Full Paper

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β-Selective One-Pot Fluorophosphorylation of D,D-Heptosylglycals Mediated by Selectfluor

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Abstract: This study describes the development of a novel procedure of glycal fluorophosphorylation applied to the synthesis of a fluorinated analogue of an important bacterial metabolite. This procedure was applied to several heptose-derived glycals, and the stereochemical outcome of the reaction was analyzed. Under optimized conditions, the reaction is β-*gluco* selective, but a significant amount of the α-*gluco* diastereomer is also generated.

Keywords: antibiotics · fluorosugars · LPS · phosphorylation · Selectfluor

1. Introduction

Lipopolysaccharide (LPS) is the main polysaccharide present at the surface of gram-negative bacteria.[1] This molecule may play a major role in the mortality of many infectious diseases, as well as in the virulence of numerous human pathogens.[2] Moreover, LPS ensures protection against hydrophobic molecules and participates in the bacterial cell integrity.

LPS is an amphipathic molecule that can be decomposed into three main substructures: lipid A, the oligosaccharide core, and the O-antigen. The oligosaccharide core can be divided into two parts: the inner core is formed at least of one molecule of 3-deoxy-α-D-*manno*-oct-2-ulosonic acid (Kdo) and two to three molecules of L-*glycero*-α-D-*manno*-heptose (heptose), and the outer core is composed of hexoses. Importantly, Kdo and heptoses are not present in mammals; targeting the enzymes involved in their biosynthesis may thus lead to selective antibacterial inhibitors.[3]

Gram-negative bacteria lacking heptose biosynthesis display the so-called deep-rough phenotype,[4] and show an increased sensitivity towards antibiotics.[1a, 5] They also become more susceptible to the bactericidal effect of the host, as well as to phagocytosis by macrophages.[6] Therefore, the inhibition of the heptose biosynthetic pathway is a novel approach to develop new antibacterial agents with a novel mechanism of action; instead of targeting the central metabolism or the cell wall biosynthesis, this approach consists of attenuating or even annihilating the virulence of the microorganism, without the need to kill it.[7]

With this concept in mind, we developed the first inhibitors of heptosyltransferase WaaC as a novel approach to inhibit the bacterial cell wall resistance to the innate immune response.[8] Later on, we designed and synthesized heptose analogues as inhibitors of the two first enzymes of this bacterial biosynthetic pathway.[9] Thus, the inhibition of heptose biosynthesis seems to be a very promising field for the development of antivirulence drugs.[7d,10] Interestingly, the inhibition of this pathway has been relatively overlooked for two reasons: i) the enzymes involved in the heptose biosynthesis have been cloned and characterized only recently (Figure 1); and ii) their substrates are not commercially available and their synthesis is not straightforward.[11]

The biosynthesis of bacterial heptoses starts from sedoheptulose-7-phosphate **1**, derived from the central metabolism.[12] A keto-aldose isomerase, GmhA, transforms **1** into D-*glycero*-D-*manno*-heptose 7-phosphate **2**, which is then phosphorylated by the kinase HldE. After hydrolysis of the 7-phosphate of **3**, intermediate **4** is transformed into nucleotide-sugar **5**. Some bacterial strains, such as *E. coli*, use the same HldE enzyme for two non-consecutive steps. A regioselective D to L epimerization is then catalyzed by HldD, yielding ADP-L-heptose **6**, the donor substrate of heptosyltransferases (WaaC, WaaF, and WaaQ).[13]

In 2008, our group described the synthesis and the inhibition properties of nucleotide-sugar **7**, the 2-fluoro analogue of **6**.[8a] Fortunately, we were able to obtain a 3D-structure of WaaC, in complex with **7**, which allowed us

