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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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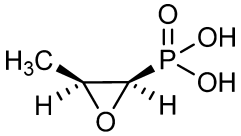

Fig. 1. Structure of (1*R*,2*S*)-1,2-epoxypropylphosphonic acid (Fosfomycin).

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