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Synthesis and spectral properties of fluorinated α,β-epoxyphosphonates☆

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ABSTRACT

The methods of synthesis of two type of monofluorinated α,β-epoxyphosphonates, fosfomycin analogues, with the vicinal and geminal arrangement of fluorine and phosphorus atoms have been developed. The electrophilic monofluorination of enamine or β-enaminophosphonate using Selectfluor® have been evaluated. The selective bromination of resulting α-fluoro ketone followed by addition of phosphite and cyclization gave first desired α,β-epoxyphosphonate. The α-fluoro-β-ketophosphonate has been converted into various fluorinated haloalcohols *via* halogenation and reduction with borane complex. The reaction of ring closure of fluorohalohydrin has yielded oxirane or appropriate phosphates. The products structure has been confirmed by ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy.

1. Introduction

The three-membered oxirane ring can serve as a very useful building block offering combination of reactivity and synthetic application in organic synthesis. One of the examples of compounds with phosphonate moiety directly attached to the oxirane ring could be fosfomycin distinguishing a broad spectrum of antibiotic properties against both Gram-positive and Gram-negative bacterial infections in mammals and a synergistic effect to other classes of antibiotics (Fig. 1) [1,2]. Fosfomycin [(1*R*,2*S*)-(*Z*)-1,2-epoxypropylphosphonic acid, EPPA] is a phosphoenolpyruvate (PEP) analogue that interferes the cell wall synthesis in bacteria by inhibiting the initial step involving UDP-*N*-acetylglucosamine-3-enolpyruvyltransferase, also known as MurA [3]. Additionally it shows almost no binding to proteins. Racemic fosfomycin was obtained for the first time by Christensen in 1969 [4]. Since then, due to the advancing antimicrobial resistance, the interest in its use has fluctuated and has risen recently [5].

Presently, a number of methods are available for synthesis of EPPA and its analogues [6]. Among them, only few compounds containing fluorine atom are known [7]. Generally, the main strategies of synthesis of α,β-epoxyalkylphosphonates [8] may be classified into the reactions of dialkyl phosphites anions with α-halo ketones [9], the reaction of dialkyl halohydrinphosphonates with bases [10], the Darzens reaction of dialkyl chloromethylphosphonates with carbonyl compounds [9a,11] and the oxidation of 1,2-unsaturated phosphonates derivatives [8,12].

The first method of the formation of α,β-epoxyalkylphosphonates with concomitant introduction of phosphonate group has been reported in case of such α-halo or α-tosyl ketones as chloroacetone [9b–f] or phenacyl chloride [8,9c] and more complicated carbohydrate [9b,g] or coumarine [9h] derivatives. This reaction has been reported to involve the initial attack of nucleophilic dialkylphosphite anions [$:P(O)(OR)_2^-$] at the carbonyl carbon atom, followed by the intramolecular cyclization and displacement of leaving group leading to the desired α,β-epoxyphosphonates in moderate to good yields [9]. The reaction conditions required for the generation of dialkylphosphite anion have featured the use of alkali metals [9c,e,f], sodium metoxide [9b], sodium hydroxide [9b,h] or K_2CO_3 [9e] in two-phase system. Alternative formation of α,β-epoxyphosphonate has been accomplished by using fluoride ion-deprotonation reaction in DMF [with $HP(O)(OEt)_2$ and the α-halo ketone] [9d] or with $HP(O)(OBu)_2$ in the presence of titanium isopropoxide [with α-tosyl aldehyde and subsequent treatment with DBU] [9i]. This group of reactions sometimes proceeds with a lack of regiospecificity, in some cases the formation of the vinyl phosphates [9c,f] and β-oxophosphonates [9c] as by-products have been reported.

Other widely used approach leading to α,β-epoxyphosphonates has been based on the formation of 1,2-bisfunctional compounds

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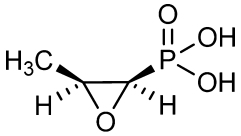


Fig. 1. Structure of (1*R*,2*S*)-1,2-epoxypropylphosphonic acid (Fosfomycin).

containing already phosphonate moiety, such as halohydrins and related structures with subsequent cyclization reactions [8]. Several variants of this approach have been reported [10]. The epoxidation cyclization was studied using a variety of α- or β-hydroxy halohydrin and bases (NaH [10b], KOH [9c,10b], EtO^- [10b], K_2CO_3 [10c], DMAP [10d], *n*-BuLi [10e]). Generally the conversion of bromohydrinphosphonates gave better results than corresponding chlorohydrinphosphonates [8], although other leaving group such as $ArSO_3^-$ [10c], TfO^- [10d] or $MeSO_3^-$ [10f,g] have been also applied. Alternative formation of α,β-epoxyphosphonate has been accomplished by cyclization of 1,2-bisfunctional hydrin obtained from silylated alcohols after deprotection with TBAF, however this strategy involves additional protection step [10h]. The chiral α,β-epoxyphosphonates obtained by this method have served mainly for the synthesis of fosfomycin analogues (from *threo* halohydrin) [10c,e,f,11] and in carbohydrate [10d,g] or nucleoside [10i] chemistry.

We were interested in synthesis of fluorinated α,β-epoxyphosphonates as fosfomycin and phosphoenolpyruvate analogues, because the substitution of hydrogen atom by fluorine atom(s) very often causes dramatic changes in the physical and biological properties of obtained organic compounds [13]. The particular role of fluorine is especially apparent in the fluorinated alkylphosphonates frequently used as nonhydrolysable surrogates of naturally occurring phosphates where C–O–P bridge has been replaced by C–CHF–P or C–CF_2–P linkages. Due to the comparable acidity of the monofluoromethylenephosphonic acids ($pK_a \sim 6.2$) to the parent phosphates ($pK_a \sim 6.45$) and the similar angle of C–CHF–P bridge ~113° analogous to C–O–P ~118° in phosphate [14], the monofluorinated alkylphosphonates have already been studied as substrate analogues in inhibition of several enzymes [14,15].

Several methods of the introduction of fluorine into target compounds are known and have been a subject of numerous reviews [16,17]. Among them the α-monofluorination of the ketones *via* electrophilic fluorination reactions is frequently carried out [18] with such reagents as Selectfluor® [F-TEDA-BF_4, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)] [19] or *N*-fluorobenzenesulfonimide [NFSI, $(PhSO_2)_2NF$] [20]. Also the application of enamines has proved to be useful alternative for the introduction of fluorine on the α carbon to a carbonyl group [19,21]. Similarly, the synthesis of α-monofluoroalkylphosphonate derivatives are associated mainly with electrophilic fluorination of phosphonate carbanions [22] or enantioselective formation of stable chiral enolates with complexes of palladium with BINAP or SEGPHOS ligands [23] or zinc (II) with bis(oxazolines) ligands [24] with NFSI. The metal catalysis has also been used for asymmetric synthesis of *gem*-chlorofluoromethylene-β-ketophosphonates [25].

During our synthesis of *gem*-α,α-difluoro-β-iminophosphonates *via* electrophilic fluorination of β-enaminophosphonates [26] we were surprised by the lack of monofluorinated products in the reaction mixtures. We decided to expand the scope of enamine fluorination towards preparation of monofluorinated, biologically active molecule. We have designed the synthesis of fluorinated α,β-epoxyphosphonates with the vicinal and geminal arrangement of fluorine and phosphorus atoms. Herein, we present our results concerning the synthesis of two categories of fluorine containing α,β-epoxyphosphonates with the application of enamine reactivity.

