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A Facile and Efficient Synthesis of Diethyl α,α-Chlorofluoroalkanephosphonates

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ABSTRACT: *A facile and efficient synthetic methodology for the preparation of diethyl α,α-chlorofluoroalkanephosphonates is described. A wide variety of diethyl α-hydroxyphosphonates were investigated by a two-step halogenation procedure, which includes nucleophilic chlorination with PPh_3 and CCl_4 and electrophilic fluorination with* N*-fluorobisbenzenesulfonimide. Aromatic and aliphatic α,α-chlorofluorophosphonates could be prepared by this method with acceptable yields.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:250–255, 2010; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20604

INTRODUCTION

In the past few years, the α-functionalized phosphonates have attracted considerable attention in the field of biology, pharmacology, and organic chemistry [1–7]. In particular, α-halogenated phosphonates, which are widely utilized as synthetic reagents and especially as good precursors for the synthesis of symmetrical or unsymmetrical α-halogenoalkenes and alkynes in mild conditions by the Wittig–Horner reaction [8–11], are fascinating organophosphorus compounds. Moreover, the α-monohalogenated and α,α-dihalogenated phosphonates are often designed as phosphate mimics to be used as enzyme inhibitors and metabolite probes because of their structural and electronic similarities to the parent phosphate groups [12–21]. A number of methods for the introduction of a halogen and two same halogens at the α-CH_2 position of phosphonates by the nucleophilic and electrophilic halogenations have been reported. The nucleophilic halogenation is effectively achieved usually starting with α-hydroxyphosphonates or α-ketophosphonates using nucleophilic halogenating reagents, such as Et_2N-SF_3 (DAST) [22–24] for fluorination, PPh_3/CCl_4 [25] and $SOCl_2$ [26] for chlorination, $SOBr_2$ [26], PPh_3/CBr_4 [27], PPh_3/Br_2/pyridine [27], $CH_2{=}CHCH_2Br/N,N'$-carbonyldiimidazole (CDI) [28], and PPh_3/DDQ/*n*-Bu_4NBr [29] for bromination, MeI/CDI [28], PI_3 [26], and PPh_3/DDQ/*n*-Bu_4NI [29] for iodination. Meanwhile, electrophilic halogenation is a more powerful method to generate α-halogenated phosphonates and α,α-dihalogenated phosphonates, which directly started with phosphonates. Electrophilic halogenating reagents usually are *N*-fluorobisbenzenesulfonimide (NFSI), selectfluor, and a lot of other electrophilic fluorinating reagents for fluorination [30–33], hexachloroethane ($C1_3C{-}CC1_3$) [32], and CCl_4[34] for chlorination, tetrachlorodibromoethane ($BrC1_2C{-}CC1_2Br$) [32] for bromination, and iodine [32] for iodination. However, little attention has been given to explore more complicated α,α-chlorofluorophosphonates as yet. As part of our program to extend new potent and nonpeptidyl inhibitors of protein tyrosine phosphatases (PTPs), it is necessary to synthesize a wide variety of α,α-chlorofluorophosphonate molecules. According to the literature, the α-monobromophosphonates [35], α-monofluorophosphonates [4,23], and α,α-difluorophosphonates [36–38] as natural phosphate mimetics can potentially target phosphate-binding

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pockets and are directed to an enzyme active site for covalent modification in an activity-dependent fashion. But these compounds have respective drawbacks. For example, the radius of bromine atom is much larger than hydrogen, which resulted in the probes having a difficulty to approach target pockets, and the fluorine atom is a poor leaving group. On the basis of both electronic and steric considerations, α,α-chlorofluorophosphonates as enzyme inhibitors and phosphate mimics will have their own special advantages. Therefore, it is a desirable and unfulfilled goal to develop a general method to obtain a wide variety of α,α-chlorofluorophosphonates.

This paper reports a new and efficient approach to synthesize diethyl α,α-chlorofluorophosphonates, which includes a two-step halogenation procedure. We found that a wide range of α,α-chlorofluorophosphonates could be prepared by this method with acceptable yields. Diethyl α,α-chlorofluoroalkylphosphonates can be easily synthesized, besides diethyl α,α-chlorofluoro benzylphosphonates that we reported recently [39].

