CH_3	63



7 $R^1 \neq H, R^2 = H$ **8** $R^1, R^2 \neq H$ **9** $R^1 \neq H, R^2 = H$ **10** $R^1, R^2 \neq H$ **11** $R^1 \neq H, R^2 = H$ **12** $R^1, R^2 \neq H$

Scheme 5.

3. Conclusion

When bromodifluoromethylphosphonate (**1**) is treated with ^{i}PrMgCl in THF, and the resulting magnesium species **2** reacted with an electrophile, the product formation will be influenced by stoichiometry, temperature and the presence or absence of salts. The right balance between these three factors seems crucial for the synthetic applications of **2**, and has led to the development of an efficient system for the formation of 1,1-difluoro-2-hydroxyethylphosphonates. However, the aim of this work was to improve the efficiency of the conditions leading to the formation of 1,1-difluoroolefines. The reported results indicate that no improvement was obtained by using a step-by-step process, and no additional benefit was achieved in comparison with previous results.

4. Experimental section

NMR spectra were recorded on a Brucker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon and 81.01 MHz for phosphorus. ^{31}P downfield shifts (δ) are expressed with a positive sign, in ppm, relative to external 85% H_3PO_4 in H_2O. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to $CDCl_3$ as internal standard. ^{19}F NMR spectra were recorded on a Brucker AC 250 spectrometer operating at 235 MHz. ^{19}F chemical shifts (δ) are expressed in ppm with a positive sign relative to $CFCl_3$ as internal standard in $CDCl_3$. Positive values of the coupling constants (J) are given in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; p, pentuplet and m, multiplet.

Low-resolution mass spectra were recorded on a Hewlett–Packard 5989 B mass spectrometer.

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.

4.1. Diethyl 1,1-difluoro-1-bromomethylphosphonate (1)

A 1 l reactor equipped with a mechanical stirrer, thermometer, efficient reflux condenser, and an addition funnel was charged with dibromodifluoromethane (115 g, 0.55 mol) and THF (300 ml) and flushed with nitrogen. Stirring was initiated and the solution was warmed by immersing the flask in an oil bath heated at 60 °C, triethyl phosphite (83 g, 0.5 mol) was then added dropwise over 1 h. After an additional 30 min at 60 °C, the reaction mixture was cooled and the solvent was removed under reduced pressure. The crude product **1** (99%) was purified by bulb-to-bulb distillation (b.p. 145–155 °C/0.5 mm Hg). Yield 96%.

^{31}P NMR ($CDCl_3$): δ −2.6 (t, ^{2}J(P–F) = 93); ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 6H, ^{3}J(H–H) = 7.1, CH_3CH$_2$O), 4.35 (qd, 4H, ^{3}J(H–H) = 7.1, ^{3}J(H–P) = 8.2, CH$_3$CH_2O); ^{13}C NMR ($CDCl_3$): δ 17.0 (d, ^{3}J(C–P) = 5.8, CH_3CH$_2$O), 67.0 (d, ^{2}J(C–P) = 6.4, CH$_3$$CH_2$O), 117.3 (td, ^{1}J(C–F) = 328.9, ^{1}J(C–P) = 238.2, PCF_2Br).

m/z (EI) 269 (M + H$^+$, 5%), 267 (M + H$^+$, 5%), 137 (80), 109 (100).

4.2. Diethyl 1,1-difluoromethylphosphonate (3)

A 500 ml reactor equipped with a mechanical stirrer, thermometer, reflux condenser, and an addition funnel was charged with previously standardised ^{i}PrMgCl (29 ml of 1.90 M Et_2O solution, 0.055 mol) and THF (120 ml). The solution was cooled to −78 °C and a solution of **1** (13.4 g, 0.05 mol) in THF (50 ml) was added dropwise. The resulting mixture was stirred for 10 min at −78 °C then at this temperature a solution of EtOH (10 ml) in THF (10 ml) was added dropwise. The reaction mixture was poured into an ice-cold mixture of HCl (40 ml of 3 M solution) and CH_2Cl_2 (50 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **3** which was purified by bulb-to-bulb distillation (b.p. 50–55 °C/0.5 mm Hg). Yield 85%.

^{31}P NMR ($CDCl_3$): δ +3.1 (t, ^{2}J(P–F) = 91); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 6H, ^{3}J(H–H) = 7.1, CH_3CH$_2$O), 4.26 (qd, 4H, ^{3}J(H–H) = 7.1, ^{3}J(H–P) = 8.2, CH$_3$CH_2O), 5.89 (td, 1H, ^{2}J(H–F) = 48.7, ^{2}J(H–P) = 26.9, PCF_2H); ^{13}C NMR ($CDCl_3$): δ 16.9 (d, ^{3}J(C–P) = 5.7, CH_3CH$_2$O), 65.1 (d, ^{2}J(C–P) = 7.0, CH$_3$$CH_2$O), 112.0 (td, ^{1}J(C–F) = 257.9, ^{1}J(C–P) = 213.6, PCF_2H).

m/z (EI) 189 (M + H$^+$, 1%), 137 (60), 160 (100).

4.3. Diethyl 1,1-difluoro-1-trimethylsilylmethylphosphonate (4)

A 500 ml reactor equipped as above was charged with ^{i}PrMgCl (29 ml of 1.90 M Et_2O solution, 0.055 mol) and THF (120 ml). The solution was cooled to −78 °C and a solution of **1** (13.4 g, 0.05 mol) and chlorotrimethylsilane (6 g, 0.055 mol) in THF (50 ml) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C then poured into an ice-cold stirred mixture of HCl (40 ml of 3 M solution) and CH_2Cl_2 (50 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **4** which was purified by bulb-to-bulb distillation (b.p. 90–95 °C/0.5 mm Hg). Yield 90%.

^{31}P NMR ($CDCl_3$): δ +7.7 (t, ^{2}J(P–F) = 92); ^{1}H NMR ($CDCl_3$): δ 0.24 (s, 9H, Si(CH_3)$_3$), 1.34 (t, 6H,

^3J(H–H) = 7.1, CH_3CH$_2$O), 4.23 (qd, 4H, ^3J(H–H) = 7.1, ^3J(H–P) = 7.1, CH$_3$CH_2O); ^{13}C NMR (CDCl$_3$): δ −4.8 (s, Si(CH_3)$_3$), 16.2 (d, ^3J(C–P) = 5.4, CH_3CH$_2$O), 63.5 (d, ^2J(C–P) = 7.5, CH$_3$$CH_2$O), 126.5 (td, ^1J(C–F) = 271.5, ^1J(C–P) = 165.1, PCF_2Si(CH$_3$)$_3$).

m/z (EI) 260 (M$^+$, 2%), 69 (100).

4.4. Diethyl 1,1-difluoro-1-chloromethylphosphonate (5)

A 250 ml reactor equipped as above was charged with ^{i}PrMgCl (5.5 ml of 2.0 M Et$_2$O solution, 0.011 mol) and THF (10 ml). The solution was cooled to −78 °C and a solution of **1** (2.67 g, 0.01 mol) in THF (15 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C. Then a solution of hexachloroethane (2.61 g, 0.011 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C and then allowed to warm up to 0 °C within 2 h. It was poured into an ice-cold mixture of HCl (20 ml of 3 M solution) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **5** which was purified by bulb-to-bulb distillation (b.p. 50–55 °C/0.5 mm Hg). Yield 60%.

^{31}P NMR (CDCl$_3$): δ −2.7 (t, ^2J(P–F) = 101); ^{1}H NMR (CDCl$_3$): δ 1.37 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 4.31 (p, 4H, ^3J(H–H) = 7.1, ^3J(H–P) = 7.1, CH$_3$CH_2O); ^{13}C NMR (CDCl$_3$): δ 16.0 (d, ^3J(C–P) = 6.0, CH_3CH$_2$O), 66.0 (d, ^2J(C–P) = 6.3, CH$_3$$CH_2$O), 123.0 (td, ^1J(C–F) = 316.7, ^1J(C–P) = 249.1, PCF_2Cl).

m/z (EI) 223 (M$^+$, 2%), 137 (43), 109 (100).

4.5. Diethyl 1,1-difluoro-1-iodomethylphosphonate (6)

A 250 ml reactor equipped as above was charged with ^{i}PrMgCl (5.5 ml of 2.0 M Et$_2$O solution, 0.011 mol) and THF (10 ml). The solution was cooled to −78 °C and a solution of **1** (2.67 g, 0.01 mol) in THF (15 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C. Then a solution of iodine (2.54 g, 0.011 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C and then allowed to warm up to 0 °C within 2 h. It was poured into an ice-cold mixture of HCl (20 ml of 3 M solution) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The extracts were washed with an aqueous sodium bisulfite solution, dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **6** which was purified by bulb-to-bulb distillation (b.p. 95–100 °C/0.5 mm Hg). Yield 48%.

