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Synthesis of 1-Phosphonoalkylidene and -arylidene Derivatives of Nucleosides

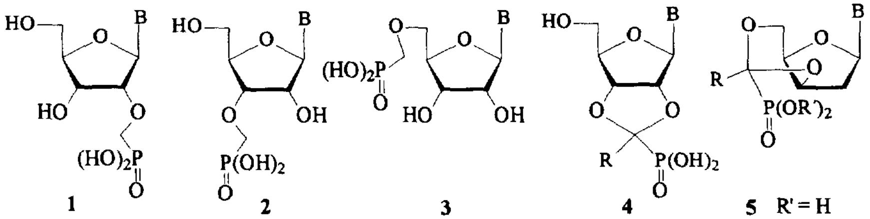
Magdalena Endová, Milena Masojídková, Miloš Buděšínský and Ivan Rosenberg*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic
Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

Abstract: Redox reaction of chlorodiethylphosphite with nucleoside orthoesters results in efficient synthesis of 2', 3'- or 3', 5'-O-((1-diethylphosphono)aralkyl)methylene derivatives of nucleosides as a novel type of isopolar phosphonate-based nucleotide analogues. The configuration of products was determined by 2D-ROESY NMR experiments. Copyright © 1996 Elsevier Science Ltd

Search for the compounds exhibiting antiviral and/or anticancer activities has led to the preparation of a number of nucleoside and nucleotide analogues. Among them, the nucleoside phosphonates[1] containing phosphonic acid residue mimicking the regular phosphate group of nucleotides showed strong antiviral activities against DNA viruses and retroviruses, and are in the foreground of interest of many laboratories[2].

A longstanding attention given to the synthesis of nucleotide analogues with enhanced enzymatic stability has led us to the preparation of 2'-O-, 3'-O- and 5'-O-phosphonomethyl derivatives of nucleosides **1**, **2**, **3**[3]. Conservation of the 5'-oxygen atom in the molecule of the analogue and conformational adaptability of the P-C-O bond seem to be important for the interaction of these compounds with various enzymes[4]. Although insertion of methylene group lengthens the "parent" phosphomonoester or phosphodiester bond, our NMR spectroscopy studies[5] revealed the close conformational similarities of phosphonate analogues to natural nucleotides.

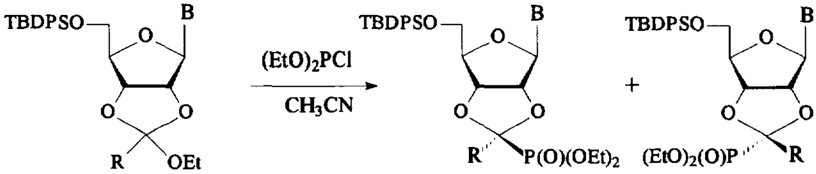


1 **2** **3** **4** **5** R' = H

R = H, CH_3, C_6H_5 **6** R' = Et

Within the framework of our investigation, we report now a novel type of the nucleotide analogues **4** and **5**. These compounds can be considered as conformationally restricted congeners of phosphonates **1**, **2** and **3**, respectively.

Although general procedures for the chemical synthesis of 2-dialkylphosphonoderivatives of 1,3-dioxolanes and 1,3-dioxanes have already been described[6], their application in the nucleoside chemistry completely failed. On the other hand, chlorodiethylphosphite is known to give diethyl diethoxymethylphosphonate in a redox reaction with triethylorthoformate; orthoesters of other carboxylic acids react under transesterification of the P^{III} compound[7].



7 $R = H, CH_3, C_6H_5$ 8 *exo*-isomer 8 *endo*-isomer
$B = T, U, C^{Bz}, G^{Bz}, A^{Bz}$

Scheme 1.
Synthesis of Protected Phosphonates.

Surprisingly, in our hands, the reaction of chlorodiethylphosphite proceeded very smoothly with all three types of nucleoside orthoesters[8] 7 used (ethoxymethylene (EM, R = H), -ethylidene (EE, $R = CH_3$) and -benzylidene (EB, $R = C_6H_5$) derivatives), and desired 2',3'-O-((1-diethylphosphono)alkyl)methylene derivatives **8** (see Scheme 1) were isolated in good yields[9] (50-98%, for examples see Table 1).

A complete set of protected **8** and deprotected **4** phosphonates was prepared. We found that the reactivity of nucleoside orthoesters 7 depends both on the type of nucleobase [10] and orthoester; it decreases in the order T, U, $C^{Bz} > G^{Bz} >> A^{Bz}$ and EB ≈ EE >> EM. In the case of adenine ethoxymethylene-derivative 7 ($B = A^{Bz}$, R=H), as the orthoester with the lowest reactivity, we found that Lewis acids (tin tetrachloride, boron trifluoride diethyl etherate, trimethylsilyl trifluoromethanesulphonate, etc.), sodium iodide, or silver trifluoromethanesulphonate, if present in the equimolar amount, strongly accelerated the course of the reaction. This phenomenon could be explained by the activation of orthoester moiety by Lewis acids, either by classical ones or those generated *in situ* from chlorodiethylphosphite (diethyliodophosphite or diethyltrifluoromethanesulphonylphosphite). Neither low temperature in the combination with Lewis acid nor diastereomeric composition of the starting orthoester 7 ($B = A^{Bz}$, R=H) exerted any influence on the ratio of the *exo*- and *endo*-phosphonate **8** ($B = A^{Bz}$, R=H); the *exo*-compound always prevailed. The *exo*-isomer appeared to be the major one in the whole series of phosphonates **8**.