RESULTS AND DISCUSSION

Since electrophilic monohalogenation at the α-CH_2 position of phosphonates could directly form complex mixtures of monohalogeno-, dihalogeno-, and nonhalogenophonates, we started our preparation with nucleophilic halogenation of α-hydroxyphosphonates (**1**) to give monohalogenophonates (**2**), which underwent electrophilic halogenation to give diethyl α,α-chlorofluorophosphonates (**3**). The strategy is shown in Scheme 1.

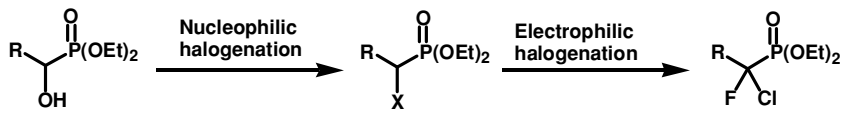
A variety of starting diethyl α-hydroxyphosphonates, with different length of carbon alkyl chains or substituted aromatic rings, were involved in the reaction sequence. They could be easily prepared in excellent yields from corresponding aldehydes and diethyl phosphite (the Pudovik reaction) on a laboratory scale [40]. With these starting materials in hand, the diethyl α,α-chlorofluorophosphonates were prepared by a nucleophilic halogenation procedure and then electrophilic halogenation procedure (Scheme 1).

Our initial approach to the introduction of fluorine atom relied on a nucleophilic fluorination to prepare the α-fluorophosphonates (**2**) with Et_2N-SF_3 (DAST), and this step worked quite well. However, the subsequent electrophilic chlorination of α-monofluorophosphonates with $C1_3C$—$CC1_3$ and sodium hexamethyldisilazane (NaHMDS) did not proceed as smoothly as expected. Thereby, the two-step halogenation procedure that included a nucleophilic fluorination and electrophilic chlorination is not advisable, because of weak nucleophilicity of intermediate α-fluorophosphonate carbanions and the weak electrophilicity of the $C1_3C$—$CC1_3$.

The poor results led us to seek an alternate preparation of α,α-chlorofluorophosphonates **3**. We decided to exchange the sequence of halogenations. Therefore, the appropriate α-chlorophosphonates were formed by treatment of α-hydroxyphosphonates with triphenylphosphine in CCl_4 [25,39] at 80°C in high yields (**2a–2i**, Table 1, Scheme 2).

In the last step, the diethyl α-chlorophosphonate carbanions, the key intermediates in the synthesis of α,α-chlorofluorophosphonates **3**, were very selectively formed from diethyl α-chlorophosphonates **2** by using sodium hexamethyldisilazane (NaHMDS, 1.5–2 equiv) as metallating agent at −78°C (Scheme 3). The fluorination step took place at low temperature (−78° to −30°C) using excess fluorinating reagents (NFSI, 1.3 equiv). After warming to room temperature, the reaction was quenched with dilute aqueous HCl (0.01 N) to neutralize excess NaHMDS. The crude diethyl α,α-chlorofluorophosphonates **3** could be isolated through a silica gel column with EtOAc/hexane (1:5). Fortunately, this procedure worked well and a wide variety of α,α-chlorofluoroalkylphosphonates and α,α-chlorofluorobenzylphosphonates (**3a–3i**, Table 2) were obtained in reasonable to good yields except **3a** and **3d**. All the structures were confirmed by the analytical and spectral data.

The compounds were stable at 4°C for at least several weeks. An array of electron-withdrawing or electron-donating functional groups, such as ether, halogen, and cyano, on aromatic rings could be tolerated. We also investigated the influence of steric



