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Synthesis and Selective Lipozyme® TL IM Catalyzed Acylation Studies on 4-*C*-Hydroxymethylated *xylo*-Furanosides

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Abstract—*In this work, a novel chemo-enzymatic strategy to manipulate the hydroxyl groups in 4-C-hydroxymethyl-1,2-O-isopropylidene-3-O-alkyl-β-L-threo-xylofuranosides has been developed. Lipozyme® TL IM selectively catalyzed the transfer of acetyl group from vinyl acetate to OH of 4-C-hydroxymethyl group over C-5 OH group in 4-C-hydroxymethyl-1,2-O-isopropylidene-3-O-alkyl-β-L-threo-xylofuranose. It was observed that on increasing the alkyl chain length the diastereoselectivity of the Lipozyme® TL IM towards acylation of C-1′ OH group increases. The reaction time also increased with increase in the alkyl chain length.*

1. INTRODUCTION

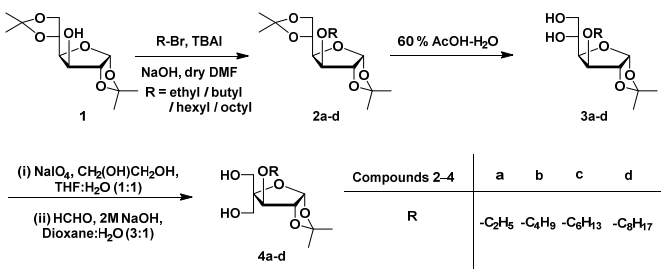
Carbohydrates are abundant in nature and have been found to play an important role in various types of biochemical recognition processes. These include growth, immune response, infection, cell adhesion, metastasis and numerous signal transduction events.[i] They are present in polymers such as starch, pectin, cellulose, and chitin and are also key components of DNA and RNA. They occur in combination with lipids to form glycolipids and with proteins to form glycoproteins. In the plant kingdom, digalactosyl diacylglycerol and sulfoquinovosyl diacyglycerol are the two major membrane components.[ii]

Polymers based on carbohydrates have emerged as an exciting topic in polymer research as they are processible, biocompatible and biodegradable.[iii] Some of the important applications of polymers of this class are used as drug-delivery agents, cell surface mimics and as therapeutic and diagnostic agents.[iv] Enzyme catalysis has been widely explored for the preparation of monomers and polymers.[v] We have recently designed and synthesized a sugar-PEG copolymer which is useful for the delivery of nonpolar drugs at a particular pH.[vi]

Our continued interest of study of enzyme catalyzed regio- and stereoselective reactions on different bioactive compounds led us to develop a novel chemo-enzymatic strategy to manipulate the different hydroxyl groups in 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-pentofuranose, a precursor for the synthesis of sugar-PEG copolymer useful in drug delivery applications.[vii]

2. RESULT AND DISCUSSION

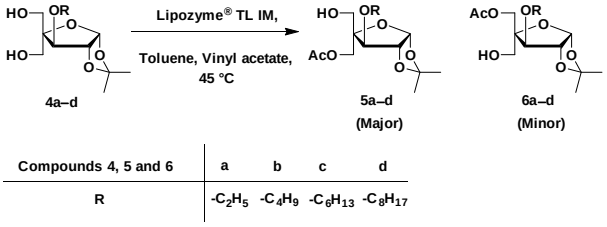
The substrate for the enzymatic reactions, 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose and 4-*C*-acetoxymethyl-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose derivatives were synthesized through a multistep sequence starting from commercially available 1,2:5,6-di-*O*-isopropylidene-D-glucose (**1**). In the first step, synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose **2a-b** was carried out by the reaction of 1,2:5,6-di-*O*-isopropylidene-D-glucose (**1**) with alkyl bromide in dry DMF in the presence of sodium hydroxide and phase transfer catalyst, *i.e.* tetrabutyl ammonium iodide to afford the desired products in 84 to 92 % yields (**Scheme 1**). The removal of the more acid labile 5,6-*O*-isopropylidene acetal in *C*-3 alkyloxy sugar derivatives **2a-d** was done by stirring the compounds in 60 % aqueous acetic acid for 24 hr to obtain 1,2-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose **3a-d** in 83 to 88 % yields. Oxidative cleavage of the two vicinal hydroxyl groups by sodium periodate in compounds **3a-d** afforded the corresponding aldehydes, which on subsequent *in-situ* aldol-cannizzaro reaction with formaldehyde produced 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose **4a-d** in 69 to 75 % yields (**Scheme 1**).



