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Synthesis of Triazole-Containing Furanosyl Nucleoside Analogs and Their Phosphate, Phosphoramidate or Phoshonate Derivatives as Potential Sugar Diphosphate or Nucleotide Mimetics

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Abstract: The synthesis of novel, rather stable and potentially bioactive xylofuranosyl nucleoside analogs and potential sugar diphosphate or nucleotide mimetics comprising a 1,2,3-triazole moiety is reported. 3'-*O*-Methyl-branched *N*-benzyltriazole isonucleosides were accessed in 5-7 steps and 42-54% overall yields using a Cu(I)-catalyzed cycloaddition of 3-*O*-propargyl-1,2-*O*-isopropylidene-α-D-xylofuranose with benzyl azide as key step. Related isonucleotides were obtained by 5-*O*-phosphorylation of acetonide-protected 3-*O*-propargyl xylofuranose and further "click" cycloaddition or by Staudinger-phosphite reaction of a 5-azido *N*-benzyltriazole isonucleoside. Hydroxy-, amino- or bromomethyl triazole 5'-isonucleosides were synthesized by thermal cycloaddition of 5-azido 3-*O*-benzyl/dodecyl xylofuranoses with propargyl alcohol, propargylamine or propargyl bromide. Better yields (82-85%) were obtained when using propargyl alcohol and a high 1,4-regioselectivity was attained with propargyl bromide. Further *O*/*N*-phosphorylation or Arbuzov reaction led to (triazolyl)methyl phosphates, phosphoramidates or phosphonates. The latter were converted into uracil nucleoside 5'-(triazolyl)methyl phosphonates as prospective nucleoside diphosphate mimetics.

Introduction

Nucleosides and nucleotides are key molecules in essential biological events including nucleic acid synthesis, cell division, cell signalling, and metabolism. The development of synthetic analogues of these molecules, aiming at inhibiting nucleotide-dependent processes/enzymes that are overactivated and play crucial roles in diseases such as cancer or viral infections, has been significantly explored. Various nucleoside and nucleotide analogs have reached clinical application as chemotherapeutic agents, acting mostly as nucleic acid antimetabolites, from which cytarabine, gemcitabine or azidothymidine can be highlighted.[1] Their mechanism of action involves a kinase-mediated conversion into di- and triphosphate nucleoside metabolites and further incorporation into nucleic acids or alternatively, inhibition of polymerases or other enzymes involved in nucleic acid or nucleotide biosynthesis, inducing inhibition of cell division or viral replication.[1]

Despite the proven chemotherapeutic efficacy of nucleos(t)ide analogs, some drawbacks are associated with their use, namely their high polarity which results in low oral bioavailability and the resistance that cancer or virus-infected cells exert against their action. Among the relevant nucleoside-specific chemoresistance mechanisms are the downregulation of nucleoside transporters,[2] hindering their passage to the intracellular medium, and of nucleoside kinases,[3] leading to a decreased formation of nucleoside phosphates, or the overexpression of nucleotidases, which mediate dephosphorylation of the former metabolites.[4] Nucleoside analogs or mimetics possessing structural features that may allow them to overcome these issues have been synthesized. Modifications at the nucleobase, sugar moiety or the insertion of phosphate group analogs have been performed aiming at nucleos(t)ide analogs of improved bioavailability, cell-penetrating ability or stability to enzymatic hydrolysis. These molecules include acyclic nucleos(t)ides,[5] carbocyclic derivatives[6] or other sugar heteroanalog-containing nucleosides,[7] nucleosides comprising uncommon glycosyl units,[8] *C*-nucleosides,[9] nucleoside alkyl/aryl phosphodi/triesters,[10] phosphoramidates or H- or C-phosphonates.[10,11]

Other biological effects of therapeutic relevance have been reported for nucleos(t)ides and analogs, including antibiotic properties, acting as inhibitors of crucial microbial cell processes,[12] or ability to inhibit cholinesterases,[13] which are important therapeutic targets for Alzheimer's disease symptomatic treatment. Among the described cholinesterase inhibitors are our previously reported 5'/6'-isonucleosides,[13c–f] which comprise a nucleobase or an analogous nitrogeneous heteroaromatic moiety N-linked to a sugar moiety at C-5 or C-6, and D-glucofuranuronamide-based *N*-glycosyl triazoles.[13e] Isonucleosides are rather stable nucleoside regioisomers since their N-C bond linking the sugar and nucleobase units is less susceptible to chemical or enzymatic hydrolysis than the Nglycosidic bond present in nucleosides. Furanosyl 2'/3'-isonucleosides displaying anticancer[14] and antiviral[15] properties were reported.

The biological profile and efficacy of nucleos(t)ide analogs encourage the development of new structures that may circumvent the limitations of the clinically-used ones, exhibit alternative mechanisms of action, and offer new therapeutic opportunities. In this context, we report herein on the synthesis of a variety of xylofuranose-based isonucleosides (**A**, **B**) together with potential mimetics of sugar diphosphates (**D**) and nucleotides (**C**, **E**) comprising a 1,2,3-triazole moiety (Figure 1). The broad bioactivity profile associated with this motif,[16] its ability for hydrogen-bond, ion-dipole, cation-π or π-stacking interactions with amino acid residues or to coordinate metals, enabling molecular recognition by enzymes or receptors, and its high chemical and enzymatic stability are relevant aspects that motivate its inclusion in new potentially bioactive structures. Furthermore, this moiety can be straightforwardly accessed by means of a Huisgen azide-alkyne cycloaddition reaction.[17] Reported examples on furanosyl nucleoside analogs containing a 1,2,3-triazole moiety[17h] revealed their propensity to exhibit antiviral,[18] anticancer[19] or antifungal activities,[20] and to inhibit nucleotide-dependent enzymes.[21] This N-heteroaromatic system was included as a surrogate of a nucleobase in isonucleosides of types **A** and related isonucleotides **C**, comprising a benzyltriazole motif linked by an oxymethylene spacer to the xylofuranose unit at C-3 (3'-*O*-methyl-branched isonucleosides), and in 5'-isonucleosides **B** containing hydroxy-, amino- or bromomethyl triazole systems. A terminal aminomethyl triazole isonucleoside was previously reported as a moderate acetylcholinesterase inhibitor,[13c] which shows the biological interest of this type of structure.

Moreover, the triazole unit was also aimed as a potential neutral and rather stable surrogate of a phosphate group in compounds of types **D** and **E**. Such bioisosteric replacement was already demonstrated to be feasible in the mimicry of glycosyl phosphates,[22] nucleic acid oligonucleotides,[23] nucleoside mono- or diphosphates,[21d] or nucleoside triphosphates.[24] Non-charged phosphate group analogs such as di-*O*-ethyl/phenyl phosphate, di-*O*-ethyl phosphoramidate or phosphonate moieties were installed in the molecules, which may solve polarity and low cell-penetrating ability concerns. Moreover, the di-*O*-alkyl/aryl phosph(on)ate and phosphoramidate moieties may undergo intracellular cleavage by phosphodiesterase-mediated hydrolysis, releasing the free phosph(on)ate and phosphoramidate isonucleosides, similarly to what occurs with ester-type nucleoside phosph(on)ate prodrugs.[11b] In compounds of types **D** and **E**, the combination of a phosphate group analog with a triazole unit was intended to establish new potential neutral diphosphate mimetics of higher stability, namely the (triazolyl)methyl phosphate, phosphoramidate and phosphonate systems. The (triazolyl)methyl phosphonate fragment may render the molecules particularly stable due to their non-hydrolytically cleavable P-C bond, which encouraged the synthesis of prospective nucleoside diphosphate mimetics of type **E**. Motivated by previous studies showing the biological efficacy of 3-*O*-benzyl and 3-*O*-dodecyl-containing furanosyl nucleoside analogs,[8b, 8c, 13e] 3-*O*-benzyl and 3-*O*-dodecyl groups were included in molecules having a xylofuranos-5'-yl triazole scaffold.

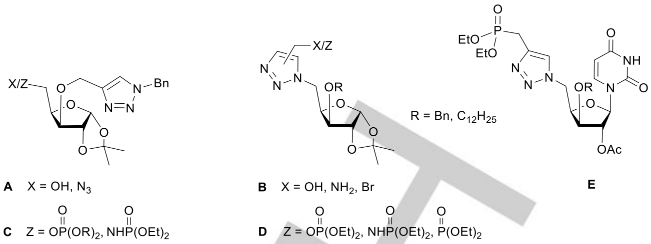
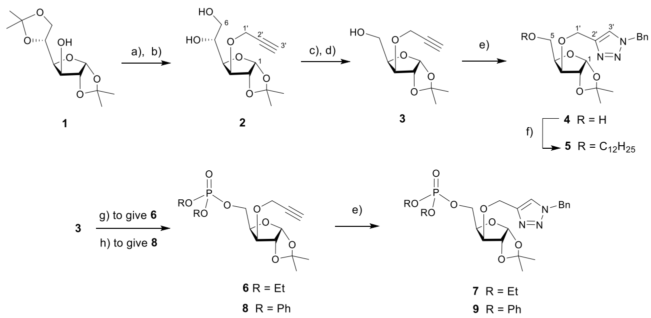


Figure 1. General skeletons of triazole-containing isonucleosides (**A**, **B**), isonucleotides (**C**), potential sugar diphosphate mimetics (**D**) and nucleotide mimetics (**E**) exploited herein.

Results and Discussion

The synthesis of isonucleosides and related isonucleotides comprising an *O*-(*N*-benzyltriazolyl)methyl system at a pentoxylofuranosyl template at C-3 (compounds of types **A** and **C**, Figure 1) involved the access to 3-*O*-propagyl xylofuranosyl derivatives as key synthons. Thus, diacetone-D-glucose (**1**, Scheme 1) was subjected to *O*-propargylation (propargyl bromide/sodium hydride), which was followed by selective mild acidic hydrolysis of the primary acetonide (75% acetic acid aqueous soln.) to furnish the 5,6-diol **2**. Oxidative cleavage of **2** with sodium periodate and subsequent reduction of the formed dialdofuranose with sodium borohydride afforded the 3-*O*-propargyl xylofuranose **3**. “Click” 1,3-dipolar cycloaddition between **3** and benzyl azide in the presence of a copper iodide/Amberlyste A-21 catalytic system provided the *N*-benzyl triazole derivative **4** in quantitative yield.

The synthesis of C-5 functionalized derivatives of this isonucleoside was then exploited. In order to increase its lipophilicity, a dodecyl moiety was introduced at OH-5 through alkylation (dodecyl bromide/sodium hydride), affording **5**. Phosphorylation of the 3-*O*-propargylated derivative **3** with diethyl phosphorochloridate in the presence of trimethylamine and 4-dimethylaminopyridine (DMAP) gave the corresponding phosphate triester **6**, which upon Cu(I)-catalyzed cycloaddition with benzyl azide provided the triazole-containing isonucleoside 5'-diethyl phosphate **7** in 92% yield. On the other hand, treatment of **3** with diphenylphosphoryl azide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 40 ºC afforded the 5-*O*-diphenylphosphono xylofuranose derivative **8**. Even at a prolonged reaction time (16 h), no formation of a secondary product resulting from the nucleophilic replacement of the phosphate group by the azide anion occurred, as reported for this methodology,[25] being the xylofuranos-5-yl diphenyl phosphate **8** obtained as the sole product in 68% yield. Further “click” cycloaddition with benzyl azide furnished the 5'-diphenyl phosphate isonucleoside **9** in 74% yield, as a diphenyl counterpart of isonucleotide **7**.



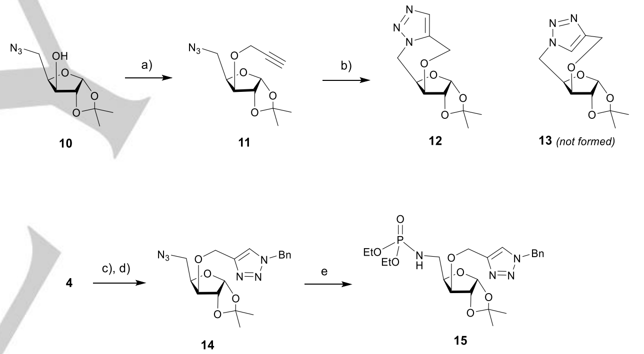
Scheme 1. Reagents and conditions: (a) C_3H_3Br, NaH, DMF, r. t., 16 h; (b) AcOH (75% aq. soln.), r. t. 16 h., 96%, 2 steps. (c) $NaIO_4$, THF/H_2O (3:1), r. t. 4 h; (d) $NaBH_4$, $EtOH/H_2O$ (2:1), r. t., 1 h, 57%, 2 steps; (e) BnN_3, CuI/A-21, CH_2Cl_2, r. t., 24 h, 98% (**4**), 92% (**7**), 74% (**9**); (f) $C_{12}H_{25}Br$, NaH, DMF, r. t., 16 h, 95%; (g) $ClPO(OEt)_2$, NEt_3, DMAP, CH_2Cl_2, r. t., 16 h, 98%; (h) DPPA, DBU, toluene, r. t., 24 h, then 40 ºC, 16 h, 68%.

For the synthesis of an isonucleoside phosphoramidate analog of isonucleotide **7**, the use of the 5-azido 3-*O*-propargyl xylofuranose derivative **11** as precursor was firstly attempted (Scheme 2). It was synthesized by 3-O-propargylation (propargyl bromide/sodium hydride) of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**10**),[26] which was completed within a considerable shorter reaction time (5 min) than that previously reported (2 h) under similar conditions.[27] However, due to the presence of both alkynyl and azide moieties, this compound was found to be unstable at room temperature and in dichloromethane solution in the presence of the CuI/A-21 catalyst, envolved towards the fused tetracyclic 1,5-dissubstituted triazole **12** through intramolecular 1,3-dipolar cycloaddition. The ^{13}C NMR signals for C-4 and C-5 of the triazole moiety at 132.2 ppm and 135.2 ppm, respectively, were indicative of a 1,5-disubstituted derivative,[28] while the fused system in **12** was confirmed by the HMBC correlations between protons H-5 of the sugar moiety with C-5 of the triazole unit and between the oxymethylenic protons and both C-4/C-5 of the triazole motif. The sole formation of **12** was previously reported *via* an intramolecular thermal Huisgen cycloaddition of **11** in toluene at 100 ºC, [27,29] a protocol which in our hands led to **12** in 67% yield.

Although our NMR data for this compound were in conformity with those reported,[27] no concordance was verified between our single crystal X-ray structure (CCDC number 2004694, **A**, Figure 2) with the published structure (CSD refcode DAQJOV; CCDC number 264130) which corresponds to the L-*xylo*-configured derivative (see Figure S36, in the Supporting Information). The crystal structure of **12** obtained in this work corresponds to the D-*xylo*-configured molecule with a fused tetracyclic framework containing a 7-membered ring (1,4-oxazepane) between the triazole motif and the xylofuranose ring, which adopts a C3-endo conformation. The bond lengths and angles for the two enantiomers are analogous (see CIF file).

To gain insight into the observed experimental regioselectivity in the thermal cycloaddition, density functional theory (DFT) calculations (PBE1PBE/6-311G**) were performed on 1,5- and 1,4-disubstituted triazoles (**12**, **13**) to investigate their relative stability. The three-dimensional structures of **12** and **13** were built using Pymol[30] and geometry optimization (**B**, **C**, Figure 2) was performed using Gaussian 09[31] (see Computational Details in the Exptl. Sect. for more informations). The DFT-optimised structure of **12** (**B**, Figure 2) was compared with the X-ray structure (**A**, Figure 2) and the agreement was excellent with a root-mean square deviation (RMSD) of atomic positions of ~ 0.09 Å (see Figure S37, in the Supporting Information). The calculated values for the enthalpy (ΔH) and free energy (ΔG) of the 1,4-disubstituted regioisomer (**C**, Figure 2) in toluene are higher by *ca.* 55 kcal/mol relative to those obtained for the 1,5-regioisomer (**B**, Figure 2), thereby supporting the observed regioselectivity and indicating that **12** is most certainly the thermodynamic product (Table 1). Similar energy differences in favour of the 1,5-regioisomer were obtained when chloroform was considered as solvent in the study, indicating that solvent polarity has no effect on the regiochemical course of this intramolecular 1,3-dipolar cycloaddition.

Since the installation of the *N*-benzyltriazole moiety on the bisfunctionalized template **11** towards the desired 5-azido isonucleoside appeared not to be feasible, an alternative pathway consisting on the introduction of an azide functionality on the 5-hydroxylated 3-*O*-(*N*-benzyltriazolyl)methyl isonucleoside **4** was undertaken. Thus, **4** was subjected to a sequence of tosylation (tosyl chloride/pyridine) and nucleophilic displacement with sodium azide, leading to **14** in 78% overall yield. Staudinger-type reaction of **14** with triethyl phosphite afforded quantitatively the isonucleoside 5-phosphoramidate **15**.



Scheme 2. Reagents and conditions: (a) C_3H_3Br, NaH, DMF, r. t., 5 min., 95%; (b) toluene, 100 ºC, 2 h, 67%; (c) TsCl, py, r. t., 16 h; (d) NaN_3, DMF, 80 ºC, 16 h, 78%, 2 steps; (e) $P(OEt)_3$, CH_2Cl_2, r. t., 48 h, 96%.

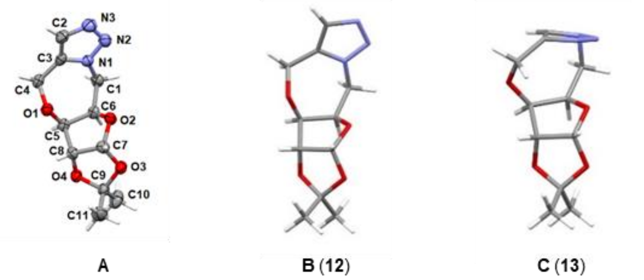


Figure 2. (**A**) X-ray molecular structure of **12**. (**B**, **C**) Optimized structures of **12** and **13** in toluene (PBE1PBE/6-311G**).