1 2 3

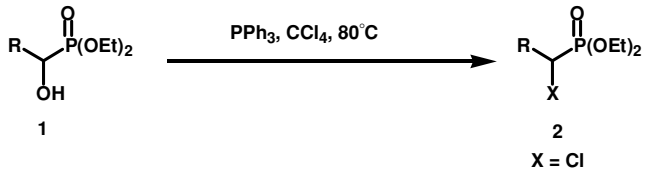
R = aryl or alkyl, X = Cl or F

SCHEME 1

TABLE 1 Diethyl α-Chlorophosphonates **2**

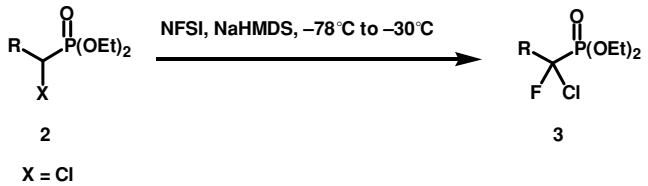
2	*R*	*^1H NMR ($CDCl_3$) $\delta\alpha_{CH}$ ($^2J_{PH}$)*	*^{13}C NMR ($CDCl_3$) $\delta\alpha_{CH}$ ($^1J_{PC}$)*	*Yield[a] (%)*
a	2-$CH_3OC_6H_4$-	5.64 (d, $^2J_{PH} = 14.0$)	45.5 (d, $^1J_{PC} = 162.5$)	77
b	3-$CH_3OC_6H_4$-	4.87 (d, $^2J_{PH} = 14.1$)	53.3 (d, $^1J_{PC} = 158.6$)	81
c	3-NCC_6H_4-	4.91 (d, $^2J_{PH} = 14.8$)	52.3 (d, $^1J_{PC} = 157.6$)	85
d	2-ClC_6H_4-	5.58 (d, $^2J_{PH} = 14.8$)	48.9 (d, $^1J_{PC} = 161.0$)	80
e	3-ClC_6H_4-	4.86 (d, $^2J_{PH} = 14.4$)	52.7 (d, $^1J_{PC} = 158.2$)	83
f	Et-	3.78 (dt, $^2J_{PH} = 10.3$)	54.1 (d, $^1J_{PC} = 158.7$)	89
g	*i*-Pr-	3.86 (dd, $^2J_{PH} = 12.1$)	59.0 (d, $^1J_{PC} = 156.6$)	82
h	*n*-Pr-	3.86 (dt, $^2J_{PH} = 10.7$)	51.7 (d, $^1J_{PC} = 159.1$)	76
i	*i*-Bu-	3.92 (dt, $^2J_{PH} = 11.3$)	50.3 (d, $^1J_{PC} = 159.7$)	79

[a]Isolated yields.



SCHEME 2

hindrance of the substituents (R). The reaction was general for substrates **2** with *m*-substituted aromatic rings or with alkyl substituents. However, *o*-methoxy derivative **3a** and *o*-chloro derivative **3d** were not obtained by flash column chromatography of silica gel, and only trace products were observed by TLC. This decrease in yield could be attributed to the increased steric demands of the *o*-substituted phosphonates. Under these conditions, the step of deprotonation to form diethyl α-chlorophosphonates carbanions was slowed down because of a difficult approach of NaHMDS in a highly crowded position. α,α-Chlorofluoroalkylphosphonates (**3f–3i**) were obtained in moderate yields.



SCHEME 3

CONCLUSION

In conclusion, we have demonstrated that a wide variety of diethyl α,α-chlorofluorophosphonates can be synthesized by two steps from the corresponding α-hydroxyphosphonates via nucleophilic chlorination and then electrophilic fluorination. This procedure is applicable to preparation of a wide range of aromatic and aliphatic substituted α,α-chlorofluorophosphonates. These compounds could be potential inhibitor of PTPs. Attempts toward the asymmetric version of the reaction, as well as the extension of this method, are currently underway.

EXPERIMENTAL

General

NMR spectra were operated at 300 MHz for proton, 75 MHz for carbon, 121.5 MHz for phosphorus,

TABLE 2 Diethyl α,α-Chlorofluorophosphonate **3**

3	*R*	*^{19}F NMR ($CDCl_3$) $\delta\alpha_{CClF}$ ($^2J_{FP}$)*	*^{31}P NMR ($CDCl_3$) $\delta\alpha_{CClF}$ ($^2J_{PF}$)*	*Yield (%)[a]*
a	2-$CH_3OC_6H_4$-			Trace
b	3-$CH_3OC_6H_4$-	−132.04 (d, $^2J_{FP} = 93.1$)	2.23 (d, $^2J_{PF} = 90.6$)	79
c	3-NCC_6H_4-	−128.38 (d, $^2J_{FP} = 90.2$)	1.35 (d, $^2J_{PF} = 89.2$)	82
d	2-ClC_6H_4-			Trace
e	3-ClC_6H_4-	−130.60 (d, $^2J_{FP} = 93.1$)	4.10 (d, $^2J_{PF} = 90.3$)	80
f	Et-	−127.94 (dq, $^2J_{FP} = 87.4$)	4.06 (d, $^2J_{PF} = 90.2$)	62
g	*i*-Pr-	−124.20 (d, $^2J_{FP} = 90.2$)	3.74 (d, $^2J_{PF} = 90.2$)	72
h	*n*-Pr-	−127.71 (dq, $^2J_{FP} = 90.2$)	5.54 (d, $^2J_{PF} = 90.4$)	65
i	*i*-Bu-	−126.78 (dq, $^2J_{FP} = 90.2$)	4.73 (d, $^2J_{PF} = 90.5$)	52

