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Synthesis of Novel Xylofuranosyloxymethyl Nucleosides

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ABSTRACT

The ability to selectively trap xylofuranosyloxy carbocation instead of the xylofuranosyl cation by activation of acetoxymethoxy leaving group at the anomeric centre is demonstrated for the synthesis of xylofuranosyloxymethyl nucleosides. The use of $SnCl_4$ as an activator gives both xylofuranosyloxymethyl and natural nucleosides, whereas use of TMSOTf exhibits selectivity to give xylofuranosyloxymethyl nucleosides in case of uracil, thymine, guanine and a mixture of nucleosides in case of cytosine and adenine.

Key words: Glycosyloxymethyl nucleosides, Lewis acid, Glycosylation, Thymine, Adenine.

INTRODUCTION

The chemistry of nucleosides[1] was revolutionized after the discovery of modified nucleosides[2] as effective therapeutic agents for the treatment of AIDS and cancer.[3,4] Examples of modified nucleosides approved by US Food and Drug administration are: 3'-azidothymidine **(AZT),** dideoxycytidine **(ddC)**, dideoxyinosine **(ddI),** 2',3'-didehydro-2',3'-dideoxythymidine **(d_4T)**, 3'-azido-2',3'-dideoxyuridine **(AzddU).**[5] Another important class of sugar modified nucleosides are acyclic nucleosides, where a sugar unit is replaced by acyclic group.[6] The first acyclic nucleoside 9-[(2-hydroxyethoxy) methyl] guanine **(ACV)** is a highly specific inhibitor of herpes simplex virus proliferation (Figure 1). Ganciclovir (**GCV**), structurally different from acyclovir by the addition of a hydroxymethyl group to the acyclic side chain is effective for cytomegalovirus infections.

Glycosylation reaction [7] is crucial for the synthesis of complex glycoconjugates, including the nucleosides. Although there has been fairly significant advancement in the field of glycoconjugate synthesis, the efficiency of glycosidic bond formation in achieving high chemical yield, stereoselectivity and regioselectivity[8] still remains challenging.[9] The classical aspects of carbohydrate chemistry centers around the anomeric carbon where glycosidic bond formation takes place via glycosyl cation[10] and

stereochemical outcome depends on attaching the aglycones to give either α- or β–glycosides.[11] We were interested in developing efficient glycosylation methods for the synthesis of glycoconjugates.[12] In continuation of our efforts to develop efficient glycosylation reactions, we designed an acetoxymethoxy leaving group at the anomeric centre and demonstrated its ability as glycosyl donor.[13] During our investigations, we found that when a glycosylation reaction was performed with *O*-nucleophiles, it resulted into *O*-glycosides, whereas *N*-nucleophiles afforded glycosyloxymethyl derivatives.[13,14] The formation of glycosyloxymethyl derivatives was explained based on capturing the glycosyloxymethyl cation 'b' by *N*-nucleophiles such as nucleic acid bases (Scheme 1).[14] In order to confer generality to the concept developed for synthesis of novel nucleosides and to probe the reactivity of other glycosyl donors we report the activation of xylofuranosyl donor. Furthermore, given the medicinal importance of acylic nucleosides, synthesis of modified glycosyloxymethyl nucleosides may provide new therapeutic agents that can inhibit herpes simplex virus.

RESULTS AND DISCUSSION

The key substrate xylofuranosyl donor **4** was prepared starting from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-xylofuranoside (**1**).[14] Compound **1** on reaction with propargyl alcohol and $BF_3.OEt_2$ at room temperature gave 2-propynyl 2,3,5-tri-*O*-benzoyl-β-D-xylofuranoside (**2**) (Scheme 2).[15] Compound **2** on further reaction with a catalytic amount of $Hg(OCOCF_3)_2$ in acetone-H_2O (2:1) at room temperature gave the corresponding 2-(oxopropoxy)-2,3,5-tri-*O*-benzoyl-²-D-xylofuranoside (**3**). Baeyer-Villiger rearrangement of **3** with m-CPBA in $CHCl_3$ at room temperature gave 1-[(2,3,5-tri-*O*-benzoyl-β-D-(xylofuranosyloxy) methyl]acetate (**4**) in 45% overall yield from compound **1**. Compound **4** was characterized by ^{1}H NMR spectrum from the appearance of methylene protons at δ 5.40-5.48 (m, 2H), anomeric proton (H-1) at δ 5.50 as a singlet indicating the β-anomeric configuration and by ^{13}C NMR from the appearance of methylene carbon at δ 85.1 and anomeric carbon (C-1) at δ 104.9.

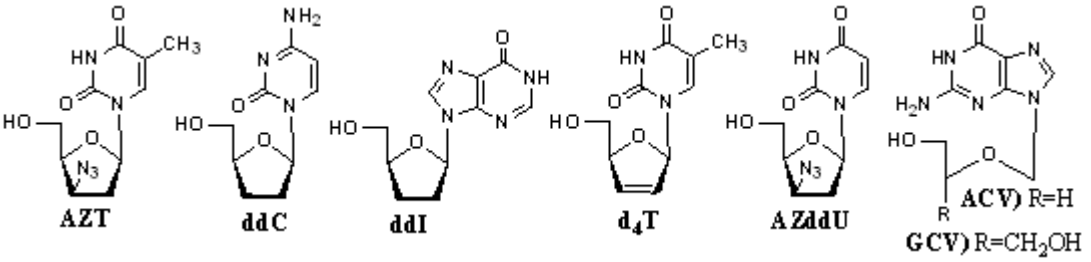
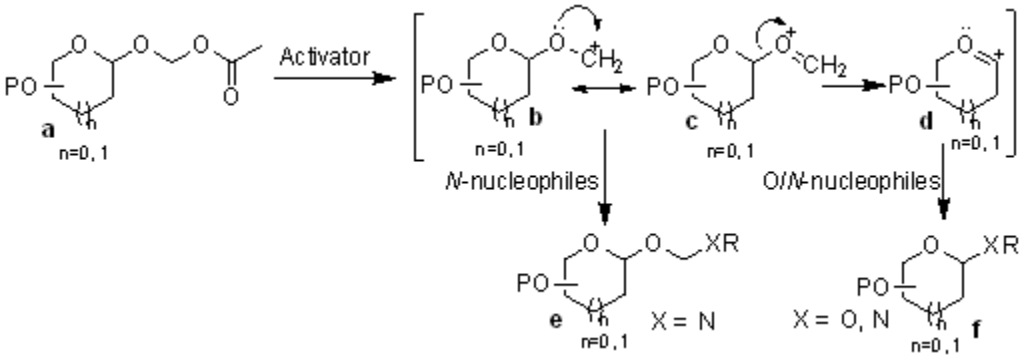