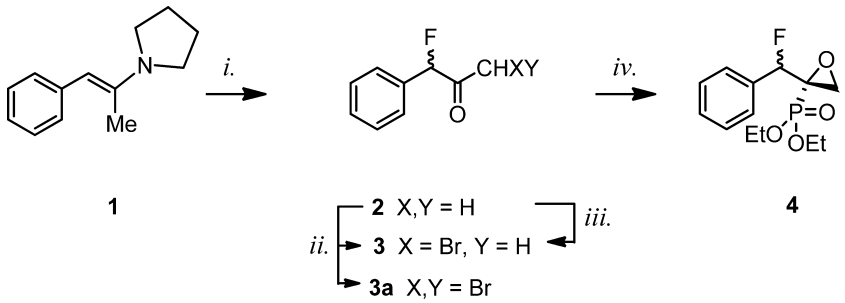
2. Results and discussion

The synthesis of monofluorinated α,β-epoxyphosphonates having the vicinal and geminal arrangements of fluorine and phosphorus atoms could be achieved by different approaches. Our first strategy was based on the reaction of sodium dialkyl phosphite with the appropriate fluorinated α-bromo ketone. We started with the application of enamine **1** obtained from benzyl methyl ketone (BMK) and pyrrolidine [27]. Next, the fluorination of enamine **1** with Selectfluor® [19] followed by hydrolysis gave 1-phenyl-1-fluoro-2-propanone **2** [28] with 41% yield as racemic mixture. The application of enamine has proved to be useful alternative for the introduction of fluorine atom on the carbon α to the carbonyl group [19,21]. Due to the attack of enamine double bond on fluorinating reagent, this electrophilic fluorination led to one regioisomer with fluorine atom in benzylic position as indicated by the spectral analysis of product **2** (Scheme 1).

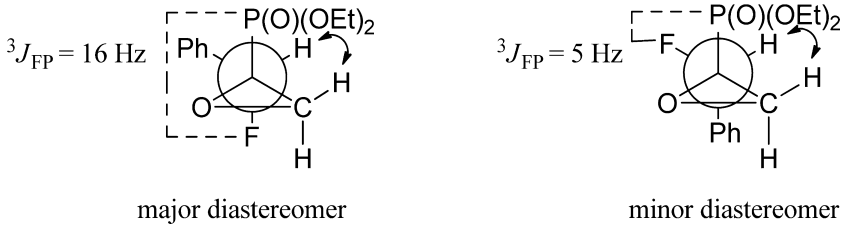
Thus, the signal located at δ: −183.25 as dq (J = 49 Hz, 4 Hz) in ^{19}F NMR as well as a distinctive doublet (J = 49 Hz) at δ: 5.68 in ^1H NMR confirmed the structure of compound **2** [28b]. Interestingly, analogous reaction of enamine derived from monocarbonyl- or β-dicarbonyl compounds with Selectfluor® (2 equiv.) and addition of TEA (1 equiv.) gave corresponding *gem*-α,α-difluorinated carbonyl compounds with high yields [29]. It is noteworthy, that the electrophilic fluorination reaction of BMK with Selectfluor® did not lead to the corresponding α-monofluoroketone **2**. In the next step, the nonselective bromination of terminal methyl group (Br_2, HBr_{aq}, 20 h, rt) gave a mixture of compounds **3** and **3a** (69%), which after selective debromination (acetone, 48 h, rt) led to **3** with 69% yield [30]. On the other hand, while the bromination of **2** was performed using bromine in acetic acid the compound **3** was obtained as well, but with 59% yield. Subsequent Michaelis–Becker reaction of **3** with $NaP(O)(OEt)_2$ in THF (60 °C, 24 h) yielded the terminal α,β-epoxyphosphonate **4** as a mixture of two diastereomers (1:0.3 ratio) with 52% yield.

The structure of major and minor diastereomers of **4** has been determined basing on the NMR spectra analysis and Nuclear Overhauser Enhancement Spectroscopy (NOESY) experiments (Scheme 2).

Thus, the signals of major diastereomer of **4** located at δ: −183.76 (as ddd) in ^{19}F NMR and in ^{31}P NMR (δ: 16.42, d), with $^2J_{FH}$ 46 Hz and $^3J_{FP}$ 16 Hz (values typical for two- (F–H) and three-bond (F–P) coupling constants) compared to the signal of **4** minor isomer appearing in ^{31}P NMR (δ: 16.83, d) with $^3J_{FP}$ 5 Hz indicated the vicinal arrangement of fluorine and phosphonate group, similarly to the result obtained for α-amino-β-fluoroalkylphosphonates [31]. Moreover, the different values of F–P coupling constants indicated the *anti* arrangement of fluorine and phosphorous atoms in major ($^3J_{FP}$ 16 Hz) and *gauche* conformation ($^3J_{FP}$ 5 Hz) for minor isomer of **4** – according to Karplus dihedral angle relationship (Scheme 2) [32]. NOESY experiments supported the stereochemical assignment at *C*1 and *C*2 of the major diastereomer of **4** as being 1*R*,2*S* since correlations were observed between one of the oxirane protons (–C*H*H– at δ: 3.12) and the proton –C*H*F– (δ: 5.81), as well as a weak correlation was noted between one of the oxirane protons (–C*H*H– at δ: 3.09) and the proton –C*H*F– (δ: 5.94), for compound **4** minor isomer. Also, a long-range coupling between the second methylenic proton –CH*H*– and fluorine ($^4J_{HF}$ 3.5/3 Hz) was observed for both the major and minor diastereomers of **4**. At the same time, location of signal of –*C*HF– carbon in ^{13}C NMR spectrum of major isomer of **4** appearing at δ: 90.6 (dd) with typical J values equal $^1J_{CF}$ 183 Hz, $^2J_{CP}$ 22 Hz and a chemical shift of –*C*P– carbon signal at δ: 55.5 (dd) with values $^1J_{CP}$ 198 Hz and $^2J_{CF}$ 27 Hz



Scheme 1. (i) Selectfluor®, MeCN, reflux, 24 h, work up (**2**, 41%); (ii) Br_2, HBr, AcOH, 20 h, rt (**3**/**3a** 1:1, 69%); (iii) Br_2, HBr, AcOH, 20 h, rt, next $Me_2C(O)$, 48 h, rt (69%); (iv) NaH, $HP(O)(OEt)_2$, THF, 60 °C, 24 h (*d.r.* 1:0.3, 52%).

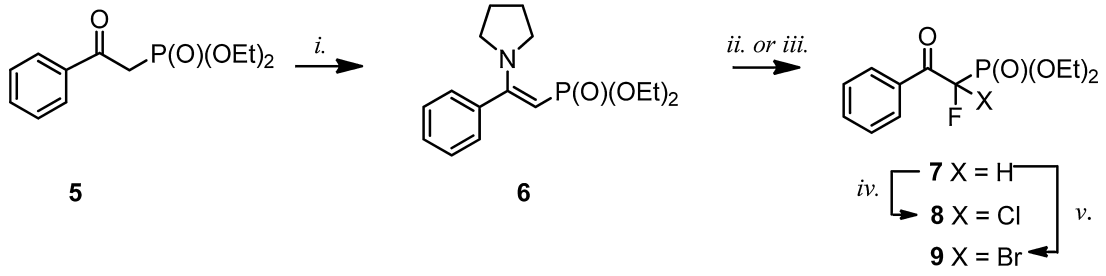


Scheme 2.

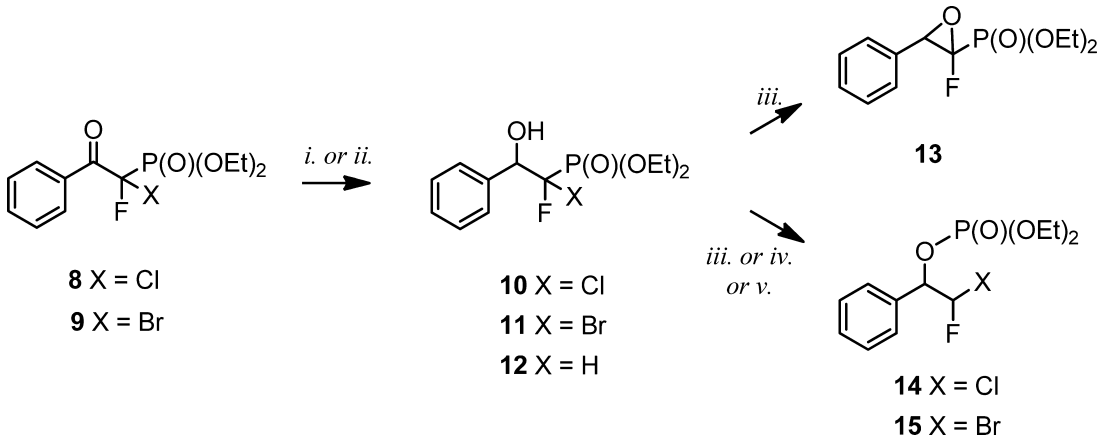
additionally confirmed the arrangement of substituents. These data are consistent with analogous J_{CP} values for the fosfomycin analogue such as α,β-epoxyphosphonate derivatives, where the phosphonate group bounded directly to an oxirane ring exemplified the specific effect upon spin–spin coupling constants [10f]. This strategy appears as an interesting variant of the synthesis leading to desired oxirane with moderate yields and without formation of other by-products, but it seems that diastereoselectivity depends strongly on the stereochemistry of prochiral precursors. The analogous additions of: $P(O)(OR)_2^-$ preferentially to the carbonyl group, instead of substitution of such good leaving groups as chloride or tosylate, have been already reported in the synthesis of non-fluorinated α,β-epoxyphosphonates [9]. However, the few reported stereoselectivity of α,β-epoxyphosphonates synthesis by this approach has been obtained from chiral substrates *e.g.* carbohydrates [9b,g]. At the same time, the reaction of ketone **3** with diethyl hydrogen phosphite $HP(O)(OEt)_2$ [with and without the addition of *p*-toluenesulfonic acid (PTSA)] gave only traces of oxirane **4**, whereas the application of $HP(O)(OEt)_2$ and triethylamine as a base caused the decomposition of starting material.

