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Synthesis of new 2-phosphono-α-D-glycoside derivatives by stereoselective oxa-Michael addition to a D-galacto derived enone

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Abstract—The synthesis of new 2-phosphono-α-D-glycoside derivatives by stereoselective oxa-Michael addition to an enone derived from D-galactal and containing a phosphonate group is described. Retro-Michael reactions were prevented by tandem acetylation to trap the unstable enolic intermediates. The stereochemistry of the addition products was established by NOESY experiments and explained with molecular mechanics (MM) and density functional theory (DFT) calculations.

Keywords: Oxa-Michael Addition; 3-Oxo-2-phosphono-α-glycosides; Alcohols; O-Glycosylation

1. Introduction

For a long time, carbohydrates have excited the interest of researchers.[1] Being among the most abundant natural products, they are implicated in many cellular processes such as cell–cell recognition, cellular adhesion, and transport. They also play a fundamental role in vital processes, being present, for example, in nucleic acids or as a component of bacterial cellular walls.[2] The importance, complexity, and variety of natural carbohydrates make their synthesis a challenging and worthy task.

In Nature, carbohydrates are found mainly in the form of *O*-glycosyl derivatives, and, therefore, organic chemistry has witnessed a noticeable increase in research addressed to the development of new stereocontrolled O-glycosylation methods.[3]

Furthermore, among unnatural carbohydrates those containing a phosphonate group appear very interesting. The phosphonate group is a useful and versatile tool for the studies of metabolic regulation, enhancement, and inhibition.[4] It is, in fact, a stable analogue of the naturally occurring phosphate, as the C–P bond is inerted to the enzymes involved in phosphate cleavage. At present, the interest of the chemists and biologists is mainly concerned with glycosyl phosphonates, which are the analogues of glycosyl phosphates involved in the biosynthesis of oligo- and polysaccharides and glycoconjugates.[5]

Although there are a number of naturally occurring sugar 2-phosphates,[6] principally in Gram-negative bacteria lipopolysaccharides, to the best of our knowledge, the literature concerning 2-phosphono sugar analogues is rather scarce,[7] and nothing is known about their biological activity. In this respect, we believe that the development of new methodologies for the stereoselective preparation of 2-phosphono sugars might be an appealing target.

Recently, we have reported on the stereocontrolled preparation from 2-(diethoxyphosphoryl)hex-1-en-3-ulose (**1**)[8] of 3-oxo-2-phosphono-α-C-glycosides through a Michael-type addition of organocopper reagents and have shown that the phosphonate group has a remarkable activating effect on the Michael addition. Hereafter,

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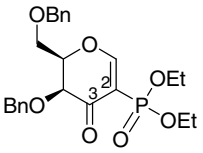
we wish to describe the extension of these studies to the addition of a series of alcohols to **1**. To the best of our knowledge, the literature concerning the O-glycosylation via Michael addition of O-nucleophiles to hex-1-en-3-uloses derived from carbohydrates is scarce[9] and mainly limited to the addition of MeOH.



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2. Results and discussion

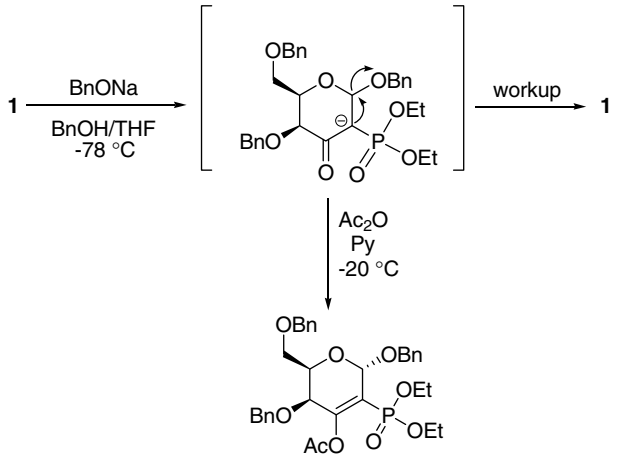
We started this work with the addition at −78 °C of BnONa in BnOH–THF to the Michael acceptor **1**. Nevertheless, though the reaction according to TLC monitoring appeared to proceed,[†] after the workup only the starting material was recovered. After several attempts in which the workup conditions were varied, an ensuing retro-Michael reaction was considered responsible for the results obtained. Thus, quenching the reaction with Ac_2O and pyridine, we were able to obtain the enol acetate **2** as the only product, confirming the above hypothesis (see Scheme 1 and Table 1, entry 1).

Prompted by these findings, the addition to **1** was performed with various alcohols leading to the results presented in Table 1. The yields ranged from moderate to good with an excellent α:β ratio except in the case of propargyl alcohol (entries 8 and 9) in which an α:β ratio of 90:10 was recorded. No change in the diastereoisomeric ratio was observed by varying the reaction time. (Table 1, entries 8 and 9).

Good results were obtained with both primary and secondary alcohols. It is worth noting that yields were shown to depend on reaction temperature. With the exception of the addition of BnOH (Table 1, entries 1 and 2), the best results were obtained at −30 °C. On the other hand, the reaction does not proceed at lower temperature (Table 1, entries 3 and 5), while at 0 °C a rapid decomposition of the starting material occurs.

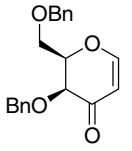
To evaluate the activating effect of the phosphonate group, the reactivity of enones **1** and **8** was compared. BnOH was used as the nucleophile, and the reaction was carried out under the same conditions for both enones: in the case of **1** a total conversion of the starting material was observed, whereas for **8**, which lacked the C-2 phosphonate group, only a 30% conversion was recorded.

[†]TLC (SiO_2, 2:8 hexanes–EtOAc) showed the disappearance of the starting material together with the appearance of a product with a higher R_f.



2 α/β 100/0

Scheme 1. Michael addition of BnONa to 2-(diethoxyphosphoryl)-hex-1-en-3-ulose **1**.



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To test the general applicability of the above procedure, the addition of the more sterically hindered D-glucal-derived[10] nucleophile **9a** was performed on enone **1**. Also in this case the reaction showed complete stereoselectivity with the formation of **10** in a 99:1 α:β ratio (Scheme 2).

The diastereoisomeric ratio of the oxa-Michael addition turned out to be unaffected by the reaction time as shown by the results in Table 1 for the addition of BnOH and propargyl alcohol (entries 1, 2 and 8, 9, respectively). Moreover, as stated before, the reaction was completely reversible after workup, and the addition products could not be isolated unless acetylation of the enol intermediate was performed. These results show that the oxa-Michael additions described above are equilibrium processes. To confirm this conclusion, an additional experiment was performed: enone **1** was allowed to react at −30 °C with BnOH for 5 h in order to ensure that all the starting material was consumed (Table 1, entry 2). After this time, MeOH was added, and the reaction was allowed to continue for an additional 5 h at −30 °C. As usual, the addition product was acetylated for 12 h at −20 °C with Ac_2O and pyridine. The ^1H NMR spectrum of the crude reaction mixture showed the presence of a 4:6 mixture of **2** and **3**, confirming thermodynamic control during the Michael addition. As a consequence, the observed α:β stereoselectivity in the Michael addition (Table 1) is simply due to the relative stability of the two anomers