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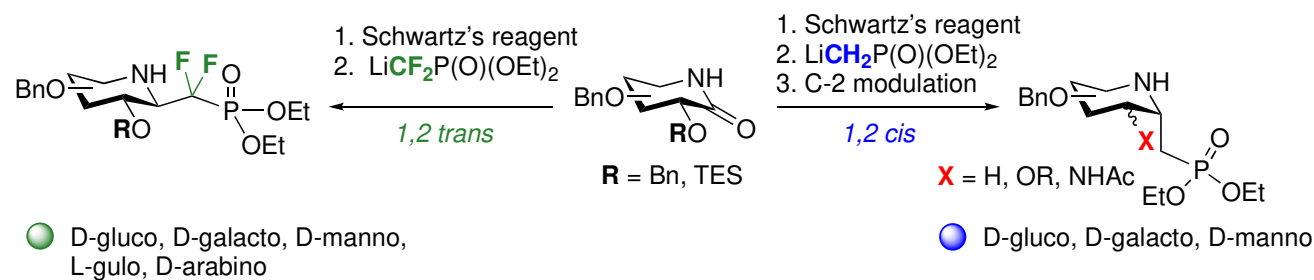
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# Stereoselective Synthesis of 1-C-Diethylphosphonomethyl and -difluoromethyl Iminosugars from Sugar Lactams

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Supporting Information Placeholder

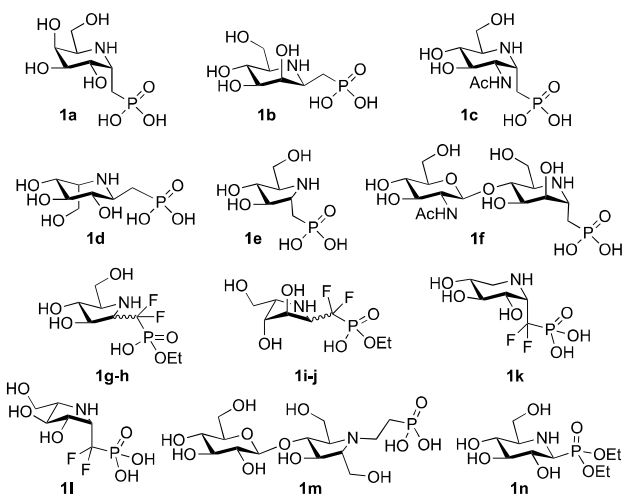


**ABSTRACT:** A strategy allowing the straightforward synthesis of 1-C-phosphonomethyl and 1-C-phosphonodifluoromethyl iminosugars is reported. Conversion of sugar lactams to the corresponding imines with the Schwartz's reagent followed by their reaction with  $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$  and  $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$  stereoselectively afforded the 1,2-*cis* and 1,2-*trans* glycosyl phosphonates respectively in modest to good yield. Application of this methodology to C-2 orthogonally protected sugar lactams paved the way to 2-acetamido- and 2-deoxy-1-C-phosphonomethyl iminosugars.

Glycosyl 1-phosphates, key structural motifs in a wide range of biological processes that involve carbohydrates,<sup>1,2</sup> are commonly used by glycosyltransferases (GTs) to build up cell-surface polysaccharides and peptidoglycans. These enzymes catalyze the transfer of the sugar moiety from the activated sugar donor to an acceptor molecule.<sup>3,4</sup> Since the pioneering work of Blackburn<sup>5</sup> and Mc Kenna<sup>6</sup> in the early 1980's, hydrolytically stable glycosyl phosphate mimics have progressively appeared as attractive targets and inhibitors of glycosyl 1-phosphate processing enzymes and many examples of phosphonomethyl-C-glycosides have been reported.<sup>7,8,9,10,11,12,13,14</sup> Due to the pivotal role of GT enzymes in the biosynthesis of polysaccharides and glycoconjugates, the rational design of potent glycosyltransferase inhibitors has attracted increasing interest during the last two decades. Since glycosyl transfer reactions are thought to proceed through transition states with an oxocarbenium ion character<sup>15</sup> closely related to those of glycosidases,<sup>3</sup> iminosugars<sup>16</sup> have been envisaged as potential inhibitors. These small molecules must be able to mimic, at the transition state, the charge and shape of the carbohydrate moiety of the sugar-nucleotide. To mimic the pyrophosphate part of the natural substrate, incorporation of phosphonic acids as isosteric analogs in terms of geometry and polarity<sup>17</sup> has been pursued. In contrast to the naturally occurring and hydrolyzable P–O bond, the strength of the P–C bond provides these synthetic surrogates metabolic resistance to phosphatase hydrolysis.<sup>18</sup> Nevertheless, this area is still rather underexplored and only a few examples of so called 1-C-phosphonomethyl iminosugars have been reported so far (Figure 1). This includes six-membered derivatives **1a–d** designed respectively as  $\alpha$ -D-Gal,<sup>19</sup>  $\beta$ -D-Man,<sup>19</sup>  $\alpha$ -D-GlcNAc<sup>20</sup> and  $\alpha$ -L-Ido<sup>21</sup> analogs, five-membered compounds<sup>22</sup> such as **1e**, and a pseudodisaccharide **1f**.<sup>23</sup> Of note other analogs have also

