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Stereoselective Glycal Fluorophosphorylation: Synthesis of ADP-2-fluoroheptose, an Inhibitor of the LPS Biosynthesis

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Abstract: Heptosides are found in important bacterial glycolipids such as lipopolysaccharide (LPS), the biosynthesis of which is targeted for the development of novel antibacterial agents. This work describes the synthesis of a fluorinated analogue of ADP-L-*glycero*-β-D-*manno*-heptopyranose, the donor substrate of the heptosyl transferase WaaC, which catalyzes the incorporation of this carbohydrate into LPS. Synthetically, the key step for the preparation of ADP-2F-heptose is the simultaneous and stereoselective installation of both the fluorine atom at C-2 and the phosphoryl group at C-1 through a selectfluor-mediated (selectfluor = 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(triflate)) electrophilic addition/nucleophilic substitution involving a heptosylglycal. Therefore, we detail in this article 1) the stereoselective preparation of the key intermediates heptosylglycals, 2) the development of a new fluorophosphorylation procedure allowing an excellent β-*gluco* stereoselectivity with "all-equatorial" glycals, 3) the synthesis of the target ADP-2F-heptose, and 4) some comments on the contacts observed between the fluorine atom of the final molecule and the protein in the crystallographic structure of heptosyltransferase WaaC.

Keywords: fluorine · glycal · glycosyl transferases · nucleotides · polysaccharides · selectfluor

Introduction

Lipopolysaccharide (LPS) is a key component of the outer membrane of Gram-negative bacteria.[1] The mortality of many infectious diseases is closely related to the amount of circulating LPS endotoxins found in patient sera.[2]

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 of at least one molecule of 3-deoxy-α-D-*manno*-oct-2-ulopyranosonic acid (Kdo) and two molecules of L-*glycero*-α-D-*manno*-heptopyranose (heptose), and the outer core is composed of hexoses. Lipid A and one Kdo is the minimal structure for maintaining cell viability. Gram-negative bacteria that lack heptose display the deep-rough phenotype[3] and show a reduction in outer membrane protein content, an increased sensitivity towards detergents or hydrophobic antibiotics, and are much more susceptible to phagocytosis by macrophages.[4] Therefore, the heptosyltransferases implied in LPS biosynthesis represent attractive targets, the inhibition of which could attenuate the virulence of diverse bacterial strains.

In a more general perspective, the discovery of glycosyltransferase (GT) inhibitors[5] as well as the understanding of their intimate mechanism still represent challenging tasks.[6,7] To date, one of the most general class of GT inhibitors is the family of NDP-2-fluoro-sugars (NDP = nucleoside diphosphate), which are analogues of the donor substrates (NDP-sugars).[7–10] NDP-2-fluoro-sugars generally display low micromolar inhibition levels in the range of the K_m of

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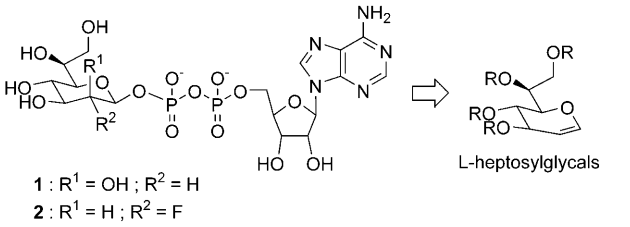
GT's donor substrates.[7] Interestingly, they are also valuable tools for co-crystallisation experiments with GTs, since they are both competitive inhibitors and very close analogues of their substrates. To date, the structures of six GTs in complex with NDP-2F-sugars have been resolved.[11,12] It is worth noting that the co-crystallization of glycosyltransferases with NDP-sugar analogues revealed substrate-induced conformational changes of the protein. These results are extremely important, since they provide the binding mode and the conformation of the donor within the catalytic pocket, which can facilitate the design of inhibitors and the understanding of the mechanism.

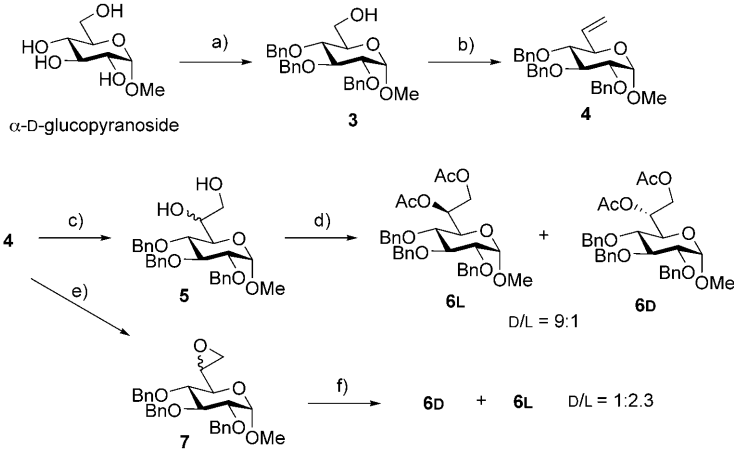
For Gram-negative bacteria, the donor substrate of heptosyltransferases is ADP-L-*glycero*-β-D-*manno*-heptose **1**, the anomeric configuration of which has been recently demonstrated by Kosma et al.[13] To obtain a low-micromolar inhibitor that will be used to develop and calibrate a high-throughput inhibition assay against WaaC, the first heptosyl transferase of LPS biosynthesis, we designed and synthesized molecule **2**, the fluorinated analogue of the bacterial heptosyltransferases donor substrate. Moreover, we have recently reported the crystallographic structure of heptosyltransferase WaaC in complex with **2**.[12]



Synthetically, the key step for the preparation of **2** is the simultaneous and stereoselective installation of both fluorine atom at C-2 and the phosphoryl group at C-1 through a selectfluor-mediated (selectfluor = 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(triflate)) electrophilic addition/nucleophilic substitution involving a heptosylglycal.[14] Therefore, we detail in this article 1) the stereoselective preparation of the key intermediates heptosylglycals, 2) the development of a new fluorophosphorylation procedure allowing an excellent β-*gluco* stereoselectivity with "all-equatorial" glycals, 3) the synthesis of the target ADP-2F-heptose **2**, and 4) some comments on the contacts observed between the fluorine atom of **2** and the protein in the crystallographic structure of heptosyltransferase WaaC in complex with **2**.

Results and Discussion

Synthesis of L-heptosylglycals: Due to their involvement in the LPS biosynthesis, several synthetic procedures for 6-D- and 6-L-*glycero*-mannosylheptoses have been developed mainly using stereoselective Grignard additions or osmium dihydroxylation.[15] In contrast, the synthesis of glucosylheptoses has been much less investigated.[16,17] Thus, we first explored the stereoselective preparation of L-*glycero*-D-*gluco*-heptoses from a key olefin intermediate **4** derived from D-glucose. Alcohol **3** was prepared in 80% yield from commercial methyl α-D-*gluco*-pyranoside by installation of triisopropylsilyl (TIPS) group at O-6 position, followed by a *per-O*-benzylation and a desilylation (Scheme 1). Swern oxidation of **3** afforded an intermediate aldehyde that was immediately subjected to a Wittig reaction to afford the olefin **4** in 72% yield. Treatment of olefin **4** with OsO_4 (2.5 mol%) and *N*-methylmorpholine-*N*-oxide (NMO) at room temperature furnished diol **5** in 92% yield as a 9:1 mixture of two diastereomers. Asymetric dihydroxylations were also tested but without success: both ADmix-α and ADmix-β[18] gave poorer yields and lower diastereoselectivities than OsO_4. The separation of the epimeric diols **5** being difficult, the mixture was O-peracetylated then separated by standard silica gel chromatography to afford *gluco*-heptoses **6D** and **6L**.



Scheme 1. Reagents and conditions: a) TIPSCl, Im, DMF, RT; BnBr, NaH, DMF, RT; TBAF, THF RT, 80% for 3 steps; b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78°C→0°C; $Ph_3CH_3P^+$, Br^-, *n*BuLi, THF, 0°C→RT, 72% for two steps; c) OsO_4, NMO, acetone, H_2O, 0°C→RT, 92%; d) Ac_2O, Py, RT, quant; e) mCPBA, CH_2Cl_2, 0°C→RT, 87%; f) CsOAc, [18]crown-6, DMF, 100°C; Ac_2O, Py, RT, 84% for 2 steps.