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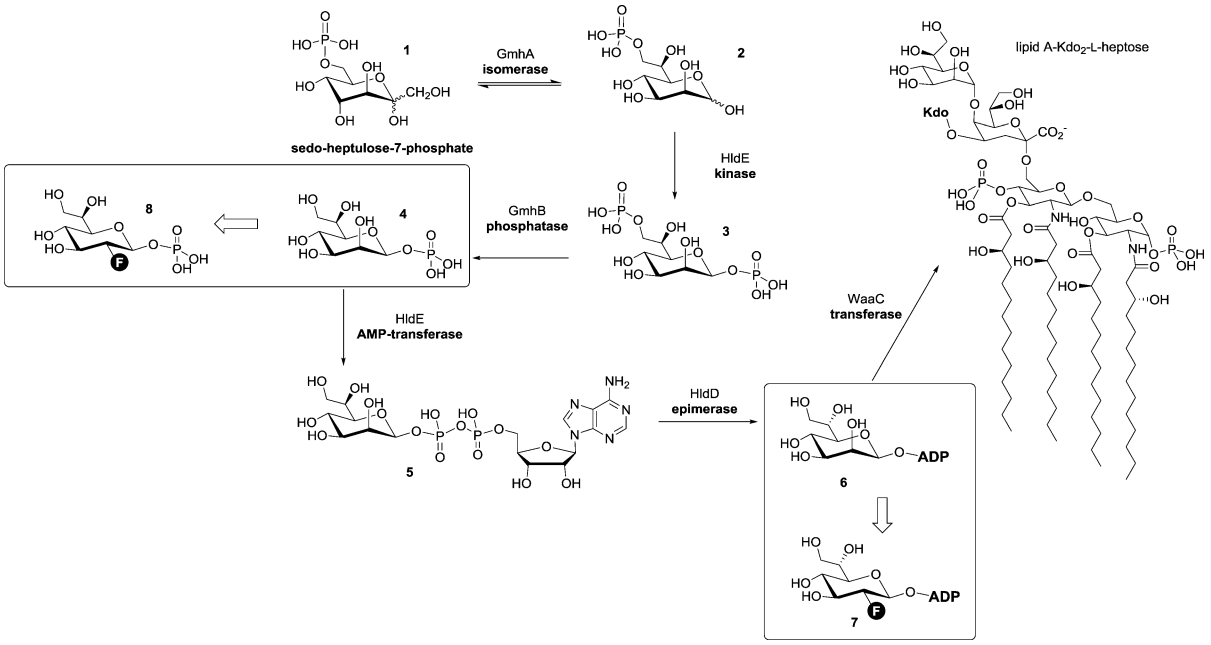


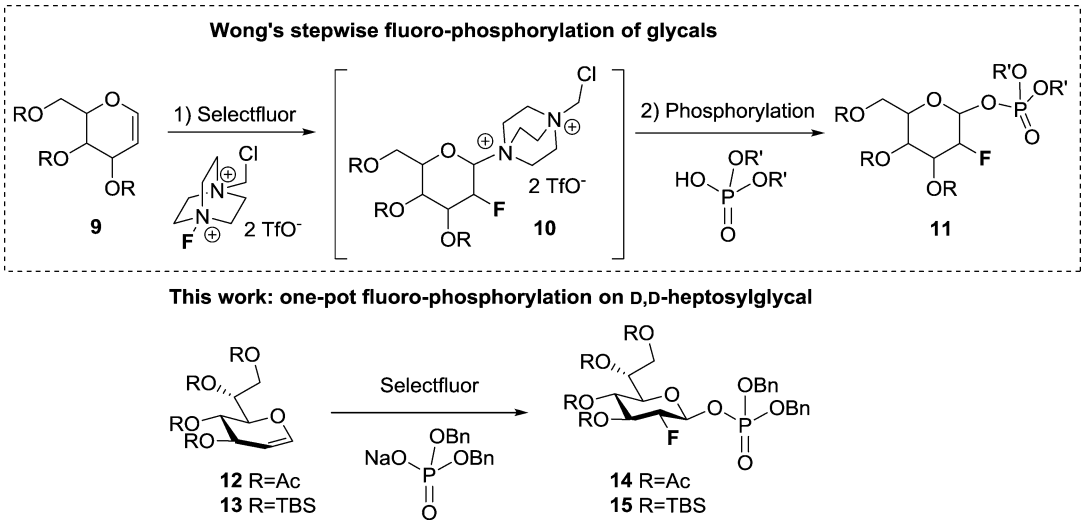
Figure 1. Biosynthesis of bacterial L-heptosides found in LPS.

to map the interactions of the glycosyltransferase and its donor substrate **6**.[14]

The preparation of fluorinated analogue **7** required an 18-step synthesis whose central step was Wong's Selectfluor mediated fluorophosphorylation of glycals (Scheme 1).[15] This reaction allows the installation, in a single synthetic operation, of the fluorine atom at the 2-position and the protected phosphate at the 1-position, regio- and stereoselectively.