^{31}P NMR (CDCl$_3$): δ −3.8 (t, ^2J(P–F) = 86); ^{1}H NMR (CDCl$_3$): δ 1.39 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 4.34 (p, 4H, ^3J(H–H) = 7.1, ^3J(H–P) = 7.1, CH$_3$CH_2O); ^{13}C NMR (CDCl$_3$): δ 16.2 (d, ^3J(C–P) = 5.4, CH_3CH$_2$O), 66.1 (d, ^2J(C–P) = 6.4, CH$_3$$CH_2$O), 97.2 (td, ^1J(C–F) = 331.2, ^1J(C–P) = 218.1, PCF_2I).

m/z (EI) 315 (M + H$^+$, 3%), 187 (60).

4.6. General procedure for the condensation of 2 with aldehydes

A 250 ml reactor equipped as above was charged with ^{i}PrMgCl (7.5 ml of 1.90 M Et$_2$O solution, 0.015 mol) and THF (20 ml). The solution was cooled to −78 °C and a solution of **1** (4.00 g, 0.015 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C and at this temperature a solution of aldehyde (0.01 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C then allowed to warm up to 0 °C within 1 h and from 0 °C to room temperature for an additional hour. The reaction mixture* was poured into an ice-cold mixture of HCl (20 ml of 2 M solution) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **7** mixed with **3** which was previously eliminated by heating the crude mixture at 70 °C under 0.5 mm Hg for 1 h. Then **7** was purified either by bulb-to-bulb distillation or by column chromatography (see Table 2).

[* Work-up was performed in a different manner for the 2-(4′-dimethylamino)phenyl- (**7h**) and the 2-2′-pyridyl- (**7k**) phosphonates: ice-cold HCl (7.5 ml of 2 M solution, 0.015 mol) was rapidly added to the reaction mixture of **7h** before extraction; whereas the reaction mixture of **7k** was poured into an ice-cold mixture of saturated ammonium salt solution (20 ml) and CH_2Cl_2 (20 ml)].

4.6.1. Diethyl 1,1-difluoro-2-heptyl-2-hydroxyethylphosphonate (7a)

^{31}P NMR (CDCl$_3$): δ +5.4 (t, ^2J(P–F) = 104); ^{19}F NMR (CDCl$_3$): δ −116.8 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 7.6, PCF_AF$_B$CHOH), −125.6 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 106.6, ^3J(F–H) = 19.0, PC$F_A$$F_B$CHOH); ^{1}H NMR (CDCl$_3$): δ 0.87 (t, 3H, ^3J(H–H) = 6.3, (CH$_2$)$_6$CH_3), 1.29 (s, 8H, (CH_2)$_4$CH$_3$), 1.38 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 1.64 (m, 4H, CHOH(CH_2)$_2$), 3.4 (m, 1H, PCF$_2$CHOH), 3.9 (m, 1H, PCF$_2$CHOH), 4.29 (p, 4H, ^3J(H–H) = ^3J(H–P) = 7.1, CH$_3$CH_2O); ^{13}C NMR (CDCl$_3$): δ 14.0 (s, (CH$_2$)$_6$$CH_3$), 16.3 (d, ^3J(C–P) = 5.5, CH_3CH$_2$O), 22.7 (s, CH_2), 25.4 (s, CH_2), 28.9 (s, CH_2), 29.4 (d, ^3J(C–P) = 7.5, CHOHCH_2), 29.8 (s, CH_2), 31.9 (s, CH_2), 64.6 (s, CH$_3$$CH_2$O), 71.2 (m, X part of ABMX system, $^2J \approx 23.3$, P$_M$CF_AF$_B$$C_X$HOH), 119.7 (ddd, X

part of ABMX system, ^1J(C–F) = 268.6, ^1J(C–F) = 264.0, ^1J(C–P) = 207.6, $P_M C_X F_A F_B$CHOH).

m/z (EI) 317 ($M + H^+$, 6%), 188 (100), 161 (95).

*4.6.2. Diethyl 1,1-difluoro-2-(2'-butyl)-2-hydroxyethylphosphonate (two diastereomers) (**7b**)*

^{31}P NMR ($CDCl_3$): δ +5.5 (t, ^2J(P–F) = 105, P_{maj}), +5.0 (dd, ^2J(P–F) = 99 and 105, P_{min}); ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, ^3J(H–H) = 7.4, CH_2CH_3), 0.98 (d, 3H, ^3J(H–H) = 6.7, $CHCH_3$), 1.35 (t, 6H, ^3J(H–H) = 7.1, CH_3CH_2O), 1.5 (m, 2H, CH_2CH_3), 1.9 (m, 1H, CHOHC*H*), 3.5 (m, 1H, PCF_2CHOH), 3.7 (m, 1H, PCF_2CHOH), 4.25 (m, 4H, ^3J(H–H) = 7.1, CH_3CH_2O); ^{13}C NMR ($CDCl_3$): δ 11.7 (s, CH_2CH_3 $_{min}$), 12.3 (s, CH_2CH_3 $_{maj}$), 14.1 (s, $CHCH_3$ $_{maj}$), 16.3 (s, $CHCH_3$ $_{min}$), 17.1 (d, ^3J(C–P) = 5.3, CH_3CH_2O), 24.7 (s, CH_2CH_3 $_{min}$), 27.8 (s, CH_2CH_3 $_{maj}$), 34.9 (s, CHOH–CH_{maj}), 35.7 (s, CHOH–CH_{min}), 65.5 (s, CH_3CH_2O), 73.3 (m, $CHOH_{maj}$), 75.3 (m, $CHOH_{min}$), 120.9 (ddd, X part of ABMX system, ^1J(C–F) = 270.6, ^1J(C–F) = 265.4, ^1J(C–P) = 208.4, $P_M C_X F_A F_B$CHOH$_{maj}$), 121.4 (ddd, X part of ABMX system, ^1J(C–F) = $^1J \approx$ 272.2, ^1J(C–F) = 266.0, ^1J(C–P) = 210.0, $P_M C_X F_A F_B$CHOH$_{min}$).

m/z (EI) 274 (M^+, 2%), 217 (46), 188 (61), 161 (100).

*4.6.3. Diethyl 1,1-difluoro-2-tertbutyl-2-hydroxyethylphosphonate (**7c**)*

^{31}P NMR ($CDCl_3$): δ +5.8 (t, ^2J(P–F) = 104); ^{1}H NMR ($CDCl_3$): δ 1.05 (d, 9H, J = 0.9, $C(CH_3)_3$), 1.36 (t, 6H, ^3J(H–H) = 7.1, CH_3CH_2O), 3.5 (m, 1H, PCF_2CHOH), 3.71 (ddd, 1H, X part of ABMX system, ^3J(C–P) = 28.5, ^3J(C–F) = 3.7, ^3J(C–F) = 1.4, $P_M CF_A F_B CH_X OH$), 4.27 (qd, 4H, ^3J(H–P) = 12.0, ^3J(H–H) = 7.1, CH_3CH_2O); ^{13}C NMR ($CDCl_3$): δ 17.0 (d, ^3J(C–P) = 5.7, CH_3CH_2O), 27.3 (s, $C(CH_3)_3$), 36.0 (d, $C(CH_3)_3$), 65.2 (d, ^2J(C–P) = 7.0, CH_3CH_2O), 65.5 (d, ^2J(C–P) = 6.6, CH_3CH_2O), 76.9 (m, X part of ABMX system, ^2J(C–F) = 24.9, ^2J(C–F) = 20.8, ^2J(C–P) = 10.0, $P_M CF_A F_B C_X$HOH), 122.9 (m, X part of ABMX system, ^1J(C–F) = 277.0, ^1J(C–F) = 267.4, ^1J(C–P) = 209.2, $P_M C_X F_A F_B$CHOH).

m/z (EI) 275 ($M + H^+$, 100%), 188 (19), 161 (56), 132 (39).

*4.6.4. Diethyl 1,1-difluoro-2-(1'-propenyl)-2-hydroxyethylphosphonate (**7d**)*

^{31}P NMR ($CDCl_3$): δ +5.0 (t, ^2J(P–F) = 103); ^{19}F NMR ($CDCl_3$): δ −116.4 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, ^3J(F–H) = 7.6, $PCF_A F_B$CHOH), −124.3 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0, $PCF_A F_B$CHOH); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 6H, ^3J(H–H) = 7.1, CH_3CH_2O), 1.77 (d, 3H, ^3J(H–H) = 6.7, $=CHCH_3$), 3.20 (d_{large}, 1H, ^3J(H–H) = 3.8, PCF_2CHOH), 4.28 (p, 4H, ^3J(H–P) = ^3J(H–H) = 7.1, CH_3CH_2O), 4.4 (m, 1H, PCF_2CHOH), 5.59 (ddq, 1H, ^3J(H–H)$_{trans}$ = 15.4, ^3J(H–H) = 6.5, ^4J(H–H) = 1.5, $CH=CHCH_3$), 5.95 (dqd, 1H, ^3J(H–H)$_{trans}$ = 15.4, ^3J(H–H) = 6.7, ^4J(H–H) = 1.0, $CH=CHCH_3$); ^{13}C NMR ($CDCl_3$): δ 16.3 (d, ^3J(C–P) = 5.2, CH_3CH_2O), 17.9 (s, $=CHCH_3$), 64.7 (d, ^2J(C–P) = 7.1, CH_3CH_2O), 72.5 (ddd, X part of ABMX system, ^2J(C–F) = 25.8, ^2J(C–F) = 22.8, ^2J(C–P) = 15.1, $P_M CF_A F_B C_X$HOH), 118.9 (ddd, X part of ABMX system, ^1J(C–F) = 269.5, ^1J(C–F) = 264.2, ^1J(C–P) = 207.8, $P_M C_X F_A F_B$CHOH), 125.0 (d, ^3J(C–P) = 2.3, $CH=CHCH_3$), 132.0 (s, $CH=CHCH_3$).

m/z (CI +ve) 259 ($M + H^+$, 100%).