been disclosed in which the phosphonate moiety is connected to the nitrogen atom (**1m**)<sup>24</sup> or directly attached to the C-1 position (**1n**).<sup>25</sup> This limited number of structures can be tentatively attributed to the lack of a general and efficient synthetic strategy to access  $\alpha$ - and  $\beta$ -phosphonomethyl iminosugars in pyrrolidine or piperidine series. The main routes developed so far include a chemo-enzymatic approach,<sup>19</sup> the early introduction of the phosphonate moiety on glycosylamines followed by the ring closure of the resulting acyclic molecule (Figure 2a),<sup>26</sup> an intramolecular iodoamination followed by iodine displacement (Figure 2b).<sup>20</sup> Interestingly, two examples describe the addition of lithiated methylphosphonate on a furanose-derived nitron<sup>27</sup> and imine<sup>28</sup> (Figure 2c). Sugar-derived imines are attractive synthons to access natural products owing to their stereochemical diversity and enantiomeric purity.<sup>29</sup> Several methods have been developed to access these chemical species including *N*-chlorination/elimination of cyclic amines,<sup>30</sup> Staudinger/azaWittig cyclization<sup>31,32,33</sup> and deoxygenation of the corresponding nitrones.<sup>34</sup> However, these methods have their own limitations, respectively formation of regioisomeric mixtures, multistep synthesis of starting materials and phosphine contamination of the products. In last decade, Furman explored the potential of *O*-protected sugar lactams, that can be readily obtained from the corresponding 2,3,4,6-tetra-*O*-benzylated pyranoses,<sup>35,36</sup> as imine precursors. Their reduction with Schwartz's reagent ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ ), that has a great functional group tolerance, provided in good yield the corresponding imines that were further reacted with various C-nucleophiles to furnish a library of iminosugar C-glycosides.<sup>37,38</sup> We anticipated this efficient methodology could be exploited to rapidly access 1-C-phosphonomethyl iminosugars using lithiated phosphonates as nucleophiles

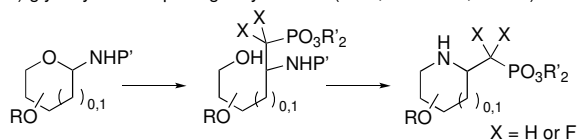
(Figure 2).



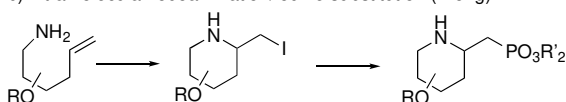
**Figure 1.** Structures of 1-C-phosphonomethyl and 1-C-phosphonodifluoromethyl iminosugars and their analogues reported to date

#### Previous work

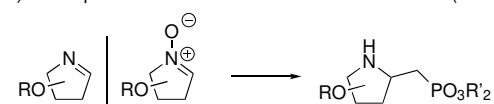
a) glycosylamine opening/recyclisation (Behr, Eustache, Martin)



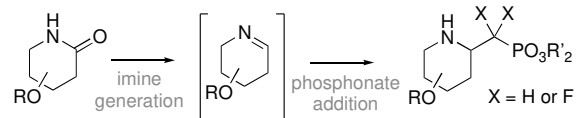
b) intramolecular iodoamination/iodine substitution (Wong)



c) nucleophilic addition to furanose imine and nitron (Eustache, Defoin)



