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FULL PAPER

Acyl and Benzyl-*C*-β-*D*-Glucosides: Synthesis and Biostudies for Glucose-Uptake Promoting Activity in C2C12 Mytotubes

Mannem Rajeswara Reddy,[a] Shanmugam Hemaiswarya,[b] Harikrishna Kommidi,[a] Indrapal Singh Aidhen,[a]* Mukesh Doble[b]*

Dedication ((optional))

Abstract: A convenient and scalable synthetic approach has been developed for the synthesis of acyl-*C*-β-D-glucosides and benzyl-*C*-β-D-glucosides. The use of Weinreb-amide (WA) functionality was crucial for this accomplishment as the other apparently capable alternatives, had severe limitations for the access to acyl-*C*-glucosides. The synthesized compounds, acyl and benzyl-*C*-glucosides promote glucose-uptake activity in the C2C12 (mouse skeletal muscle) cell lines through PPAR-γ mediated GLUT4 expression. The developed synthetic scheme for acyl-and benzyl-C-*β*-D-glucosides and biostudies evaluating their activity as glucose-uptake promoters are disclosed herein.

Introduction

Glucose uptake is the rate-limiting step in glucose utilization in diabetic and non-diabetic skeletal muscle.[1] Skeletal muscle has major contribution in postprandial glucose uptake which accounts for more than 80% of insulin-dependent glucose disposal in human.[2] The glucose uptake here is the result of the enhanced translocation and redistribution of glucose transporter 4 (GLUT4) from intracellular vesicles to plasma membrane, where it facilitates the entry of the glucose inside the cells.[3] The impairment in the insulin-stimulated translocation of glucose transporters (GLUT4) to cell surface and there by reduced/poor uptake of glucose in the peripheral tissues including skeletal muscle has contributed to the elevated glucose levels. The discovery of natural product, Demethylasterriquinone **1** in 1999 created a sensation of being an excellent insulin mimic.[4] Although it mimicked the action of a protein, it was soon realized that the presence of potentially problematic quinone substructure, therein, posed severe safety concerns. Extensive structure modification by Pirrung and co-workers identified indolylkojic acid **2** as a safer small molecule insulin mimic, in which the quinone in demethylasterriquinone **1** was replaced with kojic acid unit (Figure 1).[5] Further structural variations in 2014, by Mukherjee and co-workers through the introduction of one carbon spacer between indole/substituted-indole/aryl/heteroaryl moiety and kojic acid, represented by structure **3** lead to identification of new molecules promoting glucose-uptake by cells, not necessarily through insulin-initiated pathways.[6] Inspired from structural lead **3**, we envisaged exploring compounds **4/5**, wherein the kojic acid unit present in **2** and **3** has been replaced by non-planer glucosyl residue. Barring the oxidative state of the pyranyl unit, the close similarity in the oxygenation pattern, prompted us to target the synthesis and biological evaluation of compounds **4** and **5** as possible mimics of **2**. Moreover, the proposed acyl-*C*-β-D-glucosides **4** and benzyl-*C*-β-D-glucoside **5** are new molecules in the literature not studied for this objective.

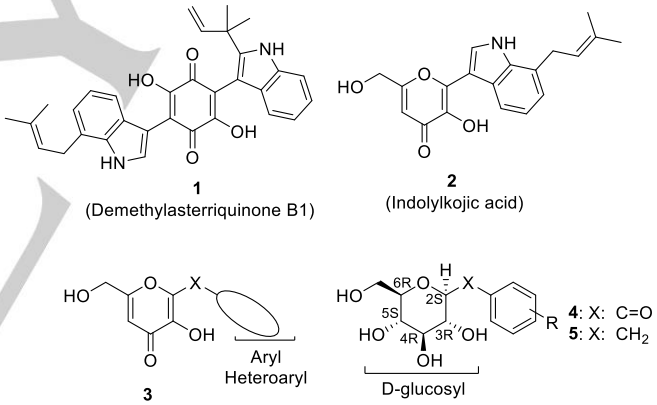

Figure 1. Structure of natural product demethylasterriquinone B1 (**1**), Indolyl kojic acid (**2**), its derivative (**3**) and our proposed molecules **4** and **5.**

Theoretically four disconnections are possible for the synthesis of acyl-*C*-β-D-glucosides (Figure 2). Disconnection I and II visualizes the incorporation of acyl unit at the anomeric center, with D-glucosyl unit appearing either as nucleophile (synthon A) or as an electrophilic unit (synthon B). The synthetic route based on disconnection I demands stringent reaction conditions for the formation of C1-carbanionic organometallic equivalent for the synthon A. Although successful, formation of C1-carbanion is accompanied by elimination of the C-2-benzyloxy group, under basic conditions and poses purification difficulties for the isolation of acyl-*C*-β-D-glucosides.[7] Although there are no reports on direct addition of nucleophilic acyl-unit onto synthon B, Dondoni's work involving addition of benzothiazole as masked formyl anion onto protected lactone (equivalent of synthon B) and also enabling synthesis of acyl-*C*-β-D-glucosides, merits a special mention.[8] Elegantly, the C-2 position of benzothiazole plays a dual role, first

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

as nucleophilic center and later as electrophilic center, for successful synthesis of acyl-*C*-β-D-glucosides. Genuine difficulties and concerns arise from the use of toxic mercury salts for unmasking of the carbonyl functionality, particularly while scaling-up of this method has limitation.[9] No synthetic route is available based on disconnection III, through utilization of synthon C.

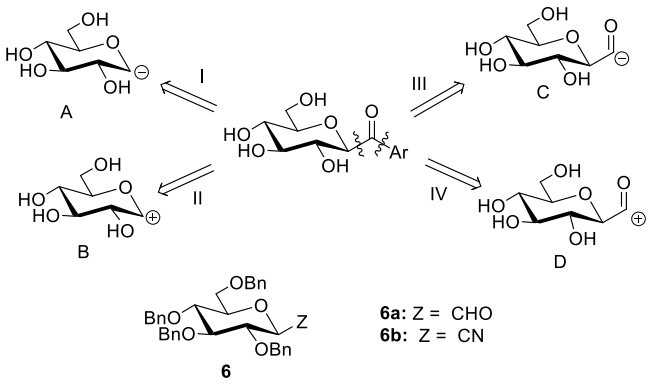


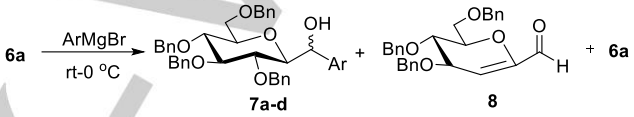
Figure2. Theoretical disconnection for acyl-*C*-β-D-glucosides.

Disconnection IV envisaging use of synthon D seems to be the most attractive, as it demands mere addition of ArMgX onto *C*-1-functionalized D-glucose building blocks such as **6a** or **6b**. The direct addition of the nucleophile on to the 1-formyl-*C*-glycoside building block with D-galacto configuration on glycoside residue at low temperatures (-78 ºC) followed by oxidation has been used for access to acyl-*C*-β-D-galactosides.[10] Similarly, the use of 1-formyl-α-*C*-glucoside has been made in an attempt to access the corresponding 1-acyl-α-*C*-glucosides.[11] Although use of building block **6b** was explored for the same objective by us,[12] with the rationale that low electrophilicity of cyano group (vs CHO) may obviate the elimination side product, successful use of the same has been reported only recently by Guillarme and coworkers.[13] Our observation, parallels with those reported by Guillarme, that the addition of organometallic agents (M= Li or Mg) onto **6b**, is accompanied by formation of the glycal side product. Gong co-workers reported a novel Ni-catalyzed coupling of two electrophilic substrates, viz D-glycosyl bromides and acid derivatives for the synthesis of acyl-*C*-glycoside synthesis.[14] Walczak and co-worker have synthesized acyl-*C*-β-glucosides using stereoretentive cross coupling reaction of glycosyl stannanes and thio esters with palladium catalyst.[15] Although cross-coupling reactions, such as these are emerging for the said objectives, the use of expensive transition metal catalyst and scaling up of the reactions are the associated limitations.The synthesis as well as the biological study assessing glucose-uptake promoting activity of **4** and **5** in C2C12 (mouse skeletal muscle) cell lines is presented herein.

Results and Discussion

The succesful addition of ArMgBr on to 1-formyl-α-*C*-glucoside, and isolated report of addition onto 1-formyl-β-*C*-glucoside,[16] tempted us to use the building block **6a** for the synthesis of our targeted compounds **4** and **5.** Multigram quantities of building block **6a**, 1-formyl-β-*C*-glucoside were prepared according to the method described by Frederic Labeguere.[17] The addition of simple alkynylmagnesium bromide and phenylmagnesium bromide at 0 ºC, led to the formation of corresponding addition products **7a**[9] and **7b**[16] along with recovery of starting material **6a** (10-15%)(entry 1 and 2 in Table 1). However, in an attempt to optimize and generalize the addition of few other Grignard reagents, extensive formation of elimination product **8** was also observed. Lowering of temperature did prevent formation of the side product **8**, however the yields of the addition products**7c** and **7d** was only moderate (entry 3 and 4, in Table 1). All these reactions, when attempted on gram scales, had problems of side product formation and recovery of unreacted started material **6a**.

Table 1. Addition of various Grignard reagents on to the aldehyde **6a.**



Entry	Ar	t	**7** (Yield)[a]	**8** (Yield)	**6a**
1	TMS—	0 ºC-rt	**7a** (68%)	-	10%
2		0 ºC-rt	**7b** (53%)	trace	10%
3	BnO	0 ºC-rt -15 ºC	**7c** (10%) 36%	21% -	-
4	MeO, BnO, OMe	0 ºC-rt -50 ºC	- **7d** (50%)	55% -	-

[a] Isolated

With the above-mentioned unsatisfactory use of aldehyde **6a**, we were intrigued to see, if the Weinreb-amide (WA)-based building block **6c**, as an alternative, would have any advantage. This was with the rationale that its reactivity would be lower compared to **6a** and would be better than nitrile-based building block **6b** (Figure 3).

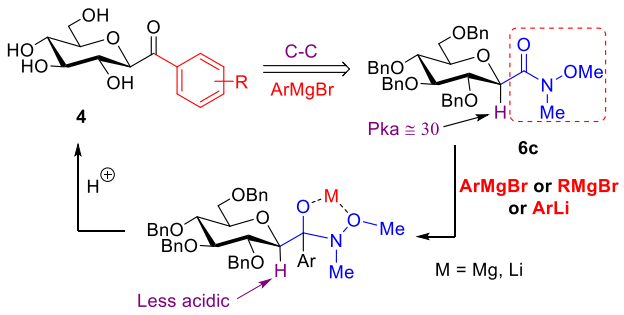
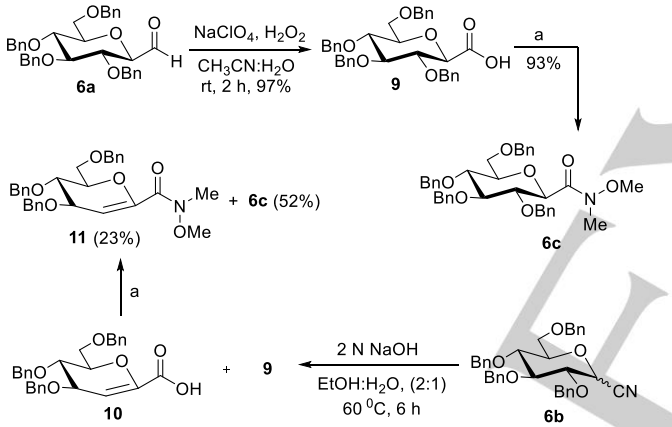


Figure 3. Synthesis of acyl-C-β-D-glucosides from Weinreb amid **6c.**

To our delight, the oxidation of aldehyde **6a**, under Pinnick oxidation reaction with $NaClO_4$,[18] using H_2O_2 as scavenger, afforded the carboxylic acid **9** in quantitative yield and same could be converted to the desired amide **6c** in one pot, with an isolated yield of 93% (Scheme 1). The Weinreb amide-based building **6c** is a light-yellow color gum, bench stable. Multi-grams (10 g) of this WA-based building block can be prepared and stored. The nitrile based building block **6b**, being more readily made compared to aldehyde **6a**, was also explored as a starting material to arrive at WA-amide **6c**. Base hydrolysis of compound **6b** with alcoholic NaOH, resulted in the inseparable mixture of acids **9** and **10.** The inevitable glycal derivative **10** is presumably formed from α-anomer of starting nitrile (or from the corresponding acid) under the basic hydrolysis conditions. The inseparable mixture of acids, **9** and **10** were directly converted to the corresponding amides, with the hope that **6c** and **11** will be separable.[12] Unfortunately, they could be separated only on a small-scale using silica-gel based chromatography. The scale, purification difficulties and low yields of **6c** through this approach prevented any further optimization of this reaction sequence for our needs of **6c** as a building block (Scheme 1).

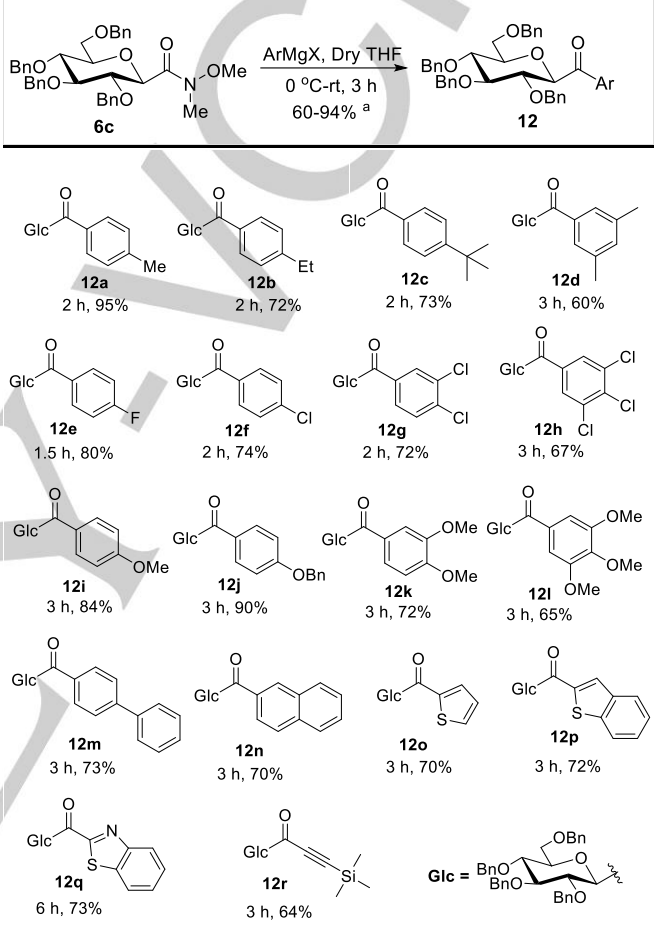


(a) Pivolylchloride, NEt_3, 3 h followed by HCl.NH(Me)(OMe), NEt_3, dry CH_2Cl_2, 3 h, 0 °C-rt

Scheme 1. Synthesis of glucosylated Weinreb amide building block **6c**.

During initial attempts, three equivalents of 4-methylphenylmagnesium bromide was added onto **6c**, at low temperature (-10 °C). It led to the formation of acyl-*C*-β-D-glycoside **12a** in 6 h. The same addition reaction when performed at room temperature, the reaction was completed in 1.5 hours and resulted in the formation of desired product **12a** as a single product. There was no formation of the glycal as the side product. Using these optimized conditions, the amide **6c**,was now subjected to various Grignard reagents. It is noteworthy that Grignard reagents with different substituents on phenyl ring, including electron donating groups, halogens and alkyl substituents, afforded the ketones **12a-12l** in good yields. Moreover, the addition of 4-biphenylmagnesium bromide, 2-naphthylmagnesium bromide and benzothiazol-2-ylmagnesium bromide (2-BTMgBr) onto the amide **6c** also resulted in the formation of corresponding ketone product **12m, 12n** and **12q** respectively in good yields. Even the freshly prepared, 2-lithio derivative of benzo[b]thiphene reacted with amide **6c**, affording the corresponding ketone **12p** in good yields. The building block was equally useful towards addition of alkynyl Grignard reagents, such as ((trimethylsilyl)ethynyl)magnesium bromide, to give expected ketone **12r** in good yield (Table 2).

