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ONE POT SOLID PHASE CLEAVAGE OF alpha-DIOLS TO PRIMARY ALCOHOLS. AN ATTRACTIVE ROUTE TO TRIHYDROXY-NUCLEOSIDES, ANTIVIRAL PRECURSORS.

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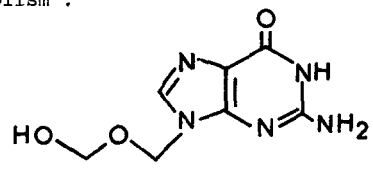
Summary :
The preparation of the trihydroxy derivatives of adenosine, guanosine, uridine and cytidine was effected, using a 1:1 mixture of periodate and borohydride supporting resins.

Since the recent discovery of the important antiviral Acyclovir[1] 1, many preparations of related acyclic nucleosides have been reported[2]. Among them trihydroxy-nucleosides 2 have been studied for their potentialities as antiviral agents and inhibitors of nucleic acid metabolism[3].



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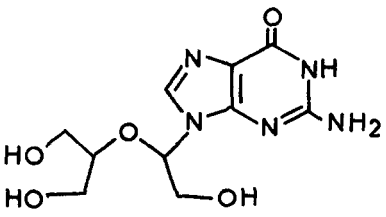

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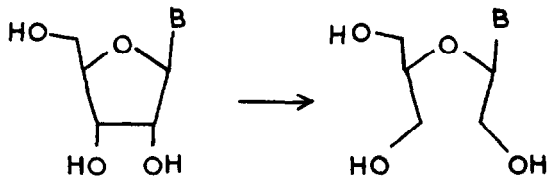
However the preparation of these compounds still suffers from tedious purification and low yield. The problem deals mainly with the separation of the products from the minerals, and the unstability of the intermediate dialdehyde[4]. We now describe an improved preparation of these compounds.

Polymer supported reagents have recently taken a larger part in the panoply of the synthetic chemist[5]. In particular periodate[6] and borohydride[7] supporting resins have been described, but surprisingly they have been seldom used in synthetic chemistry. Although they are supporting antagonist reagents, we assumed that the two resins would not react with each other. Thus a mixture of periodate and borohydride supporting resins would allow in situ reduction of the nucleoside dialdehyde as soon as it is formed. Indeed this is what happened and we report in this letter an application of this procedure to the synthesis of some trihydroxynucleosides.

From a practical point of view the nucleoside 3a-d (1mmol) was dissolved (or suspended) in 10 ml of water, then continuously pumped through a column of 6 ml of the 1:1 mixture of dry resins[8]. At the end of the reaction, monitored by TLC[9], the resin was rinsed with 10 ml of water and the combined solutions evaporated to dryness leading to the corresponding trihydroxy-nucleosides[10] 4a-d.



3a-d 4a-d

	B	yield
a :	adenine	70 %
b :	cytosine	79 %
c :	guanine	40 % *
d :	uracil	73 %

*Heated in suspension at 50° for 2 hours

To the best of our knowledge, this is the first report on the concomitant use of two antagonist reagents. In addition to the easy workup this approach provides the advantage of a very short lifetime for the intermediate dialdehyde. It is therefore the method of choice for the cleavage of glycols leading to unstable products.

References and notes

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8- The resins were obtained by slowly passing a solution of excess reagent ($NaIO_4$ or $NaBH_4$) in water through a column of amberlyst A-27 (chloride form), rinsing with water, ethanol, then dried under vacuum at 60° overnight. We found this technique superior to those described[6-7] since stirring can lead to appreciable grinding of the polymer beads.
9- Reaction times were in the range of 2 to 10 hours depending on the solubility of the compounds and the pump flow rate.
10- ^1H nmr (DMSO) of 4a : δ = 3.0-4.7 (m,9H:3CH_2,3OH), 5.3 (m,1H :OCH), 5.8 (m,1H:NCH), 7.2 (bs,2H:NH_2), 8.0 (s, 1H:H2), 8.2 (s,1H:H8). 4b: δ = 3.1-4.0 (m,6H:3CH_2), 4.0-5.3 (m,4H:3OH,OCH), 4.8 (m,1H:OCH), 5.5-5.8 (d,1H:H6, m,1H:NCH), 7.0 (b, 2H:NH_2), 7.5 (d, 1H:H5). 4c: δ = 3.6-4.0 (m,7H:3CH_2,OCH), 5.7 (m,1H:NCH) 6.4-6.6 (b, 5H:3OH,NH_2), 7.8 (s,1H:H8), 10.5 (b,1H:NH). 4d: δ = 3.1-3.8 (m,7H:3CH_2,OCH), 4.2-5.0 (bm, 4H:3OH,NH), 5.6-5.7 (d,1H:H6, t,1H:NCH), 7.6 (d,1H:H5).
AcOD was used to identify exchangeable protons. Other physical data of 4a-d were in agreement with the litterature.

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