Assignment of the stereochemistry at C-6: The stereochemistry at C-6 of each diastereomer was determined by comparison with analytical data of related *gluco*-heptosides found in the literature.[17] Strengthening this stereochemical assignment by standard X-ray crystallography was unfortunately unsuccessful, since all attempts to obtain monocrystals of heptoses **6D** and **6L**, or even intermediates **7** to **15**, failed. To our delight, we finally obtained suitable monocrystals of final-ADP-2F-heptose **2** in complex with the heptosyl-transferase WaaC (Figure 1), thus demonstrating the L

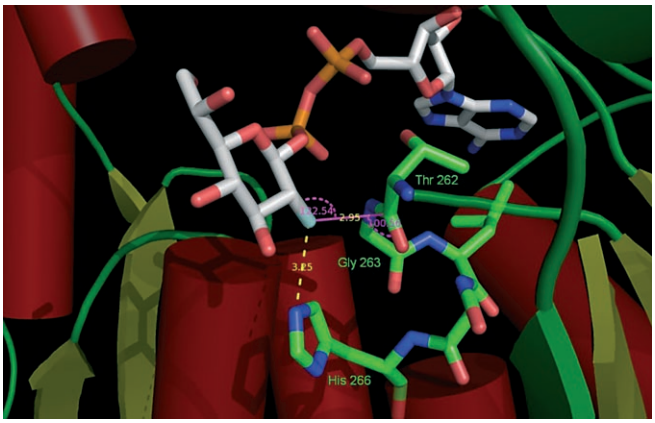


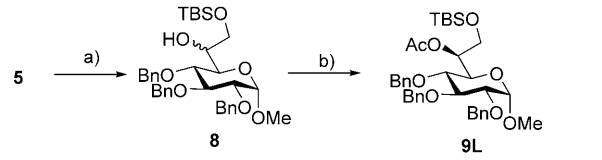
Figure 1. Structure of heptoside **2** in the active site of heptosyl transferase WaaC demonstrating the L configuration at C-6 (red: oxygen; blue: nitrogen; light blue: fluorine). The contacts between the fluorine atom and the protein (imidazole ring of His266 and peptidic backbone) are also represented.

configuration of **2**, and therefore the stereochemistry of all intermediate molecules **6** to **15**.[12]

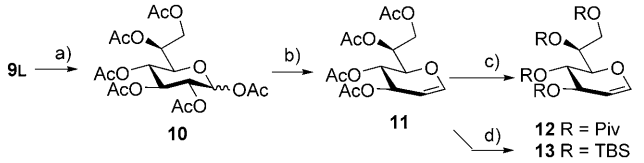
Optimization of the L selectivity: Thus, the 9:1 D diastereoselectivity of the dihydroxylation of **5** follows Kishi's rules.[19] To obtain a better L diastereoselectivity, olefin **4** was subjected to mCPBA to afford epoxides **7** in 87% yield as an inseparable 2.3:1 mixture. Nucleophilic opening of **7** with cesium acetate in presence of acetic anhydride yielded **6** with a 1:2.3 diastereoselectivity in favor of the L diastereoisomer.

To improve the overall yield in L-*glycero*-heptose **6L**, we then developed an epimerization procedure of diol **5** (Scheme 2). The mixture of diols **5** was first selectively protected as a silylated ether **8** in 91% yield, which was treated with trifluoromethanesulfonic anhydride followed by a S_N2 substitution with cesium acetate to afford pure silyl acetate **9L** in 64% isolated yield. The two diastereoisomers **9L** and **9D** were independently transformed into **6L** and **6D** by a simple desilylation followed by an acetylation to demonstrate their stereochemistry at C-6.

Synthesis of heptosylglycals: One-pot deprotection of all protective groups and O-peracetylation of **9L** (or **6L**) with acetic anhydride and sulfuric acid in chloroform gave the O-peracetylated heptopyranose **10** in 82% yield (Scheme 3). Thus, a series of L-heptosylglycals **11**–**13** could be efficiently prepared by using a known zinc-mediated glycal formation,[20] followed by protective group manipulations.

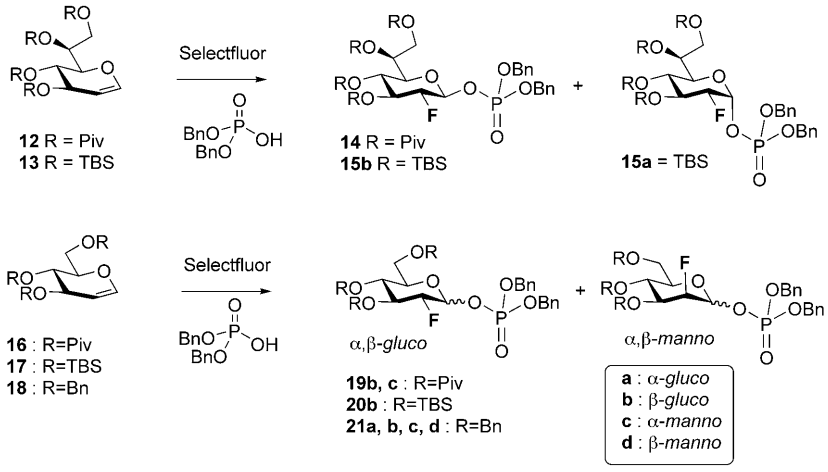


Scheme 2. Reagents and conditions: a) TBDMSCl, DMAP, Py, CH_2Cl_2, 0°C→RT, 91%; b) Tf_2O, Py, CH_2Cl_2, −40°C→RT; CsOAc, 18-crown-6, PhMe, ultrasonication, 64%.



Scheme 3. Reagents and conditions: a) H_2SO_4, Ac_2O, $CHCl_3$, 0°C→RT, 82%; b) HBr, AcOH, Ac_2O, CH_2Cl_2, RT; Zn, $CuSO_4$, AcONa, AcOH, H_2O, RT, 91% for 2 steps; c) Na, MeOH, RT; PivCl, DMAP, Py, RT, 82% for 2 steps; d) Na, MeOH, RT; TBDMSCl, Im, DMF, 0°C→RT, 95% for 2 steps.

Diastereoselective fluorophosphorylation of L-heptosyl glycals: The procedure developed by Wong et al. was followed for the first attempts of fluorophosphorylations of glycals **11** to **13** (Scheme 4 and Table 1, entries 1–3).[14] Although the products could be detected in each case (by ^{31}P and ^{19}F NMR spectroscopy), they could not be isolated in pure form due to unexpected side reactions. Even performed in a stepwise fashion (selectfluor addition then substitution by dibenzyl phosphate),[14] these conditions seemed too harsh for heptosylglycals **11** to **13**. The complex NMR spectra of the crude reaction mixtures strongly suggested the formation of several diastereomers contaminated by fluorinated side products. In addition, the fluorophosphorylations of "all-equatorial" glycals usually suffer from low-to-moderate diastereoselectivities at both C-2 and anomeric positions (see discussion below): four diastereomers are therefore expected, thus complicating both the interpretation of NMR



Scheme 4. Fluorophosphorylation of glycals (see Table 1).

Table 1. Fluorophosphorylation of glycals (see Scheme 4).[a]

	Glycal	Phosphorylating agent	T [°C][b]	t [h]	Yield [%][c]	Products a:b:c:d[d]
1	**11**	$(BnO)_2PO_2H$	90	2	–[e]	–[e]
2	**12**	$(BnO)_2PO_2H$	90	2	–[e]	–[e]
3	**13**	$(BnO)_2PO_2H$	90	2	–[e]	–[e]
4	**16**	$(BnO)_2PO_2H$	90	1.5	40	**19** 0:3:2:0
5	**16**	$(BnO)_2PO_2H$, DTBP[f]	60	12	45	**19** 0:4:1:0
6	**16**	$(BnO)_2PO_2Na$[g]	60	12	61	**19** 0:6:1:0
7	**16**	$(BnO)_2PO_2Na$[g]	45	36	63	**19** 0:9:1:0
8	**18**	$(BnO)_2PO_2Na$[g]	45	120	65	**21** 2:7:10:1
9	**17**	$(BnO)_2PO_2Na$[g]	45	48	66	**20** 0:1:0:0
10	**12**	$(BnO)_2PO_2Na$[g]	60	16	58	**14** 0:93:7:0
11	**13**	$(BnO)_2PO_2Na$[g]	45	48	51	**15** 6:94:0:0

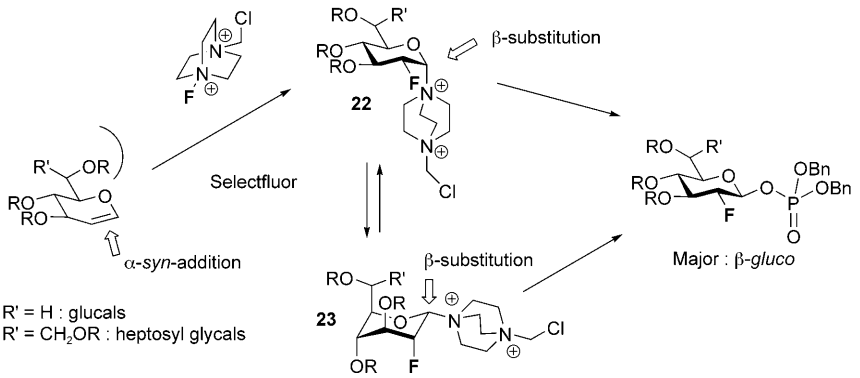
[a] Selectfluor and glycal were reacted first at room temperature; the phosphorylating reagent was then added after disappearance of the glycal and heated. [b] Temperature of the phosphorylation step. [c] Isolated yield. [d] Assessed by ^1H, ^{19}F and ^{31}P NMR spectroscopy a: α-*gluco* b: β-*gluco* c: α-*manno* d: β-*manno*. [e] Complex mixtures of non-separable products and side products. [f] 2,6-Di-*t*butylpyridine. [g] In presence of [15]crown-5.

data and the purification step. Given these unexpected difficulties we decided to modify and optimize the fluorophosphorylation experimental procedure.

When glycals bear an axial or a pseudo-axial group, the addition of selectfluor is highly diastereoselective: the mechanism of selectfluor attack upon the glycal in the first step occurs through a *syn*-addition, from the opposite face of the axial group, for steric reasons.[9,21] For glycals bearing only equatorial groups, mixtures of epimers at C-2 are always formed (*manno*-configured when the F is axial, *gluco*- when equatorial).[8,21,22] The diastereoselectivity also depends on the protective group pattern of the glycal: increasing the steric hindrance of the protective groups should influence the *gluco*/*manno* selectivity. This is the reason why we explored the fluorophosphorylation of heptosylglycals bearing pivaloyl (Piv, **12**) and *tert*-butyldimethylsilyl groups (TBS, **13**).

