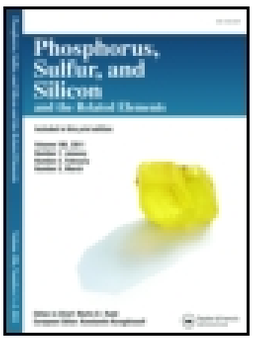

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The synthesis of new fluorinated or nonfluorinated sugar phosphonates and phosphoramidates as building blocks in the synthesis of modified hyaluronic acid subunits

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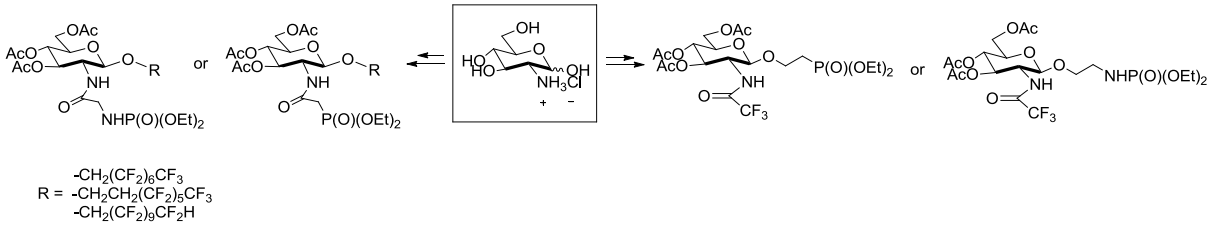
In memoriam of Harry R. Hudson.

Abstract



The synthesis of several new fluorinated or nonfluorinated sugar phosphonates and phosphoramidates as building blocks for the synthesis of modified hyaluronic acid subunits is described. These compounds were prepared from D-glucose and D-glucosamine hydrochloride. The syntheses of phosphonates and phosphoramidates are based on ARBUZOV and STAUDINGER reactions. The products were fully characterized by ^{1}H, ^{13}C, ^{19}F, ^{31}P NMR and ESI MS spectroscopy.

Keywords

fluorinated sugar phosphonates, fluorinated sugar phosphoramidates, Arbuzov reaction, neighbouring group participation

ACCEPTED MANUSCRIPT

1. Introduction

Organophosphorus compounds, especially natural phosphates play an important role in many biological processes. It is worth mentioning that glycosyl phosphates are of great interests by many researchers[1,2]. These species are key glycosylating agents in biosynthesis of oligosaccharides by glycosyl transferases. Also they can be used as metabolic intermediates or backbones for phosphorus-based biologically active compounds[3–5].

For many years, much attention has been focused on the synthesis of phosphonates and carbohydrate phosphonates as the analogues of phosphates[6,7]. Furthermore, the phosphorus-oxygen bond (P-O) is sensitive to hydrolysis by typical phosphate enzymes in contrast to the phosphorus-carbon bond (P-C) in phosphonates, which is hydrolytically stable[6,8]. Moreover, the replacement of an oxygen atom in phosphates by a methylene group changes the polarity and acidity of the compound[9] (Figure 1). Also in phosphonate analogues we can observe some changes in bond length between C - C - P atoms (1.51 Å-1.80 Å -1.50 Å), which is slightly longer comparing to C - O - P bond (1.43 Å-1.59 Å-1.49 Å)[6,8].

Another example of phosphates analogues are phosphoramidates where instead of a phosphorus-oxygen bond (P - O), a phosphorus-nitrogen bond (P - N) is present (Figure 2). This class of organophosphorus compounds plays a dominant role in many processes. Phosphoramidates have been used as catalysts[10,11], inhibitors[12,13] and as a substitute for naturally occurring phosphate group[14,15]. Additionally, these compounds play an important role in medicine and biological chemistry due to their biological activity. They have been used in the

treatments of cancer and HIV[16,17]. Additionally, they display potent cytostatic, antiviral and antifungal activities[18], which open up new inspirations for the synthesis of biologically active analogues. Among them, glycosyl phosphoramidates are used as novel phosphoramidate prodrugs[19] or isosteric analogues of glycosyl phosphates[20].

Recently, special interest has been focused on the synthesis of drug delivery platforms. One of the natural polymers, which can be successfully used in drug delivery applications is hyaluronic acid (HA). This compound is a natural polysaccharide, which consists of the repeating disaccharide subunits of β-D-*N*-acetylglucosamine and β-D-glucuronic acid (Figure 3). HA is biodegradable and biocompatible, which makes this molecule a promising drug carrier. There are several reports describing examples of modified HA-drug conjugate acting on cancer cells[21–23].

Diverse use of phosphonates and phosphoramidates shows, that they may be used successfully as compounds displaying biological activity. The introduction of these two species in building blocks of a drug delivery platform should be advantageous. It is also important, that phosphonate and phosphoramidate moiety in combination with a fluorinated motif in the molecule would lower polarity of the molecules. Because of that it is possible to increase the lipophilicity of hyaluronic acid and increase the ability to penetrate cell membranes. Additionally for such compounds, ^{19}F NMR spectroscopy can be successfully used as an efficient tool for studying the interactions between fluorinated compounds and biological systems[24,25].

2. Results and Discussion

Two routes of conversion of fluorinated and nonfluorinated monosaccharides into sugar phosphonates and sugar phosphoramidates have been explored. Our goal was to develop a synthetic methodology for some model monosaccharides as building blocks for further HA subunits synthesis. One of the common approaches for the formation of P - C bond is the ARBUZOV reaction[26]. In this reaction the nucleophilic triethyl phosphite $P(OEt)_3$ reacts in S_N2 reaction with electrophylic alkyl halides (-Cl, -Br, -I). Alternatively, the STAUDINGER reaction allows to obtain phosphoramidates with P - N bonds from azides and trivalent phosphorus e.g. $P(OEt)_3$[14,27]. In this paper we would like to present our results on the synthesis of new modified monosaccharides based on D-glucose and D-glucosamine hydrochloride derivatives.

Our initial goal was the synthesis of the monosaccharides **2** and **6** with 2-hydroxyethyl moieties, which has started from D-glucose **1** and D-glucosamine hydrochloride **5**. This procedure is known for 2-hydroxyethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **2**[28] but only partially for compound **6**[29,30]. The sugar phosphonates **4** and **8** were obtained from corresponding bromides **3**[31,32] and **7** by heating at reflux with $P(OEt)_3$ (Scheme 1). In several preparation of phosphonates, like the one described by VALÉRY et al.[32] triethyl phosphite was used in large excess (even as a 156-fold excess). Such a huge excess of reagent can cause some problems with isolation and purification of the product. In our case, evaporation of the reactant on rotavap followed by column chromatography was not sufficient. The TLC analysis showed that our products (**4**, **8**) were more polar than $P(OEt)_3$ itself. In ^{31}P NMR spectra, except signals from the main products 1-diethylphosphonoethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **4** or 1-diethylphosphonoethyl-2-trifluoroacetamido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside **8,** we have

observed a lot of signals due to impurities and by-products. However, it was found that reduced pressure distillation of excess of $P(OEt)_3$ allows the complete removal of emerging by-products. In ^{31}P NMR spectrum only two signals were observed: 27.84 pm for phosphonate **4** and 28.53 ppm for phosphonate **8**.

Sugar phosphoramidates **11** and **13** were prepared by Staudinger reaction[20] from the corresponding 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucose **10** and sugar azide having trifluoroacetamide group **12** (Scheme 2) with high yields (93-94%). It is possible to use several other methods for azide synthesis (*i*) in anhydrous DMF with heating in 60°C[33], in (*ii*) acetone with KI at room temperature[34]or (*iii*) using phase transfer catalysis (PTC)[35]. The synthesis of 2-azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **12** was reported in the literature previously. Generally azide **12** is prepared from bromide[30] or sugar protected with acetyl group[36] in reaction with 2-azidoethanol in the presence of the Lewis acid.

Nucleophilic displacement reaction are often used in carbohydrate chemistry. In the literature we can find reports on substitution reactions on anomeric carbon atoms in monosaccharide with aliphatic alcohols. It is often observed that this kind of reaction proceeds with neighboring group participation effect. In one of the stages of the reaction an oxonium ion is formed, as a relatively stable five-member ring intermediate[37]. In many cases formation of an oxazoline ring was the main product[38,39].

In our reaction with sugar **19** as a nucleophile, we have used partially fluorinated alcohols **14-18** (Figure 4). The presence of the fluorine substituents will also lead to a dramatic change in electronic properties of the molecule. In order to decrease the inductive effect caused by the

fluorine substituents, it is necessary to use a short spacer between fluorinated carbon chain and rest of the molecule (Figure 4). In our test reaction, when we have used a large excess of 2,2,3,3,4,4,5,5-octafluoropentan-1-ol **15** like (16-, 8- or 4-fold excess), ^{1}H NMR analysis of the crude product showed the desired product and some by-products derived from the fluorinated alcohol **15**. Therefore, we have decided to limit the amount of fluorinated alcohol to only 1-2 equiv. of alcohol. It turned out that 1 equiv. can be used only for alcohol with two nonfluorinated CH_2 groups in 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorooctanol **17**. In all other cases we have used 2 equiv. of fluorinated alcohols. In case of **14**-**16** and **18** the main product was 1-hydroxy-3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-α-D-glucopyranose. In ^{1}HNMR spectrum we have observed a triplet at 5.31 ppm with coupling constant $^{3}J_{H\text{-}H}$ = 3.6 Hz. In reaction with 1 equiv. of fluorinated alcohol **14**-**16** and **18**, we have obtained only a traces of products, which was confirmed only by a highly sensitive analysis ESI MS. For the reaction with 2,2,3,3,4,4,5,5-octafluoropentan-1-ol **15** e.g. m/z $[M+H]^+$ calcd for $C_{19}H_{23}ClF_8NO_9$: 596.0934; found: 596.0927; m/z $[M+Na]^+$ calcd for $C_{19}H_{22}ClF_8NNaO_9$: 618.0753; found: 618.0745. We did not observed in ^{1}H NMR spectrum a signal from the CF_2H group around 6.2 ppm. Unfortunately, for the reaction with the short chain alcohol 1,1,1,3,3,3-hexafluoropropan-2-ol **14** we did not observe the desired product neither in NMR nor MS spectra.