As more reactive fosfomycin analogues, the fluorinated α,β-epoxyphosphonates with the geminal arrangement of fluorine and phosphorus atoms has been planned. Our second strategy was based on the cyclization reactions of dialkyl halohydrinphosphonates [8]. One of the useful known methods for the synthesis of monofluorinated β-ketophosphonates is electrophilic fluorination with Selectfluor [22]. However, we decided to evaluate the fluorination of enamines towards the synthesis of the other fluorinated α,β-epoxyphosphonates (Schemes 3 and 4).

Starting from β-ketophosphonate **5** and pyrrolidine in the presence of catalytic amount of PTSA, the appropriate β-enaminophosphonate **6** has been prepared (Scheme 3) [26,33]. Next, the electrophilic fluorination with Selectfluor® (MeCN, −10 °C, 24 h) followed by enamine hydrolysis, gave known α-fluoro-β-ketophosphonate **7** with a yield of 55% [34]. It is noteworthy, that the fluorinations of **6** at increased or at room temperature have caused the formation of *gem*-α,α-difluoro-β-ketophosphonate analogue of **7** (X = F). These results are analogous to our previously reported studies concerning the fluorination of imino/enamino phosphonates towards *gem*-α,α-difluoro-β-iminophosphonate derivatives with Selectfluor® (MeCN, reflux, 3.5 – 4 h) [26]. However, this particular fluorination of enamine **6** appeared not to be as efficient as known enol-mediated synthesis of racemic **7** with Selectfluor® (yield 65%) [22] and comparable with the enantioselective fluorination of corresponding β-ketophosphonates **5** using chiral complexes of palladium or zinc (yields 57% and 86% *ee* or 97% and 97% *ee*, respectively) [23,24]. Subsequent reaction of **7** with NCS and triethylamine in MeCN (reflux, 2 h) gave **8** [25] with 97%. To extend the enamine application, the one-pot chlorofluorination reaction of β-enaminophosphonate **6** has been investigated as well. Thus, the reaction of **7** with Selectfluor® (2 equiv., −10 °C) and NCS (1 equiv., rt) in MeCN gave compound **8** with 41% yield. On the other hand, the asymmetric approach basing on one-pot chlorofluorination of ketone **5** using copper(II) complex of SPYMOX catalyst gave **8** with a 78% yield and



Scheme 3. (i) Pyrrolidine, toluene, PTSA, Dean-Stark, 12 h (95%); (ii) Selectfluor®, MeCN, −10 °C, 24 h, work up (**7**, 55%); (iii) Selectfluor®, MeCN, −10 °C, 24 h, then NCS, rt, 24 h (**8**, 41%); (iv) NCS, TEA, MeCN, reflux, 2 h (97%); (v) Br_2, $CHCl_3$, 24 h, rt (66%).



Scheme 4. (i) $BH_3{\cdot}SMe_2$, CH_2Cl_2, rt, 48 h (**10** d.r. 1:1, 98%, **11** d.r. 1:1, 98%); (ii) $NaBH_4$, 2 equiv., EtOH, rt, 24 h (**12** d.r. 1:0.9, 91%); (iii) TEA, EtOH, rt, 24 h (**13** d.r. 1:0.6, 39%, or **15** d.r. 1:1, 20%); (iv) NaH, THF, reflux, 2 h, then rt (**14** 1:0.05, 43%; **15** d.r. 1:0.3, 48%) (v) K_2CO_3, KI, DMF, rt, 24 h (**15** d.r. 1:0.7, 98%).

85% *ee* [25a]. Alternatively, the α-bromination reaction of **7** (Br_2, $CHCl_3$, rt, 24 h) yielded *gem*-α,α-bromofluoro-β-ketophosphonate **9** (66%). The analysis of ^{19}F NMR and ^{31}P NMR spectra of product **9** confirmed the presence of bromine on the same carbon as that bearing the fluorine substituent giving rise to spectacular deshielding effect [35]. Thus, in ^{19}F NMR spectrum the signal deriving from **9** is located at δ: −134.6 (d), while in ^{31}P NMR spectrum it is placed at δ: 5.93 as doublet $^2J_{FP}$ 80 Hz. The spectral properties of **9** are analogous to the data reported for **8** (δ: −129.6 in ^{19}F NMR, δ: 6.92 in ^{31}P NMR and $^2J_{FP}$ 85 Hz) [25]. The bromination of **7** at lower temperature (−20 °C) gave **9** with 26% yield, while the reaction of **7** accomplished by using NBS and TEA gave **9**, but with 21% yield.

Next, the reduction of α,α-halofluoroketones **8** and **9** and with borane complex ($BH_3{\cdot}SMe_2$) gave fluorinated chloro- or bromohydrin **10** and **11** respectively as a mixture of two diastereomers (1:1 ratio) with 98% yields (Scheme 4). In ^1H NMR spectrum of the reaction mixture, the new signals of two diastereomers of **11** have appeared at δ: 5.10/5.12 (doublets) with $^3J_{FH}$ 4 Hz, matching the signals (dd) at δ: −133.01/−133.10 in ^{19}F NMR spectrum and doublets at δ: 9.76/9.78 with $^2J_{PF}$ 78 Hz in ^{31}P NMR spectrum. This data has clearly indicated the coupling of fluorine atom with vicinal hydrogen and geminal phosphorous nuclei. Additionally, the lack of carbonyl group signal, and a new signal appearance at δ: 105.5 with $^1J_{CF}$ 272 and $^1J_{CP}$ 179 Hz and at δ: 74.4 with $^2J_{CF}$ 23 Hz and $^2J_{CP}$ 7 Hz in ^{13}C NMR spectrum of **11** have supported the formation of halofluorohydrin. While the one-bond coupling constant values are consistent with analogous *J* values for diethyl α,α-difluoro-n-hexylphosphonate equal $^1J_{CF}$ 260 Hz, $^1J_{CP}$ 215 Hz, and the $^2J_{CF}$ 21 Hz, $^2J_{CP}$ 14 Hz, the value of $^2J_{CP}$ in **11** is relatively smaller [35].