Heptosylglycals belong to the family of "all-equatorial" glycals for which the control of the *manno*/*gluco* and the α/β selectivities remains a problem. We reasoned that better yields and diastereoselectivities should be obtained if the reaction could be performed at lower temperature. The fluorophosphorylation of glycals requires a stepwise procedure in which the fluorination is first conducted at room temperature, the dialkylphosphate is then added and heated at 90°C (entry 4). To optimize a new procedure, we selected known D-glucals **16**–**18** bearing pivaloyl, *tert*-butyldimethylsilyl (TBS), and benzyl protective groups, respectively (Scheme 4). The results are summarized in Table 1. When the *per*-pivaloated D-glucal **16** was engaged in the reaction in the presence of 2,6-di-*tert*-butylpyridine (entry 5), the temperature could be lowered to 60°C resulting in a significant improvement of the β-*gluco* selectivity compared to standard conditions (entry 4), with comparable yields.

We anticipated that the temperature of the phosphorylation step could be further lowered if the nucleophilicity of the phosphate was increased. Therefore, we employed the sodium salt of dibenzyl phosphate in presence of [15]crown-5 ether (15C5) and decreased the temperature of the reaction. With this new procedure (entry 6), we could observe that, starting from the same glucal **16**, the yield and the stereoselectivity were both improved at 60°C. Lowering the temperature to 45°C (entry 7) yielded an optimized β-*gluco*/α-*manno* 9:1 selectivity. Surprisingly, when benzylated glucal **18**[23] was used under the same conditions (entry 8), the same global yield in fluorophosphates was obtained, but the four diastereomers were generated. These stereoisomers could not be separated, but their relative configurations could be assessed by ^1H and ^{19}F NMR analysis. On the other hand, silylated glucal **17** yielded the β-*gluco*-fluorophosphate **20b** as a single diastereomer in 66% isolated yield (entry 9). To our knowledge, this level of diastereoselectivity is the highest reported to date in the literature for "all-equatorial" glycals. In this last case, the starting glucal **17** was totally consumed. Inspection of ^{31}P and ^{19}F NMR spectra of the crude reaction mixture clearly indicated that the intermediate adduct between selectfluor and glycal **17** (such as **22** or **23**, Scheme 5) was still present when the reaction was stopped. From this methodological study, it can be concluded that using sterically demanding protective groups on all-equatorial glycals and performing the phosphorylation step at moderate temperatures give rise to good to excellent β-*gluco* selectivities. In all the cases (Table 1 entries 4–9), including the less selective ones (entries 4 and 8), the 1,2-*trans* products (β-*gluco* or α-*manno*) are always produced in significantly higher ratio than the 1,2-*cis* products (α-*gluco* and β-*manno*). As illustrated in Scheme 5, the β-stereoselectivity may be rationalized by invoking 1) a *syn*-addition of selectfluor from the α-face, as demonstrated by Wong et al.,[14] yielding intermediate adducts **22** (in a $^1C_4$ conformation) and/or **23** (in a $^4C_1$ conformation), and 2) a nucleophilic sub-

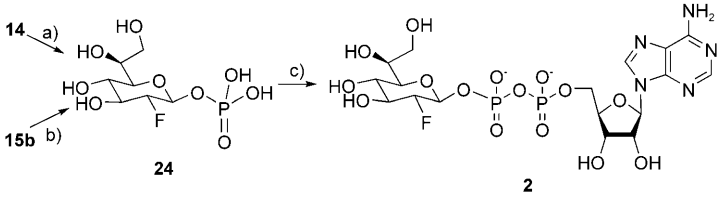


Scheme 5. Rationalization of the β-*gluco* stereoselectivity of the fluorophosphorylation.

stitution by the phosphate, implying an inversion of the anomeric configuration.

Given the high β-selectivity of this new procedure, we were confident that we could efficiently complete the synthesis of our target molecule **2**. After optimization of the reaction temperatures with starting heptosylglycals **12** and **13** (entries 10 and 11), we obtained results that nicely corroborate the glucal series. The pivaloylated and the silylated glycals gave an excellent β-*gluco* selectivity. The yields are moderate, but consistent with the literature data for this reaction.

Completion of the synthesis of 2: Although the most reasonable deprotection sequence consists of deprotecting the carbohydrate first and then the phosphate by hydrogenolysis,[7,24] a reverse sequence gave far better results (Scheme 6). After screening various nucleophiles (MeLi, $LiAlH_4$, diisobutylaluminum hydride (DIBAL), NaOH) for the deprotection of the four pivaloates of **14**, tetrabutylammonium hydroxide was found to be the only one that could achieve cleanly this deprotection. Surprisingly, the tetrabutyl ammonium fluoride (TBAF) deprotection of **15b** was troublesome, especially if performed before the hydrogenolysis. After optimization of the conditions, we could obtain the fully deprotected fluorophosphate **25** in pure form in quantitative and 55% yields from **14** and **15b**, respectively. Target molecule **2** was obtained in 56% yield by using the tetrazole-catalyzed morpholidate coupling procedure.[25]



Scheme 6. Reagents and conditions: a) H_2, Pd/C; TBAOH, H_2O, RT, quant; b) H_2, Pd/C; TBAF, THF, 55% for 2 steps; c) AMP-morpholidate, 1H-tetrazole, Py, RT (56%).

Analysis of the contacts between the fluorine atom and the protein: It should be noted that final molecule **2** is a *gluco*-heptoside, whereas the natural substrate of bacterial heptosyltransferase WaaC, molecule **1**, is a *manno*-heptoside. Nevertheless, due to the electron-withdrawing character of the fluorine atom, ADP-2F-heptose **2** displayed competitive inhibition against WaaC with an IC_{50} of 30 μmol.[12] Gratifyingly, the structure of WaaC in complex with **2** was obtained and allowed the analysis of the interactions between the transferase and its substrate. To our surprise, the equatorial fluorine of the pyranose contacts the side chain of His266 and the amide group of Gly263/Thr262 peptidic bond. The lengths and angles of the C–F bond and the neighboring protein residues are summarized in Table 2. We were first surprised by the short distance between the F atom and the carbonyl group of the peptidic backbone, which is significantly lower than the sum of the van der Waals radii of C and F atoms.

Table 2. Structural characteristics of the contacts between the fluorine atom of **2** and heptosyltransferase WaaC.

Distances	[Å]	Angles	[°]
F···N (His 266)	3.25		
F···O (Thr262)	3.40	C-F···C_{WaaC}	122.5
F···C=O (Thr262)	2.95	F···C=O	100.6
F···Cα-C=O (Thr262)	3.23	torsional angle C-F···C=O	126.4
F···H-Cα-C=O (Thr262)	2.67		

On the one hand, the implication of hydrogen bonds between organofluorines and proteins has been the subject of controversies.[26] In this structure, a hydrogen bond with the C-H of Thr262 cannot be reasonably invoked. On the other hand, unexpected attractive interactions between organofluorines and the carbon atom of carbonyl groups have been clearly evidenced in the recent literature.[27–29] This type of interaction was discovered by Diederich, Müller, and collaborators after analyzing the X-ray crystal structure of thrombin in complex with a fluorinated inhibitor, followed by a database mining of the Cambridge Structural Database. Moreover, their attractive character has been shown by NMR spectroscopy and measurement of free enthalpies.[28,30] As illustrated in Table 2, the contact observed between ADP-2-fluoro-heptose **2** and WaaC nicely corresponds to what has been evidenced as orthogonal multipolar interactions:[27] a short F···C=O distance, an orthogonal position of the fluorine atom above the pseudotrigonal axis of the carbonyl group and a C–F/C=O torsional angle between 100 and 140°.

Given these geometrical data, this C-F···C=O interaction is not fortuitous and contributes to the binding of inhibitor **2** into the catalytic pocket of WaaC. At this stage, it is difficult to discuss whether this interaction slightly modifies the positioning of the heptose moiety compared to the natural substrate **1**, since all attempts to cocrystallize **1** and WaaC failed.[12]

Conclusion

In a general perspective, this work contributes to the growing field of the synthesis of biologically relevant fluorinated molecules. A survey of the recent literature data highlights 1) the need for developing new efficient and stereoselective fluorination methodologies,[31] and 2) the very broad range of applications exploiting fluorinated molecules, going from drug design[29,32] to supramolecular chemistry. Fluorinated carbohydrates themselves have found many applications from mechanistic enzymology[7,10,33] to positron emission tomography (PET).[34] The work detailed in this study required both the development of a β-stereoselective fluorophosphorylation methodology and the synthesis of a challenging

NDP-sugar analogue of an important intermediate of the LPS biosynthesis. To the best of our knowledge, this molecule is the best inhibitor of heptosyl transferase reported to date[35] and its co-crystallization with the target bacterial enzyme will allow us to rationally design a new generation of inhibitors of the LPS biosynthetic pathway.

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere. Yields refer to chromatographically and spectroscopically homogeneous materials. Tetrahydrofuran, diethyl ether, and toluene were freshly dried over sodium benzophenone, dichloromethane over P_2O_5, and acetonitrile and nitromethane over CaH_2. Reagents were purchased at the highest commercial quality from Sigma-Aldrich or Acros, and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck aluminum roll silica gel 60-F_{254} using UV light and ethanoic phosphomolybdic acid or ethanoic sulfuric acid for visualization. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded with a Bruker AC-250 and AMX-400 spectrometer. All compounds were characterized by ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR as well as by ^{1}H–^{1}H correlation experiment. The following abbreviations were used to describe the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, brs = broad singlet. Merck silica gel (60, particle size 0.040–0.063 mm) was employed for flash column chromatography using cyclohexane-ethyl acetate as eluting solvents. Size-exclusion chromatography was performed with a Pharmacia Biotech Äkta FPLC apparatus on Sephadex G15 column (2.5 × 60 cm), and the fractions containing adenine derivatives were detected by UV light. Purifications of nucleotide sugars were realized by semipreparative HPLC using a Waters Delta prep 4000 chromatography system equipped with a NovaPack C18 column (eluent: triethylammonium acetate 50 mM, pH 6.8).

