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Nucleoside 5′-*C*-phosphonates: reactivity of the α-hydroxyphosphonate moiety

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Abstract—We found that various dialkyl phosphites, dialkyl trimethylsilyl phosphites, and tris-trimethylsilyl phosphite reacted smoothly with nucleoside 5′-aldehydes to afford epimeric nucleoside 5′-*C*-phosphonates in high yields. A number of these compounds in both the 2′-deoxyribo and *ribo* series were prepared. In the case of 2′-deoxythymidine-5′-aldehyde, a thorough study was made on the influence of the 3′-hydroxyl protecting group, type of phosphite, base, and solvent, on the yield and epimeric ratio of the resulting 5′-hydroxyphosphonates. Partial stereoselectivity in favour of either *R* or *S* epimers was observed. An attempt to transform the α-hydroxyl of the phosphonate moiety into a halo or azido moiety was not successful. Only intramolecular substitution reaction of the mesyloxy group for an alkoxy residue of the 2-hydroxyethyl ester took place in a low yield.
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1. Introduction

Nucleoside phosphonic acids, the well-known structurally diverse analogues of natural nucleotides, exhibit virtually absolute stability against enzymes of nucleotide catabolism, such as phosphomonoesterases and nucleotidases.[1] Among them, several types exhibit, after in vivo phosphorylation, remarkable antiviral properties.[2] The potential biological effects of nucleoside phosphonic acids have been the driving force in the search for novel nucleotide analogues with the P–C linkage. Nucleoside α-hydroxyphosphonic acids bearing a phosphoryl moiety attached directly to one of the carbon atoms of the sugar ring could undoubtedly be interesting compounds in this respect. Wiemer[3] and Králíková[4] reported 3′- and 2′-α-hydroxyphosphonate derivatives of nucleosides (Fig. 1). These 2′- and 3′-nucleotide analogues, however, did not exhibit any antiviral properties. A short account on the synthesis of regioisomeric compounds bearing the 5′-hydroxyphosphonate moiety **4a** was also reported by Králíková.[5,6] Recently Wiemer[7] described the synthesis of arabinosylcytosine 5′-hydroxyphosphonate **4b** which showed interesting biochemical properties. The nucleoside 5′-hydroxyphosphonates are related to the known 5′-deoxynucleoside 5′-phosphonates[8] **5** that lack chirality on the C5′ atom (Fig. 1).

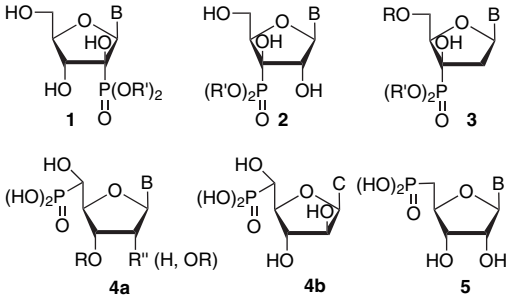

Figure 1. Examples of isopolar non-isosteric nucleoside phosphonic acids.

Herein, we present the synthesis of a number of nucleoside 5′-*C*-phosphonates (5′-hydroxyphosphonates) in 2′-deoxyribo **12–15** and *ribo* series **48–53** bearing an additional chiral centre on the C5′ atom (Schemes 1 and 4, Tables 1 and 3), and demonstrate the reactivity of the 5′-hydroxy group of the hydroxyphosphonate moiety. We prepared these compounds employing the general method of nucleophilic addition of phosphites to carbonyl compounds.[9–11] We found it interesting to subject these compounds to further transformation reactions to obtain a variety of new derivatives. In addition, the free nucleoside 5′-*C*-phosphonic acids **38–41** and **54–58** represent a pool of potential antimetabolites which could inhibit, for instance, different mammalian 5′-nucleotidases, as described earlier[12] for another type of nucleoside 5′-phosphonic acids prepared in our laboratory.[13,14] Also the inhibition of thymidine phosphorylase, the enzyme involved in angiogenesis,[15] by nucleoside 5′-*C*-phosphonic acids could be expected, similarly to recently reported case of acyclic nucleoside phosphonic acids.[16]

Keywords: Nucleoside 5′-aldehydes; Oxidation; Phosphonates; Addition reaction; Nucleophilic substitution.
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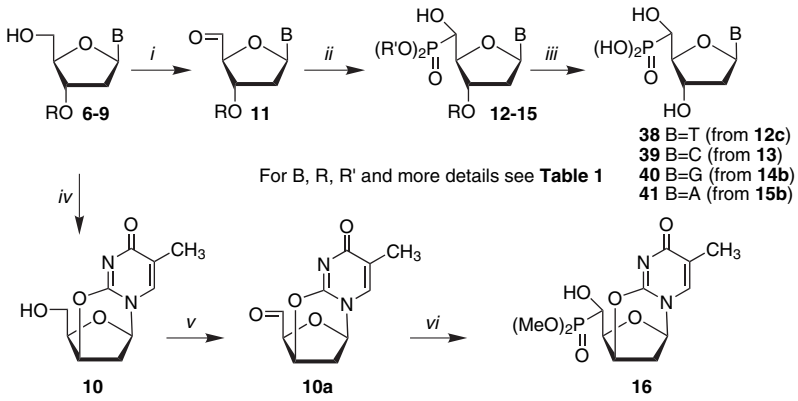

Scheme 1. (i) DMSO–$(COCl)_2$ or DMSO–DCC method; (ii) $(R'O)_2(O)PH$, Et_3N; (iii) (a) Me_3SiBr, CH_3CN, 24 h, rt, (b) satd ammonia in 50% aq ethanol, 48 h, rt, (c) 1 M TBAF in THF, 16 h, rt; (iv) Ph_3P, DEAD (from **10** R=H, B=T); (v) DMSO, DCC, pyridine, TFA; (vi) $(MeO)_2(O)PH$, Et_3N.