Moreover, the attempt to reduction of the carbonyl bond in **9** with 1 equiv. or 2 equiv. of sodium borohydride led to the concomitant substitution of bromine by: H^- and resulted in the formation of fluorohydrin **12** with 35% and 91% yield respectively, as a mixture of two diastereomers (1:0.9 ratio). Next, the ring closure reaction of **11** with TEA in EtOH gave the desired oxirane **13** as a mixture of two diastereomers (1:0.6 ratio) with a yield of 39%. Although, the ^{19}F NMR and ^{31}P NMR spectra of **13** comparing to starting alcohol **11** (less polar on TLC) are similar, the differences between the compounds are visible in ^1H NMR and ^{13}C NMR. Thus, the new signal of benzylic proton appears at δ: 5.17 (dd) with $^3J_{HP}$ 3 Hz and $^3J_{HF}$ 5 Hz in ^1H NMR. At the same time, in the ^{13}C NMR spectrum, the signals of carbons –*C*PFO– and –*C*H(Ph)O are located at δ: 105.5 (dd) and at δ: 74.4 (dd) respectively. Similarly to oxirane **4**, in compound's **13** spectrum the large coupling constants values $^1J_{CF}$ 273 Hz and $^2J_{CF}$ 22 Hz are observed, while $^1J_{CP}$ 178 Hz and $^2J_{CP}$ 7 Hz are relatively smaller. Analogous reaction of **10** or **11** with NaH in THF led to α,α-halofluoromethylphosphates **14** with 43% yield (two diastereomers, 1:0.05 ratio) or **15** with 48% yield as two diastereomers mixture (with 1:0.3 ratio) respectively. Also, the reaction of **10** with TEA in EtOH or with K_2CO_3 in addition to KI in DMF gave compound **14** as a mixture of two diastereomers (1:0.7 ratio). This data is confirmed by distinctive up-field shifted signals in ^{19}F NMR (δ: −145.49/−144.33) comparing to **10** or **11**, and typical for phosphates localization of signals at δ: −1.6/−2.1 in ^{31}P NMR [36]. The hydrolysis of C–P bond under basic conditions and rearrangement yielding phosphate derivatives have already been reported [37]. The reactions of dialkyl halohydrinphosphonates with TEA appears to be useful alternative route of the synthesis of fluorinated α,β-epoxyphosphonates with the geminal arrangement of fluorine and phosphorus atoms since the application of other bases (NaH or K_2CO_3) caused the migration of a phosphorus substituent. Additionally, it seems that this method depends also on the type of leaving group and the presence of other substituents that influence on even well-established reactions.

In summary, we have developed the method for the synthesis of two type of monofluorinated α,β-epoxyphosphonates having the vicinal arrangement of fluorine and phosphorus atoms 4 with moderate yield and good diastereoselectivity and geminal fluoroalkylphosphonate possessing an oxiran ring **13** as a mixture of two diastereomers with moderate yield. The introduction of fluorine atom has been accomplished by electrophilic fluorination of corresponding enamine **1** or β-enaminophosphonate **6** with Selectfluor®. Moreover, the introduction of chlorine has been accomplished by two methods: chlorination of **7** and chlorofluorination of β-enaminophosphonate **6** with Selectfluor® and NCS to give **8**. Additionally, the results concerning bromination of **2** and **7** and reduction of appropriate fluorohaloketone **8** and **9** leading to **10** and **11** have been presented. While, the treatment of fluorohalohydrin **11** with TEA gave desired α,β-epoxyphosphonate **13**, analogous reactions of **10** or **11** with other bases gave corresponding phosphates **14** and **15**. The structures of products have been determined by ^1H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR. The obtained compounds could be employed as building blocks for further synthesis and be applied as potential enzyme inhibitor as fosfomycin analogues.

3. Experimental

3.1. General procedures

^1H (Me_4Si) NMR spectra were determined with solutions in $CDCl_3$ at 300 MHz, ^{13}C (Me_4Si) at 75 MHz and ^{19}F NMR (CCl_3F) at

282 MHz and ^{31}P NMR (85% H_3PO_4 as an external standard) at 121 MHz on Varian GEMINI 300, or ^{13}C NMR (Me_4Si) at 151 MHz and ^{31}P NMR (85% H_3PO_4) at 242 MHz on Bruker Avance 600 spectrometer, as is noted. The yields of reaction and purity of the obtained products were conveniently evaluated by ^{19}F NMR in $CDCl_3$ or by GC–MS method. GC–MS spectra were performed on Varian GC–MS 4000 spectrometer (conditions: flow rate of 1 mL/min, injector temperature = 220 °C, column oven temperature 40 °C (3 min) → 15 °C/min → 280 °C (10 min), using chloroform as the solvent). Reagent grade chemicals were used and solvents were dried by refluxing with sodium metal-benzophenone (THF), with CaH_2 (CH_3CN) and distilled under an argon atmosphere. All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Reaction temperatures below 0 °C were performed using a cooling bath (liquid N_2/*m*-xylene or NaCl/ice). TLC was performed on Merck Kieselgel 60-F_{254} with EtOAc/hexane as developing systems, and products were detected by inspection under UV light (254 nm) and a standard procedure (solution of $KMnO_4$). Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. All starting materials were supplied by Sigma Aldrich. Sodium hydride as 60% dispersion in mineral oil, and 48% aqueuos hydrobromic acid were used.

Compounds **1** [27] was prepared as described. The spectroscopic data for **2** [28], **7** [34] and **9** [25] were in accordance with the values reported earlier in the literature.

3.2. Preparation of 1-fluoro-1-phenylpropan-2-one **2**

To a solution of an enamine **1** (1.39 mmol) in acetonitrile (20 mL) Selectfluor® (1.03 g, 2.9 mmol) was added and the reaction mixture was refluxed for 24 h. Next, the resulting mixture was partitioned ($NH_4Cl/H_2O//CH_2Cl_2$). The combined extracts were washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated. The crude product was purified by silica column chromatography (5% EtOAc/hexane) to give **2** as a slightly green oil (86 mg, yield 41%). Compound **2** had: ^{19}F NMR: δ −183.25 (dq, 1F, J = 49, 4 Hz).

3.3. Preparation of 3-bromo-1-fluoro-1-phenylpropan-2-one **3** and 1,1-dibromo-3-fluoro-3-phenylpropan-2-one **3a**

Bromine (0.06 mL, 199 mg, 1.24 mmol) was added to the solution of **2** (86 mg, 0.57 mmol) in a mixture of acetic acid (0.47 mL) and 48% aqueuos HBr (0.1 mL). The reaction mixture was stirred for 20 h at room temperature. Next, acetone (0.95 mL) was added and stirring was continued for another 48 h. Then, the resulting mixture was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The combined extracts were washed with brine, dried ($MgSO_4$), evaporated and column chromatographed (hexane) to give **3** (90 mg, 69%) as slightly yellow oil. Compound **3** had: ^{1}H NMR: δ 4.13 (dd, 1H, J = 14, 2 Hz, CH_2Br), 4.20 (dd, 1H, J = 14, 3 Hz, CH_2Br), 6.01 (d, 1H, J = 48 Hz, CHF), 7.41–7.48 (m, 5H, arom. H); ^{13}C NMR (151 MHz): δ 30.7 (s, CH_2Br), 94.5 (d, J = 188 Hz, CHF), 126.8 (d, J = 6 Hz, arom. C), 129.13 (s, arom. C), 130.2 (d, J = 2 Hz, arom. C), 133.2 (d, J = 14 Hz, arom. C), 197.3 (d, J = 27 Hz, CO); ^{19}F NMR: δ −185.01 (ddd, 1F, J = 48, 3, 2 Hz); GC–MS (EI) m/z = 137 [M-Br-CH_2]$^+$; R_t 12.0 min.

Note 1: Analogous reaction of **2** with bromine (1 equiv.), acetic acid and 48% aqueous hydrobromic acid at room temperature for 20 h followed by work up ($CH_2Cl_2//NaHCO_{3aq}/NaCl_{aq}$, Na_2SO_4) gave a mixture of compounds **3** and **3a** as an yellow oil (1:1 ratio, yield 69%). Compound **3a** had: ^{1}H NMR: δ 6.21 (d, 1H, J = 47 Hz, CHF), 6.27 (d, 1H, J = 1 Hz, $CHBr_2$), 7.41–7.48 (m, 5H, arom. H); ^{13}C NMR (151 MHz): δ 37.3 (s, $CHBr_2$), 92.2 (d, J = 190 Hz, CHF), 126.2 (d, J = 7 Hz, arom. C), 129.1 (s, arom. C), 129.8 (d, J = 2 Hz, arom. C), 133.0 (d, J = 14 Hz, arom. C), 191.4 (d, J = 27 Hz, CO); ^{19}F NMR: δ −181.30 (dd, J = 47, 3 Hz).

Note 2: Analogous reaction of **2** with bromine (1 equiv.) and acetic acid at room temperature for 48 h gave compound **3** (yield 59%).

