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Nucleoside Phosphonates

Synthesis and Antiviral Evaluation of 3′-*C*-Hydroxymethyl-3′-*O*-Phosphonomethyl-β-D-5′-deoxyxylose Nucleosides

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Abstract: L-2′-deoxythreose nucleoside phosphonates PMDTA and PMDTT possess potent anti-HIV activity. Herein, a novel class of 3′-*C*-branched-L-threose nucleoside phosphonate analogs, 5′-deoxy-3′-*C*-hydroxymethyl-3′-*O*-phosphonomethyl-D-xylose nucleosides, were synthesized and biologically evaluated. The key sugar intermediate 3-*C*-benzyloxymethyl-3-*O*-diethylphosphonomethyl-1,2-*O*-isopropylidene-α-D-5-deoxyxylose (**8**) was firstly synthesized, which may be an interesting scaffold for access to diverse 3′-*C*-branched L-threosyl nucleoside phosphonate derivatives. And the key synthesis involved Wittig olefination of 1,2-*O*-isopropylidene-3-oxo-α-D-5-deoxyxylose, stereoselective dihydroxylation of alkenes by aqueous $KMnO_4$, selective benzylation of hydroxymethyl group under activation of dibutyltin oxide, and introduction of phosphonate group by nucleophilic substitution. Eventually, glycosylation under Vorbrüggen conditions provided 3′-*C*-hydroxymethyl-3′-*O*-phosphonomethyl-β-D-5′-deoxyxylose nucleoside analogs in satisfying yield.

Introduction

Viral infections are a leading cause of death worldwide and significantly affect global health. Despite the rapid progress in the development of various vaccines and antiviral drugs, there are often no effective vaccines or antiviral therapies available to control fatal outbreaks due to the generation of viral mutants, the emergence of new strains and developing resistance towards drugs. Therefore the search for new antiviral compounds that are more potent and effective against viruses with low cytotoxicity is always necessary and significant. Evidence has shown that effective drug treatment can not only control the development of viral disease but also reduce its transmission.[1] Nucleoside analogs are a key class of agents for the treatment of viral diseases.[2] To date, many nucleoside drugs have been widely used in clinical practice,[3] such as Clevudi, telbivudine, chidovudine, and cidofovir (Figure 1). In addition, Remdesivir, a small-molecule broad-spectrum antiviral drug developed by Gilead Sciences, is also a nucleoside analog that is expected to be used to treat COVID-19 and Ebola viruses.[4] The nucleoside drugs that are currently also used in antitumor and antifungal therapy,[5] which makes nucleoside analogs more attractive[6] in the pharmaceutical field.

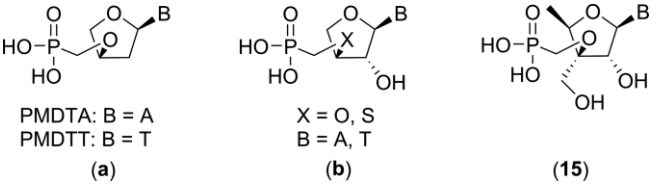

Figure 1. Structures for PMDTA and PMDTT (**a**), their 2′-hydroxyl analogs (**b**) and target compounds **15**.

Effective structural modification of sugar rings or bases is an important method to obtain new nucleoside analogs.[7] In our research, L-threose was selected as the basic motif for sugar modifications, and a series of modified L-threose nucleoside phosphonate analogs were synthesized and evaluated for their antiviral activities. It is well known that most nucleoside analogs undergo three consecutive phosphorylation reactions to produce biologically active triphosphate analogs, which exhibits antiviral effects as a substrate for viral RNA or DNA polymerase. In this process, the first phosphorylation reaction is generally inefficient and is a rate-limiting step.[8] Meanwhile, nucleoside monophosphate molecules are extremely unstable in human blood or cells due to the effect of phosphatase. In order to address the above problems, a phosphonate, the isosteric analog of a nucleoside monophosphate, was first selected as a good alternative for mononucleotide by Clercq and Holy.[9]

Herdewijn and co-workers[10] were the first to report that 1-(Adenin-9-yl)-3′-O-phosphonomethyl-L-2′-deoxythreose (PMDTA, EC_{50} = 2.5 μM) and 1-(Thymin-1-yl)-3′-O-phosphonomethyl-L-2′-deoxythreose (PMDTT, EC_{50} = 6.59 μM) selectively inhibit HIV without affecting normal cell proliferation (Figure 1a). Meanwhile, the 2′-hydroxyl counterpart (3′-O-phosphonomethyl-L-threose nucleosides)[10] and 3′-S-phosphono-

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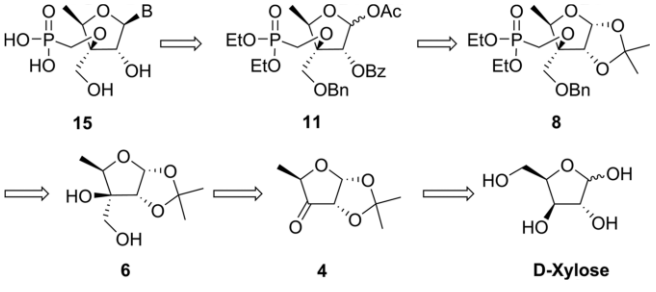
methyl-L-threose nucleosides[11] (Figure 1b) showed no significant antiviral and antitumor activity. Being interested in the nucleoside phosphonate with modification of the L-threose skeleton, we designed and synthesized a series of novel L-threose nucleoside analogs: 3′-C-hydroxymethyl-3′-O-phosphonomethyl-D-5′-deoxyxylose nucleosides (Figure 1, **15**). Herein we report the synthesis and the result for the biological evaluation of the target compounds.

Results and Discussion

The retro-synthetic analysis for the target compounds **15** starting from D-xylose is shown in Scheme 1. Target nucleoside phosphonates **15** can be obtained by glycosylation of the sugar phosphonate **11** and subsequent deprotection. Compound **11** is prepared by acetolysis of 1,2-O-isopropylidenylfuranose intermediate **8** and the following benzoylation. Compound **8** is derivatived from **6** by selective introduction of phosphonate function to 3-hydroxy group. Compound **6** is synthesized from sugar ketone **4**. Compound **4** is obtained by a consecutive four-step modification of D-xylose.



Scheme 1. Retrosynthesis route of target compound **15**.

As shown in Scheme 2, intermediate **6** was synthesized via key sugar ketone **4** starting from commercially available D-xylose. The 1,2-dihydroxyl groups of D-xylose were selectively protected with isopropylidene group by using acetone according to the ref.[12] with some modifications, to generate 1,2-O-isopropylidene-D-xylose (**1**) in 79 % yield. Tosylation of the free primary hydroxyl group at C-5 of **1** by tosyl chloride in pyridine gave compound **2**. Reductive removal of tosylate group using LAH (lithium aluminum hydride) afforded 4-methylfuranose **3** in 94 % yield. Oxidation of 3-hydroxyl group of **3** with PDC furnished sugar ketone **4** in 77 % yield. 3-Methene furanose **5** was obtained through a Wittig reaction of **4** with the ylide generated from a phosphonium salt. Oxidation of compound **5** with dilute neutral potassium permanganate gave oily vicinal diol **6** with a yield of 58 %.

Attempts to determine of the absolute configuration of C-3 in compound **6** was unsuccessful by NOESY analysis, thus the X-ray single-crystal diffraction method was used to confirm the configuration further. Conversion of the oily compound **6** into a crystallizable solid was achieved by selective tosylation of 3-C-hydroxymethyl group to produce tosylate of **6**. Single crystal of the tosylated **6** was obtained by vapor-phase diffusion method using *n*-hexane and ethyl acetate co-solvent system. The absolute configuration of C-3 was well established as the desired *3S*-configuration by X-ray crystallographic analysis of the suitable single crystal of tosylated **6** (as shown in Figure 2, CCDC No. 2012122). This result indicated that the permanganate attacked C=C bond from the less-hindered face (opposite to isopropylidene group) of furanose ring to form two vicinal C–O bonds, resulting in the stereoselective formation of 3*S*-carbon stereogenic center.