With this methodology in hand, we decided to synthesize the fluorinated analogue **8** of the biosynthetic intermediate **4**, displaying the D-*glycero*-D-*manno* configuration (Figure 1). To do so, we explored a new synthetic methodology, consisting of performing Wong's fluorophosphorylation with the concomitant presence of the fluorinating and the phosphorylating agents, which had never previously been realized. In this article, we wish to describe this novel methodology for L- and D-heptosyl glycals, the comparative stereoselectivities between Wong's initial stepwise procedure and this new protocol, and finally the synthesis of the deprotected molecule **8**.

In this study, we will first describe the synthesis of D,D-heptosylglycals **12** and **13**, then the fluorophosphorylation reaction, and finally, the synthesis of heptose-phosphate **8**.



Scheme 1. The fluorophosphorylation of glycals.

2. Results and Discussion

2.1 Synthesis of D,D-Heptosylglycals 12–13

The synthesis of D,D-heptosylglycal followed the same global strategy of the synthesis of its L-*glycero*-D-*manno* epimer that we previously published.[8a] The synthesis began with the known alkene **16**,[16] easily prepared on a large scale, in a few steps, from D-glucose.[17] The dihydroxylation of **16** under standard conditions, followed by an acetylation of the resulting diol, yielded intermediate **18** in 80% yield for the D-epimer. The observed D/L selectivity (9/1) corroborates literature data.[18] A direct conversion of benzylated intermediate **18** into D-*glycero*-D-*manno*-heptose peracetate **19** could directly be achieved under acetolysis conditions. Bromination of the anomeric position, followed by a zinc-mediated β-elimination, afforded the D,D-heptal tetraacetate **12** in 87 % yield. Protective group manipulation finally yielded the corresponding tetrasilylated glycal **13**.

2.2 Fluorophosphorylation of Heptose Glycals

In their pioneering work on the Selectfluor mediated regioselective fluorination of glycals, Wong *et al.* developed the first protocol, on a wide range of glycals, adapted for weak nucleophiles, such as alcohols, including protected sugars.[19] Two years later, the same team described a second procedure, allowing the use of more challenging nucleophiles such as amines, thiols and phosphates.[15a] Thanks to this improvement, the access to nucleotide-fluorosugars became more straightforward, and was eventually exploited to study the mechanism of glycosyltransferases.[20]

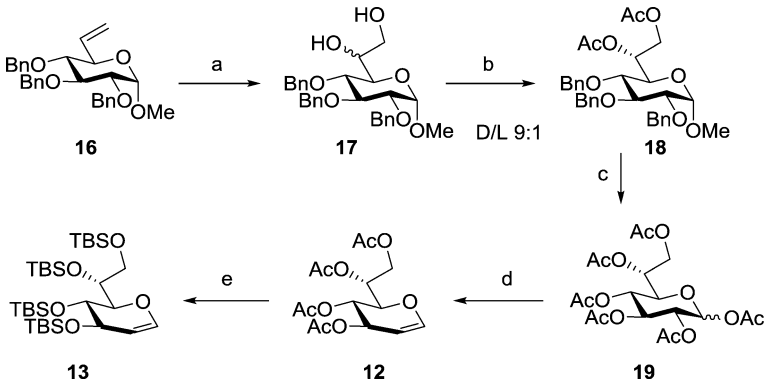
The difficulty that can be encountered in the one-pot fluorophosphorylation of glycals is that two nucleophilic species might be in competition for a single electrophile: indeed, dialkylphosphates are nucleophilic enough to react with Selectfluor, thus yielding undesired side-reactions. This problem was resolved by using a stepwise procedure represented in Scheme 1: 1) a *syn*-addition of Selectfluor is first performed under anhydrous conditions, yielding intermediate **10**; and 2) a substitution of the anomeric DABCO biscation by a dialkylphosphate is performed, usually at 100 °C.[15a]