Table 1. Calculated enthalpy and Gibbs free energy for structures **B** and **C**. The values for the lowest energy regioisomer (**12**, structure **B**) were set as reference.

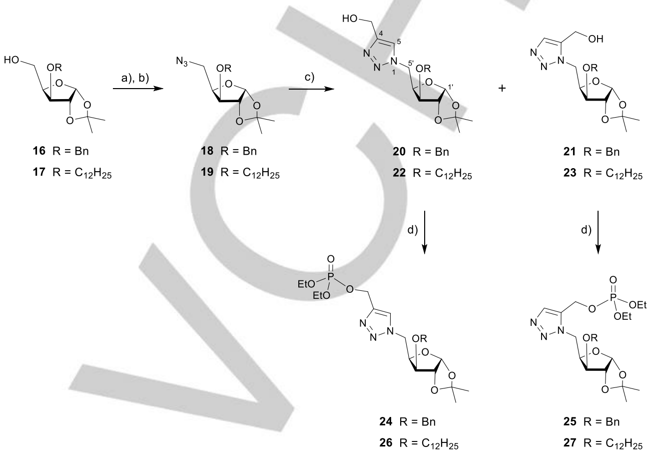
	1,5-disubstituted triazole (**B**)	1,4-disubstituted triazole (**C**)
Δ*H* (kcal/mol)	0	55.7
Δ*G* (kcal/mol)	0	55.1

5-Azido xyfuranoses were the precursors used for the synthesis of a variety of xylofuranos-5'-yl triazole isonucleosides **B** (Figure 1) and their derivatives comprising phosphate, phosphoramidate or phosphonate groups as potential mimetics of sugar diphosphates (**D**, Figure 1). Thus, the 5-azido 3-*O*-benzyl and 3-*O*-dodecyl xylofuranose derivatives (**18**, **19**) were synthesized by tosylation of the partially protected xylofuranoses **16**[13e] and **17**[8c] and subsequent tosylate substitution with sodium azide (Scheme 3). Thermal cycloaddition between the 3-*O*-benzylated precursor **18** and propargyl alcohol in refluxing toluene afforded the 4-hydroxymethyl-1-xylofuranosyl triazole **20** and the 1,5-regioisomer **21** in 46% and 36% yields, respectively, which were clearly identified based on the ^{13}C NMR chemical shifts of their triazole carbon signals. While in the 1,4-disubstituted triazole **20**, the signals for C-4 and C-5 appeared at 147.5 ppm and 123.0 ppm, respectively, in the 1,5-dissubstituted counterpart **21**, C-4 and C-5 resonated at 133.3 ppm and 137.3 ppm, respectively. These characteristic ^{13}C NMR chemical shift differences between 1,4- and 1,5-disubstituted triazoles were considered for the structural assignment of the different regioisomers of the further triazole derivatives described below.

Compound **20** was obtained as colourless crystals (prisms), allowing its X-ray crystallographic analysis which confirmed the 1,4-regiochemistry at the triazole unit and revealed that the xylofuranose ring adopts a C3-endo conformation (CCDC number 2004693, Figure 3a). The crystal packing of this compound revealed that the molecules forms $C_1^1(5)$ infinite linear chains that are sustained by a OH···N1 hydrogen bond ($d_{OH\cdots N1}$ = 2.02(5) Å) (Figure 3b). This motif is reinforced by a non-classical H-bond C3H···N2 ($d_{C3H\cdots N2}$ = 2.59(3) Å). The overall packing is completed by other four non classical H-bonds of the type CH···O (two intermolecular bonds), CH···N and CH···π ($d_{C1H\cdots O4}$ = 2.47(4) Å, $d_{C7H\cdots O1}$ = 2.49(3) Å, $d_{C16H\cdots N2}$ = 2.62(3) Å, $d_{C12H\cdots\pi}$ = 3.3(1) Å, respectively). A similar cycloaddition procedure was applied to the 3-O-dodecyl counterpart **19**, leading again to the 1,4-disubstituted triazole **22** in a higher yield (54%) than that obtained for the 1,5-dissubstituted congener **23** (31%).

The hydroxymethyltriazole 5'-isonucleosides **20**-**23** were then subjected to phosphorylation with diethyl phosphorochloridate under basic conditions as already mentioned for **3**. The corresponding [(xylofuranos-5-yl)triazolyl]methyl phosphates **24**-**27** were obtained in good to excellent yields (68-93%).

It is noteworthy to mention that in the case of the ^{1}H NMR spectra of the 4-phosphonoxymethyl-1-xylofuranosyl triazoles **24** and **26**, the signal corresponding to the protons of the oxymethylene group linked to the triazole unit appeared as a doublet at *ca*. 5.2 ppm with a coupling constant of $J_{CH2,P}$ = 8.8 Hz, while in the case of the 1,5-disubstituted regioisomers **25** and **27**, these protons resonated as doublet of doublets each (δ = *ca*. 5.3 and 5.2 ppm) from an ABX system resulting from the geminal coupling ($^2J_{a,b}$ = ca. 13 Hz) and the individual couplings with the phosphorous atom ($J_{H\text{-}a,P}$ = 9.2 Hz and $J_{H\text{-}b,P}$ = 8.4 Hz). Moreover, the ^{13}C NMR signals for the triazole quaternary carbon atom atoms (C-4 or C-5) of the (triazolyl)methyl phosphates **24**-**27** appeared as doublets due to coupling with the phosphorous atom ($J_{C,P}$ = *ca*.7.5 Hz).



Scheme 3. Reagents and conditions: (a) TsCl, py, r. t., 16 h; (b) NaN_3, DMF, 80 ºC, 16 h, 80% (**18**), 77% (**19**)[8c], 2 steps; (c) C_3H_3OH, toluene, 110 ºC, 24 h, 46% (**20**), 36% (**21**), or 48 h, 54% (**22**), 31% (**23**); (d) ClPO(EtO)$_2$, NEt_3, DMAP, CH_2Cl_2, r. t., 16 h, 78% (**24**), 68% (**25**), 81% (**26**), 93% (**27**).

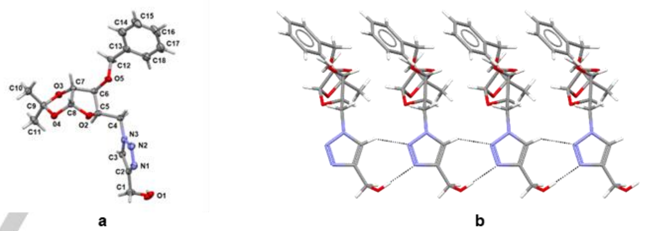
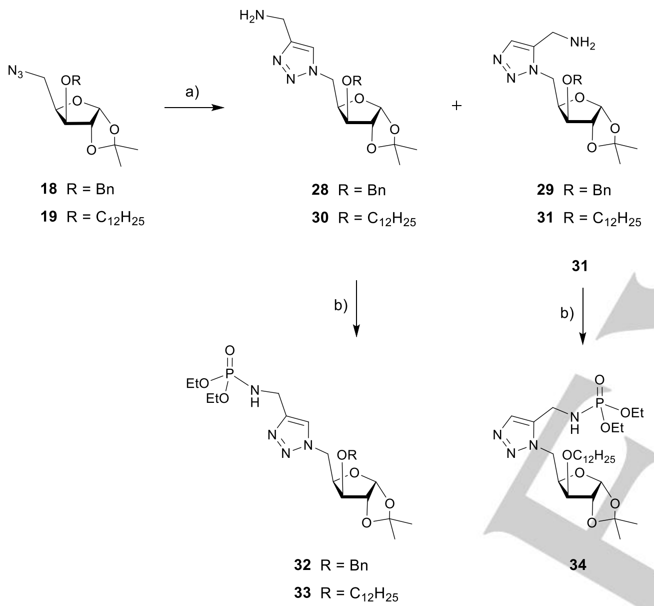


Figure 3. (**a**) X-ray molecular structure of the 4-hydroxymethyl-1-xylofuranosyl triazole **20**; (**b**) $C_1^1(5)$ infinite chain synthon that is formed through OH···N1 hydrogen bonds.

The 5-*O*-protected azido furanoses **18** and **19** were also subjected to thermal cycloaddition with propargylamine in refluxing toluene (Scheme 4). The 5-azido-3-*O*-benzyl xylofuranose derivative **18** were converted within 24 h into the 4- and 5-aminomethyl-1-xylofuranosyl triazoles **28**-**29** in a modest total yield of 6% and in a regioisomeric ratio of 1:1. This low conversion could not be improved either with longer reaction times or with an increase in the amount of propargylamine, with most of **18** remaining unreacted. The 1,5-regioisomer **29** could not be isolated, being inseparably contaminated with traces of the starting material. On the other hand, when the 3-*O*-dodecylated derivative **19** was subjected to similar cycloaddition conditions, the 1,4- and the 1,5-disubstituted triazoles **30** and **31** were obtained in 20% yield each. Treatment of the aminomethyltriazole 5'-isonucleosides **28**, **30** and **31** with diethyl phosphorochloridate furnished the expected phosphoramidate derivatives **32**-**34** in moderate yields (50-56%). The reaction proceeded reasonably without base. In fact the addition of

trimethylamine and DMAP to the reaction medium proved to promote the formation of side products, as detected by TLC.
In the ^{1}H NMR spectra of the 4-phosphonoaminomethyl-1-xylofuranosyl triazoles **32** and **33**, the aminomethylenic protons appeared as a doublet of doublet at *ca.* 4.2 ppm with coupling with the phosphorous atom ($J_{CH2,P}$ = *ca.* 11 Hz) and with the nitrogen-bound proton ($J_{CH2,NH}$ = 7 Hz). On the other hand, the methylenic protons in the 1,5-disubstituted triazole **34** gave signals corresponding to the parts A and B of an ABMX system (ABM = ^{1}H, X = ^{31}P), showing the geminal coupling ($^2J_{a,b}$ = 15.7) in addition to the individual ^3J couplings with the phosphorous atom ($J_{H\text{-}a,P}$ = 9.5, $J_{H\text{-}b,P}$ = 12.1) and with the phosphonoamino proton ($J_{H\text{-}a,NH}$ = 9.5, $J_{H\text{-}b,NH}$ = 5.4). Similarly to that observed in the ^{13}C NMR spectra of their phosphate counterparts **24**-**27**, the triazole quaternary carbon atoms of the (triazolyl)methyl phosphoramidates **32**-**34** resonated as doublets with $J_{C,P}$ = *ca*. 6 Hz.



Scheme 4. Reagents and conditions: (a) propargylamine, toluene, 110 ºC, 24 h, 3% (**28**), 3% (**29**), or 16 h, 20% (**30**), 20% (**31**); (b) $ClPO(EtO)_2$, CH_2Cl_2, r.t., 2 h, 56% (**32**), 50% (**33**), 52% (**34**).

Towards the access to phosphonate analogs of **24**-**27** and **32**-**34**, the 5-azido xylofuranoses **18** and **19** were engaged in thermal cycloaddition with propargyl bromide (Scheme 5). The reactions employing both the 3-*O*-benzyl and 3-*O*-dodecyl precursors led to 4-bromomethyl-1-xylosyl-1,2,3-triazoles **35**, **37** as major products in moderate yields (48-58%), along with the 1,5-disubstituted regioisomers **36** and **38** obtained in only 2% and 5% yields, respectively.
X-ray diffraction analysis of the crystals obtained for the 3'-*O*-benzyl bromomethyl triazole 5'-isonucleoside **35** proved its structure in which the xylofuranose ring is in the C3-endo conformation (CCDC number 2004692, Figure 4a). Although in the packing of this compound the only intermolecular contacts observed are non-classical H-bonds, there are similarities between the crystalline structures of compounds **20** and **35**. The 3D arrangement of **35** is composed by $C_1^1(5)$ infinite non linear chains which are supported by a non-classical C1H···N2 interaction ($d_{C1H\cdots N2}$ = 2.40 Å). In these chains the adjacent molecules are rotated 180º in order to have a more effective packing (Figure 4b). These chains are linked to neighboring ones by non-classical hydrogen bonds of the type CH···O ($d_{C6H\cdots O1}$ = 2.53 Å and $d_{C4H\cdots O2}$ = 2.64 Å) and of the genre CH···π between the triazole group and the phenyl group ($d_{C3H\cdots\pi}$ = 3.03 Å), fulfilling the 3D packing.
A distinct ^{13}C NMR spectral feature observed for the 1,4- and 1,5-regioisomers is the chemical shift for the bromomethylenic carbon, which appears at *ca.* *δ* 21.7-21.8 ppm in the 4-bromomethyl triazole derivatives **35**/**37** and at *δ* 17.5 ppm in the 5-bromomethyl congeners **36**/**38**.
The different regiochemical outcome of the 1,3-dipolar cycloaddition reactions of **18**-**19** with propargyl bromine relatively to that achieved when using propargyl alcohol and propargylamine, may be explained by the possibility of stabilization of the 1,5-disubstituted hydroxy- (**21**, **23**) and aminomethyl (**29**, **31**) triazole derivatives through hydrogen bond interactions between the terminal hydroxyl or amino groups and the furanose endocyclic oxygen atom. In the 5-bromomethyl-1-xylosyl triazoles, not only these interactions are absent, but also lone pair repulsions between the bromine and the ring oxygen atoms, which are closer in the 1,5-regioisomers, may destabilize their formation, resulting therefore in a high regioselectivity for the 1,4-disubstituted derivatives.
The bromomethyl triazoles **35**, **37** and **38** were submitted to a Michaelis-Arbuzov reaction with triethylphosphite at 110 ºC to afford the [(xylofuranos-5-yl)triazolyl]methyl phosphonates **39**-**41** in yields ranging from 76% to 96%.
In the ^{1}H NMR spectra of **39**-**41**, the phosphonomethylenic protons resonate between *δ* 3.5 to 3.2 ppm as parts A and B of an ABX system, with geminal couplings ($^2J_{a,b}$) of *ca.* 21 Hz and individual three-bond ^{31}P-^{1}H couplings ($J_{H\text{-}a,P}$ and $J_{H\text{-}b,P}$) of *ca.* 16 Hz. Their ^{13}C NMR spectra showed both quaternary and methinic carbon atoms of the triazole units resonating as doublets with $J_{C,P}$ of *ca.* 7 Hz and 3-4 Hz, respectively. Moreover, a large $J_{C,P}$ coupling of *ca.* 143-144 Hz was detected for the phosphonomethylenic carbon atoms, whose signals appeared at *δ* 24.3 ppm in the 1,4-dissubstituted phosphonomethyl triazoles **39**-**40** and at 21.9 ppm in the 1,5-disubstituted derivative **41**.
The structural arrangement of [(furanos-5-yl)triazolyl]methyl phosphonates as potential stable mimetics of sugar diphosphates comprising a hydrolytically-resistant (triazolyl)methyl phosphonate system, motivated the insertion of a nucleobase at the anomeric position at the skeleton towards prospective nucleotide mimetics of type **E** (Figure 1). A 7-methylguanosine-based molecule of this type of structure was previously synthesized through cycloaddition between 5-azido methylguanosine and propargylphosphonate in the context of accessing potential inhibitors of a cytosolic 5'-nucleotidase.[21d]
Thus, compounds **39-40** were converted into the corresponding 1,2-di-*O*-acetyl xylofuranosyl donors **42-43** through acidic hydrolysis (65% trifluoroacetic acid aqueous soln.) of the 1,2-acetonide group followed by acetylation (Ac_2O/pyridine). Further Vorbrüggen-type *N*-glycosidation[32] with uracil, which was activated by silylation with bis(trimethylsilyl)acetamide (BSA), was performed in the presence of trimethylsilyl triflate (TMSOTf) in acetonitrile using a previously described microwave-assisted protocol (65 ºC, 150 W, Pmax 250 Psi),[13a,13b] leading to the N^1-linked uracil nucleosides **44** and **45** in yields of 36% and 16%, respectively. HMBC correlations between the anomeric proton

(H-1) and both C-2/C-6 of the uracil unit confirmed the regiochemistry of the nucleosidic linkage.

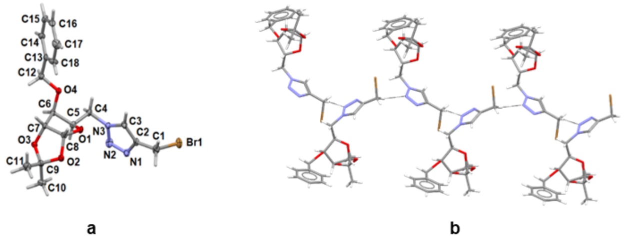
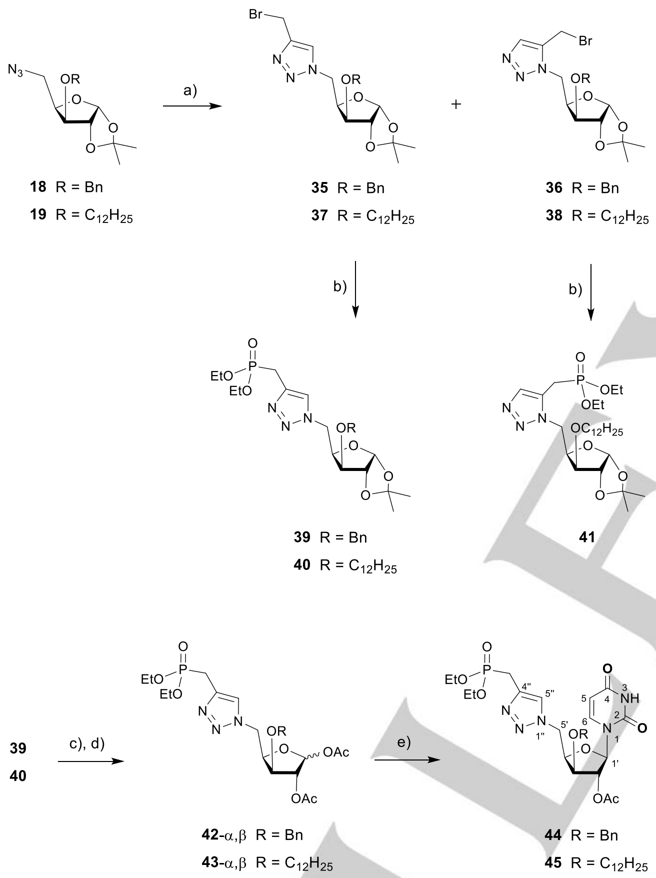


Figure 4. (**a**) X-ray molecular structure of the bromomethyl triazole 5'-isonucleoside **35**; (**b**) $C_1^1(5)$ infinite non-linear chains that compose the 3D packing of this compound.