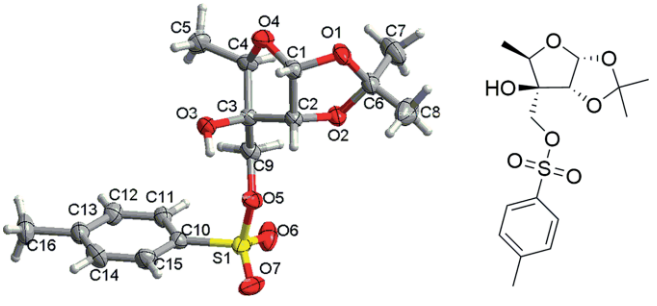
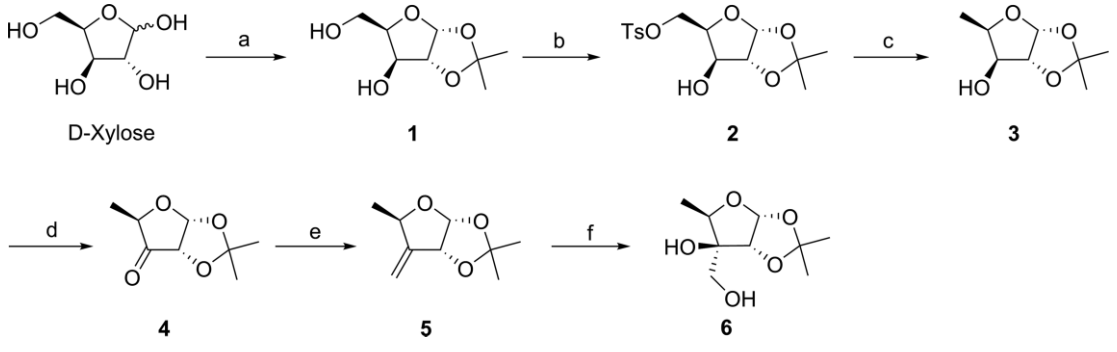


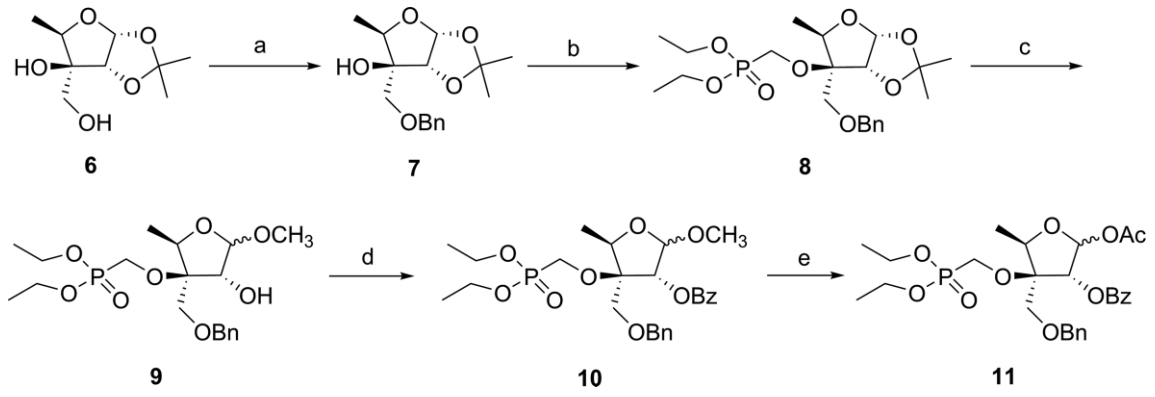
Figure 2. The absolute configuration of tosylated **6**.

Deposition Number 2012122 (for **6**) contains 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.

Phosphonate furanose **11** was obtained by selective introduction of phosphonate group to 3-hydroxyl of **6** and further conversion of 1,2-*O*-isopropylidene into 1,2-*O*-diacyl groups as



Scheme 2. Synthesis of 3-C-hydroxymethyl-1,2-O-isopropylidene-D-5-deoxyxylose. (a) H_2SO_4, acetone, r.t., 9 h, 79 %; (b) TsCl, Pyr, 0 °C to r.t., 10 h, 84 %; (c) $LiAlH_4$, THF, 0 °C to r.t., 6 h, 94 %; (d) PDC, Ac_2O, DCM, reflux, 6 h, 77 %; (e) $Ph_3P^+CH_3Br^-$, NaH, *tert*-amyl alcohol, THF, 0 °C to r.t., 7 h, 76 %; (f) $KMnO_4$, acetone, 0 °C, 4 h, 58 %.

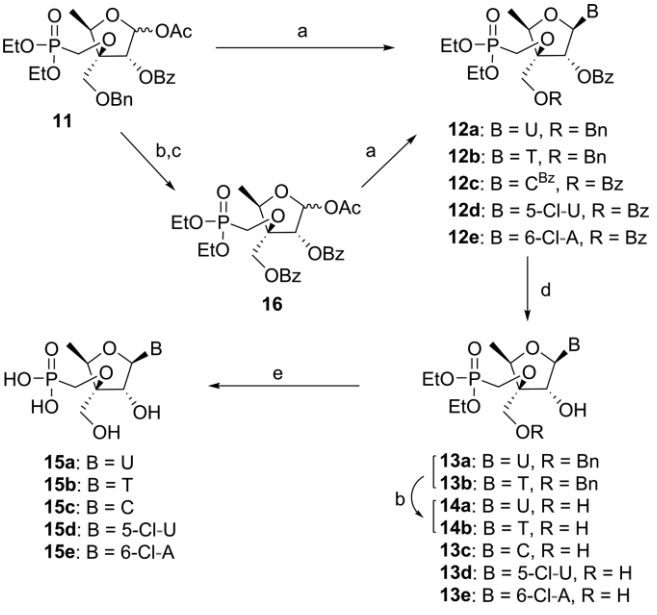


Scheme 3. Synthesis of 1-*O*-acetyl-2-*O*-benzoyl-3-*C*-hydroxymethyl-3-*O*-phosphonomethyl-D-5-deoxyxylose (**11**). (a) (1) Bu_2SnO, toluene, 140 °C, 2 h; (2) TBAB, BnBr, 100 °C, 8 h, 90 %. (b) NaH, $(EtO)_2P(=O)CH_2OTs$, THF, 45 °C, 72 h, 52 %; (c) H_2SO_4, MeOH, 50 °C, 17 h, 68 %; (d) BzCl, Pyr, 0 °C to r.t., 6.5 h, 96 %; (e) Ac_2O, AcOH, H_2SO_4, r.t., 8 h, 89 %.

shown in Scheme 3. In order to selectively functionalize 3-hydroxyl group of compound **6**, the primary hydroxyl group of **6** was selectively protected with benzyl group via dibutyltin oxide activation according to the procedure described in ref.[13] to afford compound **7** in 90 % yield. Alkylation of 3-hydroxyl group of **7** with tosylate of diethylphosphonomethanol in the presence of NaH gave compound **8** with a yield of 52 %. Alcoholysis of **8** by methanol under the catalysis of sulfuric acid allowed to provide methyl glycoside **9** as an α/β anomeric mixture in 68 % yield. It was known that the presence of the 2-*O*-acyl group in sugar precursor would allowed stereoselective introduction of the base moiety on C1-position of sugar during Vorbrüggen glycosylation for nucleoside synthesis, and especially 2-O-benzoyl sugar will be more advantageous than 2-O-acetoxy counterpart. Therefore compound **9** was benzoylated with benzoyl chloride in pyridine to provide **10** in 96 % yield, and then acetoxy exchange of 1-methoxy afforded more reactive sugar precursor **11** as an α/β anomeric mixture in 89 % yield.

Target nucleoside phosphonates **15a**–**15e** were obtained by Vorbrüggen glycosylation of sugar precursor **11** or its altenative **16** with various base moieties and followed by deprotection reactions as shown in Scheme 4.

Vorbrüggen glycosylation of sugar precursor **11** with uracil and thymine using N,O-bis(trimehtylsilyl)acetamide (BSA) as a silylating agent and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid gave corresponding protected nucleoside **12a** and **12b**, in 78 % and 89 % yields, respectively. Likewise, glycosylation of 4-Benzoylcytosine, 5-Cl-uracil and 6-Cl-purine also afforded corresponding protected nucleosides successfully, however, further deprotection of benzyl group by catalytic hydrogenation didn't succeed, and the undesired reduction of the chlorine from 5-chlorouracil and 6-chloroadenine was observed. Therefore, the deprotection of the benzyl group in **11** by catalytical hydrogenation, followed by protection with benzoyl group to provide precursor **16**. Replacement of **11** with precursor **16** in the Vorbrüggen glycosylation gave **12c**, **12d**, and **12e** smoothly. Deprotection of benzoyl groups of **12a**–**12e** by saturated ammonia in methanol produced **13a**–**13e**. Reductive removal of benzyl group of **13a** and **13b** by Pd/C catalytic hydrogenation afforded **14a** and **14b**. The diethyl ester groups



Scheme 4. Synthesis of target nucleoside phosphonates **15a**–**15e**. (a) BSA, TMSOTf, uracil for **12a**, thymine for **12b**, N^4-benzoylcytosine for **12c**, 5-chlorouracil for **12d**, 6-chloroadenine for **12e**, CH_3CN; (b) Pd/C, H_2, MeOH, r.t.; (c) BzCl, Pyr, r.t.; (d) NH_3/CH_3OH, r.t.; (e) TMSBr, 2,6-lutidine, CH_3CN, r.t.

on phosphonate compounds **14a**–**14b** and **13c**–**13e** were hydrolyzed with TMSBr/2,6-lutidine at room temperature. After purification by C18-silica gel chromatography, nucleoside phosphonic acids **15a**–**15e** were obtained as white foamy solids.