In our preliminary synthesis of 2-fluoro-L,D-heptose **7**, we found that we could improve the stereoselectivity of the stepwise fluorophosphorylation by decreasing the reaction temperature (down to 45–60 °C), and by enhancing the nucleophilicity of the phosphate (using the phosphate sodium salt and [15]-crown-5).[8a]

In view of the synthesis of 2-fluoro-D,D-heptoside **8**, we decided to investigate again the opportunity to perform the fluorophosphorylation in a one-pot fashion. Indeed, we were interested to determine whether the stereochemical outcome of the reaction (α/β and *gluco*/*manno*) would be affected if all the reagents are present from the very beginning of the reaction. We reasoned that at lower temperatures (compared to the initial stepwise procedure), it might be possible to start the reaction with the two nucleophilic species (the glycal and the phosphate), in competition for the electrophilic fluorinating agent.

The results of this investigation are gathered in Table 1. The first attempts using acetylated glycal **12** were unsuccessful (entry 1). This result was tentatively attributed to the fact that, in general, peracetylated glycals are poor substrates in Selectfluor mediated reactions, due to the lability of the acetates under these specific reaction conditions.[8a,15a,21]

The following attempts employing persilylated glycal **13** were more encouraging, but generally suffered from low conversions and, depending on the reaction temperature, some unidentified side-products were also observed (data not shown). However, we could clearly observe the formation of the desired 2-fluoro-heptose phosphates **15** by ^{31}P- and ^{19}F-NMR of the crude reaction mixtures. Our main conclusion from these preliminary assays was that this reaction could indeed be performed in a one-pot fashion, at 60 °C. To resolve the conversion problem, we assumed that the fluorinating reagent might slowly de-



Scheme 2. Synthesis of D,D-heptose glycals **12** and **13**. Reagents and conditions: (a) OsO_4, NMO, acetone, H_2O, 0 °C and rt, 92%; (b) Ac_2O, Py, rt, quant; (c) H_2SO_4, Ac_2O, $CHCl_3$, 0 °C and rt, 83%; (d) HBr-AcOH, AcOH, Ac_2O, CH_2Cl_2, rt; Zn, $CuSO_4$, AcONa, AcOH, H_2O, rt, 87%; for 2 steps; (e) Na, MeOH, rt; TBSCl, Im, DMF, 0 °C and rt, 87% for 2 steps.

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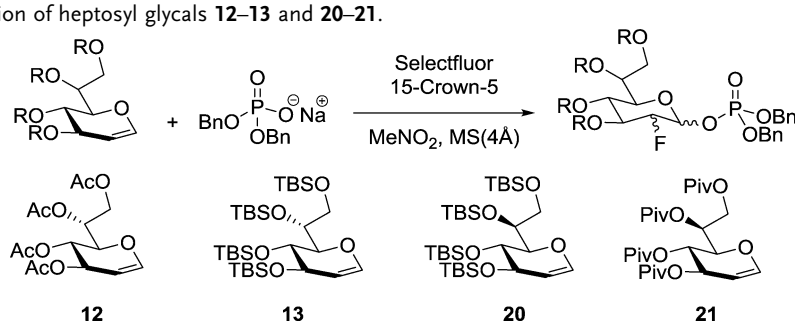
Table 1. Fluorophosphorylation of heptosyl glycals **12**–**13** and **20**–**21**.



12 **13** **20** **21**

entry	Glycal	$(BnO)_2PO_2Na$ (eq.)	Addition method[a]	T (°C)[b]	t (h)	Yield (%)[c]	Products a : b : c : d[d]
1	**12**	5	A	60	4	–[e]	**14**
2	**13**	5	A	60	4	70[d]	**15** 39 : 61 : 0 : 0
3	**20**	5	A	60	4	61	**22** 24 : 76 : 0 : 0
4	**21**	3	B	60	2	53	**23** 6 : 94 : 0 : 0