*4.6.5. Diethyl 1,1-difluoro-2-(4'-fluorophenyl)-2-hydroxyethylphosphonate (**7e**)*

^{31}P NMR ($CDCl_3$): δ +4.9 (t, ^2J(P–F) = 99); ^{19}F NMR ($CDCl_3$): δ −113.7 (m, C_6H_4F), −115.0 (dd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, $PC F_A F_B$CHOH), −125.8 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0, $PCF_A F_B$CHOH); ^{1}H NMR ($CDCl_3$): δ 1.34 (2 t, 6H, ^3J(H–H) = 7.0, $(CH_3CH_2O)_{A\text{ and }B}$), 4.0 (m, 1H, $PCF_2CHOHC_6H_4F$), 4.24 (qd, 4H, ^3J(H–P) = 8.1, ^3J(H–H) = 7.0, $(CH_3CH_2O)_{A\text{ and }B}$), 5.10 (ddd, 1H, ^3J(H–P) = 20.4, ^3J(H–F) = 5.9, ^3J(H–F) = 3.9, $PCF_2CHOHC_6H_4F$), 7.07 (t, 2H, ^3J(H–F) = ^3J(H–H) = 8.7, H_{meta} of C_6H_4F), 7.46 (dd, 2H, ^3J(H–H) = 8.4, ^4J(H–F) = 8.5, H_{ortho} of C_6H_4F); ^{13}C NMR ($CDCl_3$): δ 17.0 (d, ^3J(C–P) = 5.7, CH_3CH_2O), 65.7 (d, ^2J(C–P) = 6.8, CH_3CH_2O), 73.3 ($m_{8\text{ peaks}}$, X part of ABMX system, ^2J(C–F) = 26.4, ^2J(C–F) = 21.6, ^2J(C–P) = 14.4, $P_M CF_A F_B C_X$HOH), 115.7 (d, ^2J(C–F) = 22.0, C_{meta} of C_6H_4F), 118.6 (ddd, X part of ABMX system, ^1J(C–F) = 271.9, ^1J(C–F) = 264.9, ^1J(C–P) = 206.2, $P_M C_X F_A F_B$CHOH), 130.6 (d, ^3J(C–F) = 8.1, C_{ortho} of C_6H_4F), 131.5 (t, ^3J(C–F) = 3.0, C_{ipso} of C_6H_4F), 163.7 (d, ^1J(C–F) = 249.6, C_{para} of C_6H_4F).

m/z (EI) 312 (M^+, 1%), 188 (33), 161 (41), 132 (100).

*4.6.6. Diethyl 1,1-difluoro-2-(4'-methylphenyl)-2-hydroxyethylphosphonate (**7f**)*

^{31}P NMR ($CDCl_3$): δ +5.2 (t, ^2J(P–F) = 103); ^{19}F NMR ($CDCl_3$): δ −114.8 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, ^3J(F–H) = 7.6, $PC F_A F_B$CHOH), −125.6 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 106.6, ^3J(F–H) = 19.0, $PCF_A F_B$CHOH); ^{1}H NMR ($CDCl_3$): δ 1.31 (m, 6H, CH_3CH_2O), 2.35 (s, 3H, $C_6H_4CH_3$), 4.1 (m_{masked}, 1H, PCF_2CHOH), 4.23 (m, 4H, CH_3CH_2O), 5.07 (ddd, 1H, ^3J(H–P) = 20.5, ^3J(H–F) = 6.0 and 3.8, PCF_2CHOH), 7.18 (d, 2H, ^3J(H–H) = 8.0, H_{meta} of $C_6H_4CH_3$), 7.36 (d, 2H, ^3J(H–H) = 8.0, H_{ortho} of $C_6H_4CH_3$); ^{13}C NMR ($CDCl_3$): δ 16.6 (d, ^3J(C–P) = 6.1, CH_3CH_2O), 21.5 (s, $C_6H_4CH_3$), 65.0 (d, ^2J(C–P) = 7.0, CH_3CH_2O), 65.3 (d, ^2J(C–P) = 6.8, CH_3CH_2O), 73.3 (ddd, X part of ABMX system,

^2J(C–F) = 26.5, ^2J(C–F) = 21.3, ^2J(C–P) = 14.7, $P_MCF_AF_BC_XHOH$), 118.8 (ddd, X part of ABMX system, ^1J(C–F) = 272.3, ^1J(C–F) = 263.2, ^1J(C–P) = 207.4, $P_MC_XF_AF_BCHOH$), 128.5 (s, C_{meta} of $C_6H_4CH_3$), 129.1 (s, C_{ortho} of $C_6H_4CH_3$), 133.1 (d, ^3J(C–P) = 5.7, C_{ipso} of $C_6H_4CH_3$), 138.7 (s, C_{para} of $C_6H_4CH_3$).

m/z (EI) 308 (M^+, 7%), 188 (48), 161 (55), 132 (100).

*4.6.7. Diethyl 1,1-difluoro-2-(4'-methoxyphenyl)-2-hydroxyethylphosphonate (**7g**)*

^{31}P NMR ($CDCl_3$): δ +5.2 (t, ^2J(P–F) = 103); ^{19}F NMR ($CDCl_3$): δ −115.2 (dd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, PCF_AF_BCHOH), −125.6 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0, PCF_AF_BCHOH); ^{1}H NMR ($CDCl_3$): δ 1.32 (td, 6H, ^3J(H–H) = 7.1, CH_3CH_2O), 3.80 (s, 3H, OCH_3), 4.0 (m, 1H, PCF_2CHOH), 4.18 (m, 4H, ^3J(H–H) = 7.1, CH_3CH_2O), 5.06 (dm, 1H, ^3J = 20.2, PCF_2CHOH), 6.90 (d, 2H, ^3J(H–H) = 8.6, H_{meta} of $C_6H_4OCH_3$), 7.39 (d, 2H, ^3J(H–H) = 8.6, H_{ortho} of $C_6H_4OCH_3$); ^{13}C NMR ($CDCl_3$): δ 16.5 (d, ^3J(C–P) = 4.6, CH_3CH_2O), 55.5 (s, OCH_3), 65.2 (dd, ^2J(C–P) = 7.2, J = 12.0, CH_3CH_2O), 73.3 (m, X part of ABMX system, $P_MCF_AF_BC_XHOH$), 113.8 (s, C_{meta} of $C_6H_4OCH_3$), 118.2 (ddd, X part of ABMX system, ^1J(C–F) = 271.7, ^1J(C–F) = 265.8, ^1J(C–P) = 204.2, $P_MC_XF_AF_BCHOH$), 127.1 (t, ^3J(C–F) = 6.0, C_{ipso} of $C_6H_4OCH_3$), 129.6 (s, C_{ortho} of $C_6H_4OCH_3$), 160.2 (s, C_{para} of $C_6H_4OCH_3$).

m/z (CI +ve) 324 (M^+, 5%).

*4.6.8. Diethyl 1,1-difluoro-2-(4'-dimethylaminophenyl)-2-hydroxyethylphosphonate (**7h**)*

^{31}P NMR ($CDCl_3$): δ +5.5 (t, ^2J(P–F) = 104); ^{19}F NMR ($CDCl_3$): δ −115.2 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, ^3J(F–H) = 7.6, PCF_AF_BCHOH), −125.5 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 106.6, ^3J(F–H) = 19.0, PCF_AF_BCHOH); ^{1}H NMR ($CDCl_3$): δ 1.33 (td, 6H, ^3J(H–H) = 7.0, CH_3CH_2O), 2.95 (s, 6H, $N(CH_3)_2$), 4.0 (m, 1H, PCF_2CHOH), 4.24 (m, 4H, CH_3CH_2O), 5.03 (dm, 1H, ^3J(H–P) = 20, PCF_2CHOH), 6.72 (d, 2H, ^3J(H–H) = 8.8, H_{meta} of $C_6H_4N(CH_3)_2$), 7.33 (d, 2H, ^3J(H–H) = 8.3, H_{ortho} of $C_6H_4N(CH_3)_2$); ^{13}C NMR ($CDCl_3$): δ 17.0 (d, ^3J(C–P) = 5.9, CH_3CH_2O), 41.1 (s, $N(CH_3)_2$), 65.5 (dd, ^2J(C–P) = 6.7, J = 12.1, CH_3CH_2O), 73.8 (m, X part of ABMX system, ^2J(C–F) = 26.6, ^2J(C–F) = 21.3, ^2J(C–P) = 14.7, $P_MCF_AF_BC_XHOH$), 112.6 (s, C_{meta} of $C_6H_4N(CH_3)_2$), 118.8 (m, X part of ABMX system, ^1J(C–F) = 270.1, ^1J(C–F) = 264.0, ^1J(C–P) = 204.5, $P_MC_XF_AF_BCHOH$), 123.0 (d, ^3J(C–P) = 4.9, C_{ipso} of $C_6H_4N(CH_3)_2$), 129.6 (s, C_{ortho} of $C_6H_4N(CH_3)_2$), 151.6 (s, C_{para} of $C_6H_4N(CH_3)_2$).

m/z (EI) 337 (M^+, 7%), 150 (100).