According to the literature, the synthesis of 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** required introduction of the 2-chloroacetamide group, what was described by FONDY et al.[40], WONG et al.[41] or WITTE et al.[42]. Compound **19** was prepared with very good yield. Surprisingly, to the best of our knowledge we did not find ^{13}C NMR and HRMS spectra for this compound. The next set of compounds was prepared from 1,3,4,6-tetra-*O*-acetyl-

2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** as a starting material. Sugar **19** reacts with fluorinated alcohols **16**-**18** in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid. Reactant **19** itself can be obtained from D-glucosamine hydrochloride **5** in a multi-steps sequence. The results of this reaction are monosaccharides **20**-**22** with fluorinated aliphatic chains having 13, 15, 20 fluorine atoms on substituent in anomeric position (Scheme 3). In the next step we wanted to eliminate problems with excess of $P(OEt)_3$, that has been mentioned previously. In syntheses of compounds **23**-**25** we applied the reaction conditions described by LAKOUD et al.[43]. These authors reported the synthesis of phosphonates only with 5 equiv. of $P(OEt)_3$. However, we run our experiment in mild conditions, which were described by WONG et al.[41]. In some cases we have used only 2 equiv. of $P(OEt)_3$, which was sufficient. The reaction was conducted with heating in 65°C and in the presence of NaI or KI. These reaction conditions allowed us to achieve high yields even for the fluorinated monosaccharides **23**-**25** with 68–86%. It turned out that it is possible to use only 2 equiv. excess of triethyl phosphate in this kind of reaction that facilitates further purification.

Next, we have turned our attention to the syntheses of phosphoramidates **29**-**31** starting from the corresponding azides **26**-**28** (Scheme 3). The reactions were carried out according to the procedure described before[20] with excellent yields 76–92%.

Consequently we have studied the preparation of the nonfluorinated phosphonate **32**, **34** and nonfluorinated phosphoramidate **36**, **38** as the analogues of 2-chloroacetamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **19** and 2-bromopropionamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **33** (Scheme 4). These compounds were prepared as a model nonfluorinated monosaccharides. The chloride **19** was converted under ARBUZOV conditions to 2-

diethylphosphonoacetamid-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **32** according to the procedure described by WONG et al.[41] with 69% yield. Similarly, from the bromide **33** we have obtained 2-diethylphosphonopropionamid-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **34**. The syntheses of **36** and **38** were accomplished in two-step reactions with 91% and 69% yields for 2-diethylphosphoramidoacetamid-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **36** and with 92 % and 60 % yields for 2-diethylphosphoramidopropionamid-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **38** (Scheme 5). To the best of our knowledge compounds **34**, **36** and **38** are new compounds, first reported examples of this class.

3. Conclusions

In summary, we have developed an efficient synthetic route to a library of modified monosaccharides, which may be useful way in the synthesis of hyaluronic acid subunits. The starting materials 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** and 2-bromopropionamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **33** were prepared with good yields (87% and 75%) in easy multistage reaction. The synthesis of fluorinated phosphonates and phosphoramidates containing in their structure aliphatic chains with 13, 15 and 21 fluorine atoms was optimized.

4. Experimental

All chemicals were reagent grade and were used as purchased without further purification. Anhydrous dichloromethane (DCM) was prepared by pre-drying with anhydrous $CaCl_2$ followed

by distillation over CaH_2 under argon atmosphere. All moisture sensitive reactions were carried out under argon atmosphere. Thin-layer chromatography (TLC) was carried out on silica gel plates (Silica gel 60, F254, Merck) with detection by UV light or with stain solution (Cerium Molybdate Stain and Potassium Permanganate). Purification was performed with column chromatography using normal-phase silica gel (Silica gel 60, 70-230 mesh, Fluka). ^{1}H, ^{13}C, ^{19}F, ^{31}P NMR were recorded with a Varian VNMR-S 400 MHz, VARIAN Mercury 300 MHz, Varian GEMINI 300 (300 MHz) or Bruker Avance 400 (400 MHz), Bruker ASCEND 600 (600 MHz) spectrometers. Chemical shifts are reported as δ values (ppm). NMR spectra were recorded in deuterated solvents and calibrated using an internal reference: TMS (^{1}H), $CDCl_3$ (^{13}C), $CFCl_3$ (^{19}F) and 85% H_3PO_4 (^{31}P) as an external standard (δ = 0 ppm). Multiplicities of signals are described as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, td = triplet of doublets, tt = triplet of triplets, m = multiplet. Coupling constants (*J*) are given in Hz. Mass spectra (ESI) were carried out with Q-TOF (Impact HD, Bruker) and Agilent 1200 LC system with Agilent Q-TOF 6540 spectrometer with DUAL AJS ESI source. The Supplemental Materials contains some selected ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra of products. (Figures S 1 – S 23)

4.1. 1-Diethylphosphonoethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **4**

A mixture of bromide **3** (0.104 g, 0.229 mmol) and $P(OEt)_3$ (5.90 mL, 35.720 mmol) was heated under reflux for 15 h. The excess of $P(OEt)_3$ was distilled off under reduced pressure and the crude product was purified by column chromatography (DCM/MeOH 20:1, v/v) afforded **4** as an oil. Yield: (0.097 g) 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (appt, *J* = 9.5 Hz, 1H, H-3), 5.06 (t, *J* = 9.7 Hz, 1H, H-4), 4.96 (dd, *J* = 8.0 Hz, *J* = 9.5 Hz, 1H, H-2), 4.52 (d, *J* = 8.0 Hz, 1H, H-

1), 4.26 (dd, *J* = 4.8 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.14-4.00 (m, 6H, H-6b, 2xOCH_2CH_3, OCH_bCH_2), 3.85-3.74 (m, 1H, OCH_aCH_2), 3.69 (ddd, *J* = 2.4 Hz, *J* = 4.8 Hz, *J* = 9.9 Hz, 1H, H-5), 2.17-2.09 (m, 2H, $CH_2P(O)$), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.35-1.29 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 $\underline{C}(O)CH_3$, 170.2 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 100.7 C-1, 72.8 C-5, 71.9 C-2, 71.2 C-3, 68.3 C-4, 64.2 C-6, 63.6 (d, *J* = 5.8 Hz, $O\underline{C}H_2CH_2P(O)(OEt)_2$), 61.84 (d, *J* = 5.4 Hz, $O\underline{C}H_2CH_3$), 61.72 (d, *J* = 6.3 Hz, $O\underline{C}H_2CH_3$), 27.0 (d, *J* = 139.3 Hz, $OCH_2\underline{C}H_2P(O)(OEt)_2$), 20.69 $C(O)\underline{C}H_3$, 20.66 $C(O)\underline{C}H_3$, 20.57 2x$C(O)\underline{C}H_3$, 16.4 (d, *J* = 6.0 Hz, $OCH_2\underline{C}H_3$), 16.1 (d, *J* = 6.7 Hz, $OCH_2\underline{C}H_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 27.84 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{34}O_{13}P$: 513.1737; found: 513.1737 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{33}NaO_{13}P$: 535.1556; found: 535.1557.

4.2. 2-Hydroxyethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **6**

To a solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide (0.514g, 1.110 mmol) in anhydrous DCM (28.40 mL) was added anhydrous Na_2SO_4 and 1,2-ethanediol (0.62 mL, 11.100 mmol). After stirring at room temperature for 15 min, under an argon atmosphere, Ag_2CO_3 (4.60 g, 16.700 mmol) was added to the reaction mixture and stirred overnight protected from the light. The reaction mixture was filtered, washed with water (3x30 mL), dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography using a 5:1 mixture of EtOAc/cyclohexane (CH) as eluent. Compound **6** was obtained as a white solid. Yield: (0.299 g) 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 1H, NH), 5.30 (dd, *J* = 9.4 Hz, *J* = 10.6 Hz, 1H, H-3), 5.10 (t, *J* = 9.7 Hz, 1H, H-4), 4.75 (d, *J* = 9.7 Hz, 1H, H-1), 4.26 (dd, *J* = 5.2 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.20 (dd, *J* = 2.6 Hz, *J* = 12.3 Hz, 1H, H-6b), 4.07 (dd, *J* = 8.7 Hz, *J* = 19.2 Hz, 1H, H-2), 3.90 (ddd, *J* = 2.4 Hz, *J* = 4.7

Hz, *J* = 9.9 Hz, 1H, H-5), 3.84-3.72 (m, 4H, OCH_2CH_2OH), 2.83 (t, *J* = 5.2 Hz, 1H, OH), 2.11 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1 $\underline{C}(O)CH_3$, 170.8 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 157.7 (q, *J* = 37.8 Hz, $\underline{C}(O)CF_3$), 115.6 (q, *J* = 289.1 Hz, $\underline{C}F_3$), 101.0 C-1, 72.4 C-5, 72.0 C-3, 71.9 C-4, 68.4 $O\underline{C}H_2CH_2OH$, 62.0 C-6, 61.7 $OCH_2\underline{C}H_2OH$, 54.8 C-2, 20.7 $C(O)\underline{C}H_3$, 20.6 $C(O)\underline{C}H_3$, 20.4 $C(O)\underline{C}H_3$; ^{19}F NMR (376 MHz, $CDCl_3$): δ -76.03 (s, 3F, CF_3); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}F_3NO_{10}$: 446.1275; found: 446.1271 *m/z* $[M+Na]^+$ calcd for $C_{16}H_{22}F_3NNaO_{10}$: 468.1094; found: 468.1101.

4.3. 2-Bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **7**

To a solution of alcohol **6** (0.124 g, 0.279 mmol) in anhydrous DCM (3.50 mL) were added PPh_3 (0.146 g, 0.558 mmol) and CBr_4 (0.204 g, 0.614 mmol) under an argon atmosphere. After stirring for 2 h at room temperature, the reaction mixture was diluted with DCM (11 mL) and washed with water (2x12 mL). The organic layer was then dried over Na_2SO_4 and concentrated. Purification by column chromatography (CH/EtOAc 2:1,v/v) afforded **7** as a white solid. Yield: (0.105 g) 75%; ^1H NMR (300 MHz, $CDCl_3$): δ 6.66 (d, *J* = 8.6 Hz, 1H, NH), 5.31 (dd, *J* = 9.3 Hz, *J* = 10.7 Hz, 1H, H-3), 5.11 (t, *J* = 9.6 Hz, 1H, H-4), 4.77 (d, *J* = 8.3 Hz, 1H, H-1), 4.28 (dd, *J* = 4.8 Hz, *J* = 12.4 Hz, 1H, H-6a), 4.24-4.13 (m, 2H, H-6b, OCH_aCH_2Br), 4.02 (dd, *J* = 8.7 Hz, *J* = 19.3 Hz, 1H, H-2), 3.87-3.72 (m, 2H, H-5, OCH_bCH_2Br), 3.40-3.44 (m, 2H, CH_2Br), 2.11 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 157.4 (q, *J* = 37.5 Hz, $\underline{C}(O)CF_3$), 115.5 (q, *J* = 286.3 Hz, $\underline{C}F_3$), 100.4 C-1, 72.1 C-5, 71.5 C-3, 69.7 C-4, 68.2 $O\underline{C}H_2CH_2Br$, 61.8 C-6, 54.9 C-2, 30.0 $OCH_2\underline{C}H_2Br$, 20.7 $C(O)\underline{C}H_3$, 20.6 $C(O)\underline{C}H_3$, 20.4 $C(O)\underline{C}H_3$; ^{19}F NMR (282 MHz, $CDCl_3$): δ -

76.50 (s, 3F, CF_3); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}BrF_3NO_9$: 508.0431; found: 508.0501 *m/z* $[M+Na]^+$ calcd for $C_{16}H_{21}BrF_3NNaO_9$: 530.0249; found: 530.0250.

