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β-Stereoselective Phosphorylations Applied to the Synthesis of ADP- and Polyprenyl-β-Mannopyranosides

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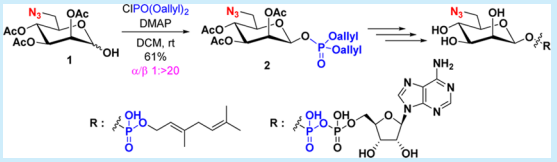
Supporting Information

ABSTRACT: An efficient and convenient synthetic route to glycosyl 1-β-phosphates has been developed using diallyl chlorophosphate as a phosphorylating agent with 4-*N*,*N*-dimethylaminopyridine under mild conditions. Diallyl-glycosyl 1-β-phosphate triesters of D-manno, L-*glycero*-D-*manno*-hepto-, D-gluco-, D-galacto-, and L-fuco-pyranose as well as lactose have been obtained by this strategy in good yields and excellent β-selectivities. Furthermore, the diallyl 6-azido-mannosyl 1-β-phosphate **2** was deprotected under mild conditions and converted into potentially clickable analogues of β-mannosyl phosphoisoprenoids **I** and ADP-heptose **II**.



Glycosyl-1-phosphates play a central role in glycobiology because they are involved in carbohydrate metabolism and the biosynthesis of oligosaccharides.[1,2] Glycosyl-1-phosphates are key intermediates in the enzymatic[3] and the chemical[4,5] preparations of nucleotide sugars and some important glycolipids. However, they are generally quite expensive and rarely commercially available.

Therefore, the stereoselective phosphorylation of carbohydrates at the anomeric position has naturally been a topic of intense research aimed at the preparation of enzyme substrates or at the synthesis of analogues of natural metabolites.[2] Yet, the synthesis of β-mannosyl phosphates remains a difficult challenge of considerable importance. For instance, β-mannosyl phosphoisoprenoid **I** is involved as a substrate in the biosynthesis of the mannan core of the lipoarabinomannan found in the cell wall of major pathogens such as *Mycobacterium tuberculosis* (Figure 1).[6]

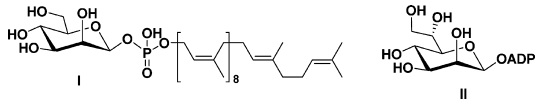


Figure 1. Structures of β-manno-configured phosphates **I** and **II**.

Another important metabolite that displays a mannose-β-1-phosphate structure is ADP-L-*glycero*-β-D-*manno*-heptopyranose **II**, the donor substrate of heptosyl transferases. The latter catalyze the incorporation of heptose units into the inner core of lipopolysaccharide (LPS), a key component of the outer membrane of Gram-negative bacteria (Figure 1).[7,5]

Furthermore, the synthesis of clickable analogues of metabolites has become a powerful tool in glycosciences for applications that include the development of enzyme inhibitors as well as *in vivo* cell imaging.[8] Therefore, any synthetic methodology that allows both the preparation of natural molecules and their clickable analogues is of considerable scientific value. As detailed below, this study reports a methodology that allows the β-stereoselective preparation of 1-phospho mannosides bearing an azido or an alkynyl group as potentially clickable functionalities. To demonstrate the applicability of this approach, two clickable analogues of **I** and **II** have been prepared.

The conversion of glycopyranosides into their corresponding glycosyl 1-phosphates has been accomplished by two main strategies. The first uses glycosylation reactions that employ nucleophilic phosphates and electrophilic glycosides such as glycosyl bromide,[9] thioglycosides,[10] trichloroacetimidates,[11] and activated glycals.[5] The second involves the treatment of anomeric lactols with electrophilic phosphates P(V) or phosphites/phosphoramidites P(III).[12] In general, most anomeric phosphorylations yield α-glycopyranosides as the major product, especially mannopyranosides.[12a]

Among all the methods that use electrophilic phosphorylating reagents, Sabesan *et al.* developed the first efficient β-selective phosphorylation of mannopyranosyl lactols using diphenyl chlorophosphate and DMAP as a base.[12a] More recently, Crich *et al.* developed a β-selective phosphorylation of electrophilic mannosides.[10b] The high stereoselectivity of the latter approach requires the presence of a 4,6-*O*-benzylidene protecting group in the sugar unit, as is the case for the general β-mannosylation reaction developed by the same team.[13] Unfortunately these two methods cannot be readily applied for the synthesis of azido/alkynyl containing mannosides because the deprotection of diphenyl or benzylidene groups requires hydrogenolytic or harsh conditions that are frequently not compatible with the presence of an anomeric phosphate.

