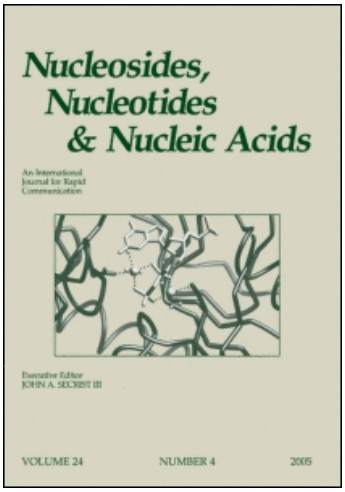

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STUDIES ON THE PHOSPHONATE ISOSTERE OF NUCLEOSIDE 3′- AND 2′-PHOSPHATES AS PRECURSORS OF THE RELATED OLIGONUCLEOTIDES

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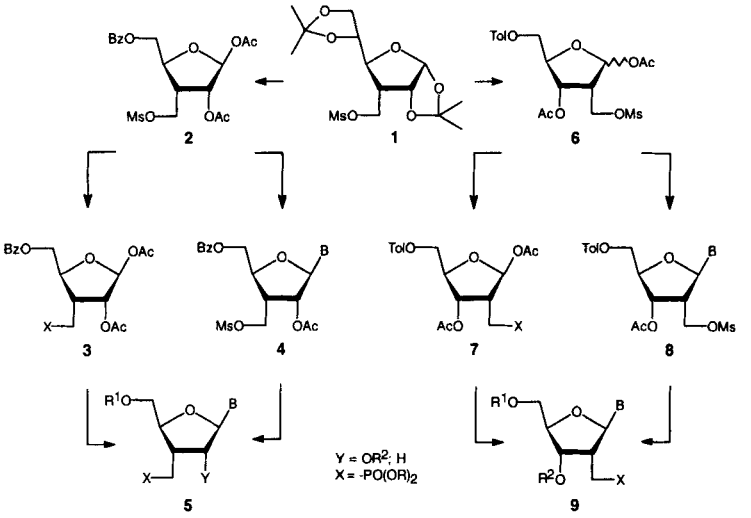
ABSTRACT: Synthesis of 2',3'-dideoxy-3'-C-(dihydroxyphosphinylmethyl)-adenosine and -thymidine **5**, as well as of 2'-deoxy-2'-C-(dihydroxyphosphinylmethyl)-adenosine and -thymidine **9** was accomplished with the use of the universal carbohydrate precursor 3-deoxy-1,2;5,6-di-O-isopropylidene-3-C-(mesyloxymethyl)-α-D-allofuranose (**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 N^6-benzoyl-adenine gave the corresponding nucleoside phosphonates **5** a [R^1 = Bz; Y = OAc; X: R = iPr; B = Thy (Σ39%) or Ade^{Bz}(Σ69%)]. The second route comprised an introduction of the phosphonate diester function on the nucleoside level. This involved condensation of persilylated thymine or N^6-benzoyladenine with **2**, followed by nucleophilic displacement of the mesyloxy group in nucleosides thus obtained by treatment with NaI/Bu_4I 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 = Tol; R^2 = Ac; X: R = iPr; B = 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 described[2] 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 = Bz; Y = H; B = Thy (Σ48%) or Ade (Σ43%)]. Successive treatment with trimethylbromosilane[3] in DMF at room temperature and then with methanolic ammonia afforded, after ion exchange column chromatography, the phosphonic acids **5** c (R^1 = Y = H; X: R = H; B = Thy or Ade) in *ca.* 60% yield. Similarly, complete deblocking of **9** a gave the phosphonates **9** b [R^1 = R^2 = H; X: R = H; B = Thy (76%) or Ade (58%)].

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