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Synthesis of Nucleoside α-Hydroxy Phosphonates

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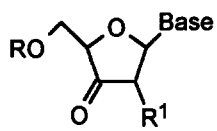
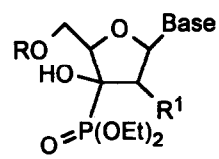
Abstract: Nucleophilic addition of a dialkyl phosphite anion to 2'- or 3'-keto nucleosides results in an efficient synthesis of 2'-hydroxy-2'-phosphono- or 3'-hydroxy-3'-phosphononucleosides. The stereochemistry of one such adduct, 5'-O-trityl-3'-ß-hydroxy-3'-α-(diethyl)phosphonothymidine, was determined by single crystal diffraction analysis.

In recent years there has been a tremendous resurgence of interest in synthesis of modified nucleosides, primarily because of their potential anti-viral activity. In fact, three modified nucleosides, 3'-azidothymidine (AZT),[1] dideoxyinosine (DDI),[2] and dideoxycytidine (DDC),[3] are the only drugs of recognized therapeutic value in treatment of AIDs thus far. However, the usefulness of these compounds is limited by their toxic side effects,[4] stimulating the development of new nucleoside derivatives with the potential to be more selective anti-HIV agents. These observations, together with our longstanding interest in methods for C-P bond formation,[5,6] have led us to attempt synthesis of a variety of modified nucleosides containing phosphonate groups. While methylenephosphonate analogues of both nucleoside 5'- and 3'-phosphates have been known for a long time,[7] direct attachment of a phosphono group at the 2'- and 3'-positions is apparently unknown. In particular, phosphite additions to 3'-ketones (1) would be expected to afford geminal hydroxy phosphonates (2) that could be viewed as new analogues isomeric to nucleoside 3'-phosphates (3), and thus may have some potential to interfere with viral replication. In this paper, the first examples of 2'- and 3'-nucleoside phosphonates are reported.



1



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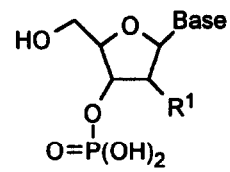
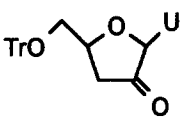
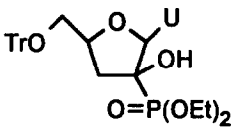
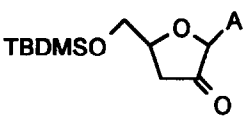
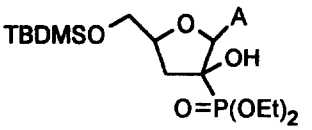
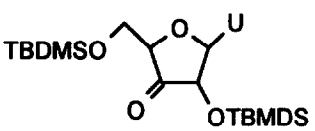
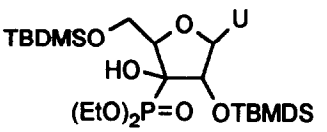
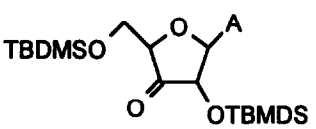
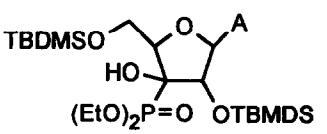
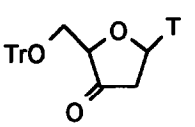
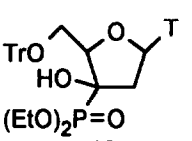


3

Nucleophilic addition of a dialkyl phosphite anion to a carbonyl group, the Abramov reaction, is a well-known method for preparation of geminal hydroxy phosphonates.[8] However, phosphite additions can be complicated by an alkyl transfer that generates alkyl phosphonates,[9] and at least the 3'-keto nucleosides have a certain notoriety for the ease with which they undergo elimination of the base moiety under basic conditions.[10a] Nonetheless, these unstable ketones have been prepared and shown to undergo some carbonyl addition reactions.[10]

This investigation was begun with uridine (**4**)[10c] and adenosine derivatives (**6**) because these 2'-ketones are believed to be somewhat more stable than the 3'-analogues, and both can be prepared from the commercially available nucleosides. At low temperature (-78°), reaction of the 2'-ketone **4** with diethyl phosphite and lithium bis(trimethylsilyl)amide gave the desired product **5** as a single diastereomer in 80% isolated yield.[11] At higher temperature, a mixture of diastereomers was obtained. The protected adenosine derivative **6** also undergoes smooth reaction, affording the analogous phosphonate **7** in 82% yield (Table 1).

