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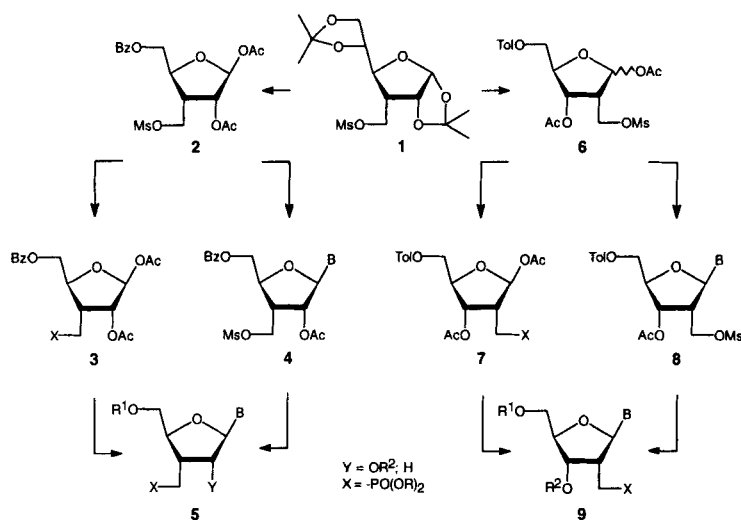
STUDIES ON THE PHOSPHONATE ISOSTERE OF NUCLEOSIDE 3'- AND 2'-PHOSPHATES AS PRECURSORS OF THE RELATED OLIGONUCLEOTIDES

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ABSTRACT: Synthesis of 2',3'-dideoxy-3'-C-(dihydroxyphosphinylmethyl)-adenosine and -thymidine **5**, as well as of 2'-deoxy-2'-C-(dihydroxyphosphinylmethyl)-adenosine and -thymidine **9** was accomplished with the use of the universal carbohydrate precursor 3-deoxy-1,2;5,6-di-O-isopropylidene-3-C-(mesyloxymethyl)- α -D-allofuranose (**1**).

In this communication we describe a versatile route for the preparation of isosteric phosphonate analogs **5** [$R^1 = Y = H$; X: R = H] and **9** [$R^1 = R^2 = H$; X: R = H] of the respective 3'- and 2'-phosphates from the universal sugar precursor **1**.¹



Two alternative synthetic routes were studied for the preparation of the phosphonates **5**. The first one includes an intermediary formation of the sugar-

phosphonate derivative **3** from **2**¹ condensation of which with persilylated thymine or N⁶-benzoyl-adenine gave the corresponding nucleoside phosphonates **5 a** [$R^1 = \text{Bz}$; $Y = \text{OAc}$; $X: R = \text{iPr}$; $B = \text{Thy}$ ($\Sigma 39\%$) or Ade^{Bz} ($\Sigma 69\%$)]. The second route comprised an introduction of the phosphonate diester function on the nucleoside level. This involved condensation of persilylated thymine or N⁶-benzoyladenine with **2**, followed by nucleophilic displacement of the mesyloxy group in nucleosides thus obtained by treatment with NaI/Bu₄I and the Arbuzov reaction of iodides with triisopropyl phosphite to afford the nucleoside phosphonates **5 a** in 30-35% combined yield. Both of these routes were also applied for the synthesis of the fully blocked phosphonates **9 a** [$R^1 = \text{Tol}$; $R^2 = \text{Ac}$; $X: R = \text{iPr}$; $B = \text{Ade}$ or Thy]. In this case, the key sugar intermediate **6** was prepared from **1** in 8 steps through the selective cleavage of the C(1)-C(2) bond (32%, combined) as previously described² with slight modifications. By the route through intermediate preparation of sugar phosphonate **7**, the desired adenine and thymine nucleoside phosphonates **9 a** were obtained in 10 and 29% combined yield, respectively. Alternatively, by the Arbuzov reaction at the nucleoside level the same phosphonates **9 a** were prepared in 23 and 55% combined yield, respectively.

Removal of the 2'-O-acetyl group in **5 a**, followed by the Barton deoxygenation of the secondary hydroxyl group gave **5 b** [$R^1 = \text{Bz}$; $Y = \text{H}$; $B = \text{Thy}$ ($\Sigma 48\%$) or Ade ($\Sigma 43\%$)]. Successive treatment with trimethylbromosilane³ in DMF at room temperature and then with methanolic ammonia afforded, after ion exchange column chromatography, the phosphonic acids **5 c** ($R^1 = Y = \text{H}$; $X: R = \text{H}$; $B = \text{Thy}$ or Ade) in *ca.* 60% yield. Similarly, complete deblocking of **9 a** gave the phosphonates **9 b** [$R^1 = R^2 = \text{H}$; $X: R = \text{H}$; $B = \text{Thy}$ (76%) or Ade (58%)].

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