Table 1. Reaction Conditions and Results of the Phosphonate Synthesis.

R	B	Reaction temp. (°C)	Ratio[a] of *exo*- to *endo*-orthoester 7	Ratio[a] of *exo*- to *endo*-phosphonate **8**	Yield[b] of **8** (%)
H	T	0 to 20	1.1	2.8	74
	A^{Bz}	reflux	0.04	3	91
CH_3	T	-40 to 20	1.3	8	78
	A^{Bz}	20	1.2	10	98
C_6H_5	T	-40 to 20	1.2	6	84
	A^{Bz}	20	1.2	10	96

[a] determined from ^1H NMR spectra; [b] isolated yield

Similar results were obtained with 3',5'-orthoesters of 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[11] under very mild conditions (-40 to 0°C); desired 2'-deoxy-3',5'-O-((1-diethylphosphono)aryl)methylene derivatives **6** (B = T) were prepared in equally good yields (66-90%).

Complete removal of protecting groups from phosphonates **8** and **6** and purification of free phosphonates **4** and **5** was accomplished according to standard procedures[12] (50-96% yield).

The configuration of *exo*- and *endo*-isomers of phosphonates **8** was determined from proton 2D-ROESY NMR spectra[13]. For example in the case of diastereomeric pair of 5'-deprotected compounds **8** (R = H, B = A^{Bz}) an *exo*-isomer showed ROE-cross peaks of proton H* with ribose H-1' and H-4' protons, while for *endo*-isomer ROE-cross peaks with H-2' and H-3' ribose protons were observed (see Figure 1). The configurational assignment is also supported by chemical shifts differences of ribose protons in isomeric pairs: proximity of $O{=}P(OR)_2$ group induces downfield shifts (cca 0.1 ppm) of H-2' and H-3' protons in *exo*-isomer and of H-1' and H-4' protons in *endo*-isomer (see Figure 1). ^1H and ^{13}C NMR data of orthoesters 7 and phosphonates **8**, **6** will be discussed elsewhere.

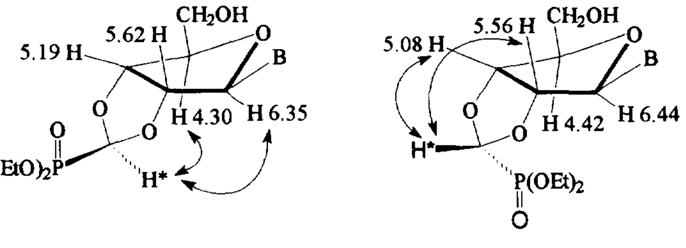


Figure 1.
Characteristic ROE-cross peaks of proton H* and chemical shifts of ribose protons in *exo*- and *endo*-isomers of 5'-deprotected compound **8** (B = A^{Bz}).

The phosphonomethylene derivatives of nucleosides reported here represent a novel class of isopolar, nonisosteric nucleotide analogues resistant towards the cleavage by phosphomonoesterases and nucleotidases. The evaluation of physico-chemical and antiviral properties of compounds **4** and **5** is in the progress.

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9. Typical procedure: 5'-O-*tert*-Butyldiphenylsilyl (TBDPS) derivatives of ribonucleosides[8a] were converted to the 2',3'-orthoesters **7** according to general procedures[8b,c] and these compounds (1 mmol) were treated with chlorodiethylphosphite (2 mmol) in acetonitrile (10 ml) under argon atmosphere. Reaction temperature was varied according to the reactivity of the orthoester (see Table 1). The course of the reaction was followed by TLC (chloroform-ethanol mixture). After disappearance of the starting material the reaction was quenched by addition of the mixture of 1M TEAB-ethanol (1:1; 5 ml). The resulting mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (chloroform-ethanol gradient mixture).

10. T ... thymin-1-yl; U ... uracil-1-yl; C^{Bz} ... N-4-benzoylcytosin-1-yl; G^{Bz} ... N-2-benzoylguanin-9-yl; A^{Bz} ... N-6-benzoyladenin-9-yl.

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12. a) bromotrimethylsilane in acetonitrile (phosphoester group); concentrated aqueous ammonia (N-benzoyl group); c) tetrabutylammonium fluoride in tetrahydrofurane (TBDPS group); d) chromatography on DEAE-Sephadex A25 in triethylammonium hydrogen carbonate buffer; e) Dowex 50 in Na^+ form.

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