Conclusion

An effective synthetic methodology to obtain 3′-*C*-branched-3′-O-phosphonomethyl-L-threosyl nucleoside phosphonates was developed starting from D-xylose. A series of novel 3′-*C*-branched L-threosyl nucleoside phosphonate analogs (**15a**–**15e**) bearing a 3′-*C*-hydroxylmethyl group and diverse base moieties have been synthesized. The absolute configuration of the newly generated stereocenter at C-3′ was confirmed by X-ray single-crystal diffraction method. Unfortunately, no significant in vitro biological activities were observed against HBV,

HSV, and RSV as well as against tumor cells MCF-7 and PC-3. The possible reason for lack of biological activity may be due to the poor cellular permeability of these negative charged phosphonic acid groups at physiological pH. Further bioactive evaluation of the target compounds is undergoing in our laboratory. Moreover, the key intermediate 1,2-*O*-isopropylidene-3-*O*-phosphonomethyl-3-*C*-hydroxymethyl-D-5-deoxyxylose will provide a useful platform for access to diverse 3′-*C*-branched L-threosyl nucleoside phosphonate derivatives bearing interesting 3′-C modifications such as a vinyl, ethynyl or alkyl group.

Experimental Section

General Information: Except in special cases, all reactants and reagents were obtained commercially and were not reprocessed. The required anhydrous reagents are all treated by standard methods. Dichloromethane, acetonitrile, and pyridine are treated with calcium hydride, THF is treated with sodium particles, and benzophenone is used as an indicator. Moisture-sensitive reactions are carried in dried glassware and are protected with nitrogen. Thin-layer chromatography (TLC) was performed on a glass plate precoated with silica gel GF 254 (5–40 μm) and detected by placing it under an ultraviolet lamp or by spraying the chromatogram with 5 % ethanol phosphomolybdic acid and charring them using a heat gun. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AVANCE III 400 MHz spectrometer with tetramethylsilane as the internal standard. 300–400 mesh silica gel was used as the stationary phase of the chromatography column.

X-ray Diffraction Experiment: X-ray diffraction analysis was carried out on a Rigaku Oxford Xcalibur Gemini, Eos CCD diffractometer with graphite-monochromated Cu-K_α (λ = 1.54184Å) radiation. A monoclinic crystal was selected and mounted on a glass fiber. The crystal was kept at 293(2) K during data collection. The structure was solved with the ShelXS structure solution program[14] using direct methods and refined with the ShelXL refinement package[15] using Least Squares minimization. The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydroxyl hydrogen atoms were refined with isotropic thermal parameters. Other hydrogen atoms were included but not refined. All calculations were performed using the CrysAlisPro crystallographic software system.[16]

1,2-*O*-Isopropylidene-α-D-xylose (1): D-xylose (50 g, 333 mmol) was suspended in 500 mL of acetone in an ice-water bath, then concentrated sulfuric acid (40 mL, 747 mmol) was added dropwise in 30 min. The reaction mixture was stirred at room temperature for 6 h. 140 mL of a 30 % aqueous sodium hydroxide was added dropwise in an ice-water bath to adjust the pH of the mixture to 1–2. The reaction was stirred at room temperature for 2 h and then 3 g solid NaOH was added to adjust the pH to 7–8. The precipitate was filtered out, and the cake was washed with acetone. The combined filtrate was concentrated, the residue was purified by silica gel column chromatography (PE/EA = 3:1–1:1) to give compound **1** (50 g, 263 mmol) in 79 % yield as a yellowish oil.

1: ^{1}H NMR (400 MHz, [d_6]DMSO): δ = 5.80 (d, J = 3.7 Hz, 1H, H-1), 5.14 (d, J = 4.8 Hz, 1H, OH), 4.62 (t, J = 5.7 Hz, 1H, H-3), 4.37 (d, J = 3.7 Hz, 1H, H-2), 4.02–3.93 (m, 2H, H-4, OH), 3.60 (m, 1H, H-5a), 3.51 (m, 1H, H-5b), 1.38 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). ^{13}C NMR (101 MHz, [d_6]DMSO): δ = 110.2 (CMe_2), 104.2 (C-1), 85.0 (C-2), 81.3 (C-4), 73.4 (C-3), 58.8 (C-5), 26.6 (CH_3), 26.1 (CH_3).

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-xylose (2): Compound **1** (20 g, 105 mmol) was dissolved in 200 mL of anhydrous pyridine, p-toluenesulfonyl chloride (22 g, 116 mmol) was added in portions at 0 °C under nitrogen. After the mixture was stirred at room temperature for 10 h, 10 mL of water was added to quench the reaction. The resulted mixture was concentrated under reduced pressure, the residue was partitioned between 100 mL of saturated sodium chloride solution and 50 mL of dichloromethane (DCM). The water layer was extracted with 50 mL of DCM three times. The combined organic layer was dried with Na_2SO_4, concentrated to dryness. The residue was recrystallized with PE and EA (3:1) to provide most of the target compound. The filtrate was concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5:1–1:1) to allow the second part of **2**. Compound **2** (30.5 g in total, 88 mmol) was obtained as a white solid with a yield of 84 %.

2: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 2H, Ar-H), 7.36 (d, J = 8.0 Hz, 2H, Ar-H), 5.88 (d, J = 3.6 Hz, 1H, H-1), 4.51 (d, J = 3.6 Hz, 1H, H-2), 4.40–4.26 (m, 3H, H-5a, H-3, H-4), 4.14 (dd, J = 14.0, 8.9 Hz, 1H, H-5b), 2.46 (s, 3H, Ar-CH_3), 2.40 (d, J = 5.1 Hz, 1H, OH), 1.46 (s, 3H, CH_3), 1.30 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.3, 132.4, 130.0, 128.0 (Ar-C), 112.1 (CMe_2), 105.0 (C-1), 85.0 (C-2), 77.6 (C-4), 74.3 (C-3), 66.2 (C-5), 26.8 (CH_3), 26.2 (CH_3), 21.7 (Ar-CH_3).

5-Deoxy-1,2-O-isopropylidene-α-D-xylose (3): $LiAlH_4$ (6.61 g, 174 mmol) was added to the cold anhydrous tetrahydrofuran (350 mL) in portions under nitrogen. After the mixture was stirred in an ice-water bath for 30 min, compound **2** (40 g, 116 mmol) was added. The mixture was stirred in an ice-water bath for another 30 min, then continued to stir at room temperature for 5 h. The reaction was quenched by dropwise addition of water (20 mL) under ice-water cooling. Then 20 mL of 15 % aqueous NaOH was added and stirred for 40 minutes. The resulted slurry was filtered through Celite, the cake was dispersed in 100 mL of ethyl acetate and filtered. The dispersion and filtration were repeated twice. The combined filtrate was dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (PE/EA= 5:1–2:1) to give off-white crystalline solid **3** (18.9 g, 108.5 mmol) in 94 % yield.

3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89 (d, J = 3.8 Hz, 1H, H-1), 4.53 (d, J = 3.8 Hz, 1H, H-2), 4.32 (qd, J = 6.5, 2.5 Hz, 1H, H-4), 3.99 (s, 1H, H-3), 1.50 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3), 1.30 (d, J = 6.5 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 111.4 (CMe_2), 104.4 (C-1), 85.5 (C-2), 76.4 (C-4), 75.9 (C-3), 26.6 (CH_3), 26.1 (CH_3), 12.7 (C-5).

5-Deoxy-1,2-O-isopropylidene-3-oxo-α-D-xylose (4): To a solution of **3** (3.5 g, 20.1 mmol) in 80 mL of anhydrous dichloromethane was added Pyridinium dichromate (9.07 g, 24.1 mmol) and acetic anhydride (2.83 mL, 30 mmol) at 0 °C under nitrogen. After stirring at the same temperature for 20 min, the mixture was heated to reflux and maintained for 6 h. Most of the solvent was evaporated under reduced pressure. 100 mL of ethyl acetate was added to the residue and stirred for 30 min, the resulting slurry was filtered. Chromium salt cake was washed with ethyl acetate twice. The combined filtrate was dried with Na_2SO_4, concentrated and purified by silica gel column chromatography (PE/EA= 5:1–1:1) to obtain compound **4** (2.68 g, 15.6 mmol) in 77 % yield as pale yellow oil.

4: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.05 (d, J = 4.5 Hz, 1H, H-1), 4.44 (q, J = 6.8 Hz, 1H, H-4), 4.35 (d, J = 4.4 Hz, 1H, H-2), 1.51 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.32 (d, J = 6.8 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.6 (C-3), 112.8 (CMe_2), 101.2 (C-1), 74.6 (C-2), 72.6 (C-4), 26.1 (CH_3), 25.9 (CH_3), 14.4 (C-5).