3.4. Preparation of diethyl ((R)-2-((S)-fluoro(phenyl)methyl)oxiran-2-yl)phosphonate and diethyl ((R)-2-((R)-fluoro(phenyl)methyl)oxiran-2-yl)phosphonate **4**

To a stirred dispersion of sodium hydride (60% solution in mineral oil, 18 mg, 0.44 mmol) in THF (7 mL) diethyl phosphite (56 μL, 60 mg, 0.44 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. Next, the obtained solution was added dropwise to a stirred solution of compound **3** (65 mg, 0.28 mmol) dissolved in THF (2 mL). The reaction mixture was heated at 60 °C for 24 h and then extracted with methylene chloride (3× 10 mL). The organic layers were dried ($MgSO_4$) and purified on silica gel (20% → 30% EtOAc/hexane) to give compound **4** as two diastereomers (slightly yellow oil, 42 mg, yield 52%). Major diastereomer of compound **4** had: ^{1}H NMR: δ 1.37 (t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.12 (dd, 1H, J = 6, 4 Hz, CH_2), 3.20 (ddd, 1H, J = 6, 5, 3.6 Hz, CH_2), 3.90–4.10 (m, 4H, $OC\underline{H}_2CH_3$), 5.81 (dd, 1H, J = 46, 5 Hz, CHF), 7.35–7.43 (m, 5H, arom. H); ^{13}C NMR: δ 16.1 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 16.2 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 48.2 (d, J = 8 Hz, CH_2), 55.5 (dd, J = 197, 27 Hz, CP), 63.1 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 63.4 (d, J = 6 Hz, $O\underline{C}H_2CH_3$), 90.6 (dd, J = 183, 22 Hz, CHF), 127.3 (d, J = 7 Hz, arom. C), 128.2 (s, arom. C), 129.2 (d, J = 2 Hz, arom. C), 134.9 (d, J = 1.8 Hz, arom. C); ^{31}P NMR: δ 16.42 (d, J = 16 Hz); ^{19}F NMR: δ −183.76 (ddd, J = 45, 16, 3.5 Hz); GC–MS m/z = 288 [M−H]$^+$; R_t 15.4 min. Minor diastereomer of compound **4** had: ^{1}H NMR: δ 1.37 (t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.09 (dd, 1H, J = 5, 3 Hz, CH_2), 3.20 (ddd, 1H, J = 6, 5, 3.6 Hz, CH_2), 3.90–4.10 (m, 4H, $OC\underline{H}_2CH_3$), 5.94 (dd, 1H, J = 46, 3 Hz, CHF), 7.35–7.43 (m, 5H, arom. H); ^{13}C NMR: δ 16.3 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 48.5 (d, J = 5 Hz, CH_2), 54.8 (dd, J = 199, 28 Hz, CP), 63.4 (d, J = 6 Hz, $O\underline{C}H_2CH_3$), 63.6 (d, J = 6 Hz, $O\underline{C}H_2CH_3$), 91.7 (dd, J = 178, 16 Hz, CHF), 127.6 (d, J = 6 Hz, arom. C), 128.2 (s, arom. C), 129.4 (d, J = 2 Hz, arom. C), 135.1 (d, J = 2.0 Hz, arom. C); ^{31}P NMR: δ 16.83 (d, J = 5 Hz); ^{19}F NMR: δ −183.76 (ddd, J = 46, 5, 3.5 Hz); GC–MS m/z = 288 [M−H]$^+$; R_t 15.4 min.

Note 1: Analogous reaction of **3** with diethyl hydrogen phosphite (1.5 equiv.) [with and without the addition of *p*-toluenesulfonic acid (PTSA, 5% mol) at 60 °C gave traces of compound **4**.

Note 2: Analogous reaction of **3** with diethyl phosphite (1.5 equiv.) and triethylamine (1.5 equiv.) as a base (THF, 60 °C) caused the decomposition of starting material.

3.5. Preparation of diethyl (2-phenyl-2-(pyrrolidin-1-yl)vinyl)phosphonate **6**

To a solution of a ketone **5** (356 mg, 1.39 mmol) in toluene (20 mL), pyrrolidine (171 μL, 148 mg, 2.09 mmol) and *p*-toluenesulfonic acid monohydrate PTSA (13 mg, 0.07 mmol) were added. The reaction mixture was heated under Dean-Stark adapter at reflux for 24 h. Next, the PTSA was neutralized with TEA (10 μL, 7 mg, 0.07 mmol) and toluene and excess of amine were removed from the reaction mixture under reduced pressure to give crude enaminophosphonate **6** (407 mg, 95%) as confirmed by GC–MS analysis. Compound **6** had: ^{1}H NMR: δ 1.08 (t, 6H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.80–1.90 (m, 4H, CH_2), 4.02 (d, 1H, J = 10.5 Hz, CHP), 3.68–3.75 (m, 2H, CH_2), 3.76–3.82 (m, 2H, CH_2), 4.12 (quintet, 4H, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 7.28–7.36 (m, 5H, arom. H); ^{31} P NMR: δ 24.9 (s, 1P), GC–MS (EI) m/z = 294 [M−Me]$^+$.

3.6. Preparation of diethyl 1-fluoro-2-oxo-phenylethylphosphonate **7** by enamine fluorination

To the enaminophosphonate **6** (386 mg, 1.25 mmol), the acetonitrile (20 mL) and Selectfluor® (664 mg, 1.87 mmol) were added at −10 °C, and the cooling was continued for 24 h. Next, methylene chloride (20 mL) and water (10 mL) were added and the reaction mixture was extracted with methylene chloride (3× 10 mL). The organic layer was dried (Na_2SO_4) and column chromatographed (30% EtOAc/hexane) to give compound **7** (188 mg, yield 55%).

Note: Analogous reaction of **6** with Selectfluor® (1.5 equiv.) at room temperature or at 60 °C gave diethyl 1,1-difluoro-2-oxo-phenylethylphosphonate with a yield 37%.

3.7. Preparation of diethyl 1-chloro-1-fluoro-2-oxo-phenylethylphosphonate ***8***

To the stirred solution of **7** (108 mg, 0.39 mmol) in MeCN (10 mL) triethylamine (0.11 mL, 79 mg, 0.78 mmol) and NCS (104 mg, 0.78 mmol) were added. The reaction mixture was refluxed for 2 h. Then, methylene chloride (20 mL) and water (10 mL) were added and the reaction mixture was extracted with methylene chloride (3× 10 mL). The organic layer was dried (Na_2SO_4) to give known compound **8** (118 mg, yield 97%).

Note: The reaction of enaminophosphonate **6** (386 mg, 1.25 mmol) with Selectfluor® (664 mg, 1.87 mmol) in MeCN (20 mL) at −10 °C with cooling for 24 h and addition of NCS (167 mg, 1.25 mmol) with continued stirring for 24 h at room temperature followed by extraction gave known compound **8** (158 mg, yield 41%) as an yellow oil.

3.8. Preparation of diethyl 1-bromo-1-fluoro-2-oxo-phenylethylphosphonate ***9***

Bromine (34 μL, 107 mg, 0.67 mmol) was added to the stirred solution of **7** (184 mg, 0.67 mmol) in chloroform (10 mL). The reaction mixture was stirred for 24 h at room temperature. Then, the resulting mixture was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The combined extracts were washed with brine, dried ($MgSO_4$), evaporated and column chromatographed (30% EtOAc/hexane) to give compound **9** (156 mg, 66%) as an yellow oil. Compound **9** had: ^{1}H NMR: δ 1.31 (td, 3H, J = 6, 1 Hz, $OCH_2C\underline{H}_3$), 1.36 (td, 3H, J = 6, 1 Hz, $OCH_2C\underline{H}_3$), 4.20–4.43 (m, 4H, $OC\underline{H}_2CH_3$), 7.39–8.13 (m, 5H, arom. H); ^{13}C NMR (151 MHz): δ 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 65.7 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 65.9 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 96.2 (dd, J = 284, 181 Hz, CFBr), 128.5 (s, arom. C), 130.5 (d, J = 5 Hz, arom. C), 131.9 (dd, J = 4, 4 Hz, arom. C), 134.4 (s, arom. C), 189.2 (dd, J = 25, 6 Hz, CO); ^{31}P NMR (243 MHz): δ 5.93 (d, J = 80 Hz); ^{19}F NMR: δ −134.59 (d, J = 80 Hz); GC–MS m/z = 201 $[M+4H-F-Br-2Et]^+$; R_t 16.2 min.

Note 1: The reaction of **7** with *N*-bromosuccynimide (1.5 equiv.) and triethylamine (1.5 equiv.) in acetonitrile at reflux for 24 h gave **9** (yield 21%).

Note 2: Analogous reaction of **7** (Br_2, $CHCl_3$) at low temperature (−20 °C) gave **9** (yield 26%).