Methyl 2,3,4-tri-*O*-benzyl-D/L-*glycero*-α-D-*gluco*-heptopyranoside (5): OsO_4 (2.5 % in *t*BuOH, 1.82 mL) was added to a solution of olefin **4**[36] (2.18 g, 4.72 mmol) and NMO (1.27 g, 9.44 mmol) in acetone (25 mL) and water (3 mL). After 13 h at room temperature, the reaction mixture was poured into aq. $Na_2S_2O_3$ (5 %, 20 mL) and stirred for 30 min. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:1) to give diol **5** as a colorless syrup (2.15 g, 92 %, diastereomeric mixture D/L = 9:1). This molecule has been previously described in the literature.[16]

Methyl 6,7-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-*glycero*-α-D-*gluco*-heptopyranoside (6D) and methyl 6,7-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-*glycero*-α-D-*gluco*-heptopyranoside (6L)

Peracetylation procedure: Acetic anhydride (3 equiv) and a catalytic amount of DMAP was added to a solution of diol **5** (950 mg, 1.92 mmol) in anhydrous pyridine (9.0 mL). After stirring overnight at room temperature, the reaction mixture was poured into ice water and extracted with dichloromethane. The combined organic layers were washed with 1 N aq. HCl, satd aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to chromatography on a silica gel column (cyclohexane/ethyl acetate = 5:1) to afforded a mixture of diacetates **6D** and **6L** (ratio 9:1) as a colorless syrup (quantitative).

*From methyl 6,7-*anhydro-*2,3,4-tri-*O-*benzyl-*D/L-glycero-D-gluco-*heptopyranoside (7)*: A solution of epoxide **7** (1.24 g, 2.60 mmol), cesium acetate (2.49 g, 13.0 mmol), and [18]crown-6 (3.44 g, 13.0 mmol) in DMF (20 mL) was stirred vigorously at 100 °C for 3 h. The reaction mixture was poured into brine, and the organic layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved into pyridine (15 mL), and the mixture was added acetic anhydride (10 mL). After stirring at room temperature for 13 h, the reaction mixture was poured into ice water and extracted with dichloromethane. The combined organic layers were washed with 1 N aq. HCl, satd aq. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to chromatography on a silica gel column (cyclohexane/ethyl acetate = 5:1) to afford a mixture of diacetates **6D** and **6L** (ratio 3:7) as a colorless syrup (1,26 g, 84 %).

Data for ***6D***: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 15H; ArH), 5.51 (ddd, $J_{5,6}$ = 2.2 $J_{6,7a}$ = 3.1 $J_{6,7b}$ = 8.4 Hz, 1H; H-6), 4.68–5.08 (m, 6H; $ArCH_2$), 4.59 (d, $J_{1,2}$ = 3.6 Hz, 1H; H-1), 4.28 (dd, $J_{6,7a}$ = 3.1 $J_{7a,7b}$ = 12.1 Hz, 1H; H-7a), 4.15 (dd, $J_{6,7b}$ = 8.4 $J_{7a,7b}$ = 12.1 Hz, 1H; H-7b),4.03 (t, $J_{2,3}$ = $J_{3,4}$ = 9.4 Hz, 1H; H-3), 3.86 (dd, $J_{5,6}$ = 2.2 $J_{4,5}$ = 10.3 Hz, 1H; H-5), 3.53 (t, $J_{3,4}$ 9.4 Hz, $J_{4,5}$ 9.8 Hz, 1H; H-4), 3.51 (dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.4 Hz, 1H; H-2), 3.42 (s, 3H; OMe), 2.08 (s, 3H; Ac), 2.05 ppm (s, 3H; Ac); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 170.6, 169.9, 138.5, 138.0, 137.8, 128.4, 128.3, 128.2, 128.0 × 2, 127.9, 127.7, 127.6, 97.7, 82.1, 79.7, 77.7, 75.8, 74.7, 73.4, 70.5, 70.3, 62.5, 55.1, 20.9, 20.8 ppm; MS(DCI): *m*/*z*: 596 $[M+NH_4]^+$.

Data for ***6L***: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 15H; ArH), 5.51 (ddd, $J_{5,6}$ = 2.0 Hz $J_{6,7a}$ = 7.3 $J_{6,7b}$ = 6.3 Hz, 1H; H-6), 4.68–5.08 (m, 6H; $ArCH_2$), 4.70 (d, $J_{1,2}$ = 3.0 Hz, 1H; H-1), 4.31 (dd, $J_{6,7a}$ = 7.3 $J_{7a,7b}$ = 11.1 Hz, 1H; H-7a), 4.26 (dd, $J_{6,7b}$ = 6.3 $J_{7a,7b}$ = 11.1 Hz, 1H; H-7b), 4.08 (t, $J_{2,3}$ = $J_{3,4}$ = 9.7 Hz, 1H; H-3), 3.90 (dd, $J_{4,5}$ = 10.3 Hz $J_{5,6}$ = 2.0 Hz, 1H; H-5), 3.59 (dd, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.7 Hz, 1H; H-2), 3.46 (dd, $J_{3,4}$ = 10.0 Hz $J_{4,5}$ = 10.3 Hz, 1H; H-4), 3.39 (s, 3H; OMe), 2.16 (s, 3H; Ac), 2.08 ppm (s, 3H; Ac); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 170.4, 170.0, 138.3, 137.8, 137.5, 128.5, 128.48, 128.41, 128.37, 128.1, 128.0, 127.9, 127.8, 98.1, 82.1, 79.5, 76.7, 75.9, 75.3, 73.4, 68.4, 68.0, 62.1, 55.3, 20.9, 20.7 ppm; MS(DCI): *m*/*z*: 596 $[M+NH_4]^+$.

Methyl 6,7-anhydro-2,3,4-tri-*O*-benzyl-D/L-*glycero*-D-*gluco*-heptopyranoside (7): mCPBA (7.53 g, 30.6 mmol) was added to a solution of olefin **4** (4.69 g, 10.2 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was then stirred for 12 h at room temperature. After addition of potassium carbonate, the solution was poured into water and extracted by dichloromethane three times. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:1 then 1:1) to give epoxide **7** (7:3 diastereomeric mixture) as a colorless syrup (4.21 g, 8.8 mmol, 87 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.60–7.35 (m, 15H; ArH), 4.68–5.04 (m, $ArCH_{2\,L,D}$), 4.61 (d, $J_{1,2}$ = 3.6 Hz, 0.7H; H-1_L), 4.58 (d, $J_{1,2}$ = 3.6 Hz, 0.3H; H-1_D), 4.01–4.07 (m, H-$3_{L,D}$), 3.72 (dd, J = 4.0, 9.9 Hz, 0.3H; H-5_D), 3.45–3.58 (m, H-$2_{L,D}$, H-4_L, H-5_L), 3.47 (dd, $J_{4,5}$ = 8.9 Hz $J_{4,3}$ = 9.6 Hz, 0.3H; H-4_D), 3.40 (s, 3H; OMe_L), 3.39 (s, 3H; OMe_D), 3.16 (m, H-$6_{L,D}$), 2.81 and 2.87 (ABX, $J_{6,7a}$ = 2.8 Hz, $J_{6,7b}$ = 4.3 Hz Hz, $J_{7a,7b}$ = 5.4 Hz, 1.4H; H-7_L), 2.67–2.75 ppm (ABX, $J_{6,7a}$ = 2.7 Hz, $J_{6,7b}$ = 4.0 Hz $J_{7a,7b}$ = 5.4 Hz, 0.3H; H-7_D); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 138.7, 138.1, 138.0, 137.8, 133.4, 130.1, 130.0, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 98.1 (L), 97.8 (D), 81.9 (L), 81.8 (D), 80.3 (D), 79.9 (D), 79.7 (L), 79.5 (L), 75.9 (L), 75.5 (D), 75.0 (D), 73.5 (L), 70.3 (L), 68.7 (D), 55.5 (L), 55.3 (D), 52.1 (D), 51.6 (L), 44.5 (L), 43.9 ppm (D); MS (DCI-NH_3): *m*/*z*: 494 $[M+NH_4]^+$; HRMS calcd for $C_{29}H_{36}O_6N$ $[M+NH_4]^+$: 494.2543; found: 494.2549.

Methyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-7-*O*-*tert*-butyldimethylsilyl-L-*glycero*-α-D-*gluco*-heptopyranoside (9L): TBDMSCl (94 mg, 0.607 mmol) was gradually added to a solution of diol **5** (200 mg, 0.404 mmol), DMAP (4.9 mg, 0.040 mmol), and triethylamine (165 μL, 1.21 mmol) in pyridine (35 mL) at 0 °C. After stirring 13 h at room temperature, the reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ and the aqueous phase was extracted by dichloromethane. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 5:1) to furnish intermediate silyl ether **8**[37] as a colorless syrup (224 mg, 91 %). Trifluoromethanesulfonic anhydride (188 μL, 1.15 mmol) was added dropwise to a solution of silyl ether **8** (234 mg, 0.384 mmol) in pyridine (10 mL) at −40 °C, then the reaction mixture was allowed to warm to 0 °C and stirred for 1 h. After concentration in vacuo, the residue was subjected to chromatography on silica gel (cyclohexane/ethyl acetate

5:1), and all the fractions were successively concentrated and dried in vacuo. The resulting triflate was dissolved into anhydrous toluene (10 mL), and cesium acetate (223 mg, 1.16 mmol) and 18-crown-6 (305 mg, 1.16 mmol) were added. The reaction mixture was sonicated for 6 h at room temperature, and diluted into ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 8:1) to give acetate **9L** as a colorless syrup (160 mg, 64%): $[\alpha]_{23}^{D}=-4.0$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.40$ (m, 15H; ArH), 5.43 (t, $J_{5,6}=J_{6,7}=7.1$ Hz, 1H; H-6), 4.71–5.09 (m, 5H; $ArCH_2$), 4.74 (d, $J_{1,2}=3.6$ Hz, 1H; H-1), 4.54 (d, $J=10$ Hz, 1H; CH_2-Ar), 4.11 (t, $J_{2,3}=J_{3,4}=9.2$ Hz, 1H; H-3), 4.04 (br d, $J_{4,5}=10.1$ Hz, 1H; H-5), 3.80 (m, 2H; H-7), 3.62 (dd, $J_{1,2}=3.5$ Hz, $J_{2,3}=9.7$ Hz, 1H; H-2), 3.49 (dd, $J_{3,4}=9.6$ Hz, $J_{4,5}=10$ Hz, 1H; H-4), 3.46 (s, 3H; OMe), 2.15 (s, 3H; Ac), 0.94 (s, 9H; Si*t*Bu), 0.11 and 0.13 ppm (s×2, 6H; SiMe); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=170.0$, 138.5, 138.0, 137.8, 128.4, 128.3, 128.2, 128.0×2, 127.9, 127.7, 127.6, 97.9, 82.3, 79.6, 76.9, 75.8, 75.1, 73.1, 70.7, 67.2, 60.0, 55.1, 25.7, 20.9, 18.0, −5.4, −5.6 ppm; MS(DCI): *m/z*: 668 $[M+NH_4]^+$; HRMS calcd for $C_{37}H_{54}O_8NSi$ $[M+NH_4]^+$: 668.3619; found: 668.3628.

1,2,3,4,6,7-Hexa-*O*-acetyl-L-*glycero*-D-*gluco*-heptopyranose (10): Conc. H_2SO_4 (2.93 mL) was added dropwise to a solution of silyl ether **9L** (3.91 g, 5.99 mmol) and acetic anhydride (7.53 mL) in chloroform (4.89 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After addition of potassium carbonate, the solution was poured into water and extracted by dichloromethane three times. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:1 then 1:1) to give acetate **10** as a colorless syrup (2.27 g, 82%, α/β=88:12): ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=$ 6.34 (d, $J_{1,2}=3.8$ Hz, 1H; H-1α), 5.66 (d, $J_{1,2}=8.3$ Hz, 0.14H; H-1β), 5.46 (d, $J_{2,3}=J_{3,4}=10.0$ Hz, 1H; H-3α), 5.25 (ddd, $J_{5,6}=2.1$ Hz, $J_{6,7}=5.2$, 7.2 Hz, 1H; H-6α), 5.12 (dd, $J_{1,2}=3.6$ Hz, $J_{2,3}=9.1$ Hz, 1H; H-2α), 5.10 (t, $J_{3,4}=J_{4,5}=9.8$ Hz, 1H; H-4α), 4.27 (dd, $J_{6,7}=5.0$ Hz, $J_{gem}=11.7$ Hz, 1H; H-7α), 4.19 (dd, $J_{4,5}=10.2$ Hz, $J_{5,6}=2.1$ Hz, 1H; H-5α), 4.15 (dd, $J_{6,7}=7.6$ Hz, $J_{gem}=11.7$ Hz, 1H; H-7α), 2.02–2.19 ppm (m, 20H; $COCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=170.4$, 170.2, 170.1, 169.6, 169.3, 168.5, 92.0 (C-1β), 88.7 (C-1α), 70.0, 69.9, 69.0, 66.9, 66.5, 62.1, 20.7, 20.6×3, 20.4, 20.3 ppm; MS(DCI): *m/z*: 480 $[M+NH_4]^+$; HRMS calcd for $C_{19}H_{30}O_{13}N$ $[M+NH_4]^+$: 480.1717; found: 480.1711.

1,5-Anhydro-2-deoxy-3,4,6,7-tetra-*O*-acetyl-L-*galacto*-hept-1-enitol (11): HBr-AcOH (9.68 mL, 56.3 mmol) was added to a solution of heptose **10** (2.17 g, 4.69 mmol), acetic anhydride (1.32 mL), and acetic acid (1.12 mL) in dichloromethane (4 mL), and the reaction mixture was stirred for 12 h at room temperature. The reaction was quenched by addition of sodium acetate (4.61 g, 56.3 mmol). The suspension was transferred into a suspension of $CuSO_4$ (186 mg, 1.17 mmol), zinc powder (11.7 g, 178 mmol), and sodium acetate (8.78 g, 113 mmol) in water (9.2 mL) and acetic acid (13.8 mL). The mixture was vigorously stirred for 4 h at room temperature then filtered through a pad of Celite, which was washed with ethyl acetate and water. The organic layer of the filtrate was washed with saturated aqueous solution of $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate 3:1) to furnish glycal **11** as a colorless syrup (1.47 g, 91%): $[\alpha]_{23}^{D}=-13.8$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=6.44$ (dd, $J_{1,2}=6.2$ Hz, $J_{1,3}=1.6$ Hz, 1H; H-1), 5.48 (ddd, $J_{1,3}=1.8$ Hz, $J_{2,3}=2.4$ Hz, $J_{3,4}=7.2$ Hz, 1H; H-3), 5.38 (m, 1H; H-6), 5.25 (dd, $J_{3,4}=7.3$ Hz, $J_{4,5}=9.9$ Hz, 1H; H-4), 4.79 (dd, $J_{1,2}=6.2$ Hz, $J_{2,3}=2.4$ Hz, 1H; H-2), 4.35 (dd, $J_{6,7}=4.8$ Hz, $J_{gem}=11.7$ Hz, 1H; H-7a), 4.19 (m, 2H; H-5, H-7b), 2.03–2.09 ppm (4s, 12H; $COCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=170.6$, 170.4, 170.2, 169.6, 145.5, 100.0, 74.6, 69.4, 66.6, 66.1, 62.3, 20.9, 20.6 ppm; MS(DCI): *m/z*: 362 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{15}H_{20}O_9$: C 52.32, H 5.85; found: C 52.32, H 5.84.

1,5-Anhydro-2-deoxy-3,4,6,7-tetra-*O*-pivaloyl-L-*galacto*-hept-1-enitol (12): Sodium (10 mg) was added to a suspension of acetate **11** (488 mg, 1.42 mmol) in MeOH (5 mL), and the reaction mixture was stirred for 2 h. The solution was concentrated in vacuo, and the residue was dissolved in pyridine (20 mL). Pivaloyl chloride (2.10 mL, 17.0 mmol) was added dropwise to this solution at 0°C, and the mixture was allowed to warm to room temperature. After 12 h at room temperature under argon, cold saturated aq. $NaHCO_3$ was added, and the mixture was extracted twice with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/ethyl acetate 10:1) to afford pivaloate **12** as a white powder (598 mg, 82%): $[\alpha]_{23}^{D}=-17.6$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=6.46$ (d, $J_{1,2}=6.0$ Hz, $J_{1,3}=1.4$ Hz, 1H; H-1), 5.44 (ddd, $J_{1,3}=1.6$ Hz, $J_{2,3}=2.3$ Hz, $J_{3,4}=7.0$ Hz, 1H; H-3), 5.40 (ddd, $J_{5,6}=2.9$ Hz, $J_{6,7}=4.3$, 7.4 Hz, 1H; H-6), 5.28 (dd, $J_{3,4}=7.0$ Hz, $J_{4,5}=9.5$ Hz, 1H; H-4), 4.79 (dd, $J_{1,2}=6.0$ Hz, $J_{2,3}=2.5$ Hz, 1H; H-2), 4.38 (dd, $J_{6,7}=4.4$ Hz, $J_{gem}=11.7$ Hz, 1H; H-7), 4.23 (dd, $J_{4,5}=9.6$ Hz, $J_{5,6}=2.9$ Hz, 1H;H-5), 4.20 (dd, $J_{6,7}=7.4$ Hz, $J_{gem}=$ 11.6 Hz, 1H; H-7), 1.26, 1.20, 1.19 and 1.18 ppm (4s, 36H; *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=178.0$, 177.9, 177.0, 176.2, 145.5, 99.9, 75.2, 69.2, 66.2, 65.5, 62.9, 38.7×2, 27.1, 27.0×2, 26.9 ppm; MS(DCI): *m/z*: 530 $[M+NH_4]^+$; HRMS calcd for $C_{27}H_{48}O_9N$ $[M+NH_4]^+$: 530.3329; found: 530.3336; elemental analysis calcd (%) for $C_{27}H_{44}O_9$: C 63.26, H 8.65; found: C 63.13, H 8.81.