To generate potentially clickable glycosides, a protective group strategy that avoids hydrogenation steps should be followed.

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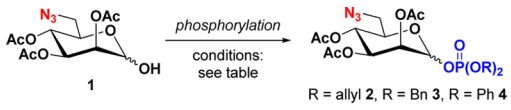
Inspection of the recent literature shows that diallyl phosphates have been prepared to resolve this problem. For instance, Macmillan *et al.* have successfully prepared GDP-2-, 3-, 4-, and 6-azidomannoses from GTP and the corresponding azidomannose-1-α-phosphate, which were generated after deallylation.[14] Recently, Lowary *et al.* have reported the synthesis of UDP-2-azido-2-deoxy-α-D-galactofuranose (UDP-Gal*f*N_3) using galactofuranosyl diallyl 1-α-phosphate triesters as a precursor.[15] However, these phosphorylation techniques give only α-phosphates.

Therefore, to develop a novel β-selective phosphorylation methodology, we first decided to screen allyl-protected phosphorylating reagents on the protected 6-azido-mannose **1** (see Table 1) easily prepared from D-mannose.[14] Sabesan's method was selected as a starting strategy, and we thus selected electrophilic P(III) and P(V) reagents **5**−**11** for this purpose. The efficiency and stereoselectivity of the phosphorylations of **1** were evaluated and compared with dibenzyl and diphenyl chlorophosphates **9** and **11**.

Table 1. Optimization of β-Phosphorylation Conditions of 1



1

R = allyl **2**, R = Bn **3**, R = Ph **4**

entry	phosphorylating agent	t (h)	ratio (α/β)	product (yield[e] (%))
1[a,b]	$((i\mathrm{Pr})_2\mathrm{N})_2\mathrm{PCl}$ **5**	12	4:1	**2** (18)[f]
2[a,c]	$(\mathrm{AllylO})_2\mathrm{PN}(i\mathrm{Pr})_2$ **6**	6	2:1	**2** (53)
3[a,c]	$(\mathrm{BnO})_2\mathrm{PN}(i\mathrm{Pr})_2$ **8**	10	2:1	**3** (46)
4[a]	$(\mathrm{AllylO})_2\mathrm{POCl}$ **7**	4	1:20	**2** (30)
5[a]	$(\mathrm{BnO})_2\mathrm{POCl}$ **9**	4	1:5	**3** (18)
6[a]	$\mathrm{PhO}_2\mathrm{POCl}$ **10**	5		NI[g]
7[a]	$(\mathrm{PhO})_2\mathrm{POCl}$ **11**	3	1:4	**4** (75)
8[a,d]	**$(\mathrm{AllylO})_2\mathrm{POCl}$ 7**	**4**	**1:20**	**2 (61)**

[a]To a solution of **1** and DMAP (5 equiv) in DCM, 3.0 equiv of phosphorylating agent was slowly added via a syringe pump.[18,12a] [b]Allyl alcohol (2.5 equiv) and 1*H*-tetrazole (2.5 equiv) were added after 5 h, then *t*-BuOOH.[16] [c]1*H*-Tetrazole (2.5 equiv) was added after 5 h, then *t*-BuOOH.[14] [d]Here, 7.5 equiv of phosphorylating agent and 10.0 equiv of DMAP were used. [e]Isolated yield. [f]In this reaction, the β anomer could not be isolated in pure form. [g]The products could not be isolated because of a very low conversion of lactol **1** and the transformation of the chlorophosphate into many side products.