4.4. 1-Diethylphosphonoethyl-2-trifluoroacetamido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside **8**

A mixture of bromide **7** (0.099 g, 0.194 mmol) and $P(OEt)_3$ (5.20 mL, 30.260 mmol) was heated under reflux for 15 h. The excess of $P(OEt)_3$ was distilled off under reduced pressure and crude product was purified by column chromatography (DCM/MeOH 20:1, v/v) afforded **8**. Yield: (0.094 g) 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, *J* = 8.4 Hz, 1H, NH), 5.23 (appt, *J* = 9.9 Hz, 1H, H-3), 5.11 (t, *J* = 9.6 Hz, 1H, H-4), 4.82 (d, *J* = 8.5 Hz, 1H, H-1), 4.29 (dd, *J* = 4.5 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.18-4.03 (m, 7H, H-6b, OCH_bCH_2, 2xOCH_2CH_3, H-2), 3.91-3.78 (m, 1H, OCH_aCH_2), 3.71 (ddd, *J* = 2.4 Hz, *J* = 4.3 Hz, *J* = 9.9 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.10-2.02 (m, 2H, $CH_2P(O)$), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.37-1.31 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 157.8 (q, *J* = 37.4 Hz, $\underline{C}(O)CF_3$), 115.9 (q, *J* = 288.0 Hz, $\underline{C}F_3$), 99.9 C-1, 72.9 C-5, 72.1 C-3, 68.4 C-4, 63.7 (d, *J* = 5.7 Hz, $O\underline{C}H_2CH_2P(O)(OEt)_2$), 62.3 (d, *J* = 6.5 Hz, $O\underline{C}H_2CH_3$), 61.9 C-6, 61.8 (d, *J* = 6.8 Hz, $O\underline{C}H_2CH_3$), 54.1 C-2, 26.4 (d, *J* = 141 Hz, $OCH_2\underline{C}H_2P(O)(OEt)_2$), 20.7 $C(O)\underline{C}H_3$, 20.6 $C(O)\underline{C}H_3$, 20.4 $C(O)\underline{C}H_3$, 16.38 (d, *J* = 6.1 Hz, $OCH_2\underline{C}H_3$), 16.25 (d, *J* = 6.0 Hz, $OCH_2\underline{C}H_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ -76.21 (s, 3F, CF_3); ^{31}P NMR (121 MHz, $CDCl_3$): δ 28.53 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{32}F_3NO_{12}P$: 566.1614; found: 566.1615 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{31}F_3NNaO_{12}P$: 588.1434; found: 588.1434.

4.5. 1-Diethylphosphoramidoethoxy-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside **11**

The mixture of azide **10** (0.080 g, 0.192 mmol) in anhydrous DCM (8.20 mL) with powdered molecular sieves 4Å (0.017 g) was stirred for 1h under an argon atomosphere at room

temperature. Then $P(OEt)_3$ was added (0.16 mL, 0.960 mmol) and stirred overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by column chromatography (DCM/MeOH 20:1,v/v) afforded **11** as a white foam. Yield: (0.095 g) 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (t, *J* = 9.3 Hz, 1H, H-3), 5.08 (appt, *J* = 9.7 Hz, 1H, H-4), 4.99 (dd, *J* = 8.0 Hz, *J* = 9.6 Hz, 1H, H-2), 4.53 (d, *J* = 8.0 Hz, 1H, H-1), 4.26 (dd, *J* = 4.8 Hz, *J* = 12.4 Hz, 1H, H-6a), 4.14 (dd, *J* = 2.4 Hz, *J* = 12.4 Hz, 1H, H-6b), 4.09-4.02 (m, 5H, 2xOCH_2CH_3, NHP(O)), 3.92-3.83 (m, 1H, OCH_aCH_2), 3.71 (ddd, *J* = 2.4 Hz, *J* = 4.7 Hz, *J* = 9.9 Hz, 1H, H-5), 3.64 (m, 1H, OCH_bCH_2), 3.18-3.06 (m, 2H, OCH_2CH_2), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.35-1.29 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6 $\underline{C}(O)CH_3$, 170.2 $\underline{C}(O)CH_3$, 169.41 $\underline{C}(O)CH_3$, 169.35 $\underline{C}(O)CH_3$, 101.0 C-1, 72.7 C-5, 71.9 C-2, 71.3 C-3, 70.7 (d, *J* = 5.4 Hz, $O\underline{C}H_2CH_2NHP(O)(OEt)_2$), 68.3 C-4, 62.3 (d, *J* = 5.5 Hz, $O\underline{C}H_2CH_3$), 61.8 C-6, 41.1 $OCH_2\underline{C}H_2NHP(O)(OEt)_2$, 20.7 $C(O)\underline{C}H_3$, 20.63 $C(O)\underline{C}H_3$, 20.55 2x$C(O)\underline{C}H_3$, 16.2 (d, *J* = 7.0 Hz, 2x$OCH_2\underline{C}H_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 9.50 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{36}NO_{13}P$: 529.1925; found: 529.1873 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{35}NNaO_{13}P$: 551.1744; found: 551.1691.

4.6. 2-Azidoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **12**

To a solution of 2-bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **7** (0.082 g, 0.162 mmol) in DCM (0.82 mL) and aq. sat. $NaHCO_3$ (0.82 mL), TBASH (0.051 g, 0.149 mmol) and NaN_3 (0.031 g, 0.483 mmol) were added. The reaction mixture was stirred at room temperature for 48 h. It was subsequently diluted with EtOAc (5 mL) and washed with H_2O (8 mL) and aq. sat. $NaHCO_3$ (8 mL), dried over Na_2SO_4 and

concentrated in vacuo. The crude product was purified by column chromatography (CH/EtOAc 1:1, v/v) and afforded **12** as a white solid. Yield: (0.066 g) 87%; ^{19}F NMR (282 MHz, $CDCl_3$): δ -76.63 (s, 3F, CF_3).

4.7. 1-Diethylphosphoramidoethoxy-3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside **13**

The mixture of azide **12** (0.055 g, 0.117 mmol) in anhydrous DCM (5.10 mL) with powdered molecular sieves 4Å (0.025 g) was stirred for 1 h under an argon atmosphere at room temperature. Then $P(OEt)_3$ was added (0.1 mL, 0.585 mmol) and stirred overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by column chromatography (DCM/MeOH 20:1,v/v) afforded **13** as a white solid. Yield: (0.063 g) 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 8.6 Hz, 1H, NH), 5.32 (dd, *J* = 9.4 Hz, *J* = 10.5 Hz, 1H, H3), 5.10 (t, *J* = 9.7 Hz, 1H, H-4), 4.85 (d, *J* = 8.4 Hz, 1H, H-1), 4.28 (dd, *J* = 4.6 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.19-3.97 (m, 6H, H-6b, H-2, 2xOCH_2CH_3), 3.95-3.86 (m, 1H, OCH_bCH_2), 3.73 (ddd, *J* = 2.4 Hz, *J* = 4.5 Hz, *J* = 10.0 Hz, 1H, H-5), 3.67-3.53 (m, 2H, OCH_aCH_2, NHP(O)), 3.13-3.04 (m, 2H, OCH_2CH_2), 2.11 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.37-1.29 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 157.8 (q, *J* = 37.5 Hz, $\underline{C}(O)CF_3$), 115.8 (q, *J* = 289.3 Hz, $\underline{C}F_3$), 100.0 C-1, 72.1 C-5, 72.0 C-3, 70.0 (d, *J* = 5.3 Hz, $O\underline{C}H_2CH_2NHP(O)(OEt)_2$), 68.5 C-4, 62.61 (d, *J* = 4.5 Hz, $O\underline{C}H_2CH_3$), 62.54 (d, *J* = 4.4 Hz, $O\underline{C}H_2CH_3$), 62.0 C-6, 54.7 C-2, 41.0 $OCH_2\underline{C}H_2NHP(O)(OEt)_2$, 20.7 $C(O)\underline{C}H_3$, 20.6 $C(O)\underline{C}H_3$, 20.4 $C(O)\underline{C}H_3$, 16.2 (d, *J* = 6.9 Hz, $OCH_2\underline{C}H_3$), 16.0 (d, *J* = 7.4 Hz, $OCH_2\underline{C}H_3$); ^{19}F NMR (282 MHz, $CDCl_3$): δ -76.22 (s, 3F, CF_3);

^{31}P NMR (121 MHz, $CDCl_3$): δ 9.33 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{33}F_3N_2O_{12}P$: 581.1724; found: 581.1737 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{32}F_3N_2O_{12}P$: 603.1543; found: 603.1555.

4.8. 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy- β-D-glucopyranoside **19**

Et_3N (0.61 mL) was added to a solution of 2-deoxy-2-amino-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl hydrochloride (0.844 g, 2.200 mmol) in anhydrous DCM (10 mL) at 0 °C. After 5 min chloroacetic anhydride (0.640 g, 3.740 mmol) was added. The reaction mixture was stirred for 3.5 hours at room temperature and controlled by TLC. Next, the solution was diluted with DCM (50 mL), washed successively with 1N HCl (2 x 50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and solvent was evaporated. The resulting crude product was crystallized from EtOAc/CH giving **19** as a light grey and white solid. Yield: (0.807 g) 87%; ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9 $\underline{C}(O)CH_3$, 170.7 $\underline{C}(O)CH_3$, 169.3 2x$\underline{C}(O)CH_3$, 166.6 $\underline{C}(O)CH_2Cl$, 92.1 C-1, 72.9 C-5, 71.9 C-3, 67.9 C-4, 61.7 C-6, 53.3 C-2, 42.3 $\underline{C}H_2Cl$, 20.9 C(O)$\underline{C}H_3$, 20.7 C(O)$\underline{C}H_3$, 20.58 C(O)$\underline{C}H_3$, 20.57 C(O)$\underline{C}H_3$; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{23}ClNO_{10}$: 424.1010; found: 424.1011 *m/z* $[M+Na]^+$ calcd for $C_{16}H_{22}ClNNaO_{10}$: 446.0830; found: 446.0843.