1,5-Anhydro-2-deoxy-3,4,6,7-tetra-*O*-*tert*-butyldimethylsilyl-L-*galacto*-hept-1-enitol (13): Sodium (10 mg) was added to a suspension of acetate **11** (894 mg, 2.6 mmol) in MeOH (5 mL), and the reaction mixture was stirred for 2 h. The solution was concentrated in vacuo, and the residue was dissolved in anhydrous *N*,*N*-dimethylformamide (20 mL). imidazole (2.83 g, 41.6 mmol) then TBDMSCl (4.70 g, 31.1 mmol) was added to this suspension at 0°C. After stirring 12 h at room temperature, the solution was poured into brine and the aqueous phase was extracted by ethyl acetate three times. The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ then brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by silica gel chromatography (cyclohexane/ethyl acetate 3:1 then 1:1) gave glycal **13** as a white powder (1.56 g, 2,47 mmol, 95%). $[\alpha]_{23}^{D}=-21.1$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=6.37$ (d, $J_{1,2}=6.4$ Hz, 1H; H-1), 4.75 (ddd, $J_{1,2}=6.4$ Hz, $J=1.6$, 5.0 Hz, 1H; H-2), 4.22 (m, 2H; H-5 and H-6), 4.03 (dd, $J=1.8$, 4.0 Hz, 1H; H-4), 3.71 and 3.96 (2dd, $J_{6,7b}=$ 2.0 Hz, $J_{6,7a}=2.1$ Hz, $J_{gem}=8.6$ Hz, 2H; H-7), 3.87 (m, 1H; H-3), 0.94 (s, 18H; Si*t*Bu), 0.91 (s, 9H; Si*t*Bu), 0.90 (s, 9H; Si*t*Bu), 0.06–0.14 ppm (7s, 24H; SiMe); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=143.4$, 100.5, 79.4, 69.4, 69.3, 66.4, 65.9, 26.9, 26.2, 26.0, 25.8, 25.78, 18.6, 18.2, 18.0, 17.9, −4.3, −4.4×3, −4.6×2, −5.1, −5.5 ppm; MS(DCI): *m/z*: 650 $[M+NH_4]^+$; HRMS calcd for $C_{31}H_{68}O_5Si_4Na$ $[M+Na]^+$: 655.4041; found: 655.4057; elemental analysis calcd (%) for $C_{31}H_{68}O_5Si_4$: C 58.80, H 10.82; found: C 58.77, H 10.97.

2-Deoxy-1-*O*-dibenzylphosphoryl-2-fluoro-3,4,6,7-tetra-*O*-pivaloyl-L-*glycero*-β-D-*gluco*-heptopyranose (14): A mixture of pivaloate **12** (543 mg, 1.06 mmol) and MS 4 Å (200 mg) in anhydrous nitromethane (15 mL) was stirred for 2 h at room temperature under argon atmosphere. Selectfluor-$(TfO)_2$ (761 mg, 1.59 mmol) was added very quickly at 0°C, and the reaction mixture was allowed to warm to room temperature. After 12 h of stirring, sodium dibenzylphosphate (955 mg, 3.18 mmol) and [15]crown-5 (700 mg, 3.18 mmol) was added with flowing argon gas, and the mixture was heated to 60°C and stirred for 16 h. The suspension was filtered through a pad of Celite, and the pad was washed with dichloromethane. The filtrate was concentrated in vacuo, and the residue was subjected to chromatography on silica gel (hexane/ethyl acetate 5:1) to give fluorophosphate **14** (497 mg, 58%) as a colorless syrup. $[\alpha]_{23}^{D}=-1.7$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.38$ (m, 10H; ArH), 5.43 (ddd, $J_{1,2}=7.7$ Hz, $J_{1,F}=2.8$ Hz, 1H; H-1), 5.38 (dt, $J_{2,3}=J_{3,4}=$ 9.3 Hz, $J_{3,F}=13.3$ Hz, 1H; H-3), 5.26 (ddd, $J_{5,6}=1.9$ Hz, $J_{6,7}=4.6$, 8.0 Hz, 1H; H-6), 5.06–5.18 (m, 4H; $ArCH_2$), 5.11 (t, $J_{3,4}=J_{4,5}=9.8$ Hz, 1H; H-4), 4.45 (ddd, $J_{1,2}=7.8$ Hz, $J_{2,3}=9.0$ Hz, $J_{2,F}=50.6$ Hz, 1H; H-2), 4.28 (dd, $J_{6,7}=4.7$ Hz, $J_{gem}=11.7$ Hz, 1H; H-7), 4.04 (dd, $J_{6,7}=8.1$ Hz, $J_{gem}=$ 11.6 Hz, 2H; H-7), 3.91 (dd, $J_{4,5}=10.1$ Hz, $J_{5,6}=2.0$ Hz, 1H; H-5), 1.18–1.25 ppm (4s, 12H; *t*Bu); ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): $\delta=177.7$, 177.0, 176.7, 176.0, 135.2 (d), 135.1 (d), 128.6×2, 128.0, 127.9, 96.2 (dd, $J_{1,F}=4.9$ Hz, $J_{1,P}=24.3$ Hz), 89.6 (dd, $J_{2,F}=193$ Hz, $J_{1,P}=9.0$ Hz), 73.6, 72.0 (d, $J_{3,F}=19$ Hz),, 69.7? (d), 69.6(d), 65.8, 65.6 (d, $J_{4,F}=7$ Hz), 62.7,

38.8, 38.74, 38.65, 38.6, 30.1, 27.1, 26.95, 26.92, 26.85 ppm; ^{19}F NMR (235 MHz, D_2O, 25 °C): $\delta = -199.2$ ppm (dd, $J_{2,F} = 51.7$ Hz, $J_{3,F} = 14.1$ Hz); ^{31}P NMR (101 MHz, D_2O, 25 °C): $\delta = -2.93$ ppm (s); MS(DCI): *m/z*: 826 $[M+NH_4]^+$; HRMS calcd for $C_{41}H_{59}O_{13}FP$ $[M+H]^+$: 809.3677; found: 809.3682.

2-Deoxy-1-*O*-dibenzylphosphoryl-2-fluoro-3,4,6,7-tetra-*O*-*tert*-butyldimethylsilyl-L-*glycero*-β-D-*gluco*-heptopyranose (15b) and 2-deoxy-1-*O*-dibenzylphosphoryl-2-fluoro-3,4,6,7-tetra-*O*-*tert*-butyldimethylsilyl-L-*glycero*-α-D-*gluco*-heptopyranose (15a): The procedure described for the preparation of **14** was applied to glycal **13** (342 mg, 0.540 mmol). The final residue was subjected to chromatography on silica gel (toluene then cyclohexane/ethyl acetate 10:1) to give fluorophosphates **15b** (256 mg, 51 %) and **15a** (15 mg, 3 %) as colorless syrups.

Data for ***15b***: $[\alpha]_{23}^{D} = +2.6$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.37$ (m, 10H; ArH), 5.41 (td, $J_{1,2} = J_{1,P} = 7.7$ Hz, $J_{1,F} = 3.2$ Hz, 1H; H-1), 5.01–5.17 (m, 4H; $ArCH_2$), 4.21 (td, $J_{1,2} = J_{2,3} = 7.7$ Hz, $J_{2,F} = 50.7$ Hz, 1H; H-2), 4.06 (ddd, $J_{5,6} = 1.6$ Hz, $J_{6,7} = 5.5$, 7.4 Hz, 1H; H-6), 3.95 (td, $J_{2,3} = 7.7$ Hz, $J_{3,4} = 8.0$ Hz, $J_{3,F} = 16.0$ Hz, 1H; H-3), 3.89 (t, $J_{3,4} = J_{4,5} = 8.0$ Hz, 1H; H-4), 3.72 (dd, $J_{6,7} = 7.7$ Hz, $J_{gem} = 9.7$ Hz, 1H; H-7), 3.59 (m, 2H; H-5, H-7), 0.96 (s, 9H; Si*t*Bu), 0.92 (s, 9H; Si*t*Bu), 0.91 (s, 9H; Si*t*Bu), 0.90 (s, 9H; Si*t*Bu), 0.04–0.19 ppm (7s, 24H; SiMe); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 135.6$, 135.5, 128.5, 128.4×2, 127.9, 127.8, 96.4? (dd, $J_{1,F} = 4.8$ Hz, $J_{1,P} = 26.2$ Hz), 92.5 (dd, $J_{2,F} = 189$ Hz, $J_{1,P} = 8$ Hz), 77.1 (d, $J_{3,F} = 17$ Hz), 76.7, 72.0 (d, $J_{4,F} = 7$ Hz), 71.3, 69.4 (d), 69.3(d), 26.2, 26.0, 25.91, 25.89, 18.6, 18.3, 18.27, 18.1, −2.5, −3.2, −3.3, −3.35, −3.4, −3.5, −3.7, −4.0 ppm; ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C): $\delta = 191.5$ ppm (dd, $J_{2,F} = 50.0$ Hz, $J_{3,F} = 14.0$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = -2.79$ ppm (s); MS(DCI): *m/z*: 946 $[M+NH_4]^+$; HRMS calcd for $C_{45}H_{86}O_9NFSi_4P$ $[M+NH_4]^+$: 946.5101; found: 946.5095.