*4.6.9. Diethyl 1,1-difluoro 2-(2'-furyl) 2-hydroxyethylphosphonate (**7i**)*

^{31}P NMR ($CDCl_3$): δ +4.3 (t, ^2J(P–F) = 101); ^{19}F NMR ($CDCl_3$): δ −115.9 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, ^3J(F–H) = 7.6, PCF_AF_BCHOH), −123.6 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0, PCF_AF_BCHOH); ^{1}H NMR ($CDCl_3$): δ 1.34 (td, 6H, ^3J(H–H) = 7.0, ^4J(H–P) = 4.5, CH_3CH_2O), 4.09 (m, 1H, PCF_2CHOH), 4.25 (qd, 4H, ^3J(H–P) = 8.9, ^3J(H–H) = 7.0, CH_3CH_2O), 5.15 (dm, 1H, PCF_2CHOH), 6.40 (dd, 1H, ^3J(H–H) = 3.3, ^3J(H–H) = 1.8, H_4 of C_4H_3O), 6.52 (d_{large}, 1H, ^3J(H–H) = 3.3, H_3 of C_4H_3O), 7.45 (m, 1H, H_5 of C_4H_3O); ^{13}C NMR ($CDCl_3$): δ 16.6 (d, ^3J(C–P) = 6.0, CH_3CH_2O), 65.4 (d, ^2J(C–P) = 6.5, CH_3CH_2O), 68.1 (ddd, X part of ABMX system, ^2J(C–F) = 27.1, ^2J(C–F) = 21.9, ^2J(C–P) = 16.6, $P_MCF_AF_BC_XHOH$), 110.3 (s, C_3 of C_4H_3O), 110.9 (s, C_4 of C_4H_3O), 118.3 (ddd, X part of ABMX system, ^1J(C–F) = 271.7, ^1J(C–F) = 265.0, ^1J(C–P) = 209.8, $P_MC_XF_AF_BCHOH$), 143.3 (s, C_5 of C_4H_3O), 149.6 (dd, ^3J(C–P) = 6.2, ^3J(C–P) = 2.7, C_2 of C_4H_3O).

m/z (EI) 284 (M^+, 10%), 188 (73), 161 (75), 132 (100).

*4.6.10. Diethyl 1,1-difluoro 2-(2'-thienyl) 2-hydroxyethylphosphonate (**7j**)*

^{31}P NMR ($CDCl_3$): δ +4.8 (t, ^2J(P–F) = 101); ^{19}F NMR ($CDCl_3$): δ −115.0 (ddd, ^2J(F–F) = 299.0, ^2J(F–P) = 99.0, ^3J(F–H) = 7.6, PCF_AF_BCHOH), −125.2 (ddd, ^2J(F–F) = 299.0, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0, PCF_AF_BCHOH); ^{1}H NMR ($CDCl_3$): δ 1.34 (q, 6H, ^3J(H–H) = ^4J(H–P) = 7.0, CH_3CH_2O), 1.8 (m, 1H, PCF_2CHOH), 4.25 (p, 4H, ^3J(H–P) = ^3J(H–H) = 7.0, CH_3CH_2O), 5.39 (dm, 1H, ^3J(H–P) = 19.5, PCF_2CHOH), 7.03 (dd, 1H, ^3J(H–H) = 5.0, ^3J(H–H) = 3.6, H_4 of C_4H_3S), 7.18 (d, 1H, ^3J(H–H) = 3.6, H_3 of C_4H_3S), 7.36 (dd, 1H, ^3J(H–H) = 5.0, ^4J(H–H) = 1.2, H_5 of C_4H_3S); ^{13}C NMR ($CDCl_3$): δ 16.9 (d, ^3J(C–P) = 5.6, CH_3CH_2O), 65.7 (d, ^2J(C–P) = 7.0, CH_3CH_2O), 70.7 (ddd, X part of ABMX system, ^2J(C–F) = 27.5, ^2J(C–F) = 22.4, ^2J(C–P) = 16.2, $P_MCF_AF_BC_XHOH$), 118.1 (ddd, X part of ABMX system, ^1J(C–F) = 272.6, ^1J(C–F) = 264.8, ^1J(C–P) = 206.6, $P_MC_XF_AF_BCHOH$), 127.1 (s, C_3 of C_4H_3S), 127.2 (s, C_4 of C_4H_3S), 127.7 (s, C_5 of C_4H_3S), 138.4 (d, ^3J(C–P) = 6.7, C_2 of C_4H_3S).

m/z (EI) 300 (M^+, 13%), 188 (80), 161 (93), 132 (100).

*4.6.11. Diethyl 1,1-difluoro 2-(2'-pyridyl) 2-hydroxyethylphosphonate (**7k**)*

^{31}P NMR ($CDCl_3$): δ +4.3 (t, ^2J(P–F) = 101); ^{19}F NMR ($CDCl_3$): δ −114.6 (dd, ^2J(F–F) = 304.7, ^2J(F–P) = 99.0, PCF_AF_BCHOH), −125.6 (ddd, ^2J(F–F) = 304.7, ^2J(F–P) = 102.8, ^3J(F–H) = 19.0,

PCF_AF_BCHOH); ^1H NMR ($CDCl_3$): δ 1.35 (td, 6H, $^3J(H-H) = 7.1$, $^4J(H-P) = 2.7$, CH_3CH_2O), 4.26 (qd, 4H, $^3J(H-P) = 8.0$, $^3J(H-H) = 7.1$, CH_3CH_2O), 5.20 (dt, 1H, $^3J(H-P) = 20.8$, $^3J(H-F) = 4.5$, PCF_2CHOH), 5.67 (s_{large}, 1H, PCF_2CHOH), 7.35 (dd, 1H, $^3J(H-H) = 7.7$ and 4.8, H_5 of C_5H_4N), 7.48 (d_{large}, 1H, $^3J(H-H) = 7.7$, H_3 of C_5H_4N), 7.78 (tt, 1H, $^3J(H-H) = 7.7$, $^4J(H-H) = {}^6J(H-P) = 1.2$, H_4 of C_5H_4N), 8.60 (dd, 1H, $^3J(H-H) = 4.8$, $^4J(H-H) = 1.2$, H_6 of C_5H_4N); ^{13}C NMR ($CDCl_3$): δ 15.9 (d, $^3J(C-P) = 5.4$, CH_3CH_2O), 64.3 (d, $^2J(C-P) = 6.3$, CH_3CH_2O), 72.5 (ddd, X part of ABMX system, $^2J(C-F) = 26.1$, $^2J(C-F) = 21.9$, $^2J(C-P) = 13.6$, $P_MCF_AF_BC_XHOH$), 118.4 (ddd, X part of ABMX system, $^1J(C-F) = 272.6$, $^1J(C-F) = 264.8$, $^1J(C-P) = 209.2$, $P_MC_XF_AF_BCHOH$), 123.0 (s, C_3 of C_5H_4N), 123.5 (s, C_5 of C_5H_4N), 136.5 (s, C_4 of C_5H_4N), 147.9 (s, C_6 of C_5H_4N), 153.9 (d, $^3J(C-P) = 6.1$, C_2 of C_5H_4N).

m/z (EI) 296 ($M + H^+$, 5%), 161 (8), 132 (17), 108 (100).

4.7. General procedure for the condensation of 2 with ketones

A 250 ml reactor equipped as above was charged with anhydrous LiBr (1.31 g, 0.015 mol, dried by heating at 150 °C under 0.1 mm Hg vacuum over 1 h) and THF (15 ml) and heated at 50 °C until complete dissolution. ^iPrMgCl (7.5 ml of 1.90 M Et_2O solution, 0.015 mol) and THF (10 ml) were added to the reactor at −20 °C. The solution was cooled to −78 °C and a solution of **1** (4.00 g, 0.015 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 5 min at −78 °C then allowed to warm up to −40 °C. At this temperature a solution of ketone (0.01 mol) in THF (20 ml) was added dropwise. The resulting mixture was stirred for 15 min at −40 °C then allowed to warm up to 0 °C within 1 h and from 0 °C to room temperature for an additional hour. The reaction mixture was poured into an ice-cold mixture of HCl (20 ml of 2 M solution) and CH_2Cl_2 (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product **8** and the excess of **3** which was previously eliminated by heating the crude mixture at 70 °C under 0.5 mm Hg for 1 h. Then **8** was purified either by bulb-to-bulb distillation or by column chromatography (see Table 3).