Scheme 5. Reagents and conditions: (a) C_3H_3Br, toluene, 110 ºC, 16 h, 48% (**35**), 2% (**36**), or 48 h, 58% (**37**), 5% (**38**); (b) $P(EtO)_3$, 110 ºC, 3 h, 83% (**39**), 96% (**40**), 76% (**41**); (c) TFA (65% aq. soln), r.t., 2 h (d) Ac_2O, py, r.t., 1.5 h, 51% (**42**), 68% (**43**), 2 two steps; (e) uracil, BSA, TMSOTf, CH_3CN, 65 °C, MW, max. 150 W, 45 min, 36% (**44**), 16% (**45**).

Conclusion

This contribution showed the synthesis of a diversity of new isonucleosides, isonucleotides and potential nucleotide mimetics based on xylofuranosyl moieties and containing a 1,2,3-triazole unit, comprising a total of 30 molecules.

3'-*O*-Methyl-branched *N*-benzyltriazole isonucleosides and their isonucleotides comprising 5'-di-*O*-ethyl/phenyl phosphate and 5'-di-*O*-ethyl phosphoramidate groups, which are previously unreported types of structural frameworks, were accessed by efficient synthetic pathways from a 1,2-diacetonide-protected 3-*O*-propargyl xylofuranose precursor. The CuI/Amberlyst A21-catalyzed cycloaddition reactions with benzyl azide occurred in high yields (92-98%) for the partially protected 3-*O*-propargyl xylofuranose derivative and for its corresponding xylofuranos-5-yl diethyl phosphate, while the xylofuranos-5-yl diphenyl phosphate led to the corresponding triazole-containing isonucleotide in a relatively lower yield (74%) most likely due to the hiher steric hindrance arising from the diphenyl phosphate moiety.

Triazole xylofuranos-5'-yl isonucleosides containg C4/C5-linked hydroxy-, amino- or bromomethyl groups were synthesized from 5-azido 1,2-*O*-isopropylidene xylofuranoses containing 3-*O*-benzyl or 3-*O*-dodecyl groups. In general lower total yields (6%-82%) were obtained for the thermal cycloaddition reactions starting from the 3-*O*-benzylated xylofuranose precursor than when using the 3-*O*-dodecyl counterpart (40-85%), which reflects the higher steric constrain created by the *O*-benzyl substituent. Significant lower conversions were achieved when using propargyl amine, which is in accordance with its lower electron-deficient character relatively to that of propargyl alcohol or propargy bromide, being therefore the less reactive propargyl derivative herein used in the Huisgen cycloaddition reactions. Hydrogen-bond interactions, which may stabilize 5-hydroxy- and 5-aminomethyl-1-xylosyl triazoles, and lone electron pair repulsions, which eventually destabilize their bromomethyl counterparts, might explain the higher regioselectivity to 1,4-dissubstitued triazoles when using propargyl bromide.

The hydroxy-, amino- and bromomethyl 5'-triazole isonucleosides were efficiently converted into their [(xylofuranos-5'-yl)triazolyl]methyl phosphate, phosphoramidate and phosphonates, respectively, in which the structural fragment linked at the furanose unit at C-5 is envisioned as potential and relatively stable bioisostere of a disphosphate moiety. The (triazolyl)methyl phosphoramidate skeleton is herein reported for the first time. *N*-Glycosylation of uracil with 1,2-di-*O*-acetylated 5-[4-(phosphonomethyl)triazolyl] xylofuranoses afforded the corresponding N^1-linked uracil nucleosides as nucleotide-like molecules. The low yields (16-36%) obtained in the nucleosidation reactions may be due to the presence of the electron-withdrawing (triazolyl)methyl phosphonate moiety in the glycosyl donors, which affects their reactivity by destabilizing the intermediate glycosyl oxocarbenium ion formed during the reaction.

In view of the bioactivity profile of nucleoside and nucleotide analogs, the structures of the newly synthesized compounds, which include innovative skeletons, make them interesting candidates for biological evaluation.

Experimental Section

Chemistry

General methods: Chemicals were purchased from *Sigma-Aldrich* and *Alfa Aesar*. The progress of the reactions was monitored by thin layer chromatography (TLC) using Merck 60 F_{254} silica gel aluminum plates with detection under UV light (254 nm) and/or by immersion on a solution of 10 % H_2SO_4 in EtOH or with the Hanessian stain (solution of cerium (IV) sulfate (0.2% w/v) and ammonium molybdate (5% w/v) in H_2SO_4 (6% aq.) followed by heating (200 ºC). Flash column chromatography was performed on silica gel 60 G (0.040–0.063 mm, E. Merck). NMR spectra were acquired with a BRUKER Avance 400 spectrometer operating at 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and at 161.91 MHz for ^{31}P. Chemical shifts are given in parts per million and are reported relative to internal TMS, in the case of ^{1}H NMR spectra in $CDCl_3$, or relative to the respective solvent peak as reference. ^{31}P NMR Spectra were calibrated according to the IUPAC recommendations for chemical shift referencing.[33] Coupling constants (*J*) are reported in Hertz (Hz). Signal assignments were made with aid from 2D NMR experiments (COSY, HSQC, HMBC). High-resolution mass spectrometry (HRMS) analyses were performed on a High Resolution QqTOF Impact II mass spectrometer from Bruker Daltonics equipped with an electrospray ion source (ESI). Spectra were recorded in positive mode with external calibration. Melting points were determined with a Stuart Scientific SMP 3 apparatus and are uncorrected. Optical rotations (589 nm, 20 ºC) were acquired on a Perkin–Elmer 343 polarimeter.

1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-glucofuranose (2): To a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**, 3 g, 11.5 mmol) in DMF (20 mL), at 0º C and under nitrogen atmosphere, sodium hydride (60% 0.55 g, 13.8 mmol) was added. After stirring during 10 min, propargyl bromide (80 wt.% soln. in toluene, 1.49 mL, 13.8 mmol) was added. The reaction was stirred at room temperature overnight. Then, it was diluted with diethyl ether and water was added. The phases were separated and the aqueous phase was extracted with diethyl ether (2 ×). The combined organic layers were died with anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuum. The obtained crude was dissolved in aq. acetic acid soln (75%, 30 mL) and the reaction mixture was stirred at room temperature overnight. After co-evaporation with toluene, the residue was purified by column chromatography (EtOAc/hexane, 1:4) to afforded the title compound (2.85 g, 96%, 2 steps) as a yellow oil. $[\alpha]_D^{20}$ = – 35 (c =1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.90 (d, 1 H, H-1, $^3J_{1,2}$ = 3.4), 4.60 (d, 1H, H-2), 4.34 (br. d, 1 H, H-1′a, $^2J_{1'a,1'b}$ = 15.9), 4.27- 4.20 (m, 2 H, H-3, H-1′b), 4.15 (dd, 1 H, H-4, $^3J_{3,4}$ = 2.8, $^3J_{4,5}$ = 8.2), 3.97 (ddd, 1 H, H-5), 3.87 (dd, part A of AB system, 1 H, H-6a, $^2J_{6a,6b}$ = 11.5, $^3J_{5,6a}$ = 2.5), 3.75 (ddd, 1 H, H-6b, $^3J_{5,6b}$ = 5.7), 2.64-2.42 (m, 3 H, H-3′, *O*H-5, *O*H-6), 1.49 (s, 3 H, C*H*$_3$, *i*-Pr), 1.31 (s, 3 H, C*H*$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.1 (Cq, *i*-Pr), 105.3 (C-1), 82.2 (C-2), 81.6 (C-3), 79.9 (C-4), 79.2 (C-2′), 75.7 (C-3′), 69.1 (C-5), 64.4 (C-6), 57.7 (C-1′), 26.8, 26.3 (2 × *C*H$_3$, *i*-Pr). HRMS: calcd for $C_{12}H_{18}O_6$ [M + H]$^+$ 259.1176, found 259.1181; calcd. for $C_{12}H_{18}O_6$ [M + Na]$^+$ 281.0996; found 281.1003.

1,2-*O*-Isopropylidene-3-*O*-propargyl-α-D-xylofuranose (3): To a solution of 1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-glucofuranose (**2**, 2.85 g, 11 mmol) in THF/H_2O (22 mL, 3:1) at 0 ºC, sodium metaperiodate ($NaIO_4$, 4 g, 18.7 mmol) was added and the mixture was stirred at room temperature for 4 h. The mixture was then diluted with EtOAc and it was filtered over celite. The phases were separated and the aqueous phase was extracted with EtOAc (2 ×). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under vacuum. The resulting residue was dissolved in EtOH/H_2O (22 mL, 2:1) and at 0ºC, sodium borohydride ($NaBH_4$, 567 mg, 15 mmol) was added. The mixture was stirred at room temperature for 1 h. Then, EtOAc was added. The mixture was washed with water and the aqueous phase was extracted with EtOAc (2 ×). The combined organic layers were washed with brine soln. and were dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvents under vacuum, the residue was subjected to column chromatography (EtOAc/hexane, 1:4) to afford the title compound (1.44 g, 57%, 2 steps) as a colourless oil. $[\alpha]_D^{20}$ = – 62 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.84 (d, 1 H, H-1, $^3J_{1,2}$ = 3.0), 4.54 (d, 1 H, H-2), 4.27-4.15 (m, 2 H, H-4, H-1′a, $^2J_{1'a,1'b}$ = 16.4), 4.16-4.04 (m, 2 H, H-1′b, H-3), 3.83-3.69 (m, 2 H, C*H*$_2$-5, $^2J_{5a,5b}$ = 11.8, $^3J_{4,5a}$ = 5.9, $^3J_{4,5b}$ = 5.4), 2.80 (br. s, 1 H, *O*H), 2.47 (m, 1 H, H-3′), 1.41 (s, 3 H, CH$_3$, *i*-Pr), 1.23 (s, 3 H, C*H*$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 112.0 (Cq, *i*-Pr), 105.2 (C-1), 82.4 (C-2), 82.2 (C-3), 80.1 (C-4), 79.0 (C-2′), 75.6 (C-3′), 60.7 (C-5), 57.5 (C-1′), 26.9, 26.4 (2 × *C*H$_3$, *i*-Pr). HRMS: calcd. for $C_{11}H_{18}O_5$ [M + Na]$^+$ 251.0890; found 251.0895.

General procedure for the CuI/Amberlyst A-21 catalyzed cycloaddition between 3-*O*-propargyl xylofuranose derivatives and benzyl azide: To a solution of 3-*O*-propargyl derivative (0.88 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere, benzyl azide (0.14 mL, 1.06 mmol) and CuI/Amberlyst A-21 (0.5 mmol.g^{-1}, 0.1 mmol CuI, 200 mg) were added. The mixture was stirred at room temperature for 24 h. The catalyst was filtered off, the solvent was evaporated and the crude residue was subjected to column chromatography.

3-*O*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl-1,2-*O*-isopropylidene-α-D-xylofuranose (4): Obtained according to the general CuI/A21 cycloaddition procedure, starting from 1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**3**, 200 mg, 0.88 mmol), benzyl azide (0.14 mL, 1.06 mmol) and in the presence of CuI/A-21 catalyst (0.1 mmol CuI, 200 mg). Purification by column chromatography (EtOA/petroleum ether, 1:1) afforded the title compound (310 mg, 98%) as a colourless oil. $[\alpha]_D^{20}$ = – 33 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48 (s, 1 H, H-3′), 7.42-7.33 (m, 3 H, Ph), 7.31-7.23 (m, 2 H, Ph), 5.92 (d, 1 H, H-1, $^3J_{1,2}$ = 3.7), 5.52 (s, 2 H, C*H*$_2$Ph), 4.81 (d, 1 H, part A of AB system, H-1′a, $^2J_{1'a,1'b}$ = 12.9), 4.67-4.59 (m, 2 H, H-1′b, H-2), 4.32 (ddd, 1 H, H-4), 4.08 (d, 1 H, H-3, $^3J_{3,4}$= 3.3), 3.91-3.77 (m, 2 H, C*H*$_2$-5, $^2J_{5a,5b}$ = 11.7, $^3J_{4,5a}$ = 7.0, $^3J_{4,5b}$ = 5.5), 1.46 (s, 3 H, C*H*$_3$, *i*-Pr), 1.29 (s, 3 H, C*H*$_3$, *i*-Pr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.6 (C-2'), 134.3 (Cq, Ph), 129.2, 128.9, 128.1 (*C*H, Ph), 122.3 (C-3'), 111.7 (Cq, *i*-Pr), 105.1 (C-1), 82.4 (C-2), 82.3 (C-3), 80.1 (C-4), 63.1 (C-1'), 59.5 (C-5), 54.4 (*C*H$_2$Ph), 26.8, 26.3 (2 × CH$_3$, *i*-Pr). HRMS: calcd. for $C_{18}H_{23}N_3O_5$ [M + H]$^+$ 362.1710, found 362.1713; calcd. for $C_{18}H_{23}N_3O_5$ [M + Na]$^+$ 384.1530; found 384.1532.

3-*O*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (5): To a solution of 3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**4**, 30 mg, 0.08 mmol) in DMF (2 mL), at 0º C and under nitrogen atmosphere, sodium hydride (60%, 4 mg, 0.1 mmol) was added. After stirring during 10 min, dodecyl bromide (0.02 mL, 0.12 mmol) was added. The reaction was stirred at room temperature overnight. Then, it was diluted with diethyl ether and water was added. The phases were separated and the aqueous phase was extracted with diethyl ether (2 ×). The combined organic layers were died with anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuum. The residue was purified by column chromatography (EtOAc/hexane, 1:3) to afford the title compound (42 mg, 95%) as a white solid. $[\alpha]_D^{20}$ = – 15 (c = 1, in CH_2Cl_2). m.p.: 42.7–43.4 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.44 (s, 1 H, H-3′), 7.42-7.32 (m, 3 H, Ph), 7.30-7.22 (m, 2 H, Ph), 5.87 (d, 1 H H-1, $^3J_{1,2}$ = 3.7), 5.51 (s, 2 H, C*H*$_2$Ph), 4.75 (d, part A of AB system, 1 H, H-1'a, $^2J_{1'a,1'b}$ = 12.4), 4.65 (d, of AB system, 1 H, H-1'b), 4.60 (d, 1 H, H-2), 4.33 (td, 1 H, H-4), 3.99 (d, 1 H, H-3, $^3J_{3,4}$ = 3.0), 3.65-3.54 (m, 2 H, C*H*$_2$-5, $^2J_{5a,5b}$ = 10.1, $^3J_{4,5a}$ = 6.2, $J_{4,5b}$ = 6.0), 3.48-3.32 (m, 2 H CH$_2$-1″), 1.57-1.44 (m, 5 H, CH$_2$-2″, C*H*$_3$, *i*-Pr), 1.34-1.17 (m, 21 H, C*H*$_3$, *i*-Pr, C*H*$_2$-3'' to C*H*$_2$-11''), 0.87 (t, 3 H, C*H*$_3$-12'', *J* = 6.8). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 145.3 (C-2′), 134.6 (Cq, Ph) 129.3, 128.9, 128.2 (*C*H, Ph), 122.4 (C-3′), 111.8 (Cq, *i*-Pr), 105.1 (C-1), 82.5 (C-2), 82.2 (C-3), 79.0 (C-4), 71.9 (C-1''), 67.8 (C-5), 64.0 (C-1'), 54.3 (*C*H$_2$Ph), 32.0, 29.8, 29.8, 29.7, 29.6, 29.5 (C-2″ to C-9″) 26.9, 26.4 (2 × CH$_3$, *i*-Pr), 26.2 (C-10''), 22.8 (C-11''), 14.3 (C-12''). HRMS: calcd for $C_{30}H_{47}N_3O_5$ [*M* + H]$^+$ 530.3588, found 530.3594; calcd for $C_{30}H_{47}N_3O_5$ [*M* + Na]$^+$ 552.3408, found 552.3421.