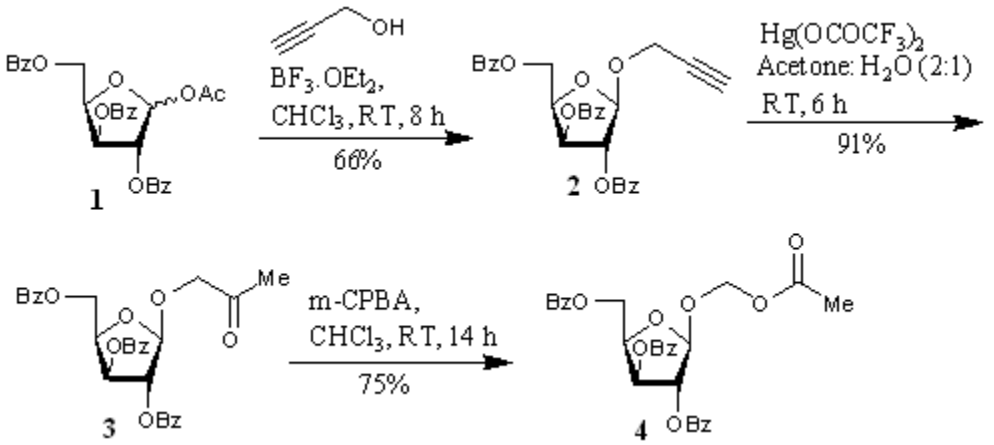
Fig .1. Therapeutically important nucleoside analogues



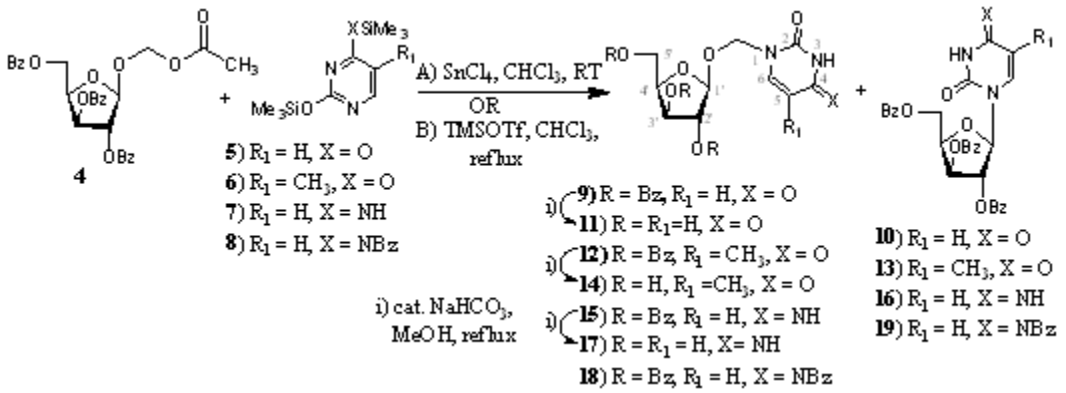
Scheme 1: Activation of acetoxymethoxy glycosyl donor

To envisage the concept, we first investigated the coupling reactions of xylofuranosyl donor **4** with pyrimidine bases 5-8.[16] Thus, coupling reaction of **4** with **5** in $CHCl_3$ and using activator $SnCl_4$ at room temperature gave 1-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy)methyl]uracil (9) and 1-(2',3',5'-tri-*O*-benzoyl-β-D-xylofuranosyl)uracil (10) in a ratio of 1.0:1.9 (78% yield) (Scheme 3). A similar coupling reaction of **4** with *bis*(trimethylsilyl) thymine (6) by use of $SnCl_4$ gave 1-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl]thymine (12) and 1-(2',3',5'-tri-*O*-benzoyl-β-D-xylofuranosyl) thymine **(13)** in a ratio of 1.0:2.1 (66% yield) (Scheme 3). Coupling reaction of 4 with *bis* (trimethylsilyl) cytosine **(7)** by use of $SnCl_4$ gave 1-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl]cytosine (15) and 1-(2',3',5'-tri-*O*-benzoyl-β-D-xylofuranosyl)cytosine **(16)** in a ratio 1.0:2.4 (62% yield) respectively (Scheme 3).

The xylofuranosyloxymethyl pyrimidine nucleosides **9, 12, 15** were separated from pyrimidine nucleosides **10, 13, 16** by column chromatography and characterized by ^1H and ^{13}C NMR. The methylene protons, characteristic of xylofuranosyloxymethyl nucleosides 9, 12, 15 appeared at δ 5.20-5.40 (2H, AB type quartet, J_{gem} = 9.6-11.0 Hz). Compounds **10, 13, 16** were characterized as natural nucleoside by comparison of ^1H NMR, melting point and specific rotation with that reported in the literature.[16-18] Compound **9, 12, 15** on debenzoylation gave 1-[(β-D-xylofuranosyloxy)methyl]uracil (**11**), 1-[(β-D-xylofuranosyloxy)methyl]thymine **(14)**, 1-[(β-D-xylofuranosyloxy)methyl]cytosine (**17**) respectively in good yields. Regiochemistry (*N*^{1} or *N*^{3} linked nucleosides) of the newly formed xylofuranosyloxymethyl nucleosides 9, 12, 15 were assigned as *N*-1 linked nucleosides based on the