Data for ***15a***: $[\alpha]_{22}^{D} = +16.2$ ($c = 0.43$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.37$ (m, 10H; ArH), 5.94 (dd, $J_{1,2} = 2.7$ Hz, $J_{1,P} = 7.0$ Hz, 1H; H-1), 5.04–5.17 (m, 4H; $ArCH_2$), 4.25 (dddd, $J_{1,2} = 2.4$ Hz, $J_{2,3} = 9.1$ Hz, $J_{2,F} = 47.8$ Hz, $J_{2,P} = 3.3$ Hz, 1H; H-2), 4.18 (m, 1H; H-3), 4.09 (t, $J_{6,7} = 6.5$ Hz, 1H; H-6), 3.86 (s, 1H; H-5), 3.82 (t, $J_{3,4} = J_{4,5} = 10.0$ Hz, 1H; H-4), 3.61 (d, $J_{6,7} = 6.5$ Hz, 2H; H-7), 0.90–0.96 (4s, 36H; Si*t*Bu), 0.04–0.19 ppm (7s, 24H; SiMe). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = 135.6$, 128.5, 128.4×2, 127.9, 127.8, 94.8 (dd, $J_{1,F} = 5.2$ Hz, $J_{1,P} = 24.2$ Hz), 89.5 (dd, $J_{2,F} = 191$ Hz, $J_{1,P} = 6.7$ Hz), 73.7, 73.6 (d, $J_{3,F} = 17$ Hz), 71.7, 71.5 (d, $J_{4,F} = 7$ Hz), 69.3, 69.2, 64.31, 26.3, 26.2, 26.0, 25.9, 18.6, 18.5, 18.3, 18.2, −2.5, −2.7, −2.8, −3.3, −3.4, −3.8, −5.4, −5.5 ppm; ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C): $\delta = -193.9$ ppm (dd, $J_{2,F} = 44.7$ Hz, $J_{3,F} = 14.0$ Hz); ^{31}P NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = -2.64$ ppm (s). MS-(DCI): *m/z*: 946 $[M+NH_4]^+$; HRMS calcd for $C_{45}H_{83}O_9FSi_4P$ $[M+H]^+$: 929.4836; found: 929.4844.

Dibenzyl(2-deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-β-D-*gluco*-pyranosyl)phosphate (19b) and dibenzyl(2-deoxy-2-fluoro-3,4,6-tri-*O*-pivaloyl-α-D-*manno*-pyranosyl)phosphate (19c): A solution of *tri*-pivaloyl-D-glucal **16**[14] (1 g, 2.50 mmol) in nitromethane (35 mL) was stirred with 4 Å molecular sieves (2 g) under argon during 15 minutes. Selectfluor (1.8 g, 3.70 mmol) was added at 0 °C and the reaction mixture was stirred for 20 h at ambient temperature. [15]Crown-5 (1.5 mL, 7.50 mmol) and dibenzylphosphate (sodium salt, 2.25 g, 7.50 mmol) were then added and the resulting solution was warmed to 45 °C for 36 h. The mixture was diluted with EtOAc (200 mL), filtered, and concentrated under low pressure. The residue was finally purified by flash chromatography (hexane/EtOAc, 3:1, 3:2) to yield **19b** (990 mg, 57 %) and **19c** (110 mg, 6 %) as white solids.

Data for ***19b***: White solid, m.p. 176 °C; $[\alpha]_{20}^{D} = +23°$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.42$–7.30 (m, 10H; C_6H_5), 5.48 (td, $J_{1,2} = J_{1,P} = 7.6$ Hz, $J_{1,F} = 3.0$ Hz, 1H; H-1), 5.43 (ddd, $J_{3,F} = 13.7$ Hz, $J_{3,4} = 9.4$ Hz, $J_{2,3} = 9.1$ Hz, 1H; H-3), 5.20–5.08 (m, 5H; OCH_2Ph, H-4), 4.47 (ddd, $J_{2,F} = 50.8$ Hz, $J_{1,2} = 7.6$ Hz, $J_{2,3} = 9.1$ Hz, 1H; H-2), 4.25 (dd, $J_{5,6a} = 2.0$ Hz, $J_{6a,6b} = 13.0$ Hz, 1H; H-6a), 4.11 (dd, $J_{5,6b} = 5.0$ Hz, 1H; H-6b), 3.90 (ddd, $J_{4,5} = 10.0$ Hz, $J_{5,6a} = 2.0$ Hz, $J_{5,6b} = 5.0$ Hz, 1H; H-5), 1.22 (s, 9H; CH_3), 1.21 (s, 9H; CH_3), 1.20 ppm (s, 9H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 177.8$, 177.0, 176.4 (*C*O), 135.3, 135.2 (C_{ipso}), 128.6–127.5 (m, C_6H_5), 95.9 (dd, $J_{P1} = 23.7$ Hz, $J_{F,1} = 4.8$ Hz, C-1), 89.7 (dd, $J_{F,2} = 191$ Hz, $J_{P,2} = 9.0$ Hz, C-2), 73.2 (C-5) ; 71.8 (d, $J_{F,3} = 19.4$ Hz, C-3), 69.62 (d, $J = 5.7$ Hz, CH_2Ph), 69.54 (d, $J = 5.5$ Hz, CH_2Ph), 66.6 (d, $J_{F,4} = 7.4$ Hz, C-4), 61.17 (C-6), 38.80, 38.76 ($C(CH_3)_3$), 27.02, 26.98 ppm ($C(CH_3)_3$); ^{31}P NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = -2.83$ ppm (d, $J_{P,1} = 7.6$ Hz); ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C); $\delta = -201.20$ ppm (ddd, $J_{F,2} = 50.8$ Hz, $J_{F,3} = 13.7$ Hz, $J_{F,1} = 3.0$ Hz); MS-CI: *m/z* (%): 712 (100) $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{35}H_{48}FO_{11}P$ (%): C 60.51, H 6.96; found: C 60.37, H 7.14.

Data for ***19c***: White solid, m.p. 78 °C; $[\alpha]_{20}^{D} = +78°$ (c = 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.42$–7.30 (m, 10H; C_6H_5), 5.76 (td, $J_{1,2} = 1.9$ Hz, $J_{1,P} = J_{1,F} = 5.2$ Hz, 1H; H-1), 5.50 (dd, $J_{3,4} = 10.1$ Hz, $J_{4,5} = 10.1$ Hz, 1H; H-4), 5.16 (ddd, $J_{3,4} = 10.3$ Hz, $J_{3,F} = 28.5$ Hz, $J_{2,3} = 2.5$ Hz, 1H; H-3), 5.15–5.08 (m, 4H; OCH_2Ph), 4.54 (ddd, $J_{2,3} = J_{1,2} = 2.2$ Hz, $J_{2,F} = 49.0$ Hz, 1H; H-2), 4.08–3.96 (m, 3H; H5, H-6), 1.23 (s, 9H; CH_3), 1.22 (s, 9H; CH_3), 1.18 ppm (s, 9H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 177.9$, 177.4, 176.1 (*C*O), 135.2, 135.17 (C_{ipso}), 128.84–127.94 (m, C_6H_5), 94.50 (dd, $J_{P,1} = 31.7$ Hz, $J_{F,1} = 5.4$ Hz, C-1), 86.00 (dd, $J_{F,2} = 180.4$ Hz, $J_{P,2} = 9.0$ Hz, C-2), 70.60 (C-5), 70.1, (d, $J = 5.5$ Hz, CH_2Ph), 69.9 (d, $J = 5.6$ Hz, CH_2Ph), 68.8 (d, $J_{F,3} = 16.5$ Hz, C-3), 63.77 (C-4), 60.74 (C-6), 38.8, 38.7, 27.0, 26.9 ppm; ^{31}P NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = -2.99$ ppm (d, $J_{P,1} = 5.2$ Hz); ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C); $\delta = -204.90$ ppm (ddd, $J_{F,2} = 49.0$ Hz, $J_{F,3} = 28.5$ Hz, $J_{F,1} = 4.3$ Hz); MS-CI: *m/z* (%): 712 (100) $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{35}H_{48}FO_{11}P$: C 60.51, H 6.96; found: C 60.41, H 7.11.

Dibenzyl(2-deoxy-2-fluoro-3,4,6-tri-*O*-*tert*-butyldimethylsilyl-β-D-*gluco*-pyranosyl)phosphate (20b): Compound **17**[38] (600 mg, 1.23 mmol) was solubilized in nitromethane (24 mL) and stirred with 4 Å molecular sieves (1 g) under argon for 15 min. Selectfluor (500 mg, 1.04 mmol) was added at 0 °C and the reaction mixture was stirred for 4 h at ambient temperature. [15]Crown-5 (736 μL, 3.68 mmol) and dibenzylphosphate (sodium salt, 1.0 g, 3.33 mmol) were then added and warmed to 45 °C for 48 h. The mixture was diluted with EtOAc (100 mL), filtered, and concentrated under low pressure. The residue was finally purified by flash chromatography (hexane/EtOAc, 5.5:1) to yield **20b** (607 mg, 66 %) as a white syrup. $[\alpha]_{20}^{D} = 1.4°$ ($c = 0.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.42$–7.27 (m, 10H; C_6H_5), 5.50 (td, $J_{1,2} = J_{1,P}$ 7.3 Hz, $J_{1,F} = 4.0$ Hz, 1H; H-1), 5.17–5.05 (m, 4H; OCH_2Ph), 4.20 (ddd, $J_{2,F} = 49.7$ Hz, $J_{2,3} = 7.1$ Hz, 1H; H-2), 3.90 (ddd, $J_{3,F} = 16.0$ Hz, $J_{2,3} = J_{3,4} = 7.1$ Hz, 1H; H-3), 3.88 (dd, $J_{5,6a} = 4.0$ Hz, $J_{6a,6b} = 11.1$ Hz, 1H; H-6a), 3.78 (dd, $J_{5,6b} = 4.8$ Hz, 1H; H-6b), 3.73 (dd, $J_{3,4} = J_{4,5} = 7.1$ Hz, 1H; H-4), 3.51 (ddd, $J = 4.0$ Hz, $J = 4.8$ Hz, $J = 7.1$ Hz, 1H; H-5), 0.98 (s, 9H; *t*Bu), 0.94 (s, 9H; *t*Bu), 0.90 (s, 9H; *t*Bu), 0.19–0.04 ppm (6s, 18H; CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 135.66$, 135.58 (C_{ipso}), 128.44–127.88 (m, C_6H_5), 95.90 (dd, $J_{P,1} = 27.6$ Hz, $J_{F,1} = 4.7$ Hz, C-1), 92.8 (dd, $J_{F,2} = 187.1$ Hz, $J_{P,2} = 8.3$ Hz, C-2), 79.13 (C-5), 76.34 (d, $J_{F,3} = 18.3$ Hz, C-3), 70.38 (d, $J_{F,4} = 5.5$ Hz, C-4), 69.36 (d, $J = 5.6$ Hz, CH_2Ph), 69.27 (d, $J = 5.5$ Hz, CH_2Ph), 62.03 (C6), 18.53, 18.28, 17.97, 18.53, 18.28, 17.97, −3.11, −3.14, −3.39, −3.97, −4.03, −4.43, −5.18, −5.40 ppm; ^{31}P NMR (101 MHz, $CDCl_3$, 25 °C): $\delta = -2.64$ ppm (d, $J_{P,1}$ 7.3 Hz); ^{19}F NMR (235 MHz, $CDCl_3$, 25 °C): $\delta = -190.39$ ppm (ddd, $J_{F,2} = 49.7$ Hz, $J_{F,3} = 16.0$ Hz, $J_{F,1} = 4.0$ Hz); elemental analysis calcd (%) for $C_{38}H_{66}FO_8PSi_3$: C 58.13, H 8.47; found C 57.64, H 9.06.