Diethyl (5-deoxy-1,2-O-isopropylidene-3-O-propargyl-α-D-xylofuranos-5-yl)phosphate (6): To a solution of 1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**3**, 100 mg, 0.44 mmol) in dichloromethane (5 mL) under nitrogen atmosphere, triethylamine (0.09 mL, 0.66 mmol) was added. The mixture was cooled at 0 ºC and diethyl phosphorochloridate (0.08 mL, 0.53 mmol) and DMAP (catalytic amount, a spatula tip) were added. The solution was stirred at room temperature for 16 h. Then, water was added to the solution, the phases were

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separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under vacuum. Purification by column chromatography (EtOAc/hexane, 1:3) afforded the title compound (157 mg, 98 %) as a colourless oil. $[\alpha]_D^{20}$ = – 24 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.86 (d, 1 H, H-1, $^3J_{1,2}$ = 3.7), 4.58 (d, 1 H, H-2), 4.39 (ddd, 1 H, H-4), 4.24-4.00 (m, 9 H, H-3, H-5a, H-5b, 2 × C*H*$_2$, Et, C*H*$_2$-1'), 2.47 (t, 1 H, H-3', $^4J_{1'a,3'}$ = $^4J_{1'b,3'}$ = 2.3), 1.44 (s, 3 H, C*H*$_3$, *i*-Pr), 1.32-1.23 (m, 9 H, 2 × C*H*$_3$, Et, CH$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.0 (Cq, *i*-Pr), 105.2 (C-1), 82.0 (C-2), 81.1 (C-3), 78.8 (C-2'), 78.7 (d, C-4, $^3J_{C-4,P}$ = 8.5), 75.5 (C-3′), 64.8 (d, C-5, $^2J_{C-5,P}$ = 5.3), 63.99 (d, *C*H$_2$, Et, $^2J_{C-P}$ = 5.9), 63.97 (d, *C*H$_2$, Et, $^2J_{C-P}$ = 5.9), 57.5 (C-1′), 26.8, 26.3 (2 × CH$_3$, *i*-Pr), 16.1 (d, 2 × *C*H$_3$, 2 × Et, $^3J_{C,P}$ = 6.9). ^{31}P-RMN (162 MHz, $CDCl_3$): *δ* – 1.28. HRMS: calcd. for $C_{15}H_{25}O_8P$ [M + H]$^+$ 387.1179, found 387.1179; calcd. for $C_{15}H_{25}O_8P$ [M + Na]$^+$ 365.1360, found 365.1358.

Diethyl [3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl]phosphate (7): Obtained according to the general CuI/A21 cycloaddition procedure, starting from 5-*O*-diethylphosphono-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**6**, 100 mg, 0.27 mmol), benzyl azide (0.06 mL, 0.44 mmol) in the presence of CuI/A-21 catalyst (0.05 mmol CuI, 100 mg). Purification by column chromatography (EtOAc/petroleum ether, 1:2) afforded the title compound (125 mg, 92%) as pale yellow oil. $[\alpha]_D^{20}$ = – 23 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.58 (s, 1 H, H-3′), 7.41-7.25 (m, 5 H, Ph), 5.89 (d, 1 H, H-1, $^3J_{1,2}$ = 3.7), 5.55, 5.50 (2 d, AB system, 2 H, C*H*$_2$Ph, $^2J_{a,b}$ = 15.0), 4.77 (d, 1 H, part A of AB system, H-1'a, $^2J_{1'a,1'b}$ = 12.2), 4.66-4.59 (m, 2 H, H-1'b, H-2), 4.40 (ddd, 1 H, H-4), 4.25-4.00 (m, H-3, C*H*$_2$-5, 2 × C*H*$_2$, Et), 1.48 (s, 3 H, C*H*$_3$, *i*-Pr), 1.34-1.26 (m, 9 H, 2 × CH$_3$, Et, CH$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.7 (C-2'), 134.7 (Cq, Ph), 129.2, 128.8, 128.2 (*C*H, Ph), 122.9 (C-3'), 112.0 (Cq, *i*-Pr), 105.2 (C-1), 82.1 (C-2), 81.6 (C-3), 78.6 (d, C-4, $^3J_{C-4,P}$ = 8.8), 64.4 (d, C-5, $^2J_{C-5,P}$ = 5.3), 64.09 (d, *C*H$_2$, Et, $^2J_{C-P}$ = 5.9), 64.05 (d, *C*H$_2$, Et, $^2J_{C-P}$ = 5.7), 63.8 (C-1'), 54.3 (*C*H$_2$Ph), 26.9, 26.3 (2 × CH$_3$, *i*-Pr), 16.2 (d, 2 × *C*H$_3$, 2 × Et, $^3J_{C,P}$ = 6.8). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* –1.26 ppm. HRMS: calcd for $C_{22}H_{32}N_3O_8P$ [M + H]$^+$ 498.2000, found 498.2009.

Diphenyl (5-deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranos-5-yl)phosphate (8): To a solution of 1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**3**, 100 mg, 0.44 mmol) in toluene (6 mL) under nitrogen, at 0 ºC, diphenylphosphoryl azide (0.11 mL, 0.53 mmol) and DBU (0.08 mL, 0.53 mmol) were added and the mixture was stirred at room temperature for 24 h. Additional DBU (0.05 mL, 0.8 equiv.) was then added at 0 ºC and stirring was continued at 40 ºC for 16 h. The mixture was then washed twice with 2 M HCl soln. and water. The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated under vacuum. The crude residue was purified by column chromatography (EtOAc/hexane, 1:4) to afford the title compound (138 mg, 68%) as a colourless oil. $[\alpha]_D^{20}$ = – 46 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.42-7.15 (m, 10 H, 2 × Ph), 5.94 (d, 1 H, $^3J_{1,2}$ = 3.7), 4.65 (d, 1 H, H-2), 4.54-4.40 (m, 3 H, H-4, H-5a, H-5b), 4.19-4.09 (m, 3 H, C*H*$_2$-1′, H-3), 2.47 (t, 1 H, H-3′, $^4J_{1'a,3'}$ = $^4J_{1'b,3'}$ = 2.2), 1.49 (s, 3 H, CH$_3$, *i*-Pr), 1.33 (s, 3 H, C*H*$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 150.52 (d, Cq, Ph, $^2J_{C,P}$ = 7.3), 150.49 (d, Cq, Ph, $^2J_{C,P}$ = 7.1), 129.8, 125.4, 120.2, 120.2 (*C*H, 2 × Ph) 112.2 (Cq, *i*-Pr), 105.3 (C-1), 82.1 (C-2), 81.1 (C-3), 78.8 (C-2′), 78.5 (d, C-4, $^3J_{C-4,P}$ = 8.6), 75.6 (C-3′), 66.2 (d, C-5, $^2J_{C-5,P}$ = 6.2), 57.6 (C-1′), 26.9, 26.4 (2 × CH$_3$, *i*-Pr). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 12.06. HRMS: calcd. for $C_{23}H_{25}O_8P$ [M + H]$^+$ 461.1360, found 461.1362; calcd. for $C_{23}H_{25}O_8P$ [M + Na]$^+$ 483.1179, found 483.1183.

Diphenyl [3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl]phosphate (9): Obtained according to the general CuI/A21 cycloaddition procedure, starting from 1,2-*O*-isopropylidene-5-*O*-diphenylphosphono-3-*O*-propargyl-α-D-xylofuranose (**8**, 124 mg, 0.27 mmol), benzyl azide (0.04 mL, 0.32 mmol) in the presence of CuI/A-21 catalyst (0.06 mmol CuI, 120 mg). Purification by column chromatography (EtOAc/petroleum ether, 1:3) afforded the title compound (118 mg, 74%) as a colourless oil. $[\alpha]_D^{20}$ = – 21 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.54 (s, 1 H, H-3′), 7.39-7.12 (m, 15 H, 3 × Ph), 5.90 (d, 1 H, H-1, $J_{1,2}$ = 3.6), 5.49, 5.44 (2 d, AB system, 2 H, C*H*$_2$Ph, $J_{a,b}$ = 15.1), 4.73 (d, part A of AB system, 1 H, H-1'a, $J_{1'a,1'b}$ = 11.9), 4.65 (d, 1H, H-2), 4.57-4.33 (m, 4 H, H-1'b H-4, H-5a, H-5b), 4.01 (br. s, 1 H, H-3), 1.48 (s, 3 H, CH$_3$, *i*-Pr), 1.32 (s, 3 H, CH$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.44 (d, Cq, Ph, $^2J_{C,P}$ = 7.5), 150.36 (d, Cq, Ph, $^2J_{C,P}$ = 7.4), 134.6 (Cq, Ph), 129.9, 129.1, 128.8, 128.2, 125.6 (*C*H, 3 × Ph), 123.0 (C-3') 120.12 (d, *C*H-*o*, Ph, $^3J_{C-P}$ = 4.9), 120.10 (d, *C*H-*o*, Ph, $^3J_{C-P}$ = 4.9), 112.1 (Cq, *i*-Prop), 105.3 (C-1), 81.9 (C-2), 81.4 (C-3), 78.2 (d, C-4, $^3J_{C-4,P}$ = 9.4), 65.6 (d, C-5, $^2J_{C-5,P}$ = 5.7), 63.7 (C-1'), 54.2 (*C*H$_2$Ph), 26.9, 26.3 (2 × *C*H$_3$, *i*-Pr). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* – 12.1 ppm. HRMS: calcd for $C_{30}H_{32}N_3O_8P$ [*M* + H]$^+$ 594.2000, found 594.2004.

5-Azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (11): To a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**10**,[26] 600 mg, 2.8 mmol) in DMF (15 mL), at 0º C and under nitrogen atmosphere, sodium hydride (60% in mineral oil, 132 mg, 3.3 mmol) was added. After stirring during 10 min, propargyl bromide (0.36 mL, 3.3 mmol) was added. The reaction was stirred at room temperature during 5 min, whereupon completed conversion was shown by TLC. Then, the mixture was diluted with diethyl ether and water was added. The phases were separated and the aqueous phase was extracted with diethyl ether (2×). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuum. The crude was subjected to column chromatography (EtOAc/hexane, 1:5) to afford the title compound (673 mg, 95 %) as a yellow oil. $[\alpha]_D^{20}$ = – 25 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$)*: *δ* 5.88 (d, 1 H, H-1, $J_{1,2}$ = 3.8), 4.61 (d, 1 H, H-2), 4.32-4.22 (m, 2 H, H-4, H-1'a), 4.18 (dd, 1 H, H-1'b, $^2J_{1'a,1'b}$= 16.0, $J_{1'b,3'}$ = 2.4), 4.07 (d, 1H, H-3, $^3J_{3,4}$ = 3.2), 3.54 (dd, part A of ABX system, 1 H, H-5a, $^2J_{5a,5b}$ = 12.6, $^3J_{4,5a}$ = 6.8), 3.46 (dd, part B of ABX system 1 H, H-5b, $^3J_{4,5b}$= 6.3), 2.49 (t, 1 H, H-3', ^4J = 2.4), 1.47 (s, 3 H, C*H*$_3$, *i*-Pr), 1.29 (s, 3 H, C*H*$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$)*: δ = 112.0 (Cq, *i*-Pr), 105.1 (C-1), 82.0 (C-2), 81.2 (C-3), 78.8 (C-2′), 78.7 (C-4), 75.5 (C-3′), 57.4 (C-1′), 49.3 (C-5), 26.8, 26.3 (2 × *C*H$_3$, *i*-Pr). HRMS: calcd. for $C_{11}H_{15}N_3O_4$ [M + H]$^+$ 254.1135, found 254.1137. *NMR data were in accordance with published data.[29]

3,5'-Anhydro-5-deoxy-5-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (12)[27]: A solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**11**, 60 mg, 0.23 mmol) in toluene (5 mL) was stirred at 110 ºC for 2 h. The solution was concentrated under vacuum, the solid was filtered off and washed with petroleum ether, affording the title compound as a white powder (40 mg, 67%). Crystallization from EtOAc resulted in colourless monocrystals of **12-a**. $[\alpha]_D^{20}$ = – 12 (c = 1, in CH_2Cl_2). m.p.: 201.0–203.1 ºC. HRMS: calcd for $C_{11}H_{15}N_3O_4$ [M + H]$^+$ 254.1135, found 254.1136. NMR data were in accordance with the published data.[27]

5-Azido-3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (14): To a solution of 3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**4**, 300 mg, 0.83 mmol) in pyridine (12 mL), tosyl chloride (320 mg, 1.66 mmol) was added. The solution was left stirring at room temperature and under nitrogen atmosphere for 16 h. It was then diluted with ethyl acetate and washed with 2 M HCl soln. and water. The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated under vacuum. The crude residue was dried under vacuum and then it was dissolved in DMF (20 mL). To the resulting solution and under nitrogen atmosphere, sodium azide (162 mg, 2.5 mmol) was added and the mixture was stirred at 80 ºC for 16 h. Then, the mixture was diluted with diethyl ether and water was added. The phases were separated and the aqueous phase was extracted with diethyl ether (2 ×). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuum. The crude was subjected to column chromatography (EtOAc/hexane, 1:2) to afford the title compound

(251 mg, 78 %, 2 steps) as a yellow oil. $[\alpha]_D^{20}$ = –23 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1 H, H-3′), 7.42-7.33 (m, 3 H, Ph), 7.31-7.26 (m, 2 H, Ph), 5.88 (d, 1 H, H-2, $^3J_{1,2}$ = 3.7), 5.53 (s, 2 H, CH_2, Bn), 4.77 (d, 1 H, part A of AB system, H-1′a, $^2J_{1'a,1'b}$ = 12.3), 4.67-4.60 (m, 2 H, H-1′b, H-2), 4.28 (td, 1 H, H-4), 4.00 (d, 1 H, H-3, $^3J_{3,4}$ = 3.2), 3.49 (dd, 1 H, part A of ABX system ABX, H-5a, $^2J_{5a,5b}$ = 12.3, $^3J_{4,5a}$ = 6.6), 3.41 (dd, 1H, part B of ABX system, H-5b, $^3J_{4,5b}$ = 6.9), 1.49 (s, 3 H, CH_3, *i*-Pr), 1.31 (s, 3 H, CH_3, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (C-2′), 134.4 (Cq, Ph), 129.2, 128.9, 128.1 (*C*H, Ph), 122.6 (C-3′), 112.0 (Cq, *i*-Pr), 105.1 (C-1), 82.0 (C-2), 81.7 (C-3), 78.5 (C-4), 63.4 (C-1′), 54.3 (*C*H_2, Bn), 49.0 (C-5), 26.8, 26.2 (2 × *C*H3, *i*-Pr). HRMS: calcd. for $C_{18}H_{22}N_6O_4$ [M + H]$^+$ 387.1775, found 387.1779; calcd. for $C_{18}H_{22}N_6O_4$ [M + Na]$^+$ 409.1595, found 409.1599.

Diethyl *N*-[3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuran-5-yl]phosphoramidate (15): To a solution of 5-azido-3-*O*-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**14**, 30 mg, 0.08 mmol) in CH_2Cl_2 (5 mL), triethyl phosphite (0.07 mL, 0.39 mmol) was added. The reaction was stirred at room temperature for 48 h. The solution was concentrated under vaccum and the residue was subjected to column chromatography (EtOAc/MeOH, 20:1) to afford the title compound (37 mg, 96%) as a colourless oil. $[\alpha]_D^{20}$ = –3.6 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1 H, H-3′), 7.40-7.32 (m, 3 H, Ph), 7.30-7.24 (m, 2 H, Ph), 5.87 (d, 1 H, $^3J_{1,2}$ = 3.8), 5.51 (s, 2 H, CH_2Ph), 4.76 (d, 1 H, part A of AB system, H-1′a, $^2J_{1'a,1'b}$ = 12.4), 4.63-4.54 (m, 2 H, H-1′b, H-2), 4.25 (td, 1 H, H-4, $^3J_{4,5a}$ = $^3J_{4,5b}$ = 6.7, $^3J_{3,4}$ = 3.3), 4.08-3.94 (m, 5 H, H-3, 2 × CH_2, Et), 3.35 (dt, 1 H, N*H*, $^2J_{NH,P}$ = 10.7, $^3J_{NH,5a}$ = $^3J_{NH,5b}$ = 7.3), 3.24-3.06 (m, 2 H, H-5a, H-5b), 1.46 (s, 3 H, CH_3, *i*-Pr), 1.32-1.24 (m, 3 H, CH$_3$, *i*-Pr, 2 × CH_3, Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6 (C-2′), 134.5 (Cq, Ph), 129.3, 128.9, 128.3 (*C*H, Ph), 122.5 (C-3′), 111.8 (Cq, *i*-Pr), 105.1 (C-1), 82.1 (C-2), 82.0 (C-3), 79.8 (d, C-4, $^3J_{C\text{-}4,P}$ = 5.1), 63.2 (C-1′), 62.47, 62.44 (2 d, 2 × CH$_2$, Et, $^2J_{CH2,P}$ = 5.3), 54.3 (CH$_2$, Bn), 39.7 (C-5), 26.8, 26.4 (2 × *C*H$_3$, *i*-Pr), 16.3 (d, 2 × *C*H$_3$, Et, $J_{C,P}$ =7.2). ^{31}P NMR (162 MHz, $CDCl_3$): δ 9.11. HRMS: calcd. for $C_{22}H_{33}N_4O_7P$ [M + H]$^+$ 497.2160, found 497.2176; calcd. for $C_{22}H_{33}N_4O_7P$ [M + Na]$^+$ 519.1979, found 519.1990.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (15): To a solution of 1,2-*O*-isopropylidene-3-*O*-propargyl-α-D-xylofuranose (**3**, 100 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) under nitrogen, triphenilphosphine (230 mg, 0.88 mmol) and carbon tetrabromide (292 mg, 0.88 mmol) were added. The mixture was stirred at room temperature and under nitrogen atmosphere for 24 h. The mixture was concentrated under vacuum and the crude residue was subjected to column chromatography (EtOAc/hexane, 1:5) to afford the title compound (30 mg, 24%) as a colourless oil. $[\alpha]_D^{20}$ = –37 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (d, 1 H, H-1, $^3J_{1,2}$ = 3.6), 4.68 (d, 1 H, H-2), 4.46 (ddd, 1 H, H-4), 4.34-4.24 (br.s, 2 H, H-1′a, H-1′b, $^2J_{1'a,1'b}$ = 16.1, $^4J_{1'a,3'}$ = 2.3, $^4J_{1'b,3'}$ = 2.3), 4.17 (d, 1 H, H-3, $^3J_{3,4}$ = 2.9), 3.57-3.49 (m, 2 H, H-5a, H-5b, $^2J_{5a,5b}$ = 9.7, $^3J_{4,5a}$ = 8.7, $^3J_{4,5b}$ = 5.9), 2.50 (m, 1 H, H-3′, ^4J = 2.3), 1.51 (s, 3 H, CH_3, *i*-Pr), 1.33 (s,3 H, CH_3, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.3 (Cq, *i*-Pr), 105.6 (C-1), 82.3 (C-2), 81.1 (C-3), 80.4 (C-4), 79.0 (C-2′), 75.4 (C-3′), 58.3 (C-1′), 27.0 (*C*H$_3$, *i*-Pr), 26.9 (C-5), 26.4 (*C*H$_3$, *i*-Pr). HRMS: calcd. for $C_{11}H_{15}BrO_4$ [M + Na]$^+$ 313.0046, found 313.0040.

