## 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)- $\alpha$ -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.<sup>1</sup>



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 persilvlated thymine or N<sup>6</sup>benzoyl-adenine gave the corresponding nucleoside phosphonates 5 a  $[R^1 = Bz; Y =$ OAc; X: R = iPr; B = Thy ( $\Sigma$ 39%) or Ade<sup>Bz</sup>( $\Sigma$ 69%)]. The second route comprised an introduction of the phosphonate diester function on the nucleoside level. This involved condensation of persilvlated thymine or  $N^6$ -benzovladenine with 2, followed by nucleophilic displacement of the mesyloxy group in nucleosides thus obtained by treatment with NaI/Bu<sub>4</sub>I 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  $IR^1$  = 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<sup>2</sup> 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 [ $\mathbb{R}^1 = \mathbb{B}z$ ; Y = H; B = Thy ( $\Sigma 48\%$ ) or Ade ( $\Sigma 43\%$ )]. Successive treatment with trimethylbromosilane<sup>3</sup> in DMF at room temperature and then with methanolic ammonia afforded, after ion exchange column chromatography, the phosphonic acids 5 c ( $\mathbb{R}^1 = Y = H$ ; X:  $\mathbb{R} = H$ ; B = Thy or Ade) in *ca*. 60% yield. Similarly, complete deblocking of 9 a gave the phosphonates 9 b [ $\mathbb{R}^1 = \mathbb{R}^2 = H$ ; X:  $\mathbb{R} = H$ ; B = Thy (76%) or Ade (58%)].

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