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Oxidative cleavage of ribofuranose 5-(α-hydroxyphosphonates): a route to erythrofuranose-based nucleoside phosphonic acids

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Abstract—We report here an oxidative cleavage of (5*R*)- and (5*S*)-ribofuranosyl-5-*C*-phosphonate derivatives with periodate anion under both strong acidic and neutral conditions. In both cases, only (5*R*)-configured compound underwent the expected oxidation reaction and afforded the desired (4*R*)-erythrofuranosylphosphonate, whereas the second epimer, (5*S*)-ribofuranosyl-5-*C*-phosphonate did not provide the corresponding (4*S*)-erythrofuranosylphosphonate derivative. This different behavior of epimers toward oxidative cleavage is an important phenomenon. The obtained (4*R*)-erythrofuranosylphosphonate was used for the preparation of phosphonate mimic of adenosine 5′-phosphate via classical nucleosidation reaction. Condensation of the protected shortened AMP analogue with adenosine derivatives, however, provided only the 2′,5′-linked ApA analogue. Study on hybridization of the modified 2′-5′ ApA with polyU revealed its ability to form stable triplex-like complex, similar to natural 2′-5′ r(ApA) and 3′-5′ r(ApA). NMR spectroscopy study showed that the erythrofuranose part of the phosphonate nucleotide unit of modified 2′-5′ ApA was predominantly in the C2′-*endo* conformation, which is characteristic for B-DNA.

1. Introduction

Structurally diverse isopolar phosphonate nucleotide analogues containing a bridging *P–C* bond have attracted our attention for many years.[1–7] This class of compounds, known as nucleoside phosphonic acids, represents a pool of potential antimetabolites exhibiting absolute stability against phosphomonoesterase and nucleotidase cleavage.[8] Some of these compounds have already found clinical use as potent antivirals.[9–11] The search for novel nucleotide analogues can reveal new biologically active compounds capable of discriminating between cellular and viral or tumor enzymes of nucleic acid metabolism, which could be used as antiviral and/or anticancer agents. In addition, novel phosphonate nucleotide analogues can be used for the construction of isopolar chimeric oligonucleotides containing nuclease-stable internucleotide linkages,[7] for instance, similar to already prepared phosphonate 2′,5′-oligoadenylates, which are potent, enzyme stable RNase L activators[12] intended for RNase L-mediated cleavage of pathogenic RNA.[13]

Here we present the synthesis of the isopolar, nonisosteric AMP analogue **13**, a representative of a new class of modified nucleoside 5′-phosphates, the structure of which resembles the features of the earlier reported nucleoside phosphonic acids **1**[14,15] and **2**[16,17] (Fig. 1), and the *ribo* ApA dimer **18a** with the isopolar, shortened phosphonate internucleotide linkage.

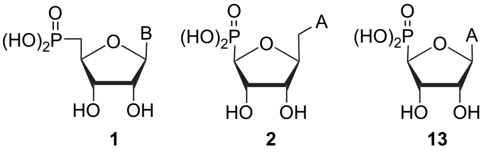

Figure 1.

2. Results and discussion

The strategy for the synthesis of **13** originated from the suitably protected ribofuranosyl-5-*C*-phosphonate derivative **7a**, the key compound obtained by a four-step synthesis from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**).[18] Benzoylation of **3** afforded compound **4**, which was selectively deprotected in 60% aqueous acetic acid at 50 °C to give **5**. Oxidation of the vicinal diol of **5** with sodium periodate in aqueous acetone resulted in the aldehyde **6**. Subsequent addition of diethyl phosphite to aldehyde **6** in the presence of triethylamine provided a 1:1 epimeric mixture of (*R*)- and (*S*)-5-*C*-phosphonates **7a** and **7b**, respectively, in an overall 54% yield (Scheme 1). The epimers were

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Keywords: AMP analogue; Nucleoside phosphonic acid; Sugar phosphonate; Periodate oxidation; NMR conformational analysis.

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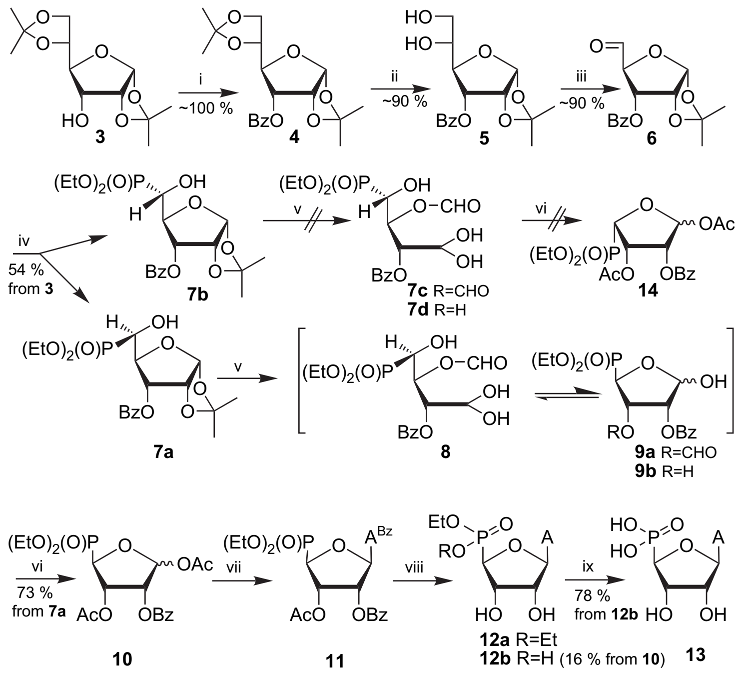