5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (18): To a solution of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**16**,[13e] 785 mg, 2.8 mmol) in pyridine (17 mL), tosyl chloride (640 mg, 3.4 mmol) was added. The solution was left stirring at room temperature and under nitrogen atmosphere for 16 h. It was then diluted with ethyl acetate and washed with 2 M HCl soln. and water. The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated under vacuum. The crude residue was dried under vacuum and then it was dissolved in DMF (12 mL). To the resulting solution and under nitrogen atmosphere, sodium azide (546 mg, 8.4 mmol) was added and the mixture was stirred at 80 ºC for 16 h. Then, the mixture was diluted with diethyl ether and water was added. The phases were separated and the aqueous phase was extracted with diethyl ether (2 ×). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated in vacuum. The crude was subjected to column chromatography (EtOAc/hexane, 1:7) to afford the title compound (684 mg, 80%, 2 steps) as a colourless oil. The NMR data were in accordance with the reported data.[8b]

General procedure for the thermal azide-alkyne cycloaddition between 5-azido-3-*O*-protected 1,2-*O*-isopropylidene-α-D-xylofuranoses and propargyl derivatives: To a solution of 5-azido-3-*O*-protected 1,2-*O*-isopropylidene-α-D-xylofuranose (1 mmol) in toluene (7 mL) under nitrogen, propargyl alcohol, propargylamine or propargyl bromide (2 equiv.) was added. The reaction mixture was stirred under reflux for 16-48 h. After concentration under vacuum, the residue was subjected to column chromatography.

3-*O*-Benzyl-5-deoxy-5-(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (20) and 3-*O*-benzyl-5-deoxy-5-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (21): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**18**, 300 mg, 0.98 mmol) and propargyl alcohol (0.11 mL, 1.96 mmol). The reaction was stirred for 24 h. Purification by column chromatography (EtOAc/Hex, 1:1) afforded the 1,4-disubstituted triazole **20** (163 mg, 46%) as colourless crystals and the 1,5-disubstituted regioisomer **21** (126 mg, 36%) as a colourless oil.

Data for 20: $[\alpha]_D^{20}$ = – 40 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1 H, H-5), 7.43-7.29 (m, 5 H, Ph), 5.98 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.7), 4.80-4.60 (m, 5 H, H-a, from CH_2Ph, CH_2OH, H-2′, H-5′a), 4.59-4.46 (m, 3 H, H-4′, H-b from CH_2Ph, H-5′b), 4.00 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.7), 1.43 (s, 3 H, CH_3, *i*-Pr.), 1.31 (s, 3 H, CH_3, *i*-Pr.). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9 (C-4), 136.8 (Cq, Ph), 128.7, 128.3, 128.0 (*C*H, Ph), 123.0 (C-5), 112.1 (Cq, *i*-Pr.), 105.2 (C-1′), 81.9 (C-2′), 81.5 (C-3′), 78.8 (C-4′), 71.9 (*C*H$_2$Ph) 56.0 (*C*H$_2$OH), 49.2 (C-5′), 26.7, 26.2 (2 × *C*H$_3$, *i*-Pr). HRMS: calcd. for $C_{18}H_{23}N_3O_5$ [M + H]$^+$ 362.1710, found 362.1716; calcd. for [M + Na]$^+$ 384.1530, found 384.1535.

Data for 21: $[\alpha]_D^{20}$ = – 32 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1 H, H-4), 7.44-7.27 (m, 5 H, Ph), 5.99 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.7), 4.74-4.49 (m, 8 H, H-2′, H-4', CH_2Ph, CH_2OH, CH_2-5′, $^2J_{a,b\ (Bn)}$ = 11.8), 4.10 (d, 1 H, H-3′, $^3J_{3',4'}$ = 1.8), 1.41 (s, 3 H, CH_3, *i*-Pr), 1.30 (s, 3 H, CH$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3 (C-5), 136.8 (Cq, Ph), 133.3 (C-4), 128.7, 128.4, 128.0 (*C*H, Ph), 123.0 (C-1′), 112.4 (Cq, *i*-Pr), 105.1 (C-1'), 82.0 (C-2'), 81.7 (C-3'), 79.6 (C-4'), 72.1 (*C*H$_2$Ph) 52.6 (*C*H$_2$OH), 47.7 (C-5'), 26.7, 26.2 (2 ×CH$_3$, *i*-Pr). HRMS: calcd. for $C_{18}H_{23}N_3O_5$ [M + H]$^+$ 362.1710, found 362.1715; calcd. for [M + Na]$^+$ 384.1530, found 384.1537.

5-Deoxy-3-*O*-dodecyl-5-(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (22) and 5-deoxy-3-*O*-dodecyl-5-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (23): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**19**,[8c] 400 mg, 1.04 mmol) and propargyl alcohol (0.12 mL, 2.09 mmol). The reaction was stirred for 48 h. Purification by column chromatography (EtOAc/Hex, 1:3) afforded the 1,4-disubstituted triazole **22** (248 mg, 54%) and the 1,5-disubstituted regioisomer **23** (143 mg, 31%) as colourless oils.

Data for 22: $[\alpha]_D^{20}$ = – 17 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1 H, H-5), 5.93 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.78-4.69 (m, 3 H, CH_2OH, H-5'a, $^2J_{5'a,5'b}$ = 18.9, $^3J_{4,5'a}$ = 8.4), 4.58 (d, 1 H, H-2′), 4.54-4.43 (m, 2 H, H-4′, H-5′b), 3.84 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.0), 3.63 (dt, 1 H, H-1″a, $^2J_{1''a,1''b}$ = 9.1, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.5), 3.41 (dt, 1H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7), 1.63-1.49 (m, 2 H, H-2″), 1.41 (s, 3 H, CH_3, *i*-Pr), 1.36-1.16 (m, 21 H, CH_3, *i*-Pr, H-3″ to H-11″), 0.86 (t, 3 H, CH_3-12", ^3J = 6.8). ^{13}C

NMR (100 MHz, $CDCl_3$): *δ* 147.9 (C-4), 123.0 (C-5), 112.1 (Cq, *i*-Pr), 105.3 (C-1′), 82.6 (C-3′), 82.1 (C-3′), 79.2 (C-4′), 70.6 (C-1″), 56.5 (CH_2OH), 49.5 (C-5′), 32.0, 29.8, 29.8, 29.7, 29.7, 29.7, 29.5, 29.5, 26.3 (C-2″ to C-10″), 26.8, 26.2 (2 × CH_3, *i*-Pr), 22.8 (C-11"), 14.2 (C-3″). HRMS: calcd. for $C_{23}H_{41}N_3O_5$ [M + H]$^+$ 440.3119, found 440.3125; calcd. for [M + Na]$^+$ 462.2938, found 462.2941.

Data for 23: $[\alpha]_D^{20}$ = – 25 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.60 (s, 1 H, H-4), 5.92 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.5), 4.77-4.65 (m, 3 H, CH_2OH, H-5′a), 4.61-4.45 (m, 3 H, H-2′, H-4′, H-5′b, $^2J_{5'a,5'b}$ = 14.2, $^3J_{4,5'b}$ = 8.6), 3.94 (d, 1 H, H-3′, $^3J_{3',4'}$ = 3.0), 3.63 (dt, 1 H, H-1″a, $^2J_{1''a,1''b}$ = 9.1, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.6), 3.43 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7), 1.60-1.49 (m, 2 H, CH_2-2″), 1.38 (s, 3 H, CH_3, *i*-Pr), 1.34-1.16 (m, 21 H, CH_3, *i*-Pr, CH_2-3″ to CH_2-11″), 0.85 (t, 3 H, CH_3-12", ^3J = 6.5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (C-5), 133.6 (C-4), 112.5 (Cq, *i*-Pr), 105.2 (C-1′), 82.8 (C-3′), 82.1 (C-2′), 80.0 (C-4′), 70.8 (C-1″), 52.6 (CH_2OH), 47.9 (C-5′), 32.0, 29.7, 29.7, 29.7, 29.5, 29.4, 26.3 (C-2″ to C-10″), 26.8, 26.2 (2 × CH_3, *i*-Pr), 22.8 (C-11"), 14.2 (C-2″). HRMS: calcd. for $C_{23}H_{41}N_3O_5$ [M + H]$^+$ 440.3119, found 440.3130; calcd. for [M + Na]$^+$ 462.2938, found 462.2953.

General procedure for the phosphorylation of 3-*O*-protected 5-(hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranoses with diethyl phosphorochloridate: To a solution of 5-(hydroxymethyl-1H-1,2,3-triazol-1-yl)-xylofuranose derivative (0.14 mmol) in dichloromethane (3 mL) and under nitrogen atmosphere, triethylamine (1.5 equiv.) was added. The reaction mixture was cooled to 0ºC and diethyl phosphorochloridate (1.5 equiv) and DMAP (catalytic amount, one spatula point) were added. The reaction was stirred at room temperature overnight. The solution was concentrated under vacuum and the residue was purified by column chromatography.

3-*O*-Benzyl-5-deoxy-5-[4-(diethoxyphosphoryloxy)methyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (24): According to the general procedure, the treatment of 3-*O*-benzyl-5-deoxy-5-(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**20**, 50 mg, 0.14 mmol) with triethylamine (0.03 mL, 0.21 mmol) and diethyl phosphorochloridate (0.03 mL, 0.21 mmol) and purification by flash column chromatography (EtOAc /Hexane, 1:2) afforded the title compound (54 mg, 78%) as a colourless oil. $[\alpha]_D^{20}$ = – 20 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.72 (s, 1 H, H-5), 7.43-7.30 (m, 5 H, Ph), 5.97 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.6), 5.16 (d, 2 H, CH_2OP, $^3J_{CH2,P}$ = 8.8), 4.74 (d, part A of AB system, 1 H, H-a, CH_2Ph, $^2J_{a,b}$ = 11.7), 4.70-4.62 (m, 2 H, H-2′, H-5′a), 4.59-4.49 (m, 3 H, H-5′b, H-4′, H-b from CH_2Ph), 4.15-4.04 (m, 4 H, 2 × CH_2, 2 × Et), 3.99 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.2), 1.42 (s, 3 H, CH_3, *i*-Pr), 1.35-1.27 (m, 9 H, 2 × CH_3, 2 × Et, CH_3, *i*-Pr) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.4 (d, C-4, $^3J_{C,P}$ = 7.5), 136.9 (Cq, Ph), 128.9, 128.5, 128.1 (*C*H, Ph), 124.8 (C-5), 112.3 (Cq, *i*-Prop), 105.4 (C-1′), 82.1 (C-2′), 81.6 (C-3′), 78.9 (C-4′), 72.1, (CH_2, Bn), 64.1 (d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 5.9), 60.6 (d, CH_2OP, $^2J_{C,P}$ = 5.1), 49.6 (C-5′), 26.9, 26.3 (2 × CH_3, *i*-Pr), 16.1 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.9). ^{31}P NMR (162 MHz, $CDCl_3$): δ = – 1.15. HRMS: calcd. for $C_{22}H_{32}N_3O_8P$ [M + H]$^+$ 498.2000, found 498.1995; calcd. for [M + Na]$^+$ 520.1819, found 520.1814.

3-*O*-Benzyl-5-deoxy-5-[5-(diethoxyphosphoryloxy)methyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (25): According to the general procedure, the treatment of 3-*O*-benzyl-5-deoxy-5-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**21**, 50 mg, 0.14 mmol) with triethylamine (0.03 mL, 0.21 mmol) and diethyl phosphorochloridate (0.03 mL, 0.21 mmol) and purification by flash column chromatography (EtOAc/hexane, 1:2) afforded the title compound (47 mg, 68%) as a colourless oil. $[\alpha]_D^{20}$ = – 23 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.70 (s, 1 H, H-4), 7.42-7.28 (m, 5 H, Ph), 5.95 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 5.24 (dd, 1 H, part A of ABX system, H-a from CH_2OP, $^2J_{a,b}$ = 13.1, $^3J_{H-a,P}$ = 9.2) 5.11 (dd, part B of ABX system, 1 H, H-b from CH_2OP, $^3J_{H-b,P}$ = 8.4), 4.76-4.55 (m, 5 H, H-a from CH_2Ph, CH_2-5′, H-2′, H-4′, $^2J_{a,b}$ = 11.7), 4.50 (d, 1 H, H-b from CH_2Ph), 4.11-3.96 (m, 5 H, 2 × CH_2, 2 × Et, H-3′), 1.40 (s, 3 H, CH_3, *i*-Pr), 1.32-1.20 (m, 9 H, 2 × CH_3 from 2 × Et, CH_3, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.9 (Cq, Ph), 134.3 (C-4), 133.0 (d, C-5, $^3J_{C-5,P}$ = 7.8), 128.8, 128.5, 128.1 (*C*H, Ph), 112.3 (Cq, *i*-Pr), 105.3 (C-1′), 82.2 (C-2′), 81.9 (C-3′), 79.7 (C-4′), 72.2 (CH_2Ph), 64.3 (d, 2× CH_2, 2× Et, $^2J_{C,P}$ = 5.9), 57.0 (d, CH_2OP, $^2J_{C,P}$ = 4.9), 47.9 (C-5′), 26.8, 26.3 (2 × CH_3, *i*-Pr) 16.2 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.8). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* –1.17. HRMS: calcd. for $C_{22}H_{32}N_3O_8P$ [M + H]$^+$ 498.2000, found 498.2010; calcd. for [M + Na]$^+$ 520.1819, found 520.1830.

5-Deoxy-5-[4-(diethoxyphosphoryloxy)methyl-3-*O*-dodecyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (26): According to the general procedure, the treatment of 5-deoxy-3-*O*-dodecyl-5-(4-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**22**, 50 mg, 0.11 mmol) with triethylamine (0.02 mL, 0.17 mmol) and diethyl phosphorochloridate (0.02 mL, 0.17 mmol) and purification by column chromatography (EtOAc/Hexane, 1:2) afforded the title compound (53 mg, 81%) as a colourless oil. $[\alpha]_D^{20}$ = – 15 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.80 (s, 1H, H-5), 5.93 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 5.18 (d, 2 H, CH_2OP, $^3J_{CH2,P}$ = 8.8), 4.72 (dd, part A of ABX system,1 H, H-5′a, $^3J_{4',5'a}$ = 7.5, $^2J_{5'a,5'b}$ = 17.5), 4.59 (d, 1 H, H-2′), 4.56-4.45 (m, 2 H, H-4′, H-5′b), 4.15-4.04 (m, 4 H, 2 × CH_2, 2 × Et), 3.85 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.4), 3.64 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.5, $^2J_{1''a,1''b}$ = 9.2), 3.43 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.6), 1.62-1.52 (m, 2 H, CH_2-2″), 1.42 (s, 3 H, CH_3, *i*-Pr), 1.38-1.18 (m, 27 H , 2 × CH_3, 2 × Et, CH_3, *i*-prop, CH_2-3″ to CH_2-11″), 0.90 (t, 3 H, CH_3-12", ^3J = 6.6). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.4 (d, C-4, $^3J_{C-4,P}$ = 7.3), 124.8 (C-5), 112.2 (Cq, *i*-Pr), 105.4 (C-1′), 82.6 (C-3′), 82.2 (C-2′), 79.0 (C-4′), 70.7 (C-1″), 64.1 (d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 5.9), 60.6 (d, CH_2OP, $^2J_{C,P}$ = 5.2), 49.6 (C-5′), 32.1, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 26.3 (C-2″ to C-10″), 26.9, 26.3 (2 × CH_3, *i*-Pr), 22.8 C-11″), 16.2 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.8), 14.3 (C-12″). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* –1.13. HRMS: calcd. for $C_{27}H_{50}N_3O_8P$ [M + H]$^+$ 576.3408, found 576.3405; calcd. for [M + Na]$^+$ 598.3228, found 598.3224.