Scheme 1: Synthesis of 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose

Lipozyme® TL IM was screened for diastereoselective acetylation of one of the two primary hydroxyl groups in 4-*C*-hydroxymethyl-l,2-*O*-isopropylidene-3-*O*-ethyl-*β*-L-*threo*-pentofuranose (**4a**) in different organic solvents, *i.e.* THF, 1,4-dioxane, DIPE, toluene and acetonitrile at 45, 50 and 60 °C and at 200 rpm in an incubator shaker. It was observed that reaction in toluene was relatively faster as compared to that in DIPE.

Thus in a typical reaction, a mixture of **4a/ 4b/ 4c/ 4d**, vinyl acetate and Lipozyme® TL IM (substrate-enzyme ratio, 1:0.5 w/w) in dry toluene was incubated in an incubator shaker at 45 °C (**Scheme 2**, **Table 1**). The reaction was stopped after the disappearance of the starting compound and concomitant appearance of a prominent spot of the product on analytical TLC at higher R_f value than the starting compound. The reaction was quenched by filtering off the enzyme and the solvent was removed under reduced pressure.



Scheme 2: Lipozyme® TL IM catalyzed acetylation of 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose

Table 1: Lipozyme® TL IM mediated diastereoselective acylation of 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranoses 4a-d in toluene at 45 °C[a]

Entry	Substrate	R	Time (hr)	Product	Yield of 5 (%)
1.	**4a**	C_2H_5	15	**5a**	55
2.	**4b**	C_4H_9	12	**5b**	69
3.	**4c**	C_6H_{13}	17	**5c**	75
4.	**4d**	C_8H_{17}	21	**5d**	79

[a]All these reactions, when performed under identical conditions but without adding enzyme did not yield any product.
[b]Calculated on the basis of integration of anomeric protons in the ^{1}H NMR

The crude product thus obtained was a mixture of two monoacetylated compounds **5a** & **6a** / **5b** & **6b** / **5c** & **6c** / **5d** & **6d** in different diastereomeric ratio. The mixture was thus purified by silica gel column chromatography using ethyl acetate in petroleum ether as gradient solvent system to obtain the major product **5a** / **5b** / **5c** / **5d** in 55 to 79 % isolated yields (**Scheme 2**).

It was observed that on increasing the 3-*O*-alkyl chain length the diastereoselectivity of the Lipozyme® TL IM towards acylation of C-1' OH group increases. The reaction time also increased with increase in the alkyl chain length (**Table 1**). The NOESY NMR spectrum (**Figure 1**) of **5b** showed the cross peaks for the interaction of the methylene protons which shifted downfield due to acetylation and hydrogen at C-3 position. Appearance of this cross peak confirmed that the acetylation had taken place on C-1' hydroxyl group and not on the C-5 hydroxyl group.