Table 2. Addition of various organometallic reagents on to the amide **6c**

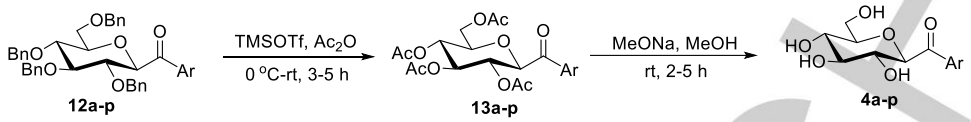


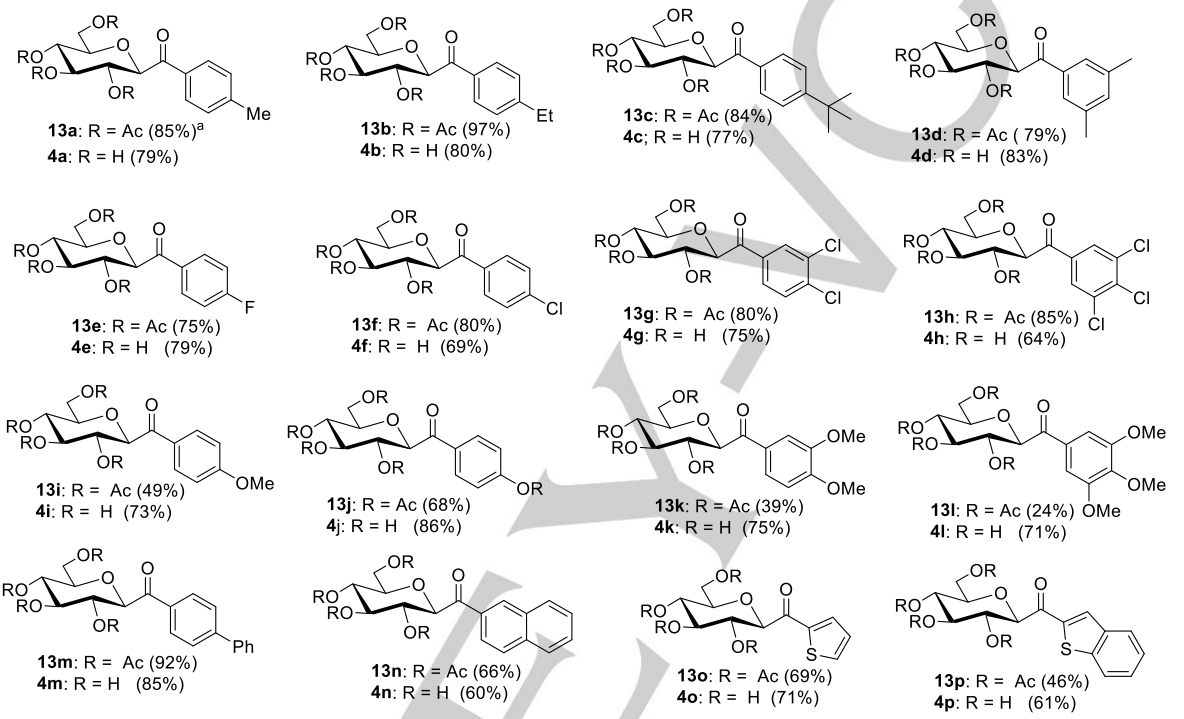
[a] Isolated yield

For the targeted acyl-*C*-β-D-glucoside **4**, removal of the benzyl ether under hydrogenation condition was explored on **12a** as an illustrative example. This condition resulted in removal of benzyl ether as well as concomitant reduction of the carbonyl group too. To circumvent this over reduction, Lewis acid promoted debenzylation was attempted using 10 equivalents of BBr_3 (1 M solution in heptane) in anhydrous dichloromethane as solvent. The desired product **4a** was formed but it was found to be contaminated with inseparable borate impurities. With these difficulties in the background, alternative protocol was explored for debenzylation. The ketone **12a** was treated with TMSOTf (1.5 eq) in presence of acetic anhydride as solvent at 0 °C for 3 h. The reaction afforded the corresponding per-acetyl derivative **13a** in good yield and subsequent deacetylation was easily achieved

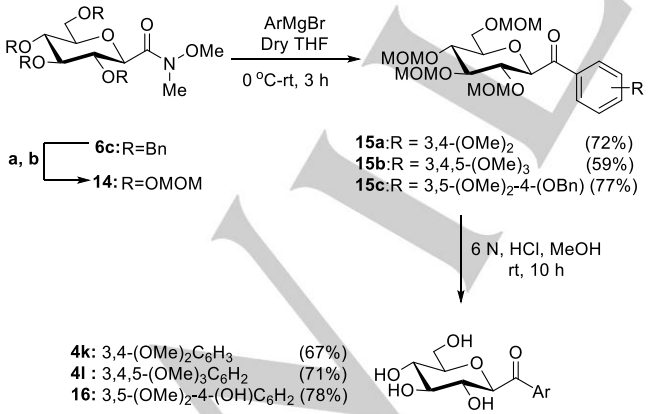
using 0.5 equivalents of sodium methoxide in methanol. The two-step protocol allowed convenient access to acyl-*C*-β-D-glucoside **4a** in good yield. This two steps protocol enabled convenient access to several other acyl-*C*-β-D-glucosides **4b-p** without any epimerization at the anomeric position.(Table3). The di and tri methoxy-substituted substrates **12k** and **12l,** afforded poor yields

Table 3. Acyl-*C*-β-D-glucosides **4a-p** and corresponding per-acetylated compounds **13a-p** from benzyl protected compounds **12a-p.**





[a] Isolated yield



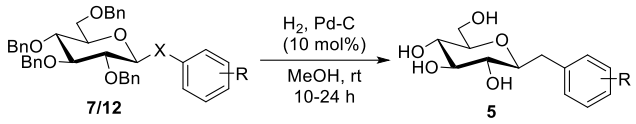
a) H_2, Pd-C (10 mol %), THF, rt, 10 h, 94%, b) MOMCl, DIPEA, dry CH_2Cl_2, TBAI, 0 °C- rt, 72 h, 77%

Scheme 2. Synthesis of methoxy substituted acyl-*C*-β-D-glucosides **4k**, 4**l** and **16.**

of the corresponding per acetylated products **13k** (39%) and **13l (**24%) respectively, using this method. (Table3). The substrate **12q** also decomposed under these reaction condition of debenzylation. Since the methoxy-substituents are important in biological activities, an alternative was necessary for the efficient access to **4k** and **4l** and other methoxy substituted compounds. This was rendered possible by way of changing the benzyl ether protection in building block **6c** to methoxymethyl ether (MOM) protection, since MOM protections can be removed under acidic conditions. The MOM ether protected amide **14** underwent clean addition reaction with methoxy-substituted arylmagnesium bromides to afford the corresponding MOM protected acyl-*C*-β-D-glucoside **15a-c** in good yields. The facile removal of MOM protection in compound **15a** and **15b** with aq. HCl (6 N) afforded the corresponding compounds **4k** and **4l** respectively. With ketone **15c**, the same acidic conditions also enabled additional removal of benzyl ether protection of a phenolic hydroxyl on the aromatic unit, affording **16** as the only isolated product, in.78% yield (Scheme 2).

For our targeted benzyl-*C*-β-D-glucosides, complete reduction of carbonyl group along with the benzyl ether deprotection, in one pot was the most convenient way. The hydrogenation conditions indeed afforded the benzyl-*C*-β-D-glucosides **5a-e** from the corresponding acyl-*C*-β-D-glucosides **12i-l** and **7d** respectively (Table 4).

Table 4. Synthesis of benzyl-*C*-β-D-glucosides **5a-e** using reductive hydrogenolysis.



S.No	**12/7d** (R)	**X**	**5a (R)**	Yield[a]
1	**12i;** R=4-OMe	C=O	**5a** R = 4-OMe	80%
2	**12j:** R =4-OBn	C=O	**5b**: R = 4-OH	93%
3	**12k:** R =3,4-$(OMe)_2$	C=O	**5c:** R = 3,4-$(OMe)_2$	68%
4	**12l:** R=3,4,5-$(OMe)_3$	C=O	**5d:** R = 3,4,5-$(OMe)_3$	87%
5	**7d:** R=3,5-$(OMe)_2$-4-(OBn)	C-OH	**5e:** R= 3,5-$(OMe)_2$-4-(OH)	64%

[a] isolated yield.

Incidentally, the obtainment of product **5b**, and **5e** constitutes the first synthesis of *C*-analogues of natural products, Arbutin[19] and Koarboside.[20] Both are *O*-glucosides, while the former is present in large abundance and is isolated from various sources,[21] displays diverse pharmacological properties, the latter has been recently isolated from the stem bark of *I.difengpi,* known for use in Chinese traditional medicine for rheumatic arthritis. The roots of perennial herb, Averrhoa carambola L. (Oxalidaceae), commonly prevalent in India, China, Malaysia, etc also contains the same, along with other *O*-glycosides.[22]

Biological Studies:

Insulin stimulated glucose (NBDG:2-(N-{7-Nitrobenz-2-oxa-1,3-diazol-4-yl]amino}-2-deoxyglucose) uptake was assessed in differentiated C2C12 myoblasts, after treatment with 5 and 10 μM of acyl and benzyl-*C*-β-D-glucosides,**4a-p**, **16** and **5a-e**, after16h of incubation. The uptake was measured in a fluorescence spectrophotometer and the results are expressed with respect to control (without compound treatment). Pioglitazone and metformin were used as positive control. Few acyl-*C*-β-D-glucosides (**4a-b**, **4e-g** and **4i**) showed high toxicity against the same cell line, as assessed by MTT assay at 10 μM concentration, so their NBDG uptake was evaluated at a non-cytotoxic concentration of 5 μM. At 5 μM, only compounds **4i** and **5a** showed about 1.5 fold increase in NBDG uptake when compared to the control, while other compounds showed no significant effect. Whereas, a significant increase in the NBDG uptake at 10 μM was observed under insulin stimulated conditions. The results are presented in Table 4. The compounds, **5a**, **5b**, **5c** and **5d** in particular exhibited 2.69, 2.7, 2.82 and 2.09 fold increase in glucose uptake, respectively, when compared to the untreated control. Presence of methoxy and hydroxyl groups in the aromatic ring increases the glucose uptake as evident with compounds **5a-5d**. Glucose uptake was marginal when treated with acyl series of glucosides at 10 μM. Among the acyl-*C*-β-D-glucosides evaluated at 10 μM, only three compounds **4c**, **4h** and **4j** showed increase in glucose uptake (1.5-1.87 fold) under insulin stimulated conditions. In sharp contrast to acyl-*C*-β-D-glucosides, 10 μM of lipophilic benzyl-*C*-β-D-glucosides (**5a-e**) showed negligible cytotoxicity and exhibited more than 2 fold increase in the glucose uptake when compared to control (Table 5).

The cytotoxicity associated with the drug, pioglitazone, restricts its use beyond 5 μM concentration and showed 2.6 fold increase in glucose uptake at this concentration. However the synthesized benzyl-*C*-β-D-glucosides were safe even at 10 μM. Pioglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) agonist, is a strong insulin-sensitizing agent. However, several evidences have been raised regarding the safety concerns of this agonist in therapeutics.[23-25] Metformin, a drug commonly used in the management of diabetes, exhibited 1.7 fold NBDG uptake at 600 μM concentration in comparison to untreated control. Studies have shown that metformin is required at high concentrations for *in vitro* responses as compared to that required for therapeutic doses for type 2 diabetic patients. Higher *in vivo* blood glucose lowering effect of metformin could possibly be explained by its accumulation in the muscular extracellular space, or by an effect of the drug at a step distal to that of glucose transport.[26] The effect of the four promising benzyl-*C*-β-D-glucosides, **5a-d,** on the expressions of glucose transporter 4 (GLUT4), peroxisomal proliferator-activated receptors-gamma (PPAR-γ), and phosphoinositide-3-kinase (PI3K) were determined by qPCR in order to elucidate their mechanism of action and compared with two known drugs, metformin and pioglitazone. GLUT4 is an insulin regulated glucose transporter present in the cytoplasm under basal conditions, and on activation by insulin it is translocated to the plasma membrane (Figure 4).

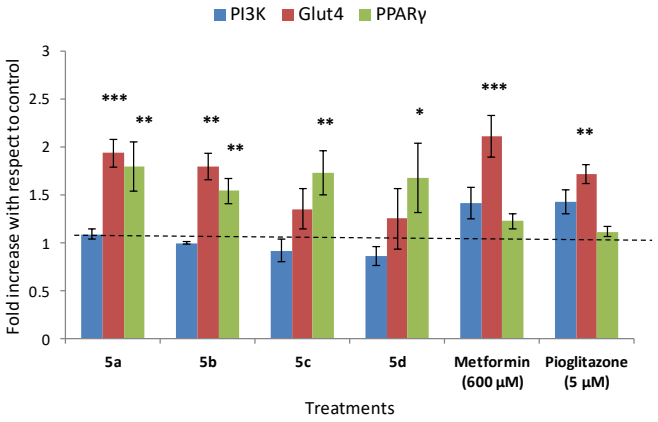


Figure 4: Effect of Compounds **5a**, **5b**, **5c** and **5d** at 10 μM, Metformin (600 μM) and pioglitazone (5 μM) on the expression of PI3K, GLUT4, PPAR-γ gene under insulin stimulated condition. The data was normalized against expression of β-actin transcript. (*p<0.05, **p<0.01, ***p<0.005 when compared to control)**.**

Table 5: Insulin stimulated NBDG uptake and cytotoxycity of acyl-*C*-β-D-glucosides **4a-p**, **16**and benzyl-*C*-β-D-glucosides**5a-e**in C2C12 mytotubes.