[a]Isolated yields.

and 282 MHz for fluorine. ^{31}P downfield shifts (δ) are expressed in ppm with a positive sign 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 chemical shifts (δ) are reported in ppm relative to $CFCl_3$ as external standard. Coupling constants (J) are given in hertz. The following abbreviations are used: s, d, t, q, p, h, and m for singlet, doublet, triplet, quadruplet, pentuplet, heptuplet, and multiplet, respectively. High-resolution electron microscopy (HRMS) spectra were recorded on a high resolution ESI-FTICR mass spectrometry (Varian 7.0T). Organic solvents were purified by standard procedures. Tetrahydrofuran (THF) was distilled under an inert atmosphere from purple solutions of sodiumbenzophenone ketyl. The synthesis of all compounds was carried out under dry N_2.

General Procedure for the Preparation of α-Hydroxyphosphonates **1**

To a solution of sodium ethoxide (1.0 mmol) in CH_2Cl_2 (10 mL), diethyl phosphite (0.912 mmol) was added via a syringe at −35°C under argon. The reaction was stirred for 30 min, and a solution of aldehyde (0.76 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 3–5 h. The reaction was quenched with 0.1 N HC1, and the resulting solution was extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, and the solvents were removed in vacuo. The crude material was purified via flash column chromatography [40].

General Procedure for the Preparation of α-Chlorophosphonates **2** *from α-Hydroxyphosphonates* **1**

A solution of **1** (3.46 mmol) and triphenylposphine (5.19 mmol) in dry CCl_4 was refluxed for 8 h under argon. Then, the mixture was evaporated under reduced pressure, and the semisolid residue was extracted with petroleum ether. The combined extracts were filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography of silica gel [25,39].

General Procedure for the Preparation of α,α-Chlorofluorophosphonates **3** *from α-Chlorophosphonates* **2**

To a solution of the α-chlorophosphonates **2** (0.94 mmol) in dry THF (10 mL) at −78°C, drop wise a solution of NaHMDS (1.69 mmol, 2.0 M in THF) in dry THF (5 mL) under argon was added. The resulting dark green solution was stirred for 1 h at −78°C. A solution of NFSI (1.31 mmol) in dry THF (5 mL) was added over a period of 10 min. After addition, the solution was stirred for 1 h and then allowed to warm to −30°C. The reaction was quenched with 0.01 N HC1, and the resulting solution was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, and solvents were removed under reduced pressure. The crude material was purified via flash column chromatography of silica gel [39].

*Diethyl α,α-Chlorofluoro-3-methoxybenzylphosphonates (***3b***).* ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, $J = 6.8$ Hz, 3H), 1.39 (t, $J = 6.7$ Hz, 3H), 3.84 (s, 3H), 3.95–4.00 (m, 1H), 4.08–4.16 (m, 1H), 4.30–4.34 (m, 2H), 6.96 (d, $J = 7.4$ Hz, 1H), 7.20 (s, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.38–7.93 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.2$ (d, $^{3}J_{PC} = 5.6$ Hz), 16.4 (d, $^{3}J_{PC} = 5.6$ Hz), 55.4, 65.2 (d, $^{2}J_{PC} = 7.0$ Hz), 65.6 (d, $^{2}J_{PC} = 6.9$ Hz), 106.7 (dd, $^{1}J_{PC} = 195.8$ Hz, $^{1}J_{FC} = 258.6$ Hz), 111.7, 116.0, 118.5, 129.4, 137.3, 159.4 ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 2.23$ (d, $^{2}J_{FP} = 90.6$) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -132.04$ (d, $^{2}J_{PF} = 93.1$ Hz) ppm; HRMS for $C_{12}H_{17}ClFO_4P$ [M + Na^+]: calculated 333.0429; found 333.0425.