3.9. General procedure for the reduction of *gem*-α,α-halofluoroketone with borane complex

The complex of borane with dimethyl sulfide (1 M in CH_2Cl_2, 0.68 mmol) was added dropwise to an appropriate *gem*-α,α-halofluoroketone (0.34 mmol). Then, the reaction mixture was stirred for 48 h at room temperature. Next, ethanol (0.45 mL) was added and stirring was continued for another 30 min and then after evaporation, the reaction mixture was passed through short silica column (EtOAc).

3.9.1. Diethyl 1-chloro-1-fluoro-2-hydroxy-2-phenylethylphosphonate ***10***

Reaction of **8** with $BH_3{\cdot}SMe_2$ carried out according to a general procedure (Section 3.9) gave compound **10** with a yield 98% as two diastereomers (1:1 ratio). Compound **10** had: ^{1}H NMR: δ 1.35–1.42 (t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.37–1.41 (t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 4.21–4.48 (m, 8H, $OC\underline{H}_2CH_3$), 5.33 (d, 1H, J = 5 Hz, C<u>H</u>OH), 5.35 (d, 1H, J = 5 Hz, C<u>H</u>OH), 7.35–7.63 (m, 10H, arom. H); ^{13}C NMR: δ 16.31 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 16.34 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 16.41 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 16.41 (d, J = 5 Hz, $OCH_2\underline{C}H_3$), 65.2 (d, J = 8 Hz, $O\underline{C}H_2CH_3$), 65.5 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 65.6 (d, J = 8 Hz, $O\underline{C}H_2CH_3$), 66.2 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 74.4 (dd, J = 24, 8 Hz, CHOH), 108.0 (dd, J = 267, 186 Hz, CFP),108.6 (dd, J = 262, 186 Hz, CFP), 127.8 (s, arom. C), 127.9 (s, arom. C), 128.4 (d, J = 2 Hz, arom. C), 128.6 (d, J = 2 Hz, arom. C), 128.8 (s, arom. C), 128.9 (s, arom. C), 135.3 (d, J = 8 Hz, arom. C); ^{31}P NMR: δ 9.38 (br d, J = 83 Hz); ^{19}F NMR: δ −130.36 (br dd, J = 82, 4 Hz); GC–MS m/z = 311 $[M]^+$; R_t 13.2 min.; GC–MS m/z = 311 $[M]^+$; R_t 13.3 min.

3.9.2. Diethyl 1-bromo-1-fluoro-2-hydroxy-2-phenylethylphosphonate ***11***

Reaction of **9** with $BH_3{\cdot}SMe_2$ carried out according to general procedure (Section 3.9) gave compound **11** as two diastereomers (1:1 ratio) with a yield 98%. Compound **11** had: ^{1}H NMR: δ 1.14 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.15 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.26 (br t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 4.02 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 4.10–4.32 (m, 7H, 3× $OC\underline{H}_2CH_3$, OH), 5.10 (d, 1H, J = 4 Hz, C<u>H</u>OH), 5.12 (d, 1H, J = 4 Hz, C<u>H</u>OH), 7.18–7.43 (m, 10H, arom. H); ^{13}C NMR: δ 16.2 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 16.3 (d, J = 7 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 65.2 (d, J = 8 Hz, $O\underline{C}H_2CH_3$), 66.5 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 74.4 (dd, J = 23, 7 Hz, CHOH), 105.5 (dd, J = 272, 179 Hz, CFP), 127.8 (s, arom. C), 128.4 (d, J = 2 Hz, arom. C), 128.8 (s, arom. C), 135.8 (d, J = 9 Hz, arom. C); ^{31}P NMR: δ 9.76 (d, J = 78 Hz), 9.78 (d, J = 78 Hz); ^{19}F NMR: δ −133.01 (dd, J = 78, 4 Hz), −133.10 (dd, J = 77, 4 Hz); GC–MS m/z = 355 $[M]^+$; R_t 16.6 min.

3.10. Preparation of diethyl 1-fluoro-2-hydroxy-2-phenylethylphosphonate ***12***

To the solution of **9** (33 mg, 0.09 mmol) dissolved in ethanol (5 mL) sodium borohydride (7 mg, 0.19 mmol) was added and a reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was quenched by the addition of water and extracted with EtOAc (3× 10 mL). Next, the mixture was dried ($MgSO_4$) and column chromatographed (50% EtOAc/hexane) to give compound **12** (30 mg) with a yield 91% as a mixture of two diastereomers (0.9:1 ratio). Compound **12** had: ^{1}H NMR: δ 1.33–1.24 (t, 12H, J = 7 Hz, $OCH_2C\underline{H}_3$), 4.02–4.30 (m, 8H, $OC\underline{H}_2CH_3$), 4.73 (ddd, 1H, J = 45, 8, 2 Hz, CHF), 4.82 (ddd, 1H, J = 45, 6, 4 Hz, CHF), 5.05–5.24 (m, 2H, C<u>H</u>OH), 7.31–7.49 (m, 10H, arom. H); ^{31}P NMR: δ 16.46 (d, J = 80 Hz), 17.47 (d, J = 73 Hz); ^{19}F NMR: δ −208.54 (ddd, J = 73, 45, 8 Hz), −220.86 (ddd, J = 80, 45, 25 Hz). GC–MS m/z = 276 $[M]^+$.

Note: Analogous reaction of **9** with $NaBH_4$ (1 equiv.) in EtOH gave **12** with a yield 35%.

3.11. Preparation of diethyl 2-fluoro-3-phenyloxiran-2-ylphosphonate ***13***

To a stirring solution of halofluoroalcohol **11** (60 mg, 0.17 mmol) in ethanol (2 mL) triethylamine (23 μL, 17 mg, 0.17 mmol) was added at room temperature. The stirring was continued for 24 h and the resulting mixture was evaporated under

reduced pressure. Then, the residue was purified by column chromatography (30% EtOAc/hexane) to give compound **13** (yellow oil) with a yield 39% as a mixture of two diastereomers (ratio 1:0.6).

Compound **13** had: ^{1}H NMR: δ 1.40 (br t, 6H, $OCH_2C\underline{H}_3$), 1.42 (br t, 6H, $OCH_2C\underline{H}_3$), 4.25–4.35 (m, 4H, $OC\underline{H}_2CH_3$), 4.35–4.48 (m, 4H, $OC\underline{H}_2CH_3$), 5.17 (dt, 2H, J = 5, 3 Hz, CH), 7.35–7.41 (m, 10H, arom. H); ^{13}C NMR (151 MHz): δ 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 16.4 (d, J = 6 Hz, $OCH_2\underline{C}H_3$), 66.6 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 66.7 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 65.2 (d, J = 8 Hz, $O\underline{C}H_2CH_3$), 65.2 (d, J = 7 Hz, $O\underline{C}H_2CH_3$), 74.4 (dd, J = 23, 8 Hz, CH), 105.5 (dd, J = 273, 178 Hz, CFP), 127.8 (s, arom. C), 128.4 (d, J = 2 Hz, arom. C), 128.9 (s, arom. C), 135.6 (d, J = 9 Hz, arom. C); ^{31}P NMR: δ 9.24 (br d, J = 77 Hz); ^{19}F NMR: δ −133.28 (dd, J = 77, 3 Hz), −133.30 (dd, J = 77, 3 Hz); GC–MS m/z = 275 $[M+H]^+$; R_t 16.6 min.

3.12. General procedure for phosphate synthesis

To a stirring solution of halofluoroalcohol (0.13 mmol) in dry THF (7 mL) the sodium hydride (60% in mineral oil, 0.13 mmol) was added. Then, the reaction mixture was heated to 75 °C for 2 h and then stirring for another 12 h at room temperature. The resulting residue was partitioned ($NaHCO_3/H_2O//CH_2Cl_2$). The combined extracts were washed with brine, dried ($MgSO_4$), evaporated and column chromatographed (20% EtOAc/hexane).