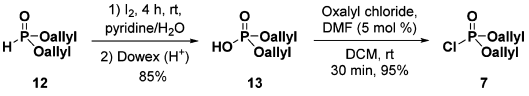
The reaction between **1** and chloro-bis(*N*,*N*-diisopropyl)-phosphoramidite **5** in the presence of DMAP, followed by the addition of allyl alcohol and 1*H*-tetrazole afforded the corresponding phosphite with the undesired α-selectivity (Table 1, entry 1).[16] Using $(\mathrm{AllylO})_2\mathrm{PN}(i\mathrm{Pr})_2$ **6** instead of $((i\mathrm{Pr})_2\mathrm{N})_2\mathrm{PCl}$ improved the α/β ratio (2:1) and provided the expected phosphate **2** in 53% yield (for the anomeric mixture), after oxidation (entry 2). A similar ratio (α/β 2:1) and a slightly lower yield were obtained with benzyl-protected phosphoramidite **8** (entry 3). Interestingly, the treatment of **1** with freshly prepared diallyl chlorophosphate **7** in the presence of 5 equiv of DMAP in dichloromethane at room temperature (rt) gave **2** in a moderate 30% yield but now the selectivity (α/β 1:20) was in favor of the desired β-anomer (entry 4). Under the same conditions, the phosphorylation of **1** with dibenzyl chlorophosphate **9** (entry 5) and *O*-phenylene chlorophosphate $\mathrm{PhO}_2\mathrm{POCl}$ **10** (entry 6) improved neither the selectivity nor the isolated yield.

Compared to the result obtained by diallyl chlorophosphate **7**, the use of diphenyl chlorophosphate yielded product **4** in 75%, but the selectivity was significantly lower (α/β 1:4, entry 7). With chlorophosphates as electrophilic reagents, the β-selectivity of the reaction can be explained by the higher nucleophilicity of β-lactols compared to their α isomers. Therefore, a slow addition of chlorophosphate into a solution of mannoside **1** could indeed be expected to favor formation of the β-phosphate **2**. However, we cannot rule out the involvement of stereoelectronic effects in this selective phosphorylation.

After a careful screening of experimental conditions, it was found that the addition rate (1.6 mL/h) and an increase in the amount of diallyl chlorophosphate **7** (7.5 equiv) and DMAP (10.0 equiv) improved the isolated yield of **2** to 61%, while maintaining an excellent 1:20 α/β selectivity (entry 8). The moderate yield can be explained by the fact that the corresponding 1-chloro-mannoside is also generated during the reaction.[17] Consequently, these optimal conditions (Table 1, entry 8) were selected for further investigation.

From this initial screening, diallyl chlorophosphate **7** gave the most promising results for the challenging β-stereoselectivity, and this reagent was selected to study the scope of the reaction. In contrast to diphenyl chlorophosphate, diallyl chlorophosphate **7** is not commercially available. We thus developed a convenient and scalable synthetic method for obtaining it; it is depicted in Scheme 1.

Scheme 1. Synthesis of Diallyl Chlorophosphate 7



12 13 7

We first tried to obtain **7** in one step, by the direct chlorination of the commercially available diallyl phosphite **12**. Despite several attempts with sulfuryl chloride,[19] trichloroisocyanuric acid,[20] and carbon tetrachloride,[21] the purity of the final diallyl chlorophosphate **7** never exceeded 50% because of the formation of side products. Therefore, we investigated a stepwise procedure that involved the oxidation of phosphite **12** followed by chlorination. The oxidation was realized in the presence of iodine in pyridine/water (20:1), followed by a reprotonation by a Dowex 50WX8 (H^+) resin that provided diallyl phosphate **13** in 85% yield. The optimized chlorination conditions for **13** entailed using oxalyl chloride in CH_2Cl_2 at rt. We found that 5 mol % equiv of DMF as a catalyst was necessary to minimize the formation of tetraallyl pyrophosphate (<5%), the usual by-product of this reaction. The reaction could be easily monitored by ^{31}P NMR: in $CDCl_3$, the chemical shifts of diallyl chlorophosphate and its corresponding pyrophosphate were 5.50 and −12.50 ppm, respectively.

Noteworthy, the addition order of reagents and the amount of DMF happened to be very important parameters for the quality of the final chlorophosphate (see Supporting Information (SI) for a detailed procedure). It was also found that diallyl chlorophosphate **7** was more stable than its dibenzylated analogue **9**, which is advantageous for synthetic procedures that require long reaction times or long addition times. Indeed, after 2 days in $CDCl_3$ at rt under argon, the ^{31}P NMR spectrum of **7** showed less than 10% decomposition.