4.7.1. Diethyl 1,1-difluoro 1-(1'-hydroxy)cyclohexyl methylphosphonate (8a)

^{31}P NMR ($CDCl_3$): δ +5.5 (t, $^2J(P-F) = 107$); ^{19}F NMR ($CDCl_3$): δ −121.5 (d, $^2J(F-P) = 106.6$, PCF_2COH); ^1H NMR ($CDCl_3$): δ 1.2 (m, 1H, $COH(CH_2CH_2)_2CH_{ax}H_{eq}$), 1.37 (t, 6H, $^3J(H-H) = 7.1$, CH_3CH_2O), 1.61 (m, 7H, $COH(CH_{ax}H_{eq}CH_2)_2CH_{ax}H_{eq}$), 1.87 ($d_{large}$, 2H, $^2J(H-H) = 11.9$, $COH(CH_{ax}H_{eq}CH_2)_2CH_2$), 2.99 (s, 1H, PCF_2COH), 4.28 (p, 4H, $^3J(H-P) = {}^3J(H-H) = 7.1$, CH_3CH_2O); ^{13}C NMR ($CDCl_3$): δ 16.9 (d, $^3J(C-P) = 5.9$, CH_3CH_2O), 21.1 (s, $COH(CH_2CH_2)_2CH_2$), 26.0 (s, $COH(CH_2CH_2)_2CH_2$), 30.3 (d, $^3J(C-P) = 2.7$, $COH(CH_2CH_2)_2CH_2$), 65.5 (d, $^2J(C-P) = 6.8$, CH_3CH_2O), 74.5 (td, $^2J(C-F) = 20.9$, $^2J(C-P) = 13.4$, PCF_2COH), 120.9 (td, $^1J(C-F) = 271.0$, $^1J(C-P) = 200.3$, PCF_2COH).

m/z (EI) 287 ($M + H^+$, 6%), 188 (100), 161 (90), 132 (79).

4.7.2. Diethyl 1,1-difluoro 1-(1'-hydroxy-4'-tertiobutyl)cyclohexyl methylphosphonate (8b)

^{31}P NMR ($CDCl_3$): δ +5.6 (t, $^2J(P-F) = 106$); ^{19}F NMR ($CDCl_3$): δ −121.5 (d, $^2J(F-P) = 106.6$, PCF_2COH); ^1H NMR ($CDCl_3$): δ 0.93 (s, 9H, $C(CH_3)_3$), 1.05 (t_{large}, 1H, $^3J(H_{ax}-H_{ax}) = 11.4$, $COH(CH_2CH_2)_2CH_{ax}$), 1.45 (t, 6H, $^3J(H-H) = 7.1$, CH_3CH_2O), 1.52–1.75 (m, 6H, $COH(CH_{ax}H_{eq}CH_2)_2CH_{ax}$), 2.01 ($d_{large}$, 2H, $^2J(H-H) = 12.4$, $COH(CH_{ax}H_{eq}CH_2)_2CH_{ax}$), 2.85 ($s_{large}$, 1H, PCF_2COH), 4.36 (p, 4H, $^3J(H-P) = {}^3J(H-H) = 7.1$, CH_3CH_2O); ^{13}C NMR ($CDCl_3$): δ 17.0 (d, $^3J(C-P) = 5.9$, CH_3CH_2O), 22.0 (s, $COH(CH_2CH_2)_2CH$), 28.1 (s, $C(CH_3)_3$), 30.8 (d, $^3J(C-P) = 2.3$, $COH(CH_2CH_2)_2CH$), 33.3 (s, $C(CH_3)_3$), 48.0 (s, $CHC(CH_3)_3$), 65.5 (d, $^2J(C-P) = 6.9$, CH_3CH_2O), 74.3 (td, $^2J(C-F) = 20.8$, $^2J(C-P) = 13.3$, PCF_2COH), 121.0 (td, $^1J(C-F) = 270.9$, $^1J(C-P) = 200.4$, PCF_2COH).

m/z (CI +ve) 343 ($M + H^+$, 100%).

4.7.3. Diethyl 1,1-difluoro 1-(1'-hydroxy-1',2',3',4'-tetrahydro)naphtyl methylphosphonate (8c)

^{31}P NMR ($CDCl_3$): δ +5.4 (dd, $^2J(P-F) = 133$ and 99); ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H, $^3J(H-H) = 7.1$, $CH_3CH_2O_A$), 1.36 (t, 3H, $^3J(H-H) = 7.1$, $CH_3CH_2O_B$), 1.8–2.0 (m, 3H, $H_{3'}$ and $H_{2'\ pseudo\ eq}$), 2.5 (m, 1H, $H_{2'\ pseudo\ ax}$), 2.79 (t, 2H, $^3J(H-H) = 6.0$, $H_{4'}$), 3.29 (s, 1H, PCF_2COH), 4.2 (m, 2H, $CH_3CH_2O_A$), 4.26 (p, 2H, $^3J(H-P) = {}^3J(H-H) = 7.1$, $CH_3CH_2O_B$), 7.10 (m, 1H, $H_{6'}$), 7.23 (m, 2H, $H_{5'\ and\ 7'}$), 7.75 (m, 1H, $H_{8'}$); ^{13}C NMR ($CDCl_3$): δ 16.4 (d, $^3J(C-P) = 5.9$, CH_3CH_2O), 18.8 (d, $^4J(C-P) = 3.4$, $C_{3'}$), 29.4 (s, $C_{4'}$), 33.8 (d, $^3J(C-P) = 3.7$, $C_{2'}$), 64.6 (d, $^2J(C-P) = 5.9$, CH_3CH_2O), 73.7 (q, $^2J(C-F) = 20.7$, $^2J(C-P) = 17.5$, PCF_2COH), 111.6 (q, $^1J(C-F) = 257.8$, $^1J(C-P) = 212.3$, PCF_2COH), 125.7 (s, $C_{6'}$), 128.3 (s, $C_{7'}$), 128.7 (s, $C_{5'}$), 129.4 (d, $^4J(C-P) = 2.9$, $C_{10'}$), 134.2 (d, $^3J(C-P) = 5.2$, $C_{9'}$), 139.2 (s, $C_{8'}$).

m/z (EI) 334 (M^+, 2%), 161 (29), 147 (100).

*4.7.4. Diethyl 1,1-difluoro 2-hydroxy 2-methyl 2-(2'-thienyl) ethylphosphonate (**8d**)*

^{31}P NMR ($CDCl_3$): δ +5.2 (t, ^2J(P–F) = 103); ^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_A$), 1.37 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_B$), 1.73 (t, 3H, CH_3), 3.7–4.2 (m, 2H, CH$_3$CH_2O$_A$), 4.29 (p, 2H, ^3J(H–P) = ^3J(H–H) = 7.1, CH$_3$CH_2O$_B$), 7.00 (dd, 1H, ^3J(H–H) = 5.0, ^3J(H–H) = 3.7, H_4 of C$_4$CH$_3$S), 7.10 (d, 1H, ^3J(H–H) = 3.7, H_3 of C$_4$CH$_3$S), 7.29 (d, 1H, ^3J(H–H) = 5.0, ^4J(H–H) = 1.2, H_5 of C$_4$CH$_3$S); ^{13}C NMR ($CDCl_3$): δ 16.2 (d, ^3J(C–P) = 6.3, *C*H$_3$CH$_2$O$_A$), 16.2 (d, ^3J(C–P) = 5.8, *C*H$_3$CH$_2$O$_B$), 24.6 (t, ^3J(C–P) = 2.2, *C*H$_3$), 64.9 (d, ^2J(C–P) = 6.5, CH$_3$*C*H$_2$O$_A$), 64.9 (d, ^2J(C–P) = 7.1, CH$_3$*C*H$_2$O$_B$), 75.6 (td, ^2J(C–F) = 23.2, ^2J(C–P) = 15.0, PCF$_2$*C*OH), 118.8 (td, ^1J(C–F) = 273.0, ^1J(C–P) = 202.9, P*C*F$_2$COH), 125.5 (s, C_3 of C$_4$H$_3$S), 125.6 (s, C_4 of C$_4$H$_3$S), 126.8 (s, C_5 of C$_4$H$_3$S), 145.2 (s, C_2 of C$_4$H$_3$S).

m/z (EI) 314 (M^+, 22%), 188 (66), 161 (95), 127 (100).