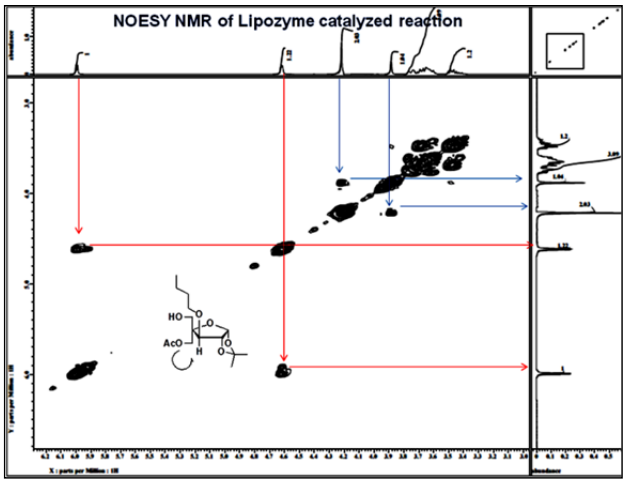


Figure 1: NOESY NMR spectrum of 5b

3. EXPERIMENTAL

General procedure for the synthesis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose (2a-d)

Bromoalkane (60 mmol) was added dropwise to a mixture of 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**1**, 20 mmol), sodium hydroxide (30 mmol), molecular sieves 4Å (4g) and tetrabutyl ammonium iodide (0.2 mmol) in dry DMF (10 ml) at 0 °C. Reaction mixture was stirred at 25 °C for 24 hr. After completion of the reaction as indicated by TLC examination, DMF was evaporated under reduced pressure. Water was added to the residue and the reaction mixture was extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product thus obtained, was purified by column chromatography over silica gel (100-200 mesh) by eluting with ethyl acetate: petroleum ether to afford the pure desired products **2a-d**.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-ethyl-D-glucofuranose (2a)[7]
It was obtained as colorless oil (5.30 g) in 92 % yield.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-butyl-D-glucofuranose (2b)[7]
It was obtained as colorless oil (5.62 g) in 89 % yield

1,2:5,6-Di-*O*-isopropylidene-3-*O*-hexyl-D-glucofuranose (2c)
It was obtained as colorless oil (5.91 g) in 86 % yield; IR (cm^{-1}, thin film): 2980, 2943, 2895, 1372, 1210, 1072 and 845; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, t, J = 7.32 Hz), 1.23-

1.30 (9H, m), 1.32 (3H, s,), 1.40 (3H, s), 1.47-1.56 (5H, m), 3.45 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.54 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz,), 3.82 (1H, d, *J* = 2.93 Hz), 3.93 (1H, dd, *J* = 8.05 Hz & *J* = 5.86 Hz), 4.03 (1H, dd, *J* = 8.79 Hz & *J* = 6.59 Hz), 4.09 (1H, dd, *J* = 7.32 Hz & *J* = 2.93 Hz), 4.26-4.30 (1H, m, C-5H), 4.49 (1H, d, *J* = 3.66 Hz, C-2H), 5.84 (1H, d, *J* = 3.66 Hz, C-1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.01, 22.56, 25.35, 25.68, 26.21, 26.72 & 26.81, 29.65, 31.55, 67.16, 70.65, 72.50, 81.15, 82.05, 82.50, 105.23, 108.83 & 111.66; HR-ESI-TOF-MS *m/z* 367.2075 ([M+Na]$^+$), calcd for $[C_{18}H_{32}O_6+Na]^+$ 367.2091.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-octyl-D-glucofuranose (2d)

It was obtained as colorless oil (6.25 g) in 84 % yield; IR (cm^{-1}, thin film): 2982, 2939, 2890, 1368, 1213, 1077 and 852; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.32 Hz), 1.27-1.31 (13H, m), 1.35 (3H, s), 1.42 (3H, s), 1.49-1.57 (5H, m), 3.47 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.57 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.84 (1H, d, *J* = 2.93 Hz), 3.96 (1H, dd, *J* = 8.05 Hz & *J* = 5.86 Hz), 4.06 (1H, dd, *J* = 8.79 Hz & *J* = 6.59 Hz), 4.11 (1H, dd, *J* = 7.32 Hz & *J* = 2.93 Hz), 4.28-4.33 (1H, m), 4.52 (1H, d, *J* = 3.66 Hz), 5.86 (1H, d, *J* = 3.66 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.04, 22.60, 25.33, 26.00, 26.19, 26.70 & 26.79, 29.21, 29.31, 29.67, 31.77, 67.14, 70.64, 72.49, 81.13, 82.02, 82.48, 105.21, 108.80 & 111.63; HR-ESI-TOF-MS *m/z* 395.2391 ([M+Na]$^+$), calcd for $[C_{20}H_{36}O_6+Na]^+$ 395.2404.