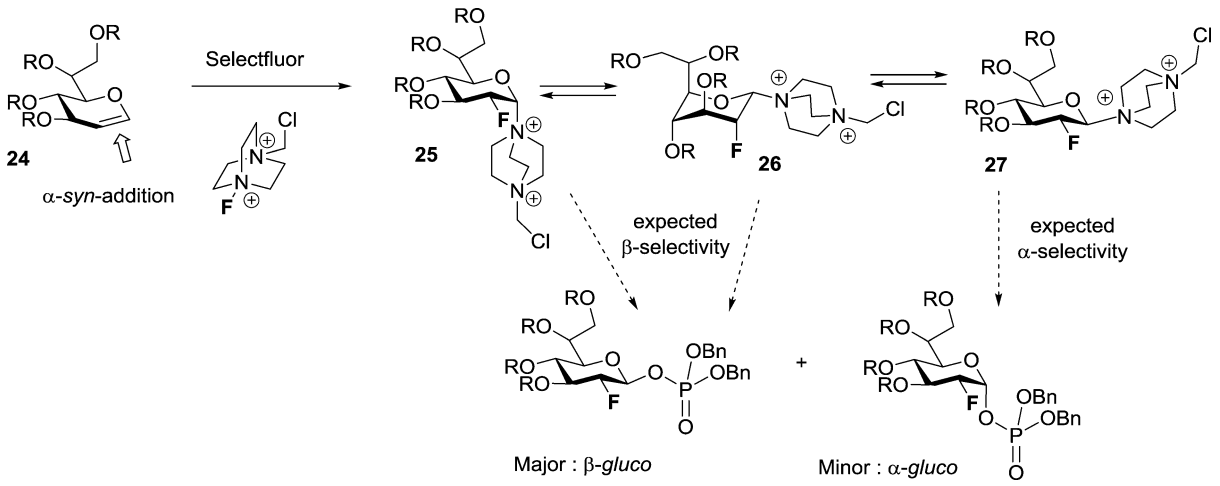
[a] A: No-stepwise method, all the reagents were simultaneously added, and 1 eq. Selectfluor was added every hours; B: Stepwise method, Selectfluor and glycal were reacted first at room temperature; the phosphorylating reagent was then added after disappearance of the glycal and heated. [b] The temperature was maintained during all the reaction. [c] Isolated yield. [d] Assessed by ^{1}H-, ^{19}F- and ^{31}P-NMR. a: α-*gluco*, b: β-*gluco*, c: α-*manno*, d: β-*manno*. [e] Complex mixtures of non-separable products and side-products.

compose under the reaction conditions. We therefore decided to use an excess of Selectfluor, by adding 1 equivalent of fluorinating reagent every hour (entry 2) until the starting glycal totally disappeared (as monitored by TLC). Gratifyingly, we could generate the desired 2-fluoro-heptose phosphate **15** in 70% as a mixture of two diastereomers. Similar results were obtained with the L-*glycero*-heptosyl glycal **20** that we had previously synthesized (entry 3).[8a] The yields were in the same range than with the stepwise procedures of Selectfluor mediated glycal fluorophosphorylation.

However, the stereochemical outcome of the reaction is slightly different when the reaction is conducted in a non-stepwise manner. For both epimeric glycals **13** and **20** the major product were the desired β-*gluco* configured fluorophosphates (entries 2 and 3). The α-*gluco* diastereomers are always the sole side-products of these reactions, indicating that, as initially proposed by Wong *et al.*, a *syn*-addition of Selectfluor occurs first, yielding a single *gluco*-configured intermediate **10**. The following nucleophilic substitution by the phosphate gives an anomeric α/β mixture in favor of the β-product.

The β-*gluco* stereoselectivity of the fluorophosphorylation, following this one-pot procedure, is moderate and lower than similar reactions performed under stepwise conditions.[8a] A typical example is detailed in entry 4, with a pivaloylated glycal **21**. In the latter case, a much higher β-*gluco* selectivity was achieved, while the yield was slightly lower than with the novel non-stepwise procedure.