Scheme 2: Preparation of xylofuranosyl donor 4

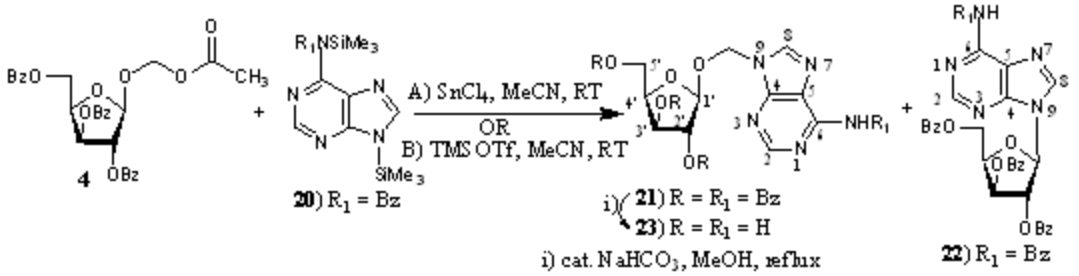


Scheme 3: Coupling of xylose donor 4 with pyrimidine bases 5-8

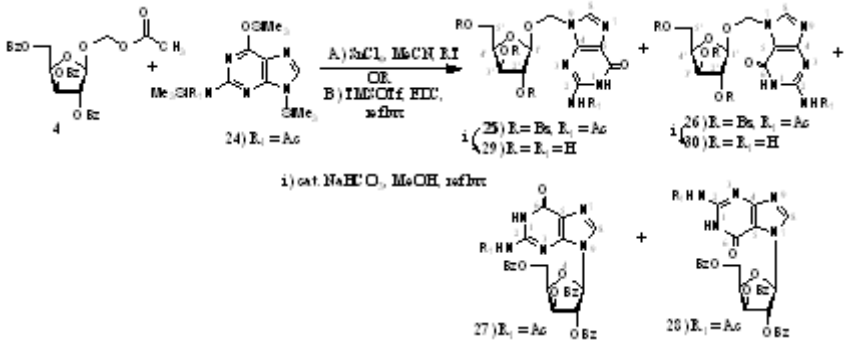
(2 nm or less) absorption difference observed in UV spectra of the compounds 11, 14, 17 in neutral vs. 0.1 N alkali.[18]

Once we accomplished the synthesis of xylofuranosyloxymethyl pyrimidines, we studied the coupling reactions of **4** with purine bases. Thus, coupling reaction of **4** with *bis*(trimethylsilyl)-*N*^{6}-benzoyladenine[19] (20) using $SnCl_4$ in MeCN at room temperature resulted in the isolation of *N*^{6}-benzoyl-9-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy)methyl]adenine **(21)** and 9-(2',3',5'-tetra-*O*-benzoyl-β-D-xylofuranosyl) adenine (22) in a ratio of 1.0:2.27 (59%) (Scheme 4). Compound **21** was characterized as xylofuranosyloxymethyl adenine by ^{1}H NMR and nucleoside **22** was characterized as *N*^{9}-isomer by comparison of its ^{1}H NMR, melting point and specific rotation with that of reported in the literature.[18b] Compound **21** on debenzoylation gave 9-[(-β-D-xylofuranosyloxy)methyl]adenine (**23**) and the regiochemistry was assigned based on ^{1}H NMR spectrum from the appearance of H-2 at δ 8.30 and H-8 at δ 8.28 (Scheme 4). A chemical shift difference of δ 0.02 ppm between H-2 and H-8 observed in the ^{1}H NMR spectrum is characteristic of *N*^{9} regioisomer.[20]

Coupling of 4 with guanine derivative 24 using $SnCl_4$ in MeCN at room temperature resulted in the isolation of oxymethylguanine nucleosides, *N*^{2}-acetyl-9-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy)methyl]guanine (**25**), *N*^{2}-acetyl-7-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy)methyl] -guanine (**26**) and natural nucleosides, *N*^{2}-acetyl-9-(2',3',5'-tri-*O*-benzoyl-β-D-xylofuranosyl) guanine (**27**) and *N*^{2}-acetyl-7-(2',3',5'-tri-*O*-benzoyl-β-D-xylofuranosyl) guanine (**28**). The ratio of xylofuranosyloxymethyl guanine derivatives **25**, **26** to natural nucleosides **27**, **28** was found to be 1.0:2.2 in 57% yield (Scheme 5). Compound **25**, **26** were characterized as xylofuranosyloxymethyl guanine by ^{1}H NMR spectra and compounds 27, **28** were characterized as natural nucleosides by comparison of their ^{1}H NMR spectra with that reported in the literature. Compounds 25, 26 on debenzoylation gave 9-[(-β-D-xylofuranosyloxy) methyl]guanine (**29**) and 7-[(-β-D-xylofuranosyloxy) methyl] guanine (**30**) respectively. The regiochemistry of compounds 25, 26 and 29, 30



Scheme 4: Coupling of 4 with adenine derivative 20



Scheme 5: Coupling of 4 with guanine derivative 24

were assigned by ^{1}H NMR. In case of the compound 29 derived from compound 25, the appearance of H-8 at δ 7.78 as a singlet (^{1}H NMR) and C-5 at δ 116.4 (^{13}C NMR) was characteristic of N^9-regioisomer.[21] In case of compound 30 derived from compound 26, the appearance of H-8 at δ 8.30 as a singlet (^{1}H NMR) and C-5 at δ 106.5 (^{13}C NMR) was characteristic of N^7-regioisomer.[21]