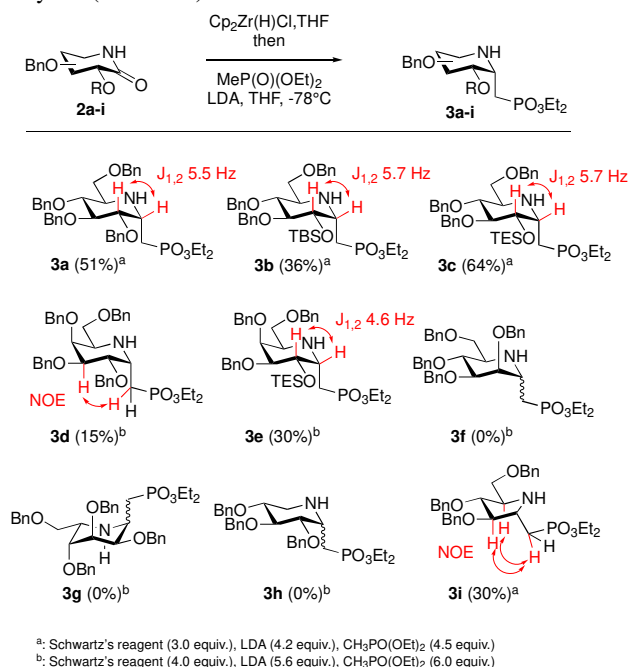
#### This work:



**Figure 2.** Most common methods for 1-C-phosphonomethyl and phosphonodifluoromethyl iminosugars synthesis and proposed strategy developed herein

Optimisation of the reaction conditions, including generation of the sugar-derived imine followed by its reaction with  $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$ , was performed on the 2-OTES tri-*O*-benzylated D-gluconolactam **2c**<sup>39</sup> for synthetic purposes. It allowed to identify LDA as the base of choice for the formation of lithiated methylphosphonate (see Table S1). Treatment of gluconolactam **2c** with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  (3 equiv.) in THF at room temperature furnished the resulting imine (TLC and MS monitoring) that was not isolated and directly added to a THF solution of  $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$  at  $-78^\circ\text{C}$  and stirred at this

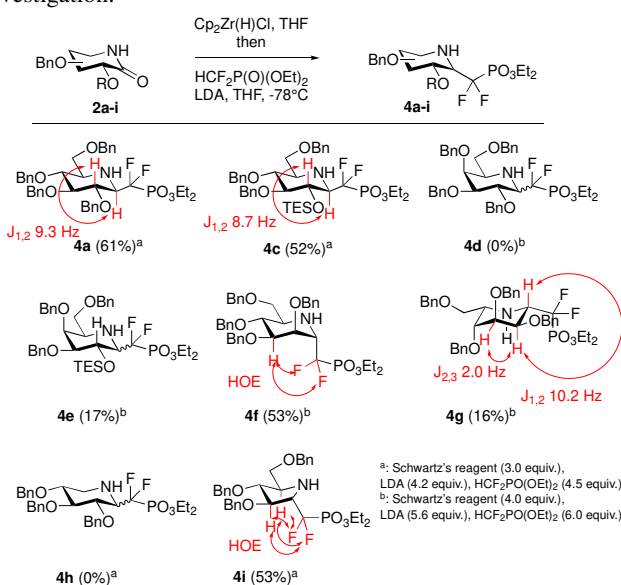
temperature for 30 min to produce the  $\alpha$ -1-C-phosphonomethyl iminosugar **3c** ( $J_{1,2} = 5.7$  Hz) in 64% yield over two steps. To evaluate the impact of the C-2 protecting group on the outcome of the reaction, this sequence was applied to 2-OBn and 2-OTBS<sup>39</sup> gluconolactams **2a** and **2b** and afforded the  $\alpha$ -configured iminosugars **3a** and **3b** in 51% and 36% yields respectively over two steps. D-galactonolactams **2d** (2-OBn) and **2e** (2-OTES) proved less reactive and required more equivalents of Schwartz's reagent for the reaction to be successful (Scheme 1, conditions b), providing the  $\alpha$ -configured iminosugars **3d** (15%) and **3e** (30%) in modest yield. Interestingly, the 2-OTES sugar lactams gave better yields compared to the 2-OBn derivatives. This reaction was not successful with D-mannonolactam, D-xylonolactam and L-gulonolactam and compounds **3f**, **3g** and **3h** could not be isolated although the corresponding imines were observed by MS and TLC suggesting a lower reactivity of these imines towards nucleophiles. Satisfyingly, this methodology was also compatible with a five-membered sugar lactam and the D-arabinolactam **2i** furnished the  $\alpha$ -configured iminosugar **3i** in 30% yield (Scheme 1).