4.9. 3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **20**

To a stirred solution of 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** (0.048 g, 0.113 mmol) in anhydrous DCM (0.23 mL) under an argon atmosphere and room temperature $BF_3{\cdot}Et_2O$ (0.03 mL, 0.226 mmol) and 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluorooctanol **16** (0.090 g, 0.226 mmol) were added and stirred for 24 h. The reaction mixture was diluted with EtOAc (2 mL) and washed with aq. sat. $NaHCO_3$ (2mL). The organic

phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/CH 1:1, v/v) afforded **20** as a white solid. Yield: (0.052 g) 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 8.5 Hz, 1H, NH), 5.44 (appt, *J* = 9.9 Hz, 1H, H-3), 5.10 (t, *J* = 9.5 Hz, 1H, H-4), 4.94 (d, *J* = 8.2 Hz, 1H, H-1), 4.37-4.25 (m, 2H, H-6a,H-6b), 4.21-4.02 (m, 2H, $OCH_2(CF_2)_6CF_3$), 3.98 (s, 2H, CH_2Cl), 3.93-3.84 (m, 1H, H-2), 3.78 (ddd, *J* = 2.5 Hz, *J* = 4.6 Hz, *J* = 9.8 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.04 (s, 6H, 2xOAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 $\underline{C}(O)CH_3$, 170.5 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 166.5 $\underline{C}(O)CH_2Cl$, 122.7-106.8 (m, $(CF_2)_6CF_3$), 100.4 C-1, 72.2 C-5, 71.0 C-3, 68.2 C-4, 65.3 (t, *J* = 26.2 Hz, $O\underline{C}H_2(CF_2)_6CF_3$), 61.7 C-6, 54.8 C-2, 42.2 CH_2Cl, 20.64 $C(O)\underline{C}H_3$, 20.56 $C(O)\underline{C}H_3$, 20.53 $C(O)\underline{C}H_3$; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -80.77, -119.86, -122.02, -122.73, -123.13, -126.10; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}ClF_{15}NO_9$: 764.0744; found: 764.0734; *m/z* $[M+Na]^+$ calcd for $C_{22}H_{21}ClF_{15}NNaO_9$: 786.0563; found: 786.0559.

4.10. 3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **21**

To a stirred solution of 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** (0.091 g, 0.214 mmol) in anhydrous DCM (4.3 mL) under an argon atmosphere and room temperature $BF_3{\cdot}Et_2O$ (0.06 mL, 0.428 mmol) and 1,1,1,2,2,3,3,4,4,5,5-pentadecafluorooctanol **17** (0.076 g, 0.214 mmol) were added and stirred for 24 h. The reaction mixture was diluted with EtOAc (3 mL) and washed with aq. sat. $NaHCO_3$ (3 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/CH 1:1, v/v) gave **21** as a white solid. Yield: (0.106 g) 69%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (d, *J* = 8.6 Hz, 1H, NH), 5.40 (dd, *J* = 10.5 Hz, *J* = 9.3 Hz, 1H, H-3), 5.09 (t, *J* =

9.6 Hz, 1H, H-4), 4.83 (d, *J* = 8.2 Hz, 1H, H-1), 4.29 (dd, *J* = 12.3 Hz, *J* = 4.9 Hz, 1H, H-6a), 4.21-4.12 (m, 2H, H-6b, H-2), 4.00 (d, *J* = 2.7 Hz, 2H, CH_2Cl), 3.91-3.82 (m, 2H, $OCH_2CH_2(CF_2)_5CF_3$), 3.77 (ddd, *J* = 9.9 Hz, *J* = 4.9 Hz, *J* = 2.4 Hz, 1H, H-5), 2.53-2.37 (m, 2H, $CH_2(CF_2)_5CF_3$), 2.11 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.60 $\underline{C}(O)CH_3$, 170.58 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 166.4 $\underline{C}(O)CH_2Cl$, 121.7-106.4 (m, $(CF_2)_5CF_3$), 100.4 C-1, 72.0 C-5, 71.4 C-3, 68.4 C-4, 61.9 C-6, $O\underline{C}H_2CH_2(CF_2)_5CF_3$, 55.0 C-2, 42.3 $\underline{C}H_2Cl$, 31.3 (t, *J* = 21.5 Hz, $OCH_2\underline{C}H_2(CF_2)_5CF_3$), 20.63 $C(O)\underline{C}H_3$, 20.60 $C(O)\underline{C}H_3$, 20.55 $C(O)\underline{C}H_3$; ^{19}F NMR (377 MHz, $CDCl_3$) δ -80.77, -113.39, -121.89, -122.86, -123.53, -126.12; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}ClF_{13}NO_9$: 728.0932; found: 728.0930; *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}ClF_{13}NNaO_9$: 750.0751; found: 750.0748.

4.11. 3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **22**

To a stirred solution of 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose **19** (0.059 g, 0.139 mmol) in anhydrous DCM (0.60 mL) under an argon atmosphere and room temperature, $BF_3{\cdot}Et_2O$ (0.17 mL, 1.390 mmol) and 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-eicosafluoroundecanol **18** (0.074 g, 0.139 mmol) gave **22** as a white solid. Yield: (0.081 g) 55%; ^{1}H NMR (403MHz, $CDCl_3$) δ 6.70 (d, *J* = 8.5 Hz, 1H, NH), 6.06 (tt, *J* = 5.0 Hz, *J* = 51.9 Hz, 1H, CF_2H), 5.43 (dd, *J* = 10.6 Hz, *J* = 9.2 Hz, 1H, H-3), 5.10 (t, *J* = 9.5 Hz, 1H, H-4), 4.93 (d, *J* = 8.2 Hz, 1H, H-1), 4.34-4.23 (m, 3H, H-6a, $OCH_2(CF_2)_9CF_2H$), 4.18 (dd, *J* = 12.4 Hz, *J* = 2.5 Hz, 1H, H-6b), 3.99 (apps, 2H, CH_2Cl), 3.87 (m, 1H, H-2), 3.77 (ddd, *J* = 9.9 Hz, *J* = 4.9 Hz, *J* = 2.4 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.04 (s, 6H, 2xOAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 $\underline{C}(O)CH_3$, 170.5 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 166.5 $\underline{C}(O)CH_2Cl$, 118.2-105.8 (m, $(CF_2)_9CF_2H$),

100.3 C-1, 72.2 C-5, 70.9 C-3, 68.2 C-4, 65.3 (t, *J* = 25.9, O<u>C</u>$H_2(CF_2)_9CF_2H$), 61.7 C-6, 54.9 C-2, 42.2 <u>C</u>H_2Cl, 20.7 C(O)<u>C</u>H_3, 20.64 C(O)<u>C</u>H_3, 20.58 C(O)<u>C</u>H_3; ^{19}F NMR (379 MHz, $CDCl_3$) δ -120.33, -122.35, -123.70, -129.74, -137.47; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}ClF_{20}NO_9$: 896.0742; found: 896.0731; *m/z* $[M+Na]^+$ calcd for $C_{25}H_{22}ClF_{20}NNaO_9$: 918.0561; found: 918.0558.

4.12. General procedure for the synthesis of fluorinated phosphonates **23**, **24**, **25**

To a solution of sugar with fluorinated aliphatic chain **20**, **21**, **22** (1 equiv.) in MeCN (29.70 mL for 1 mmol of sugar), KI (2.26 equiv.) and $P(OEt)_3$ (5 equiv.) were added. The reaction mixture was heated in 65 °C for 4 h. Solvent was evaporated and the crude product was purified by column chromatography using a 20:1 mixture of DCM/MeOH as eluent to afforded compounds **23**, **24**, **25**.

4.12.1. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphonoacetamido-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **23**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **20** (0.069 g, 0.090 mmol) and $P(OEt)_3$ (0.08 mL, 0.450 mmol) gave **23** as a white solid. Yield: (0.062 g) 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.2 Hz, 1H, NH), 5.44 (dd, *J* = 10.5 Hz, *J* = 9.1 Hz, 1H, H-3), 5.10 (t, *J* = 9.5 Hz, 1H, H-4), 5.00 (d, *J* = 8.2 Hz, 1H, H-1), 4.28 (dd, *J* = 4.8 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.23-3.95 (m, 7H, $OCH_2(CF_2)_6CF_3$, H-6b, 2xOCH_2CH_3), 3.83-3.72 (m, 2H, H-2, H-5), 2.78 (d, *J* = 21.6 Hz, 2H, $CH_2P(O)$), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.38-1.29 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 <u>C</u>(O)CH_3, 170.5 <u>C</u>(O)CH_3, 169.5 <u>C</u>(O)CH_3, 169.4 (d, *J* = 3.4 Hz, <u>C</u>(O)$CH_2P(O)(OEt)_2$), 122.0-106.4 (m, $(CF_2)_6CF_3$), 100.5 C-1, 72.0 C-5, 71.2 C-3, 68.8

C-4, 62.4 C-6, 61.9 (d, *J* = 6.6 Hz, O<u>C</u>H_2CH_3), 61.6 (d, *J* = 6.4 Hz, O<u>C</u>H_2CH_3), 64.6 (appm, O<u>C</u>$H_2(CF_2)_6CF_3$), 54.6 C-2, 34.4 (d, *J* = 129.2 Hz, C(O)<u>C</u>$H_2P(O)(OEt)_2$), 20.6 C(O)<u>C</u>H_3, 20.4 C(O)<u>C</u>H_3, 20.3 C(O)<u>C</u>H_3, 16.2 (d, *J* = 4.8 Hz, OCH_2<u>C</u>H_3), 16.1 (d, *J* = 4.4 Hz, OCH_2<u>C</u>H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -81.23, -120.56, -122.51, -123.23, -123.70, -126.62; ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.53 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{32}F_{15}NO_{12}P$: 866.1423; found: 886.1430 *m/z* $[M+Na]^+$ calcd for $C_{26}H_{31}F_{15}NNaO_{12}P$: 888.1242; found: 888.1253.

4.12.2. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphonoacetamido-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **24**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **21** (0.105 g, 0.144 mmol) and $P(OEt)_3$ (0.05 mL, 0.288 mmol) gave **24** as a white solid. Yield: (0.103 g) 86 %; ^{1}H NMR (403MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.2 Hz, 1H, NH), 5.38 (dd, *J* = 9.2 Hz, *J* = 10.5 Hz, 1H, H-3), 5.03 (t, *J* = 9.6 Hz, 1H, H-4), 4.84 (d, *J* = 8.3 Hz, 1H, H-1), 4.26 (dd, *J* = 5.0 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.17-4.06 (m, 6H, H-6b, 2xOCH_2CH_3, H-2), 3.89-3.78 (m, 2H, $OCH_2CH_2(CF_2)_5CF_3$), 3.75 (ddd, *J* = 9.9 Hz, *J* = 4.9 Hz, *J* = 2.4 Hz, 1H, H-5), 2.79 (d, *J* = 21.0 Hz, 2H, $CH_2P(O)$), 2.53-2.38 (m, 2H, $CH_2(CF_2)_5CF_3$), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.33 (td, *J* = 1.7 Hz, *J* = 7.1 Hz, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 <u>C</u>(O)CH_3, 170.4 <u>C</u>(O)CH_3, 169.5 <u>C</u>(O)CH_3, 164.4 (d, *J* = 3.3 Hz, <u>C</u>(O)$CH_2P(O)(OEt)_2$), 122.0-106.7 (m, $(CF_2)_5CF_3$), 100.5 C-1, 71.8 C-5, 71.7 C-3, 68.8 C-4, 62.8 (d, *J* = 6.6 Hz, O<u>C</u>H_2CH_3), 62.7 (d, *J* = 7.1 Hz, O<u>C</u>H_2CH_3), 62.0 C-6, 61.8 (app m, O<u>C</u>$H_2CH_2(CF_2)_5CF_3$), 54.9 C-2, 34.9 (d, *J* = 129.6 Hz, C(O)<u>C</u>$H_2P(O)(OEt)_2$), 31.4 (t, *J* = 21.4 Hz, OCH_2<u>C</u>$H_2(CF_2)_5CF_3$), 20.7 C(O)<u>C</u>H_3, 20.61 C(O)<u>C</u>H_3, 20.59 C(O)<u>C</u>H_3, 16.21 (d, *J* = 4.7 Hz, OCH_2<u>C</u>H_3), 16.15 (d, *J* = 4.8 Hz, OCH_2<u>C</u>H_3); ^{19}F NMR (379 MHz, $CDCl_3$) δ -81.30, -113.85, -

122.56, -123.38, -124.10, -126.65; ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.52 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}F_{13}NO_{12}P$: 830.1611; found: 830.1584 *m/z* $[M+Na]^+$ calcd for $C_{26}H_{33}F_{13}NNaO_{12}P$: 852.1430; found: 852.1404.