In order to probe the reactivity of xylofuranosyl donor **4**, we carefully studied the coupling reactions using organic Lewis acid, TMSOTf. Thus, coupling of **4** with **5, 6** by use of TMSOTf afforded the xylofuranosyloxymethyl pyrimidine nucleosides **9** and **12** exclusively. Formation of the corresponding natural nucleosides 10 and 13 were not observed. Coupling of **4** with **7** under similar conditions using TMSOTf showed poor selectivity. It resulted into the formation of xylofuranosyloxymethyl cytosine derivative **15** and natural nucleoside **16** in a ratio of 1.0:1.8. The formation of mixture of cytosine nucleosides may be due to the basicity of cytosine. Therefore, we protected cytosine as N^4-bz-cytosine 8 and used for coupling with 4, which resulted in the formation of N^4-benzoyl-1-[(2,3,5-tri-*O*-benzoyl-β-D-xylofuranosyloxy)-methyl]cytosine (18) in a higher yield compared to natural nucleoside 1-(N^4,2',3',5'-tetra-*O*-benzoyl-β-D-xylofuranosyl)cytosine **(19)** in a ratio of 2.9:1.0. Similarly, coupling of **4** with **20** using TMSOTf as an activator gave xylofuranosyloxymethyl adenine **21** and natural nucleoside **22** in a ratio of 1.0:1.27. Coupling of 4 with **24** using TMSOTf gave oxymethyl guanine nucleosides **25, 26** and natural nucleoside **27**, formation of **28** was not observed (Scheme 5). The ratio of natural nucleosides to oxymethyl guanine nucleosides was 1.0:14.0. Thus, synthesis of xylofuranosyloxymethyl nucleosides was achieved by coupling of xylofuranosyl donor 4 with nucleic acid bases similar to ribofuranosyl donor[14]. It was observed that the formation of glycosyloxymethyl nucleosides was in a higher ratio to natural nucleosides in case of ribofuranosyl donor when compared to xylofuranosyl donor during coupling reactions performed using $SnCl_4$. This may be due to subtle difference in the reactivity of xylose donor to the ribose donor. There is no significant difference observed between ribose and xylose donors when activated by TMSOTf.

EXPERIMENTAL

General

^{1}H NMR spectra were recorded using the following instruments: at 200 MHz on a Varian Gemini, at 300 MHz on a Bruker Avance; at 400 MHz on a Varian Unity; at 500 MHz on a Varian Inova, with tetramethyl silane as internal standard for solutions in $CDCl_3$. J values are given Hz. ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz), Bruker Avance (75 MHz) spectrometer with $CDCl_3$ as internal standard (C 77.0) for solutions in deuteriochloroform, DMSO-*d6* (C 39.7) for solutions in deuteriodimethyl sulfoxide, dioxane (C 67.3) for solutions in D_2O. Optical rotations were measured with a JASCO DIP-370 instrument. Melting points were determined by using Fischer–John's melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. UV spectra were recorded on a Shimadzu UV 160A spectrometer. Organic solutions were dried over anhydrous Na_2SO_4.

2-Propynyl 2,3,5-tri-O-benzoyl-β-D-xylofuranoside (2)

To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-α/β-D-xylofuranoside (**1**) (30.0 g, 59.5 mmol) in dry $CHCl_3$ (300 mL) was added propargyl alcohol (4.2 mL, 71.4 mmol) and $BF_3.OEt_2$ (9 mL, 71.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 8 h. After completion of the reaction, anhydrous K_2CO_3 (9.0 g) was added, stirred for a further 30 min., filtered, and the residue was washed with $CHCl_3$ (75 mL). The filtrate was transferred to a separating funnel, washed with water (2x150 mL) and brine (150 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated to obtain a residue. The residue was chromatographed [SiO_2; 60-120 mesh; hexane-ethyl acetate (9:1)] to isolate the title compound **2** as syrup (19.2 g, 66%). $[\pm]_D$ +10.0° (c 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1723; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (1H, t, CºC*H*), 4.40 (2H, m, C*H*$_2$-CºC), 4.50 (1H, dd, $J_{5,5'}$ = 13.0, $J_{4,5}$ = 6.0, H-5), 4.65 (1H, dd, $J_{4,5'}$ = 4.7, H-5'), 4.96 (1H, 2d, $J_{3,4}$ = 4.8, H-4), 5.42 (1H, s, H-1), 5.60 (1H, s, H-2), 5.82 (1H d, H-3), 7.20-8.20 (15H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.6 (H*C*ºC-), 63.4 (C-5), 75.0 (C-4), 75.2 (C-3), 78.6 (O-*C*H$_2$-C), 79.2 (HC*º*C-), 81.1 (C-2), 104.1 (C-1), 125-135 (aromatic), 164.9, 165.2 and 166.1 (C=O, ester);

Mass (FAB-MS): m/z 523 [M^++Na]; Anal. Calcd for $C_{29}H_{24}O_8$: C, 69.59; H, 4.83. Found: C, 69.38; H, 4.80.

2-(Oxopropoxy) 2,3,5-tri-O-benzoyl-β-D-xylofuranoside (**3**)

To a solution of **2** (19.0 g, 38.0 mmol) in acetone:H_2O (300 mL, 2:1) was added $Hg(OCOCF_3)_2$ (3.16 g, 7.60 mmol). The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction, acetone was evaporated; the resulting residue was dissolved in ethyl acetate (300 mL), washed with 10% aq. KI solution (2x150 mL), 20% aq. hypo solution (2x150 mL) and brine (150 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to obtain the title compound **3** as syrup (18.2 g, 91%). $[\pm]_D$ +18.0° (c 1.0, $CHCl_3$); $½_{max}$ (KBr)/cm^{-1} 1715 and 1600; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.25 (3H, s, CH_3), 4.20, 4.40 (2H, AB type quartet, J_{gem} = 15.0, OCH_2C), 4.60 (1H, dd, $J_{5,5'}$ = 13.0, $J_{4,5}$ = 5.0, H-5), 4.70 (1H, dd, $J_{4,5'}$ = 6.0, H-5'), 5.00 (1H, 2d, $J_{3,4}$ = 5.0, H-4), 5.30 (1H, s, H-1), 5.65 (1H, s, H-2), 5.90 (1H, d, H-3), 7.20-8.20 (15H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.5 (CH_3), 63.2 (C-5), 72.5 (C-4), 75.0 (C-3), 79.3 (C-2), 80.9 (-OCH_2-), 105.7 (C-1), 125-133 (aromatic), 164.9, 165.2 and 165.9, 205.2 (C=O, ester); Mass (FAB-MS): m/z 541 [M^++Na]; Anal. Calcd for $C_{29}H_{26}O_9$: C, 67.17; H, 5.05. Found: C, 66.97; H, 5.16.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl] acetate (4)