Having established the optimal conditions for β-phosphorylation, the scope of the reaction was examined with various mannopyranosides (compounds **14**−**18**, Table 2). All starting

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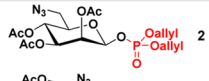
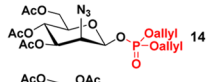
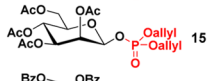
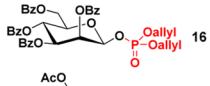
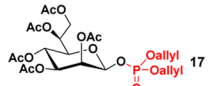
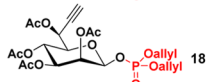
Table 2. Phosphorylation of Mannopyranosides

entry	product	t (h)	yield (%)	ratio[a] (α/β)
1	 **2**	4	61	1:>20
2	 **14**	5	53	1:>20
3	 **15**	3	65	1:>20
4	 **16**	2	80	1:30
5	 **17**	4	55	1:>20
6	 **18**	5	56	1:>20

[a]The α/β ratios were determined by ^{31}P NMR of the crude reaction mixture.

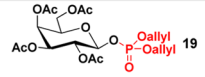
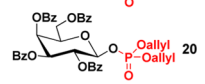
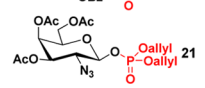
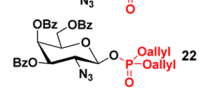
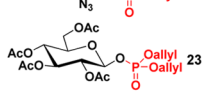
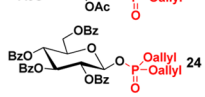
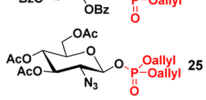
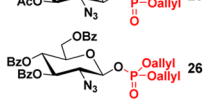
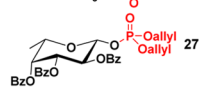
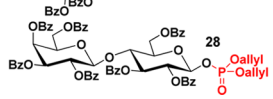
lactols were prepared from the corresponding peracetylated or perbenzoylated hexopyranoses by selective anomeric deprotection using ammonium acetate or methylamine (see SI).

The results presented in Table 2 show that, in all cases, the phosphorylation is always highly 1,2-*cis*-stereoselective, whatever axial group is present at the 2-position. Switching the azido group from the C-6 (in **1**, entry 1) to the C-2 position (in **14**, entry 2) affected neither the overall performance, nor the stereoselectivity, of the phosphorylation. The results reported in entries 3 and 4 indicate that protecting groups may influence the reaction. Indeed, a good yield (80%) and an excellent selectivity (α/β 1:30) were observed when benzoates were used as protecting groups instead of acetates. Furthermore, reaction of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose did not produce any phosphorylation product after 3 h at rt (data not shown).

However, we were pleased to find that D-manno-heptopyranose-β-1-phosphate **17**, suitable for the preparation of ADP-heptose **I**, was isolated in 55% yield with an excellent selectivity (Table 2, entry 5). Similar yield and selectivity was obtained in the preparation of the acetylated mannopyranoside **18** bearing a triple bond at C-6, indicating the compatibility of this clickable functional group under these phosphorylation conditions (Table 2, entry 6). For all products **2** and **14**−**18**, the corresponding α-phosphates could not be isolated. However, from the ^{31}P NMR spectra of the final crude reaction mixtures, we cannot rule out that trace amounts of the α-anomers were also formed. Therefore, in all the cases, we estimated that the α/β selectivity was at least 1:20.

Encouraged by the results obtained with the different mannopyranosides, we explored the synthetic potential of this selective β-phosphorylation with other glycosides. The results are gathered in Table 3. Interestingly, all the reactions (entries 1−10) produced exclusively the corresponding β-phosphates **19**−**28**, in moderate-to-good yields in a few hours. Once again, as for the mannopyranosides, phosphorylations of benzoylated

Table 3. β-Phosphorylation of D-Gluco-, D-Galacto-, and L-Fuco-Pyranosides and Lactose

entry	product	t (h)	yield (%)	ratio (α/β)
1	 **19**	3	62	β only
2	 **20**	4	70	β only
3	 **21**	4	60	β only
4	 **22**	4	65	β only
5	 **23**	4	58	β only
6	 **24**	6	81	β only
7	 **25**	4	55	β only
8	 **26**	4	58	β only
9	 **27**	3	36	β only
10	 **28**	4	65	β only

glucosides and galactosides gave better yields than the corresponding tetra-acetates (Table 3, entries 1−8).