General procedure for the synthesis of 1,2-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose (3a-d) 1,2:5,6-Di-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose (**2a-d**, 18 mmol) was added to a solution of 60 % acetic acid in water (30 ml) at 0 °C and the reaction mixture was stirred for 24 hr at room temperature. On completion of the reaction, as indicated by TLC examination, AcOH-H_2O was completely evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography using ethyl acetate: petroleum ether as gradient solvent system to obtain **3a-d** as pure product.

1,2-*O*-Isopropylidene-3-*O*-ethyl-D-glucofuranose (3a)[7]

It was obtained as colorless oil (3.94 g) in 88 % yield

1,2-*O*-Isopropylidene-3-*O*-butyl-D-glucofuranose (3b)[7]

It was obtained as colorless oil (4.28 g) in 86 % yield

1,2-*O*-Isopropylidene-3-*O*-hexyl-D-glucofuranose (3c)

It was obtained as colorless oil (4.55 g) in 83 % yield; IR (cm^{-1}, thin film): 3428, 2981, 2935, 2890, 1370, 1217, 1087, 1016, 899 and 854; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, t, *J* = 7.32 Hz), 1.29-1.35 (9H, m), 1.49-1.60 (5H, m) , 2.23 & 2.89 (2H, 2s), 3.45 (1H, dt, *J* = 9.52 Hz & *J* = 7.32 Hz), 3.62 (1H, dt, *J* = 8.79 Hz & *J* = 6.59 Hz), 3.70 (1H, dd, *J* = 10.98 Hz & *J* = 5.13 Hz), 3.81 (1H, dd, *J* = 10.98 Hz & *J* = 2.93 Hz), 3.97 (1H, d, *J* = 2.93 Hz), 4.01-4.05 (1H, m), 4.13 (1H, dd, *J* = 7.32 Hz & *J* = 2.93 Hz), 4.56 (1H, d, *J* = 4.39 Hz), 5.92 (1H, d, *J* = 4.39 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.99, 22.51, 25.72, 26.19, 26.72 & 29.65, 31.52, 64.42, 69.80, 70.47, 79.72, 81.94, 83.15, 104.99, 111.70; HR-ESI-TOF-MS *m/z* 327.1772 ([M+Na]$^+$), calcd for $[C_{15}H_{28}O_6+Na]^+$ 327.1778.

1,2-*O*-Isopropylidene-3-*O*-octyl-D-glucofuranose (3d)

It was obtained as colorless oil (5.02 g) in 84 % yield; IR (cm^{-1}, thin film): 3425, 2980, 2933, 2892, 1371, 1219, 1088, 1014, 879 and 864; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (3H, t, *J* = 7.32 Hz), 1.27-1.32 (13H, m), 1.49-1.61 (5H, m), 2.36 & 2.95 (2H, 2s), 3.45 (1H, dt, *J* = 8.79 Hz & *J* = 6.59 Hz), 3.61 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.70 (1H, dd, *J* = 10.98 Hz & *J* = 5.13 Hz), 3.80 (1H, dd, *J* = 10.98 Hz & *J* = 3.66 Hz), 3.97 (1H, d, *J* = 3.66 Hz), 4.01-4.05 (1H, m), 4.12 (1H, dd, *J* = 7.32 Hz & *J* = 3.66 Hz), 4.56 (1H, d, *J* = 3.66 Hz), 5.92 (1H, d, *J* = 3.66 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.05, 22.59, 26.04, 26.17, 26.70, 29.15, 29.30 & 29.68, 31.75, 64.37, 69.73, 70.48, 79.70, 81.94, 83.09, 104.98, 111.69; HR-ESI-TOF-MS *m/z* 355.2083 ([M+Na]$^+$), calcd for $[C_{17}H_{32}O_6+Na]^+$ 355.2091.