Entry	Compound	Fold increase in NBDG uptake compared to control	Percentage cytotoxicity	Fold increase in NBDG uptake compared to control	Percentage cytotoxicity
		5 μM		10 μM	
1	**4a**	1.12±0.07	11.65±0.55	NT	16.59±1.67
2	**4b**	1.06±0.02	18.21±11.9	NT	30.11±4.4
3	**4c**	0.95±0.14	< 1%	1.49±0.29*	6.3±0.69
4	**4d**	0.86±0.06	< 1%	1.18±0.21	9±0.6
5	**4e**	1.00±0.13	10.91±5.14	NT	< 1%
6	**4f**	0.86±0.08	10.47±2.48	NT	< 1%
7	**4g**	1.03±0.11	2.48±1.14	NT	10.44±1.31
8	**4h**	0.99±0.02	< 1%	1.57±0.67	< 1%
9	**4i**	1.42±0.11*	7.28±3.5	NT	16.3±2.62
10	**4j**	0.87±0.13	< 1%	1.87±0.13*	3.77±0.24
11	**4k**	1.10±0.75	< 1%	1.28±0.49	< 1%
12	**4l**	0.99±4.9	< 1%	1.17±0.68	< 1%
13	**4m**	1.07±0.12	2.48±1.14	NT	17.55±1.56
14	**4n**	0.94±0.13	16.99±6.42	NT	12.85±0.95
15	**4o**	0.87±0.07	< 1%	NT	20.21±2.91
16	**4p**	0.99±0.099	11.30±1.31	NT	12.45±1.71
17	**16**	1.12±3.4	< 1%	1.1±0.36	< 1%
18	**5a**	1.48±0.3*	< 1%	2.69±0.09*	< 1%
19	**5b**	1.04±0.09	< 1%	2.70±0.13*	6.08±1.33
20	**5c**	1.02±0.19	< 1%	2.82±0.03*	8.83±2.62
21	**5d**	0.89±0.12	< 1%	2.09±0.49*	< 1%
22	**5e**	1.0±0.08	< 1%	1.86±0.36*	< 1%
23	Metformin	1.7±0.36 (600μM)			
24	Pioglitazone	2.6±0.06** (5μM)			

NT-Not Tested; *P<0.05, **P<0.01

At 10 μM concentration, compound **5a** significantly (2 fold) enhanced the mRNA expression of GLUT4, followed by compound **5b** (1.8 fold). Metformin and pioglitazone caused a 2.11 and 1.71 fold increase in GLUT4 expression when compared to β-actin expression (house keeping gene). On the other hand, PI3K is a downsignaling molecule in the insulin cascade which is known to enhance glucose uptake through GLUT4 mRNA expression and translocation. None of the compounds caused significant changes in the PI3K mRNA expression, while the commercial drugs increased its expression by 1.4 fold. Compounds **5a, 5b, 5c** and **5d** enhanced glucose uptake by increasing PPAR-γ mRNA expression by approximately 1.6 to 1.7 fold in comparison to the insulin treated control. PPARs are known to interact with the peroxisome proliferator element (PPRE) in the promoter region of the target genes involved in lipid catabolism, fatty acid transport, and glucose homeostasis.Here pioglitazone did not show an effect in the PPAR-γ mRNA expression levels which has been proved true in previous studies.[27,28] Pioglitazone the known ligand for the protein PPAR-γ, upon binding, upregulates GLUT4, mediated glucose uptake.[29]

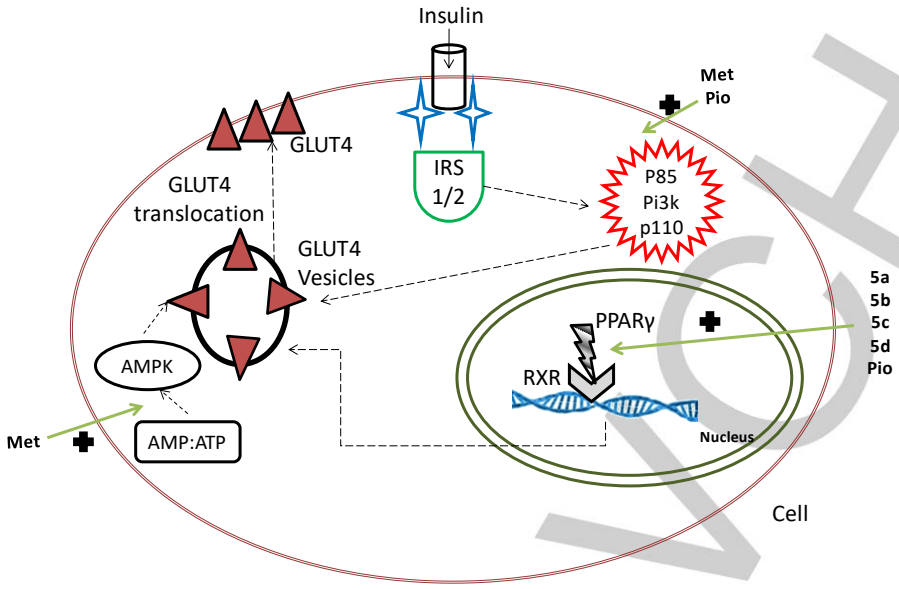


Figure 5. Proposed mechanism of action of compounds **5a**, **5b**, **5c** and **5d** based on mRNA expression of PI3K, GLUT4 and PPARγ genes. The compounds enhance NBDG uptake through PPAR-γ mediated increase in GLUT4 expression. Pioglitazone (Pio) acts through PPAR-γ mediated and metformin (Met) through AMPK mediated increase in GLUT4 expression. + means increase in expression.

Metformin on the other hand is known to enhance glucose uptake by GLUT4 via the AMPK pathway.[30] Although, we have observed an increase in PI3K mRNA expression with metformin and pioglitazone, as also reported by others,[31,32] the same was not observed with our set of compounds (**5a-d**). The gene expression studies are in corroboration with NBDG uptake, where the compounds **5a**, **5b**, **5c** and **5d** seems to act through PPAR-γ mediated enhancement of GLUT4 expression (Figure 5).

Conclusions

Finally, to conclude, we have developed a convenient synthetic route for the synthesis of acyl and benzyl-*C*-β-D-glucosides on multi gram scale, using a key building block, carrying Weinreb-amide functionality at anomeric position of D-Glucose. The initial biostudies reveal benzyl-*C*-β-D-glucosides **5a-e** being far superior in promoting glucose uptake at 10 µM, when compared to the corresponding acyl-*C*-β-D-glucosides. The studies further indicate that benzyl-*C*-glucosides **5a-e** enhance glucose uptake through PPAR-γ mediated enhancement of GLUT4 expression. The efficacy of the compounds **5a-e** needs to be further ascertained using *in vivo* animal models, for their possible development as new antidiabetic lead substances.

Experimental Section

2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(benzyloxy)phenyl)-D-glycero-D-gulo-heptitol 7c:

The oven dried two necked round bottom flask was charged with magnesium turnings (0.26 g, 10.86 mmol) and a catalytic amount of molecular iodine was added under nitrogen atmosphere. The reaction flask was pre-heated under vacuum to activate the magnesium.4-(benzyloxy)phenyl bromide (1.42 g, 5.43 mmol) in anhydrous THF was added into the activated magnesium under stirring. To that solution, 1,2-dibromoethane (0.81 mL, 5.43 mmol) was added at 50 °C, and heating was continued until the complete consumption of magnesium.After complete consumption of magnesium, the requisite aldehyde **6a**(1.0 g, 1.81 mmol) in anhydrous THF was added to the reaction mixture at 0 °C. After 3 h, saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product obtained was purified by silica-gel column chromatography to yield the alcohol **7c** (0.48 g, 36.0%) as colorless gum. R_f = 0.5 (EtOAc/ hexanes, 1:4); $[\alpha]^{25}_D$ =38.4 (c 0.5, $CHCl_3$);^{1}H NMR: (400 MHz, $CDCl_3$)**;** δ = 3.38 (d, J = 9.5 Hz,1 H),3.45-3.47 (m,1 H), 3.61-3.64 (m, 1 H), 3.65 (s, 2 H),3.71-3.75 (m, 1 H), 3.78-3.83 (m, 1 H), 4.42-4.48 (m, 2 H), 4.57 (d,J = 11.0 Hz,1 H), 4.74-4.77 (m, 1 H), 4.81-4.86 (m, 2 H), 4.91-4.93 (m, 3 H), 4.95 (s, 2 H),6.87-6.90 (m, 2 H), 7.18-7.19 (m, 2 H), 7.26-7.31 (m, 21 H), 7.36-7.37 (m, 2 H), 7.39-7.41 (m, 2 H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$); δ = 69.0 (CH_2), 70.0 (CH-OH), 70.9 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.6 (CH_2), 78.2 (CH), 78.6 (CH), 78.7 (CH), 81.5 (CH), 87.2 (CH), 114.5 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (2xCH), 127.9 (CH), 128.4 (CH), 128.5 (2xCH), 128.5 (CH), 128.6 (CH), 134.6 (C), 137.1 (C), 138.1 (2xC),138.2 (C), 138.6 (C), 153.3 (C) ppm.IR ($CHCl_3$): 1118, 1421, 1526, 2896, 2957, 3388 cm^{-1}. HRMS: Calcd for $C_{48}H_{49}O_7$ $[M+H]^+$737.3478, found 737.3363.

2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,5-(dimethoxy)-4-(benzyloxy)phenyl)-D-glycero-D-gulo-heptitol 7d:

The oven dried two necked round bottom flask was charged with magnesium turnings (0.35 g, 13.5 mmol) and a catalytic amount of molecular iodine was added under nitrogen atmosphere. The reaction flask was pre-heated under vacuum to activate the magnesium. 4-(benzyloxy)-3,5-dimethoxyphenyl bromide (4.38 g, 13.5 mmol.) in

anhydrous THF was added into the activated magnesium under stirring. To that solution, catalytic amount of MeI was added at 50 °C, and heating was continued until the color change of the reaction mixture. After complete consumption of magnesium, the requisite aldehyde **6a** (1.5 g, 2.71 mmol) in anhydrous THF was added to the reaction mixture at -50°C. After 3 h, saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product obtained was purified by silica-gel column chromatography to yield the corresponding alcohol **7d** (1.09 g, 50.0%) as light yellow color gum. R_f **=** 0.3 (EtOAc/ hexanes, 3:7); $[\alpha]^{25}_D$ **=**82.3 (c 0.5, $CHCl_3$);^{1}H NMR: (400 MHz, $CDCl_3$)**;** δ = 3.41 (d, *J* = 9.6 Hz, 1 H), 3.51 (d, *J* = 8.8 Hz, 1 H), 3.65-3.68 (m, 3 H), 3.97 (s, 6 H), 3.75-3.82 (m, 3 H), 4.45 (s, 2 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 4.72 (d, *J* = 11.2 Hz, 1 H), 4.82-4.89 (m, 2 H), 4.93-4.96 (m, 4 H), 6..64 (s, 2 H), 7.17-7.19 (m, 3 H), 7.27-7.32 (m, 21 H), 7.46-7.48 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 56.1 (CH_3), 69.0 (CH_2), 71.3 (CH-OH), 73.5 (CH_2), 75.0 (CH_2), 75.1 (CH_2), 75.3 (CH_2), 75.6 (CH_2), 78.2 (CH), 78.6 (CH), 78.7 (CH), 81.5 (CH), 87.2 (CH), 103.6 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.5 (2xCH), 128.6 (CH), 136.0 (C), 137.8 (C), 137.9 (C), 138.0 (C), 138.1 (2xC), 138.5 (C), 153.3 (C) ppm.IR ($CHCl_3$): 1118, 1421, 1526, 2896, 2957, 3388 cm^{-1}. HRMS: Calcd for $C_{50}H_{52}O_9Na$ $[M+Na]^+$819.3509, found 819.3485.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(*N*-methoxy-*N*-methyl)-aldehydo-D-glycero-D-gulo-heptose (6c) from aldehyde 6a:

Step 1: Into a round bottom flask with aldehyde **6a** (9.5 g, 17.2 mmol) in acetonitrile (60 mL) was added NaH_2PO_4 (1.8 g) and H_2O_2 (0.48 mL, 20.6 mmol) at rt. To the reaction mixture, a solution of sodium chlorite in water (2.16 g, 24.1 mmol, 24 mL) was added at 0 °C for 30 min slowly. The reaction was allowed to stir at rt for 3 h and then a solution of sodium sulfite was added. Finally, the reaction was quenched with 10% HCl and then aqueous layer was extracted with ethyl acetate (3x200 mL), the organic layer was dried over Na_2SO_4, concentrated under reduced pressure to yield the acid **9** (9.6 g, 97.8 %). The resultant acid **9** was used for next step without further purification.

Step 2: An oven dried round bottom flask was charged with acid **9** (9.5 g, 16.7 mmol) in anhydrous CH_2Cl_2 followed by pivaloyl chloride (2.6 mL, 21.7 mmol) and triethyl amine (3.62 mL, 25.0 mmol)) at 0 ° C for 10 min. The reaction mixture was warmed to rt and stirred for 3 h. Then, *N, O*-dimethylhydroxlamine hydrochloride (2.44 g, 25.0 mmol) and triethylamine (1.5 equiv.) were added slowly at 0 °C, and the mixture was stirred for 3 h at rt. The reaction mixture was quenched with water. The organic layer was extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica, eluting with ethyl acetate:hexanes, to give the title compound **6c**.(9.5 g , 93%) as light yellow viscous gum. R_f = 0.27 (EtOAc/Hexanes, 1:4); $[\alpha]^{25}_D$ **=** 86.6 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.14 (s, 3 H, *NCH*$_3$), 3.44-3.55 (m, 2 H), 3.57 (s, 3 H, *OCH*$_3$), 3.61-3.72 (m, 2 H), 3.94 (t, *J* = 9.6 Hz, 1 H), 4.29 (d, *J* = 9.6 Hz, 1 H), 4.38-4.51 (m, 3 H), 4.61 (d, *J* = 10.8 Hz, 1 H), 4.72 (t, *J* = 8.0 Hz, 2 H,), 4.83 (d, *J* = 11.2 Hz, 2 H,), 7.02-7.12 (m, 2 H, ArH), 7.12-7.20 (m, 9 H), 7.20-7.38 (m, 10 H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$); δ = 32.2 (*NCH*$_3$), 62.1 (*OCH*$_3$), 69.1 (CH_2), 73.4 (CH_2), 74.1 (CH), 75.1 (CH_2), 75.2 (CH_2), 75.6 (CH), 78.0 (CH), 79.5 (CH), 79.7 (CH), 86.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.48 (CH), 138.0 (C), 138.3 (C), 138.5 (C), 168.7 (-CO-) ppm. IR ($CHCl_3$): 1216, 1421, 1526, 1656, 2896, 3988 cm^{-1}. HRMS: Calcd for $C_{37}H_{42}NO_7$ $[M+H]^+$ 612.2961, found 612.2966.

General procedure A for the addition of Grignard reagents on to Amide 6c:

The oven dried two necked round bottom flask was charged with magnesium turnings (3 equiv.) and a catalytic amount of molecular iodine was added under nitrogen atmosphere. The reaction flask was pre-heated under vacuum to activate the magnesium. Substituted aryl bromide (3 equiev.) in anhydrous THF was added into the activated magnesiumunder stirring. After complete consumption of magnesium, the requisite amide **6c** (1 equiv.) in anhydrous THF was added to the reaction mixture at 0 °C. After 3 h, saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The product obtained was purified by silica-gel column chromatography to yield the corresponding ketones.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(methyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12a):

Building block **6c** (0.6 g, 0.98 mmol), magnesium turnings (0.08 g, 3.92 mmol) and 4-bromotoluene (0.49 ml, 3.9 mmol) were treated according to the general procedure A to give the title compound 36a, after column chromatography on silica gel to provide **12a** (0.59 g, 94.9 %), as a colorless solid. R_f **=** 0.5 (EtOAc/ hexanes, 1:4); m.p. = 86-88 °C; $[\alpha]^{25}_D$ **=** 12.6 (c 0.5, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 3.58-3.65 (m, 3 H), 3.78 (t, *J* = 8.8 Hz , 1 H,), 3.96 (t, *J* = 9.2 Hz,1 H), 4.45 (d, *J* = 8.8 Hz, 2 H), 4.51 (dd, *J* = 10.8, 8.8 Hz, 2 H), 4.58 (d, *J* = 9.6 Hz, 1 H), 4.64 (d, *J* = 10.4 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 1 H), 4.85 (bs, 2 H), 6.89-6.94 (m, 2 H), 7.08-7.15 (m, 5H), 7.17-7.30 (m, 13 H), 7.35 (t,*J* = 8.0 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz,2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.1 (CH_2), 73.5 (CH_2), 75.1 (CH_2), 75.3 (CH_2), 75.8 (CH_2), 78.1 (CH), 79.0 (CH), 79.0 (CH), 79.7 (CH), 80.1 (CH), 87.1 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 129.4 (CH), 133.6 (CH), 136.0 (C), 137.8 (C), 138.2 (C), 138.5 (C), 195.0 (CO) ppm.IR ($CHCl_3$):1355, 1421, 1526, 1701, 3018 cm^{-1}. HRMS:Calcd for $C_{42}H_{43}O_6$ $[M+H]^+$ 643.3060, found 643.3038.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(ethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12b):