*Diethyl α,α-Chlorofluoro-3-cyanobenzylphosphonates (***3c***).* ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.0$ Hz, 3H), 1.40 (t, $J = 7.0$ Hz, 3H), 4.06–4.19 (m, 2H), 4.30–4.40 (m, 2H), 7.58 (t, $J = 7.7$ Hz, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.80 (d, $J = 11.0$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.2$ (d, $^{3}J_{PC} = 5.5$ Hz), 16.4 (d, $^{3}J_{PC} = 5.5$ Hz), 65.4 (d, $^{2}J_{PC} = 7.1$ Hz), 66.1 (d, $^{2}J_{PC} = 7.2$ Hz), 105.7 (dd, $^{1}J_{PC} = 193.9$ Hz, $^{1}J_{FC} = 259.0$ Hz), 112.8, 117.9, 129.3, 129.8, 130.7, 133.5, 137.8 ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 1.35$ (d, $^{2}J_{FP} = 89.2$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -128.38$ (d, $^{2}J_{PF} = 90.2$ Hz) ppm; HRMS for $C_{12}H_{14}ClFNO_3P$ [M + Na^+]: calculated 328.0276; found 328.0280.

*Diethyl α,α-Chlorofluoro-3-chlorobenzylphosphonates (***3e***).* ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.1$ Hz, 3H), 1.39 (t, $J = 7.0$ Hz, 3H), 4.01–4.19 (m, 2H), 4.30–4.38 (m, 2H), 736 (d, $J = 7.8$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.65 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.2$ (d, $^{3}J_{PC} = 5.6$ Hz), 16.4 (d, $^{3}J_{PC} = 5.6$ Hz), 65.3 (d, $^{2}J_{PC} = 7.1$ Hz), 65.8 (d, $^{2}J_{PC} = 7.2$ Hz), 106.0 (dd, $^{1}J_{PC} = 195.6$ Hz, $^{1}J_{FC} = 258.6$ Hz), 124.6 (d, $^{3}J_{FC} = 8.0$ Hz), 126.4 (d, $^{3}J_{FC} = 8.8$ Hz), 129.6, 130.2, 134.4, 137.6 ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 4.10$ (d, $^{2}J_{FP} = 90.3$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): $\delta = -130.60$ (d, $^{2}J_{PF} = 93.1$ Hz) ppm; HRMS

for $C_{11}H_{14}Cl_2FO_3P$ [M + Na^+]: calculated 336.9934; found 336.9927.

*Diethyl α,α-Chlorofluoroethylphosphonates (**3f**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.3 Hz, 3H), 1.36–1.42 (m, 6H), 2.05–2.37 (m, 2H), 4.24–4.38 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.6 (d, $^3J_{PC}$ = 6.1 Hz), 16.3 (d, $^3J_{PC}$ = 6.3 Hz), 32.0 (d, $^2J_{PC}$ = 20.6 Hz), 64.6 (d, $^2J_{PC}$ = 7.0 Hz), 65.1 (d, $^2J_{PC}$ = 7.0 Hz), 110.0 (dd, $^1J_{PC}$ = 195.9 Hz, $^1J_{FC}$ = 255.4 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 4.06 (d, $^2J_{FP}$ = 90.2 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −127.94 (dq, $^2J_{PF}$ = 87.4 Hz, $^3J_{HF}$ = 11.3 Hz) ppm; HRMS for $C_7H_{15}ClFO_3P$ [M + Na^+]: calculated 255.0324; found 255.0325.

*Diethyl α,α-Chlorofluoroisopropylphosphonates (**3g**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (dd, J_1 = 3.8 Hz, J_2 = 6.4 Hz, 6H), 1.36–1.42 (m, 6H), 2.53–2.60 (m, 2H), 4.24–4.37 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (d, $^3J_{PC}$ = 6.8 Hz), 16.3 (d, $^3J_{PC}$ = 5.7 Hz), 17.4 (d, $^3J_{PC}$ = 6.0 Hz), 36.4 (d, $^2J_{PC}$ = 19.2 Hz), 64.4 (d, $^2J_{PC}$ = 7.5 Hz), 65.0 (d, $^2J_{PC}$ = 10.8 Hz), 113.5 (dd, $^1J_{PC}$ = 192.2 Hz, $^1J_{FC}$ = 255.8 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 3.74 (d, $^2J_{FP}$ = 90.2 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −124.20 (d, $^2J_{PF}$ = 90.2 Hz) ppm; HRMS for $C_8H_{17}ClFO_3P$ [M + Na^+]: calculated 269.0480; found 269.0483.

