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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

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To cite this Article Laux, W. H. G. , Périgaud, C. , Imbach, J. -L. and Gosselin, G.(1999) 'Synthesis of New PME A Diphosphate Mimics', *Nucleosides, Nucleotides and Nucleic Acids*, 18: 4, 1003 — 1004

To link to this Article: DOI: 10.1080/15257779908041629

URL: <http://dx.doi.org/10.1080/15257779908041629>

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SYNTHESIS OF NEW PME A DIPHOSPHATE MIMICS

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ABSTRACT: We synthesized and characterized new diphosphate mimics of the acyclic nucleoside phosphonate PME A [Adefovir, 9-(2-phosphonylmethoxyethyl)adenine].

The acyclic nucleoside phosphonate PME A [Adefovir, 9-(2-phosphonylmethoxyethyl)-adenine] is a broad-spectrum antiviral agent. Its antiviral activity encompasses both retroviruses and hepadnavirus, as well as herpesviruses^{1,2}. After entering the cells, nucleoside phosphonates like PME A are phosphorylated by cellular enzymes³. Two consecutive phosphorylation steps give rise to PMEApp (1a, Table 1), which has been shown to be active against a number of different viral DNA polymerases or reverse transcriptases.

We wish to report here the synthesis of various substituted methanediphosphonates of PME A as new mimics of PMEApp incorporating nonhydrolysable phosphorus-carbon bonds between the atoms P_β and P_γ. The synthesis of PME A diphosphate 1a and its mimics 1b-k was accomplished by a modification of the morpholidate method which was first published by Mofatt⁴. The morpholidate of PME A 2 was obtained in 71 % yield as its 4-morpholine *N,N'*-dicyclohexylcarboxamidinium salt by the method published by A. Holy⁵. As only the acids 3a-d were commercially available, the halogeno substituted methanediphosphonates 3e-k were synthesized from tetraethyl methanediphosphonate. The bromo and chloro substituted compounds were obtained following the procedures published by McKenna⁶. The synthesis of the fluorinated compounds 3i and 3k was effected by treating the anion of tetraethyl methanediphosphonate with 1.3 eq of N-fluoro-

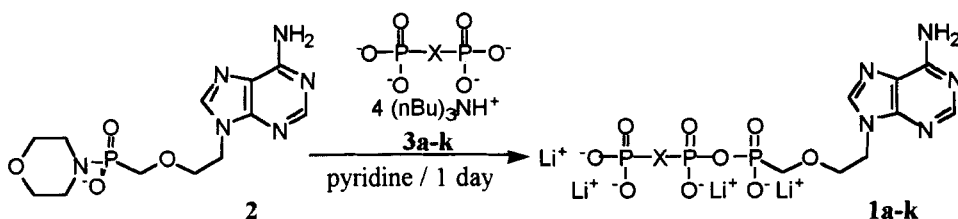


FIG.: Synthesis of PMEApp (1a) and its mimics 1b-k

TABLE 1: Results of the synthesis of PMEAs diphosphate mimics **1a-k**

<i>product</i>	<i>X</i>	<i>yield</i>	¹³ C NMR (D ₂ O)	³¹ P NMR (D ₂ O)		
			δ(CYZ)	δ(P _α)	δ(P _β)	δ(P _γ)
1a	O	32 %	—	9.6	-21.7	-9.4
1b	NH	18 %	—	9.5	-6.3	0.5
1c	CH ₂	65 %	30.8	9.2	14.7	13.7
1d	C(OH)CH ₃	33 %	72.4	9.9	16.4	17.6
1e	CCl ₂	50 %	78.0	9.8	4.0	9.5
1f	CHCl	53 %	49.5	9.4	8.8	10.2
1g	CBr ₂	54 %	57.4	9.8	4.2	9.3
1h	CHBr	43 %	38.2	9.3	8.5	9.7
1i	CF ₂	34 %	118.7	10.1	-3.8	3.9
1k	CHF	56 %	89.3	9.5	6.6	8.6

benzenesulfonimide, a reagent developed by Differding⁷. After removal of the ester groups by TMSBr the free acids **3i** and **3k** were obtained in 23 % and 28 % yields, respectively.

For the coupling reaction, pyrophosphate or one of its analogues, were converted to their pyridinium salts by Dowex 50WX2 chromatography. The residue of this chromatography was coevaporated with tri-*n*-butylamine and pyridine. Then, the morpholidate **2** was added in pyridine solution. The reaction was stirred at ambient temperature for one day. Afterwards a prepurification by a Dowex 1X2 chromatography was carried out⁵ using a gradient of aqueous lithium chloride in 0.01 M hydrochloric acid. This prepurification step was used in order to remove polar and nonpolar impurities. After a DEAE-Sephadex A25 chromatography the PMEAs diphosphate mimics were isolated in 18 % - 65 % yield.

ACKNOWLEDGMENT: W. L. is indebted to the "Fonds der Chemischen Industrie" for a Post-Doc scholarship.

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