3.12.1. Diethyl 2-chloro-2-fluoro-1-phenylethyl phosphate *14*

Reaction of **10** with sodium hydride carried out according to general procedure (Section 3.12) gave compound **14** with a yield 48% as two diastereomers (1:0.3 ratio). Major diastereomer of compound **14** had: ^{1}H NMR: δ 1.30 (td, 3H, J = 7, 1 Hz, $OCH_2C\underline{H}_3$), 1.31 (td, 3H, J = 7, 1 Hz, $OCH_2C\underline{H}_3$), 4.13–4.23 (m, 4H, $OC\underline{H}_2CH_3$), 5.48–5.55 (m, 1H, CH), 6.31 (dd, 1H, J = 50, 4 Hz, CHFCl), 7.43–7.48 (m, 5H, arom. H); ^{31}P NMR: δ −2.10 (s); ^{19}F NMR:δ −144.32 (dd, J = 50, 13 Hz). Minor diastereomer of compound **14** had: ^{1}H NMR: δ 1.13 (td, 3H, J = 7, 1 Hz, $OCH_2C\underline{H}_3$), 1.16 (td, 3H, J = 7, 1 Hz, $OCH_2C\underline{H}_3$), 4.03–4.13 (m, 4H, $OC\underline{H}_2CH_3$), 5.48–5.55 (m, 1H, CH), 6.27 (dd, 1H, J = 50, 6 Hz, CHFCl), 7.43–7.48 (m, 5H, arom. H); ^{31}P NMR: δ −2.11 (s); ^{19}F NMR: δ −144.33 (dd, J = 50, 13 Hz).

Note 1: Reaction of **10** with triethylamine carried out according to procedure (Section 3.11) gave compound **14** (yellow oil) with a yield 20% as a mixture of two diastereomers (1:1 ratio).

Note 2: Reaction of **10** with K_2CO_3 (1 equiv.) and KI (1 equiv.) in DMF at room temperature for 24 h gave compound **14** (yellow oil) with a yield 98% as a mixture of two diastereomers (1:0.7 ratio).

3.12.2. Diethyl 2-bromo-2-fluoro-1-phenylethyl phosphate *15*

Reaction of **11** with sodium hydride carried out according to general procedure (Section 3.12) gave compound **15** with a yield 43% as a two diastereomers (1:0.05 ratio). Major diastereomer of compound **15** had: ^{1}H NMR: δ 1.19–1.27 (t, 6H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.94–4.20 (m, 4H, $OC\underline{H}_2CH_3$), 5.52 (ddd, 1H, J = 11, 9, 6 Hz, CH), 6.47 (dd, 1H, J = 49, 6 Hz, CHFBr), 7.29–7.39 (m, 5H, arom. H); ^{31}P NMR: δ −1.59 (s), ^{19}F NMR: δ −145.40 (dd, J = 49, 13 Hz); GC–MS m/z = 275 $[M-Br]^+$ R_t = 15.4 min. Minor diastereomer of compound **15** had: ^{31}P NMR: δ −1.68 (s). ^{19}F NMR: δ −145.49 (dd, J = 49, 11 Hz); GC–MS m/z = 275 $[M-Br]^+$ R_t = 15.4 min.

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References

[1] D. Hendlin, E.O. Stapley, M. Jackson, H. Wallick, A.K. Miller, F.J. Wolf, T.W. Miller, L. Chalet, F.M. Kahan, E.L. Foltz, H.B. Woodruff, J.M. Mata, S. Hernandez, S. Mochales, Science 166 (1969) 122–123.
[2] S.C. Fields, Tetrahedron 55 (1999) 12237–12273.
[3] E.D. Brown, E.I. Vivas, C.T. Walsh, R.J. Kolter, Bacteriology 177 (1995) 4194–4197.
[4] B.G. Christensen, W.J. Leanza, T.R. Beattie, A.A. Patchett, B.H. Arison, R.E. Ormond, F.A. Kuehl, G. Albers-Schonberg, O. Jardetzky, Science 166 (1969) 123–125.
[5] A.S. Michalopoulos, I.G. Livaditis, V. Gougoutas, Int. J. Infect. Dis. 15 (2011) e732–e739.
[6] For some examples see:
(a) P Savignac, B. Iorga, Modern Phosphonate Chemistry, CRC Press, Boca Raton, 2003, pp. 139–181 (Chapter 4);
(b) C. Marocco, E.V. Davis, J.E. Finnell, P.-H. Nguyen, S.C. Mateer, I. Ghiviriga, C.W. Padgett, B.D. Feske, Tetrahedron: Asymmetry 22 (2011) 1784–1789;
(c) Y. Yamauchi, T. Kawate, T. Katagiri, K. Uneyama, Tetrahedron 59 (2003) 9839–9847;
(d) M. Obayashi, E. Ito, K. Matsui, K. Kondo, Tetrahedron Lett. 23 (1982) 2323–2326;
(e) H. Kawai, S. Okusu, Z. Yuan, Angew. Chem. Int. Ed. 52 (2013) 2221–2225;
(f) Y. Nishikawa, H. Yamamoto, J. Am. Chem. Soc. 133 (2011) 8432–8435.
[7] (a) I.D. Titanyuk, I.P. Beletskaya, A.S. Peregudov, S.N. Osipov, J. Fluorine Chem. 128 (2007) 723–728;
(b) Y. Yamauchi, T. Kawate, T. Katagiri, K. Uneyama, Tetrahedron 59 (2003) 9839–9847;
(c) M. Obayashi, E. Ito, K. Matsui, K. Kondo, Tetrahedron Lett. 23 (1982) 2323–2326.
[8] B. Iorga, F. Eymery, P. Savignac, Synthesis (1999) 207–224.
[9] (a) D. Redmore, Chem. Rev. 71 (1971) 315–337;
(b) B. Springs, P. Haake, J. Org. Chem. 41 (1976) 1165–1168;
(c) B.A. Arbuzov, V.S. Vinogradova, N.A. Polezhaeva, A.V. Shamsutdinova, Izv. Akad. Nauk SSSR, Ser. Khim. (1963) 1380 (Chem. Abstr. 59 (1963) 15306);
(d) F. Texier-Boullet, A. Foucaud, Tetrahedron Lett. 21 (1980) 2161–2164;
(e) K. Kossev, K. Troev, D.M. Roundhill, Phosphorus Sulfur 83 (1993) 1–8;
(f) A. Meisters, J.M. Swan, Aust. J. Chem. 18 (1965) 168;
(g) Z.I. Glebova, O.V. Eryuzheva, Y.A. Zhdanov, Russ. J. Gen. Chem. 63 (1993) 1172–1174;
(h) R. Nikolova, A. Bojilova, N.A. Rodios, Tetrahedron 54 (1998) 14407–14420;
(i) T. Hanaya, Y. Nakamura, H. Yamamoto, Heterocycles 74 (2007) 983–989.
[10] (a) C. Giordano, G.J. Castaldi, Org. Chem. 54 (1989) 1470–1473;
(b) G. Sturtz, A. Pondaven-Raphalen, Phosphorus Sulfur 20 (1984) 35–48;
(c) Y. Kobayashi, A. William, Y. Tokoro, J. Org. Chem. 66 (2001) 7903–7906;
(d) C. Ansiaux, I. N'Go, S.P. Vincent, Chem.-Eur. J. 18 (2012) 14860–14866;
(e) M. Sekine, K. Okimoto, K. Yamada, T. Hata, J. Org. Chem. 46 (1981) 2097–2107;
(f) A.E. Wroblewski, I.I. Bak-Sypien, Tetrahedron: Asymmetry 18 (2007) 520–526;
(g) J.-C. Monbaliu, B. Tinant, J. Marchand-Brynaert, J. Org. Chem. 75 (2010) 5478–5486;
(h) E. Bandini, G. Martelli, G. Spunta, M. Panunzio, Tetrahedron: Asymmetry 6 (1995) 2127–2130;
(i) F. Gallier, J.A.C. Alexandre, C. ElAmri, D. Deville-Bonne, S. Peyrottes, C. Perigaud, ChemMedChem 6 (2011) 1094–1106.
[11] (a) A.S. Demir, M. Emrullahoglu, E. Pirkin, N. Akca, J. Org. Chem. 73 (2008) 8992–8997;
(b) A. Ulman, M.J. Sprecher, Org. Chem. 44 (1979) 3703–3707;
(c) R.H. Churi, C.E. Griffin, J. Am. Chem. Soc. 88 (1966) 1824–1830.
[12] (a) E.J. Glamkowski, G. Gal, R. Purick, A.J. Davidson, M.J. Sietzinger, Org. Chem. 35 (1970) 3510–3512;
(b) H.-J. Cristau, X.Y. Mbianda, A. Geze, Y. Beziat, M.-B. Gasc, J. Organomet. Chem. 571 (1998) 189–193;
(c) H.-J. Cristau, J.-L. Pirat, M. Drag, P. Kafarski, Tetrahedron Lett. 41 (2000) 9781–9785.
[13] (a) J.-P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, 1st ed., Wiley & Sons, New Jersey, 2008;
(b) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330;
(c) D. O'Hagan, Chem. Soc. Rev. 37 (2008) 308–319, and references therein.
[14] D. O'Hagan, H.S. Rzepa, Chem. Commun. (1997) 645–652.
[15] For some examples see:
(a) VK. Batra, L.C. Pedersen, W.A. Beard, S.H. Wilson, B.A. Kashemirov, T.G. Upton, M.F. Goodman, C.E. McKenna, J. Am. Chem. Soc. 132 (2010) 7617–7625;
(b) S.M. Forget, D. Bhattasali, V.C. Hart, T.S. Cameron, R.T. Syvitskiad, D.L. Jakeman, Chem. Sci. 3 (2012) 1866–1878;
(c) D.B. Berkowitz, M.J. Bose, Fluorine Chem. 112 (2001) 13–33;
(d) P. Van der Veken, K. Senten, I. Kertèsz, A. Haemers, K. Augustyns, Tetrahedron Lett. 44 (2003) 969–972;
(e) P. Cui, W.F. McCalmont, K.R. Lynch, J.L. Tomsig, T.L. Macdonald, Bioorg. Med. Chem. 26 (2008) 2212–2225;
(f) D.B. Berkowitz, M. Bose, T.J. Pfannenstiel, T.J. Doukov, J. Org. Chem. 65 (2000) 4498–4508.