Building block **6c** (0.530 g, 0.866 mmol), magnesium turnings (0.104 g, 4.33 mmol), 1-bromo-4-ethylbenzene (0.801 g, 4.33 mmol) were treated according to the general procedure A to give the title compound **12b** (0.4g, 72%), after column chromatography on silica gel as a colorless solid; R_f **=** 0.7 (EtOAc/hexanes, 1:4); m.p = 77-79 °C; $[\alpha]^{27}_D$ **=** 1.79°(c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.26 (t, 3 H), 2.70 (q, 2 H), 3.67-3.70 (m, 3 H), 3.76 (d, *J* = 10.0 Hz, 1 H), 3.85 (t, *J* = 8.8 Hz1 H,), 4.02 (t, *J* = 9.2 Hz, 1 H), 4.49-4.57 (m, 3 H), 4.60 (d, *J* = 10.8 Hz, 1 H), 4.69 (d, *J* = 10.4 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.89-4.96 (m, 2 H), 6.96-6.98 (d, *J* = 7.2 Hz, 1 H), 7.15-7.34 (m, 20 H), 8.00 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$);δ = 15.2 (CH_3), 29.0 (CH_2), 69.1 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 78.0 (CH), 78.8 (CH), 79.7 (CH), 79.9 (CH), 87.0 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.6 (CH), 133.6 (C), 137.7 (C), 137.9 (C), 138.1 (C), 138.5 (C), 150.7 (C), 194.6 (CO) ppm. IR ($CHCl_3$)**:** 1266, 1421, 1526, 17698, 3018 cm^{-1}. Elemental analysis**:**calcd (%) for $C_{43}H_{44}O_6$ (656.31): C 78.63, H 6.75; found: C 78.42, H 6.27.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(tetr-butyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12c):

Building block **6c** (0.6 g, 0.98 mmol), magnesium turnings (0.118 g, 4.9 mmol), 1-bromo-4-tert-butylbenzene (0.98 g, 4.9 mmol) were treated according to general procedure A to give the title compound **12c** (0.49 g, 73%), after column chromatography on silica gel as a colorless solid; R_f **=** 0.7 (EtOAc/hexanes, 1:4); m.p = 78-80 °C; $[\alpha]^{27}_D$**=** -53.4 (c 0.3, $CHCl_3$); ^{1}H

NMR (500 MHz, $CDCl_3$); δ = 1.33 (s, 9 H, $C(CH_3)_3$), 3.67-3.71 (m, 3 H), 3.77 (d, *J* = 10.0 Hz, 1 H), 3.85 (t, *J* = 8.5 Hz, 1 H), 4.0 (t, *J* = 9.5 Hz, 1 H), 4.50-4.57 (m, 3 H), 4.56 (t, *J* = 11.0 Hz, 1 H), 4.64 (d, *J* = 11.0 Hz, 1 H), 4.68 (d, *J* = 10.5 Hz, 1 H), 4.85 (d, *J* = 10.5 Hz, 1 H), 4.90-4.95 (m, 2 H), 6.9-6.97 (m, 2 H), 7.14-7.34 (m, 18 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 8.0 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$);δ = 31.0 (3 x CH_3), 35.1 (CH), 69.0 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.7 (CH_2), 78.0 (CH), 79.0 (CH), 79.7 (CH), 80.0 (CH), 87.0 (CH), 125.5 (CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 133.3 (C), 137.7 (C), 137.9 (C), 138.2 (C), 138.5 (C), 157.3 (C), 194.5 (CO) ppm. IR ($CHCl_3$): 1202, 1456, 1562, 1688, 2998 cm^{-1}. Elemental analysis: calcd (%) for $C_{45}H_{48}O_6$ (684.8): C 78.92, H 7.06; found: C 79.23, H 7.20.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,5-(dimethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12d):

Building block **6c** (0.6 g, 0.98 mmol), magnesium turnings (0.164 g, 6.86 mmol), 1-bromo-3,5-dimethylbenzene (0.67 g, 4.9 mmol) were treated according to the general procedure A to give the title compound **12d** (0.38 g, 60%), after column chromatography on silica gel as a colorless solid**.** R_f = 0.7 (EtOAc/hexanes 1:4); m.p = 84-86 °C; $[\alpha]^{27}_D$= 66.2 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 2.31 (s, 6 H), 3.67-3.70 (m, 3 H), 3.76 (d, *J* = 10.0 Hz, 1 H), 3.85 (t, *J* = 8.8 Hz, 1 H), 4.02 (d, *J* = 9.2 Hz, 1 H), 4.50-4.57 (m, 3 H), 4.59 (t, *J* = 10.8 Hz, 1 H), 4.64 (d, *J* = 9.6 Hz, 1 H), 4.69 (d, *J* = 10.0 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.89-4.95 (m, 2 H), 6.98-6.99 (m, 2 H), 7.17-7.20 (m, 6 H), 7.24-7.33 (m, 13 H), 7.6 (s, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$);δ = 21.0 (2xCH_3), 69.0 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.7 (CH_2), 78.0 (CH), 79.0 (CH), 79.9 (CH), 80.0 (CH), 87.0 (CH), 127.0 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 135.3 (CH), 136.1 (CH), 137.7 (C), 137.9 (C), 138.1 (C), 138.2 (2xC), 138.5 (C), 195.6 (CO) ppm. IR ($CHCl_3$): 1196, 1413, 1523, 1696, 2996 cm^{-1}.Elemental analysis:calcd (%) for $C_{43}H_{44}O_6$ (656.8): C 78.63, H 6.75; found: C 78.81, H 6.98.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(fluoro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12e):

Building block **6c** (0.45 g, 0.74 mmol), magnesium turnings (0.09 g, 3.68 mmol) and 1-bromo-4-fluro benzene (0.40 mL, 3.68 mmol) were treated according to the general procedure A to give the title compound **12e** (0.38 g, 79.8%), after column chromatography as a colorless solid. R_f =0.5 (EtOAc/ hexanes, 1:4); m.p = 77-79 °C; $[\alpha]^{25}_D$=12.1 (c 0.5, $CHCl_3$); All spectroscopic data for our synthetic molecule (^{1}H, ^{13}C, HRMS) were well in agreement with those reported for the same.[15]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(chloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12f):

Building block **6c** (0.53 g, 0.87 mmol), magnesium turnings (0.103 g, 4.33 mmol) and 1-bromo-4-chloro benzene (0.83 mL, 4.33 mmol) were treated according to the general procedure A to give the title compound **12f (**0.42 g, 73.7%), after column chromatography on silica as a colorless solid. R_f = 0.4 (EtOAc/ hexanes, 1:4); m.p = 75-77 °C; $[\alpha]^{25}_D$=6.1 (c 0.5, $CHCl_3$);All spectroscopic data for our synthetic molecule (^{1}H, ^{13}C, HRMS) were well in agreement with those reported for the same.[15]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,4-(dichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12g):

Building block **6c** (0.50 g, 0.866 mmol), magnesium turnings (0.097 g, 4.05 mmol), 1-bromo-3,4-dichlorobenzene (0.52 g, 4.05 mmol) were treated according to the general procedure A to give the title compound **12g**, after column chromatography on silica gel (0.41g, 72%) as a colorless solid. R_f = 0.7 (EtOAc/hexanes, 1:4); m.p = 77-79 °C; $[\alpha]^{27}_D$= 4.13 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.63-3.71 (m, 3 H), 3.74 (d, *J* = 9.2 Hz, 1 H), 3.84 (t, *J* = 8.4 Hz, 1 H), 3.95 (t, *J* = 9.2 Hz, 1 H), 4.48-4.53 (m, 3 H), 4.56 (d, *J* = 10.8 Hz, 1 H), 4.60 (d, *J* = 10.8 Hz, 1 H), 4.74 (d, *J* = 10.4 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.93 (s, 2 H), 7.0-7.02 (m, 2 H), 7.18-7.34 (m, 18 H), 7.4 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 8.10 (d, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$);δ = 68.8 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 77.8 (CH), 79.2 (CH), 79.5 (CH), 79.8 (CH), 86.9 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 130.6 (CH), 131.2 (CH), 133.2 (C), 135.0 (C), 137.4 (C), 137.8 (C), 137.9 (C), 138.1 (C), 138.3 (C), 192.9 (CO) ppm. IR ($CHCl_3$): 1092, 1422, 1528, 1710, 3021 cm^{-1}. Elemental analysis:calcd (%) for $C_{41}H_{38}Cl_2O_6$ (697.6): C 70.59, H 5.49; found: C 70.28, H 5.06.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,4,5-(trichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12h):

To an oven dried two necked round bottom flask was charged with magnesium turning (0.14 g, 5.88 mmol), under nitrogen atmosphere. 1-bromo-3,4,5-trichlorobenzene (1.28 g, 4.9 mmol) in anhydrous THF was added into the activated magnesium. To that solution 1,2-dibromoethane (0.09 mL, 098 mmol) was added at 50 ºC, heating was continued until the complete consumption of magnesium. Building block **6c** (0.5 g, 1.13 mmol) in anhydrous THF was added to reaction mixture. After 3h saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc, the organic layer was dried over Na_2SO_4 and concentrated in vacuum. The crude residue was purified by column chromotography on silica gel to yield title compound **12h** (0.48g, 67%) as color less solid. R_f = 0.8 (EtOAc/hexanes, 1:4); m.p = 101-103 °C; $[\alpha]^{27}_D$= 98.6 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.62-3.72 (m, 4 H), 3.83 (t, *J* = 8.8 Hz, 1 H), 3.92 (t, *J* = 9.2 Hz, 1 H), 4.43 (d, *J* = 9.6 Hz, 1 H), 4.58-4.60 (m, 4 H), 4.75 (d, *J* = 10.8 Hz, 1 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 4.93 (s, 2 H), 7.04-7.19 (m, 7 H), 7.2-7.32 (m, 13 H), 7.9 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 68.6 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 77.8 (CH), 79.0 (CH), 79.8 (CH), 80.1 (CH), 86.9 (CH), 127.7 (CH), 127.8 (2xCH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 134.6 (C), 134.7 (2xC), 136.7 (C), 137.3 (C), 137.8 (C), 138.2 (C), 191.9 (CO) ppm. IR ($CHCl_3$):1088, 1496, 1566, 1722, 3078 cm^{-1}Elemental analysis:calcd (%) for $C_{41}H_{37}Cl_3O_6$ (730.17): C 67.27, H 5.09; found: C 67.34, H 4.66.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(methoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12i):

Building block **6c** (0.7 g, 1.14 mmol), magnesium turnings (0.14 g, 5.72 mmol) and 1-bromo-4-methoxy benzene (0.72 mL, 5.72 mmol) were treated according to the general procedure A to give the title compound **12i**, after column chromatography on silica gel to provide the title compound (0.63 g, 84%). as a colorless solid. R_f = 0.3 (EtOAc/ hexanes, 1:4); m.p = 66-68 °C; $[\alpha]^{25}_D$=17.1 (c 0.5, $CHCl_3$); All spectroscopic data for our synthetic molecule (^{1}H, ^{13}C, HRMS) were well in agreement with those reported for the same.[15]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(benzyloxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12j):

Building block **6c** (0.5 g, 1.17 mmol), magnesium turnings (0.168 g, 7.02 mmol) and 1-bromo-4-benzyloxy benzene (1.23 mL, 7.02 mmol) were treated according to the general procedureA, to give the title compound **12j**, after column chromatography on silica gel to provide the title

compound (0.539 g, 90%). as a colorless solid. R_f = 0.3 (EtOAc/ hexanes, 1:4); m.p = 82-84 ºC; $[\alpha]^{25}_D$ = 37.1 (c 0.3, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.65-3.77 (m, 2 H), 3.74 (d, *J* = 10.4 Hz, 1 H), 3.84 (t, *J* = 8.8 Hz, 1 H), 4.02 (t, *J* = 9.6 Hz,1 H), 4.49 (d, *J* = 12.0 Hz, 1 H), 4.54 (d, *J* = 10.4 Hz, 1 H), 4.56-4.67 (m, 3 H), 4.69 (d, *J* = 10.8 Hz, 1 H),), 4.84 (d, *J* = 10.8 Hz, 1 H), 4.89-4.92 (m, 2 H), 4.99 (d, *J* = 10.4 Hz, 1 H), 5.10 (s, 2 H), 6.95 (d, *J* = 9.2 Hz, 2 H), 6.99-7.01 (m, 2 H), 7.15-7.20 (m, 6 H), 7.25-7.28 (m, 8 H), 7.31-7.35 (m, 4 H), 7.36-7,41 (m, 5H), 8.05 (d, *J* = 8.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 69.2 (CH_2), 70.2 (CH_2), 73.5 (CH_2), 75.7 (CH_2), 78.1 (CH), 79.1 (CH), 79.8 (CH), 80.1 (CH), 87.1 (CH), 114.6 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 131.8 (C), 136.2 (C), 137.9 (C), 138.1 (C), 138.3 (C), 138.6 (C), 163.1 (C), 193.4 (CO) ppm. IR ($CHCl_3$):1119, 1460, 1570, 1689, 2934 cm^{-1}. Elemental analysis:calcd (%) for $C_{48}H_{46}O_7$ (734.89): C 78.45, H 6.31; found: C 78.93, H 5.90.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,4-(dimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12k):

Building block **6c** (0.7 g, 1.64 mmol), magnesium turnings (0.157 g, 6.55 mmol) and 1-bromo-3,4-dimethoxy benzene (0.95 mL, 6.55 mmol) were treated according to the general procedure A to give the title compound **12k** (0.83 g, 71.67%), after column chromatography on silica gel as a light brown color solid. R_f = 0.3 (EtOAc/ hexanes, 2:3); m.p = 88-90 ºC; $[\alpha]^{25}_D$ = -48.6 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.67-3.70 (m, 3 H), 3.77 (d, *J* = 10.0 Hz, 1 H), 3.86 (s, 3 H), 3.91-3.94 (s, 5 H), 4.03 (t, *J* = 9.2 Hz, 1 H), 4.52 (d, *J* = 4.8 Hz, 1 H), 4.56-4.61 (m, 3 H), 4.71 (d, *J* = 10.4 Hz, 1 H), 4.86 (d, *J* = 10.4 Hz, 1 H), 4.93-4.94 (m, 2 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 7.02-7.11 (m, 3 H), 7.12-7.21 (m, 5 H), 7.28-7.34 (m, 12 H), 7.62 (d, *J* = 1.2 Hz, 1 H), 7.74 (dd, *J* = 8.0, 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 55.9 (OCH_3), 56.1 (CH_3), 69.1 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 78.0 (CH), 79.1 (CH), 79.8 (CH), 80.0 (CH), 87.0 (CH), 110.0 (CH), 111.1 (CH), 124.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (2xCH), 128.4 (CH), 128.5 (CH), 129 0 (C), 134.2 (C), 137.8 (C), 137.9 (C), 138.1 (C), 138.5 (C), 148 (C), 153.7 (C), 193.3 (CO) ppm. IR ($CHCl_3$: 1120, 1460, 1570, 1689, 2934, 3020 cm^{-1}. Elemental analysis:calcd (%) for $C_{43}H_{44}O_8$ (688.3): C 74.98, H 6.44; found: C 75.30, H 6.53.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(3,4,5-(trimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12l):

A oven dried two necked round bottom flask was charged with magnesium turnings (0.078 g, 3.3 mmol) and catalytic amount of molecular iodine under nitrogen atmosphere. 1-bromo-3, 4, 5-trimethoxybenzene (0.81 g, 3.3 mmol) in anhydrous THF was added into the activated magnesium. To that solution catalytic amount of MeI was added at 50 ºC, and heating was continued until the colour change of the reaction mixture. After complete consumption of magnesium, building block**6c** (0.5 g, 0.82 mmol) in anhydrous THF was added to reaction mixture. After 3 h saturated NH_4Cl solution was added and the aqueous layer was extracted with EtOAc, the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel to give the title compound **12l** (0.38 g, 65.2%) as colorless solid. R_f = 0.3 (EtOAc:hexanes, 3:7); m.p = 98-100 ºC; $[\alpha]^{26}_D$ = 97.5(c 1.0, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$);δ = 3.74 (m, 3 H), 3.82 (s, 6 H, 2 × OCH_3), 3.86-3.95 (m, 2 H), 3.97 (s, 3 H, *OCH_3*), 4.09 (t, *J* = 9.6 Hz, 1 H), 4.55-4.70 (m, 5 H), 4.79 (d, *J* = 10.8 Hz, 1 H), 4.91-5.00(m, 3 H), 7.10-7.16 (m, 2 H), 7.24-7.28 (m, 5 H), 7.30-7.44 (m, 15 H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$); δ = 56.2, 61.0, 69.1, 73.6, 75.0, 75.2, 75.9, 78.0, 79.7, 80.0, 80.2, 87.0, 106.9, 127.82, 127.86, 127.95, 127.98, 128.0, 128.1, 128.3, 128.5, 128.6, 137.8, 137.9, 138.0, 138.4, 143.0, 153.0, 193.7 ppm. IR ($CHCl_3$): 1120, 1480, 1568, 1663, 2936, 3010 cm^{-1}. HRMS: Calcd for $C_{44}H_{47}O_9$ $[M+H]^+$ 719.3220, found 719.3224.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(phenyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (12m):