To a solution of **3** (17.5g, 33.7 mmol) in dry $CHCl_3$ (175 mL) was added m-CPBA (14.0 g, 81.1 mmol). The reaction mixture was stirred at room temperature for 14 h. After completion of the reaction, the reaction mixture was diluted with $CHCl_3$ (150 mL), washed with saturated aq. $NaHCO_3$ solution (150 mLx3, water (150 mL), brine (150 mL) and dried (Na_2SO_4). The solvent was concentrated to give a residue which was purified by silica gel chromatography [SiO_2; 60-120 mesh; hexane:ethyl acetate (9:1)] to obtain the title compound **4** as a solid (13.4 g, 75%). mp 115-117 °C; $[\pm]_D$ +14.0° (c 1.0, $CHCl_3$); λ_{max} (KBr)/cm^{-1} 1723; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (3H, s, CH_3), 4.58 (1H, dd, $J_{5,5'}$ = 13.0, $J_{4,5}$ = 4.65, H-5), 4.68 (1H, dd, $J_{4,5'}$ = 6.0, H-5'), 4.98 (1H, 2d, $J_{3,4}$ = 5.0, H-4), 5.40 - 5.48 (2H, m, OCH_2O), 5.50 (1H, s, H-1), 5.55 (1H, s, H-2), 5.88 (1H, d, H-3), 7.20-8.20 (15H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9 (CH_3) 63.2 (C-5), 74.9 (C-4), 79.5 (C-3), 81.0 (C-2), 85.1 (OCH_2O), 104.9 (C-1), 128-135 (aromatic), 164.8, 165.1, 166.0 and 170.2 (C=O, ester); Mass (FAB-MS): m/z 535 [M^++H]; Anal. Calcd for $C_{29}H_{26}O_{10}$: C, 65.16; H, 4.90. Found: C, 65.17; H, 5.14.

A typical procedure for coupling of xylofuranoside donor 4 with nucleic acid bases 5–8, 20, and 24. Method A: $SnCl_4$; Method B: Trimethylsilyltrifluoro methanesulfonate (TMSOTf)

To a solution (20 mL) of xylofuranoside donor 4 (1.0 mmol) and silylated nucleic acid bases 5–8, 20, 24 (1.2 mmol) at 0 °C was added the catalyst (1.2–2.0 mmol, 0.5N in $CHCl_3$ or MeCN or 1,2-dichloroethane) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4–18 h or reflux temperature for 1–6 h, progress of the reaction was monitored by TLC. After completion of the reaction it was neutralized with saturated aqueous $NaHCO_3$ solution and filtered through a celite pad. The filtrate was extracted into $CHCl_3$ (30 ml), organic phase was separated, washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to obtain a residue. The residue was separated by column chromatography [SiO_2, 60–120 mesh, ethyl acetate:chloroform] to isolate the title compounds.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl]uracil (**9**)

Compound **9**: Mp 83-85 °C; $[\pm]_D$ +17.5° (c 1.0, $CHCl_3$); λ_{max}/nm 259 (MeCN); $½_{max}$ (KBr)/cm^{-1} 1730; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.50 (1H, dd, $J_{5',5''}$ = 13.0, $J_{4',5'}$ 5.0, H-5'), 4.64 (1H, dd, $J_{4',5''}$ = 6.0, H-5"), 4.92 (1H, m, H-4'), 5.26, 5.40 (2H, AB type quartet, J_{gem} = 11.0, OCH_2N), 5.44 (1H, s, H-1'), 5.52 (1H, s, H-2'), 5.64 (1H, d, $J_{3',4'}$ = 5.1, H-3'), 5.80 (1H, d, $J_{5,6}$ = 5.0, H-5), 7.24-8.10 (16H, m, H-6, Ar-H); Mass (FAB-MS): m/z 609 [M^++Na]; Anal Calcd for $C_{31}H_{26}O_{10}N_2$: C, 63.48; H, 4.47; N, 4.78 Found: C, 63.26; H, 4.38; N, 4.59.

Compound **10**: Mp. 108-111 °C [lit.,[13] Mp 112-118 °C]; $[\pm]_D$ +73.3° (c 1.0, $CHCl_3$) [lit.,[13] $[\pm]_D$ +75.0° (c 0.8, $CHCl_3$)].

1-[(β-D-Xylofuranosyloxy)methyl]uracil (**11**)