4.12.3. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphonoacetamido-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **25**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **22** (0.065 g, 0.073 mmol) and $P(OEt)_3$ (0.03 mL, 0.146 mmol) gave **25** as a white solid. Yield: (0.050 g) 68 %; ^{1}H NMR (403MHz, $CDCl_3$) δ 6.86 (d, *J* = 9.2 Hz, 1H, NH), 6.07 (tt, *J* = 4.9 Hz, *J* = 51.7 Hz, 1H, CF_2H), 5.37 (dd, *J* = 10.8 Hz, *J* = 9.5 Hz, 1H, H-3), 5.15 (t, *J* = 9.4 Hz, 1H, H-4), 4.87 (d, *J* = 8.2 Hz, 1H, H-1), 4.27 (dd, *J* = 4.8 Hz, *J* = 12.3 Hz, 1H, H-6a), 4.33-4.21 (m, 6H, H-6b, 2xOCH_2CH_3, H-2), 4.17-4.08 (m, 2H, $OCH_2(CF_2)_9CF_2H$), 3.69-3.65 (m, 1H, H-5), 2.77 (d, *J* = 21.1 Hz, 2H, $CH_2P(O)$), 2.11 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 $\underline{C}(O)CH_3$, 170.9 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 166.2 (d, *J* = 3.6 Hz, $\underline{C}(O)CH_2P(O)(OEt)_2$), 116.2-96.0 (m, $(CF_2)_9CF_2H$), 100.4 C-1, 70.5 C-5, 68.3 C-3, 67.8 C-4, 62.0 (d, *J* = 6.6 Hz, $O\underline{C}H_2CH_3$), 62.1 (d, *J* = 6.5 Hz, $O\underline{C}H_2CH_3$), 62.4 C-6, 60.5 (m, $O\underline{C}H_2(CF_2)_9CF_2H$), 52.6 C-2, 34.8 (d, *J* = 129.4 Hz, $C(O)\underline{C}H_2P(O)(OEt)_2$), 20.9 $C(O)\underline{C}H_3$, 20.5 $C(O)\underline{C}H_3$, 20.4 $C(O)\underline{C}H_3$, 16.21 (d, *J* = 4.8 Hz, $OCH_2\underline{C}H_3$), 16.18 (d, *J* = 4.6 Hz, $OCH_2\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.91, -121.88, -123.28, -129.22, -137.05; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.18 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{33}F_{20}NO_{12}P$: 998.1421; found: 998.1423 *m/z* $[M+Na]^+$ calcd for $C_{29}H_{32}F_{20}NNaO_{12}P$: 1020.1240; found: 1020.1248.

4.13. General procedure for the synthesis of fluorinated sugar azides **26**, **27**, **28**

Monosaccharides with 2-chloroacetamido group **20**, **21**, **22** (1 equiv.) were heated overnight with KI (2.3 equiv.) and NaN_3 (3 equiv.) in anhydrous DMF (12 mL for 1 mmol of sugar) under an argon atmosphere in 80 °C. The solvent was evaporated from the reaction mixture and the residue diluted with EtOAc (2 mL for 1 mmol of sugar) washed with brine (2x3 mL for 1 mmol of sugar). The organic phase was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using a 3:1 mixture of EtOAc/CH as eluent to afforded compounds **26**, **27**, **28**.

4.13.1. 3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **26**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **21** (0.032 g, 0.042 mmol), KI (0.016 g, 0.096 mmol) and NaN_3 (0.008 g, 0.126 mmol) gave **26** as a white solid. Yield: (0.030 g) 93 %; ^{1}H NMR (403 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.6 Hz, 1H, NH), 5.42 (dd, *J* = 9.2 Hz, *J* = 10.6 Hz, H, H-3), 5.09 (t, *J* = 9.6 Hz, 1H, H-4), 4.95 (d, *J* = 8.2 Hz, 1H, H-1), 4.33-4.23 (m, 2H, H-6a, $OCH_2(CF_2)_6CF_3$), 4.17 (dd, *J* = 12.7 Hz, *J* = 2.7 Hz, 1H, H6b), 3.94-3.83 (m, 3H, H-2, CH_2N_3), 3.77 (ddd, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 9.9 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.038 (s, 3H, OAc), 2.036 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.59 $\underline{C}(O)CH_3$, 170.54 $\underline{C}(O)CH_3$, 169.2 $\underline{C}(O)CH_3$, 169.2 $\underline{C}(O)CH_2N_3$, 122.5-109.5 (m, $(CF_2)_6CF_3$), 100.4 C-1, 72.4 C-5, 71.3 C-3, 68.3 C-4, 65.2 C-6, 65.3 (t, *J* = 65.3 Hz, $\underline{C}H_2(CF_2)_6CF_3$), 54.5 C-2, 52.5 $\underline{C}H_2N_3$, 20.64 C(O)$\underline{C}H_3$, 20.57 C(O)$\underline{C}H_3$, 20.54 C(O)$\underline{C}H_3$; ^{19}F NMR (379 MHz, $CDCl_3$) δ: -81.24, -120.38, -122.52, -123.22, -123.62, -126.60; MS (ESI) *m/z*

$[M+H]^+$ calcd for $C_{22}H_{22}F_{15}N_4O_9$: 771.1147; found: 771.1155 *m/z* $[M+Na]^+$ calcd for $C_{22}H_{21}F_{15}N_4NaO_9$: 793.0967; found: 793.0977.

4.13.2. 3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **27**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **21** (0.114 g, 0.157 mmol), KI (0.060 g, 0.361 mmol) and NaN_3 (0.031 g, 0.471 mmol) gave **27** as a white solid. Yield: (0.108 g) 94 %; ^{1}H NMR (403 MHz, $CDCl_3$) δ 6.43 (d, *J* = 8.7 Hz, 1H, NH), 5.36 (dd, *J* = 10.6 Hz, *J* = 9.3 Hz, 1H, H-3), 5.08 (t, *J* = 9.6 Hz, 1H, H-4), 4.80 (d, *J* = 8.3 Hz, 1H, H-1), 4.27 (dd, *J* = 12.3 Hz, *J* = 4.8 Hz, 1H, H-6a), 4.18-4.11 (m, 3H, H-6b, $OCH_2CH_2(CF_2)_5CF_3$), 3.93 (s, 2H, CH_2N_3), 3.87-3.80 (m, 1H, H-2), 3.74 (ddd, *J* = 10.0 Hz, *J* = 4.9 Hz, *J* = 2.5 Hz, 1H, H-5), 2.52-2.34 (m, 2H, $CH_2(CF_2)_5CF_3$), 2.09 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 167.1 $\underline{C}(O)CH_2N_3$, 121.7-106.4 (m, $(CF_2)_5CF_3$), 100.5 C-1, 72.0 C-5, 71.6 C-3, 68.4 C-4, 61.9 C-6, $O\underline{C}H_2CH_2(CF_2)_5CF_3$, 54.7 C-2, 52.5 $\underline{C}H_2N_3$, 31.3 (t, *J* = 21.4 Hz, $OCH_2\underline{C}H_2(CF_2)_5CF_3$), 20.6 C(O)$\underline{C}H_3$, 20.59 C(O)$\underline{C}H_3$, 20.57 C(O)$\underline{C}H_3$; ^{19}F NMR (379 MHz, $CDCl_3$) δ -81.30, -113.91, -122.41, -123.38, -124.12, -126.64; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}F_{13}N_4O_9$: 735.1336; found: 735.1330 *m/z* $[M+Na]^+$ calcd for $C_{22}H_{23}F_{13}N_4NaO_9$: 757.1155; found: 757.1148.

4.13.3. 3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **28**

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **22** (0.090 g, 0.101 mmol), KI (0.037 g, 0.225

mmol) and NaN_3 (0.033 g, 0.505 mmol) gave **28** as a white solid. Yield: (0.081 g) 89 %; ^{1}H NMR (403MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.6 Hz, 1H, NH), 6.06 (tt, *J* = 5.1 Hz, *J* = 51.8 Hz, 1H, CF_2H), 5.42 (dd, *J* = 10.6 Hz, *J* = 9.2 Hz, 1H, H-3), 5.11 (t, *J* = 9.4 Hz, 1H, H-4), 4.95 (d, *J* = 8.2 Hz, 1H, H-1), 4.34-4.25 (m, 3H, H-6a, $OCH_2(CF_2)_9CF_2H$), 4.17 (dd, *J* = 12.4 Hz, *J* = 2.5 Hz, 1H, H-6b), 3.96-3.84 (m, 3H, CH_2N_3, H-2), 3.76 (ddd, *J* = 9.9 Hz, *J* = 4.9 Hz, *J* = 2.4 Hz, 1H, H-5), 2.11 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 $\underline{C}(O)CH_3$, 170.9 $\underline{C}(O)CH_3$, 169.5 $\underline{C}(O)CH_3$, 169.5 $\underline{C}(O)CH_2N_3$, 116.2-98.0 (m, $(CF_2)_9CF_2H$), 100.4 C-1, 70.5 C-5, 68.2 C-3, 67.7 C-4, 65.0 C-6, 61.5 $\underline{C}H_2(CF_2)_9CF_2H$, 53.6 C-2, 52.3 $\underline{C}H_2N_3$, 20.7 C(O)$\underline{C}H_3$, 20.5 C(O)$\underline{C}H_3$, 20.4 C(O)$\underline{C}H_3$; ^{19}F NMR (379 MHz, $CDCl_3$) δ -120.36, -122.40, -123.76, -129.60, -137.41; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}F_{20}N_4O_9$: 903.1146; found: 903.1144; *m/z* $[M+Na]^+$ calcd for $C_{25}H_{22}F_{20}N_4NaO_9$: 925.0965; found: 925.0962.

4.14. General procedure for the synthesis of fluorinated phosphoramidates **29**, **30**, **31**

Corresponding florinated azides **26**, **27**, **28** in anhydrous DCM (43.3 mL for 1 mmol of sugar), molecular sieves 4Å (0.213 g for 1 mmol of sugar) was added and the reaction mixture was stirred for 1 h at room temperature. Next, $P(OEt)_3$ (5 equiv.) was added and stirring was continued overnight. Then, it was diluted with DCM, passed through a pad of Celite and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH 20:1, v/v) gave **29**, **30**, **31**.

