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Synthesis of Unnatural 2- and 3-Deoxyfuranose Analogues

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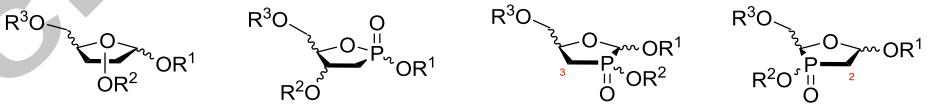
deoxysugars analogs; oxaphospholane; Pudovik reaction; *P*-alkylation reaction.

Abstract
This paper describes the synthesis of two racemic analogues of unnatural 3'-deoxy and 2'-deoxy sugars, where a phosphorus atom replaces the carbon atom in the 2'- or 3'-positions. Two methods of four- and 5-steps were developed affording these new unnatural sugar analogues.

Introduction
Carbohydrates are an ubiquitous class of biomolecules with a great array of diversity, both in structure and biological functions. 2'- or 3'-deoxypentofuranoses **1** and furthermore deoxynucleosides are of great interest in medicinal chemistry.[1] In this context, cyclic sugar analogues in which the anomeric carbon atom is replaced by a phosphorus have received continuous attention in the literature.[2] We have already explored the synthesis of acyclic nucleoside phosphonates,[3] and unnatural cyclic sugar analogues containing a phosphorus atom at the anomeric position, both in the deoxyribose and deoxyxylose series **2**.[4] Herein, we report the preparation of new deoxyfuranoses in their racemic form, with the phosphorus atom replacing the carbon atom at the 2'-position (**3**) or 3'-position (**4**) of the heterocyclic tetrahydrofurane core (Figure 1).



1 **2** **3** **4**

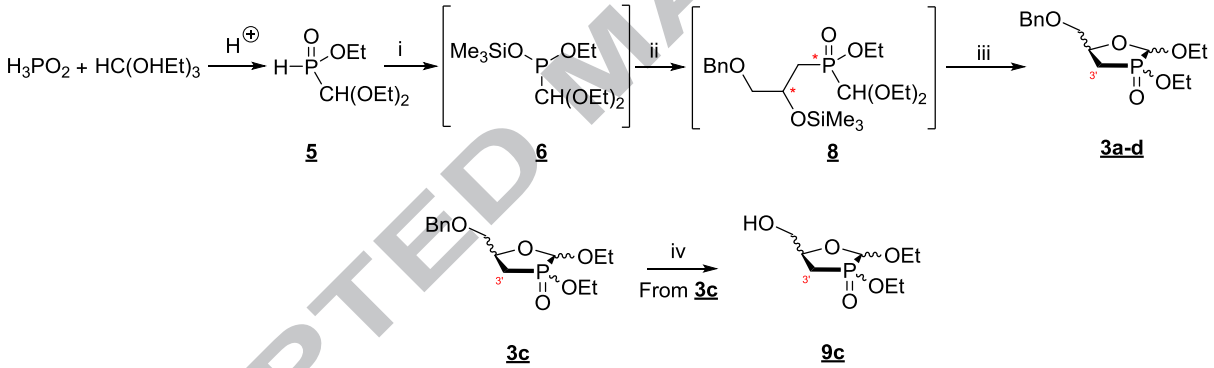
Figure 1. Natural sugar **1** and unnatural deoxyfuranose analogues **2**-**4**

A) ***Synthesis of targeted unnatural 2-deoxyfuranoses 3***

First of all, hypophosphorous acid has been dried from the commercial aqueous solution (50% w/w), scrupulously complying a temperature below 35°C to avoid disproportionation during concentration.[5] Then, ethyl-diethoxymethyl *H*-phosphinate **5**,[6] rather unstable[7] but more reactive than the corresponding hypophosphorous ester,[8] was preferred as starting precursor. This *P*-protected *H*-phosphinate **5** was obtained from an esterification and a *P*-alkylation reaction catalyzed by *p*-toluenesulfonic acid (PTSA) between dry hypophosphorous acid (1 eq.) and triethyl orthoformate (2 eq.) (Scheme 1). Ethyl-diethoxymethyl hydrogenophosphinate **5** which was purified by distillation under reduced pressure in 48% yield and 94% of purity (determined by ^{31}P-NMR) can be used immediately or stored under nitrogen atmosphere in the fridge.

