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INTRODUCTION OF α-FLUOROPHOSPHONOMETHYL ETHER FUNCTIONALITY AND ITS APPLICATION TO THE SYNTHESIS OF FLUORINATED ACYCLIC PHOSPHONATE NUCLEOSIDES

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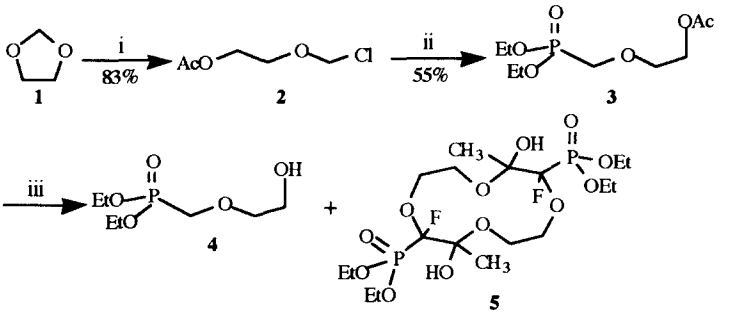
Abstract: *Introduction of the α-fluorophosphonomethyl ether functionality has been achieved by electrophilic fluorination of the corresponding phosphonomethyl ether carbanion. Coupling of the synthesized 2-[(diethoxyphosphono)fluoromethoxy]ethanol (9) with adenine and 6-chloropurine under Mitsunobu conditions afforded novel fluorinated acyclic phosphonate nucleosides 11a and 11b, respectively.* Copyright © 1996 Elsevier Science Ltd

Since Blackburn[1,2] and Chambers[3] demonstrated that α-fluoromethyl and α,α-difluoromethylene phosphonates were superior analogues, both electronically and structurally, to phosphates, considerable attention has been drawn to the synthesis of α-fluorinated phosphonate analogues of biologically important phosphates[4,5] such as nucleotides and sugar phosphates. In addition to the Arbuzov reaction between fluoroalkyl halides and trialkyl phosphites,[6,7] a number of methods have been developed for the synthesis of α-fluorinated phosphonates. These include alkylation[4,8-10] and Wittig reactions[11] of fluoroalkyl phosphonate anions, palladium-catalyzed addition of iododifluoromethyl phosphonate[12] to alkenes or addition of phosphonyl radical to fluoroolefins,[13] replacement of the hydroxyl or keto group by fluorine(s) in α-hydroxy- or α-ketoalkyl phosphonates using DAST,[14-16] and direct fluorination of alkyl phosphonate carbanions with electrophilic fluorinating agents such as perchloryl fluoride,[8,11,17,18] and a class of N-fluoro compounds.[19-21]

The functional group α-fluorophosphonomethyl ether [-OCFHP(O)$(OH)_2$] has been of recent interest during our search for hydrolytically stable and more effective phosphate analogues. Since there have been no previous reports on the introduction of such a functionality, herein we wish to communicate our results concerning the synthesis of 2-[(diethoxyphosphono)fluoromethoxy]ethanol (**9**), the first example of compounds possessing the α-fluorophosphonomethoxy group, and its coupling reaction with adenine and 6-chloropurine to afford the corresponding fluorinated acyclic phosphonate nucleosides.

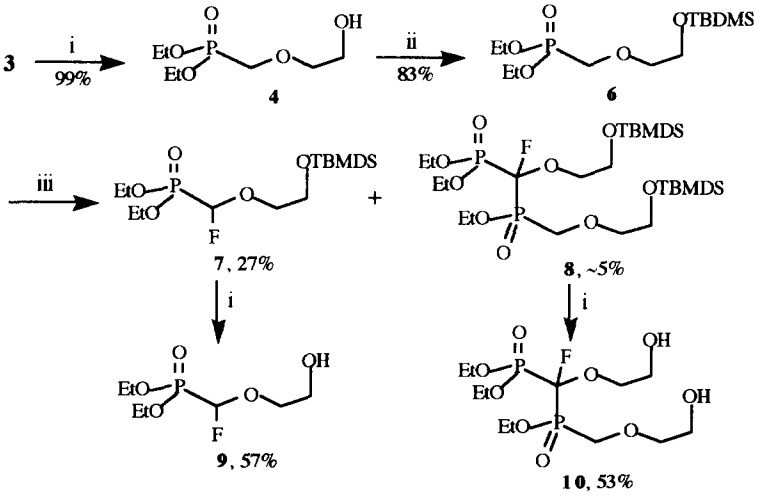
Thus, electrophilic fluorination of diethyl 2-acetoxyethoxymethanephosphonate (**3**) was initially attempted. Compound **3** was prepared according to a literature procedure,[22] starting from 1,3-dioxolane (**1**), *via* chloromethyl ether **2** (**Scheme 1**). A modified method utilizing a catalytic amount of $ZnCl_2$ was found to be more efficient for acylative cleavage of **1** to yield **2**.[23] Electrophilic fluorination of **3** using N-fluorobenzenesulphonimide [$(PhSO_2)_2NF$] in the presence of NaH as a base did occur, but the desired product was not isolated. Instead, ester hydrolysis afforded the alcohol **4** and acyl transfer from O to C^{24} led to the dimeric fluorine-substituted hemiacetal **5**.[25,26] Changing the base from NaH to

LDA, LHMDS, KHMDS, or *sec*-BuLi did not affect the course of the reaction. It was apparent that the acetyl group was not suitable for protection of the hydroxyl group under these fluorination reaction conditions.