4.14.1. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphoramidoacetamido-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **29**

3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7-pentadecafluoromethoxy)-β-D-glucopyranoside **26** (0.051 g, 0.066 mmol) and $P(OEt)_3$ (0.06 mL,

0.330 mmol) gave **29** as a white solid. Yield: (0.044 g) 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 1H, NH), 5.42 (dd, *J* = 10.4 Hz, *J* = 9.3 Hz, 1H, H-3), 5.08 (t, *J* = 9.6 Hz, 1H, H-4), 4.99 (d, 1H, *J* = 8.2 Hz, H-1), 4.28 (dd, *J* = 12.3 Hz, *J* = 4.8 Hz, 1H, H-6a), 4.16 (dd, *J* = 2.4 Hz, *J* = 12.3 Hz, 1H, H-6b), 4.12-4.03 (m, 6H, 2xCH_2CH_3, $OCH_2(CF_2)_6CF_3$), 3.94-3.84 (m, 1H, H-2), 3.76 (ddd, *J* = 9.9 Hz, *J* = 5.0 Hz, *J* = 2.3 Hz, 1H, H-5), 3.53-3.99 (m, 3H, CH_2NHP(O)), 2.09 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.36-1.28 (m, 6H, 2xCH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6 $\underline{C}(O)CH_3$, 170.5 $\underline{C}(O)CH_3$, 169.5 $\underline{C}(O)CH_3$, 169.4 (d, *J* = 9.4 Hz, $\underline{C}(O)CH_2NHP(O)(OEt)_2$), 122.8-108.6 (m, $(CF_2)_5CF_3$), 100.6 C-1, 72.3 C-5, 71.7 C-3, 68.7 C-4, 63.0 (d, *J* = 6.6 Hz, $O\underline{C}H_2CH_3$), 62.9 (d, *J* = 6.6 Hz, $O\underline{C}H_2CH_3$), 62.1 C-6, 64.5 (m, $O\underline{C}H_2(CF_2)_6CF_3$), 54.5 C-2, 44.8 (s, $C(O)\underline{C}H_2NHP(O)(OEt)_2$), 20.6 $C(O)\underline{C}H_3$, 20.5 $C(O)\underline{C}H_3$, 20.3 $C(O)\underline{C}H_3$, 16.09 (d, *J* = 6.8 Hz, $O\underline{C}H_2CH_3$), 16.06 (d, *J* = 6.7 Hz, $O\underline{C}H_2CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -81.29, -120.68, -122.54, -123.27, -123.80, -126.65; ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.51 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}F_{15}N_2O_{12}P$: 881.1532; found: 881.1555 *m/z* $[M+Na]^+$ calcd for $C_{26}H_{32}F_{15}N_2NaO_{12}P$: 903.1351; found: 903.1372.

4.14.2. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphoramidoacetamido-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **30**

3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoroethoxy)-β-D-glucopyranoside **27** (0.102 g, 0.139 mmol) and $P(OEt)_3$ (0.12 mL, 0.695 mmol) gave **30** as a white solid. Yield: (0.100 g) 85%; ^{1}H NMR (403 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.8 Hz, 1H, NH), 5.34 (dd, *J* = 10.3 Hz, *J* = 9.4 Hz, 1H, H-3), 5.06 (t, *J* = 9.6 Hz, 1H, H-4), 4.83 (d, *J* = 8.3 Hz, 1H, H-1), 4.26 (dd, *J* = 12.3 Hz, *J* = 5.1 Hz, 1H, H-6a), 4.15 (dd, *J* = 2.4 Hz, *J* = 12.3 Hz, 1H, H-6b), 4.12-4.03 (m, 4H, 2xCH_2CH_3), 3.92-3.82 (m, 3H, H-2, $OCH_2CH_2(CF_2)_5CF_3$), 3.73 (ddd, *J* =

9.9 Hz, *J* = 5.0 Hz, *J* = 2.3 Hz, 1H, H-5), 3.58-3.43 (m, 3H, $CH_2NHP(O)$), 2.52-2.36 (m, 2H, $CH_2(CF_2)_5CF_3$), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.36-1.29 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 170.5 $\underline{C}(O)CH_3$, 169.4 (d, *J* = 9.4 Hz, $\underline{C}(O)CH_2NHP(O)(OEt)_2$), 120.8-107.6 (m, $(CF_2)_5CF_3$), 100.6 C-1, 72.2 C-5, 71.9 C-3, 68.6 C-4, 62.95 (d, *J* = 6.6 Hz, $O\underline{C}H_2CH_3$), 62.90 (d, *J* = 6.5 Hz, $O\underline{C}H_2CH_3$), 62.0 C-6, 61.6 (appm, $O\underline{C}H_2CH_2(CF_2)_5CF_3$), 54.4 C-2, 44.8 (s, $C(O)\underline{C}H_2NHP(O)(OEt)_2$), 31.4 (t, *J* = 21.7 Hz, $OCH_2\underline{C}H_2(CF_2)_5CF_3$), 20.64 $C(O)\underline{C}H_3$, 20.61 $C(O)\underline{C}H_3$, 20.57 $C(O)\underline{C}H_3$, 16.09 (d, *J* = 6.8 Hz, $O\underline{C}H_2CH_3$), 16.04 (d, *J* = 6.8 Hz, $O\underline{C}H_2CH_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -81.29, -113.99, -122.42, -123.40, -124.15, -126.66; ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.59 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{35}F_{13}N_2O_{12}P$: 845.1720; found: 845.1706 *m/z* $[M+Na]^+$ calcd for $C_{26}H_{34}F_{13}N_2NaO_{12}P$: 867.1539; found: 867.1530.

4.14.3. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-diethylphosphoramidoacetamido-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **31**

3,4,6-Tri-*O*-acetyl-2-azidoacetamido-2-deoxy-1-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-eicosafluorononylmethoxy)-β-D-glucopyranoside **28** (0.052 g, 0.058 mmol) and $P(OEt)_3$ (0.05 mL, 0.290 mmol) gave **30** as a white solid. Yield: (0.053 g) 92%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.65 (d, *J* = 8.6 Hz, 1H, NH), 6.06 (tt, *J* = 5.1 Hz, *J* = 51.8 Hz, CF_2H), 5.44 (dd, *J* = 10.6 Hz, *J* = 9.2 Hz, 1H, H-3), 5.10 (t, *J* = 9.4 Hz, 1H, H-4), 4.96 (d, *J* = 8.2 Hz, 1H, H-1), 4.34-4.23 (m, 7H, H-6a, 2xCH_2CH_3, $OCH_2(CF_2)_9CF_2H$), 4.17 (dd, *J* = 12.4 Hz, *J* = 2.5 Hz, 1H, H-6b), 3.96-3.84 (m, 3H, H-2, $CH_2NHP(O)$), 3.77 (ddd, *J* = 9.9 Hz, *J* = 4.9 Hz, *J* = 2.4 Hz, 1H, H-5), 2.10 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{19}F NMR (379 MHz, $CDCl_3$) δ -120.36, -122.42, -

123.74, -129.72, -137.39; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{34}F_{20}N_2O_{12}P$: 1013.1530; found: 1013.1529 *m/z* $[M+Na]^+$ calcd for $C_{29}H_{33}F_{20}N_2NaO_{12}P$: 1035.1349; found: 1035.1349.

4.15. General synthesis of phosphonates **32** and **34**

To a solution of sugar chloride **19** (1 equiv.) or sugar bromide **33** (1 equiv.) in MeCN (30 mL for 1 mmol of sugar), KI (2.26 equiv.) and $P(OEt)_3$ (2 equiv.) were added. The reaction mixture was heated in 65 °C for 3.5-4 h. The solvent was evaporated and the crude product was purified by column chromatography using a 20:1 mixture of DCM/MeOH as eluent.

4.15.1. 2-Diethylhosphonoacetamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranoside **32**

1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranoside **19** (0.021 g, 0.050 mmol) and $P(OEt)_3$ (0.02 mL, 0.100 mmol) gave **32** as a white solid. Yield: (0.018 g) 69%; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (d, *J* = 9.0 Hz, 1H, NH), 5.85 (d, *J* = 8.8 Hz, 1H, H-1), 5.33 (dd, *J* = 9.3 Hz, *J* = 10.6 Hz, 1H, H-4), 5.10 (t, *J* = 9.6 Hz, 1H, H-3), 4.29 (dd, *J* = 4.5 Hz, *J* = 12.5 Hz, 1H, H-6a), 4.20-4.14 (m, 1H, H-2), 4.13-4.09 (m, 5H, H-6b, 2xOCH_2CH_3), 3.87 (ddd, *J* = 2.2 Hz, *J* = 4.5 Hz, *J* = 10.0 Hz, 1H, H-5), 2.81 (d, *J* = 21.0 Hz, 2H, $CH_2P(O)(OEt)_2$), 2.13 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.37-1.32 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.7 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_3$, 164.5 (d, *J* = 4.1 Hz, $\underline{C}(O)CH_2P(O)(OEt)_2$), 91.9 C-1, 72.6 C-5, 72.0 C-3, 68.2 C-4, 62.9 (d, *J* = 6.4 Hz, $O\underline{C}H_2CH_3$), 61.6 C-6, 53.3 C-2, 35.3 (d, *J* = 129.9 Hz, $C(O)\underline{C}H_2P(O)(OEt)_2$), 20.9 $C(O)\underline{C}H_3$, 20.71 $C(O)\underline{C}H_3$, 20.68 $C(O)\underline{C}H_3$, 20.60 $C(O)\underline{C}H_3$, 16.28 (d, *J* = 6.1 Hz, $OCH_2\underline{C}H_3$); ^{31}P NMR (243 MHz, $CDCl_3$): δ 21.53 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{33}NO_{13}P$: 526.1690; found: 526.1698 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{32}NNaO_{13}P$: 548.1509; found: 548.1522.