Table 1. Epimeric ratios and yields of prepared 2′-deoxynucleoside 5′-*C*-phosphonates (for general structures see Scheme 1)

Starting nucleoside	Oxidation method	Phosphite	Product	B	R	R′	*R*/*S* ratio[a]	Yield %[b]
6a	A[c]	$(Me_3SiO)_3P$	**12a**	T	TBDPS	H	37/63	85
		$(MeO)_2POH$	**12b**			Me	21/79	78
		$(EtO)_2POH$	**12c**			Et	19/81	77
		$(i\text{PrO})_2POH$	**12d**			*i*Pr	13/87	67
6b		$(MeO)_2POH$	**12e**		TBDMS	Me	20/80	71
6c	B[d]	$(MeO)_2POH$	**12f**		Bz	Me	42/58	52
		$(EtO)_2POH$	**12g**			Et	50/50	58
6d		$(EtO)_2POH$	**12h**		Piv	Et	33/67	54
6e		$(MeO)_2POH$	**12i**		DMTr	Me	19/81	60
7	A[c]	$(MeO)_2POH$	**13**	C^{Bz}	TBDPS	Me	15/85	84
8a			**14a**	G^{Bz}			34/66	82
8b			**14b**	G^{iBu}			40/60	76
9a			**15a**	A^{Bz}			25/75	69
9b	B[d]		**15b**	A^{Bz}	DMTr		22/78	80
10			**16**	T	—	—	37/63	34

[a] Epimeric ratio determined from ^1H NMR spectra.
[b] Isolated yield.
[c] DMSO–$(COCl)_2$.
[d] DMSO–DCC–pyridine–TFA.

2. Results and discussion

2.1. Preparation of 2′-deoxyribonucleoside 5′-*C*-phosphonates

The synthesis of protected nucleoside hydroxyphosphonates **12–16** in the 2′-deoxy series was accomplished by nucleophilic addition of various phosphites to nucleoside 5′-aldehydes **11** and **10a** (Scheme 1, Table 1) obtained by oxidation of protected nucleosides **6–9**, **10** using the Swern (DMSO–$(COCl)_2$)[17] or modified[18] Moffatt procedures (DMSO–DCC).[19,20] They were used in further reaction without purification and characterization. Whereas the 3′-*O*-silyl-protected 2′-deoxyribonucleosides **6a**, **6b**, **7**, **8a**, **8b** and **9a** were smoothly oxidized by the Swern procedure[17] (Method A), for the oxidation of 2′-deoxynucleosides bearing 3′-*O*-acyl protecting groups **6c**, **6d**, 3′-*O*-DMTr derivatives **6e** and **9b**, and 2,3′-anhydrothymidine (**10**) the DMSO–DCC method[18] was used (Method B) (Table 1). In contrast to literature data, [17] the 3′-*O*-acyl-protected 2′-deoxynucleosides **6c** and **6d** were not stable under conditions of the Swern oxidation procedure.[17]

We attempted to increase the stereoselectivity of the addition of dialkyl phosphites to nucleoside 5′-aldehydes (Table 1) by changing several factors, such as the solvent and the base used, and the type of phosphorus acid esters. We found that the solvent did not have any effect on the stereoselectivity, but the yields of phosphonates were different. Thus, DCM provided better yields of 5′-*C*-phosphonates than THF and acetonitrile. Increasing the amount of triethylamine (from 1 to 5 equiv) or the use of saturated ammonia in dioxane as a weak base did not influence the ratio of epimers. The use of DBU instead of triethylamine caused destruction of the starting nucleoside 5′-aldehyde. No change in the ratio of the epimeric phosphonates under the addition of diethyl phosphite in the presence of either lithium bis (trimethylsilyl)amide or *tert*-butylmagnesium chloride at −78 °C was found, but the yields of 5′-*C*-phosphonates were significantly reduced. On the other hand, only little changes in epimeric ratios were found if various dialkyl phosphites were used in the presence of triethylamine (Table 1); however, tris-trimethylsilyl phosphite exhibited significantly lower stereoselectivity in the addition reaction. The comparison of various types of 3′-*O*-protecting groups revealed (Table 1) that the use of 3′-*O*-acyl groups resulted in decrease of reaction preferences for the (*S*)-epimers.

The epimeric, protected nucleoside 5′-*C*-phosphonates **12–15** were separable by RP-HPLC, but on silica gel the

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