2-Deoxy-1-*O*-phosphoryl-2-fluoro-L-*glycero*-β-D-*gluco*-heptopyranose (24): Triethylamine (42 μL, 0.309 mmol) was added to a suspension of fluorophosphate **14** (125 mg, 0.155 mmol) and Pd/C (10 %, 62 mg) in ethyl acetate (1 mL) and ethanol (2 mL). The mixture was hydrogenated under H_2 atmosphere (1 bar) for 12 h, and filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford a triethylammonium salt, which was dissolved in water (1 mL). Tetrabutylammonium hydroxide (40 % in H_2O, 1.34 mL, 2.07 mmol) was added to this solution, and the mixture was stirred at room temperature for 26 h. After neutralization by IR-120 A (H^+) resin, the solution was filtered and concentrated in vacuo. The residue was dissolved in ethanol (4 mL), and tributylamine (74 μL, 0.310 mmol) was added. Concentration of the mixture in vacuo afforded a monophosphate **24** (112 mg, quantitative yield) as a syrup.

Alternatively, compound **24** was prepared from **15b**: Triethylamine (43 μL, 0.312 mmol) was added to a suspension of fluorophosphate **15b** (145 mg, 0.156 mmol) and Pd/C (10 %, 20 mg) in ethyl acetate (1 mL) and ethanol (2 mL). The mixture was hydrogenated under H_2 atmosphere

for 12 h, and filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford a triethylammonium salt that was dissolved in tetrahydrofuran (5 mL). Tetrabutylammonium fluoride (236 mg, 0.90 mmol) was added to this solution, and the mixture was stirred at room temperature for 3 h. After neutralization by IR-120 A (H^+) resin, the solution was filtered and concentrated in vacuo. The residue was dissolved in ethanol (4 mL), and tributylamine (74 μL, 0.312 mmol) was added. Concentration of the mixture in vacuo afforded a monophosphate **24** (57 mg, 55%) as a bis(tributylammonium) salt. $[\alpha]_{23}^{D} = -1.7°$ ($c = 0.5$ in H_2O); ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 5.14$ (td, $J_{1,2} = J_{1,P} = 7.7$ Hz, $J_{1,F} = 2.6$ Hz, 1H; H-1), 4.18 (ddd, $J_{1,2} = 7.7$ Hz $J_{2,3} = 8.0$ Hz, $J_{2,F} = 51.0$ Hz, 1H; H-2), 3.98 (td, $J_{6,7a} = J_{6,7b} = 6.8$ Hz, $J_{5,6} = 1.5$ Hz, 1H; H-6), 3.85 (td, $J_{2,3}$ 8.0 Hz, $J_{3,4}$ 9.2 Hz, $J_{3,F} = 24.9$ Hz, 1H; H-3), 3.72 (m, 2H; H-7), 3.66 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, 1H; H-4), 3.53 ppm (dd, $J_{4,5} = 9.5$ Hz, $J_{5,6} = 1.5$ Hz, 1H; H-5); ^{13}C NMR (100 MHz, D_2O, 25 °C): δ 95.3 (dd, $J_{1,F} = 4.7$ Hz, $J_{1,P} = 23.9$ Hz), 92.8 (dd, $J_{2,F} = 186$ Hz, $J_{1,P} = 8.1$ Hz), 75.0, 74.5 (d, $J_{3,F} = 17$ Hz), 68.8 (d, $J_{4,F} = 7.8$ Hz), 68.6, 62.5, 53.1, 25.6, 19.6, 13.1 ppm; ^{19}F NMR (235 MHz, D_2O, 25 °C): $\delta = -199.2$ ppm (dd, $J_{2,F} = 51.7$ Hz, $J_{3,F} = 14.1$ Hz); ^{31}P NMR (101 MHz, D_2O, 25 °C): $\delta = 0.83$ ppm (s); MS (FAB−): m/z: 291 $[M-H]^+$; HRMS (FAB−) calcd for $C_7H_{13}O_9FP$ $[M-H]^+$: 291.0281; found: 291.0283.

Adenosine 5′-diphospho-2-deoxy-2-fluoro-L-*glycero*-β-D-*gluco*-heptopyranoside (2): Monophosphate **24** (51 mg, 0.077 mmol) was dissolved in anhydrous pyridine under argon atmosphere and concentrated under vacuum. This azeotropic removal of residual water was repeated three times. AMP-morpholidate (214 mg, 0.302 mmol) and 1H-tetrazole (42 mg, 0.603 mmol) was added to the dried monophosphate **24**, and the mixture was left under high vacuum for 24 h. Anhydrous pyridine (2 mL) was added, and the mixture was stirred under argon atmosphere for 52 h. After concentration, the residue was precipitated and washed with ethyl acetate. The resulting solid was purified by preparative HPLC (RP-C18, isocratic elution: triethylammonium acetate buffer (pH 6.8)/2% acetonitrile) to give a mixture of sugar nucleotide **2** and AMP dimer. The mixture was separated by size exclusion chromatography (Sephadex G-15, elution: water) to furnish sugar nucleotide **2** as a syrup. Repeated lyophilizations of the syrupy product afforded pure sugar nucleotide **2** as a white solid (31 mg, 56%). ^{1}H NMR (400 MHz, D_2O, 25 °C): $\delta = 8.25$ (s, 1H; adenine), 8.49 (s, 1H; adenine), 6.13 (d, $J_{1',2'} = 6.0$ Hz, 1H; H-1′), 5.21 (td, $J_{1,2} = J_{1,P} = 7.8$ Hz, $J_{1,F} = 2.6$ Hz, 1H; H-1), 4.75 (m, 1H; H-2′), 4.52 (dd, $J_{2',3'} = 5.1$ Hz, $J_{3',4'} = 3.5$ Hz, 1H; H-3′), 4.39 (t, $J_{3',4'} = J_{4',5'} = 3.1$ Hz, 1H; H-4′), 4.21 (dd, $J_{4',5'} = 3.2$ Hz, $J_{gem} = 5.2$ Hz, 1H; H-5′), 4.15 (ddd, $J_{1,2} = 7.9$ Hz, $J_{2,3} = 8.7$ Hz, $J_{2,F} = 50.7$ Hz, 1H; H-2), 3.91 (dt, $J_{5,6} = 1.3$ Hz, $J_{6,7a} = J_{6,7b} = 6.9$ Hz, 1H; H-6), 3.78 (dd, $J_{2,3} = J_{3,4} = 9.2$ Hz, $J_{3,F} = 15.0$ Hz, 1H; H-3′), 3.69 (dd, $J_{6,7a} = 7.1$ Hz, $J_{gem} = 11.6$ Hz, 1H; H-7a), 3.68 (dd, $J_{6,7} = 7.1$ Hz, $J_{gem} = 11.6$ Hz, 1H; H-7b), 3.63 (t, $J_{3,4} = J_{4,5} = 9.5$ Hz, 1H; H-4), 3.48 ppm (dd, $J_{4,5} = 9.8$ Hz, $J_{5,6} = 1.5$ Hz, 1H; H-5); ^{13}C NMR (101 MHz, D_2O, 25 °C): $\delta = 181.9$, 156.0, 153.4, 153.3, 95.6 (dd, $J_{P1} = 22.6$ Hz, $J_{F1} = 4.4$ Hz, C1), 92.4 (dd, $J_{F2} = 184$ Hz, $J_{P2} = 8.8$ Hz, C2), 87.2, 84.3 (d, $J = 9.4$ Hz,), 75.1, 74.6, 74.3 (d, $J_{F3} = 17.3$ Hz, C3), 70.8, 68.7 (d, $J_{F4} = 7.8$ Hz, C4), 68.5, 65.6 (d, $J = 5.6$ Hz, C5′), 62.4; ^{19}F NMR (235 MHz, D_2O, 25 °C): δ −199.9 ppm (dd, $J_{2,F} = 50.8$ Hz, $J_{3,F} = 13.9$ Hz); ^{31}P NMR (101 MHz, D_2O, 25 °C): $\delta = -11.3$ (d, $J = 22.2$ Hz), −13.3 ppm (d, $J = 22.2$ Hz); MS-ESI: m/z: 620 $[M-H]^+$; ESI-HRMS calcd for $C_{17}H_{25}N_5O_{15}FP_2$ $[M-H]^+$: 620.0806; found: 620.0817.

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