Building block **6c** (0.52 g, 0.85 mmol), magnesium turnings (0.108 g, 4.25 mmol), 4-bromobiphenyl (0.99 g, 4.25 mmol) were treated according to the general procedure in A to give the title compound **12m** (0.43g, 73%), after column chromatography on silica gel as a colorless solid; R_f = 0.6 (EtOAc/hexanes, 1:4); m.p = 110-112 ºC; $[\alpha]^{27}_D$= 3.89 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.69-3.70 (m, 3 H), 3.78 (d, *J* = 10.5 Hz, 1 H), 3.87 (t, *J* = 8.5 Hz, 1 H), 4.04 (t, *J* = 9.5 Hz, 1 H), 4.50-4.62 (m, 4 H), 4.68 (d, *J* = 9.5 Hz, 1 H), 4.72 (d, *J* = 10.5 Hz, 1 H), 4.86 (d, *J* = 10.5 Hz, 1 H), 4.91-4.96 (m, 2 H), 6.9-7.0 (m, 2 H), 7.15-7.16 (m, 3 H), 7.19-7.21 (m, 2 H), 7.25-7.43 (m, 14 H), 7.47-7.49 (m, 2 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.63 (d, *J* = 8.5 Hz, 2 H), 8.14 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$)**;**δ = 69.0 (CH_2), 73.4 (CH_2), 75.0 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 78.0 (CH), 79.1 (CH), 79.7 (CH), 80.0 (CH), 87.0 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.9 (CH), 134.6 (C), 137.7 (C), 137.9 (C), 138.1 (C), 138.5 (C), 139.8 (C), 146.2 (C), 194.5 (CO) ppm. IR ($CHCl_3$):1120, 1480, 1568, 1663, 2936, 3010 cm^{-1}. Elemental analysis:calcd (%) for $C_{47}H_{44}O_6$ (704.8): C 80.09, H 6.29; found: C 80.30, H 5.90.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(naphthalen-2-yl)-aldehydo-D-glycero-D-gulo-heptose (12n):

Building block **6c** (0.58 g, 0.95 mmol), magnesium turnings (0.114 g, 4.73 mmol), 2-bromonapthalane (0.98 g, 4.73 mmol) were treated according to the general procedure in A to give the title compound **12n** (0.45g, 70%), after column chromatography on silica gel as a colorless solid. R_f = 0.5 (EtOAc/hexanes, 1:4); m.p = 98-100 ºC; $[\alpha]^{27}_D$ = -78.6 (c 0.3, $CHCl_3$); All spectroscopic data for our synthetic molecule (^{1}H, ^{13}C, HRMS) were well in agreement with those reported for the same.[15]

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(2-thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (12o):

Building block **6c** (0.51 g, 0.83 mmol), magnesium turnings (0.1 g, 4.16 mmol) and 2-bromothiophene (0.40 mL, 4.16 mmol) were treated according to the general procedure A to give the title compound **12o** (0.37 g, 70%), after column chromatography on silica gel as a brown color solid. R_f = 0.3 (EtOAc/ hexanes, 1:4); m.p = 72-74 ºC; $[\alpha]^{25}_D$ = 8.4(c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.51-3.58 (m, 1 H). 3.61-3.71 (m, 3 H), 3.75 (t, *J* = 8.8 Hz, 1 H), 3.87 (t, *J* = 9.6 Hz, 1 H), 4.43 (d, *J* = 6.8 Hz, 2 H), 4.47 (d, *J* = 8.8 Hz, 2 H,), 4.50-4.55 (m, 1H), 4.58 (d, *J* = 10.0 Hz, 1 H), 4.77 (d, *J* = 10.8 Hz, 1 H), 4.84 (ABq, *J* =11.2, 6.0 Hz, 2 H), 6.94-7.01 (m, 3 H), 7.09-7.14 (m, 5 H), 7.17-7.28 (m, 13 H), 7.57- 7.61 (m, 1 H,), 7.86 - 7.88 (m, 1 H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$); δ = 68.9 (CH_2), 73.5 (CH_2), 75.2 (CH_2), 75.3 (CH_2), 75.8 (CH_2), 77.8 (CH), 79.7 (CH), 80.1 (CH), 81.1 (CH), 86.7 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.37 (CH), 128.4 (CH), 128.5 (CH), 134.5 (CH), 134.9 (CH), 137.5 (C), 138.0 (C), 138.1 (C), 138.5 (C), 142.5 (C), 188.4 (CO) ppm. IR ($CHCl_3$);1345, 1434, 1524, 1711, 2094 cm^{-1}. HRMS: Calcd for $C_{39}H_{39}O_6S$ $[M+H]^+$: 635.2467, found 635.2450.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(2-benzo[b]thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (12p):

To an oven dried round bottom flask was charged with 2-benzo[b]thiophene (0.65 g, 4.9 mmol) in anhydrous THF (8 mL) at room temperature. The flask was allowed to cool at -60 ºC, n-BuLi (1.96 mL, 2.5 M in hexane) was added to the solution and stirred for 1 h at same temperature. To the reaction mixture, building block **6c** (0.6 g, 0.98 mmol)

was added and stirring was continued at 0 °C for 3 h. Then, reaction mixture was diluted with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel to give the title compound **12p** (0.48 g, 71.7%) as a colorless solid. R_f = 0.8 (EtOAc/hexanes, 1:4);m.p = 104-106 °C; $[\alpha]^{27}_D$ = -93.6 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 3.65-3.80 (m, 4 H), 3.85 (t, *J* = 8.8 Hz, 1 H), 3.99 (t, *J* = 9.2 Hz, 1 H), 4.51-4.60 (m, 4 H), 4.62-4.67 (m, 2 H), 4.88 (d, *J* = 11.2 Hz, 1 H), 4.93-4.97 (m, 2 H), 7.01-7.11 (m, 5 H), 7.21-7.24 (m, 2 H), 7.29-7.37 (m, 14 H), 7.44-7.48 (m, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 8.2-8.4 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 68.9 (CH_2), 73.5 (CH_2), 75.1 (CH_2), 75.2 (CH_2), 75.8 (CH_2), 77.8 (CH), 79.6 (CH), 80.1 (CH), 81.3 (CH), 86.7 (CH), 122.8 (CH), 124.9 (CH), 126.4 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 131.9 (CH), 137.3 (C), 137.9 (C), 138.1 (C), 138.4 (C), 139.1 (C), 141.7 (C), 142.7 (C), 189.9 (CO) ppm. IR ($CHCl_3$); 1421, 1578, 1711, 2094, 3010 cm^{-1}. HRMS:Calcd for $C_{43}H_{40}O_6SNa$ $[M+Na]^+$707.2443, found 707.2448.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(2-benzo[d]thiozole)-aldehydo-D-glycero-D-gulo-heptose (12q):

A dried two necked round bottom flask was charged with magnesium turnings (0.085 g, 3.464 mmol) and a catalytic amount of I_2 was added. The flask was pre-heated under vacuum to activate the magnesium and anhydrous THF (25 mL) was added. At stirring isopropylbromide (0.325 mL, 3.46 mmol) was added slowly, after 5 min the mixture was strongly self-heated As the magnesium turnings were finished, benzo[d]thiazole (0.285 mL, 2.6 mmol) was added to the reaction mixture at 0 °C slowly and stirring was continued for 30-45 min at the same temperature. To the resulting yellow color precipitation was added amide **6c** (0.53 g, 0.866 mmol) in anhydrous THF for 15 min at 0 °C, and the solution was warmed to rt, allowed to stir 6 h at same temperature. The solution was diluted with cold aq. NH_4Cl solution, aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layer was washed with brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexanes, 1:3) affording the ketone **12q (**0.246 g, 73.2%) as the light-yellow color gum. R_f = 0.5 (EtOAc/hexanes, 1:4); $[\alpha]^{27}_D$ =-39.7 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 3.74-3.75 (m, 4 H), 3.92-3.95 (m, 1 H), 4.08 (t, *J* = 9.5 Hz, 1 H), 4.47-4.51 (m, 2 H), 4.57-4.62 (m, 2 H), 4.75 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 10.5 Hz, 1 H), 4.92 (s, 2 H), 5.32 (d, *J* = 10.0 Hz, 1 H), 6.87-6.89 (m, 2 H), 6.99-7.02 (m, 2 H), 7.18-7.19 (m, 2 H), 7.23-7.32 (m, 15 H), 7.56-7.57 (m, 1 H), 7.96-7.97 (m, 1 H), 8.20-8.21 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 68.8 (CH_2), 73.5 (CH_2), 74.9 (CH_2), 75.1 (CH_2), 75.6 (CH_2), 77.5 (CH), 78.0 (CH), 80.0 (CH), 80.1 (CH), 86.7 (CH), 122.3 (CH), 126.0 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 137.5 (C), 138.0 (C), 138.1 (C), 138.4 (C), 153.5 (C), 165.0 (C), 190.0 (CO) ppm. IR ($CHCl_3$); 1421, 1578,1614, 1702, 2112, 2968, 3010 cm^{-1}. HRMS: Calcd for $C_{42}H_{40}O_6NS$ $[M+H]^+$ 686.2576, found 686.2595.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-trimethylsilylethynyl-aldehydo-D-glycero-D-gulo-heptose (12r):

(Trimethylsilyl)ethynyl]magnesiumbromide was prepared from magnesium turnings (0.069 g, 2.88 mmol),ethylbromide (0.219 mL, 2.88 mmol) and trimethylsilyl acetylene (0.282 mL, 2.88 mmol according to the reported procedure. To this solution,the building block **6c** (0.430 g, 0.72 mmol) in anhydrous THF (4 mL) was added for 15 min at 0 °C, and the solution was allowed to stir 3 h at 0 °C. The solution was diluted with cold aq. NH_4Cl solution, aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic layer was washed with brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting yellow color residue was purified by column chromatography on silica gel (EtOAc/hexanes, 85:15 then 1:4) affording the title compound **12r (**0.298 g, 63.9%) as a colorless solid. R_f = 0.7 (EtOAc/hexanes 1:4); m.p = 98-100 °C; $[\alpha]^{27}_D$ =-113.1 (c 0.3, $CHCl_3$); All spectroscopic data for our synthetic molecule (^{1}H, ^{13}C, HRMS) were well in agreement with those reported for the same.[8]

General procedure B for the synthesis of per acetylated compounds 13a-p:

An oven dried round bottom flask was charged with compound **12a-p** (1 equiv.) in acetic anhydried (8 mL, for 1 mmol) at room temperature. To that solution, trimethylsilyl trifluoromethanesulfonate (1.5 equiv.) was added at 0 °C, slowly. Then the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was diluted with H_2O, dropwise, and extracted with EtOAc. The combined organic layer was washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant crude product was purified by column chromatography on silica gel (EtOAc/hexanes) to afford the peracetylated compound **13a-p**.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(methyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13a):

Compound **12a** (0.44 g, 0.68 mmol), trimethylsilyl trifluoromethanesulfonate (0.187 mL, 1.03 mmol), acetic anhydried (7 mL) were treated according to the general procedure in B to give the title compound **13a** (0.26 g, 84.6%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 110-112°C; $[\alpha]^{27}_D$ = -98.3 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.84 (s, 3 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.42 (3 H), 3.89-3.92 (m, 1 H), 4.17 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.23 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.72 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 10.0 Hz, 1 H), 5.35 (t, *J* = 9.5 Hz, 1 H), 5.49 (t, *J* = 9.5 Hz, 1 H), 7.27 (d, *J* = 8.5 Hz, 2 H), 7.89 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.8 (CH_3), 62.2 (CH_2), 68.2 (CH), 69.0 (CH), 74.3 (CH), 76.7 (CH), 77.8 (CH), 129.3 (CH), 129.5 (CH), 132.5 (C), 145.1 (C), 169.0 (C), 169.4 (C), 170.5 (C), 170.6 (C), 190.5 (C). IR ($CHCl_3$): 1284, 1568, 1662, 1668, 2956, 2996 cm^{-1}; HRMS**:**Calcd for $C_{22}H_{26}O_{10}Na$ $[M+Na]^+$ 473.1423, found 473.1419.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(ethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13b):

Compound **12b** (0.35 g, 0.532 mmol), trimethylsilyl trifluoromethanesulfonate (0.144 mL, 0.79 mmol), acetic anhydried (6 mL) were treated according to the general procedure in B to give the title compound **13b** (0.24 g, 97.2%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 135-137 °C; $[\alpha]^{27}_D$= -103.9 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.26 (t, *J* = 8.0 Hz, 3 H), 1.84 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.72 (q, *J* = 8.0 Hz, 2 H), 3.89-3.93 (m, 1 H), 4.15 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.24 (dd, *J* = 12.4, 5.6 Hz, 1 H), 4.74 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 10.0 Hz, 1 H), 5.36 (t, *J* = 9.2 Hz, 1 H), 5.50 (t, *J* = 9.6 Hz, 1 H), 7.30 (d, *J*= 8.0 Hz, 2 H), 7.91 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$); δ = 15.2 (CH_3), 20.4 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 29.0 (CH_2) ppm. 62.2 (CH_2), 68.2 (CH), 68.9 (CH), 74.2 (CH), 76.6 (CH), 77.6 (CH), 128.1 (CH), 129.5 (CH), 132.6 (C), 151.2 (C), 168.9 (C=O), 169.4 (C=O), 170.5 (C+O), 170.6 (C=O), 191.4 (C=O) ppm. IR ($CHCl_3$): 1479, 1589, 1662, 1663, 2889, 2996 cm^{-1}. Elemental analysis:calcd (%) for $C_{23}H_{28}O_{10}$ (464.47): C 59.48, H 6.08; found: C 60.01, H 5.87.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(tetr-butyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13c):

Compound **12c** (0.45 g, 0.657 mmol), trimethylsilyl trifluoromethanesulfonate (0.18 mL, 0.985 mmol), acetic anhydried (8 mL) were treated according to the general procedure B to give the title compound **13c** (0.27 g, 83.6%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 150-152°C; $[\alpha]^{27}_D$= -129.0 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.34 (s, 9 H), 1.84 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 3.89-3.93 (m, 1 H), 4.15 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.25 (dd, *J* = 12.4, 5.6 Hz, 1 H), 4.74 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 10.0 Hz, 1 H), 5.36 (t, *J* = 9.2 Hz, 1 H), 5.50 (t, *J* = 9.6 Hz, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 31.0 (3xCH_3), 35.2 (C), 62.2 (CH_2), 68.1 (CH), 68.9 (CH), 74.2 (CH), 76.6 (CH), 77.6 (CH), 125.6 (CH), 129.3 (CH), 132.2 (C), 157.9 (C), 169.0 (C), 169.4 (C), 170.5 (C), 170.6 (C), 191.4 (CO) ppm. IR ($CHCl_3$):1248, 1556, 1648, 1689, 2876, 2986 cm^{-1}; Elemental analysis:calcd (%) for $C_{25}H_{32}O_{10}$ (492.52): C 60.97, H 6.55; found: C 61.32, H 6.05.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(3,5-(dimethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13d):

Compound **12d** (0.34 g, 0.51 mmol), trimethylsilyl trifluoromethanesulfonate (0.141 mL, 0.77 mmol), acetic anhydried (6 mL) were treated according to the general procedure B to give the title compound **13d** (0.19 g, 79.2%), after column chromatography on silica gel as a colorless solid. *R*$_f$ = 0.3 (EtOAc/hexanes, 3:7); m.p = 160-162°C; $[\alpha]^{27}_D$ = -69.0 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.82 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.38 (6 H), 3.89-3.94 (m, 1 H), 4.16 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.23 (dd, *J* = 12.4, 1.6 Hz, 1 H), 4.76 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 9.6 Hz, 1 H), 5.36 (t, *J* = 9.2 Hz, 1 H), 5.47 (t, *J* = 9.6 Hz, 1 H), 7.24 (s, 1 H), 7.58 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.3 (2xCH_3), 62.3 (CH_2), 68.1 (CH), 69.0 (CH), 74.2 (CH), 76.6 (CH), 77.5 (CH), 127.0 (CH), 135.0 (C), 135.7 (CH), 138.3 (2xC), 168.9 (C), 169.4 (C), 170.5 (C), 170.6 (C), 192.2 (CO) ppm. IR ($CHCl_3$): 1368, 1569, 1652, 1692, 2898, 3012 cm^{-1}; Elemental analysis:calcd (%) for $C_{23}H_{28}O_{10}$ (464.47): C 59.48, H 6.08; found: C 59.74, H 5.84.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(fluoro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13e):