*Diethyl α,α-Chlorofluoropropylphosphonates (**3h**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.40 (t, J = 7.0 Hz, 3H), 1.66–1.77 (m, 2H), 2.04–2.36 (m, 2H), 4.24–4.38 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 15.8 (d, $^3J_{PC}$ = 6.0 Hz), 16.4 (d, $^3J_{PC}$ = 5.8 Hz), 40.4 (d, $^2J_{PC}$ = 7.0 Hz), 40.7 (d, $^2J_{PC}$ = 7.0 Hz), 64.5 (d, $^2J_{PC}$ = 7.1 Hz), 65.1 (d, $^2J_{PC}$ = 7.0 Hz), 109.6 (dd, $^1J_{PC}$ = 195.5 Hz, $^1J_{FC}$ = 255.4 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 5.54 (d, $^2J_{FP}$ = 90.4 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −127.71 (dq, $^2J_{PF}$ = 90.2 Hz, $^3J_{HF}$ = 8.5 Hz) ppm; HRMS for $C_8H_{17}ClFO_3P$ [M + Na^+]: calculated 269.0480; found 269.0478.

*Diethyl α,α-Chlorofluoroisobutylphosphonates (**3i**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.05 (m, 6H), 1.39 (dt, J_1 = 2.9 Hz, J_2 = 7.0 Hz, 6H), 2.08–2.28 (m, 3H), 4.26–4.51 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (d, $^3J_{PC}$ = 5.6 Hz), 23.0, 24.0 (d, $^3J_{PC}$ = 10.0 Hz), 45.8 (d, $^2J_{PC}$ = 12.2 Hz), 64.6 (d, $^2J_{PC}$ = 7.1 Hz), 65.2 (d, $^2J_{PC}$ = 7.1 Hz), 110.1 (dd, $^1J_{PC}$ = 195.9 Hz, $^1J_{FC}$ = 257.5 Hz) ppm; ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 4.73 (d, $^2J_{FP}$ = 90.5 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −126.78 (dq, $^2J_{PF}$ = 90.2 Hz, $^3J_{HF}$ = 19.7 Hz) ppm; HRMS for $C_9H_{19}ClFO_3P$ [M + Na^+]: calculated 283.0637; found 283.0634.