*4.8. General procedure for the transposition of the diethyl 1,1-difluoro 2-hydroxyethyl phosphonates **7** and **8** into **9** and **10***

Sodium hydride (0.15 g of 60% dispersion in mineral oil, 3.3 mmol) was washed with hexane (3 × 10 ml) in a three-necked round-bottomed flask equipped with a thermometer, reflux condenser and an addition funnel and flushed with nitrogen. Magnetic stirring was initiated and THF (20 ml) was added. The suspension was cooled to 0 °C, diethyl 1,1-difluoro-2-hydroxyethyl phosphonate (**7** or **8**, 3 mmol) was then added dropwise. After an additional 30 min at 0 °C, an ice-cold mixture of water (10 ml) and brine (10 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The extracts were dried ($MgSO_4$) and the solvents were removed under reduced pressure to give the crude product (**9** or **10**) which was purified by chromatography.

*4.8.1. Diethyl 1-heptyl 2,2-difluoroethylphosphate (**9a**)*

^{31}P NMR ($CDCl_3$): δ −3.4 (s); ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, ^3J(H–H) = 6.4, (CH$_2$)$_6$CH_3), 1.28 (m, 14H, (CH_2)$_4$CH$_3$ and CH_3CH$_2$O), 1.47 (m, 2H, CH(OP)CH$_2$CH_2), 1.68 (m, 2H, CH(OP)CH_2), 4.12 (qd, 4H, ^3J(H–H) = ^3J(H–P) = 7.2, CH$_3$CH_2O), 4.45 (m, 1H, HF$_2$C–C*H*), 5.80 (td, 1H, ^2J(H–F) = 55.3, ^3J(H–H) = 3.4, *H*F$_2$C); ^{13}C NMR ($CDCl_3$): δ 14.6 (s, (CH$_2$)$_6$*C*H$_3$), 16.5 (d, ^3J(C–P) = 2.7, *C*H$_3$CH$_2$O$_A$), 16.6 (d, ^3J(C–P) = 3.0, *C*H$_3$CH$_2$O$_B$), 23.2 (s, *C*H$_2$), 24.9 (s, *C*H$_2$), 29.1 (s, *C*H$_2$), 29.8 (s, *C*H$_2$), 30.0 (s, *C*H$_2$), 32.4 (s, *C*H$_2$), 64.7 (d, ^2J(C–P) = 6.1, CH$_3$*C*H$_2$O), 76.7 (td, ^2J(C–F) = 25.1, ^2J(C–P) = 5.8, HF$_2$C–*C*H), 114.7 (td, ^1J(C–F) = 245.0, ^3J(C–P) = 4.9, HF$_2$*C*).

m/z (CI +ve) 317 ($M + H^+$, 100%).

*4.8.2. Diethyl 1-(1'-methyl)propyl 2,2-difluoroethylphosphate (two diastereomers) (**9b**)*

^{31}P NMR ($CDCl_3$): δ −3.2 (s, major), −3.3 (s, minor); ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H, ^3J(H–H) = 7.3, CH$_2$–C$H_{3\ min}$), 0.94 (t, 3H, ^3J(H–H) = 7.3, CH$_2$–C$H_{3\ maj}$), 0.98 (d, 3H, ^3J(H–H) = 6.9, CH–C$H_{3\ maj}$), 1.02 (d, 3H, ^3J(H–H) = 7.0, CH–C$H_{3\ min}$), 1.3 (m$_{masked}$, 1H, C*H*H–CH$_3$), 1.32 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 1.54 (m, 1H, CH*H*–CH$_3$), 1.83 (m, 1H, C*H*–CH$_3$), 4.12 (p, 4H, ^3J(H–H) = ^3J(H–P) = 7.2, CH$_3$CH_2O), 4.4 (m, 1H, HF$_2$C–C*H*), 5.81 (td, 1H, ^2J(H–F) = 55.2, ^3J(H–H) = 4.7, *H*F$_2$C$_{maj}$), 5.85 (td, 1H, ^2J(H–F) = 54.8, ^3J(H–H) = 3.9, *H*F$_2$C$_{min}$); ^{13}C NMR ($CDCl_3$): δ 11.1 (s, CH$_2$*C*H$_{3\ min}$), 11.5 (s, CH$_2$*C*H$_{3\ maj}$), 13.4 (s, CH*C*H$_{3\ maj}$), 14.4 (s, CH*C*H$_{3\ min}$), 15.9 (d, ^3J(C–P) = 3.4, *C*H$_3$CH$_2$O$_A$), 16.0 (d, ^3J(C–P) = 4.4, *C*H$_3$CH$_2$O$_B$), 24.0 (s, *C*H$_2$CH$_{3\ min}$), 25.8 (s, *C*H$_2$CH$_{3\ maj}$), 35.2 (q, ^3J(C–F) = ^3J(C–P) = 3.0, *C*HCH$_{3\ maj}$), 35.6 (q, ^3J(C–F) = ^3J(C–P) = 3.0, *C*HCH$_{3\ min}$), 64.0 (d, ^2J(C–P) = 5.9, CH$_3$*C*H$_2$O), 78.5 (td, ^2J(C–F) = 24.1, ^2J(C–P) = 5.9, HF$_2$C–*C*H$_{maj}$), 79.5 (td, ^2J(C–F) = 23.4, ^2J(C–P) = 5.9, HF$_2$C–*C*H$_{min}$), 114.2 (td, ^1J(C–F) = 244.4, ^3J(C–P) = 4.8, HF$_2$*C*$_{min}$), 114.4 (td, ^1J(C–F) = 244.5, ^3J(C–P) = 4.5, HF$_2$*C*$_{maj}$).

m/z (CI +ve) 275 ($M + H^+$, 100%).

*4.8.3. Diethyl 1-(1',1'-dimethyl)ethyl 2,2-difluoroethylphosphate (**9c**)*

^{31}P NMR ($CDCl_3$): δ −3.2 (s); ^{19}F NMR ($CDCl_3$): δ −123.7 (ddd, A part of ABXY system, ^2J(F–F) = 289.4, ^2J(F–H) = 53.3, ^3J(F–H) = 11.4, H$_X$F$_A$F$_B$CCH$_Y$), −125.6 (ddd, B part of ABXY system, ^2J(F–F) = 289.4, ^2J(F–H) = 53.3, ^3J(F–H) = 11.4, H$_X$F$_A$F$_B$CCH$_Y$); ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, C(CH_3)$_3$), 1.33 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 4.14 (p, 4H, ^3J(H–H) = ^3J(H–P) = 7.1, CH$_3$CH_2O), 4.23 (dddd, 1H, ^3J(H–P) = 15.9, ^3J(H–F) = 10.3, ^3J(H–F) = 9.6, ^3J(H–H) = 2.8, HF$_2$C–C*H*), 5.88 (td, 1H, ^2J(H–F) = 54.0, ^3J(H–H) = 2.8, *H*F$_2$C); ^{13}C NMR ($CDCl_3$): δ 15.7 (d, ^3J(C–P) = 5.0, *C*H$_3$CH$_2$O$_A$), 15.8 (d, ^3J(C–P) = 5.0, *C*H$_3$CH$_2$O$_B$), 25.8 (s, C(*C*H$_3$)$_3$), 33.6 (t, ^3J(C–F) = 3.4, *C*(CH$_3$)$_3$), 63.7 (d, ^2J(C–P) = 6.0, CH$_3$*C*H$_2$O), 82.4 (ddd, ^2J(C–F) = 21.4, ^2J(C–F) = 18.7, ^2J(C–P) = 6.1, HF$_2$C–*C*H), 113.8 (ddd, ^1J(C–F) = 246.3, ^1J(C–F) = 243.5, ^3J(C–P) = 2.7, HF$_2$*C*).

m/z (CI +ve) 275 ($M + H^+$, 100%).

*4.8.4. Diethyl 1-(4'-fluoro)phenyl 2,2-difluoroethylphosphate (**9e**)*

^{31}P NMR ($CDCl_3$): δ −3.6 (s); ^{19}F NMR ($CDCl_3$): δ −112.6 (s, C$_6$H$_5$F), −127.5 (ddd, A part of ABXY system, ^2J(F–F) = 285.6, ^2J(F–H) = 53.3, ^3J(F–H) = 11.4, H$_X$F$_A$F$_B$CCH$_Y$), −130.3 (ddd, B part of ABXY system, ^2J(F–F) = 285.6, ^2J(F–H) = 53.3, ^3J(F–H) = 11.4, H$_X$F$_A$F$_B$CCH$_Y$); ^{1}H NMR ($CDCl_3$): δ 1.17 (t,

3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_A$), 1.28 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_B$), 3.94 (pd, 2H, ^3J(H–H) = ^3J(H–P) = 7.1, J = 2.5, CH$_3$CH_2O$_A$), 4.09 (q, 2H, ^3J(H–H) = 7.1, CH$_3$CH_2O$_B$), 5.36 (qd, 1H, ^3J(H–P) = ^3J(H–F) = 10.1, ^3J(H–H) = 4.0, HF$_2$C–CH), 5.88 (td, 1H, ^2J(H–F) = 55.2, ^3J(H–H) = 4.0, HF$_2$C), 7.09 (t, 2H, ^3J(H–H) = ^3J(H–F) = 8.7, H_{meta} of C$_6$H$_4$F), 7.41 (dd, 2H, ^3J(H–H) = ^3J(H–F) = 8.7, ^3J(H–F) = 5.3, H_{ortho} of C$_6$H$_4$F); ^{13}C NMR (CDCl$_3$): δ 16.2 (d, ^3J(C–P) = 3.0, CH$_3$CH$_2$O$_A$), 16.3 (d, ^3J(C–P) = 3.8, CH$_3$CH$_2$O$_B$), 64.6 (d, ^2J(C–P) = 6.0, CH$_3$$CH_2O_A$), 64.8 (d, ^2J(C–P) = 6.2, CH$_3$$CH_2O_B$), 77.1 (td, ^2J(C–F) = 26.6, ^2J(C–P) = 4.7, HF$_2$C–CH), 114.1 (td, ^1J(C–F) = 246.6, ^3J(C–P) = 8.7, HF$_2$$C$), 116.2 (d, ^3J(C–F) = 22.2, C_{meta} of C$_6$H$_4$F), 129.2 (s$_{large}$, C_{ipso} of C$_6$H$_4$F), 130.2 (d, ^4J(C–F) = 8.2, C_{ortho} of C$_6$H$_4$F), 163.8 (d, ^1J(C–F) = 248.7, C_{para} of C$_6$H$_4$F).

m/z (EI) 313 (M + H$^+$, 1%), 292 (44), 244 (55), 216 (84).