Scheme 1. Reagents: i) AcCl, $ZnCl_2$; ii) $(EtO)_3P$; iii) a. NaH, b. $(PhSO_2)_2NF$

Compound **3** was then converted into *tert*-butyldimethylsilyl (TBDMS)-protected compound **6** in a two-step process. Fluorination of **6** was carried out at -78 to 0°C by using $(PhSO_2)_2NF$ as the fluorinating agent and *sec*-BuLi as the base. The key intermediate 1-(*tert*-butyldimethylsiloxy)-2-[(diethoxyphosphono)fluoromethoxy]ethane (**7**)[25] was formed in moderate yield (27%) along with small amounts of dimer **8**[26] (~5% yield) (**Scheme 2**). When the reaction mixture was allowed to warm to ambient temperature, the yield of **7** was decreased to 22%; however, formation of the dimer **8** significantly increased to ~20%. The rate of addition of the fluorinating agent also affected the outcome of the reaction. When the fluorinating agent in THF was added to the anionic solution of **6** over a period of 80 min, compared with the usual 40 min, dimer **8** was isolated in 30% yield.

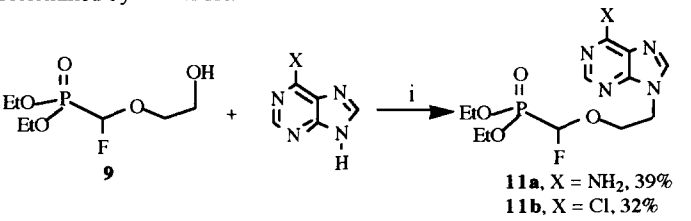


Scheme 2. Reagents: i) Dowex (H^+), EtOH; ii) TBDMS-Cl, DMAP/Et_3N; iii) a. *sec*-BuLi, b. $(PhSO_2)_2NF$

Replacement of *sec*-BuLi with LDA, LHMDS, or *n*-BuLi led to formation of more complicated mixtures, with less than 10% of **7** formation. Other N-fluoro electrophilic fluorinating agents such as $PhSO_2(Me)NF$, N-fluoro-2,4,6-trimethylpyridinium triflate, and 3,5-dichloro-1-fluoropyridinium triflate were also investigated for fluorination of compound **6**, but with limited success.

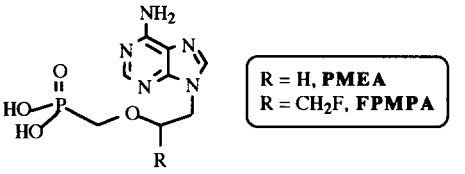
An attempted removal of the TBDMS group from compound **7** to form **9** using $(n\text{-Bu})_4NF$ under reported conditions was unsuccessful.[27] Treatment of compound **7** with acetic acid-water-THF (3:1:1), according to the procedure of Corey *et al*,[27] furnished compound **9** in 26% yield. However, treatment of **7** with Dowex (H^+) ion exchange resin at ambient temperature yielded **9**[26] in 57% yield after silica gel column chromatographic purification. Dimer **8** was also desilylated under similar conditions to yield compound **10**[26] in 53% yield (**Scheme 2**).

One of the applications of 2-[(diethoxyphosphono)fluoromethoxy]ethanol (**9**) is illustrated by the synthesis of α-fluoro acyclic phosphonate nucleosides. Thus, coupling of **9** with adenine and 6-chloropurine under Mitsunobu reaction conditions afforded compounds **11a**[26] and **11b**[26] in yields of 39% and 32%, respectively (**Scheme 3**). It is worthwhile to note that direct fluorination of the phosphonates corresponding to **11** proved to be very complicated, with less than 5% of the desired **11** being formed as determined by ^1H NMR.



Scheme 3. Reagents: i) DEAD, Ph_3P

Compound **11a** could be considered as the precursor of a fluorinated analogue of PMEA, an antiviral agent which is currently undergoing phase I/II clinical trials for the treatment of HIV infection.[28] FPMPA is the only fluorinated analogue in the acyclic nucleoside phosphonate series that has been reported to possess strong antiretroviral activity.[29]



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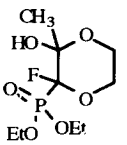

5a

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