5-Deoxy-5-[5-(diethoxyphosphoryloxy)methyl-3-*O*-dodecyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (27): According to the general procedure, the treatment of 5-deoxy-3-*O*-dodecyl-5-(5-hydroxymethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranose (**23**, 50 mg, 0.11 mmol) with triethylamine (0.02 mL, 0.17 mmol) and diethyl phosphorochloridate (0.02 mL, 0.17 mmol) and purification by column chromatography (EtOAc/Hexane, 1:2) afforded the title compound (61 mg, 93%) as a colourless oil. $[\alpha]_D^{20}$ = – 10 (c = 1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.72 (s, 1 H, H-4), 5.92 (d, 1H, H-1′ $^3J_{1',2'}$ = 3.6), 5.29 (dd, part A of ABX system, 1 H, H-a from CH_2OP, $^2J_{a,b}$ = 13.2, $^3J_{H-a,P}$ = 9.2), 5.17 (dd, part B of ABX system, 1 H, H-b from CH_2OP, $^3J_{H-b,P}$ = 8.4), 4.73 (dd, 1 H, H-5′a, $^3J_{4',5'a}$ = 8.3, $^2J_{a,b}$ = 19.3), 4.61-4.50 (m, 3 H, H-2′, H-4′,H-5′b), 4.15-4.01 (m, 4 H, 2 × CH_2, 2 × Et), 3.92 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.1), 3.63 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.6, $^2J_{1''a,1''b}$ = 9.2), 3.44 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7), 1.64-1.49 (m, 2 H, CH_2-2″), 1.41 (s, 3 H, CH_3, *i*-Pr), 1.37-1.19 (m, 27 H , 2 × CH_3, 2 × Et, CH_3, *i*-Pr, CH_2-3" to CH_2-11″), 0.87 (t, 3 H, CH_3-12", ^3J = 6.5). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 134.4 (C-4), 133.2 (d, C-5, $^3J_{C-5,P}$ = 7.8), 112.2 (Cq, *i*-P), 105.3 (C-1′), 82.7 (C-3′), 82.2 (C-2′), 79.8 (C-4′), 70.7 (C-1″), 64.4 (d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 5.9), 57.1 (d, CH_2OP, $^2J_{C,P}$ = 5.1), 48.0 (C-5′), 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 26.4 (C-2″ to C-10″), 26.8, 26.3 (2 × CH_3, *i*-Pr), 22.8 C-11″), 16.2 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.8), 14.3 (C-12″). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* – 1.13 ppm. HRMS: calcd. for $C_{27}H_{50}N_3O_8P$ [M + H]$^+$ 576.3408, found 576.3405; calcd. for [M + Na]$^+$ 598.3228, found 598.3224.

5-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (28) and 5-(5-aminomethyl-1*H*-1,2,3-triazol-1-yl)-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (29): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**18**, 600 mg, 1.97 mmol) and propargylamine (0.25 mL, 3.93 mmol). The reaction was stirred for

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24 h. Purification by column chromatography (from EtOAc to EtOAc/MeOH, 18:1) afforded the 1,4-disubstituted triazole **22** (20 mg, 3%) as a yellow oil and the 1,5-disubstituted regioisomer **29** (20 mg, 3%, not isolated from **18**), along with recovered **18** (480 mg, 80%).

Data for 28: $[\alpha]_D^{20}$ = – 12 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.61 (s, 1 H, H-5), 7.42-7.28 (m, 5 H, Ph), 5.95 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.3), 4.76-4.58 (m, 3 H, H-2′, H-a from C*H*$_2$Ph, H-5′a), 4.57-4.43 (m, 3 H, H-4′, H-b from C*H*$_2$Ph, H-5′b), 4.07-3.93 (m, 3 H, C*H*$_2$N, H-3′), 1.40 (s, 3 H, CH_3, *i*-Pr), 1.29 (s, 3H, CH_3, *i*-Prop). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.9 (C-4), 137.0 (Cq, Ph), 128.8, 128.4, 128.1 (*C*H, Ph), 123.0 (C-5), 112.2 (Cq, *i*-Pr), 105.3 (C-1′), 82.1 (C-2′), 81.6 (C-3′), 79.0 (C-4′), 72.1 (*C*H$_2$Ph), 49.4 (C-5′), 36.8 (*C*H$_2$N), 26.8, 26.3 (2 × CH_3, *i*-Pr). HRMS: calcd. for $C_{18}H_{24}N_4O_4$ [M + H]$^+$ 361.1870, found 361.1870; calcd. for $C_{18}H_{24}N_4O_4$ [M +Na]$^+$ 383.1690, found 383.1690.

NMR data for 29: ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.56 (s, 1 H, H-4), 7.41-7.28 (m, 5 H, Ph), 5.96 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.7), 4.79-4.57 (m, 4 H, H-a from C*H*$_2$Ph, H-2′, H-4′, H-5′a), 4.55-4.43 (m, 2 H, H-b from C*H*$_2$Ph, H-5′b), 4.07 (d, 1 H, H-3′, $^3J_{3',4'}$ = 3.1), 3.94 (s, 2 H, C*H*$_2$N), 1.41 (s, 3 H, C*H*$_3$, *i*-Pr), 1.29 (s, 3 H, C*H*$_3$, *i*-Pr).* ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.3 (C-5), 137.0 (Cq, Ph), 132.4 (C-4), 128.8, 128.5, 128.1 (*C*H, Ph), 112.3 (Cq, *i*-Pr), 105.2 (C-1′), 82.1 (C-2′), 82.0 (C-3′), 79.8 (C-4′), 72.1 (*C*H$_2$Ph), 47.4 (C-5′), 35.0 (*C*H$_2$N), 26.8, 26.3 (2 × *C*H$_3$, i-Pr).*

*Data extracted from the spectrum of a mixture containing **18**/**29**.

5-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (30) and 5-(5-aminomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (31): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**19**, 600 mg, 1.56 mmol) and propargylamine (0.2 mL, 3.12 mmol). The reaction was stirred for 16 h. Purification by column chromatography (from EtOAc to EtOAc/MeOH, 18:1) afforded the 1,4-disubstituted triazole **30** (140 mg, 20%) and the 1,5-disubstituted regioisomer **31** (140 mg, 20%) as yellow oils. Unreacted **19** was recovered (239 mg, 40%).

Data for **30**: $[\alpha]_D^{20}$ = – 45 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.67 (s, 1 H, H-5), 5.93 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.69 (dd, 1 H, part A of ABX system, H-5′a, $^3J_{4',5'a}$ = 8.9, $^2J_{5'a,5'b}$ = 20.9) 4.58 (d, 1 H, H-2′), 4.56-4.42 (m, 2 H, H-5′b, H-4′), 4.04 (s, 2 H, C*H*$_2$N), 3.85 (d, 1 H, H-3, $^3J_{3',4'}$ = 2.4) 3.63 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.7, $^2J_{1''a,1''b}$ = 9.1), 3.43 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.6), 1.66-1.55 (m, 2 H, C*H*$_2$-2″), 1.38 (s, 3 H, C*H*$_3$, *i*-Prop), 1.26-1.22 (m, 21 H, C*H*$_3$, *i*-Pr, C*H*$_2$-3″ to C*H*$_2$-11″), 0.87 (t, 3 H, C*H*$_3$-12″, ^3J = 6.9). ^{13}C NMHz, $CDCl_3$): *δ* 147.8 (C-4), 122.4 (C-5), 112.0 (Cq, *i*-Pr), 105.2 (C-1′), 82.5 (C-3′), 82.0 (C-2′), 79.0 (C-4′), 70.5 (C-1″), 49.3 (C-5′), 36.9 (*C*H$_2$N), 31.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 26.2 (C-2″ to C-10″), 26.7, 26.1 (2 × *C*H$_3$, *i*-Pr), 22.7 (C-11″), 14.1 (C-12″). HRMS: calcd for $C_{23}H_{42}N_4O_4$ [M + H]$^+$ 439.3279, found 439.3280.

Data for **31**: $[\alpha]_D^{20}$ = – 10 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.57 (s, 1 H, H-4), 5.92 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.5), 4.73-4.55 (m, 3 H, H-5′a, H-4′, H-2′, $^3J_{4',5'a}$ = 3.2, $^2J_{5'a,5'b}$ = 14.2), 4.45 (dd, part B of ABX system 1 H, H-5′b, $^3J_{4',5'b}$ = 7.9), 3.98 (s, 2 H, C*H*$_2$N), 3.93 (d, 1 H, $^3J_{3',4'}$ = 3.2), 3.64 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.6, $^2J_{1''a,1''b}$ = 9.2), 3.44 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7), 1.63-1.49 (m, 2 H, C*H*$_2$-2″), 1.41 (s, 3 H, C*H*$_3$, *i*-Pr), 1.38-1.16 (m, 21 H, CH_3, *i*-Prop, C*H*$_2$-3″ to C*H*$_2$-11″), 0.87 (t, 3 H, C*H*$_3$-12″, ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.2 (C-5), 132.4 (C-4), 112.2 (Cq, *i*-Pr), 105.3 (C-1′), 82.9 (C-3′), 82.2 (C-2′), 80.0 (C-4′), 70.7 (C-1″), 47.5 (C-5′), 35.0 (*C*H$_2$N), 32.1, 29.8, 29.8, 29.7, 29.5, 29.5, 26.3 (C-2″ to C-10″), 26.8, 26.2 (2 × *C*H$_3$, *i*-Pr), 22.8 (C-11″), 14.3 (C-12″). HRMS: calcd for $C_{23}H_{42}N_4O_4$[M + H]$^+$ 439.3279, found 439.3280.

General procedure for the *N*-phosphorylation of 3-*O*-protected 5-(aminomethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranoses with diethyl phosphorochloridate: To a solution of 5-(aminomethyl-1H-1,2,3-triazol-1-yl) xylofuranose derivative (0.35 mmol) in dichloromethane (5 mL) at 0 ºC and under nitrogen atmosphere, diethyl phosphorochloridate (1.2 equiv.) was added. The mixture was stirred at room temperature for 2 h. The solution was concentrated under vacuum and the residue was subjected to column chromatography.

3-*O*-Benzyl-5-deoxy-5-[4-(diethoxyphosphoryl)aminomethyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (32): Obtained according to the general procedure, starting from 5-(4-aminomethyl-1*H*-1,2,3-triazol-1-yl)-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**28**, 30 mg, 0.08 mmol) and diethyl phosphorochloridate (0.01 mL, 0.1 mmol). Purification by column chromatography (from EtOAc to EtOAc/MeOH, 25:1, then 18:1) afforded the title compound (23 mg, 56%) as a colourless oil. $[\alpha]_D^{20}$ = – 32 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.56 (s, 1 H, H-5), 7.43-7.30 (m, 5 H, Ph), 5.99 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.74 (d, 1 H, part A of AB system, H-a from C*H*$_2$Ph, $^2J_{a,b}$ = 11.7), 4.70-4.60 (m, 2 H, H-2′, H-5′a), 4.56-4.51 (m, 3 H, H-b from C*H*$_2$Ph, H-4′, H-5′b), 4.19 (dd, 2 H, C*H*$_2$NH, $^3J_{CH2,P}$ = 10.6, $^3J_{CH2,NH}$ = 6.8), 4.13-3.95 (m, 5 H, H-3′, 2 × CH_2, 2 × Et), 3.13 (dt, 1 H, N*H*, $^2J_{NH,P}$ = 10.2), 1.41 (s, 3 H, C*H*$_3$, *i*-Pr), 1.34-1.18 (m, 9 H, CH_3, *i*-Prop, 2 × C*H*$_3$, 2 × Et). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.7 (d, C-4, $^3J_{C,P}$ = 6.3), 136.9 (Cq, Ph), 128.9, 128.5, 128.1 (*C*H, Ph), 122.8 (C-5), 112.2 (Cq, *i*-Prop), 105.4 (C-1′), 82.1 (C-3′), 81.7 (C-3′), 79.0 (C-4′), 71.9 (*C*H$_2$Ph), 62.7 (d, 2 × *C*H$_2$, 2 × Et, $^2J_{C,P}$ = 5.5), 49.6 (C-5′), 37.0 (*C*H$_2$N), 26.8, 26.3 (2 × *C*H$_3$, *i*-Pr), 16.3 (d, 2 × *C*H$_3$, 2 × Et, $^3J_{C,P}$ = 7.0). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 8.19. HRMS: calcd. for $C_{22}H_{33}N_4O_7P$ [M + H]$^+$ 497.2160, found 497.2173; calcd. for [M + Na]$^+$ 519.1979, found 519.1997.

5-Deoxy-3-*O*-dodecyl-5-[4-(diethoxyphosphoryl)aminomethyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (33): Obtained according to the general procedure, starting from 5-(4-aminomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**30**, 89 mg, 0.2 mmol) and diethyl phosphorochloridate (0.04 mL, 0.24 mmol). Purification by flash column chromatography (from EtOAc to EtOAc/MeOH, 28:1, then 22:1) afforded the title compound (58 mg, 50%) as a colourless oil. $[\alpha]_D^{20}$ = – 23 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (s, 1H, H-5), 5.93 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.70 (dd, 1 H, H-5′a, $^3J_{4',5'a}$ = 8.3, $^2J_{5'a,5'b}$ = 18.9), 4.58 (d, 1 H, H-2′), 4.55-4.41 (m, 2 H, H-4′, H-5′b), 4.21 (dd, 2 H, C*H*$_2$NH, $^3J_{CH2,P}$ = 10.7, $^3J_{CH2,NH}$ = 7.0), 4.14-3.97 (m, 4 H, 2 × CH_2, 2 × Et), 3.85 (d, 1 H, H-3, $^3J_{3',4'}$ = 2.1), 3.63 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.5, $^2J_{1''a,1''b}$ = 9.1), 3.42 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.5), 3.18 (dt, 1 H, N*H*, $^2J_{NH,P}$ = 10.3), 1.61-1.50 (m, 2 H, C*H*$_2$-2″), 1.41 (s, 3 H, C*H*$_3$, *i*-Pr), 1.37-1.15 (m, 27 H, C*H*$_3$, *i*-Pr, 2 × C*H*$_3$, 2 × Et, C*H*$_2$-3″ to C*H*$_2$-11″), 0.86 (t, 3 H, C*H*$_3$-12″, ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.7 (d, C-4, $^3J_{C\text{-}4,P}$ = 6.2), 122.8 (C-5), 112.1 (Cq, *i*-Pr), 105.3 (C-1′), 82.7 (C-3′), 82.1 (C-2′), 79.1 (C-4′), 70.7 (C-1″), 62.6 (d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 5.4), 49.6 (C-5′), 37.1 (*C*H$_2$N), 32.0, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 26.3 (*C*H$_2$-3″ to *C*H$_2$-10″) 26.9, 26.2 (2× CH_3, *i*-Pr), 22.8 (*C*H$_2$-10″), 16.3 (d, 2 × *C*H$_3$, 2 × Et, $^3J_{C,P}$ = 7.1), 14.3 (C-12″). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 8.20. HRMS: calcd for $C_{27}H_{51}N_4O_7P$ [*M* + H]$^+$ 575.3568, found 575.3572; calcd for [*M* + Na]$^+$ 597.3388, found 597.3390.

5-Deoxy-3-*O*-dodecyl-5-[5-(diethoxyphosphoryl)aminomethyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (34): Obtained according to the general procedure, starting from 5-(5-aminomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**31**, 155 mg, 0.35 mmol) and diethyl phosphorochloridate (0.06 mL, 0.42 mmol). Purification by flash column chromatography (from EtOAc to EtOAc/MeOH, 28:1, then 22:1) afforded the title compound (105 mg, 52 %) as a colourless oil. $[\alpha]_D^{20}$ = – 16 (c = 1, in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (s, 1 H, H-4), 5.92 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.6), 4.73 (dd, part A of ABX system, 1 H, H-5′a, $^3J_{4',5'a}$ = 2.8, $^2J_{5'a,5'b}$ =14.7), 4.62-4.50 (m, 2 H, H-2′, H-4′), 4.40 (dd, part B of ABX system, 1 H, H-5′b, $^3J_{4',5'b}$ = 8.6), 4.29 (dt, 1 H, H-a from C*H*$_2$NH, $^3J_{H\text{-}a,NH}$ = $^3J_{H\text{-}a,P}$ = 9.5, $J_{a,b}$ = 15.7), 4.17 (ddd, 1 H, H-b from C*H*$_2$NH, $^3J_{NH,Hb}$ = 5.4, $^3J_{H\text{-}b,P}$ = 12.1), 4.11-3.89 (m, 4 H, 2 × CH_2, 2 × Et, H-3′, $^3J_{3',4'}$ = 3.0), 3.64 (dt, 1 H, H-1″a, $^2J_{1''a,1''b}$ = 9.2, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.6), 3.57-3.38 (m, 2 H, H-1″b, N*H*, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7, $^2J_{NH,P}$ = $^3J_{H\text{-}a,NH}$ = 9.5), 1.63-1.50 (m, 2 H, CH_2-2″), 1.38 (s, 3 H, CH_3, *i*-Pr), 1.35-1.19 (m, 27 H, CH_3, *i*-Pr, 2 × CH_3, 2 × Et, CH_2-3″ to CH_2-11″), 0.86 (t, 3 H, CH_3-12″, *J* = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.5 (d, C-5, $^3J_{C\text{-}5,P}$ = 6.0), 133.5 (C-4), 112.3 (Cq, *i*-Prop), 105.2 (C-1′), 82.9 (C-3′), 82.1 (C-2′), 80.0 (C-4′), 70.6 (C-1″), 62.8, 62.7 (2 d, 2 × CH$_2$, 2 × Et, $^2J_{C\text{-}P}$ = 5.2), 47.9 (C-5′), 34.2 (CH$_2$N), 32.0, 29.8, 29.7, 29.7, 29.5, 29.5, 26.3 (CH$_2$-3″ to CH$_2$-10″) 26.8, 26.2 (2 × CH$_3$, *i*-Pr), 22.8 (CH$_2$-11″), 16.30, 16.25 (d, 2 × CH$_3$, 2 × Et, $^3J_{C,P}$ = 6.8), 14.2 (C-12″). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 7.83. HRMS: calcd for $C_{27}H_{51}N_4O_7P$ [M + H]$^+$ 575.3568, found 575.3570; calcd for [M + Na]$^+$ 597.3388, found 597.3388.