Scheme 1. (i) Benzoylcyanide, CH_3CN, TEA; (ii) 60% aq acetic acid, 50 °C, 3 h; (iii) $NaIO_4$, 70% aq acetone, 0 °C, 8 h; (iv) $HP(O)(OEt)_2$, TEA, DCM, 80 °C, 24 h; (v) (a) HIO_4, 50% aq dioxane, 60 °C, 3 days; (b) 0.1 M TEAB; (vi) Ac_2O, DMAP, pyridine, 16 h, rt; (vii) silylated 6-*N*-benzoyladenine, $SnCl_4$, CH_3CN, 24 h , rt; (viii) 1 M NaOH, 48 h, rt; (ix) Me_3SiBr, CH_3CN, 24 h, rt. Yields of compounds **4**, **5**, and **6** were estimated from TLC (compounds were used for further reaction step without purification).

separated by silica gel chromatography and subjected to subsequent oxidative cleavage separately.

2.1. Oxidative cleavage of 7a (Scheme 1)

Hydrolysis of the 1,2-*O*-isopropylidene group of **7a** and subsequent oxidative cleavage of the C1–C2 bond, performed in one step by aqueous periodic acid, led to an equilibrium mixture of **8** and **9a** in which the 3-*O*-formyl group protects the acyclic form **8** (if present) from further oxidative cleavage of the C4–C5 bond. We attempted to verify the presence of the 3-*O*-formyl group in the product (**8** or **9a**) but neither treatment with 0.1 M TEAB in aqueous dioxane[19] nor heating in 80% aqueous pyridine[20] changed the mobility on TLC or RP HPLC. It did not seem that the 3-*O*-formyl group in **8** could survive in strongly acidic conditions during several days' treatment with aqueous periodic acid. Thus, we concluded that the nascent acyclic form **8** has to undergo a very fast cyclization reaction to furanose **9a**. Then both the formyl derivative **9a** and the deformylated compound **9b** are resistant against oxidative cleavage by periodic acid. Since the subsequent acetylation resulted in the expected acetyl derivative **10** in good yield, the final product of oxidative cleavage of **7a** with periodic acid must have been predominantly the furanose **9b**.

Note: the transformation of compound **9b** to **10**, which we performed several times has resulted in several cases in pure β-anomer of **10** (3-*O*-acetyl-2-*O*-benzoyl) but in several cases also in an anomeric mixture of both 3-*O*-acetyl-2-*O*-benzoyl and 2-*O*-acetyl-3-*O*-benzoyl regioisomers. We believe that each of these isomers afforded, after nucleosidation and deprotection, the identical product. The formation of the regioisomers (migration of the benzoyl group) seems to depend on the time of oxidation of **7a**, workup of **9a**, and conditions for acetylation of **9a** to **10**.

2.2. Oxidative cleavage of 7b (Scheme 1)

On the other hand, treatment of **7b** with periodic acid to obtain **14** caused a total decomposition of compound **7b** with the formation of a very complex mixture of derivatives. Application of a two-step procedure[20] using 90% aqueous TFA for hydrolysis of 1,2-*O*-isopropylidene group in **7b** in the first step, and then, after removal of TFA, sodium periodate oxidative cleavage in the second step also led to a total decomposition of **7b**. Under the same conditions, the epimer **7a** reacted as smoothly as with periodic acid alone and following acetylation provided a comparable yield of product **10**.

The nature of the very different reactivities of **7a** and **7b** toward periodic acid (or TFA–sodium periodate[20]) is not quite clear. The explanation for this phenomenon could perhaps be seen in the equilibrium between acyclic structure **7c** and its furanose form, which can be shifted in favor of the acyclic compound **7c**. Under such conditions, hydrolysis of the 3-*O*-formyl group in the acyclic structure **7c** leads to **7d** and this compound, bearing a C3–C4 vicinal diol, is immediately cleaved by periodic acid (or sodium periodate) (Scheme 2). It can be speculated that the cleavage of the *O*-formyl group could proceed in an oxidative manner via the extremely labile carbonic acid monoester (R-OCOOH) but, more likely, groupings like P=O or hydrated C1 aldehyde $CH(OH)_2$ in **7c** could facilitate the formyl group hydrolysis via intramolecular participation due to a favorable conformation (Scheme 2). Similarly, the different reactivity of epimers **7a** and **7b** toward acetolysis was described recently; whereas the epimer **7a** provided the expected