5-Deoxy-1,2-O-isopropylidene-3-methene-α-D-xylose (5): Methyltriphenylphosphine bromide (4.98 g, 13.94 mmol) and tert-amyl alcohol (1.65 mL, 15.10 mmol) were sequentially added to 60 mL of

anhydrous THF under nitrogen. To the solution, NaH (60 % in mineral oil, 0.93 g, 23.23 mmol) was added with cooling in an ice bath. The mixture was stirred at 0 °C for 30 min and at room temperature for 3 h. A solution of compound **4** (2 g, 11.62 mmol) in anhydrous THF (20 mL) was added dropwise to the above solution in an ice-water bath. The mixture was stirred at room temperature for 4 h. 30 mL of saturated ammonium chloride solution was added to quench the reaction. After rotary evaporation of THF, the residue was extracted with EA (20 mL × 4). The combined organic layer was dried with anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (PE/EA = 20:1–10:1) to obtain a colorless oil **5** (1.5 g, 8.8 mmol) in 76 % yield.

5: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (d, J = 4.1 Hz, 1H, H-1), 5.32 (d, J = 1.6 Hz, 1H, =CH_2), 5.08 (dd, J = 2.0, 0.8 Hz, 1H, =CH_2), 4.85 (d, J = 4.0 Hz, 1H, H-2), 4.75 (q, J = 6.2 Hz, 1H, H-4), 1.51 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.32 (d, J = 6.2 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.2 (C-3), 111.8 (CMe_2), 110.6 (C-1), 103.6 (=CH_2), 81.7 (C-2), 74.5 (C-4), 27.0 (CH_3), 26.7 (CH_3), 17.8 (C-5).

5-Deoxy-3-C-hydroxymethyl-1,2-O-isopropylidene-α-D-xylose (6): To a solution of **5** (5 g, 29.4 mmol) in 67 mL of acetone in an ice–water bath was added dropwise a solution of potassium permanganate (5.43 g, 34.37 mmol) in 287.5 mL of water. After stirring for 4 h in an ice-water bath, the reaction was quenched by adding 2.0 g of sodium bisulfite. The resulting mixture was filtered, and the cake was washed with 20 mL of acetone. The filtrate was combined, concentrated under reduced pressure, co-evaporated with toluene, and purified by silica gel column chromatography (PE/EA = 3:1–1:3) to allow **6** (3.5 g, 17.1 mmol, 58 %) as a colorless oil.

6: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (d, J = 3.9 Hz, 1H, H-1), 4.40 (d, J = 3.9 Hz, 1H, H-2), 4.04 (q, J = 6.4 Hz, 1H, H-4), 3.84 (d, J = 11.4 Hz, 1H, CH_2OH), 3.52 (d, J = 11.4 Hz, 1H, CH_2OH), 3.18 (s, 1H, OH), 2.96 (s, 1H, OH), 1.48 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.20 (d, J = 6.4 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 111.2 (CMe_2), 103.0 (C-1), 84.2 (C-2), 80.7 (C-4), 75.4 (C-3), 61.2 (CH_2OH), 25.7 (CH_3), 25.3 (CH_3), 11.6 (C-5).

3-C-Benzyloxymethyl-5-deoxy-1,2-O-isopropylidene-α-D-xylose (7): To a solution of compound **6** (1 g, 4.90 mmol) in anhydrous toluene (36 mL) was added dibutyltin oxide (2.01 g, 8.08 mmol) under nitrogen atmosphere. After the mixture was stirred at 140 °C for 2 hours, the reaction temperature was decreased to 100 °C. Then tetrabutylammonium bromide (0.79 g, 2.45 mmol) and benzyl bromide (0.90 mL, 7.59 mmol) were added. The mixture was stirred at 100 °C for 8 hours and then cooled to room temperature. Concentration under reduced pressure, purification by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1–6:1) provided **7** (1.3 g, 4.42 mmol) as a light yellow oil in 90 % yield.

7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5H, Ar-H), 5.89 (d, J = 3.8 Hz, 1H, H-1), 4.62 (d, J = 12.0 Hz, 1H, ArCH_2O), 4.58 (d, J = 12.0 Hz, 1H, ArCH_2O), 4.40 (d, J = 3.8 Hz, 1H, H-2), 4.05 (q, J = 6.3 Hz, 1H, H-4), 3.77 (d, J = 9.4 Hz, 1H, CCH_2O), 3.43 (d, J = 9.4 Hz, 1H, CCH_2O), 2.71 (s, 1H, OH), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.24 (d, J = 6.4 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7, 128.5, 127.9, 127.7 (Ar-C), 112.0 (CMe_2), 104.3 (C-1), 85.4 (C-2), 80.6 (C-4), 77.1 (ArCH_2), 73.7 (C-3), 69.5 (CH_2O), 26.9 (CH_3), 26.4 (CH_3), 12.9 (C-5).

3-C-Benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1,2-O-isopropylidene-α-D-xylose (8): To a solution of compound **7** (3.2 g, 10.9 mmol) in 100 mL of anhydrous THF was added NaH (60 % in mineral oil, 1.30 g, 32.62 mmol) and tosylate of diethylphosphonomethanol (4.2 g, 13.1 mmol) upon cooling in an ice-water bath under a nitrogen atmosphere. The mixture was stirred in the ice-water bath for 30 min and then heated to 45 °C for 72 h. The reaction mixture was quenched by adding 50 mL of saturated aqueous NaCl, then THF was evaporated under reduced pressure. The resulting solution was extracted with ethyl acetate (4 × 30 mL). The combined organic layer was dried with anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (PE/EA= 5:1–1:1) to give compound **8** (2.5 g, 5.62 mmol) as a pale yellow oil in 52 % yield.

8: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5H, Ar-H), 5.85 (d, J = 3.8 Hz, 1H, H-1), 4.59 (d, J = 4.0 Hz, 1H, H-2), 4.57 (d, J = 12.1 Hz, 1H, ArCH_2O), 4.52 (d, J = 12.1 Hz, 1H, ArCH_2O), 4.20 –4.08 (m, 5H, H-4, PCH_2O, OCH_2CH_3), 4.07–4.00. (m, 2H, OCH_2CH_3), 3.81 (d, J = 11.0 Hz, 1H, CCH_2O), 3.62 (d, J = 11.0 Hz, 1H, CCH_2O), 1.47 (s, 3H, CCH_3), 1.33–1.25 (m, 12H, H-5, OCH_2CH_3, CCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7, 128.4, 127.7, 127.6 (Ar-C), 111.9 (CMe_2), 104.4 (C-1), 86.5 (d, $J_{C,P}$ = 11.0 Hz, C-3), 81.7 (C-2), 79.2 (ArCH_2), 73.7 (CH_2O), 68.5 (C-4), 62.7 (d, $J_{C,P}$ = 6.4 Hz, CH_2), 62.5 (d, $J_{C,P}$ = 6.4 Hz, CH_2), 59.3 (d, $J_{C,P}$ = 169 Hz, PCH_2), 26.9 (CH_3), 26.4 (CH_3), 16.5 (d, $J_{C,P}$ = 6.4 Hz, CH_3), 16.4 (d, $J_{C,P}$ = 6.4 Hz, CH_3), 13.4 (C-5). ^{31}P NMR (162 MHz, $CDCl_3$) δ = 20.8.

3-C-Benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-O-methyl-D-xylose (9): Concentrated sulfuric acid (0.45 mL, 8.44 mmol) was added to a solution of compound **8** (2.5 g, 5.62 mmol) in 60 mL of anhydrous methanol at 0 °C under nitrogen atmosphere. The mixture was stirred at this temperature for 30 min, then heated to 50 °C and maintained for 17 h. After the reaction mixture was cooled to room temperature, solid $NaHCO_3$ (2.0 g) was added to quench the reaction. Inorganic salt was filtered off, the filtrate was dried with Na_2SO_4, concentrated by rotary evaporation, and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 1: 2–1: 5) to obtain **9** (1.6 g, 3.82 mmol, 68 %) as an oily anomeric mixture.

