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Stereoselective Synthesis of 5-Methylphosphono-D-Arabino Hydroximolactone, Inhibitor of Glucosamine-6-Phosphate Synthase and Phosphoglucose Isomerase.

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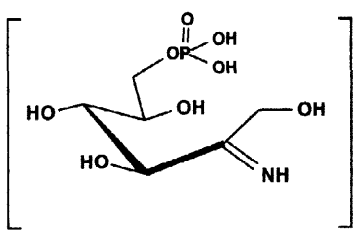
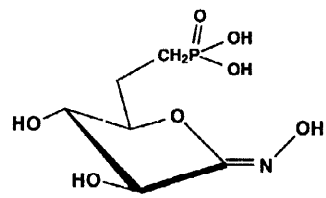
Abstract : Compound **2**, synthesized from D-arabinose in 12 steps with an overall 4% yield, is a competitive inhibitor vs fructose-6P for both phosphoglucose isomerase and glucosamine-6P synthase.

The reaction performed by glucosamine-6P synthase (L-glutamine: D-fructose-6-phosphate amidotransferase, GlmS), *i.e.* conversion of fructose-6P into glucosamine-6P, is believed to proceed through the formation of intermediate **1**, a Schiff base between the keto group of the sugar and the ammonia generated from the glutamine amide function[1]. This intermediate is then processed by the keto/aldose isomerase activity of GlmS to give glucosamine-6P. In the course of our search for specific inhibitors of this enzyme involved in microbial cell wall biosynthesis, the phosphonate **2** was considered to mimick reasonably well the putative intermediate **1** without presenting the sensitivity of the phosphate bond towards hydrolysis.



1



2

Scheme 1

We now describe the synthesis of **2** and its evaluation *in vitro* against *Escherichia coli* GlmS and commercially available rabbit muscle phosphoglucose isomerase (PGI), another member of the keto/aldose isomerase family using fructose-6P as a substrate.

Fully protected D-arabinose **3** (scheme 2), obtained according to literature (Mp 80-82°C, lit[2] 80-81°C), was detritylated in 93% yield with 6M HCl in THF[3]. The resulting primary alcohol was oxidized under Moffatt conditions[4] to afford the corresponding aldehyde which was used without further purification. The methyl phosphonate was isolated in 51% yield from the aldehyde following Horner-Emmons condensation with the tetraethyl methylenediphosphonate carbanion[5] (sodium hydride-ether) and hydrogenation over PtO_2. Hydrolysis with sulfuric acid (2M in AcOH, 60°C) afforded **4** in 73% yield as a mixture of non separable anomers. **4** was readily oxidized into the corresponding lactone unwilling, however, to give a stable adduct upon condensation with hydroxylamine.

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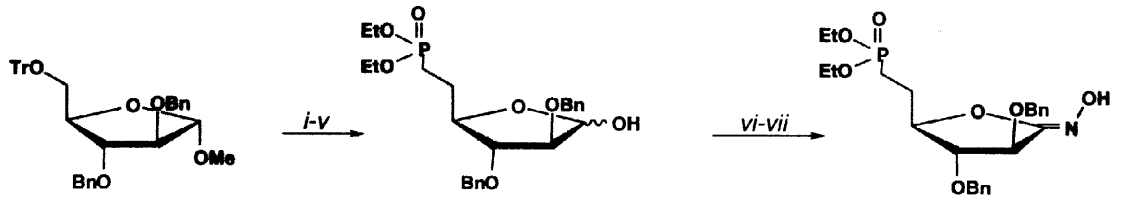

3 **4** **5**

i) 6M HCl/THF; *ii)* DCC/DMSO; *iii)* $[(EtO)_2PO]_2CHNa$/Ether; *iv)* H_2/PtO_2/EtOH; *v)* 2M H_2SO_4/AcOH; *vi)* NH_2OH,HCl-MeONa/MeOH; *vii)* $NaIO_4$-$HNaCO_3$/EtOH-H_2O

Scheme 2

Inverting the sequence of these two steps, *i.e.* reaction of **4** with hydroxylamine and oxidation by sodium metaperiodate (1.1 equivalents) in the presence of sodium bicarbonate[6], gave the protected hydroximolactone **5** in 34 % yield for the two steps.

Phosphonate ester hydrolysis was accomplished using neat bromotrimethylsilane[7] followed by anhydrous triethylamine quenching of the reaction mixture. Hydrogenolysis of the benzyl groups was finally performed (MeOH, 1 eq. triethylamine) with a large excess of Pd/C (1:1 by weight) and hydrogen gas, to give the hydroximolactone **2** in 50% yield as a monotriethyl ammonium salt after lyophilization[8].

When tested against purified *Escherichia coli* GlmS[9] or commercially available rabbit PGI, **2** behaved as a competitive inhibitor *vs* fructose-6P with respective K_i of 0.4 mM and 32 µM. These values reflect an affinity of **2** for the enzyme active site similar to that of the substrate (K_m/K_i = 1 and 3.1 respectively). Since PGI is known to recognize the cyclic form of fructose-6P[10], it can be concluded that GlmS might operate in the same way before undergoing Schiff base formation between fructose-6P and lysine 603[1].

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References and notes

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