Compound **12e** (0.15 g, 0.23 mmol), Trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.347 mmol), aceticanhydried (3 mL) were treated according to the general procedure B to give the title compound **13e** (0.079 g, 75%), after column chromatography on silica gel as a colorless solid. R_f = 0.2 (EtOAc/hexanes, 3:7); m.p = 129-131 °C; $[\alpha]^{27}_D$=78.6 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.88 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 3.89-3.92 (m, 1 H), 4.16 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.23 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.83 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 10.0 Hz, 1 H), 5.35 (t, *J* = 9.5 Hz, 1 H), 5.48 (t, *J* = 9.5 Hz, 1 H), 7.15 (t, *J* = 8.5 Hz, 2 H), 8.04 (dd, *J* = 8.5, 5.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 62.2 (CH_2), 68.1 (CH), 68.8 (CH), 74.0 (CH), 76.7 (CH), 78.1 (CH), 115.8 (d, *J*= 21.8 Hz, CH), 131.2 (C), 132.1 (d, *J* = 9.5 Hz, CH), 166.2 (d, *J* = 252.8 Hz, C), 168.9 (C), 169.3 (C), 170.4 (C), 170.5 (C), 190.4 (CO) ppm. Elemental analysis:calcd (%) for $C_{21}H_{23}FO_{10}$ (454.4): C 55.51, H 5.10; found: C 55.96, H 4.69.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(chloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13f):

Compound **12f** (0.37 g, 0.558 mmol), trimethylsilyl trifluoromethanesulfonate (0.152 mL, 0.347 mmol), acetic anhydried (6 mL) were treated according to the general procedure B to give the title compound **13f** (0.21 g, 80.16%), after column chromatography on silica gel as a colorless solid. R_f = 0.2 (EtOAc/hexanes, 3:7); m.p = 131-133 °C; $[\alpha]^{27}_D$ = -26.3 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.89 (s, 3 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.08 (s, 3 H), 3.89-3.92 (m, 1 H), 4.16 (dd, *J* = 12.5, 2.5 Hz, 1 H), 4.23 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.66 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.16 (t, *J* = 10.0 Hz, 1 H), 5.35 (t, *J* = 9.5 Hz, 1 H), 5.47 (t, *J* = 9.5 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.94 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 62.2 (CH_2), 68.1 (CH), 68.8 (CH), 74.0 (CH), 76.7 (CH), 78.2 (CH), 128.9 (CH), 130.7 (CH), 133.1 (C), 140.5 (C), 168.9 (C), 169.3 (C), 170.4 (C), 170.5 (C), 190.9 (CO) ppm. IR ($CHCl_3$):1186, 1526, 1645, 1692, 2878, 2983 cm^{-1}. Elemental analysis:calcd (%) for $C_{21}H_{23}ClO_{10}$ (470.86): C 53.57, H 4.92; found: C 53.96, H 4.60.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(3,4-(dichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13g):

Compound **12g** (0.36 g, 0.517 mmol), trimethylsilyl trifluoromethanesulfonate (0.140 mL, 0.820 mmol), acetic anhydried (6 mL) were treated according to the general procedure B to give the title compound **13g** (0.21 g, 80.45%), after column chromatography on silica gel as a colorless solid. R_f = 0.2 (EtOAc/hexanes, 3:7); m.p = 136-138 °C; $[\alpha]^{27}_D$ = 93.2 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.93 (s, 3 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.11 (s, 3 H), 3.90-3.93 (m, 1 H), 4.19-4.20 (m, 2 H), 4.60 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.15 (t, *J* = 9.6 Hz, 1 H), 5.35 (t, *J* = 9.6 Hz, 1 H), 5.46 (t, *J* = 9.2 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 8.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 62.1 (CH_2), 67.9 (CH), 68.7 (CH), 73.8 (CH), 76.7 (CH), 78.7 (CH), 128.9 (CH), 130.7 (CH), 131.4 (CH), 133.2 (C), 134.1 (C), 138.7 (C), 169.0 (C), 169.4 (C), 170.4 (C), 170.5 (C), 190.1 (CO) ppm. IR ($CHCl_3$): 996, 1552, 1664, 1702, 2896, 3016 cm^{-1}. Elemental analysis:calcd (%) for $C_{21}H_{22}Cl_2O_{10}$ (505.30): C 49.92, H 4.39; found: C 49.50, H 3.96.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(3,4,5-(trichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13h):

Compound **12h** (0.43 g, 0.587 mmol), trimethylsilyl trifluoromethanesulfonate (0.196 mL, 0.88 mmol), acetic anhydried (6 mL) were treated according to the general procedure B to give the title compound **13h**, after column chromatography on silica gel (0.27 g, 85.17%) as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 146-148 °C; $[\alpha]^{27}_D$ = -123.5 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.95 (s, 3 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.13 (s, 3 H), 3.90-3.93 (m, 1 H), 4.18-4.19 (m, 2 H), 4.54 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 5.15 (t, *J* = 10.0 Hz, 1 H), 5.34 (t, *J* = 9.2 Hz, 1 H), 5.43 (t, *J* = 9.6 Hz, 1 H), 8.02 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 62.1 (CH_2), 67.9 (CH), 68.7 (CH), 73.8 (CH), 76.9 (CH), 79.2 (CH), 129.3 (CH), 133.7 (C), 134.9 (2xC), 137.4 (C), 169.1 (C), 169.4 (C), 170.4 (C), 170.6 (C), 189.4 (CO) ppm. IR ($CHCl_3$):1022, 123, 1668, 1692, 3016 cm^{-1}. HRMS:Calcd for $C_{21}H_{21}Cl_3O_{10}Na$ $[M+Na]^+$ 561.0098, found 561.0098.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(methoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13i):

Compound **12i** (0.720 g, 1.09 mmol), trimethylsilyl trifluoromethanesulfonate (0.296 mL, 1.638 mmol), acetic anhydried (10 mL) were treated according to the general procedure B to give the title compound **13i** (0.25 g, 49.1%), after column chromatography on silica gel

as a colorless solid. R_f = 0.4 (EtOAc/hexanes, 2:3); m.p = 107-109 °C; $[\alpha]^{27}_D$ = 46.7 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.78 (s, 3 H), 1.94 (s, 3 H), 1.98 (s, 3 H), 1.99 (s, 3 H), 3.80 (s, 3 H, OMe), 3.82-3.85 (m, 1 H), 4.08 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.17 (dd, *J* = 12.5, 5.5 Hz, 1 H), 4.65 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.08 (t, *J* = 10.0 Hz, 1 H), 5.28 (t, *J* = 9.5 Hz, 1 H), 5.41 (t, *J* = 9.5 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 7.95 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 55.5 (CH3, OMe), 62.2 (CH_2), 68.2 (CH), 69.0 (CH), 74.2 (CH), 76.5 (CH), 77.6 (CH), 113.8 (CH), 127.9 (C), 131.7 (CH), 164.2 (C), 168.9 (C), 169.4 (C), 170.4 (C), 170.5 (C), 190.2 (CO) ppm. IR ($CHCl_3$):1186, 1526, 1648, 1690, 2878, 3012 cm^{-1}. Elemental analysis:calcd (%) for $C_{22}H_{26}O_{11}$ (466.44): C 56.65, H 5.62; found: C 57.09, H 5.38.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(4-(acetoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13j):

Compound **12j** (0.5 g, 0.68 mmol), trimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.36 mmol), acetic anhydried (8 mL) were treated according to the general procedure B to give the title compound **13j** (0.23 g, 68.45%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 2:3); m.p = 129-131°C; $[\alpha]^{27}_D$ = 56.8(c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.86 (s, 3 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 2.33 (3 H), 3.89-3.93 (m, 1 H), 4.15 (dd, *J* = 12.4, 2.4 Hz, 1 H), 4.23 (dd, *J* = 12.4, 7.6, Hz 1 H), 4.71 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.15 (t, *J* = 10.0 Hz, 1 H), 5.35 (t, *J* = 9.2 Hz, 1 H), 5.48 (t, *J* = 9.6 Hz, 1 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 8.03 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 21.2 (CH_3), 62.3 (CH_2), 68.2 (CH), 68.9 (CH), 74.2 (CH), 76.7 (CH), 77.9 (CH), 121.9 (CH), 131.0 (CH), 132.5 (C), 155.0 (C), 168.7 (C), 169.0 (C), 169.4 (C), 170.5 (C), 170.6 (C), 190.7 (CO) ppm. IR ($CHCl_3$)**:** 1216, 1568, 1668, 1716, 2996, 3018 cm^{-1}. HRMS:Calcd for $C_{23}H_{26}O_{12}Na$ $[M+Na]^+$517.1322, found 517.1318.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(3,4-(dimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13k):

Compound **12k** (0.25 g, 0.363 mmol), trimethylsilyl trifluoromethanesulfonate (0.1 mL, 0.544 mmol), acetic anhydried (4 mL) were treated according to the general procedure B to give the title compound **13k** (0.07 g, 39.0%), after column chromatography on silica gel as a colorless solid. *R*$_f$ = 0.3 (EtOAc/hexanes, 1:1): m.p = 150-152 °C; $[\alpha]^{27}_D$ = -86.2 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.87 (s, 3 H), 2.03 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 3.89-3.91 (m, 1 H), 3.93 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 4.15 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.26 (dd, *J* = 12.0, 5.0, Hz 1 H), 4.73 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.17 (t, *J* = 9.5 Hz, 1 H), 5.36 (t, *J* = 9.5 Hz, 1 H), 5.51 (t, *J* = 9.5 Hz, 1 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 7.55 (d, *J* = 1.5 Hz, 1 H), 7.65 (dd, *J* = 8.0, 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 56.1 (CH_3, OMe), 56.2 (CH_3, OMe) 62.3 (CH_2), 68.3 (CH), 69.1 (CH), 74.3 (CH), 76.7 (CH), 77.7 (CH), 109.9 (CH), 111.3 (CH), 124.3 (CH), 128.1 (C), 149.3 (C), 154.2 (C), 169.0 (C), 169.4 (C), 170.5 (C), 170.6 (C), 190.3 (CO) ppm. IR ($CHCl_3$): 1126, 1568, 1656, 1692, 2896, 3018 cm^{-1}. HRMS:Calcd for $C_{23}H_{28}O_{12}Na$ $[M+Na]^+$519.1478, found 519.1466.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(3,4,5-(trimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13l):

Compound **12l** (0.12 g, 0.167 mmol), trimethylsilyl trifluoromethanesulfonate (0.043 mL, 0.25 mmol), acetic anhydried (3 mL) were treated according to the general procedure B to give the title compound **13l** (0.021 g, 24.2%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 157-159°C; $[\alpha]^{27}_D$ = 183.7 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$); δ = 1.88 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 3.91 (s, 7 H, 2xOMe), 3.92 (s, 3 H, OMe), 4.13 (dd, *J* = 12.4, 2.0 Hz, 1 H), 4.27 (dd, *J* = 12.4, 5.6 Hz Hz, 1 H),4.71 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.15 (t, *J* = 10.0 Hz, 1 H), 5.36 (t, *J* = 9.2 Hz, 1 H), 5.49 (t, *J* = 9.6 Hz, 1 H), 7.27 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (2xCH_3), 56.5 (2xOMe), 61.07 (OMe), 62.1 (CH_2), 68.3 (CH), 69.1 (CH), 74.2 (CH), 76.7 (CH), 77.9 (CH), 107.2 (CH), 129.9 (C), 153.1 (C), 169.0 (C), 169.4 (C), 170.5 (2xC), 190.6 (CO) ppm. IR ($CHCl_3$): 1142, 1526, 1656, 1698, 2889, 2996 cm^{-1}. HRMS:Calcd for $C_{24}H_{30}O_{13}Na$ $[M+Na]^+$ 549.1584, found 549.1578.

2,6-Anhydro-3,4,5,7-tetra-*O*-benzyl-1-*C*-(4-(phenyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (13m):

Compound **12m** (0.35 g, 0.496 mmol), trimethylsilyl trifluoromethanesulfonate (0.165 mL, 0.744 mmol), acetic anhydried (5 mL) were treated according to the general procedure B to give the title compound **13m** 0.235 g, 92.5%), after column chromatography on silica gel as a colorless solid. R_f = 0.2 (EtOAc/hexanes, 3:7); m.p = 163-165 °C; $[\alpha]^{27}_D$ = -183.7 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 1.87 (s, 3 H), 2.04 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 3.92-3.96 (m, 1 H), 4.18 (dd, *J* = 12.4, 2.4 Hz, 1 H), 4.26 (dd, *J* = 12.4, 5.6 Hz, 1 H), 4.78 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.18 (t, *J* = 9.6 Hz, 1 H), 5.38 (t, *J* = 9.2 Hz, 1 H), 5.53 (t, *J* = 9.6 Hz, 1 H), 7.41-7.44 (m, 1 H), 7.47-7.50 (m, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2 H), 8.14 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 62.2 (CH_2), 68.1 (CH), 68.9 (CH), 74.1 (CH), 76.7 (CH), 77.8 (CH), 127.2 (CH), 127.3 (CH), 128.5 (CH), 129.0 (CH), 129.9 (CH), 133.5 (C), 139.6 (C), 146.7 (C), 169.0 (C), 169.4 (C), 170.5 (C), 170.6 (C), 191.4 (CO) ppm. IR ($CHCl_3$):1526, 1664, 1698, 2869, 2998 cm^{-1}. Elemental analysis:calcd (%) for $C_{27}H_{28}O_{10}$ (512.51): C 63.28, H 5.51; found: C 63.13, H 5.06.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(naphthalen-2-yl)-aldehydo-D-glycero-D-gulo-heptose (13n):

Compound **12n** (0.57 g, 0.84 mmol), trimethylsilyl trifluoromethanesulfonate (0.23 mL, 1.26 mmol), acetic anhydried (8 mL) were treated according to the general procedure B to give the title compound **13n** (0.27 g, 66.3%), after column chromatography on silica gel as a colorless solid. *R*$_f$ = 0.3 (EtOAc/hexanes, 3:7); m.p = 138-140 °C; $[\alpha]^{27}_D$ = -64.4 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.81 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 3.97-4.01 (m, 1 H), 4.18 (dd, *J* = 12.5, 2.5 Hz, 1 H), 4.26 (dd, *J* = 12.0, 5.5 Hz, 1 H), 4.90 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.19 (t, *J* = 9.5 Hz, 1 H), 5.41 (t, *J* = 9.5 Hz, 1 H), 5.55 (t, *J* = 10.0 Hz, 1 H), 7.56-7.59 (m, 1 H), 7.62-7.65 (m, 1 H), 7.88-7.91 (m, 2 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 8.01 (dd,*J* = 8.5, 2.0 Hz, 1 H), 7.91 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.4 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 62.3 (CH_2), 68.3 (CH), 69.1 (CH), 74.2 (CH), 76.7 (CH), 77.8 (CH), 124.4 (CH), 127.0 (CH), 127.8 (CH), 128.5 (CH), 129.0 (CH), 129.7 (CH), 131.5 (CH), 132.2 (C), 132.3 (C), 135.9 (C), 168.9 (C), 169.3 (C), 170.5 (C), 170.6 (C), 191.8 (CO) ppm. IR ($CHCl_3$): 1511, 1663, 1692, 2869, 2998 cm^{-1}. HRMS:Calcd for $C_{25}H_{26}O_{10}Na$ $[M+Na]^+$509.1423, found 509.1416.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(2-thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (13o):

Compound **12o** (0.32 g, 0.504 mmol), trimethylsilyl trifluoromethanesulfonate (0.138 mL, 0.756 mmol), acetic anhydried (6 mL) were treated according to the general procedure B to give the title compound **13o** (0.180 g, 69.2%), after column chromatography on silica

gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 75-77 °C; $[\alpha]^{27}_D$ = 36.2 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.93 (s, 3 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.10 (s, 3 H), 3.87-3.89 (m, 1 H), 4.20 (dd, *J* = 12.5, 2.5 Hz, 1 H), 4.29 (dd, *J* = 12.5, 5.0 Hz, 1 H), 4.48 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 5.18 (t, *J* = 9.5 Hz, 1 H), 5.34 (t, *J* = 9.5 Hz, 1 H), 5.41 (t, *J* = 9.5 Hz, 1 H), 7.16 (dd, *J* = 5.0, 4.0 Hz, 1 H), 7.29 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.96 (dd, *J* = 4.0, 1.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 62.3 (CH_2), 68.1 (CH), 69.2 (CH), 73.9 (CH), 76.5 (CH), 80.1 (CH), 128.1 (CH), 134.4 (CH), 135.4 (CH), 140.8 (C), 169.1 (C), 169.4 (C), 170.4 (C), 170.6 (C), 185.6 (CO) ppm. IR ($CHCl_3$):1556, 1648, 1688, 2872, 2982 cm^{-1}; HRMS:Calcd for $C_{19}H_{22}$ $SO_{10}Na$ $[M+Na]^+$ 465.0831, found 465.0826.