9: α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5H, Ar-H), 4.69 (d, J = 3.3 Hz, 1H, H-1), 4.58 (d, J = 11.8 Hz, 1H, ArCH_2O), 4.52 (d, J = 11.8 Hz, 1H, ArCH_2O), 4.28 (s, 1H, OH), 4.25 (q, J = 6.6 Hz, 1H, H-4), 4.21–4.05 (m, 5H, OCH_2CH_3, H-2), 4.05–3.93 (m, 2H, PCH_2), 3.84 (d, J = 11.0 Hz, 1H, CCH_2O), 3.68 (d, J = 11.0 Hz, 1H, CCH_2O), 3.41 (s, 3H, OCH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_3), 1.29(t, J = 7.1 Hz, 3H, CH_3), 1.26 (d, J = 6.6 Hz, 3H, H-5). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.4, 128.5, 128.0, 127.8 (Ar-C), 109.2 (C-1), 85.3 (d, $J_{C,P}$ = 10.1 Hz, C-3), 80.2 (ArCH_2), 78.9 (C-2), 73.8 (CH_2O), 69.1 (C-4), 62.9 (d, $J_{C,P}$ = 6.4 Hz, CH_2), 62.7 (d, $J_{C,P}$ = 6.4 Hz, CH_2), 59.0 (d, $J_{C,P}$ = 167 Hz, PCH_2), 56.0 (OCH_3), 16.44 (CH_3), 16.38 (CH_3), 16.0 (C-5). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5H, Ar-H), 4.93 (d, J = 4.8 Hz, 1H, H-1), 4.54 (s, 2H, ArCH_2O), 4.32–4.21 (m, 2H, H-2, H-4), 4.17 (q, J = 7.2 Hz, 2H, CH_2), 4.12 (q, J = 7.2 Hz, 2H, CH_2), 3.94–3.87 (m, 2H, PCH_2), 3.85 (d, J = 11.0 Hz, 1H, CCH_2O), 3.52 (d, J = 11.0 Hz, 1H, CCH_2O), 3.43 (s, 3H, OCH_3), 2.97 (d, J = 7.6 Hz, 1H, OH), 1.35–1.25 (m, 9H, H-5, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.9, 128.4, 127.7, 127.5 (Ar-C), 101.2 (C-1), 84.7 (d, $J_{C,P}$ = 12 Hz, C-3), 79.2 (ArCH_2), 77.9 (C-2), 73.6 (CH_2O), 69.0 (C-4), 62.7 (d, $J_{C,P}$ = 6.2 Hz, CH_2), 62.5 (d, $J_{C,P}$ = 6.2 Hz, CH_2), 58.3 (d, $J_{C,P}$ = 169 Hz, PCH_2), 55.3 (OCH_3), 16.5 (d, $J_{C,P}$ = 5.8 Hz, CH_3), 16.4 (d, $J_{C,P}$ = 5.8 Hz, CH_3), 14.9 (C-5).

2-O-Benzoyl-3-C-benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-O-methyl-D-xylose (10): Compound **9** (0.92 g, 2.20 mmol) was dissolved in 6 mL of anhydrous pyridine, benzoyl chloride (0.52 mL, 4.40 mmol) was added at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min and then at room temperature for 6 h. The reaction was quenched by adding 1 mL of water, concentrated under reduced pressure to dryness. The residue was purified by silica gel column chromatography (PE/EA = 5:1–1:1) to obtain **10** (1.1 g, 2.11 mmol, 96 %) as an oily anomeric mixture.

10: α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.85 (m, 2H, Ar-H), 7.55–7.48 (m, 1H, Ar-H), 7.37 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.29–7.18 (m, 5H, Ar-H), 5.17 (d, *J* = 4.6 Hz, 1H, H-1), 5.12 (d, *J* = 4.6 Hz, 1H, H-2), 4.52 (d, *J* = 11.8 Hz, 1H, ArCH_2O), 4.48 (d, *J* = 11.8 Hz, 1H, ArCH_2O), 4.33 (q, *J* = 6.4 Hz, 1H, H-4), 4.13–4.02 (m, 4H, OCH_2CH$_3$), 3.94 (d, *J* = 11.0 Hz, 1H, CCH_2O), 3.85 (dd, *J* = 13.1, 9.9 Hz, 1H, PCH$_2$), 3.73 (t, *J* = 12.4 Hz, 1H, PCH$_2$), 3.69 (d, *J* = 11.0 Hz, 1H, CCH_2O), 3.24 (s, 3H, OCH$_3$), 1.28 (d, *J* = 6.4 Hz, 3H, H-5), 1.24 (t, *J* = 7.1 Hz, 3H, CH$_3$), 1.21(t, *J* = 7.1 Hz, 3H, CH$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.2 (C=O), 136.8, 132.4, 128.7, 128.3, 127.5, 127.4, 126.7, 126.5 (Ar-C), 99.3 (C-1), 83.3 (d, $J_{C,P}$ = 13.4 Hz, C-3), 78.1 (C-2), 77.8 (ArCH_2), 72.7 (CH$_2$O), 68.0 (C-4), 61.7 (d, $J_{C,P}$ = 6.2 Hz, OCH_2CH$_3$), 61.6 (d, $J_{C,P}$ = 6.2 Hz, OCH_2CH$_3$), 57.2 (d, $J_{C,P}$ = 169 Hz, PCH$_2$), 54.3 (OCH$_3$), 15.43 (d, $J_{C,P}$ = 6.2 Hz, OCH$_2$CH_3), 15.37 (d, $J_{C,P}$ = 6.2 Hz, OCH$_2$CH_3), 14.1 (C-5). HRMS(ESI-TOF): calcd. for $C_{26}H_{36}O_9P$ [M + H]$^+$ 523.2097, found 523.2104.

1-O-Acetyl-2-O-benzoyl-3-C-benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-D-xylose (11): Compound **10** (1 g, 1.91 mmol) was dissolved in a solution of glacial acetic acid (6.35 mL, 111 mmol) and acetic anhydride (0.81 mL, 8.61 mmol). Concentrated sulfuric acid (0.051 mL, 0.96 mmol) were added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 10 minutes and then at room temperature for 8 h. Saturated aqueous $NaHCO_3$ was added to quench the reaction. The resulting mixture was filtered and extracted with ethyl acetate(5 × 20 mL). The combined organic layer was dried with anhydrous sodium sulfate, concentrated to dryness in vacuo, and purified by silica gel column chromatography (PE/EA = 5:1–1:1) to give **11** (0.93 g, 1.69 mmol) in 88 % yield as an oily anomeric mixture.

11: α-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2H, Ar-H), 7.62 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.46 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.2–7.23 (m, 5H, Ar-H), 6.53 (d, *J* = 4.8 Hz, 1H, H-1), 5.57 (d, *J* = 4.8 Hz, 1H, H-2), 4.53 (s, 2H, ArCH_2O), 4.50 (q, *J* = 6.4 Hz, 1H, H-4), 4.22–4.12 (m, 4H, OCH_2CH$_3$), 3.99 (dd, *J* = 13.2, 9.9 Hz, 1H, PCH$_2$), 3.93 (dd, *J* = 13.2, 11.8 Hz, 1H, PCH$_2$), 3.91 (d, *J* = 10.9 Hz, 1H, CCH_2O), 3.72 (d, *J* = 10.9 Hz, 1H, CCH_2O), 1.91 (s, 3H, COCH_3), 1.36 (d, *J* = 6.4 Hz, 3H, H-5), 1.34 (t, *J* = 7.1 Hz, 3H, CH$_3$), 1.31 (t, *J* = 7.1 Hz, 3H, CH$_3$). β-Anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.92 (m, 2H, Ar-H), 7.60 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.25–7.12 (m, 5H, Ar-H), 6.10 (s, 1H, H-1), 5.75 (s, 1H, H-2), 4.46 (q, *J* = 6.5 Hz, 1H, H-4), 4.47 (d, *J* = 11.7 Hz, 1H, ArCH_2O), 4.38 (d, *J* = 11.7 Hz, 1H, ArCH_2O), 4.26–4.13 (m, 5H, OCH_2CH$_3$, PCH$_2$), 4.03 (dd, *J* = 12.9, 10.7 Hz, 1H, PCH$_2$), 3.81 (d, *J* = 10.6 Hz, 1H, CCH_2O), 3.69 (d, *J* = 10.6 Hz, 1H, CCH_2O), 2.13 (s, 3H, Ac CH$_3$), 1.38 (d, *J* = 6.5 Hz, 3H, H-5), 1.34 (t, *J* = 7.3 Hz, 3H, CH$_3$), 1.32 (t, *J* = 7.3 Hz, 3H, CH$_3$). HRMS(ESI-TOF): calcd. for $C_{27}H_{36}O_{10}P$ [M + H]$^+$ 551.2046, found 551.2059.

2-O-Benzoyl-3-C-benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-(uracil-1-yl)-β-D-xylose (12a): To a solution of compound **11** (240 mg, 0.44 mmol) in 5 mL of anhydrous acetonitrile, uracil (73 mg, 0.65 mmol) and BSA (0.32 mL, 1.31 mmol) were added at room temperature under nitrogen atmosphere. The mixture was stirred at 65 °C for 10 min and then cooled to room temperature. TMSOTf (0.24 mL, 1.31 mmol) was added and stirred at room temperature for 6 h. After being quenched by the addition of 1 mL of water, the mixture was concentrated in vacuo and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2:1–1:4) to provide **12a** (205 mg, 0.34 mmol) in 78 % yield as a colorless syrup.