3-*O*-Benzyl-5-(4-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (35) and 3-*O*-benzyl-5-(5-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (36): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**18**, 159 mg, 0.52 mmol) and propargyl bromide (80 wt.% soln. in toluene, 0.12 mL, 1.04 mmol). The reaction was stirred for 16 h. Purification by column chromatography (EtOAc/cyclohexane, 1:6) afforded the 1,4-disubstituted triazole **35** (106 mg, 48%) as white crystals and the 1,5-disubstituted regioisomer **36** (4 mg, 2%) as yellowish oil.

Data for **35**: $[\alpha]_D^{20}$ = – 19 (c = 1, in CH_2Cl_2). m.p.: 122.2–123.7 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.57 (s, 1 H, H-5), 7.42-7.30 (m, 5 H, Ph), 5.97 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.7), 4.73 (d, part A of AB system, 1 H, H-a from CH$_2$Ph, $^2J_{a,b}$ = 11.8), 4.70-4.59 (m, 2 H, H-2′, H-5′a, $^3J_{4',5'a}$ = 7.4, $^2J_{5'a,5'b}$ = 17.1), 4.57-4.42 (m, 5 H, H-4′, H-5′b, CH_2Br, H-b from CH_2Ph), 3.97 (d, 1 H, H-3′, $J_{3',4'}$ = 2.7), 1.42 (s, 3 H, CH_3, *i*-Pr), 1.30 (s, 3 *H*, CH_3, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.6 (C-4), 136.8 (Cq, Ph), 128.8, 128.5, 128.1 (*C*H, Ph), 124.0 (C-5), 112.2 (Cq, *i*-Prop), 105.3 (C-1′), 82.0 (C-2′), 81.5 (C-3′), 78.8 (C-4′), 72.0 (*C*H$_2$Ph), 49.5 (C-5′), 26.8, 26.3 (2 × CH$_3$, *i*-Pr), 21.7 (*C*H$_2$Br). HRMS: calcd for $C_{18}H_{22}BrN_3O_4$ [M + H]$^+$ 424.0866, found 424.0867.

Data for **36**: $[\alpha]_D^{20}$ = – 26 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.65 (s, 1 H, H-4), 7.43-7.29 (m, 5 H, Ph) 5.97 (d, 1H, H-1′, $^3J_{1',2'}$ = 3.7), 4.75 (d, part A of AB system, 1 H, H-a from CH_2Ph, $^2J_{a,b}$ = 11.8), 4.71-4.56 (H-2', H-4', CH_2-5', H-a from CH_2Br), 4.54-4.42 (m, 2 H, H-b from CH_2Ph, H-b from CH_2Br, $^2J_{a,b}$ = 12.1), 4.07 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.6), 1.41 (s, 3 H, CH$_3$, *i*-Pr), 1.30 (s, 3 H, CH$_3$, *i*-Pr). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.0 (C-5), 134.2 (Cq, Ph), 134.0 (C-4), 128.9, 128.5, 128.1 (*C*H, Ph), 112.3 (Cq, *i*-Pr), 105.3 (C-1′), 82.2 (C-2′), 81.8 (C-3′), 79.6 (C-4′), 72.2 (*C*H$_2$Ph), 47.8 (C-5′), 26.8, 26.3 (2 × *C*H$_3$, *i*-Pr), 17.5 (*C*H$_2$Br).

5-(4-Bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (37) and 5-(5-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (38): Obtained according to the general procedure for thermal azide-alkyne cycloaddition, starting from 5-azido-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**19**, 300 mg, 0.78 mmol) and propargyl bromide (80 wt.% soln. in toluene, 0.17 mL, 1.56 mmol). The reaction was stirred for 48 h. Purification by column chromatography (EtOAc/cyclohexane, 1:7) afforded the 1,4-disubstituted triazole **35** (227 mg, 58%) as and the 1,5-disubstituted regioisomer **36** (20 mg, 5%) as yellowish oils.

Data for **37**: $[\alpha]_D^{20}$ = – 12 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.71 (s, 1 H, H-5), 5.95 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.7), 4.71 (m, 1 H, H-5′a, $^3J_{4',5'a}$ = 2.2, $^2J_{5'a,5'b}$ = 12.3), 4.63-4.43 (m, 5 H, H-2′, H-4′, H-5′b, CH_2Br), 3.84 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.7), 3.64 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.5, $^2J_{1''a,1''b}$ = 9.2), 3.41 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.7), 1.62-1.50 (m, 2 H, CH_2-2″), 1.43 (s, 3 H, CH_3, *i*-Pr), 1.39-1.16 (m, 21 H, CH_3, *i*-Pr, CH_2-3″ to CH_2-11″), 0.87 (t, 3 H, CH_3-12″, ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 144.7 (C-4), 124.1 (C-5), 112.2 (Cq, *i*-Pr), 105.4 (C-1′), 82.6 (C-3′), 82.1 (C-2′), 78.9 (C-4′), 70.7 (C-1″), 49.6 (C-5′), 32.1, 29.8, 29.8, 29.7, 29.5, 29.5, 26.3 (C-2″ to C-10″), 26.9, 26.2 (2 × *C*H$_3$, *i*-Pr), 22.8 (C-11''), 21.8 (*C*H$_2$Br), 14.3 (C-12''). HRMS: calcd for $C_{23}H_{40}BrN_3O_4$ [*M* + H]$^+$ 502.2275, found 502.2277.

Data for **38**: $[\alpha]_D^{20}$ = – 50 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.67 (s, 1 H, H-4), 5.93 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.7), 4.80-4.67 (m, 2 H, H-5′a, H-a from CH_2Br), 4.65-4.47 (m, 4 H, H-2′, H-4′, H-5′b, H-b from CH_2Br), 3.94 (br. s, 1H, H-3′), 3.66 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.5, $^2J_{1''a,1''b}$ = 9.1), 3.44 (dt, 1 H, H-1″b, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.6), 1.67-1.49 (m, 2 H, CH$_2$-2″), 1.42 (s, 3 H, CH_3, *i*-Pr), 1.37-1.19 (m, 21 H, CH_3, *i*-Pr, CH_2-3″ to CH_2-11″), 0.87 (t, 3 H, CH_3-12″, ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 133.4 (C-4)*, 112.2 (Cq, *i*-Pr), 105.3 (C-1′), 82.7 (C-3′), 82.2 (C-2′), 79.7 (C-4′), 70.7 (C-1″), 47.8 (C-5′), 32.0, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 27.0, 26.3 (C-2″ to C-10″), 26.8, 26.2 (2 × *C*H$_3$, *i*-Pr), 22.8 (C-11''), 17.5 (*C*H$_2$Br), 14.3 (C-12''). *inferred from HSQC. HRMS: calcd for $C_{23}H_{40}BrN_3O_4$ [*M* + H]$^+$ 502.2275, found 502.2276.

General procedure for the Michaelis-Arbuzov reaction between 3-*O*-protected 5-(bromomethyl-1*H*-1,2,3-triazol-1-yl)-1,2-*O*-isopropylidene-α-D-xylofuranoses with triethyl phosphite: A solution of 5-(bromomethyl-1*H*-1,2,3-triazol-1-yl)xylofuranose derivative (0.17 mmol) in triethyl phosphite (1.5 mL) was stirred at 110 ºC for 2 h. The solution was concentrated under vacuum and the residue was subjected to column chromatography.

3-*O*-Benzyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (39): Obtained according to the general procedure, starting from 3-*O*-benzyl-5-(4-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**35**, 80 mg, 0.19 mmol) and triethyl phosphite (1.5 mL). Purification by column chromatography (EtOAc/hexane, 1:3) afforded the title compound (75 mg, 83%) as a colourless oil. $[\alpha]_D^{20}$ = – 33 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (d, 1 H, H-5, ^4J = 2.1), 7.43-7.29 (m, 5 H, Ph), 5.98 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.7), 4.72 (d, 1 H, part A of AB system, H-a, CH_2Ph, $^2J_{a,b}$ = 11.6), 4.68-4.60 (m, 2 H, H-2', H-5′a, $^2J_{5'a,5'b}$ = 13.3, $^3J_{4',5'a}$ = 7.7), 4.57-4.46 (m, 3 H, H-4', H-5′b, H-b from CH_2Ph), 4.14-4.01 (m, 4 H, 2 × CH_2, 2× Et), 3.97 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.5), 3.38-3.21 (m, 2 H, CH_2P, $^2J_{a,b}$ = 20.5, $^2J_{H\text{-}a,P}$ = 15.8, $^2J_{H\text{-}b,P}$ = 16.0), 1.41 (s, 3 H, CH_3, *i*-Pr), 1.33-1.21 (m, 9 H, CH_3, *i*-Pr, 2 × CH_3, 2 × Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (d, C-4, $^2J_{C\text{-}4,P}$ = 7.1), 136.9 (Cq, Ph), 128.8, 128.4, 128.0 (*C*H, Ph), 123.9 (d, C-5, $^3J_{C\text{-}5,P}$ = 4.1), 112.2 (Cq, *i*-Pr), 105.3 (C-1′), 82.0 (C-2′), 81.6 (C-3′), 78.9 (C-4′), 71.9 (*C*H$_2$Ph), 62.49, 62.45 (2 d, 2 × *C*H$_2$, 2 × Et, $^2J_{C,P}$ = 6.5), 49.5 (C-5′), 26.8, 26.3 (2 × *C*H$_3$, *i*-Pr), 24.3 (d, *C*H$_2$P, $^1J_{C,P}$ = 142.6), 16.5 (d, 2 × CH$_3$, 2 × Et, $^3J_{C,P}$ = 6.0). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 24.87. HRMS: calcd for $C_{22}H_{32}N_3O_7P$ [M + H]$^+$ 482.2051, found 482.2063; calcd for $C_{22}H_{32}N_3O_7P$ [M + Na]$^+$ 504.1870, found 504.1873.

5-Deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (40): Obtained according to the general procedure, starting from 5-(4-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**37**, 85 mg, 0.17 mmol) and triethyl phosphite (1.5 mL). Purification by column chromatography (EtOAc/hexane, 1:3) afforded the title compound (91 mg, 96%) as a colourless oil. $[\alpha]_D^{20}$ = – 14 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) : *δ* 7.71 (d, 1 H, H-5, ^4J = 1.6), 5.94 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.71 (dd, 1 H, part A of ABX system, H-5′a, $^3J_{4',5'a}$ = 7.9, $^2J_{5'a,5'b}$ = 17.5), 4.59 (d, 1 H, H-2′), 4.56-4.46 (m, 2 H, H-4′, H-5′b), 4.17-4.03 (m, 4 H, 2 × CH_2, 2 × Et), 3.84 (d, 1 H, H-3', $^3J_{3',4'}$ = 2.5), 3.64 (dt, 1 H, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.6, $^2J_{1''a,1''b}$ = 9.0), 3.50-3.23 (m, 3 H, H-1″b, CH_2P, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.6, $^2J_{a,b\,(CH2P)}$ = 20.5, $^2J_{H\text{-}a,P}$ = 15.7, $^2J_{H\text{-}b,P}$ = 15.9), 1.66-1.52 (m, 2 H, CH_2-2″), 1.43 (s, 3 H, CH_3, *i*-Pr), 1.39-1.17 (m, 27 H, CH_3, *i*-Pr, CH_2-3″ to CH_2-11″, 2 × CH_3, 2 × Et), 0.88 (t, 3 H, CH_3-12'', ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.48 (d, C-4, $^2J_{C\text{-}4,P}$ = 7.2), 123.9 (d, C-5, $^3J_{C\text{-}5,P}$ = 3.4), 112.1 (Cq, *i*-Pr), 105.3 (C-1′), 82.5 (C-3′), 82.1(C-2′), 79.0 (C-4′), 70.6 (C-1″), 62.53, 62.51 (2 d, 2 × *C*H$_2$, 2 × Et, $^2J_{C,P}$ = 6.6), 49.4 (C-5′), 32.0, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 26.3 (C-2″ to C-10″), 26.9, 26.2 (2 × *C*H$_3$, *i*-Pr), 24.3 (d, *C*H$_2$P, $^1J_{C,P}$ = 142.6), 22.8 (C-11''), 16.5 (d, 2 × *C*H$_3$, 2 × Et, $^3J_{C,P}$ = 6.0), 14.3 (C-12'').

^{31}P NMR (162 MHz, $CDCl_3$): *δ* 24.91 ppm. HRMS: calcd for $C_{27}H_{50}N_3O_7P$ [*M* + H]$^+$ 560.3459, found 560.3462.

5-Deoxy-5-[5-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (41): Obtained according to the general procedure, starting from 5-(5-bromomethyl-1*H*-1,2,3-triazol-1-yl)-5-deoxy-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**38**, 90 mg, 0.18 mmol) and triethyl phosphite (1.5 mL). Purification by column chromatography (EtOAc/hexane, 1:3) afforded the title compound (76 mg, 76%) as a colourless oil. $[\alpha]_D^{20}$ = – 18 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.66 (br.s, 1 H, H-4), 5.90 (d, 1 H, H-1′, $^3J_{1',2'}$ = 3.6), 4.67 (dd, part A of ABX system, 1 H, H-5′a, $^3J_{4',5'a}$ = 7.0, $^2J_{5'a,5'b}$ = 17.8), 4.61-4.46 (m, 3 H, H-2′, H-4′, H-5′b), 4.16-3.99 (m, 4 H, 2 × CH_2, 2 × Et), 3.88 (d, 1 H, H-3′, $^3J_{3',4'}$ = 2.2), 3.61 (dt, 1 H, part A of ABX system, H-1″a, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.7, $^2J_{1''a,1''b}$ = 9.0), 3.54-3.36 (m, 2 H, H-1″b, H-a from CH_2P, $^3J_{1''b,2''a}$ = $^3J_{1''b,2''b}$ = 6.6, $^2J_{H-a,P}$ = 16.3), 3.29 (dd, H-b from CH_2P, $^2J_{a,b\,(CH2P)}$ = 21.2, $^2J_{H-b,P}$ = 16.3), 1.63-1.48 (m, 2 H, CH_2-2″), 1.44-1.16 (m, 30 H, 2 × CH_3 *i*-Pr, CH_2-3″ to CH_2-11″, 2 × CH_3, 2 × Et), 0.88 (t, 3 H, CH_3-12", ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 134.0 (d, C-4, $^3J_{C-4,P}$ = 4.3), 129.4 (d, C-5, $^2J_{C-5,P}$ = 7.4), 112.1 (Cq, *i*-Pr), 105.2 (C-1'), 82.8 (C-3'), 82.1 (C-2'), 80.1 (C-4'), 70.6 (C-1″), 62.76, 62.73 (2 d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 6.5), 47.5 (C-5'), 32.0, 29.7, 29.7, 29.5, 29.5, 26.3 (C-2″ to C-10″), 26.8, 26.2 (2 × CH_3, *i*-Pr), 22.8 (C-11"), 21.9 (d, CH_2P, $^1J_{C,P}$ = 144.1), 16.5 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.0), 14.2 (C-12"). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 22.21. HRMS: calcd for $C_{27}H_{50}N_3O_7P$ [*M* + H]$^+$ 560.3459, found 560.3479; calcd for $C_{27}H_{50}N_3O_7P$ [*M* + Na]$^+$ 582.3279, found 582.3295.

General procedure for TFA-mediated acetonide hydrolysis in 1,2-*O*-isopropylidene xylofuranose 5-(triazolyl)methyl phosphonates followed by acetylation: A solution of 3-*O*-protected 1,2-*O*-isopropylidene xylofuranose 5-(triazolyl)methyl phosphonate (0.1 mmol) in aqueous trifluoroacetic acid (1.5 mL) was stirred at room temperature for 2 h. The solvents were co-evaporated with toluene. The residue was dried under vacuum and was then treated with pyridine (2 mL) and acetic anhydride (1.5 mL). The mixture was stirred at room temp. for 90 min. The solvents were co-evaporated with toluene and the residue was subjected to column chromatography.

1,2-Di-*O*-acetyl-3-*O*-benzyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-α,β-D-xylofuranose (42-α,β): Obtained according to the general procedure starting from 3-*O*-benzyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-1,2-*O*-isopropylidene-α-D-xylofuranose (**39**, 50 mg, 0.1 mmol). Purification by column chromatography (EtOAc/hexane, 6:1) afforded the title compound (28 mg, 51%, two steps, anomeric mixture, α/β ratio, 1:0.5) as a colourless oil.
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63, 7.62 (2 d, 1.5 H, H-5 α, H-5 β), 7.42-7.29 (m, 7.5 H, Ph), 6.44 (d, 1 H, H-1'α, $^3J_{1',2'(\alpha)}$ = 4.5), 6.15 (s, 0.5 H, H-1'β), 5.32-5.27 (m, 1.5 H, H-2'α, H-2'β), 4.82 (d, 0.5 H, part A of AB system, H-a from CH_2Ph, β, $^2J_{a,b(\beta)}$ = 11.8), 4.75-4.63 (m, 4 H, H-a from CH_2Ph, α, H-5'a α, H-5'a β, H-4'α, H-4'β), 4.61-4.51 (m, 2 H, H-b from CH_2Ph, *α*, H-b from CH_2Ph, β, H-5'b β), 4.46 (dd, 1 H, part B of ABX system, H-5'b α, $^3J_{4',5'b\,(\alpha)}$ = 7.7, $^2J_{5'a,5'b(\alpha)}$ = 13.8), 4.25 (m, 1 H, H-3'α, $^3J_{2',3'\,(\alpha)}$ = 3.7, $^3J_{3',4'\,(\alpha)}$ = 5.1), 4.15-4.01 (m, 6.5 H, H-3'β, 2 × CH_2, 2 × Et, α, β), 3.38-3.21 (m, 3 H, CH_2P, α, β, $^2J_{a,b\,(CH2P)}$ = 18.0, $^2J_{H-a,P}$ = 16.3, $^2J_{H-b,P}$ = 15.8), 2.13, 2.10 (2 s, 3 H, CH_3, 2 × Ac, β), 2.07, 2.03 (2 s, 6 H, CH_3, 2 × Ac, α), 1.28 (t, 9 H, 2 × CH_3, 2 × Et, α, β, ^3J = 7.0). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.8, 169.7, 169.6, 169.3 (*C*O, Ac, α, β), 138.6 (d, C-4, α, β, $^2J_{C-4,P}$ = 6.9), 137.0, 136.8 (Cq, Ph, α, β), 128.8, 128.8, 128.5, 128.4, 128.1, 128.1 (*C*H, Ph, α, β), 124.1 (C-5 α, $^3J_{C-5,P\,(\alpha)}$ = 3.9), 124.0 (C-5 β, $^3J_{C-5,P\,(\beta)}$ = 4.3), 99.7 (C-1' β), 94.1 (C-1' α), 81.7 (C-4' β), 80.0, 80.0 (C-3' α, C-3' β), 79.1 (C- 2' β), 78.2 (C-4' α), 76.5 (C-2' α), 72.5, 72.2 (*C*H$_2$Ph, α, β), 62.52, 62.50 (2 d, 2 × CH_2, 2 × Et, α, β, $^2J_{C,P}$ = 6.7, $^2J_{C,P}$ = 6.2), 50.6, 50.1 (C-5', α, β), 24.29, 24.26 (*C*H$_2$P, α, β, $^1J_{C,P}$ = 142.8), 21.3, 21.0 , 20.9, 20.6 (*C*H$_3$, Ac, α, β), 16.5 (d, 2 × CH_3, 2 × Et, α, β, $^3J_{C,P}$ = 6.0). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 24.79. HRMS: calcd for $C_{23}H_{32}N_3O_9P$ [*M* + H]$^+$ 526.1949, found 526.1959; calcd for $C_{23}H_{32}N_3O_9P$ [*M* + Na]$^+$ 548.1768, found 548.1774.

