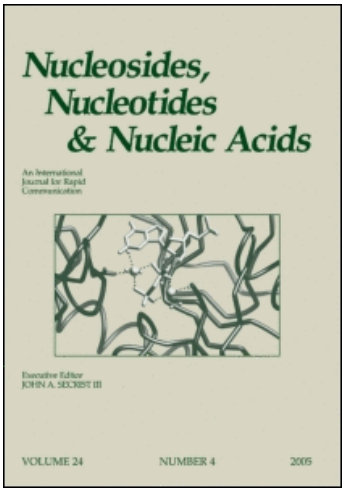

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Synthesis of New PMEA Diphosphate Mimics

W. H. G. Laux[a]; C. Périgaud[a]; J. -L. Imbach[a]; G. Gosselin[a]
[a] Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier II, Montpellier Cedex 5, France

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SYNTHESIS OF NEW PMEA DIPHOSPHATE MIMICS

W. H. G. Laux, C. Périgaud*, J.-L. Imbach, G. Gosselin
Laboratoire de Chimie Bioorganique, UMR CNRS-USTL 5625, Université Montpellier II
case courrier 008, Place E. Bataillon, 34095 Montpellier Cedex 5, France

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

The acyclic nucleoside phosphonate PMEA [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 PMEA are phosphorylated by cellular enzymes[3]. 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 PMEA as new mimics of PMEApp incorporating nonhydrolysable phosphorus-carbon bonds between the atoms P_β and P_γ. The synthesis of PMEA diphosphate **1a** and its mimics **1b-k** was accomplished by a modification of the morpholidate method which was first published by Mofatt[4]. The morpholidate of PMEA **2** was obtained in 71 % yield as its 4-morpholine *N,N'*-dicyclohexylcarboxamidinium salt by the method published by A. Holy[5]. As only the acids **3a-d** were commercialy 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 McKenna[6]. 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-

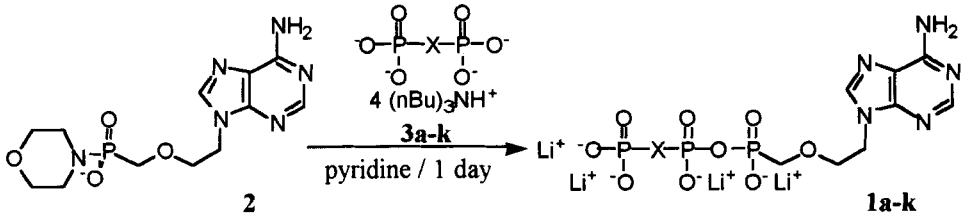

FIG.: Synthesis of PMEApp (**1a**) and its mimics **1b-k**

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

product	*X*	*yield*	^{13}C NMR (D_2O)	^{31}P NMR (D_2O)		
			δ(CYZ)	$\delta(P_\alpha)$	$\delta(P_\beta)$	$\delta(P_\gamma)$
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 developped by Differding[7]. 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 out[5] 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 PMEA diphosphate mimics were isolated in 18 % - 65 % yield.

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