12a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1H, N-H), 7.99–7.94 (m, 2H, Ar-H), 7.84 (d, *J* = 8.2 Hz, 1H, H-6), 7.61 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.26–7.20 (m, 3H, Ar-H), 7.15–7.10 (m, 2H, Ar-H), 6.12 (d, *J* = 2.5 Hz, 1H, H-1′), 5.80 (dd, *J* = 8.2, 1.9 Hz, 1H, H-5), 5.55 (d, *J* = 2.5 Hz, 1H, H-2′), 4.39 (d, *J* = 11.7 Hz, 1H, ArCH_2O), 4.34 (d, *J* = 11.7 Hz, 1H, ArCH_2O), 4.30 (q, *J* = 6.3 Hz, 1H, H-4′), 4.20–4.10 (m, 4H, OCH_2CH$_3$), 4.06 (dd, *J* = 13.2 10.7 Hz, 1H, PCH$_2$), 3.97 (dd, *J* = 13.2 11.4 Hz, 1H, PCH$_2$), 3.77 (d, *J* = 10.9 Hz, 1H, CCH_2O), 3.67 (d, *J* = 10.9 Hz, 1H, CCH_2O), 1.44 (d, *J* = 6.3 Hz, 3H, H-5′), 1.32 (t, *J* = 7.0 Hz, 6H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8 (ArCO), 163.0 (C-4), 150.2 (C-2), 140.9 (C-6), 136.8, 133.8, 129.9, 128.7, 128.6, 128.4, 128.0, 127.7 (Ar-C), 103.0 (C-5), 88.3 (C-1′), 85.1 (d, $J_{C,P}$ = 12.2 Hz, C-3′), 81.6 (C-2′), 79.0 (ArCH$_2$), 73.9 (OCH$_2$C), 67.7 (C-4′), 62.7 (d, $J_{C,P}$ = 6.4 Hz, CH$_2$CH$_3$), 62.4 (d, $J_{C,P}$ = 6.4 Hz, CH$_2$CH$_3$), 58.7 (d, $J_{C,P}$ = 170.5 Hz, PCH$_2$), 16.6 (d, $J_{C,P}$ = 5.4 Hz, CH$_3$), 16.5 (d, $J_{C,P}$ = 6.0 Hz, CH$_3$), 13.5 (C-5′). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 20.9. HRMS(ESI-TOF): calcd. for $C_{29}H_{36}N_2O_{10}P^+$ [M + H]$^+$ 603.2102, found 603.2110.

3-C-Benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-(uracil-1-yl)-β-D-xylose (13a): Compound **12a** (205 mg, 0.34 mmol) was dissolved in a saturated methanolic ammonia solution (5 mL) and stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography (DCM/MeOH = 50:1–30:1) to obtain **13a** (145 mg, 0.29 mmol) as a colorless syrup with a yield of 86 %.

13a: ^{1}H NMR (400 MHz, [d$_6$]DMSO): δ = 11.35 (d, *J* = 1.6 Hz, 1H, N-H), 7.64 (d, *J* = 8.1 Hz, 1H, H-6), 7.41–7.26 (m, 5H, Ar-H), 5.97 (d, *J* = 5.9 Hz, 1H, H-1′), 5.69 (d, *J* = 3.1 Hz, 1H, OH), 5.58 (dd, *J* = 8.1, 2.1 Hz, 1H, H-5), 4.53 (s, 2H, ArCH_2O), 4.20 (q, *J* = 6.4 Hz, 1H, H-4′), 4.13 (dd, *J* = 5.8, 3.2 Hz, 1H, H-2′), 4.08–3.96 (m, 4H, OCH_2CH$_3$), 3.87(d, *J* = 11.4 Hz, 1H, CCH_2O), 3.85 (m, 2H, PCH$_2$), 3.61 (d, *J* = 11.4 Hz, 1H, CCH_2O), 1.29 (d, *J* = 6.4 Hz, 3H, H-5′), 1.21 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3), 1.19 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (101 MHz, [d$_6$]DMSO): δ = 163.1 (C-4), 150.6 (C-2), 140.9 (C-6), 138.1, 128.2, 127.5, 127.4 (Ar-C), 101.8 (C-5), 89.6 (C-1′), 84.8 (d, *J* = 13.2 Hz, C-3′), 80.7 (C-2′), 77.6 (ArCH$_2$), 72.6 (OCH$_2$), 67.2 (C-4′), 61.9 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH$_3$), 61.7 (d, *J* = 6.1 Hz, OCH_2CH$_3$), 57.0 (d, $J_{C,P}$ = 167 Hz, PCH$_2$), 16.3 (d, $J_{C,P}$ = 5.8 Hz, OCH$_2$CH_3), 16.2 (d, $J_{C,P}$ = 5.8 Hz, OCH$_2$CH_3), 14.2 (C-5′). ^{31}P NMR (162 MHz, [d$_6$]DMSO): δ = 21.6. HRMS(ESI-TOF): calcd. for $C_{22}H_{32}N_2O_9P^+$ [M + H]$^+$ 499.1840, found 499.1835.

5-Deoxy-3-O-phosphonomethyl-3-C-hydroxymethyl-1-(uracil-1-yl)-β-D-xylose (15a): Compound **13a** (140 mg, 0.28 mmol) was dissolved in 5 mL of methanol, 50 mg of Pd-C (10 %) was added. The oscillating mixture was hydrogenated under 50 psi at room temperature for 10 h. The resulting mixture was filtered and concentrated under reduced pressure to dryness. The residue (**14a**) was directly used to next step without further purification.

The above residue **14a** was dissolved in 5 mL of anhydrous acetonitrile, 2,6-lutidine (0.18 mL, 1.57 mmol) and TMSBr (0.41 mL, 3.13 mmol) were added at 0 °C under nitrogen atmosphere. The mixture was stired at 0 °C for 30 min and then at room temperature for 5 h. After the disappearance of **14a** by TLC monitorring, the reaction was quenched by addition of a little water. The resulting solution was concentrated under reduced pressure and the residue was purified by C18-silica gel column chromatography (water/methanol = 10:1–5: 1) to obtain **15a** (50 mg, 0.14 mmol) as a white foam with a yield of 50 % (two steps).

15a: ^{1}H NMR (400 MHz, D_2O): δ = 7.83 (d, *J* = 8.1 Hz, 1H, H-6), 5.79 (d, *J* = 8.1 Hz, 1H, H-5), 5.71 (d, *J* = 2.0 Hz, 1H, H-1′), 4.36 (q, *J* = 6.4 Hz, 1H, H-4′), 4.30 (d, *J* = 2.0 Hz, 1H, H-2′), 3.99 (d, *J* = 13.4 Hz, 1H, CCH_2O), 3.69 (d, *J* = 13.4 Hz, 1H, CCH_2O), 3.58 (dd, *J* = 12.8, 11.4 Hz, 1H, PCH$_2$O), 3.32 (dd, *J* = 12.8, 9.3 Hz, 1H, PCH$_2$O), 1.36 (d, *J* = 6.4 Hz, 3H, H-5′). ^{13}C NMR (101 MHz, D_2O): δ = 166.4 (C-4), 151.6 (C-2), 142.3 (C-6), 101.7 (C-5), 90.7 (C-1′), 84.9 (d, $J_{C,P}$ = 9.1 Hz, C-3′), 82.8 (C-2′), 77.6 (C-4′), 58.5 (CH$_2$OH), 13.6 (C-5′). ^{31}P NMR (162 MHz,

D_2O): δ = 15.7. HRMS(ESI-TOF): calcd. for $C_{11}H_{16}N_2O_9P^-$ $[M - H]^-$ 351.0599, found 351.0595.

2-O-Benzoyl-3-C-benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-(thymin-1-yl)-β-D-xylose (12b): The preparation method of **12b** is as described for **12a** using thymine as starting nucleobase. **12b** was obtained (300 mg, 0.49 mmol) with a yield of 89 %.