General procedure for the synthesis of 4-*C*-hydroxymethyl-l,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose (4a-d)

Solution of 1,2-*O*-isopropylidene-3-*O*-alkyl-D-glucofuranose (**3a-d**, 16 mmol) in THF:H_2O (1:1, 50 ml) was drop-wise added to the stirred solution of sodium periodate (20 mmol) in water (30 ml) at 0 °C and stirred for 1hr, followed by addition of ethylene glycol (1.2 ml). On completion of the reaction, THF and water was evaporated under reduced pressure and the residue left was dissolved in ethyl acetate and filtered. The filtrate was evaporated under reduced pressure. The residue thus obtained was dissolved in 1,4-dioxan (30 ml) and was subjected to continuous stirring. To the stirred solution, formaldehyde (37-41%, 34 mmol) was added followed by the addition of cold 2M aqueous solution of sodium hydroxide (34 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 hr. After completion of the reaction, the reaction mixture was neutralized with formic acid and evaporated to dryness. The residue thus obtained was purified by column chromatography using ethyl acetate: petroleum ether as gradient solvent system to obtain the desired pure products **4a-d**.

4-*C*-Hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-ethyl-*β*-L-*threo*-xylofuranose (4a)[7]

It was obtained as a white solid (3.00 g) in 75 % yield; m.p. 58-62 °C

4-*C*-Hydroxymethyl-l,2-*O*-isopropylidene-3-*O*-butyl-*β*-L-*threo*-xylofuranose (4b)[7]

It was obtained as a white solid (3.25 g) in 74 % yield; m.p. 64-68 °C

4-*C*-Hydroxymethyl-l,2-*O*-isopropylidene-3-*O*-hexyl-*β*-L-*threo*-xylofuranose (4c)

It was obtained as colorless oil (3.45 g) in 71 % yield; R_f = 0.56 (25 % ethyl acetate in petroleum ether, v/v); IR (cm^{-1}, thin film) ν_{max}: 3331, 2969, 2950, 1392, 1225, 1119, 1078, 1015 and 886; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, t, *J* = 7.32 Hz), 1.25-1.34 (9H, m), 1.55-1.61 (5H, m), 2.44 & 2.53 (2H, 2s), 3.47 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.58-3.74 (5H, m), 3.96 (1H, d, *J* = 2.20 Hz), 4.64 (1H, dd, *J* = 4.39 Hz & *J* = 2.20 Hz), 5.99 (1H, d, *J* = 4.39 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.95, 22.48, 25.69, 26.66, 27.24 & 29.49, 31.48, 63.45 & 63.87, 71.01, 85.59, 85.76, 89.77, 104.87, 112.96; HR-ESI-TOF-MS *m/z* 327.1776 ([M+Na]$^+$), calcd for $[C_{15}H_{28}O_6+Na]^+$ 327.1778.

4-*C*-Hydroxymethyl-l,2-*O*-isopropylidene-3-*O*-octyl-*β*-L-*threo*-xylofuranose (4d)

It was obtained as colorless oil (3.66 g) in 69 % yield; IR (cm^{-1}, thin film): 3335, 2971, 2948, 1393, 1225, 1127, 1078, 1015 and 885; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (3H, t, *J* = 7.32 Hz), 1.24-1.34 (13H, m), 1.55-1.61 (5H, m), 2.33 & 2.48 (2H, 2s), 3.64 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.61-3.73 (5H, m), 3.96 (1H, d, *J* = 2.20 Hz), 4.64 (1H, dd, *J* = 4.39 Hz & *J* = 2.20 Hz), 5.99 (1H, d, *J* = 4.39 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.05, 22.60, 26.07, 26.70, 27.30, 29.15, 29.28 & 29.57, 31.74, 63.57 & 64.03, 71.05, 85.70, 85.81, 89.74, 104.90, 113.00; HR-ESI-TOF-MS *m/z* 355.2079 ([M+Na]$^+$), calcd for $[C_{17}H_{32}O_6+Na]^+$ 355.2091.