**Scheme 1.** Synthesis of 1-C-phosphonomethyl iminosugars

1-C-difluoromethylphosphonosugars are often considered to provide glycosyl phosphate surrogates with better mimicking abilities than the parent  $\text{CH}_2$  analogs due to steric and electronic factors.<sup>40</sup> This was recently illustrated in iminosugar series by the superior GlfT2 galactofuranosyltransferase inhibition developed by a 1-C-difluoromethylphosphonoiminosugar compared to a 1-C-methylphosphonoiminosugar.<sup>26d</sup> Indeed, the C-CF<sub>2</sub>-P linkage closely resembles the C-O-P bond of phosphates in terms of size and charge distribution. In addition, the electron withdrawing effects of  $\alpha$ -fluorination produce phosphonates with dissociation constant (pKa) values closer to those of the parent phosphate.<sup>41</sup> These promising properties led to the development of many new synthetic methods to introduce difluoromethylene phosphonate in the past ten years.<sup>42,43</sup> However, a limited range of 1-C-phosphonodifluoromethyl iminosugars **1g-l** have been reported so far (Figure 1).<sup>26b-d,44,45</sup>

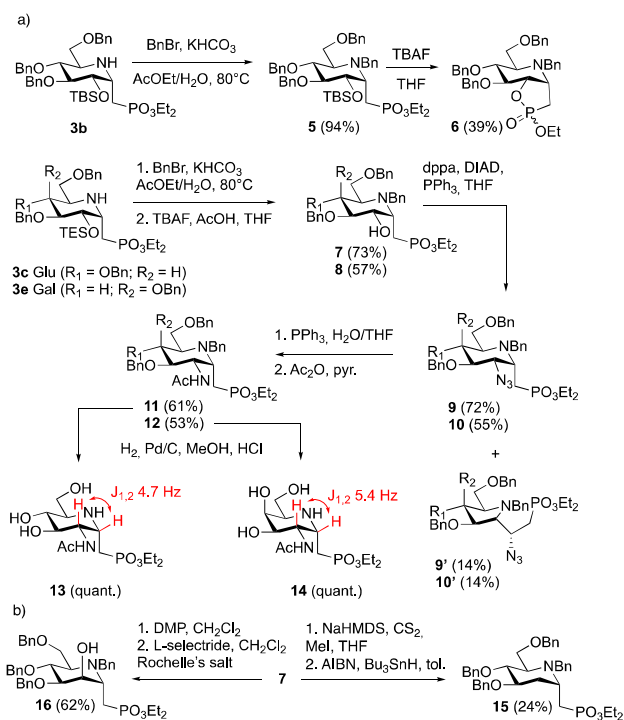
We anticipated our strategy would also work with  $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$  to furnish the corresponding fluorinated glycosyl phosphate surrogates. Lactams **2a–i** were first converted to the corresponding imines with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  and then treated with  $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$  at  $-78^\circ\text{C}$  in THF (Scheme 2). In the D-glucose series, the corresponding iminosugars **4a** (2-OBn) and **4c** (2-OTES) were obtained in satisfactory 61% and 52% yield respectively over two steps. More importantly, their extensive NMR analysis assigned a  $\beta$ -configuration for the pseudoanomeric position ( $J_{1,2} = 9.3$  Hz for **4a** and  $J_{1,2} = 8.7$  Hz for **4c**). In the D-galactose series, no trace of iminosugar **4d** (2-OBn) was detected but the iminosugar **4e** (2-OTES) was isolated in 17% yield. Unfortunately, we failed to assign its pseudoanomeric configuration either through its deprotection or extensive NMR experiments as only broad signals were obtained. Satisfyingly, this two steps transformation proved now effective in the D-mannose and L-gulose series, respectively providing the  $\alpha$ -configured iminosugar **4f** (53%) and the  $\beta$ -configured L-iminosugar **4g** (16%). It was also successful with D-arabinolactam affording  $\alpha$ -configured iminosugar **4i** (53%). However, the D-xylo-lactam was still not converted into the known 1-C-phosphonodifluoromethyl iminosugar<sup>45</sup> **4h** under these conditions. The better results, in terms of yield and substrate scope, obtained with  $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$  compared to  $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$ , can be attributed to its higher nucleophilicity resulting from its less delocalized negative charge. However, the mechanistic rationale for the opposite stereochemical outcome obtained for the  $\text{CH}_2$  and  $\text{CF}_2$  derivatives in the D-glucose and D-galactose series and the lack of reaction with the D-xylo and D-manno derivatives is still unclear and would require further investigation.