Preparation of the unnatural 3-deoxy furanose **3** took place from the protected *H*-phosphinate **5** in a convenient one pot sequence. Firstly, *H*-phosphinate **5** was quantitatively transformed into the trivalent silylphosphonite **6**, by refluxing *H*-phosphinate **5** with 1.7 equivalent of hexamethyldisilazane (HMDS).[9] After removal of excess of HMDS, the silylphosphonite **6** was diluted in THF under nitrogen and a silyl-Abramov reaction was performed by the addition of 2-(benzyloxymethyl)oxirane **7** in the presence of $ZnCl_2$ as Lewis acid catalyst. Subsequent cleavage of the trimethylsilyl (TMS) residue from the intermediate **8** was achieved by addition of a hydrochloric solution (4N) to the reaction mixture. The protected 3-deoxyfuranoses analogues **3** were obtained by a spontaneous 5-*exo-tet* cyclization in 44% yield for the overall sequence (Scheme 1). At this stage, four different diastereomers **3a**-**d** were formed in 33/37/15/14 ratio according to the presence of three chiral centers. From the mixture of the four diastereomers, two of them were isolated separately as colorless oils after column chromatography on silica gel and were entirely characterized by ^{1}H-NMR.

All the ^{1}H-NMR characteristics of both diastereomers were determined, but the J_{HH} and J_{HP} coupling constants were too close to unambiguously attribute the relative configuration of each chiral center. Even NOESY experiments revealed inconclusive. The last step of this sequence was the removal of the benzyl group by catalytic hydrogenolysis (H_2, Pd/C). Then, starting from the pure diastereomer **3c**, 5-hydroxy deoxyfuranose analogue **9c** was isolated as a single diastereomer in 94% yield. Whatever the stereochemistry, we developed a simple and affordable method for an access to racemic 3-deoxy-2-furanose where the anomeric carbon is directly linked to three heteroatoms. This particular type of phospha-acetal is known to easily release formaldehyde upon treatment in acid conditions and this is why the ethoxy group of acetal was conserved.[10]



Scheme 1. Synthesis of the 3-deoxypentofuranose**3a-d** and **9**.
i) HMDS, 3h, reflux; ii) 2-(benzyloxymethyl)oxirane **7**, $ZnCl_2$, THF, 3h 60°C, then 16h RT; iii) HCl 4N, 30min RT, 44%; iv) H_2, Pd/C, 10%, EtOH, atm. pressure, RT, 48h, 94%.

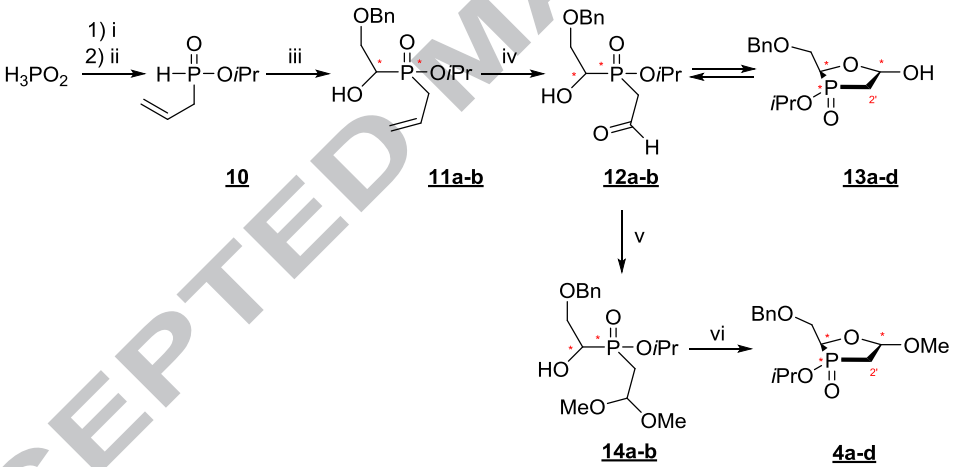
B) ***Synthesis of targeted 3-deoxyfuranoses analogue*** **4**