[16] For some examples see:
(a) PA. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, Chem. Rev. (2015), http://dx.doi.org/10.1021/cr500706a;
(b) T. Liang, C.N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 52 (2013) 8214–8264;
(c) V.A. Brunet, D. O'Hagan, Angew. Chem. Int. Ed. 47 (2008) 1179–1182;
(d) S. Lectard, Y. Hamashima, M. Sodeoka, Adv. Synth. Catal. 352 (2010) 2708–2732;
(e) H. Ibrahim, A. Togni, Chem. Commun. (2004) 1147–1155;
(f) C. Bobbio, V. Gouverneur, Org. Biomol. Chem. 4 (2006) 2065–2075;
(g) J.-A. Ma, D. Cahard, Chem. Rev. 104 (2004) 6119–6146;
(h) P.M. Pihko, Angew. Chem. Int. Ed. 45 (2006) 544–547.
[17] For some examples see:
(a) Y Hamashima, T. Suzuki, H. Takano, Y. Shimura, Y. Tsuchiya, K.-I. Moriya, T. Goto, M. Sodeoka, Tetrahedron 62 (2006) 7168–7179;
(b) V.D. Romanenko, V.P. Kukhar, Chem. Rev. 106 (2006) 3868–3935;
(c) K.V. Turcheniuk, V.P. Kukhar, G.V. Roeschenthaler, J.L. Acen, V.A. Soloshonok, A.E. Sorochinsky, RSC Adv. 3 (2013) 6693–6716;
(d) M. Rapp, T. Cytlak, M.Z. Szewczyk, H. Koroniak, Curr. Green Chem. (2015), http://dx.doi.org/10.2174/2213346102666150123230102.
[18] For some review see:
(a) PA. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, Chem. Rev. (2015), http://dx.doi.org/10.1021/cr500706a;
(b) T. Liang, C.N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 52 (2013) 8214–8264;
(c) M. Shimizu, T. Hiyama, Angew. Chem. Int. Ed. 44 (2005) 214–231;
(d) G.S. Lal, G.P. Pez, R.G. Syvret, Chem. Rev. 96 (1996) 1737–1755;
(e) K.L. Kirk, Org. Process Res. Dev. 12 (2008) 305–321;
(f) S.D. Taylor, C.C. Kotoris, G. Hum, Tetrahedron 55 (1999) 12431–12477;
(g) J. Baudoux, D. Cahard, Org. React. 69 (2007) 1–326.
[19] R.E. Banks, S.N. Mohialdin-Khaffaf, G.S. Lal, I. Sharif, R.G. Syvret, J. Chem. Soc. Chem. Commun. (1992) 595–596.
[20] E. Differding, H. Ofner, Synlett (1991) 187–189.
[21] (a) A.J. Poss, M. Van Der Puy, D. Nalewajek, G.A. Shia, W.J. Wagner, R.L. Frenette, J. Org. Chem. 56 (1991) 5962–5964;
(b) R.E. Banks, R.A. Du Boisson, W.D. Morton, E.J. Tsiliopoulos, Chem. Soc., Perkin Trans. 1 (1988) 2805–2811;
(c) T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomital, J. Am. Chem. Soc. 112 (1990) 563–575;
(d) H.Z. Alkhathlan, Tetrahedron 59 (2003) 8163–8170;
(e) S.T. Purrington, W.A. Jones, J. Fluorine Chem. 26 (1984) 43–46;
(f) D.H.R. Barton, L.S. Godinho, R.H. Hesse, M.M. Pechet, Chem. Commun. (1968) 804–806;
(g) V.C.O. Njar, T. Arunachalam, E. Caspi, J. Org. Chem. 48 (1983) 1007–1011.
[22] K. Radwan-Olszewska, F. Palacios, P. Kafarski, J. Org. Chem. 76 (2011) 1170–1173.
[23] (a) Y. Hamashima, T. Suzuki, Y. Shimura, T. Shimizu, N. Umebayashi, T. Tamura, N. Sasamoto, M. Sodeoka, Tetrahedron Lett. 46 (2005) 1447–1450;
(b) S.M. Kim, H.R. Kim, D.Y. Kim, Org. Lett. 12 (2005) 2309–2311;
(c) S.M. Kim, Y.K. Kang, K.S. Lee, J.Y. Mang, D.Y. Kim, Bull. Korean Chem. Soc. 27 (2006) 423–425.
[24] L. Bernardi, K.A. Jørgensen, Chem. Commun. (2005) 1324–1326.
[25] (a) K. Shibatomi, A. Narayama, Y. Soga, T. Muto, S. Iwasa, Org. Lett. 13 (11) (2011) 2944–2947;
(b) S.B. Woo, C.W. Suh, K.O. Koh, D.Y. Kim, Tetrahedron Lett. 54 (2013) 3359–3362.
[26] M. Rapp, M.Z. Szewczyk, H. Koroniak, J. Fluorine Chem. 167 (2014) 152–158.
[27] A.R. Reddy, G. Goverdhan, A. Sampath, Synth. Commun. 42 (2012) 639–649.
[28] (a) H. Newman, R.B. Angier, Tetrahedron 26 (1970) 825–836;
(b) B. Modarai, E. Khoshdel, J. Org. Chem. 42 (1977) 3527–3531.
[29] W. Peng, J.M. Shreeve, J. Org. Chem. 70 (2005) 5760–5763.
[30] H.Y. Choi, D.Y. Chi, Org. Lett. 5 (2003) 411–414.
[31] M. Kaźmierczak, H. Koroniak, J. Fluorine Chem. 139 (2012) 23–27.
[32] M.J. Karplus, Am. Chem. Soc. 85 (1963) 2870–2871.
[33] F. Palacios, D. Aparicio, J. de los Santos, Tetrahedron 50 (1994) 12727–12742.
[34] D.Y. Kim, Y.M. Lee, Y.J. Choi, Tetrahedron 55 (1999) 12983–12990.
[35] W.R. Dolbier Jr., Guide to Fluorine NMR for Organic Chemists, Wiley Interscience, Hoboken, 2009.
[36] E. Pretsch, P. Buhlmann, M. Badertscher, Structure Determination of Organic Compounds, Springer, Berlin, 2009p. 265.
[37] (a) P. Beier, A.V. Alexandrova, M. Zibinsky, G.K.S. Prakash, Tetrahedron 64 (2008) 10977–10985;
(b) C.E. McKenna, P.D. Shen, J. Org. Chem. 46 (1981) 4573–4576;
(c) S.R. Piettre, L. Cabanas, Tetrahedron Lett. 37 (1996) 5881–5884;
(d) S.R. Piettre, C. Girol, C.G. Schelcher, Tetrahedron Lett. 37 (1996) 4711–4712.