4.15.2. 2-Diethylphosphonopropanamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranoside **34**

1,3,4,6-tetra-*O*-acetyl-2-(3-bromopropionylamido)-2-deoxy- β-D-glucopyranoside (**33**) (0.097 g, 0.200 mmol) and $P(OEt)_3$ (0.1 mL, 0.600 mmol) gave **34** as a white solid. Yield: (0.046 g) 43 %; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 9.2 Hz, 1H, NH), 5.76 (d, *J* = 8.8 Hz, 1H, H-1), 5.23 (appt, *J* = 9.9 Hz, 1H, H-3), 5.10 (t, *J* = 9.6 Hz, 1H, H-4), 4.30-4.25 (m, 2H, H-6a, H-6b), 4.14-4.05 (m, 5H, 2xOCH_2CH_3, H-2), 3.81 (ddd, *J* = 2.2 Hz, *J* = 4.6 Hz, *J* = 9.8 Hz, 1H, H-5), 2.35-2.45 (m, 2H, $CH_2CH_2P(O)(OEt)_2$), 2.06-1.96 (m, 2H, $CH_2P(O)(OEt)_2$), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02 (s, 6H, 2xOAc), 1.37-1.26 (m, 6H, 2xCH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.4 $\underline{C}(O)CH_3$, 171.3 $\underline{C}(O)CH_3$, 170.72 $\underline{C}(O)CH_3$, 170.68 $\underline{C}(O)CH_3$, 169.4 (d, *J* = 4.4 Hz, $\underline{C}(O)CH_2CH_2P(O)(OEt)_2$), 92.4 C-1, 72.66 C-5, 72.65 C-3, 68.1 C-4, 62.05 (d, *J* = 6.5 Hz, $O\underline{C}H_2CH_3$), 61.99 (d, *J* = 6.6 Hz, $O\underline{C}H_2CH_3$), 61.7 C-6, 53.0 C-2, 29.1 (d, *J* = 3.6 Hz, $C(O)\underline{C}H_2CH_2P(O)(OEt)_2$), 20.9 $C(O)\underline{C}H_3$, 20.72 $C(O)\underline{C}H_3$, 20.74 (d, *J* = 143.8 Hz, $C(O)CH_2\underline{C}H_2P(O)(OEt)_2$), 20.65 $C(O)\underline{C}H_3$, 20.59 $C(O)\underline{C}H_3$, 16.4 (d, *J* = 5.6 Hz, 2x$OCH_2\underline{C}H_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 31.33 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{35}NO_{13}P$: 540.1846; found: 540.1852 *m/z* $[M+Na]^+$ calcd for $C_{21}H_{34}NNaO_{13}P$: 562.1665; found: 562.1674.

4.16. 1,3,4,6-tetra-*O*-acetyl-2-(3-bromopropionylamido)-2-deoxy-β-D-glucopyranoside **33**

A solution of 2-deoxy-2-amino-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl hydrochloride (0.099 g, 0.258 mmol) in anhydrous DCM (3.3 mL) was cooled to 0 °C. Next Et_3N (0.1 mL) was added followed by DCC (0.186 g, 0.903 mmol) and 3-bromopropionic acid (0.276 g, 1.806 mmol). The reaction mixture was allowed to warm up to room temperature and stirred overnight. After finishing the precipitate was filtered and the solvents were evaporated. Product was purified by column chromatography (EtOAc:CH 1:1, v/v) gave **33** as white solid. Yield: (0.092 g) 75%; ^{1}H

NMR (403 MHz, $CDCl_3$): δ 6.02 (d, *J* = 9.4 Hz, 1H, NH), 5.72 (d, *J* = 8.8 Hz, 1H, H-1), 5.21 (dd, *J* = 9.4 Hz, *J* = 10.5 Hz, 1H, H-3), 5.13 (t, *J* = 9.6 Hz, 1H, H-4), 4.41-4.32 (m, 1H, H-2), 4.28 (dd, *J* = 4.7 Hz, *J* = 12.5 Hz, 1H, H-6a), 4.13 (dd, *J* = 2.6 Hz, *J* = 12.3 Hz, 1H, H-6b), 3.85 (ddd, *J* = 2.2 Hz, *J* = 4.6 Hz, *J* = 9.8 Hz, 1H, H-5), 3.61 (t, *J* = 6.2 Hz, 1H, CH_2Br), 2.70 (t, *J* = 6.2 Hz, 1H, CH_2CH_2Br), 2.13 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 $\underline{C}(O)CH_3$, 170.7 $\underline{C}(O)CH_3$, 169.7 $\underline{C}(O)CH_3$, 169.6 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_2CH_2Br$, 92.4 C-1, 72.8 C-5, 72.4 C-3, 67.9 C-4, 61.6 C-6, 52.8 C-2, 39.6 C(O)$\underline{C}H_2CH_2Br$, 27.3 $CH_2\underline{C}H_2Br$, 21.0 C(O)$\underline{C}H_3$, 20.9 C(O)$\underline{C}H_3$, 20.7 C(O)$\underline{C}H_3$, 20.6 C(O)$\underline{C}H_3$; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}BrNO_{10}$: 482.0662; found: 482.0676 *m/z* $[M+Na]^+$ calcd for $C_{17}H_{24}BrNNaO_{10}$: 504.0481; found: 504.0485.

4.17. General synthesis of phosphoramidates **36** and **38**

To the mixture of **35** (1 equiv.) or **37** (1 equiv.) in anhydrous DCM (43.3 mL for 1 mmol of sugar), molecular sieves 4Å (0.213 g for 1 mmol of sugar) was added and the reaction mixture was stirred for 1h at room temperature. Next, $P(OEt)_3$ (5 equiv.) was added and stirring was continued overnight. Then, it was diluted with DCM, passed through a pad of Celite and solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH 20:1, v/v) gave **36** or **38.**

4.17.1. 2-diethylphosphoramidoacetamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **36**

1,3,4,6-tetra-O-acetyl-2-azidoacetamide-2-deoxy-β-D-glucopyranose **35** (0.079 g, 0.184 mmol) and $P(OEt)_3$ (0.16 mL, 0.920 mmol) gave **36** as a white solid. Yield: (0.068 g) 69%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 9.5 Hz, 1H, NH), 5.86 (d, *J* = 8.7 Hz, 1H, H-1), 5.38 (dd, *J* = 9.4 Hz, *J* = 10.5 Hz, 1H, H-3), 5.13 (t, *J* = 9.7 Hz, 1H, H-4), 4.35-4.25 (m, 1H, H-6a, H-2), 4.16-

3.95 (m, 6H, 2xOCH_2CH_3, H-6b, NHP(O)), 3.87 (ddd, *J* = 2.2 Hz, *J* = 4.7 Hz, *J* = 10.0 Hz, 1H, H-5), 3.53 (dd, *J* = 7.7 Hz, *J* = 11.2 Hz, 2H, CH_2NH), 2.11 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.37-1.27 (m, 6H, 2xCH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.98 $\underline{C}(O)CH_3$, 170.71 $\underline{C}(O)CH_3$, 170.64 $\underline{C}(O)CH_3$, 170.63 $\underline{C}(O)CH_3$, 169.3 (d, *J* = 9.4 Hz, $\underline{C}(O)CH_2NHP(O)(OEt)_2$), 92.2 C-1, 72.6 C-5, 72.5 C-3, 68.0 C-4, 62.9 (d, *J* = 5.5 Hz, $O\underline{C}H_2CH_3$), 62.8 (d, *J* = 5.6 Hz, $O\underline{C}H_2CH_3$), 61.7 C-6, 52.7 C-2, 44.6 $\underline{C}H_2NHP(O)(OEt)_2$, 20.9 $C(O)\underline{C}H_3$, 20.7 $C(O)\underline{C}H_3$, 20.6 $C(O)\underline{C}H_3$, 20.5 $C(O)\underline{C}H_3$, 16.16 (d, *J* = 5.4 Hz, $OCH_2\underline{C}H_3$), 16.07 (d, *J* = 5.4 Hz, $OCH_2\underline{C}H_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.7 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{34}N_2O_{13}P$: 541.1799; found: 541.1801 *m/z* $[M+Na]^+$ calcd for $C_{20}H_{33}N_2NaO_{13}P$: 563.1618; found: 563.1632.

4.17.2. 2-diethylphosphoramidopropionamido-1,2,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose **38**

1,3,4,6-tetra-*O*-acetyl-2-(3-azidopropionylamido)-2-deoxy-β-D-glucopyranoside (**37**) (0.073 g, 0.164 mmol) and $P(OEt)_3$ (0.14 mL, 0.820 mmol) gave **38** as a white solid. Yield: (0.055 g) 60%; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.35 (d, *J* = 9.2 Hz, 1H, NH), 5.80 (d, *J* = 8.7 Hz, 1H, H-1), 5.26 (dd, *J* = 9.4 Hz, *J* = 10.2 Hz, 1H, H-3), 5.13 (t, *J* = 9.7 Hz, 1H, H-4), 4.29 (dd, *J* = 4.7 Hz, *J* = 12.5 Hz, 1H, H-6a), 4.22 (dt, *J* = 9.0 Hz, *J* = 19.4 Hz, 1H, H-2), 4.13 (dd, *J* = 2.4 Hz, *J* = 12.4 Hz, 1H, H-6b), 4.09-4.03 (m, 4H, 2xOCH_2CH_3), 3.84 (ddd, *J* = 2.2 Hz, *J* = 4.6 Hz, *J* = 10.0 Hz, 1H, H-5), 3.31-3.25 (m, 1H, NHP(O)), 3.21-3.13 (m, 2H, CH_2NH), 2.37-2.31 (m, 2H, CH_2CH_2NH), 2.13 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.33 (appt, *J* = 7.1 Hz, 6H, 2xCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6 $\underline{C}(O)CH_3$, 171.1 $\underline{C}(O)CH_3$, 170.6 $\underline{C}(O)CH_3$, 169.4 $\underline{C}(O)CH_3$, 169.3 $\underline{C}(O)CH_2CH_2NHP(O)(OEt)_2$, 92.3 C-1, 72.8 C-5, 72.5

C-3, 67.8 C-4, 62.5 (d, *J* = 5.6 Hz, O<u>C</u>$H_2$$CH_3$), 61.8 (d, *J* = 5.6 Hz, O<u>C</u>$H_2$$CH_3$), 61.6 C-6, 53.2 C-2, 37.8 (d, *J* = 4.1 Hz, <u>C</u>$H_2$$CH_2$NHP(O)$(OEt)_2$), 37.5 CH_2<u>C</u>H_2NHP(O)$(OEt)_2$, 20.9 C(O)<u>C</u>H_3, 20.7 C(O)<u>C</u>H_3, 20.6 C(O)<u>C</u>H_3, 20.5 C(O)<u>C</u>H_3, 16.3 (d, *J* = 6.5 Hz, OCH_2<u>C</u>H_3), 16.1 (d, *J* = 6.9 Hz, OCH_2<u>C</u>H_3); ^{31}P NMR (243 MHz, $CDCl_3$): δ 8.9 (s, 1P); MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{36}N_2O_{13}P$: 555.1955; found: 555.1957 *m/z* $[M+Na]^+$ calcd for $C_{21}H_{35}N_2NaO_{13}P$: 577.1774; found: 577.1773.

