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## Nucleosides, Nucleotides and Nucleic Acids

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## Synthesis of 3'-C-Phosphono nucleosides from $\alpha,\beta$ -Unsaturated lactone

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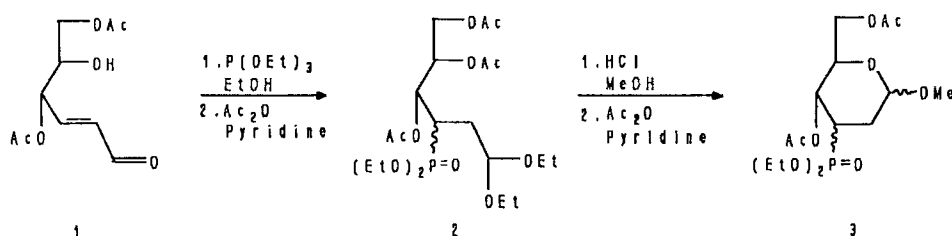
**Abstract:** The reaction of 5-protected  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone **4** with trialkylphosphite gave 3'-C-dialkylphosphono-*erythro* lactone **5** in high yields. The lactone **5** was reduced with DIBAL to the corresponding lactol, which was converted to the acetate **6** by treatment with acetic anhydride in pyridine. The acetate **6** was coupled with silylated thymine in the presence of TMS-triflate and the resulting anomeric mixture of nucleotides could be separated chromatographically and after desilylation using TBAF in THF the 3'-C-dialkylphosphono nucleosides **7** and **8** were obtained.

In the last decade there has been a tremendous interest in the synthesis of modified nucleosides, primarily because of their potential antiviral activity. All four drugs used thus far in the treatment of AIDS are nucleoside analogs: 3'-Azidothymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC) and 3'-deoxy-2',3'-didehydrothymidine (d4T).

Reaction of triethylphosphite with activated olefins in protic solvents has been reported to give  $\beta$ -substituted phosphonate esters.<sup>1,2</sup> This process, termed hydrophosphinylation, gave with simple aldehydes and ketones the product as its acetal or ketal. We were interested to see whether or not it was possible to use hydrophosphinylation in the synthesis of 3'-phosphono nucleosides as analogs to 3'-phosphate nucleosides. The replacement of a P-O bond in nucleotides by a P-C bond might be expected to have interesting biological effects. The phosphonic acids have on one hand a close structural resemblance to phosphate compounds and on the other hand, the P-C bond is in contrary to the P-O phosphate bond expected to be inert towards enzymatic cleavage.

### Results and discussion

In our research group we have developed a method in which unsaturated sugar aldehydes are used as intermediates in the synthesis of 3-substituted 2,3-dideoxyfuranoses.<sup>3-6</sup> This gave, after condensation with nucleobases, new 3'-substituted 2',3'-dideoxynucleosides. It was our initial idea to use the same  $\alpha,\beta$ -unsaturated aldehydes in hydrophosphinylation reaction for the synthesis of 3-phosphono



Scheme 1

furanoses. The first reaction was carried out with  $\alpha,\beta$ -unsaturated aldehyde **1**, prepared by Perlin transformation of tri-*O*-acetyl-D-glycal.<sup>7</sup>