Oxaphospholane derivatives **4a-d** were synthesized through a five step sequence. The first step consisted in an esterification of dry hypophosphorous acid by isopropyl alcohol, according to Gallagher and coworkers methodology.[11] Due to the disproportionation of the hypophosphorous acid upon heating, the reaction was conducted in benzene rather than toluene in order to reduce this side reaction (Scheme 2). The resulting isopropyl hypophosphite was directly reacted with allyl bromide in the presence of a solution of sodium isopropoxide in THF at room temperature. The allyl-*H*-phosphinate **10** was obtained in 70% yield and a purity of 98% determined by ^{31}P NMR. The next step was the Pudovik reaction (ie the phosphoaldol reaction) meaning the addition of the isopropyl allyl-*H*-phosphinate **10** to benzyloxyacetaldehyde in the presence of catalytic amount of triethylamine. Under thermal heating, three weeks were necessary for the complete consumption of the *H*-phosphinate **10**. By contrast, phosphinates **11a-b** were obtained in 64% yield as a mixture of two diastereomers and a 56/44 ratio, under μ-wave activation at 150°C after only 15 min.[12] This microwave-assisted Pudovik reaction was characterised by a spectacular acceleration, and interestingly no disproportionation by-products were observed, even at this high temperature.[13] The diastereomer ratio given by HPLC were in good agreement with those obtained directly by ^{31}P NMR experiments. A pure diastereomer was successfully isolated by crystallization from the crude mixture. Single crystals were analysed by X-ray experiments confirming the structure and *(±)*-P(*R*), C(*S*) relative

stereochemistry (Figure 2). The *like (±)*-P(*S*), C(*S*) and the *unlike (±)*-P(*R*), C(*S*) showed some structural differences in ^{31}P NMR chemical shift (*like*: δ = 46.48 ppm; *unlike*: δ = 46.92 ppm) and retention times on chiral HPLC (*like* pair: 12.2 min and 16.1 min and *unlike* pair: 14.9 min and 19.8 min).

Figure 2. X-ray structure of one diastereomer **11** of relative configuration *(±)*-P(*R*), C(*S*).

The following step was the ozonolysis of the diastereomeric mixture of alkenes **11a-b**, according to Malet and coworkers methodology,[14] which after treatment with PPh_3, allowed a quantitative conversion and the formation of a mixture of two acyclic diastereomers **12a-b**. In solution, the aldehydes **12a-b** were present in different forms. As classically observed with sugars, a subsequent ring closure occurred, producing the α- and β-pentafuranose forms **13a-d**. The existence of this ring-opening / ring-closure equilibrium between the aldehydes **12a-b** and cyclic furanose analogues **13a-d** has been confirmed by a NOESY experiment. The exchange connectivities in the NOESY experiment attested by the presence of correlation signals between the CH of aldehydes (open-forms) and those of the CH anomeric groups (furanose forms) suggested a dynamic equilibrium between the different diastereomers of the cyclic-forms and the acyclic-forms.[15]



Scheme 2. Synthesis of the cyclic analogues of deoxyribose.
i) *i*PrOH, benzene, 16h, reflux, 100%; ii) H_2C=CH-CH_2-Br, NaO*i*Pr, *i*PrOH, 70%; iii) Benzyloxyacetaldehyde, NEt_3, Toluene, μ-wave 15 min, 150°C, 64%; iv) a) O_3, -70°C, 10min, b) PPh_3, 65%; v) PTSA, MeOH, RT, 10 h, vi) Amberlite IR 120, toluene, 50°C, 3h, >95%.

In order to shift the equilibrium towards the cyclic deoxyribose **4a-d**, the mixture constituted by **12a-b** and **13a-d** was heated in methanol under acidic conditions forming the acetals **14a-b**. They were directly heated under thermodynamic conditions in the presence of a sulfonic acid resin. The four deoxyfuranose diastereomers analogues **4a-d** were obtained almost quantitatively and in 28% overall yield from readily affordable precursors. Nevertheless, all attempts to separate the four diastereomers by normal or reverse phase chromatography failed.

Conclusion

In conclusion, 4- or 5-step syntheses in racemic series syntheses were developed to afford new deoxyfuranoses analogues in good yields and incorporating a phosphorus atom replacing a carbon atom in the 2'-position or 3'-position of the cyclic furanose ring. Further work directed at the synthesis of nucleosides incorporating these unnatural sugar analogues and their biological applications are currently underway and will be reported in due course.

Acknowledgments

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Supplementary Material

Experimental procedures and characterization data of new compounds were provided in supplementary material.

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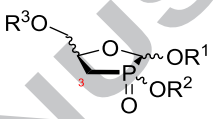

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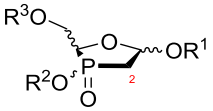

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