General procedure for Lipozyme® TL IM catalyzed acetylation of 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-alkyl-*β*-L-*threo*-xylofuranose (4a-d)

A solution of compound **4a / 4b / 4c / 4d** (4.0 mmol) and an equimolar amount of vinyl acetate in dry toluene (30 ml) was incubated with Lipozyme® TL IM (500 mg) at 45 °C and 200 rpm in an incubator shaker. The progress of the reaction was monitored by TLC. On completion, the enzyme was filtered off, the solvent was removed under reduced pressure. The product thus obtained was then purified by column chromatography using a gradient solvent system of ethyl acetate: petroleum ether.

4-*C*-Acetoxymethyl-1,2-*O*-isopropylidene-3-*O*-ethyl-*β*-L-*threo*-xylofuranose (5a)[7]

It was obtained as colorless oil (0.638 g) in 55 % yield

4-*C*-Acetoxymethyl-1,2-*O*-isopropylidene-3-*O*-butyl-*β*-L-*threo*-xylofuranose (5b)[7]

It was obtained as colorless oil (0.874 g) in 69 % yield

4-*C*-Acetoxymethyl-1,2-*O*-isopropylidene-3-*O*-hexyl-*β*-L-*threo*-xylofuranose (5c)

It was obtained as colorless oil (1.04 g) in 75 % yield; IR (cm^{-1}, thin film): 3338, 2982, 1751, 1370, 1224, 1052, 1020 and 895; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (3H, t, *J* = 7.32 Hz), 1.25-1.36 (9H, m), 1.55-1.63 (5H, m), 2.10 (3H, s), 2.40 (1H, brs), 3.45 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.59-3.78 (3H, m), 3.90 (1H, d, *J* = 1.46 Hz), 4.23 (2H, s), 4.63 (1H, dd, *J* = 4.39 Hz & *J* = 1.46 Hz), 6.01 (1H, d, *J* = 4.39 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 13.98, 20.84, 22.51, 25.71, 26.90, 27.38 & 29.50, 31.50, 63.61, 64.47, 71.28, 85.85, 86.08, 87.30, 105.07, 113.52, 170.71; HR-ESI-TOF-MS *m/z* 369.1889 ([M+Na]$^+$), calcd for $[C_{17}H_{30}O_7+Na]^+$ 369.1884.

4-*C*-Acetoxymethyl-1,2-*O*-isopropylidene-3-*O*-octyl-*β*-L-*threo*-xylofuranose (5d)

It was obtained as colorless oil (1.18 g) in 79 % yield; R_f = 0.50 (15 % ethyl acetate in petroleum ether, v/v); IR (cm^{-1}, thin film): 3336, 2981, 2939, 1745, 1374, 1231, 1120, 1047 and 893; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86 (3H, t, *J* = 7.32 Hz), 1.24-1.41 (13H, m), 1.52-1.63 (5H, m), 2.09 (3H, s), 2.38 (1H, brs), 3.45 (1H, dt, *J* = 9.52 Hz & *J* = 6.59 Hz), 3.59-3.80 (3H, m), 3.95 (1H, d, *J* = 1.46 Hz), 4.23 (2H, s), 4.62 (1H, dd, *J* = 3.66 Hz & *J* = 1.46 Hz), 6.01 (1H, d, *J* = 3.66 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 14.07, 20.84, 22.62, 26.04, 26.54, 27.15, 29.20, 29.29 & 29.56, 31.78, 63.15, 64.48, 70.99, 85.86, 86.09, 87.31, 105.10, 113.53, 170.71; HR-ESI-TOF-MS *m/z* 397.2201 ([M+Na]$^+$), calcd for $[C_{19}H_{34}O_7+Na]^+$ 397.2197.

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