2,6-Anhydro-3,4,5,7-tetra-*O*-acetyl-1-*C*-(2-benzo[b]thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (13p):

Compound **12p** (0.43 g, 0.62 mmol), trimethylsilyl trifluoromethanesulfonate (0.209 mL, 0.942 mmol), acetic anhydried (8 mL) were treated according to the general procedure B to give the title compound **13p** (0.140 g, 46.35%), after column chromatography on silica gel as a colorless solid. R_f = 0.3 (EtOAc/hexanes, 3:7); m.p = 122-124 °C; $[\alpha]^{27}_D$ = 96.5 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ = 1.93 (s, 3 H), 2.02 (s, 3 H), 2.07 (s, 3 H), 2.13 (s, 3 H), 3.90-3.94 (m, 1 H), 4.23-4.25 (m, 1 H), 4.31 (dd, *J* = 12.5, 5.5, Hz 1 H), 4.58 (d, *J* = 10.0 Hz, 1 H, anomeric proton), 5.22 (t, *J* = 9.5 Hz, 1 H), 5.38 (t, *J* = 9.5 Hz, 1 H), 5.46 (t, *J* = 9.5 Hz, 1 H), 7.41-7.43 (m, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.23 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$); δ = 20.5 (CH_3), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 62.1 (CH_2), 68.1 (CH), 69.3 (CH), 73.8 (CH), 76.5 (CH), 80.2 (CH), 122.9 (CH), 125.2 (CH), 126.3 (CH), 128.1 (CH), 131.8 (CH), 138.9 (C), 140.8 (C), 142.9 (C), 169.1 (C), 169.4 (C), 170.3 (C), 170.5 (C), 187.2 (CO). IR ($CHCl_3$):1512, 1642, 1683, 2882, 2996 cm^{-1}; Elemental analysis:calcd (%) for $C_{23}H_{24}O_{10}S$ (492.50): C 56.09, H 4.91; found: C 56.37, H 4.81.

General procedure C for the synthesis of acyl-*C*-β-D-glucosides 4a-p:

A round bottom flask was charged with compound **13a-p** (1 equiv.) in MeOH (10 mL, for 1 mmol) at room temperature. To that solution, NaOMe (0.5 equiv.) was added and stirred the reaction mixture for 2 h at rt. Then the reaction mixture was neutralized with 10% HCl (1 mL) and concentrated under reduced pressure. The resultant crude product was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:9) to afford the title compound **4a-p**.

2,6-Anhydro-1-*C*-(4-(methyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4a):

Compound **13a** (0.21 g, 0.466 mmol), sodium methoxide (0.01 g, 0.233 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4a**, after column chromatography on silica gel (0.103 g, 78.6%) as a colorless solid (hygroscopic). R_f = 0.4 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ = -36.4 (c 0.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD); δ = 2.3 (s, 3 H), 3.32 (d, *J* = 8.8 Hz, 1 H), 3.4-3.52 (m, 1 H), 3.55 (t, *J* = 8.8 Hz, 1 H), 3.68-3.73 (m, 2 H), 3.89 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.59 (d, *J* = 9.2 Hz, 1 H, anomeric proton), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 20.3 (CH_3), 61.2 (CH_2), 69.8 (CH), 71.6 (CH), 78.0 (CH), 78.8 (CH), 81.0 (CH), 128.8 (CH), 129.2 (CH), 133.6 (C), 144.7 (C), 196.5 (CO) ppm. IR (KBr):1498, 1711, 2882, 2996, 3297 cm^{-1}.HRMS: Calcd for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1181, found 283.1169.

2,6-Anhydro-1-*C*-(4-(ethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4b):

Compound **13b** (0.20 g, 0.43 mmol), sodium methoxide (0.012 g, 0.233 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4b**, after column chromatography on silica gel (0.102 g,80.3%) as a colorless solid (hygroscopic). R_f = 0.4 ($MeOH/CH_2Cl_2$ 1:9); $[\alpha]^{27}_D$ = 118.6 (c 0.2, MeOH); ^{1}H NMR (400 MHz, CD_3OD); δ = 1.27 (t, *J* = 8.8 Hz, 3 H), 2.73 (q, *J* = 7.6 Hz, 2 H), 3.46 (d, *J* = 8.8 Hz, 1 H), 3.4-3.52 (m, 1 H), 3.57 (t, *J* = 8.8 Hz, 1 H), 3.68-3.73 (m, 2 H), 3.89 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.72 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 7.36 (d, *J* = 8.0 Hz, 2 H), 8.03 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 14.3 (CH_3), 28.5 (CH_2), 61.2 (CH_2), 69.8 (CH), 71.6 (CH), 78.0 (CH), 78.8 (CH), 81.0 (CH), 127.7 (CH), 129.3 (CH), 133.8 (C), 150.8 (C), 196.5 (CO) ppm. IR (KBr): 1146, 1586, 1706, 2882, 2926, 3310 cm^{-1}. HRMS:Calcd for $C_{15}H_{20}O_6Na$ $[M+Na]^+$319.1157, found 319.1146.

2,6-Anhydro-1-*C*-(4-(tert-butyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4c):

Compound **13c** (0.213 g, 0.43 mmol), sodium methoxide (0.015 g, 0.216 mmol), methanol (4 mL) were treated according to the general procedure C to give the title compound **4c**, after column chromatography on silica gel (0.108 g, 77.14%) as a colorless solid. R_f = 0.4 ($MeOH/CH_2Cl_2$ 1:9); m.p = 80-82 °C; $[\alpha]^{27}_D$ =98.4 (c 0.6, MeOH) ; ^{1}H NMR (400 MHz, CD_3OD); δ = 1.37 (s, 9 H), 3.43 (d, *J* = 9.0 Hz, 1 H), 3.48-3.51 (m, 1 H), 3.55 (t, *J* = 9.0 Hz, 1 H), 3.69-3.71 (m, 1 H), 3.71-3.73 (m, 1 H), 3.88 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.70 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 7.57 (d, *J* = 8.5 Hz, 2 H), 8.04 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 30.0 (CH_3), 34.6 (C), 61.3 (CH_2), 69.8 (CH), 71.5 (CH), 78.1 (CH), 78.9 (CH), 81.1 (CH), 125.1 (CH), 129.0 (CH), 133.5 (C), 157.3 (C), 196.4 (CO) ppm. IR (KBr):1216, 1552, 1689, 2926, 3280 cm^{-1}; HRMS: Calcd for $C_{17}H_{25}O_6$ $[M+H]^+$: 325.1651, found 325.1652.

2,6-Anhydro-1-*C*-(3,5-(dimethyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4d):

Compound **13d** (0.18 g, 0.387 mmol), sodium methoxide (0.01 g, 0.193 mmol), methanol (3 mL) were treated according to the general procedure C to give the title compound **4d**, after column chromatography on silica gel (0.095 g, 82.6%) as a colorless solid (hygroscopic). R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ = -68.3 (c 0.3, MeOH);^{1}H NMR (500 MHz, CD_3OD); δ = 2.25 (s, 6 H), 3.31 (d, *J* = 9.0 Hz, 1 H), 3.50-3.52 (m, 1 H), 3.44 (t, *J* = 9.0 Hz, 1 H), 3.56-3.60 (m, 2 H), 3.76 (d, *J* = 12.0, 2.0 Hz 1 H), 4.58 (d, *J* = 9.0 Hz, 1 H, anomeric proton), 7.17 (s, 1 H), 7.58 (s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD $_3$); δ = 19.8 (2×CH_3), 61.3 (CH_2), 69.9 (CH), 71.6 (CH), 78.0 (CH), 78.8 (CH), 81.1 (CH), 126.7 (CH), 134.9 (CH), 136.2 (C), 138.0 (C), 194.6 (CO) ppm. IR (KBr):1196, 1556, 1701, 2926, 3296 cm^{-1}. HRMS: Calcd for $C_{15}H_{21}O_6$ $[M+H]^+$: 297.1338, found 297.1337.

2,6-Anhydro-1-*C*-(4-(fluoro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4e):

Compound **13e** (0.07 g, 0.128 mmol), sodium methoxide (0.04 mL, 0.064 mmol), methanol (3 mL) were treated according to the general procedure C to give the title compound **4e**, after column chromatography on silica gel (0.035 g, 79.5%) as a colorless solid (hygroscopic). R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ = -109.3 (c 0.4, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.44 (d, *J* = 9.5 Hz, 1 H), 3.50-3.52 (m, 1 H), 3.56 (t, *J* = 11.5 Hz, 1 H), 3.69-3.74 (m, 2 H), 3.89 (d, *J* = 13.5 Hz, 1 H), 4.70 (t, *J* = 12.0 Hz, 1 H, anomeric proton), 7.26 (t, *J* = 11.0 Hz, 2 H), 8.20 (dd, *J* = 11.0, 7.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 61.2 (CH_2), 69.8 (CH), 71.5 (CH), 78.0 (CH), 79.1 (CH), 81.1 (CH), 115.1 (d, *J* = 22.0 Hz, CH), 132.1 (d, *J* = 9.5 Hz, CH), 132.6 (C), 166.0 (d, *J* = 252.5 Hz, C), 190.4 (CO) ppm. IR (KBr):918, 1216, 1556, 1721, 2991, 3233 cm^{-1}. HRMS: Calcd for $C_{13}H_{16}FO_6$ $[M+H]^+$: 287.0930, found 287.0922.

2,6-Anhydro-1-*C*-(4-(chloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4f):

Compound **13f** (0.16 g, 0.33 mmol), sodium methoxide (0.01 g, 0.17 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4f**, after column chromatography on silica gel (0.07 g, 68.6%) as a colorless solid (hygroscopic). R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ =52.1 (c 0.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD**)**; δ = 3.43 (d, *J* = 9.2 Hz, 1 H), 3.49-3.52 (m, 1 H), 3.55 (t, *J* = 8.8 Hz, 1 H), 3.68-3.73 (m, 2 H), 3.89 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.68 (d, *J* = 12.0 Hz, 1 H, anomeric proton), 7.53 (d, *J* = 8.4 Hz, 2 H), 8.10 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 61.2 (CH_2), 69.8 (CH), 71.5 (CH), 78.0 (CH), 79.1 (CH), 81.1 (CH), 128.4 (CH), 130.7 (CH), 134.5 (C), 139.6 (C), 195.5 (CO) ppm. IR (KBr): 972, 1218, 1556, 1713, 2992, 3301 cm^{-1}. HRMS: Calcd for $C_{13}H_{15}ClO_6K$ $[M+K]^+$ 341.0194, found 341.0203.

2,6-Anhydro-1-*C*-(3,4-(dichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4g):

Compound **13g** (0.18 g, 0.356 mmol), sodium methoxide (0.01 g, 0.18 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4g**, after column chromatography on silica gel (0.09 g, 75.0%) as a colorless solid (hygroscopic). R_f = 0.2 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ = 19.5 (c 0.3, MeOH);^{1}H NMR (400 MHz, CD_3OD); δ = 3.42 (d, *J* = 9.2 Hz, 1 H), 3.50-3.52 (m, 1 H), 3.55 (t, *J* = 9.2 Hz, 1 H), 3.66-3.72 (m, 2 H), 3.89 (d, *J* = 10.0 Hz, 1 H), 4.67 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 7.69 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 8.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 61.2 (CH_2), 69.7 (CH), 71.4 (CH), 77.9 (CH), 79.2 (CH), 81.1 (CH), 128.6 (CH), 130.5 (CH), 130.8 (CH), 132.5 (C), 135.8 (C), 137.4 (C), 194.6 (CO) ppm. IR (KBr):988, 1118, 1526, 1688, 2992, 3281 cm^{-1}. HRMS: Calcd for $C_{13}H_{14}Cl_2O_6Na$ $[M+Na]^+$ 359.0065, found 359.0057.

2,6-Anhydro-1-*C*-(3,4,5-(trichloro)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4h):

Compound **13h** (0.234 g, 0.43 mmol), sodium methoxide (0.012 g, 0.217 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4h**, after column chromatography on silica gel (0.099 g, 63.97%) as a colorless solid. R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9); m.p = 66-68 °C); $[\alpha]^{27}_D$ = 33.2 (c 0.3, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.40 (d, *J* = 9.0 Hz, 1 H), 3.51-3.56 (m, 2 H), 3.66 (t, *J* = 9.0 Hz, 1 H), 3.68 (dd, *J* = 12.5, 5.5 Hz, 1 H), 3.90 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.64 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 8.1 (s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 62.8 (CH_2), 71.4 (CH), 73.0 (CH), 79.4 (CH), 80.9 (CH), 82.7 (CH), 130.6 (CH), 135.7 (C), 137.1 (C), 137.3 (C), 195.2 (CO) ppm. IR (KBr): 988, 1118, 1526, 1688, 2992, 3281 cm^{-1}. Elemental analysis:calcd (%) for $C_{13}H_{13}Cl_3O_6$ (369.98): C 42.02, H 3.53; found: C 42.54, H 3.55.

2,6-Anhydro-1-*C*-(4-(methoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4i):

Compound **13i** (0.22 g, 0.47 mmol), sodium methoxide (0.012 g, 0.236 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4i**, after column chromatography on silica gel (0.102 g, 72.85%) as a colorless solid. R_f =0.4 ($MeOH/CH_2Cl_2$, 1:9); $[\alpha]^{27}_D$ = -56.0 (c 0.3, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.43 (d, *J* = 8.5 Hz, 1 H), 3.47-3.50 (m, 1 H), 3.55 (t, *J* = 8.5 Hz, 1 H), 3.68-3.73 (m, 1 H), 3.70-3.72 (m, 1 H), 3.87 (d, *J* = 12.0 Hz, 1 H), 3.90 (s, 3 H), 4.68 (d, *J* = 9.0 Hz, 1 H, anomeric proton), 7.03 (d, *J* = 8.0 Hz, 2 H), 8.1 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 56.2 (OMe), 62.8 (CH_2), 71.4 (CH), 73.2 (CH), 79.6 (CH), 80.3 (CH), 82.6 (CH), 114.9 (CH), 130.5 (C), 133.0 (CH), 165.9 (C), 196.9 (CO) ppm. IR (KBr): 1222, 1576, 1691, 2916, 3281 cm^{-1}. HRMS: Calcd for $C_{14}H_{18}O_7Na$ $[M+Na]^+$321.095, found 321.0943.