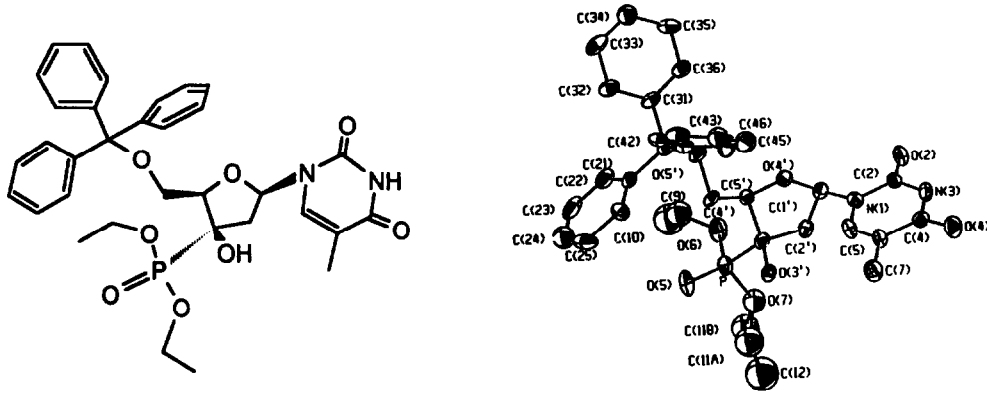
Table I. Synthesis of Nucleoside α-Hydroxy Phosphonates

keto nucleoside	product	yield %
 **4**	 **5**	80
 **6**	 **7**	82
 **8**	 **9**	90
 **10**	 **11**	93
 **12**	 **13**	76

Encouraged by this success, we prepared the somewhat less stable 3'-keto derivatives of uridine (**8**),[10a] adenosine (**10**),[10d] and 2'-deoxythymidine (**12**).[10b] With both of the ribose derivatives, the reactions with diethyl phosphite anion were clean and high-yielding. Despite the reported instability of these 3'-ketones, we found no significant elimination of the purine or pyrimidine systems under the mildly basic reaction conditions. With the 2'-deoxy compound **12**, reaction at low temperature also was straightforward, but at higher temperature a mixture of two diastereomeric addition products was obtained. One might expect the

more stable product to result from addition of the nucleophile to the less hindered α-face of the ribose ring, both on the basis of steric arguments and limited literature precedent for additions to 3'-ketones. However, previous stereochemical assignments have been based primarily on NMR data.[12-14] To determine the stereochemistry of at least one phosphonate product unambiguously, a crystalline sample of compound 13 was subjected to single crystal diffraction analysis.[15] As shown in Figure I, the X-ray analysis clearly indicates that phosphite anion has added to the carbonyl group from the sterically less hindered α-face of the nucleoside, to afford 5'-O-trityl-3'-ß-hydroxy-3'-α-(diethyl)phosphonothymidine. With this stereochemistry unequivocally established for compound 13, it would be reasonable to assume parallel additions from the α face at least for the other 3'-ketones.

Figure 1: ORTEP drawing of compound 13.



The hydroxy phosphonates reported here represent a new type of nucleoside derivative, and should be of interest for several reasons. The hydroxy phosphonate group itself offers a variety of possibilities for transformations to other functionality. Furthermore, the corresponding phosphonic acids represent a novel variation on the isomeric 3'-phosphates, but both the presence of the carbon-phosphorus bond and the slightly different atomic positions may provide stability vis-a-vis enzymatic cleavage by hydrolytic enzymes. Further chemical transformations of these nucleoside hydroxy phosphonates and their biological activity, as well as the preparation of other phosphono nucleosides, will be reported in due course.

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(11) General procedure: To a solution of diethylphosphite (1 mmol) in anhydrous THF (1ml) at -78°C was added dropwise via syringe lithium bis(trimethylsily)amide (2 equiv, 1.0M in THF) under a nitrogen atmosphere. After 10 to 15 min, a solution of the keto nucleoside (1 mmol) in 6 ml THF was added, and the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction was quenched by slow addition of acetic acid in diethyl ether and the resulting mixture was filtered. After concentration in vacuo, the residue was purified by radial chromatography.

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