Gratifyingly, the benzoylated lactoside also gave selectively the desired β-phosphate **28** in 65% (Table 3, entry 10). The yield of β-L-fucosyl-1-phosphate **27**, a key building block for the synthesis of GDP-β-fucose, the substrate of fucosyltransferases, was only 36% yield because of some difficulties encountered during the purification, probably due to the instability of the anomeric phosphate during prolonged silica gel chromatography (Table 3, entry 9). Performing this reaction under the conditions reported by Sabesan *et al.*,[12a] using diphenyl chlorophosphate **11**, provided exclusively the α-phosphate. At this stage, we have no explanation for this surprising observation. Moreover, we have observed that some 1-β-diallylphosphates (in the gluco- and galacto-series) can slowly be anomerized, at rt, to the more stable α-phosphates. Thus, it is recommended to store them at −25 °C or to deprotect them immediately after their preparation. Indeed, the corresponding phosphate triethylammonium salts were found much more stable.

The structures of all products were fully ascertained by NMR spectroscopy using ^{1}H, ^{13}C, ^{31}P, ^{1}H−^{1}H COSY, ^{1}H−^{1}H NOESY, and ^{1}H−^{13}C (HSQC, HMBC), including the mannopyranosides **2** and **14**−**18**. In fact, the stereochemistry at the anomeric position was unambiguously confirmed by NOE experiments between H-1, H-3, and H-5 for all manno-configured glycosides, and for the 1,2-*trans*-pyranosides, by the $^{3}J_{1-2}$ coupling constants showing a 1,2-*trans*-diaxial relationship.[22]

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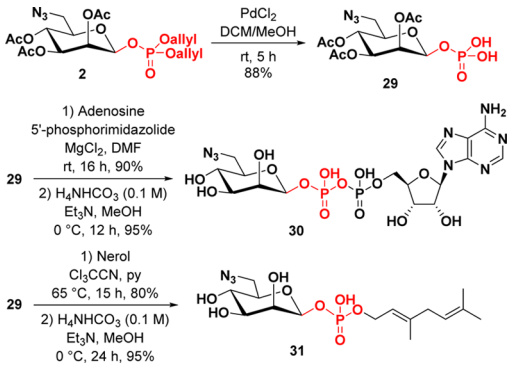
Because of the known reactivity of dialkyl chlorophosphates with carbohydrates' primary alcohols,[23] we did not attempt this reaction with unprotected sugars.

To demonstrate that this procedure can be applied to the synthesis of biologically relevant β-phosphates, we prepared deprotected glycosides **30** and **31** (Scheme 2), two potentially

Scheme 2. Synthesis of Azido Analogues 30 and 31



clickable analogues of β-mannosyl phosphoisoprenoids **I** and ADP-heptose **II** (Figure 1). The deallylation of compound **2** was carried out efficiently in the presence of $PdCl_2$ in DCM/MeOH at rt, and **29** was isolated in 88% yield (Scheme 2).[24] The coupling between **29** and adenosine 5′-phosphorimidazolide[25] in DMF in the presence of $MgCl_2$ as a Lewis acid catalyst afforded the desired protected nucleotide azido sugar, which was deacetylated to lead to **30** in 95% yield. In order to prepare the analogue of β-mannosyl phosphoisoprenoids **I**, the reaction between Nerol and phosphate **29** in the presence of trichloroacetonitrile in pyridine[26] at 65 °C, followed by deprotection, gave phospholipid **31** in 76% yield over two steps.

In conclusion, we have developed a simple regioselective 1-β-phosphorylation of acetylated or benzoylated glycopyranosides that bear an azido or an alkynyl group, using diallyl chlorophosphate as phosphorylating agent. The scope and limitations of this reaction have been described and allow various pyranosides (D-mannose, L-*glycero*-D-*manno*-heptopyranose, D-galactose, D-glycose, L-fucose, and lactose) to afford the corresponding 1-β-phosphates in moderate-to-good yields and very high β-selectivity. The interest of this transformation has been highlighted by the synthesis of a nucleotide sugar and a β-mannosyl phosphoisoprenoid. Furthermore, the findings described herein represent a significant advance in selective β-phosphorylation and will create new opportunities for the design of other complex glycolipids or nucleotide sugars.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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