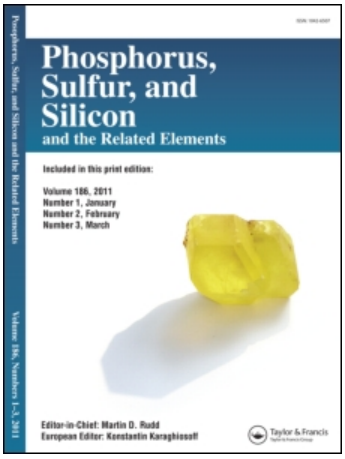

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PHOSPHONATE ANALOGUES OF CYTOSINE ARABINOSIDE MONOPHOSPHATE

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Phosphonate derivatives of cytidine and cytosine arabinoside have been prepared from the corresponding nucleoside aldehydes and tested for their ability to serve as substrates for nucleotide monophosphate kinase and for their toxicity to K562 leukemia cells.

Keywords: Cytidine; cytosine arabinoside; phosphonate

INTRODUCTION

Resistance to the therapeutic agent cytosine arabinoside (ara-C) is believed to follow from mutational loss of the ability to convert this prodrug to the corresponding monophosphate.[1] Phosphonate derivatives of ara-C may offer one way to bypass this resistance, if such compounds can function as analogs of ara-CMP. To test this hypothesis, several new phosphonate derivatives of cytidine and ara-C have been prepared. These new phosphonates bear an α-hydroxy group so that their pK_a's will more closely reflect those of ara-CMP itself.[2] Both the 5′- and 6′-α-hydroxyphosphonates were of interest, given the precedent for biological activity in both series of compounds.[3]

RESULTS AND DISCUSSION

The two epimeric 5′-α-hydroxyphosphonate derivatives of cytidine were prepared as shown in Scheme 1. After protection of commercial cytidine

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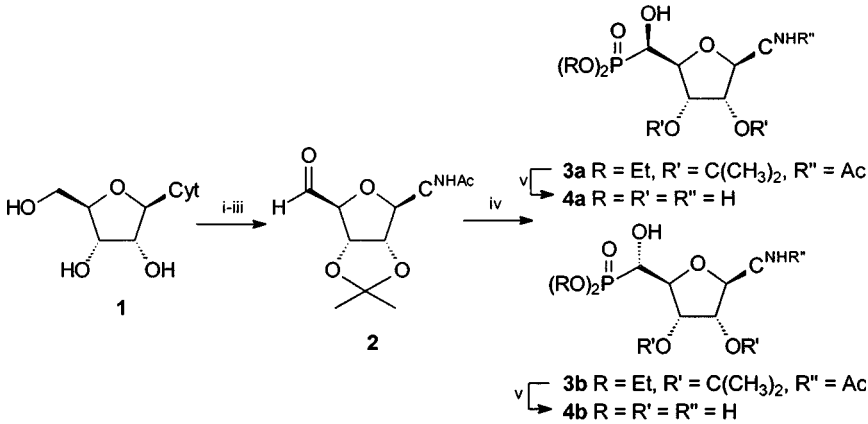
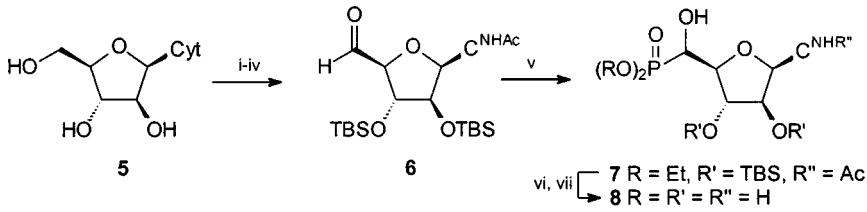
(**1**) and oxidation[4] to the corresponding aldehyde (**2**), Abramov addition of diethyl phosphite gave the desired phosphonates **3a** and **3b**.[5] These diastereomers were separated by HPLC and then deprotected to obtain phosphonic acids **4a** and **4b**. The 5′ stereochemistry of these compounds was assigned on the basis of NMR data obtained from their O-methylmandelate derivatives.[6]



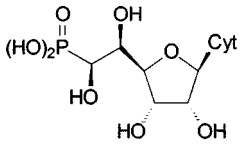
SCHEME 1 i. MeOH, Ac_2O, reflux; ii. dimethoxypropane, $HClO_4$(cat.), acetone; iii. DMSO, EDC, Pyr, TFA; iv. LiHMDS, $HP(O)(OEt)_2$, −78°C; v. TMSBr, CH_2Cl_2, then MeOH.

A similar strategy was used to prepare a 5′-α-hydroxyphosphonate derivative of Ara-C (Scheme 2). Formation of an acetonide was not possible in this arabinoside, but protection of the secondary hydroxyl groups was accomplished via formation of the 2′,3′-bis TBS ether. After oxidation to the aldehyde (**6**), phosphite addition gave a single phosphonate diastereomer (**7**), and deprotection gave the desired phosphonic acid **8**.



SCHEME 2 i. Pyr, TBDMSCI, $AgNO_3$, Et_3N, THF; ii. TFA: H_2O: THF (1:1:4), 0°C; iii. Ac_2O, MeOH, reflux; iv. DMSO, EDC, Pyr, TFA toluene; v. LiHMDS, $HP(O)(OEt)_2$, THF, −78°C; vi. TBAF, THF; vii. TMSBr CH_2Cl_2, then MeOH.

The two 6′-α-hydroxyphosphonates **9** and **10** were prepared from aldehydes **2** and **6** via Horner-Wadsworth-Emmons condensation and subsequent AD-mix α oxidation, as previously described.[7] Formation of O-methylmandelate derivatives allowed assignment of the absolute stereochemistry of the newly incorporated stereogenic centers, and this assignment was confirmed by a diffraction analysis.



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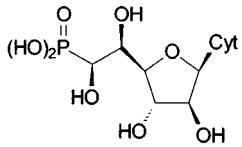

10

Each of these five α-hydroxyphosphonates was tested for the ability to serve as a substrate for nucleotide monophosphate kinase. This assay involved treatment with a mixture of the enzyme and ATP and linkage to pyruvate kinase and lactic dehydrogenase to allow determination of the rates of reaction by measurement of NAD* conversion to NADH. All five phosphonates proved to be poor substrates, with the rates of phosphorylation only about 1% of that displayed by UMP. When tested for their effect on phosphorylation of UMP, the two α-hydroxyphosphonate epimers of cytidine showed opposite effects; compound **4b** was an inhibitor of this process, but compound **4a** appeared to be an activator of this enzyme. These two epimers also differed in their toxicity to the human-derived leukemia cell line K562, where the 5′-*R* isomer **4a** showed significantly greater toxicity than the 5′-*S* isomer **4b** (IC_{50}'s of about 0.5 and >10 μM). Further studies to determine the basis of these effects will be reported in due course.

ACKNOWLEDGMENTS

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