1,2-Di-*O*-acetyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-α-D-xylofuranose (43-α,β): Obtained according to the general procedure starting from 5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**40**, 109 mg, 0.195 mmol). Purification by column chromatography (EtOAc/hexane, 6:1) afforded the title compound (80 mg, 68%, two steps, anomeric mixture, α/β ratio, 1:0.5) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63, 7.62 (2 d, 1.4 H, H-5 α, H-5 β, ^4J = 2.1, ^4J = 1.6), 6.44 (d, 1 H, H-1'α, $^3J_{1',2'(\alpha)}$ = 4.4), 6.14 (s, 0.4 H, H-1'β), 5.26-5.21 (m, 1.5 H, H-2'α, H-2'β), 4.81-4.65 (m, 2.8 H, H-5'a α, H-5'a β, H-4'α, H-4'β), 4.58-4.49 (m, H-5'b β), 4.44 (dd, 1 H, part B of ABX system, H-5'b α, $^3J_{4',5'b\,(\alpha)}$ = 8.3, $^2J_{5'a,5'b(\alpha)}$ = 14.1), 4.19-4.05 (m, 7 H, H-3'α, H-3'β, 2 × CH_2, 2 × Et, α, β), 3.79-3.59 (m, 1.4 H, H-1″a, α, β, $^3J_{1''a,2''a}$ = $^3J_{1''a,2''b}$ = 6.4, $^2J_{1''a,1''b}$ = 9.0), 3.54-3.41 (m, 1.4 H, H-1″b, α, β), 3.40-3.25 (m, 2.8 H, CH_2P, α, β, $^2J_{a,b\,(CH2P)}$ = 19.6, $^2J_{H-a,P}$ = 16.1, $^2J_{H-b,P}$ = 16.1), 2.15, 2.11, 2.06 (3 s, 5.4 H, CH_3, Ac, α, β), 1.63-1.54 (m, 2.8 H, CH_2-2″, α, β),1.41-1.21 (m, 33.6 H, CH_2-3″ to CH_2-11″, 2 × CH_3, 2 × Et, α, β), 0.88 (t, 4.2 H, CH_3-12", α, β, ^3J = 6.7).^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.9, 169.6, 169.5, 169.2 (*C*O, Ac, α, β), 138.5 (d, C-4 α, $^2J_{C-4,P\,(\alpha)}$ = 7.1), 138.4 (d, C-4 β, $^2J_{C-4,P\,(\beta)}$ = 6.6), 124.3 (C-5 β, $^3J_{C-5,P\,(\beta)}$ = 3.9), 124.1 (C-5 α, $^3J_{C-5,P\,(\alpha)}$ = 4.2), 99.7 (C-1' β), 94.0 (C-1' α), 81.4 (C-4' β), 80.6, 80.1 (C-3' α, C-3' β), 78.9 (C-2' β), 78.2 (C-4' α), 76.4 (C-2' α), 71.4, 70.9 (*C*H$_2$-1", α, β), 62.51, 62.48 (2 d, 2 × CH_2, 2 × Et, α, β, $^2J_{C,P}$ = 6.7, $^2J_{C,P}$ = 6.5), 51.1, 50.1 (C-5', α, β), 32.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 29.4, 26.2, 26.1 (C-2″ to C-10″, α, β), 24.18, 24.13 (*C*H$_2$P, α, β, $^1J_{C,P}$ = 143.0), 22.8 (C-11", α, β), 21.2, 20.9, 20.8, 20.6 (*C*H$_3$, Ac, α, β), 16.4 (d, 2 × CH_3, 2 × Et, α, β, $^3J_{C,P}$ = 6.0), 14.2 (C-12", α, β). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 24.85. HRMS: calcd for $C_{28}H_{50}N_3O_9P$ [M + H]$^+$ 604.3357, found 604.3362; calcd for $C_{28}H_{50}N_3O_9P$ [M + Na]$^+$ 626.3177, found 626.3179.

General procedure for *N*-glycosylation of uracil with 1,2-O-acetyl xylofuranose 5-(triazolyl)methyl phosphonates: To a suspension of uracil (0.15 mmol, 2 equiv. relatively to the glycosyl acetate) in anhydrous acetonitrile (1.5 mL), *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv.) was added and the mixture was stirred at room temperature for 20 min, whereupon a clear solution of the silylated derivative was obtained. A solution of 1,2-*O*-acetyl xylofuranose 5-(triazolyl)methyl phosphonate (0.1 mmol) in anhydrous acetonitrile (1.5 mL) was added to the previous solution, followed by dropwise addition of trimethylsilyl triflate (TMSOTf, 6.5 equiv.). The mixture was stirred under microwave irradiation (150 W, P max = 250 Psi) at 65 ºC for 45 min. It was then diluted with dichloromethane and neutralized with satd. aq. $NaHCO_3$ solution. The aqueous phase was extracted with dichloromethane (3x) and the combined organic phases were washed with brine and dried with anhydrous $MgSO_4$. After filtration and concentration under vacuum, the residue was subjected to column chromatography.

1-{2-*O*-Acetyl-3-*O*-benzyl-1,5-dideoxy-5-[4-(diethoxyphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-α-D-xylofuranos-1-yl}uracil (44): Obtained according to the general procedure, starting from 1,2-di-*O*-acetyl-3-*O*-benzyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-α,β-D-xylofuranose (**42**-α,β, 50 mg, 0.095 mmol) and uracil (17 mg, 0.152 mmol) and using BSA (0.07 mL, 0.297 mmol) and TMSOTf (0.12 mL, 0.644 mmol). Purification by flash column chromatography (EtOAc/MeOH, from 24:1 to 18:1) afforded the title compound (20 mg, 36%) as a colorless oil. $[\alpha]_D^{20}$ = + 6 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (br. s, 1 H, N*H*), 7.65 (d, 1 H, H-5″, ^4J = 1.7), 7.60 (d, 1 H, H-6, $^3J_{5,6}$ = 8.2), 7.43-7.28 (m, 5 H, Ph), 6.12 (s, 1 H, H-1′), 5.67 (br.d, 1 H, H-5), 5.18 (s, 1 H, H-2′), 4.78 (d, 1 H, part A of AB system, H-a from CH_2Ph, ^2Ja,b= 11.5), 4.74-4.56 (m, 3 H, CH_2-5′, H-b from CH_2Ph, $^2J_{5'a,5'b}$ = 14.3, $^3J_{4',5'a}$ = 5.0, $^3J_{4',5'b}$ = 7.4), 4.50 (ddd, 1 H, H-4′), 4.15-4.02 (m, 4 H, 2 × CH_2, 2 × Et), 3.83 (d, 1 H, H-3′, $^3J_{3',4'}$ = 3.1), 3.38-3.21 (m, 2 H, CH_2P, $^2J_{a,b\,(CH2P)}$ = 19.2, $^2J_{H-a,P}$ = 16.3, $^2J_{H-b,P}$ = 16.0), 2.13 (s, 3 H, CH_3, Ac), 1.31-1.21 (m, 6 H, 2 × CH_3, 2 × Et). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.8 (CO, Ac), 163.0 (C-4), 150.1 (C-2), 140.1 (C-6), 138.8 (d, C-4″, $^2J_{C-4'',P}$ = 6.8) 136.0 (Cq, Ph), 129.0, 128.9, 128.7 (*C*H, Ph), 123.9 (C-5″, $^3J_{C-5'',P}$ = 3.8), 103.2 (C-5), 88.9 (C-1′), 80.8 (C-4′), 79.8 (C-3′), 79.6 (C-2′), 72.2 (*C*H$_2$Ph), 62.61, 62.57 (2 d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 6.6), 48.9

(C-5′), 24.1 (CH_2P, $^1J_{C,P}$ = 142.7), 20.9 (CH_3, Ac), 16.5 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.0).^{31}P NMR (162 MHz, CDCl3): δ 24.78. HRMS: calcd for $C_{25}H_{32}N_5O_9P$ [M + H]$^+$ 578.2010, found 578.2011; calcd for $C_{25}H_{32}N_5O_9P$ [M + Na]$^+$ 600.1830, found 600.1830.

1-{2-*O*-Acetyl-1,5-dideoxy-5-[4-(diethoxyphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-α-D-xylofuranos-1-yl}uracil (45): Obtained according to the general procedure, starting from 1,2-di-*O*-acetyl-5-deoxy-5-[4-(diethylphosphono)methyl-1*H*-1,2,3-triazol-1-yl]-3-*O*-dodecyl-α-D-xylofuranose (**43**-α,β, 45 mg, 0.074 mmol) and uracil (13 mg, 0.12 mmol) and using BSA (0.06 mL, 0.24 mmol) and TMSOTf (0.09 mL, 0.50 mmol). Purification by flash column chromatography (EtOAc/MeOH, from 24:1 to 18:1) afforded the title compound (8 mg, 16%) as colorless oil. $[\alpha]_D^{20}$ = + 5 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.69 (br. s, 1 H, N*H*), 7.70 (d, 1 H, H-5″, ^4J = 1.7), 7.63 (d, 1 H, H-6, $^3J_{5,6}$ = 8.2), 6.10 (s, 1 H, H-1′), 5.76 (br.d, 1 H, H-5), 5.09 (s, 1 H, H-2′), 4.80 (d, 1 H, part A of AB system, H-5′a, $^3J_{4',5'a}$ = 4.7, $^2J_{5a',5'b}$ = 14.3), 4.64 (d, 1 H, part B of AB system, H-5′b, $^3J_{4',5'b}$ = 7.6), 4.52 (ddd, 1 H, H-4′), 4.16-4.02 (m, 4 H, 2 × CH_2, 2 × Et), 3.95 (d, 1 H, H-3′, $^3J_{3',4'}$ = 3.2), 3.74 (dt, 1 H, H-1‴a, $^3J_{1'''a,2'''a}$ = $^3J_{1'''a,2'''b}$ = 6.6, $^2J_{1'''a,1'''b}$ = 9.3), 3.52 (dt, 1 H, H-1‴b, $^3J_{1'''b,2'''a}$ = $^3J_{1'''b,2'''b}$ = 6.6), 3.39-3.23 (m, 2 H, CH_2P, $^2J_{a,b\,(CH2P)}$ = 19.9, $^2J_{H\text{-}a,P}$ = 15.9, $^2J_{H\text{-}b,P}$ = 15.8), 2.12 (s, 3 H, CH_3, Ac), 1.63-1.52 (m, 2 H, CH_2-2‴), 1.37-1.17 (m, 24 H, CH_2-3‴ to CH_2-11‴, 2 × CH_3, 2 × Et), 0.87 (t, 3 H, CH_3-12‴, ^3J = 6.9). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.6 (CO, Ac), 162.7 (C-4), 150.0 (C-2), 140.2 (C-6), 138.8 (C-4″), 123.8 (C-5″, $^3J_{C\text{-}5'',P}$ = 4.1), 103.1 (C-5), 89.0 (C-1′), 81.0 (C-4′), 80.9 (C-3′), 79.5 (C-2′), 70.9 (C-1‴), 62.60, 62.57 (2 d, 2 × CH_2, 2 × Et, $^2J_{C,P}$ = 6.5), 48.8 (C-5′), 32.0, 29.8, 29.8, 29.7, 29.5, 29.5, 26.4 (C-2‴ to C-10‴), 24.2 (d, CH_2P, $^1J_{C,P}$ = 143.5), 22.8 (C-11‴), 20.9 (CH_3, Ac), 16.5 (d, 2 × CH_3, 2 × Et, $^3J_{C,P}$ = 6.1), 14.3 (C-12‴). ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 24.79. HRMS: calcd for $C_{30}H_{50}N_5O_9P$ [*M* + H]$^+$ 656.3419, found 656.3434; calcd for $C_{30}H_{50}N_5O_9P$ [*M* + Na]$^+$ 678.3238, found 678.3254.

Crystal structure determination: X-Ray diffraction data were collected at 296 K on a Bruker AXS-KAPPA D8 QUEST diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073Å). All nonhydrogen atoms were refined anisotropically whereas the hydrogen atoms were placed in calculated positions and allowed to refine riding on the parent atom on compounds **12-a** and **20** while in compound **35** were located from the electron density map and allowed to refine freely. All the structures were solved by direct methods with Bruker SHELXTL[34] and refined by full-matrix least-squares on F^2 using SHELXL 2017/1,[35] both programs included in WINGX version 2018.3.[36] Graphics were made with MERCURY 4.3.1[37] and PLATON[38] was used for determination of hydrogen bond interactions. Deposition Numbers 2004694 (for **12**), 2004693 (for **20**), and 2004692 (for **35**), contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Data for 12: Colourless monocrystals for X-ray studies were obtained from crystallization with ethyl acetate. Crystal data: orthorhombic; space group P 2_1 2_1 2_1, a = 5.4925(4), b = 10.0614(8), c = 21.3348(16) Å; V = 1179.01(15) Å^3, Z = 4, μ = 0.110 mm^{-1}. A total of 10880 reflection intensities were collected up to $2\theta_{max}$ = 25°; for structure refinement 2583 independent reflections with I > 4σ(I) were used. The final R_{factor} was 0.0317and Rw = 0.0705.

Data for 20: Colourless monocrystals for X-ray studies were obtained. Crystal data: orthorhombic; a = 8.8217(16), b = 11.0251(18), c = 19.290(3) Å; V = 1876.2(5) Å^3, Z = 4, μ = 0.110 mm^{-1}; space group was P 21 21 21. A total of 7630 reflection intensities were collected up to $2\theta_{max}$ = 21°; for structure refinement 3473 independent reflections with I > 4σ(I) were used. The final R_{factor} was 0.0390 and Rw = 0.0811.

Data for 35: Colourless monocrystals for X-ray studies were obtained. Crystal data: monoclinic; a = 5.1766(5), b = 10.7265(13), c = 16.464(2) Å; V = 913.99(18) Å^3, Z = 2, μ = 0.110 mm^{-1}; space group was P 21. A total of 6749 reflection intensities were collected up to $2\theta_{max}$ = 25°; for structure refinement 2583 independent reflections with I > 4σ(I) were used. The final R_{factor} was 0.0372 and Rw = 0.0753.

Computational Details

All DFT calculations were perfomed with Gaussian 09.[31] Using three-dimensional structures of **12-a** and **12-b** built using Pymol,[30] the geometries were optimized using the PBE1PBE functional, also known as PBE0,[39] along with the standard 6-311G** basis set for all elements. Solvent effects (toluene or chloroform) were taken into account using a polarizable continuum model described by the SMD variation of the integral equation formalism variant (IEFPCM),[40] as implemented in Gaussian09. Frequency calculations were performed to characterize the stationary points, all corresponding to true minima. The optimized structures of **12-a** (toluene, chloroform) were compared with the experimental X-ray structure with Pymol by pair-fitting the non-hydrogen atoms, yielding RMSD values of 0.093 Å and 0.096 Å, respectively.

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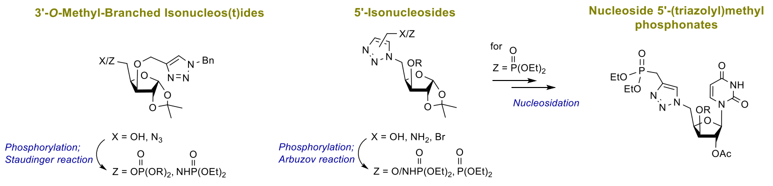

The synthesis of novel 3'/5'-isonucleosides and related prospective nucleotide or sugar diphosphate mimetics containg a triazole unit as a nucleobase surrogate or as a potential phosphate group bioisostere is described. The synthetic methodologies employed 3-*O*-propargyl or 5-azido xylofuranoses as precursors and included the azide-alkyne cycloaddition, *N*/*O*-phosphorylation, the Staudinger reaction, the Arbuzov reaction or *N*-glycosylation as key steps.