REFERENCES

[1] Olah, G. A.; Wu, A. J Org Chem 1991, 56, 902.
[2] Sprecher, M.; Kost, D. J Am Chem Soc 1994, 116, 1016.
[3] Telan, L. A.; Poon, C.-D.; Evans, S. A. J Org Chem 1996, 61, 7455.
[4] Taylor, W. P.; Zhang, Z.-Y.; Widlanski, T. S. Bioorg Med Chem 1996, 4, 1515.
[5] Sikora, D.; Nonas, T.; Gajda, T. Tetrahedron 2001, 57, 1619.
[6] Romanenko, V. D.; Kukhar, V. P. Chem Rev 2006, 106, 3868.
[7] Romanenko, V. D.; Kukhar, V. P. Tetrahedron 2008, 64, 6153.
[8] Maryanoff, B. E.; Reitz, A. B. Chem Rev 1989, 89, 863.
[9] Zimmer, H.; Bercz, P. J.; Maltenieks, O. J.; Moore, M. W. J Am Chem Soc 1965, 87, 2777.
[10] Kumaraswamy, S.; Swamy, K. Tetrahedron Lett 1997, 38, 2183.
[11] Allmendinger, T.; Fujimoto, R.; Gasparini, F.; Schilling, W.; Satoh, Y. Chimia 2004, 58, 133.
[12] Martin, S. F.; Wong, Y. L.; Wagman, A. S. J Org Chem 1994, 59, 4821.
[13] Halazy, S.; Ehrhard, A.; Danzin, C. J Am Chem Soc 1991, 113, 315.
[14] McLennan, A. G.; Taylor, G. E.; Prescott, M.; Blackburn, G. M. Biochemistry 1989, 28, 3868.
[15] Blackburn, G. M.; Perree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. Chem Scr 1986, 26, 21.
[16] Caplan, N. A.; Pogson, C. I.; Hayes, D. J.; Blackburn, G. M. Bioorg Med Chem Lett 1998, 8, 515.
[17] Wang, G.; Boyle, N.; Chen, F.; Rajappan, V.; Fagan, P.; Brooks, J. L.; Hurd, T.; Leeds, J. M.; Rajwanshi, V. K.; Jin, Y.; Prhavc, M.; Bruice, T. W.; Cook, P. D. J Med Chem 2004, 47, 6902.
[18] Liu, D. G.; Gao, Y.; Voigt, J. H.; Lee, K.; Nicklaus, M. C.; Wu, L.; Zhang, Z.-Y.; Terrence, R.; Burke, J. Bioorg Med Chem Lett 2003, 13, 3005.
[19] Yao, Z. J.; Ye, B.; Wu, X. W.; Wang, S. M.; Wu, L.; Zhang, Z.-Y.; Terrence R.; Burke, J. Bioorg Med Chem 1998, 6, 1799.
[20] Blackburn, G. M. Chem Ind London 1981, 5, 134.
[21] Berkowitz, D. B.; Bose, M. J Fluorine Chem 2001, 112, 13.
[22] Caplan, N. A.; Pogson, C. I.; Hayes, D. J.; Blackburn, G. M. J Chem Soc, Perkin Trans 1 2000, 3, 421.
[23] Pham, V.; Zhang, W.; Chen, V.; Whitney, T.; Yao, J.; Froese, D.; Friesen, A. D.; Diakur, J. M.; Haque, W. J Med Chem 2003, 46, 3680.
[24] Benayoud, F.; deMendonca, D. J.; Digits, C. A.; Moniz, G. A.; Sanders, T. C.; Hammond, G. B. J Org Chem 1996, 61, 5159.
[25] Gajda, T. Synthesis 1990, 717.
[26] Kumaraswamy, S.; Selvi, R. S.; Kumara Swamy, K. C. Synthesis 1997, 207.
[27] Gajda, T. Phophorus Sulfur Silicon Relat Elem 1990, 53, 327.

[28] Green, D.; Elgendy, S.; Patel, G.; Baban, J. A.; Skordalakes, E.; Husman, W.; Kakkar, V. V.; Deadman, J. Tetrahedron 1996, 52, 10215.
[29] Firouzabadi, H.; Iranpoor, N.; Sobhani, S. Tetrahedron 2004, 60, 203.
[30] Wang, Q.; Huang, Z.; Ramachandran, C.; Dinaut, A. N.; Taylor, S. D. Bioorg Med Chem Lett 1998, 8, 345.
[31] Taylor, S. D.; Kotoris, C. C.; Dinaut, A. N.; Chen, M. J. Tetrahedron 1998, 54, 1691.
[32] Iorga, B.; Eymery, F.; Savignac, P. Tetrahedron 1999, 55, 2671.
[33] Xu, Y.; Qian, L.; Prestwich, G. D. Org Lett 2003, 5, 2267.
[34] Petrova, J.; Coutrot, P.; Dreux, M.; Savignac, P. Synthesis 1975, 658.
[35] Kumar, S.; Zhou, B.; Liang, F.; Wang, W.-Q.; Huang, Z.; Zhang, Z.-Y. Proc Natl Acad Sci USA 2004, 101, 7943.
[36] Shen, K.; Keng, Y.-F.; Wu, L.; Guo, X.-L.; Lawrence, D. S.; Zhang, Z.-Y. J Biol Chem 2001, 276, 47311.
[37] Sun, J.-P.; Fedorov, A. A.; Lee, S.-Y.; Guo, X-.L.; Shen, K.; Lawrence, D. S.; Almo, S. C.; Zhang, Z.-Y. J Biol Chem 2003, 278, 12406.
[38] Lee, S.-Y.; Liang, F.; Guo, X.-L.; Xie, L.; Cahill, S. M.; Blumenstein, M.; Yang, H.; Lawrence, D. S.; Zhang, Z.-Y. Angew Chem, Int Ed 2005, 44, 4242.
[39] Wu, D.; He, Y. H.; Tang, R. C.; Guan, Z. Synlett 2009, 13, 2180.
[40] Drescher, M.; Li, Y.-F.; Hammerschmidt, F. Tetrahedron 1995, 51, 4933.