To a solution of **9** (0.8 g, 1.36 mmol) in methanol (15 mL) was added a catalytic amount of $NaHCO_3$ (0.1 g) and refluxed for 3 h. After completion of the reaction the reaction mixture was neutralized

with IR 120 H^+ resin, filtered, washed with methanol (15 mL) and filtrate was evaporated to a residue. The residue was dissolved in water (30 mL) washed with chloroform (2x25 mL); the water phase was concentrated to isolate the title compound **11** as a thick syrup (0.32 g, 84%). $[\pm]_D$ –55.0° (c 1.0, H_2O); λ_{max}/nm 260 (H_2O), 261 (0.1N, NaOH); ½$_{max}$ (KBr)/ cm^{-1}1685; ^{1}H NMR (400 MHz, D_2O) δ 3.60 (1H, dd, $J_{5',5''}$ = 10.0, $J_{4',5'}$ = 5.5, H-5'), 3.75 (1H, dd, $J_{4',5''}$ = 4.7, H-5"), 4.10 (1H, s, H-2'), 4.18 (1H, m, H-4'), 4.30 (1H, m, H-3'), 5.12 (1H, s, H-1'), 5.20, 5.30 (2H, AB type quartet, J_{gem} = 10.0, OCH_2N), 5.80 (1H, d, $J_{5,6}$ = 5.6, H-5), 7.65 (1H, d, H-6); ^{13}C NMR (50 MHz, D_2O) δ 66.0 (C-5'), 81.0 (C-4'), 81.2 (C-3'), 86.3 (C-2'), 89.2 (OCH_2N), 108.0 (C-1'), 113.0 (C-5), 152.0 (C-6), 158.0 (C=O,C-2), 172.0 (C=O,C-4); Mass (FAB-MS): m/z 275 [M^++H]; Anal. Calcd for $C_{10}H_{14}O_7N_7$: C, 43.80; H, 5.15; N, 10.22. Found: C, 43.56; H, 5.22; N, 10.28.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl]thymine (**12**)

Compound **12**: Mp 137-139°C; $[\pm]_D$ +14.2° (c 1.0, $CHCl_3$); λ_{max}/nm 263 (MeOH); ν_{max} (KBr)/cm^{-1} 1723; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80 (3H, s, CH_3), 4.40-4.70 (2H, m, H-5',5"), 4.85-5.10 (1H, m, H-4'), 5.22,5.34 (1H, AB type quartet, J_{gem} = 11.0, OCH_2N), 5.40 (1H, s, H-1'), 5.52 (1H, s, H-2'), 5.80 (1H, d, $J_{3',4'}$ = 5.4, H-3'), 7.10 (1H, s, H-6), 720-8.10 (15H, m, Ar-H), 9.05 (1H, br s, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.2 (CH_3), 63.5 (C-5'), 74.5 (C-3'), 75.0 (C-2'), 79.5 (C-4'), 81.0 (OCH_2N), 105.0 (C-1'), 111.5 (C-5), 125-135 (aromatic), 139.1 (C-6), 150.5 (C=O,C-2) 164.0 (C=O,C-4) 164.5, 165.0, 166.0 (C=O, ester); Mass (FAB-MS): m/z 601 [M^++H]; Anal. Calcd for $C_{32}H_{28}O_{18}N_2$: C, 63.99; H, 4.70; N, 4.66. Found: C, 63.28; H, 4.62; N, 4.73.

Compound **13**: Mp 196-199 °C [lit.[14] mp. 196-198 °C]; $[\pm]_D$ +49.3° (c 0.85, $CHCl_3$) [lit.[14] $[\pm]_D$ +50.6° (c 0.85, $CHCl_3$)].

1-[(β-D-Xylofuranosyloxy)methyl]thymine (**14**)

The benzoylated derivative 12 (0.8g, 1.33 mmol) in methanol (16 mL) was deprotected as described for 11 to isolate the title compound 14 as a white solid (0.35 g, 91.0%). mp 175-177 °C; $[\pm]_D$ –31.0° (c 1.0, H_2O); λ_{max}/nm 265 (H_2O), 266 (0.1N NaOH); ½$_{max}$ (KBr)/cm^{-1} 1690; ^{1}H NMR (200 MHz; D_2O) δ 1.88 (3H, s, CH_3), 3.70 (1H, dd, $J_{5',5''}$ = 14.0, $J_{4',5'}$ = 5.2, H-5'), 3.85 (1H, dd, $J_{4',5''}$ = 4.0, H-5"), 4.15 (1H, d, $J_{2',3'}$ = 4.65, H-3'), 4.26 (1H, d, H-2'), 4.30-4.45 (1H, m, H-4'), 5.18 (1H, s, H-1'), 5.20, 5.35 (2H, AB type quartet, J_{gem} = 14.0, OCH_2N), 7.45 (1H, s, H-6), 8.00 (1H, br s, NH); ^{13}C NMR (50 MHz, D_2O) ´ 12.5 (CH_3), 60.3 (C-5'), 73.9 (C-4'), 75.5 (C-3'), 80.5 (C-2'), 83.2 (OCH_2N), 106.5 (C-1'), 109.0 (C-5), 140.0 (C-6), 154.0 (C=O,C-2), 168.0 (C=O,C-4); Mass (FAB-MS): m/z 311 [M^++Na]; Anal. Calcd for $C_{11}H_{16}O_7N_2$: C, 45.83, H, 5.60, N, 9.2. Found: C, 45.67; H, 5.48; N, 8.91.

1-[(2,3,5-Tri-*O*-benzoyl-β-D-xylofuranosyloxy) methyl]cytosine (**15**)

Compound **15**: Mp 122-126°C; $[\pm]_D$ +44.6° (c 1.0, $CHCl_3$); λ_{max}/nm 274 (MeOH); ½$_{max}$ (KBr)/cm^{-1} 1723, 1661 and 1615; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.48 (1H, dd, $J_{5',5''}$ = 13.0, $J_{4',5'}$ = 5.0, H-5'), 4.62 (1H, dd, $J_{4',5''}$ = 6.0, H-5"), 4.90 (1H, dd, $J_{3',4'}$ = $J_{4',5'}$ 5.20, H-4'), 5.25, 5.35 (2H, AB type quartet, J_{gem} = 9.6, OCH_2N), 5.48 (1H, s, H-1'), 5.50 (1H, s, H-2'), 5.76 (1H, d, H-3'), 5.82 (1H, d, $J_{5,6}$ = 7.6, H-5), 7.20-7.60 (10H, m, H-6, Ar-H), 7.85-8.20 (6H, m, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 63.3 (C-5'), 75.1 (C-4'), 76.3 (C-3'), 79.4 (C-2'), 81.0 (OCH_2N), 95.6 (C-5), 104.8 (C-1'), 128.0-135.0 (aromatic), 144.7 (C-6), 155.9 (C-4), 165.0 (C=2, C=O), (C=O,C-2) 165.6, 166.0, 166.2 (C=O, ester); Mass (FAB-MS): m/z 586 [M^++H]; Anal. Cacld for $C_{31}H_{27}O_9N_3$: C, 63.58; H, 4.65; N, 7.18. Found: C, 63.32; H, 4.63; N, 7.11.