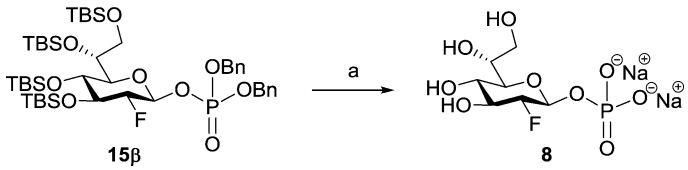
The origin of the differences of product distributions between the stepwise and non-stepwise/one-pot methods might be found in the reaction mechanism. Wong's mechanistic study, performed on fucosides, showed that Selectfluor addition occurs in a *syn* manner and that the intermediate adduct can anomerize after a ring flip.[15a] It is thus reasonable to invoke that the first intermediate of the *syn*-addition of **24** is the ammonium **25** (Scheme 3). As previously demonstrated on fucosides, the hindered DABCO ammonium can force the carbohydrate to flip to a $^1C_4$ conformation, giving a new intermediate **26**. Moreover, an anomerization can also occur to generate the β-adduct **27**, in which the leaving group is now equatorial in a relaxed $^4C_1$ conformation. The stereochemical outcome of the global reaction is directly linked to the distribution of **25**–**27** because it is expected that intermediates **25** and **26** will favor nucleophilic substitutions from their β-face, whereas **27** should give an α-selectivity. The distribution of intermediates **25**–**27** is likely to be strongly dependent on all reaction parameters, including the temperature of the two steps (Selectfluor addition and nucleophilic substitution). In contrast to the stepwise procedure in which the first step is always performed at room temperature, the temperature of the whole process has been fixed at 60 °C, which can modify the distribution of Selectfluor adducts but also the initial conformation of starting glycal **24**. The α/β selectivity may also be affected by the fact that the nucleophilic phosphate is present from the beginning of the reaction in the non-stepwise procedure, and is thus allowed to react with the intermediate adducts immediately after their formation. The results detailed in Table 1 show that, indeed, changing the reaction temperature and the addition sequence of this reaction does affect the stereoselectivity of the fluorophosphorylation.



Scheme 3. Plausible mechanism of the fluorophosphorylation of heptosides.

2.3 Synthesis of the Final D,D-Heptoside 8

The deprotection of intermediate **15β** (Scheme 4), was not so straightforward, given the polarity of the final molecule. The classical strategy, consisting of deprotecting the TBS group first to allow hydrogenolysis as the last step, failed in our hands.



Scheme 4. Synthesis of D,D-heptoside **8**. Reagents and conditions: (a) i) H_2, Pd/C, EtOAc, EtOH; ii) TBAF, THF, rt, 78% for 2 steps.

Instead, we managed to obtain the pure final molecule in 78% yield by performing the hydrogenolysis first, followed by a TBAF desilylation. After a cation exchange of the tetrabutylammoniums, the final molecule was purified by size-exclusion chromatography. Analytical data were in excellent agreement with related fluorosugars. The *gluco* and the anomeric configurations were easily deduced from the $^3J(H,H)$ coupling constants.

3. Conclusion

In conclusion, this study describes the development of a novel procedure of glycal fluorophosphorylation, in which the fluorinating and phosphorylating agents are present from the beginning of the reaction, thus avoiding a stepwise procedure. This procedure was applied to several heptose-derived glycals and allowed a comparison of the stereochemical outcome of the reaction. The β-*gluco* selectivity was less pronounced than the stepwise procedure, but allowed slightly higher yields. Thanks to this procedure, the fluorinated analogue of an important bacterial metabolite was achieved. This work contributes to the field of biochemically relevant carbohydrate mimetics:[22] the final molecule **8** will be exploited as a probe of the heptose biosynthetic pathway. This fluorophosphate will be first assessed as an inhibitor of HldE and GmhB. Then, it could be interesting to determine whether **8** is a substrate of the AMP-transfer activity of HldE, thus opening the way to the chemo-enzymatic synthesis[23] of a fluorinated analogue of ADP-D-heptose **5**.

4. Experimental Section

See the electronic supplementary information for the experimental procedures and product characterizations.

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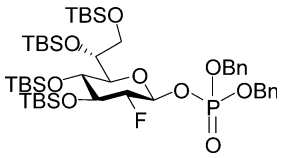

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β-Selective One-Pot Fluorophosphorylation of D,D-Heptosylglycals Mediated by Selectfluor