12b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1H, N-H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H, Ar-H), 7.58 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.55 (d, *J* = 0.9 Hz, 1H, H-6), 7.41 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.25–7.18 (m, 3H, Ar-H), 7.14–7.10 (m, 2H, Ar-H), 6.05 (d, *J* = 2.7 Hz, 1H, H-1′), 5.60 (d, *J* = 2.7 Hz, 1H, H-2′), 4.39 (d, *J* = 11.8 Hz, 1H, ArCH_2O), 4.35 (d, *J* = 11.8 Hz, 1H, ArCH_2O), 4.30 (q, *J* = 6.3 Hz, 1H, H-4′), 4.20–4.07 (m, 5H, PCH_2, OC$H_2$$CH_3$), 4.03 (dd, *J* = 13.3, 11.4 Hz, 1H, PCH_2), 3.78 (d, *J* = 10.9 Hz, 1H, CCH_2O), 3.67 (d, *J* = 10.9 Hz, 1H, CCH_2O), 1.97 (d, *J* = 0.7 Hz, 3H, T-CH_3), 1.45 (d, *J* = 6.3 Hz, 3H, H-5′), 1.29 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.1(Ar-*C*O), 164.2 (C-4), 150.5 (C-2), 136.9 (Ar-C), 136.5 (C-6), 133.8, 129.9, 128.60, 128.58, 128.4, 127.9, 127.7 (Ar-C), 111.5 (C-5), 88.4 (C-1′), 85.2 (d, $J_{C,P}$ = 12.3 Hz, C-3′), 81.6, (C-2′), 79.1 (ArCH_2), 73.8 (OCH_2C), 67.6 (C-4′), 63.1 (d, $J_{C,P}$ = 6.3 Hz, OCH_2CH_3), 62.8 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 58.4 (d, $J_{C,P}$ = 170 Hz, PCH_2), 16.4 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 16.3 (d, $J_{C,P}$ = 6.1 Hz, OCH_2CH_3), 13.6 (C-5′), 12.3 (T-*C*H_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 21.0. HRMS(ESI-TOF): calcd. for $C_{30}H_{38}N_2O_{10}P^+$ $[M + H]^+$ 617.2259, found 617.2255.

3-C-Benzyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-1-(thymin-1-yl)-β-D-xylose (13b): Compound **13b** was synthesized using **12b** as starting material following the method as described for **13a**. **13b** was obtained (204 mg, 0.40 mmol) with a yield of 82 %.

13b: ^{1}H NMR (400 MHz, [d_6]DMSO): δ = 11.34 (s, 1H, N-H), 7.44 (d, *J* = 1.0 Hz, 1H, H-6), 7.40–7.28 (m, 5H, Ar-H), 5.90 (d, *J* = 5.9 Hz, 1H, H-1′), 5.71 (d, *J* = 3.9 Hz, 1H, OH), 4.53 (s, 2H, ArCH_2O), 4.15 (q, *J* = 6.3 Hz, 1H, H-4′), 4.11 (dd, *J* = 5.8, 4.0 Hz, 1H, H-2′), 4.08–3.98 (m, 4H, OC$H_2$$CH_3$), 3.86 (d, *J* = 11.5 Hz, 1H, CCH_2O), 3.84 (d, *J* = 10.8 Hz, 2H, PCH_2), 3.60 (d, *J* = 11.5 Hz, 1H, CCH_2O), 1.83 (d, *J* = 0.72 Hz, 3H, T CH_3), 1.30 (d, *J* = 6.3 Hz, 3H, H-5′), 1.213 (t, *J* = 7.1 Hz, 3H, CH_3), 1.210 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, [d_6]DMSO): δ = 163.7 (C-4), 150.6 (C-2), 138.2 (Ar-C), 136.2 (C-6), 128.2, 127.5, 127.4 (Ar-C), 109.8 (C-5), 89.0 (C-1′), 84.8 (d, $J_{C,P}$ = 12.8 Hz, C-3′), 80.3 (C-2′), 77.7 (ArCH_2), 72.6(OCH_2C), 67.3 (C-4′), 62.1 (d, $J_{C,P}$ = 6.0 Hz, OCH_2CH_3), 61.6 (d, $J_{C,P}$ = 6.2 Hz, OCH_2CH_3), 57.1 (d, $J_{C,P}$ = 167 Hz, PCH_2), 16.24 (d, $J_{C,P}$ = 5.3 Hz, OCH_2CH_3), 16.21 (d, $J_{C,P}$ = 5.6 Hz, OCH_2CH_3), 14.2 (C-5′), 12.0 (T-*C*H_3). ^{31}P NMR (162 MHz, [d_6]DMSO): δ = 21.6. HRMS(ESI-TOF): calcd. for $C_{23}H_{34}N_2O_9P^+$ $[M + H]^+$ 513.1996, found 513.1993.

5-Deoxy-3-O-diethylphosphonomethyl-3-C-hydroxymethyl-1-(thymin-1-yl)-β-D-xylose (14b): Compound **14b** was obtained following the method as described for **14a** using **13b** as starting material and purification by column chromatography in 73 % yield.

14b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.56 (s, 1H, N-H), 7.54 (d, *J* = 0.9 Hz, 1H, H-6), 5.69 (s, 1H, H-1′), 5.49 (s, 1H, OH), 4.54 (q, *J* = 6.4 Hz, 1H, H-4′), 4.33 (s, 1H, OH), 4.29–4.09 (m, 5H, OC$H_2$$CH_3$, H-2′), 4.05 (d, *J* = 12.2 Hz, 1H, CCH_2O), 3.96 (dd, *J* = 14.1, 10.9 Hz, 1H, PCH_2), 3.89 (dd, *J* = 13.4, 9.0 Hz, 1H, CCH_2O), 3.48 (dd, *J* = 14.1, 7.5 Hz, 1H, PCH_2), 1.93 (s, 3H, T-CH_3), 1.47 (d, *J* = 6.4 Hz, 3H, H-5′), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). HRMS(ESI-TOF): calcd. for $C_{16}H_{28}N_2O_9P^+$ $[M + H]^+$ 423.1527, found 423.1521.

5-Deoxy-3-O-phosphonomethyl-3-C-hydroxymethyl-1-(thymin-1-yl)-β-D-xylose (15b): Compound **15b** was obtained following the method as described for **15a** using **14b** as starting material in 61 % yield.

15b: ^{1}H NMR (400 MHz, D_2O): δ = 7.59 (d, *J* = 0.96 Hz, 1H, H-6), 5.74 (d, *J* = 2.9 Hz, 1H, H-1′), 4.37 (q, *J* = 6.4 Hz, 1H, H-4′), 4.32 (d, *J* = 2.9 Hz, 1H, H-2′), 4.02 (d, *J* = 13.3 Hz, 1H, CCH_2O), 3.73 (d, *J* = 13.3 Hz, 1H, CCH_2O), 3.64 (dd, *J* = 12.6, 10.9 Hz, 1H, PCH_2), 3.39 (dd, *J* = 12.6, 9.8 Hz, 1H, PCH_2), 1.85 (d, *J* = 0.96 Hz, 3H, T-CH_3), 1.39 (d, *J* = 6.4 Hz, 3H, H-5′). ^{13}C NMR (101 MHz, D_2O): δ = 166.5 (C-4), 151.7 (C-2), 137.5 (C-6), 111.1 (C-5), 89.9 (C-1′), 84.8 (d, $J_{C,P}$ = 9.4 Hz, C-3′), 82.3 (C-2′), 77.7 (C-4′), 59.1 (d, $J_{C,P}$ = 162 Hz, PCH_2), 58.7 (CH_2OH), 13.7 (C-5′), 11.6 (T-CH_3). ^{31}P NMR (162 MHz, D_2O): δ = 16.2. HRMS (ESI-TOF): calcd. for $C_{12}H_{18}N_2O_9P^-$ $[M - H]^-$ 365.0755, found 365.0754.

1-O-Acetyl-2-O-benzoyl-3-C-benzoyloxymethyl-5-deoxy-3-O-diethylphosphonomethyl-D-xylose (16): Compound **11** (430 mg, 0.78 mmol) was dissolved in 10 mL of methanol, 180 mg of Pd-C (10 %) was added. The oscillating mixture was hydrogenated under 50 psi at room temperature for 5 h. The resulting mixture was filtered and concentrated under reduced pressure to dryness. The residue was evaporated with pyridine twice, then dissolved in 5 mL of anhydrous pyridine. Benzoyl chloride (0.36 mL, 3.12 mmol) was added at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min and at room temperature for 4 h, the reaction mixture was quenched by the addition of 0.5 mL of water. Concentration by rotary evaporation and purification by silica gel column chromatography (PE/EA = 5:1–1:1) allowed compound **16** (420 mg, 0.74 mmol) in ca. 95 % yield as an inseparable oily anomeric mixture.

16: HRMS(ESI-TOF): calcd. for $C_{27}H_{34}O_{11}P^+$ $[M + H]^+$ 565.1833, found 565.1838.

1-(Cytosin-1-yl)-5-deoxy-3-O-phosphonomethyl-3-C-hydroxymethyl-β-D-xylose (15c): To a solution of compound **16** (430 mg, 0.76 mmol) in 10 mL of anhydrous acetonitrile, N^4-Benzoylcytosine (246 mg, 1.14 mmol) and BSA (0.74 mL, 3.05 mmol) were added at room temperature under nitrogen atmosphere. The mixture was stirred at 65 °C for 10 min and then cooled to room temperature. TMSOTf (0.41 mL, 2.29 mmol) was added and stirred at room temperature for 10 h. After being quenched by the addition of 1 mL of water, the mixture was concentrated in vacuo and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 3:1–1:3) to provide **12c** with a small amount of impurity as a colorless syrup.