Compound **16**: Mp 137-139 °C [lit.,[14] mp 140-141 °C]; $[\pm]_D$ +61.5° (c 0.6, $CHCl_3$) [lit.,[14] $[\pm]_D$ +63.4° (c 0.6, $CHCl_3$)].

1-[(β-D-Xylofuranosyloxy)methyl]cytosine (**17**)

The benzoylated derivative 15 (0.6 g, 0.9 mmol) was debenzoylated as described for 14 to isolate the title compound 17 as a syrup (0.19 g, 81.5%). $[\pm]_D$ +17.8° (c 1, H_2O); λ_{max}/nm 268 (H_2O), 270 nm (0.1N NaOH); ½$_{max}$ (KBr)/cm^{-1} 1653; ^{1}H NMR (200 MHz, D_2O) δ 3.70 (1H, dd, $J_{5',5''}$ = 12.8, $J_{4',5'}$ = 5.0, H-5'), 3.84 (1H, dd, $J_{4',5''}$ = 6.0, H-5"), 4.20 (1H, s, H-2'), 4.22-4.40 (2H, m, H-3', H-4'), 5.20 (1H, s, H-1'), 5.24, 5.40 (2H, AB type quartet, J_{gem} = 10.0, OCH_2N), 6.20 (1H,d, $J_{5,6}$ = 7.8, H-5), 7.70 (1H, d, H-6); ^{13}C NMR (50 MHz, D_2O) δ 59.3 (C-5'), 73.5 (C-4'), 74.9 (C-3'), 78.7 (C-2'), 81.6 (OCH_2N), 104.9 (C-1'), 94.6 (C-5), 144.8 (C-6), 156.0 (C=O, C-2), 165.2 (C=O,C-4); Mass (FAB-MS) m/z 274 [M^++H];

Anal. Calcd for $C_{10}H_{15}O_6N_2$: C, 43.95; H, 5.53; N, 15.38. Found: C, 44.11; H, 5.38; N, 15.21.

N^6-Benzoyl-9-[(2,3,5-tri-O-benzoyl-β-D-xylofuranosyloxy)methyl]adenine (**21**)

Compound **21**: Mp 77-79 °C; $[\pm]_D$ +32.6° (c 1, $CHCl_3$); λ_{max}/nm 277 (MeCN); ½$_{max}$ (KBr)/cm^{-1} 1723 and 1600. ^{1}H NMR (200 MHz, $CDCl_3$) ´ 4.50 (2H, m, H-5',5"), 4.98 (1H, m, H-4'), 5.50 (1H, s, H-1'), 5.56 (1H, s, H-2'), 5.80 (1H, d, $J_{3',4'}$ = 3.5, H-3'), 5.84, 6.02 (2H, AB type quartet, J_{gem} = 9.8, OCH_2N), 7.20-7.60 (12H, m, Ar-H), 7.80-8.16 (8H, m, Ar-H), 8.22 (1H, s, H-8), 8.78 (1H, s, H-2), 9.24 (1H, br s, NH); Mass (FAB-MS): m/z 714 [M^++H]; Anal. Cacld for $C_{39}H_{31}O_9N_5$: C, 65.68; H, 4.37; N, 9.82. Found: C, 63.23; H, 4.48; N, 9.38.

Compound **22**: Mp 104-107 °C [lit.,[14,17] mp 105-110 °C]; $[\pm]_D$ +10.73° (c 1.0, $CHCl_3$) [lit.,[14,17] $[\pm]_D$ +5.2° (c 0.8, $CHCl_3$)];

9-[(β-D-Xylofuranosyloxy)methyl]adenine (**23**)

The benzoylated derivative **21** (0.6 g, 0.84 mmol) was debenzoylated as described for **11** to isolate the title compound **23** as a solid (0.19 g, 76.0%). mp 220 °C (decom.); $[\pm]_D$ –38.5° (c 1, DMSO); λ_{max}/nm 259 (H_2O); λ_{max} (KBr)/cm^{-1} 1678 and 1610; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.20-4.30 (6H, m, H-2',H-3',H-4',H-5',H-5",OH), 4.82 (1H, br s, OH), 4.98 (1H, s, H-1'), 5.15 (1H, br s, OH), 5.64, 5.85 (2H, AB type quartet, J_{gem} = 10.0, OCH_2N)), 7.30 (2H, br s, NH_2), 8.28 (1H, s, H-8), 8.30 (1H,s, H-2); ^{13}C NMR (50 MHz, DMSO-d_6) δ 63.1 (C-5'), 68.8 (C-4'), 71.8 (C-3'), 74.4 (C-2'), 86.1 (OCH_2N), 105.5 (C-1'), 119.3 (C-5), 143.1 (C-8), 149.8 (C-4), 153.6 (C-2), 156.0 (C-6); Mass (FAB-MS): m/z 298 [M^++H]; Anal. Calcd for $C_{11}H_{15}O_5N_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 43.91; H, 5.14; N, 23.42.