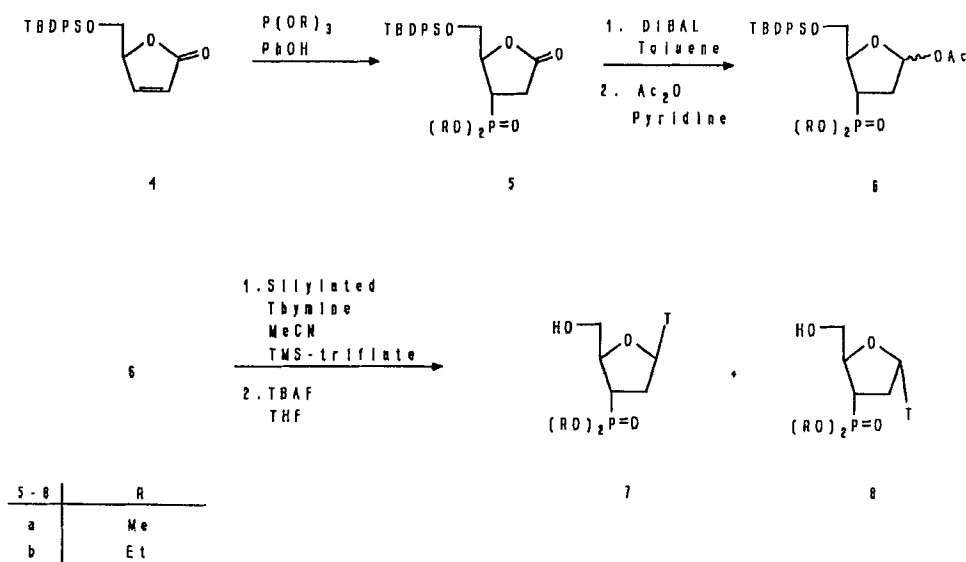
The aldehyde **1** was dissolved in abs. ethanol and treated with triethylphosphite (1 eq.). After 20 hours at room temperature the crude product was acetylated to give the  $\beta$ -substituted phosphonate ester as the diethyl acetal **2** (55%). Methanolysis of **2** resulted in deacetylation followed by ring closure. This gave unfortunately not the furanose but pyranose form, and after acetylation we obtained **3** (43%) as the sole product. To get an unprotected C-4 hydroxy group which selectively can react with the aldehyde functionality to give the desired furanoses instead of the more stable pyranoses, we would have to introduce a more stable protecting group at the C-5 hydroxy group. However, this strategy has previously been tested in the synthesis of 3-azido derivatives by Michael type addition reaction with aldehyde **1**.<sup>8</sup> The 5-hydroxy group was protected by *p*-nitrobenzoyl but an acetic induced migration from 5-*O* to 6-*O* during ring closure resulted in the formation of pyranose isomers only.

We decided instead to test the possibility of using an activated system in which the furanose ring was part of the molecule. Even though aldehydes and ketones activate olefins the most,  $\alpha,\beta$ -unsaturated esters are also reported to undergo hydrophosphinylation. Commercial available  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone complies with all the requirements for hydrophosphinylation.

5-*O*-Tert-butyldiphenylsilyl- $\alpha,\beta$ -unsaturated- $\gamma$ -lactone **4** was heated at 100 °C for 20 hours in trialkylphosphite. After silica gel chromatography, **5a** and **5b** were isolated as clear oils in 86% and 82% yield respectively. As protonating solvent, phenol proved to give a cleaner reaction and resulted in higher yields than with ethanol and methanol. No contamination by products from ester exchange was observed. The <sup>13</sup>C NMR of **5** shows the typically phosphor carbon couplings constants;  $J = 150$  Hz for C-3, 0-5 Hz for C-2 and C-4 and 7-10 Hz for C-1 and C-5.

Only the *erythro* isomer was formed which is explained by sterical reasons. It is only possible for the bulky phosphorus atom to approach the lactone **4** from the  $\alpha$  side of the ring system.

Reduction of **5** with DIBAL in THF and acylation by acetic anhydride gave **6a** in 71% yield and **6b** in 68% yield. The 1-*O*-acetyl sugar **6** provides a versatile intermediate for the synthesis of 3'-phosphono nucleosides. In the synthesis of thymine nucleotides we applied the Silyl-Hilbert-Johnson



Scheme 2

method as modified by Vorbrüggen *et al.*<sup>9,10</sup> and obtained 3'-dialkylphosphono-3'-deoxythymidine and its  $\alpha$ -anomer. The two anomers were separated by silica gel chromatography followed by desilylation using TBAF in THF (1.1M). This gave 7 (20-22%) and 8 (30-33%) as white solids. Overall yield starting from 4 was 12-13% (7) and 18-19% (8).

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