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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

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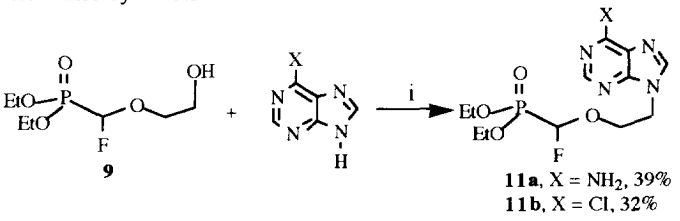
Replacement of *sec*-BuLi with LDA, LHMDS, or *n*-BuLi led to formation of more complicated mixtures, with less than 10% of **7** formation. Other N-fluoro electrophilic fluorinating agents such as $PhSO_2(Me)NF$, N-fluoro-2,4,6-trimethylpyridinium triflate, and 3,5-dichloro-1-fluoropyridinium triflate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

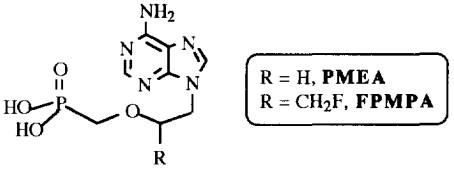
An attempted removal of the TBDMS group from compound **7** to form **9** using $(n\text{-Bu})_4NF$ under reported conditions was unsuccessful.[27] Treatment of compound **7** with acetic acid-water-THF (3:1:1), according to the procedure of Corey *et al*,[27] furnished compound **9** in 26% yield. However, 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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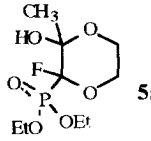
References and Notes

1. Blackburn, G. M.; Kent, D. E.; Kolkman, F., *J. Chem. Soc., Perkin Trans. 1* **1984**, 1119-1125.
2. Blackburn, G. M.; Perree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B., *Chem. Scr.* **1986**, *26*, 21-24.
3. Chambers, R. D.; O'Hagan, D.; Lamont, R. B.; Jain, S. C., *J. Chem. Soc., Chem. Commun.* **1990**, 1053-1054.
4. Otaka, A.; Miyoshi, K.; Burke, T. R.; Roller, P. P.; Kubota, H.; Tamamura, H.; Fujii, N., *Tetrahedron Lett.* **1995**, *36*, 927-930.
5. Berkowitz, D. B.; Sloss, D. G., *J. Org. Chem.* **1995**, *60*, 7047-7050 and references cited therein.
6. Burton, D. J.; Naee, D.; Flynn, R. M.; Smart, B. E.; Brittelli, D. R., *J. Org. Chem.* **1983**, *48*, 3616-3618 and references cited therein.
7. McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T., *Tetrahedron Lett.* **1990**, *31*, 5449-5452.
8. Blackburn, G. M.; Brown, D.; Martin, S. J.; Parratt, M. J., *J. Chem. Soc., Perkin Trans. 1* **1987**, 181-186 and references cited therein.
9. Burton, D. J.; Sprague, L. G., *J. Org. Chem.* **1989**, *54*, 613-617 and references cited therein.
10. Phillion, D. P.; Cleary, D. G., *J. Org. Chem.* **1992**, *57*, 2763-2764.
11. Blackburn, G. M.; Parratt, M. J., *J. Chem. Soc., Perkin Trans. 1* **1986**, 1417-1424.
12. Yang, Z.-Y.; Burton, D. J., *J. Org. Chem.* **1992**, *57*, 4676-4683.
13. Piettre, S. R., *Tetrahedron Lett.* **1996**, *37*, 2233-2236 and references cited therein.
14. Blackburn, G. M.; Kent, D. E., *J. Chem. Soc., Perkin Trans. 1* **1986**, 913-917.
15. Smyth, M. S.; Ford, H., Jr.; Burke, T. R., Jr., *Tetrahedron Lett.* **1992**, *33*, 4137-4140.
16. Wrobel, J.; Dietrich, A., *Tetrahedron Lett.* **1993**, *34*, 3543-3546.
17. Blackburn, G. M.; England, D. A.; Kolkmann, F., *J. Chem. Soc., Chem. Commun.* **1981**, 930-932.
18. McKenna, C. E.; Pham, P.-T. T.; Rassier, M. E.; Dousa, T. P., *J. Med. Chem.* **1992**, *35*, 4885-4892.
19. Xu, Z.-Q.; DesMarteau, D. D., *J. Chem. Soc., Perkin Trans. 1* **1992**, 313-315.
20. Differding, E.; Duthaler, R. O.; Krieger, A.; Ruegg, G. M.; Schmit, C., *SynLett.* **1991**, 395-396.
21. Lal, G. S., *J. Org. Chem.* **1993**, *58*, 2791-2796.
22. Holy, A.; Rosenberg, I. *Collec. Czech. Chem. Commun.* **1987**, *52*, 2801-2809.
23. Bailey, W. F.; Zarcone, L. M.; Rivera, A. D., *J. Org. Chem.* **1995**, *60*, 2532-2536.
24. Feeder, N.; Hutton, G.; Warren, S., *Tetrahedron Lett.* **1994**, *35*, 5911-5914.
25. An alternate structure for hemiacetal **5** might be its monomer **5a**, based upon the spectroscopic and analytical data. However, CI-MS indicated the molecular weitght to be 545, which corresponded to the dimer **5**.



5a

26. All the new compounds yielded satisfactory spectroscopic and analytical data.
27. Corey, E. J.; Venkateswarlu, A., *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.
28. Collier, A. C.; Coombs, R. W.; Nienow, J.; Paradise, M.; Yang, H. H.; Troxel, S.; Boggs, J.; Ebeling, D.; Jaffe, H. S.; Corey, L., First National Conference on Human Retroviruses and Related Infections, December 12-16, **1993**, Washington, D. C., Abstract 563.
29. Balzarini, J.; Holy, A.; Jindrich, J.; Dvorakova, H.; Hao, Z.; Snoeck, R.; Herdewijn, P.; Johns, D. G.; De Clercq, E., *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 4961-4965.

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