**Scheme 2.** Synthesis of 1-C-phosphonodifluoromethyl iminosugars

Taking advantage of the orthogonal protection of the C-2 position in iminosugars **3b**, **3c** and **3e**, we next explored the possibility to access 2-acetamido-1-C-phosphonomethyl iminosugars. There is only one example in the literature<sup>20</sup> and we hypothesized that the NHAc moiety could be stereoselectively introduced exploiting endocyclic nitrogen participation (Scheme 3a).<sup>46,47</sup> Iminosugar **3b** was *N*-benzylated (BnBr, K<sub>2</sub>CO<sub>3</sub>) to afford the fully protected iminosugar **5** that

led to the undesired bicyclic derivative **6** as a mixture of diastereomers upon desilylation. Efforts to open the phosphonate ring were unsuccessful as was the desilylation under acidic conditions to avoid trapping of the phosphonate group by the 2-OH group. We therefore turned our attention to the 2-OTES derivative **3c** which *N*-benzylation and *O*-desilylation under acidic conditions (TBAF, AcOH) smoothly afforded alcohol **7** (73%). Stereo-retentive displacement of the free OH in **7** with DPPA, PPh<sub>3</sub> and DIAD in THF furnished the  $\alpha$ -D-gluco-configured azidopiperidine **9** (72%) along with some azidopyrrolidine **9'** (14%) resulting from the opening of the transient fused piperidine-aziridinium ion at the methine carbon. Conversion of the azide moiety in **9** to the corresponding NHAc group was achieved in two steps (PPh<sub>3</sub>, H<sub>2</sub>O then Ac<sub>2</sub>O, pyr.) to afford the acetamido-iminosugar **11** (61%) that was quantitatively hydrogenolyzed to produce the target D-gluco-configured 2-acetamido-1-C-phosphonomethyl iminosugar **13**. To demonstrate the generality of this approach, the same sequence was applied to the D-galacto-configured iminosugar **3e** to afford the alcohol **8** (57%), azide **10** (55%) and acetamide **12** (53%). Importantly, the broad NMR signals exhibited by compounds **8**, **10** and **12** precluded their stereochemical assignment. Fortunately, hydrogenolysis of **12** quantitatively afforded the D-galacto-configured 2-acetamido-1-C-phosphonomethyl iminosugar **14** which NMR analysis confirmed its  $\alpha$ -D-GalNAc configuration and retrospectively the stereochemistry of precursors **8**, **10** and **12**. We further exploited the 2-OH position in alcohol **7** to access other novel 1-C-phosphonomethyl iminosugars (Scheme 3b). Treatment of **7** with NaHMDS, CS<sub>2</sub> and MeI followed by reaction with AIBN and Bu<sub>3</sub>SnH in toluene furnished the 2-deoxy-1-C-phosphonomethyl iminosugar **15** in modest 24% (unoptimized) yield over two steps. In addition, the free alcohol in **7** was inverted to generate the new  $\alpha$ -D-manno-configured 1-C-phosphonomethyl iminosugar, a compound that could not be obtained from D-mannonolactam by our sequence. Oxidation of **7** with Dess-Martin periodinane produced the corresponding ketone that was treated with a range of hydride reagents. While NaBH<sub>4</sub> or L-selectride failed to afford the axial alcohol **16**, treatment with L-selectride in the presence of Rochelle's salt led to the desired iminosugar **16** in 62% yield.



**Scheme 3.** Synthesis of 2-acetamido- $\alpha$ -1-C-phosphonomethyl iminosugars **13** and **14** and 2-deoxy and D-manno configured  $\alpha$ -1-C-phosphonomethyl iminosugars **15** and **16**.

In conclusion, we report the straightforward stereoselective synthesis of 1-C-phosphono-methyl and difluoromethyl iminosugars that are obtained in modest to good yields from easily available sugar lactams. The functional group tolerance of this methodology allowed us to access 2-deoxy and 2-acetamido derivatives and new sugar stereochemistries. A different reactivity and opposite stereochemical outcome were observed with the  $\text{LiCH}_2\text{P}(\text{O})(\text{OEt})_2$  and  $\text{LiCF}_2\text{P}(\text{O})(\text{OEt})_2$  reagents in the D-gluco and D-galacto series that needs to be further investigated.

## Associated content

### Supporting Information

Optimization of reaction conditions, experimental procedures, and compounds characterization (**2e**, **2h**, and **3–16**), including one- and two-dimensional NMR spectra.

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