N2-Acetyl-9-[(2,3,5-tri-O-benzoyl-β-D-xylofuranosyloxy)methyl]guanine (25) and N^2-acetyl-7-[(2,3,5-tri-O-benzoyl-β-D-xylofuranosyloxy)methyl]-guanine (**26**)

Compound **25**: Mp 149-151 °C; $[\pm]_D$ –4.89° (c 1.0, $CHCl_3$); λ_{max}/nm 276 (MeCN); λ_{max} (KBr)/cm^{-1} 1715, 1615 and 1570; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (3H, s, OCOCH_3), 4.60 (1H, dd, $J_{5',5"}$ = 12.8, $J_{4',5'}$ = 6.0, H-5'), 4.90-5.20 (2H, m, H-4', H-5), 5.30, 5.78 (2H, AB type quartet, J_{gem} = 10.0, OCH_2N), 5.50 (1H, s, H-1'), 5.54 (1H, s, H-2'), 5.84 (1H, d, $J_{3',4'}$ = 6.5, H-3'), 7.08-7.70 (10H, H-8, Ar-H), 8.00 (6H, d, Ar-H), 10.49 (1H, br s, NH), 11.90 (1H, br s, NH); Mass (FAB-MS): m/z 668 [M^++H]; Anal. Calcd for $C_{34}H_{29}O_{10}N_5$: C, 61.16; H, 4.38; N, 10.49. Found: C, 61.08; H, 4.12; N, 9.98.

Compound 26: Mp 115-120 °C; $[\pm]_D$ +2.7° (c 1.0, $CHCl_3$); λ_{max}/nm 261 (MeCN); ν_{max} (KBr)/cm^{-1} 1715, 1615 and 1570; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (3H, s, OCOCH_3), 4.38-4.52 (2H, m, H-4', H-5"), 4.94 (1H, m, H-4'), 5.58 (1H, s, H-1'), 5.62 (1H, s, H-2'), 5.80 (d, $J_{3',4'}$ 6.3, H-3'), 5.98, 6.05 (2H, AB type quartet, J_{gem} = 10.0, OCH_2N), 7.30-7.64 (9H, m, Ar-H), 7.92-8.10 (7H, m, H-8, Ar-H), 11.10 (1H, br s, NH), 12.30 (1H, br s, NH); Mass (FAB-MS): m/z 668 [M^++H]; Anal. Cacld for $C_{34}H_{29}O_{10}N_5$: C, 66.16; H, 4.38; N, 10.49. Found: C, 66.21; H, 4.23; N, 10.23.

9-[(β-D-Xylofuranosyloxy)methyl]guanine (**29**)

The benzoyl derivative **25** (0.4g, 0.59 mmol) in methanol (10 mL) was deprotected as described for 11 to isolate the title compound 29 as a solid (0.14 g, 78%). mp 201-203 °C; $[\pm]_D$ –43.4° (c 1.0, DMSO); λ_{max}/nm 251 (H_2O); ν_{max} (KBr)/cm^{-1} 3400, 1723, 1685 and 1623; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.40-3.70 (2H, m, H-5', H-5"), 3.80 (1H, m, H-2'), 3.90 (1H, m, H-3'), 4.10 (1H, dd, $J_{3',4'}$ = 3.5, $J_{4',5'}$ = 6.0, H-4'), 4.50 (1H, s, OH), 4.80 (2H, br s, 2xOH), 5.30 (1H, s, H-1'), 5.36, 5.46 (2H, AB type quartet, J_{gem} = 9.8, OCH_2N), 6.58 (2H, br s, NH_2), 7.78 (1H, s, H-8), 10.68 (1H, br s, NH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 60.5 (C-5'), 68.3 (C-4'), 75.5 (C-3'), 80.9 (C-2'), 83.3 (OCH_2N), 105.9 (C-1'), 116.4 (C-5), 137.7 (C-8), 151.3 (C-4), 153.8 (C-2), 156.7 (C-6); Mass (FAB-MS): m/z 314 [M^++H]; Anal. Calcd for $C_{11}H_{15}O_6N_5$: C, 42.17; H, 4.83; N, 22.36. Found: C, 42.31; H, 4.67; N, 23.43.

7-[(β-D-Xylofuranosyloxy)methyl]guanine (**30**)

The benzoylated derivative 26 (0.2 g, 0.29 mmol) in methanol (6 mL) was deprotected as described for 11 to isolate the title compound 30 as a white solid (0.07 g, 75.0%). Mp 235 °C (decom.); $[\pm]_D$ –47.3 (c 0.5, DMSO); λ_{max}/nm 281 (H_2O); ν_{max} (KBr)/cm^{-1} 1677 and 1485; ^{1}H; NMR (200 MHz, DMSO-d_6) δ 3.70-4.20 (5H, m, H-2', 3', 4', 5', 5"), 4.60 (1H, s, OH), 4.80 (1H, s, OH), 4.95 (1H, s, H-1'), 5.00 (1H, s, OH), 5.62, 5.70 (2H, AB type quartet, J_{gem} = 8.8, OCH_2N), 6.70 (2H, br s, NH_2), 8.30 (1H, s, H-8), 10.90 (1H, br s, NH); ^{13}C NMR (75 MHz,

DMSO-d_6) δ 60.5 (C-5'), 72.6 (C-4'), 75.4 (C-3'), 80.9 (C-2'), 83.6 (OCH_2N), 106.2 (C-1'), 106.7 (C-5), 143.2 (C-8), 154.1 (C-2), 155.2 (C-6), 160.8 (C-4); Mass (FAB-MS): m/z 314 [M^++H]; Anal. Calcd for $C_{11}H_{15}O_6N_5$: C, 42.17; H, 4.83; N, 22.36. Found: C, 42.25; H, 4.41; N, 22.62.

CONCLUSION

In summary, we have successfully demonstrated that iterative glycosylation of acetoxymethoxy xylofuranosyl donor resulted in the formation of novel xylofuranosyloxymethyl nucleosides. The coupling reactions using $SnCl_4$ as an activator resulted in the formation of a mixture of natural nucleosides and novel xylofuranosyloxymethyl nucleosides whereas use of TMSOTf resulted in the exclusive formation of novel xylofuranosyloxymethyl nucleosides (in case of uracil, thymine, guanine) and mixture of nucleosides (in case of cytosine and adenine). The application of this new method to other glycosyl donors exploring various Lewis acids and their biological functions will be reported in near future.

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