4.18. 1,3,4,6-tetra-*O*-acetyl-2-(3-azidopropionylamido)-2-deoxy-β-D-glucopyranoside **37**

To the mixture of bromide **33** (0.086 g, 0.178 mmol) in acetone (6 mL), KI (0.006 g, 0.036 mmol) and NaN_3 (0.058 g, 0.890 mmol) were added and stirred overnight. The solvent was evaporated, diluted with EtOAc and washed with aq. sat. $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and solvent was evaporated under reduced pressure. Purification by column chromatography (EtOAc/CH, 3:1,v/v) afforded **37** as a white solid. Yield: (0.073 g) 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (d, *J* = 9.4 Hz, 1H, NH), 5.74 (d, *J* = 8.8 Hz, 1H, H-1), 5.21 (dd, *J* = 9.4 Hz, *J* = 10.5 Hz, 1H, H-3), 5.13 (t, *J* = 9.6 Hz, 1H, H-4), 4.41-4.32 (m, 1H, H-2), 4.28 (dd, *J* = 4.7 Hz, *J* = 12.5 Hz, 1H, H-6a), 4.13 (dd, *J* = 2.6 Hz, *J* = 12.3 Hz, 1H, H-6b), 3.88 (ddd, *J* = 2.2 Hz, *J* = 4.6 Hz, *J* = 9.8 Hz, 1H, H-5), 3.62 (t, *J* = 6.2 Hz, 2H, CH_2N_3), 2.70 (t, *J* = 6.2 Hz, 2H, $CH_2CH_2N_3$), 2.13 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc) ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 <u>C</u>(O)CH_3, 170.6 <u>C</u>(O)CH_3, 170.0 <u>C</u>(O)CH_3, 169.5 <u>C</u>(O)CH_3, 169.2 C(O)<u>C</u>$H_2$$CH_2N_3$, 92.4 C-1, 72.9 C-5, 72.4 C-3, 67.8 C-4, 61.6 C-6, 53.0 C-2, 47.1 CH_2<u>C</u>H_2N_3, 35.8 <u>C</u>$H_2$$CH_2N_3$, 20.8 C(O)<u>C</u>$H_3$, 20.7 C(O)<u>C</u>$H_3$, 20.59 C(O)<u>C</u>$H_3$, 20.55 C(O)<u>C</u>$H_3$; MS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{25}N_4O_{10}$: 445.1571; found: 445.1567 *m/z* $[M+Na]^+$ calcd for $C_{17}H_{24}N_4NaO_{10}$: 467.1390; found: 467.1389.

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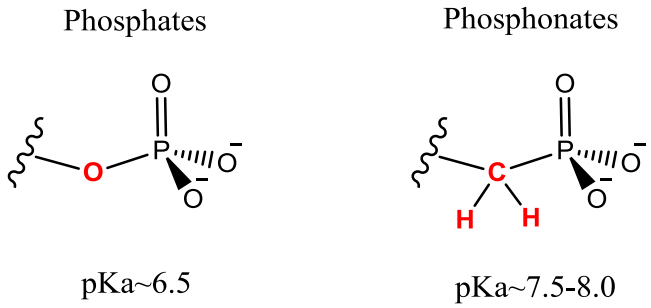


Figure 1 Diminishing of acidity P - C bond in phosphonates in relation to P - O bond in phosphates

Phosphoramidates

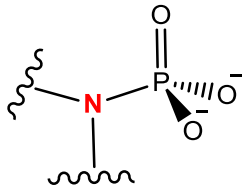


Figure 2 General structure of phosphoramidates

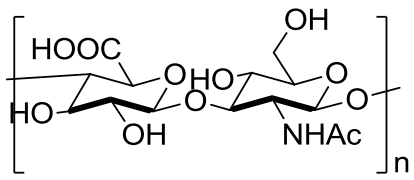
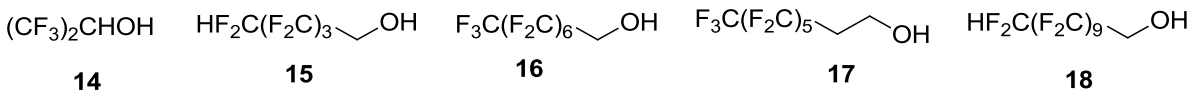
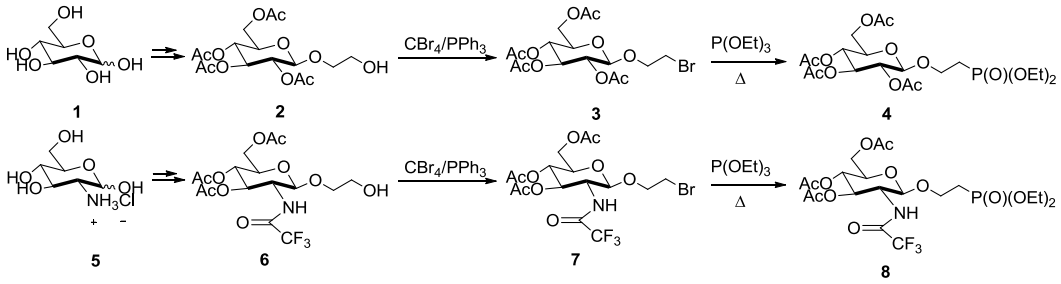


Figure 3 Hyaluronic acid (HA)

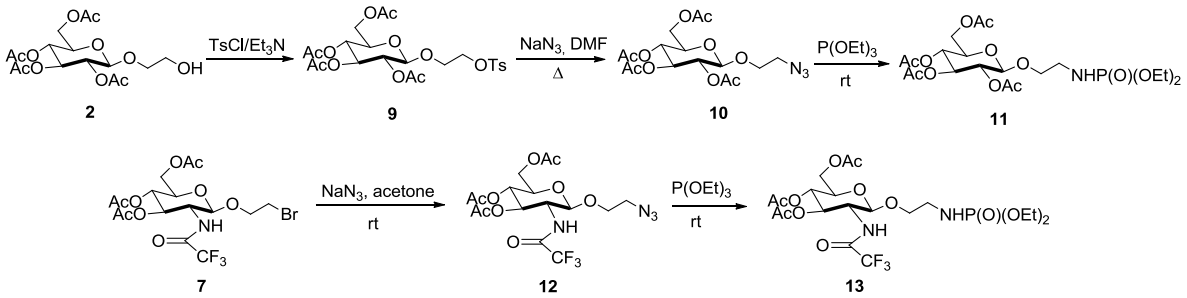


14 **15** **16** **17** **18**

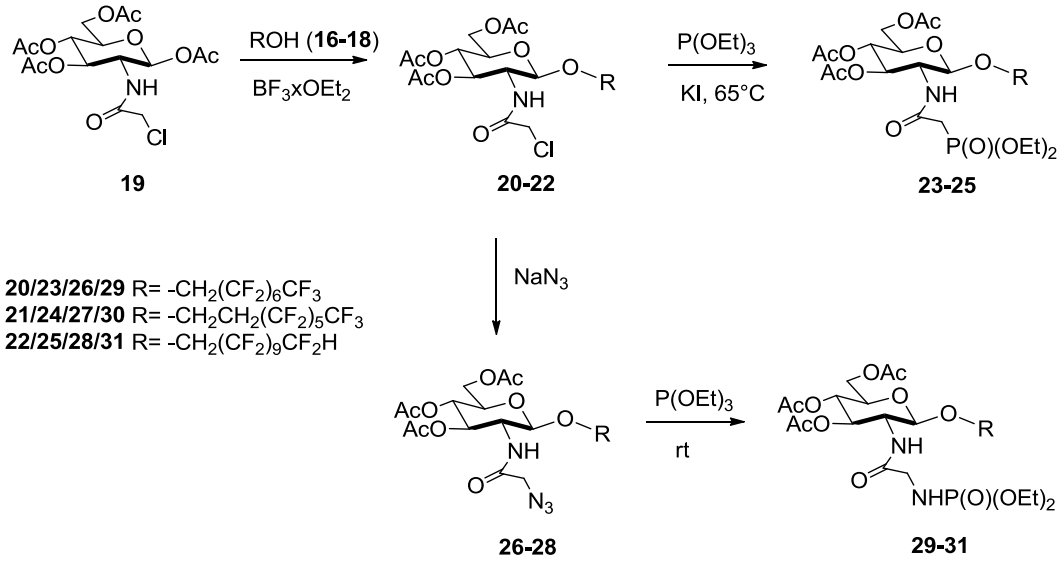
Figure 4 Partially fluorinated alcohols used in substitution reaction with sugar **19**



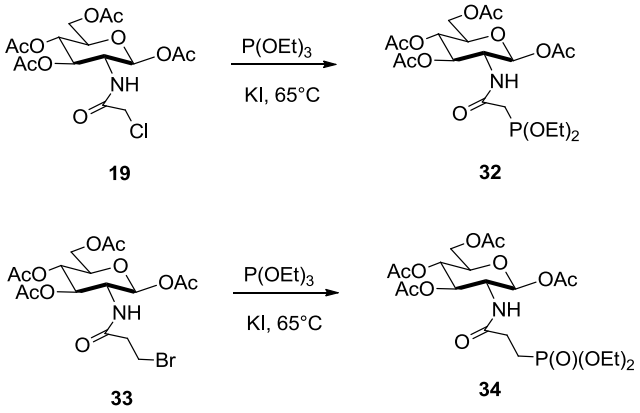
Scheme 1 Synthesis of sugar phosphonates **4** and **8** from D-glucose **1** and D-glucosamine hydrochloride **5**



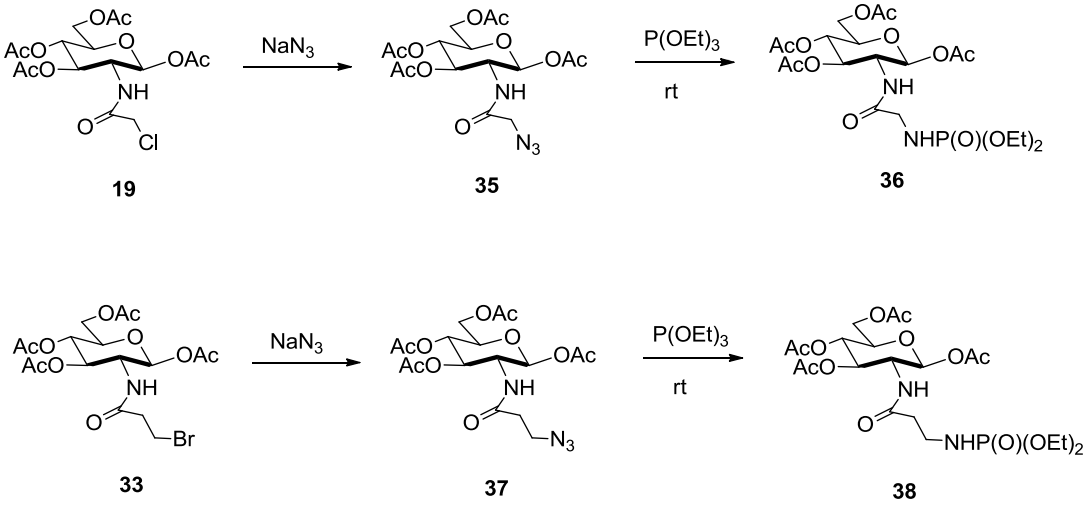
Scheme 2 Synthesis of sugar phosphoramidates **11** and **13**



Scheme 3 Synthesis of fluorinated phosphonates **23-25** and phosphoramidates **29-31**



Scheme 4 Synthesis of nonfluorinated phosphonates **32** and **34**



Scheme 5 Synthesis of nonfluorinated phosphoramidates **36** and **38**