4.8.5. Diethyl 1-(4'-methyl)phenyl 2,2-difluoroethylphosphate (9f)

^{31}P NMR (CDCl$_3$): δ −3.8 (s); ^{1}H NMR (CDCl$_3$): δ 1.16 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_A$), 1.27 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_B$), 2.35 (s, 3H, C$_6$H$_4$CH_3), 3.92 (pd, 2H, ^3J(H–H) = ^3J(H–P) = 7.1, J = 3.2, CH$_3$CH_2O$_A$), 4.10 (q, 2H, ^3J(H–H) = 7.1, CH$_3$CH_2O$_B$), 5.33 (qd, 1H, ^3J(H–P) = ^3J(H–F) = 10.0, ^3J(H–H) = 4.2, HF$_2$C–CH), 5.87 (td, 1H, ^2J(H–F) = 55.3, ^3J(H–H) = 4.2, HF$_2$C), 7.20 (d, 2H, ^3J(H–H) = 7.9, H_{meta} of C$_6$H$_4$CH$_3$), 7.30 (d, 2H, ^3J(H–H) = 7.9, H_{ortho} of C$_6$H$_4$CH$_3$); ^{13}C NMR (CDCl$_3$): δ 15.7 (d, ^3J(C–P) = 4.8, CH$_3$CH$_2$O$_A$), 15.8 (d, ^3J(C–P) = 3.6, CH$_3$CH$_2$O$_B$), 21.1 (s, C$_6$H$_4$$CH_3$), 64.1 (d, ^2J(C–P) = 6.1, CH$_3$$CH_2O_A$), 64.2 (d, ^2J(C–P) = 6.1, CH$_3$$CH_2O_B$), 77.5 (td, ^2J(C–F) = 26.2, ^2J(C–P) = 5.0, HF$_2$C–CH), 114.1 (td, ^1J(C–F) = 245.8, ^3J(C–P) = 9.0, HF$_2$$C$), 127.7 (s, C_{ortho} of C$_6$H$_4$CH$_3$), 129.4 (s, C_{meta} of C$_6$H$_4$CH$_3$), 130.1 (s$_{large}$, C_{ipso} of C$_6$H$_4$CH$_3$), 139.6 (s, C_{para} of C$_6$H$_4$CH$_3$).

m/z (EI) 309 (M + H$^+$, 1%), 288 (100).

4.8.6. Diethyl 1-(4'-methoxyphenyl) 2,2-difluoroethylphosphate (9g)

^{31}P NMR (CDCl$_3$): δ −3.7 (s); ^{1}H NMR (CDCl$_3$): δ 1.13 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_A$), 1.24 (t, 3H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_B$), 3.77 (s, 3H, C$_6$H$_4$OCH_3), 3.88 (pd, 2H, ^3J(H–H) = ^3J(H–P) = 7.1, J = 3.2, CH$_3$CH_2O$_A$), 4.07 (m, 2H, CH$_3$CH_2O$_B$), 5.30 (qd, 1H, ^3J(H–P) = ^3J(H–F) = 10.0, ^3J(H–H) = 4.1, HF$_2$C–CH), 5.85 (td, 1H, ^2J(H–F) = 55.3, ^3J(H–H) = 4.1, HF$_2$C), 6.88 (d, 2H, ^3J(H–H) = 8.7, H_{meta} of C$_6$H$_4$OCH$_3$), 7.32 (d, 2H, ^3J(H–H) = 8.7, H_{ortho} of C$_6$H$_4$OCH$_3$); ^{13}C NMR (CDCl$_3$): δ 15.7 (d, ^3J(C–P) = 4.2, CH$_3$CH$_2$O$_A$), 15.8 (d, ^3J(C–P) = 4.5, CH$_3$CH$_2$O$_B$), 55.1 (s, C$_6$H$_4$OCH$_3$), 64.0 (d, ^2J(C–P) = 6.9, CH$_3$$CH_2O_A$), 64.1 (d, ^2J(C–P) = 7.0, CH$_3$$CH_2O_B$), 77.2 (td, ^2J(C–F) = 26.2, ^2J(C–P) = 5.0, HF$_2$C–CH), 114.1 (s, C_{meta} of C$_6$H$_4$OCH$_3$), 114.1 (td, ^1J(C–F) = 245.9, ^3J(C–P) = 9.2, HF$_2$$C$), 125.0 (d, ^3J(C–P) = 2.0, C_{ipso} of C$_6$H$_4$OCH$_3$), 129.3 (s, C_{ortho} of C$_6$H$_4$OCH$_3$), 160.7 (s, C_{para} of C$_6$H$_4$OCH$_3$).

m/z (EI) 324 (M$^+$, 3%), 304 (100).

4.8.7. Diethyl 1-(2'-pyridyl) 2,2-difluoroethylphosphate (9k)

^{31}P NMR (CDCl$_3$): δ −4.0 (s); ^{1}H NMR (CDCl$_3$): δ 1.31 (q, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O$_{A\ and\ B}$), 4.1 (m, 2H, CH$_3$CH_2O$_A$), 4.21 (p, 2H, ^3J(H–H) = ^3J(H–P) = 7.1, CH$_3$CH_2O$_B$), 5.52 (qd, 1H, ^3J(H–P) = ^3J(H–F) = 10.3, ^3J(H–H) = 3.6, HF$_2$C–CH), 6.22 (td, 1H, ^2J(H–F) = 54.7, ^3J(H–H) = 3.6, HF$_2$C), 7.30 (dd, 1H, ^3J(H–H) = 7.7 and 4.8, $H_{5'}$ of C$_5$H$_4$N), 7.53 (d$_{large}$, 1H, ^3J(H–H) = 7.7, $H_{3'}$ of C$_5$H$_4$N), 7.76 (td, 1H, ^3J(H–H) = 7.7, ^4J(H–H) = 1.8, $H_{4'}$ of C$_5$H$_4$N), 8.61 (dd, 1H, ^3J(H–H) = 4.8, ^4J(H–H) = 1.8, $H_{6'}$ of C$_5$H$_4$N); ^{13}C NMR (CDCl$_3$): δ 15.8 (t, ^3J(C–P) = 7.0 and 6.0, CH$_3$CH$_2$O$_{A\ and\ B}$), 64.3 (t, ^2J(C–P) = 6.8 and 7.1, CH$_3$$CH_2O_{A\ and\ B}$), 77.4 (ddd, ^2J(C–F) = 27.1 and 22.7, ^2J(C–P) = 4.6, HF$_2$C–CH), 119.0 (td, ^1J(C–F) = 248.2, ^3J(C–P) = 5.6, HF$_2$$C$), 122.7 (s, $C_{3'}$ of C$_5$H$_4$N), 124.2 (s, $C_{5'}$ of C$_5$H$_4$N), 137.2 (s, $C_{4'}$ of C$_5$H$_4$N), 149.4 (s, $C_{6'}$ of C$_5$H$_4$N), 153.0 (d, ^3J(C–P) = 2.8, $C_{2'}$ of C$_5$H$_4$N).

m/z (EI) 295 (M$^+$, 31%), 275 (45), 250 (52), 227 (82).