Impure **12c** was dissolved in a saturated methanolic ammonia solution (5 mL) and stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure to produce **13c**, which was used directly in the next step without further purification.

Compound **13c** was hydrolyzed by using TMSBr and 2,6-lutidine following the procedure for preparation of **15a** from **14a** to yield **15c** as a white foam.

15c: ^{1}H NMR (400 MHz, D_2O): δ = 7.78 (d, *J* = 7.6 Hz, 1H, H-6), 5.99 (d, *J* = 7.6 Hz, 1H, H-5), 5.81 (s, 1H, H-1′), 4.64 (s, 1H, H-2′), 4.43 (dd, *J* = 16.1, 12.5 Hz, 1H, PCH_2), 4.28 (q, *J* = 6.4 Hz, 1H, H-4′), 4.23 (dd, *J* = 12.5, 4.7 Hz, 1H, PCH_2), 3.70 (dd, *J* = 14.5, 10.0 Hz, 1H, CCH_2O), 3.61 (dd, *J* = 14.5, 2.1 Hz, 1H, CCH_2O), 1.40 (d, *J* = 6.4 Hz, 3H, H-5′). ^{13}C NMR (101 MHz, D_2O) δ = 166.3 (C-4), 157.5 (C-2), 141.8 (C-6), 95.0 (C-1′), 92.2 (C-5), 81.2 (d, *J* = 4.1 Hz, C-3′), 79.5 (C-2′), 73.8 (C-4′), 65.9 (d, *J* = 6.2 Hz, OCH_2), 59.3 (d, *J* = 142 Hz, PCH_2), 12.0 (C-5′). ^{31}P NMR (162 MHz, D_2O): δ = 10.0. HRMS (ESI-TOF): calcd. for $C_{11}H_{17}N_3O_8P^-$ $[M - H]^-$ 350.0759, found 350.0751.

1-(5-Chlorouracil-1-yl)-5-deoxy-3-O-phosphonomethyl-3-C-hydroxymethyl-β-D-xylose (15d): Substitution of N^4-Benzoyl-

cytosine with 5-chlorouracil in Vorbrüggen glycosylation by following the procedure for preparation of **12c** gave **12d** with a small amount of impurity as a colorless syrup. Impure **12d** was deprotected with saturated methanolic ammonia and followed by hydrolysis with TMSBr/2,6-lutidine according to the method for preparation of **15c** from **12c** to allow **15d** as a white foam in 25 % yield (three steps).

15d: ^{1}H NMR (400 MHz, D_2O): δ = 7.96 (s, 1H, H-6), 5.67 (d, J = 2.0 Hz, 1H, H-1′), 4.41 (q, J = 6.4 Hz, 1H, H-4′), 4.33 (d, J = 2.0 Hz, 1H, H-2′), 4.01 (d, J = 13.4 Hz, 1H, CCH_2O), 3.72 (d, J = 13.4 Hz, 1H, CCH_2O), 3.61 (dd, J = 12.8, 11 Hz, 1H, PCH_2), 3.34 (dd, J = 12.8, 9.4 Hz, 1H, PCH_2), 1.40 (d, J = 6.4 Hz, 3H, H-5′). ^{13}C NMR (101 MHz, D_2O): δ = 164.5 (C-4), 153.2 (C-2), 141.1 (C-6), 111.0 (C-5), 93.6 (C-1′), 87.4 (d, $J_{C,P}$ = 8.9 Hz, C-3′), 85.6 (C-2′), 80.1 (C-4′), 61.8 (d, $J_{C,P}$ = 160 Hz, PCH_2), 61.0 (OCH_2), 16.2 (C-5′). ^{31}P NMR (162 MHz, D_2O): δ = 18.5. HRMS (ESI-TOF): calcd. for $C_{11}H_{15}ClN_2O_9P^-$ $[M - H]^-$ 385.0209, found 385.0211.

1-(6-Chloropurin-9-yl)-5-deoxy-3-O-phosphonomethyl-3-C-hydroxymethyl-β-D-xylose (15e): Substitution of N^4-Benzoylcytosine with 6-chloropurine in Vorbrüggen glycosylation by following the procedure for preparation of **12c** gave **12e** in 41 % yield as a colorless syrup.

12e: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 1H, H-2), 8.72 (s, 1H, H-8), 7.98–7.90 (m, 4H, Ar-H), 7.62–7.55 (m, 2H, Ar-H), 7.42 (t, J = 7.8 Hz, 4H, Ar-H), 6.40 (d, J = 2.5 Hz, 1H, H-1′), 6.03 (d, J = 2.5 Hz, 1H, H-2′), 4.79 (d, J = 13.0 Hz, 1H, CCH_2O), 4.68 (d, J = 13.0 Hz, 1H, CCH_2O), 4.60 (q, J = 6.4 Hz, 1H, H-4′), 4.25–4.14 (m, 4H, OCH_2CH$_3$), 4.12–3.99 (m, 2H, PCH_2), 1.58 (d, J = 6.4 Hz, 3H, H-5′), 1.35 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.6 (C=O), 164.8 (C=O), 152.2 (C-2), 151.5 (C-4), 151.1 (C-6), 144.4 (C-8), 134.2 (C-5), 133.7, 131.8, 129.9, 129.6, 128.8, 128.7, 128.6, 127.9 (Ar-C), 87.6 (C-1′), 84.9 (d, $J_{C,P}$ = 12.2 Hz, C-3′), 82.1 (C-2′), 79.4 (C-4′), 62.85 (d, $J_{C,P}$ = 20 Hz, OCH$_2$CH$_3$), 62.79 (d, $J_{C,P}$ = 20 Hz, OCH$_2$CH$_3$), 61.7 (OCH$_2$), 59.1 (d, $J_{C,P}$ = 171 Hz, PCH$_2$), 16.53 (d, J = 5.3 Hz, OCH$_2$CH$_3$), 16.51 (d, $J_{C,P}$ = 5.9 Hz, OCH$_2$CH$_3$), 13.7 (C-5′). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 19.9. HRMS (ESI-TOF): calcd. for $C_{30}H_{33}ClN_4O_9P^+$ $[M + H]^+$ 659.1668, found 659.1661.

Compound **12e** was deprotected with saturated methanolic ammonia and followed by hydrolysis with TMSBr/2,6-lutidine according to the method for preparation of **15c** from **12c** to allow **15e** as a white foam in 41 % yield (two steps).

15e: ^{1}H NMR (400 MHz, D_2O): δ = 8.67 (s, 1H, H-2), 8.54 (s, 1H, H-8), 6.15 (s, 1H, H-1′), 4.84 (s, 1H, H-2′), 4.41 (dd, J = 16.1, 12.6 Hz, 1H, PCH$_2$), 4.28 (q, J = 6.4 Hz, 1H, H-4′), 4.21 (dd, J = 12.6, 5.0 Hz, 1H, PCH$_2$), 3.62 (dd, J = 14.5, 10.1 Hz, 1H, CCH_2O), 3.40 (dd, J = 14.5, 2.3 Hz, 1H, CCH_2O), 1.39 (d, J = 6.4 Hz, 3H, H-5′). ^{13}C NMR (101 MHz, D_2O) δ = 151.8 (C-2), 150.5 (C-4), 149.9 (C-6), 145.6 (C-8), 131.1 (C-5), 90.6 (C-1′), 81.6 (d, $J_{C,P}$ = 4 Hz, C-3′), 79.8 (C-2′), 74.3 (C-4′), 65.7 (d, $J_{C,P}$ = 6.2 Hz, CH_2OH), 59.5 (d, $J_{C,P}$ = 142 Hz, PCH$_2$), 12.3 (C-5′). ^{31}P NMR (162 MHz, D_2O): δ = 10.2. HRMS (ESI-TOF): calcd. for $C_{12}H_{15}ClN_4O_7P^-$ $[M - H]^-$ 393.0372, found 393.0376.

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Keywords: Carbohydrates · Nucleosides · Phosphonates · Synthetic methods

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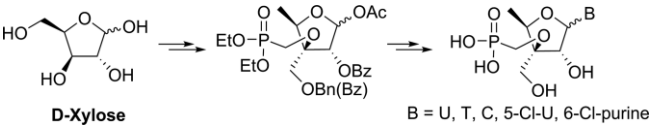

A novel class of L-threose nucleoside phosphonates, 3′-C-hydroxymethyl-3′-O-Phosphonomethyl-D-5′-deoxyxylose nucleosides, were synthesized through 15 or 16-step reactions starting from D-xylose. However, none of the target nucleoside phosphonates showed potent antiviral activity and cytotoxicity.

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