4.8.8. Diethyl (1'-difluoromethyl)cyclohexylphosphate (10a)

^{31}P NMR (CDCl$_3$): δ −7.5 (s); ^{19}F NMR (CDCl$_3$): δ −133.9 (d, ^2J(F–H) = 57.1, HF_2CCOP); ^{1}H NMR (CDCl$_3$): δ 1.18 (m, 1H, COH(CH$_2$CH$_2$)$_2$CH_{ax}H$_{eq}$), 1.32 (t, 6H, ^3J(H–H) = 7.1, CH_3CH$_2$O), 1.62 (m + d, 7H, ^3J(H–H) = 6.3, COH(CH_{ax}H$_{eq}$CH_2)$_2$CH$_{ax}$$H_{eq}$), 2.09 (d$_{large}$, 2H, ^3J(H–H) = 10.5, COH(CH$_{ax}$$H_{eq}CH_2$)$_2CH_2$), 4.10 (p, 4H, ^3J(H–H) = ^3J(H–P) = 7.1, CH$_3$CH_2O), 6.12 (t, 1H, ^2J(H–F) = 56.2, HF$_2$C); ^{13}C NMR (CDCl$_3$): δ 16.3 (d, ^3J(C–P) = 7.5, CH$_3$CH$_2$O), 20.8 (s, COH(CH$_2$$CH_2$)$_2CH_2$), 25.3 (s, COH(CH$_2CH_2$)$_2$$CH_2$), 29.1 (t, ^3J(C–F) = 3.1, COH(CH$_2$CH$_2$)$_2$CH$_2$), 64.2 (d, ^2J(C–P) = 6.2, CH$_3$$CH_2$O), 83.5 (td, ^2J(C–F) = 22.7, ^2J(C–P) = 7.5, HF$_2$C–CH), 115.3 (t, ^1J(C–F) = 247.3, HF$_2$$C$).

m/z (CI +ve) 287 (M + H$^+$, 100%).

4.8.9. 1,1-Difluoro 2-(4'-dimethylamino)phenyl ethene issued from 7h

^{1}H NMR (CDCl$_3$): δ 2.98 (s, 6H, N(CH_3)$_2$), 5.20 (dd, 1H, ^3J(H–F$_{trans}$) = 26.9, ^3J(H–F$_{cis}$) = 4.0, F$_2$C=CH), 6.72 (d, 2H, ^3J(H–H) = 8.8, H_{meta} of C$_6$H$_4$), 7.24 (d, 2H, ^3J(H–H) = 8.8, H_{ortho} of C$_6$H$_4$).

m/z (EI) 183 (M$^+$, 100%), 167 (44).

4.8.10. (1-Difluoromethylene-1,2,3,4-tetrahydro)naphthyl issued from ***8c***

^{1}H NMR ($CDCl_3$): δ 1.92 (pd, 2H, ^3J(H–H) = 6.3, ^5J(H–F) = 1.6, H_3), 2.55 (m, 2H, H_2), 2.87 (t, 2H, ^3J(H–H) = 6.3, H_4), 7.15 (m, 3H, $H_{5,\ 6\ \text{and}\ 7}$), 7.65 (d_{large}, 1H, ^5J(H–F) = 6.3, H_8); ^{13}C NMR ($CDCl_3$): δ 24.0 (s, C_3), 30.5 (s, C_4), 31.1 (s, C_2), 89.0 (dd, ^2J(C–F) = 22.4 and 10.0, C_1), 126.9 (s, C_6), 127.3 (s, C_7), 127.9 (d, ^4J(C–F) = 13.9, C_8), 129.7 (s, C_5 and C_{10}), 138.2 (d, ^3J(C–F) = 4.0, C_9), 153.6 (dd, ^1J(C–F) = 294.7 and 285.2, CF_2).

m/z (EI) 180 (M^+, 35), 147 (70), 129 (100).

Acknowledgements

We gratefully acknowledge financial support by the Centre National de la Recherche Scientifique (R.W.). We are also grateful to Miss N. Phung (URA 459) of the University of Reims for ^{19}F measurements, and Mr. M. Levard (URA 1307) of the Ecole Polytechnique for the mass spectra.

References

[1] W.F. Bailey and J.J. Patricia, *J. Organomet. Chem.*, *352* (1988) 1.
[2] D. Seyferth and R.S. Marmor, *J. Organomet. Chem.*, *59* (1973) 237.
[3] J.F. Normant, P. Perriot and J. Villieras, *Synthesis*, (1975) 458.
[4] P. Coutrot, C. Laurenco, J.F. Normant, P. Perriot, P. Savignac and J. Villieras, *Synthesis*, (1977) 615.
[5] J. Villieras, A. Reliquet and J.F. Normant, *Synthesis*, (1978) 27.
[6] J. Villieras, P. Perriot and J.F. Normant, *Synthesis*, (1978) 29.
[7] J. Villieras, P. Perriot and J.F. Normant, *Synthesis*, (1978) 31.
[8] P. Perriot, J. Villieras and J.F. Normant, *Synthesis*, (1978) 33.
[9] G.T. Lowen and M.R. Almond, *J. Org. Chem.*, *59* (1994) 4548.
[10] C. Grandin, N. Collignon and P. Savignac, *Synthesis*, (1995) 239.
[11] Y. Zanella, S. Berté-Verrando, R. Dizière and P. Savignac, *J. Chem. Soc. Perkin Trans. I*, (1995) 2835.
[12] R. Dizière and P. Savignac, *Tetrahedron Lett.*, *37* (1996) 1783.
[13] A. Marinetti and P. Savignac, Diethyl 1,1-dichloromethylphosphonate. Preparation and use in the syntheses of alkynes, *Organic Syntheses*, in press.
[14] D.J. Burton, R. Takei and S. Shin-Ya, *J. Fluorine Chem.*, *18* (1981) 197.
[15] D.J. Burton, T. Ishihara and M. Maruta, *Chem. Lett.*, (1982) 755.
[16] M. Obayashi, E. Ito, K. Matsui and K. Kondo, *Tetrahedron Lett.*, *23* (1982) 2323.
[17] G.M. Blackburn and M.J. Parratt, *J. Chem. Soc., Chem. Commun.*, (1983) 886.
[18] D.J. Burton, L.G. Sprague, D.J. Pietrzyk and S.H. Edelmuth, *J. Org. Chem.*, *49* (1984) 3437.
[19] G.M. Blackburn, D. Brown and S.J. Martin, *J. Chem. Res., Synop.*, (1985) 92.
[20] D.J. Burton and L.G. Sprague, *J. Org. Chem.*, *53* (1988) 1523.
[21] D.J. Burton and L.G. Sprague, *J. Org. Chem.*, *54* (1989) 613.
[22] R.D. Chambers, R. Jaouhari and D. O'Hagan, *J. Fluorine Chem.*, *44* (1989) 275.
[23] L.G. Sprague, D.J. Burton, R.D. Guneratne and W.E. Benett, *J. Fluorine Chem.*, *49* (1990) 75.
[24] S. Halazy, A. Ehrhard and C. Danzin, *J. Am. Chem. Soc.*, *113* (1991) 315.
[25] S.F. Martin, D.W. Dean and A.S. Wagman, *Tetrahedron Lett.*, *33* (1992) 1839.
[26] S. Chen and C. Yuan, *Phosphorus, Sulfur, and Silicon*, *82* (1993) 73.
[27] D.B. Berkowitz, M. Eggen, Q. Shen and D.G. Sloss, *J. Org. Chem.*, 58 (1993) 6174.
[28] D.J. Burton and R.M. Flynn, *J. Fluorine Chem.*, *10* (1977) 329.
[29] C.F. Bigge, J.T. Drummond and G. Johnson, *Tetrahedron Lett.*, *30* (1989) 7013.
[30] G.M. Kosolapoff, *J. Am. Chem. Soc.*, *69* (1947) 1002.
[31] G. Kamai, *Dokl. Akad. Nauk SSSR*, *79* (1951) 795; *C.A. 46* (1952) 6081.
[32] R. Rabinowitz and R. Marcus, *J. Am. Chem. Soc.*, *84* (1962) 1312.
[33] R.G. Harvey and E.R. DeSombre, *Topics in Phosphorus Chemistry*, Vol. 1, Wiley Interscience, New York, 1962, p. 57.
[34] A.F. Isbell, *US Dept. Com. Office Tech. Serv.*, Ad 266695; *C.A. 58* (1963) 11394.
[35] B. Miller, *Topics in Phosphorus Chemistry*, Vol. 2, Wiley Interscience, New York, 1965, p. 133.
[36] J. Plumb, R. Obrycki and C. Griffin, *J. Org. Chem.*, *31* (1966) 2455.
[37] R. Obrycki and C. Griffin, *J. Org. Chem.*, *33* (1968) 632.
[38] J. Fu, W. Bentrude and C. Griffin, *J. Am. Chem. Soc.*, *94* (1972) 7717.
[39] D.J. Burton and R.M. Flynn, *Synthesis*, (1979) 615.
[40] S. Bakkas, M. Juliard and M. Chanon, *Tetrahedron*, *43* (1987) 501.
[41] C.U. Kim, B.Y. Luh, P.F. Misco, J.J. Bronson, M.J.M. Hitchcock, I. Ghazzouli and J.C. Martin, *J. Med. Chem.*, *33* (1990) 1207.
[42] S. Halazy and V. Gross-Bergès, *J. Chem. Soc., Chem. Commun.*, (1992) 743.
[43] D.P. Phillion and D.G. Cleary, *J. Org. Chem.*, *57* (1992) 2763.
[44] S. Chen and C. Yuan, *Phosphorus, Sulfur, and Silicon*, *82* (1993) 73.