2,6-Anhydro-1-*C*-(4-(hydroxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4j):

Compound **13j** (0.18 g, 0.36 mmol), sodium methoxide (0.01 g, 0.18 mmol), methanol (4 mL) were treated according to the general procedure C to give the title compound **4j**, after column chromatography on silica gel (0.108 g, 85.98%) as a colorless solid. R_f = 0.2 ($MeOH/CH_2Cl_2$ 1:9);m.p = 158-160 °C); $[\alpha]^{27}_D$ = 13.4 (c 1.0, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.32 (d, *J* = 9.0 Hz, 1 H), 3.34-3.38 (m, 1 H), 3.43 (t, *J* = 9.0 Hz, 1 H), 3.54-3.57 (m, 1 H), 3.58-3.61 (m, 1 H), 3.75 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.56 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 6.75 (d, *J* = 8.5 Hz, 2 H), 7.89 (d, *J* = 9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 62.7 (CH_2), 71.3 (CH), 73.2 (CH), 79.6 (CH), 80.2 (CH), 82.4 (CH), 116.3 (CH), 129.4 (C), 133.3 (CH), 164.5 (C), 196.9 (CO) ppm. IR (KBr): 1218, 1576, 1706, 2992, 3281, 3456 cm^{-1}. HRMS: Calcd for $C_{13}H_{17}O_7$ $[M+H]^+$ 285.0974, found 285.0973.

2,6-Anhydro-1-*C*-(3,4-(dimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4k):

Compound **13k** (0.3 g, 0.594 mmol), sodium methoxide (0.02 g, 0.29 mmol), methanol (3 mL) were treated according to the general procedure C to give the title compound **4k**, after column chromatography on silica gel (0.09 g, 75.0%).as a colorless solid; R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9);.m.p = 132-134 °C; $[\alpha]^{27}_D$=84.3 (c 0.3, MeOH); ^{1}H NMR (400 MHz,CD_3OD); δ = 3.45 (d, *J* = 9.2 Hz, 1 H), 3.51-3.59 (m, 2 H), 3.70-3.73 (m, 2 H), 3.91 (s, 4 H), 3.94 (s, 3 H), 4.69 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 7.07 (d, *J* = 8.4 Hz, 1 H), 7.66 (s, 1 H). 7.82 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD); δ = 56.5 (CH_3), 56.6 (CH_3), 62.8 (CH_2), 71.4 (CH), 73.2 (CH), 79.6 (CH), 80.4 (CH), 82.6 (CH), 111.7 (CH), 112.8 (CH), 126.1 (CH), 130.6 (C), 150.4 (C), 155.7 (C), 196.8 (CO) ppm. IR (KBr):1242, 1548, 1686 2982, 3296 cm^{-1}. HRMS: Calcd for $C_{15}H_{21}O_8$ $[M+H]^+$: 329.1236, found 329.1236.

2,6-Anhydro-1-*C*-(3,4,5-(trimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4l):

Compound **13l** (0.230 g, 0.430 mmol), sodium methoxide (0.02 g, 0.22 mmol), methanol (3 mL) were treated according to the general procedure C to give the title compound **4l**, after column chromatography on silica gel **(**0.11 g, 71.4%) as a colorless solid. R_f = 0.3 ($MeOH/CH_2Cl_2$, 1:9);m.p = 152-154 °C; $[\alpha]^{27}_D$= 98.2 (c 0.2, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.41 (d, *J* = 9.5 Hz, 1 H), 3.51-3.53 (m, 1 H), 3.55 (t, *J* = 9.0 Hz, 1 H), 3.68 (dd, *J* = 12.5, 5.5 Hz 1 H), 3.73 (t, *J* = 9.0 Hz, 1 H), 3.86 (s, 3 H), 3.89-3.92 (m, 7 H), 4.63 (d, *J* = 9.6 Hz, 1 H, anomeric proton), 7.45 (s, 2 H) ppm.^{13}C NMR (125 MHz, CD_3OD); δ = 55.3 (2xCH_3), 59.7 (CH_3), 61.3 (CH_2), 69.9 (CH), 71.5 (CH), 78.0 (CH), 79.5 (CH), 81.3 (CH), 106.8 (CH), 131.2 (C), 142.8 (C), 152.9 (C), 195.2 (CO) ppm.IR (KBr): 1218, 1568, 1697 2948, 3256 cm^{-1}; HRMS: Calcd for $C_{16}H_{22}O_9K$ $[M+K]^+$ 397.0900, found 397.0902.

2,6-Anhydro-1-*C*-(4-(phenyl)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4m):

Compound **13m** (0.21 g, 0.409 mmol), sodium methoxide (0.012 g, 0.217 mmol), methanol (5 mL) were treated according to the procedure C to give the title compound **4m**, after column chromatography on silica gel (0.12 g, 85.1%) as a colorless solid. R_f = 0.4 ($MeOH/CH_2Cl_2$ 1:9); m.p = 176-178 °C); $[\alpha]^{27}_D$= -118.1 (c 0.3, MeOH); ^{1}H NMR (500 MHz, CD_3OD); δ = 3.23 (d, *J* = 9.5 Hz, 1 H), 3.39-3.42 (m, 1 H), 3.44 (t, *J* = 9.0 Hz, 1 H), 3.59-3.61 (m, 1 H), 3.62-3.64 (m, 1 H), 3.79 (dd, *J* = 12.5, 2.5 Hz, 1 H), 4.63 (d, *J* =

9.5 Hz, 1 H, anomeric proton), 7.28-7.31 (m, 1 H), 7.36-7.39 (m, 2 H), 7.59 (dd, *J* = 8.0, 1.0 Hz, 2 H)), 7.67 (d, *J* = 8.5 Hz,2 H), 8.07 (d, *J* = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); *δ* = 62.8 (CH_2), 71.4 (CH), 73.1 (CH), 79.6 (CH), 80.6 (CH), 82.7 (CH), 128.2 (CH), 128.3 (CH), 129.5 (CH), 130.2 (CH), 131.2 (CH), 136.3 (C), 141.1 (C), 147.7 (C), 195.2 (CO) ppm. IR (KBr):1496**,** 1568, 1721, 2989, 3276 cm^{-1}. HRMS**:** Calcd for $C_{19}H_{20}O_6K$ $[M+K]^+$ 383.0896, found 383.0901.

2,6-Anhydro-1-*C*-(naphthalen-2-yl)-aldehydo-D-glycero-D-gulo-heptose (4n):

Compound **13n** (0.23 g, 0.472 mmol), sodium methoxide (0.012 g, 0.217 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4n**, after column chromatography on silica gel (0.09 g, 60%) as a colorless solid. R_f = 0.3 (MeOH/CH_2Cl_2 1:9); m.p = 77-79 °C); $[\alpha]^{27}_D$= -96.3 (c 0.3, MeOH) ; ^{1}H NMR (500 MHz, CD_3OD); *δ* = 3.49 (d, *J* = 9.5 Hz, 1 H), 3.58-3.61 (m, 1 H), 3.63 (t, *J* = 9.0 Hz, 1 H), 3.75 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.79 (d, *J* = 9.5 Hz, 1 H), 3.92 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.90 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 7.56-7.60 (m, 1 H), 7.62-7.66 (m, 1 H), 7.93 (t, *J* = 8.0 Hz, 2 H)), 8.06 (d, *J* = 8.5 Hz, 1 H), 8.09 (dd, *J* = 9.5 Hz, 2.0 Hz, 1 H), 8.73 (s, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); *δ* = 61.3 (CH_2), 69.9 (CH), 71.7 (CH), 78.1 (CH), 79.0 (CH), 81.2 (CH), 123.9 (CH), 126.5 (CH), 127.3 (CH), 127.9 (CH), 128.5 (CH), 129.5 (CH), 131.6 (CH), 132.5 (C), 133.3 (C), 135.9 (C), 196.7 (CO) ppm. IR(KBr): 1496**,** 1576, 1706, 2992, 3284 cm^{-1}. HRMS: Calcd for $C_{17}H_{19}O_6$ $[M+H]^+$ 319.1181, found 319.1182.

2,6-Anhydro-1-*C*-(2-thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (4o):

Compound **13o** (0.25 g, 0.56 mmol), sodium methoxide (0.015 g, 0.28 mmol), methanol (5 mL) were treated according to the general procedure C to give the title compound **4o**, after column chromatography on silica gel (0.13 g, 71.03%) as a colorless solid. R_f =0.3 (MeOH/CH_2Cl_2 1:9); $[\alpha]^{27}_D$=-86.4 (c 0.3, MeOH); ^{1}H NMR (500 MHz, CD_3OD); *δ* = 3.43-3.49 (m, 2 H), 3.52 (t, *J* = 9.0 Hz, 1 H), 3.67 (t, *J* = 9.5 Hz, 1 H), 3.73 (dd, *J* = 12.5, 5.0 Hz, 1 H), 3.90 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.50 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 7.23 (dd, *J* = 5.0 Hz, 4.0 Hz, 1 H), 7.91 (dd, *J* = 5.0, 1.0 Hz, 1 H), 8.09 (dd, *J* = 4.0, 1.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); *δ* = 61.3 (CH_2), 69.8 (CH), 71.8 (CH), 78.0 (CH), 81.0 (CH), 81.1 (CH), 128.0 (CH), 134.9 (CH), 135.1 (CH), 142.4 (C), 189.9 (CO) ppm. IR (KBr): 1576, 1720, 2992, 3284 cm^{-1}. HRMS: Calcd for $C_{11}H_{15}O_6S$ $[M+H]^+$ 275.0586, found 275.0589.

2,6-Anhydro-1-*C*-(2-benzo[b]thiophenyl)-aldehydo-D-glycero-D-gulo-heptose (4p):

Compound **13p** (0.1 g, 0. mmol), sodium methoxide (0.009 g, 0.10 mmol), methanol (3 mL) were treated according to the general procedure C to give the title compound **4p**, after column chromatography on silica gel (0.04 g, 61.5%) as a colorless solid. R_f =0.3 (MeOH/CH_2Cl_2 1:9); m.p = 70-72 °C; $[\alpha]^{27}_D$ **=** -98.2 (c 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD); *δ* = 3.36 (d, *J* = 9.0 Hz, 1 H), 3.43-3.49 (m, 1 H), 3.45 (t, *J* = 9.0 Hz, 1 H), 3.60 (t, *J* = 9.5 Hz, 1 H), 3.62-3.65 (m, 1 H), 3.81 (dd, *J* = 12.5, 2.0 Hz, 1H), 4.54 (d, *J* = 9.5 Hz, 1 H, anomeric proton), 7.35-7.39 (m, 1 H), 7.39-7.42 (m, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.29 (s, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); *δ* = 62.8 (CH_2), 71.3 (CH), 73.4 (CH), 79.6 (CH), 82.2 (CH), 82.7 (CH), 123.9 (CH), 126.3 (CH), 127.8 (CH), 129.2 (CH), 134.1 (CH), 140.8 (CH), 143.4 (C), 144.2 (C), 193.0 (CO) ppm.IR (KBr):1584, 1718, 2979, 3213 cm^{-1}. HRMS: Calcd for $C_{15}H_{17}O_6S$ $[M+H]^+$ 325.0745, found 325.0745.

2,6-Anhydro-3,4,5,7-tetra-*O*-methoxymethyl-1-*C*-(*N*-methyl-*N*-methoxy)-aldehydo-D-glycero-D-gulo-heptose 14:

Step 1: Toastirred solution ofbuilding block **6c** (3.8 g, 6.2 mmol) in THF (40 mL) was added Pd-C (0.66 g, 10 mol %) at rt. The reaction mixture was stirred under an atmosphere of H_2 with balloon pressure until starting material was disappeared on TLC. The mixture was filtered through celite and the solvent was removed in vacuo. The resultant tetrol was used for the next step without further purification.

Step 2: In a flame dried two necked round bottom flask under nitrogen atmosphere, tetrol (1.6 g, 6.3 mmol) was combined with anhydrous dichloromethane (25 mL), upon cooling the suspension on a ice bath (0 °C) diisopropylethylamine (8.6 mL, 50.4 mmol) was added drop wise. The suspension was stirred at the same temperature for an additional 10 min and then chloromethylmethylether (4.0 mL, 50.4 mmol) was added slowly. After stirring for another 15 min at the same temperature tetrabutylammoniumiodide (8.3 g, 25.2 mmol) was added and then solution was allowed to attain rt. The reaction was stirred in darkness for 72 hours, the solution gradually turned red in color and was cooled to 0 °C, saturated NH_4Cl (30 ml) solution was added and the organic layer was extracted with dichloromethane (3x100 ml), dried over Na_2SO_4, and concentrated to give the crude product, which was further washed with Et_2O afforded the title compound **14 (**2.1 g , 77.2%) as a yellow color oil. R_f = 0.3 (EtOAc/hexanes, 1:1); **[**$\alpha]^{27}_D$ = -78.2 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$); *δ* = 3.22 (s, 3 H), 3.33 (s, 3 H), 3.34 (s, 3 H), 3.43 (2 x s, 6 H), 3.50 (s, 2 H), 3.67 (m, 2 H), 3.77 (s, 3 H), 3.87-3.96 (m, 2 H), 4.32 (d, *J* = 9.6 Hz, 1H), 4.63 (s, 2 H), 4.72-4.74 (m, 3 H), 4.85-4.90 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); *δ* = 32.2 (CH_3, N-Me), 55.2 (CH_3, OMe), 56.4 (CH_3, OMe), 56.5 (CH_3, OMe), 61.9 (CH_3, OMe), 66.9 (CH_2), 74.5 (CH), 76.6 (CH), 77.2 (CH), 79.1 (CH), 83.1 (CH), 96.7 (CH_2), 98.1 (CH_2), 98.5 (CH_2), 98.6 (CH_2), 168.4 (CO) ppm. IR ($CHCl_3$): 1214,1584, 1718, 2979, 3012 cm^{-1}. HRMS: Calcd for $C_{17}H_{33}NO_{11}Na$ $[M+Na]^+$ 450.1951, found 450.1949.

2,6-Anhydro-3,4,5,7-tetra-*O*-methoxymethyl-1-*C*-(3,4-(dimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose 15a:

Building block **14** (0.4 g, 0.936 mmol), magnesium turnings (0.107 g, 4.68 mmol), 1-bromo-3,4-dimethoxybenzene (0.68 g, 4.68 mmol) were treated according to the procedure used in compound **12l** to give the title compound **15a**, after column chromatography on silica gel (0.4 g, 72.3%)as a colorless gum. R_f = 0.3 (EtOAc/hexanes, 2:3); $[\alpha]^{27}_D$ =-14.2 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); *δ* = 3.08 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.44(s, 6 H), 3.45 (s, 2H), 3.59-3.60 (m, 1 H), 3.68-3.70 (m, 1 H), 3.77-3.81 (m, 3 H), 3.93 (s, 3 H), 3.95 (s,1 H), 3.99-4.01 (m, 1 H), 4.11-4.12, (m, 1 H), 4.55-4.65 (m, 5 H), 4.75-4.77 (m, 1 H), 4.85-4.91 (m, 3 H), 6.88-6.90 (m, 1 H), 7.61 (s, 1 H), 7.73-7.74 (m, 1 H) ppm.^{13}C NMR (125 MHz, $CDCl_3$); *δ* = 55.2 (CH_3, OMe), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 56.3(CH_3, OMe), 56.4 (CH_3, OMe), 56. 5(CH_3, OMe), 66.7 (CH_2), 76.5 (CH), 77.5(CH), 79.1 (CH), 79.3 (CH), 83.3 (CH), 96.7 (CH_2), 97.9(CH_2), 98.6 (2 x CH_2), 109.9 (CH), 111.1 (CH), 124.2 (CH), 128.9 (C), 149.0(C), 153.7 (C), 192.8 (CO) ppm. IR ($CHCl_3$):1178, 1584, 1712, 2986, 3113 cm^{-1}. HRMS: Calcd for $C_{23}H_{36}O_{12}Na$ $[M+Na]^+$ 527.2104, found 527.2106.

2,6-Anhydro-3,4,5,7-tetra-*O*-methoxymethyl-1-*C*-(3,4,5-(trimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose 15b:

Building block **14** (0.5 g, 1.17 mmol), magnesium turnings (0.107 g, 4.68 mmol), 1-bromo-3,4,5-trimethoxybenzene (1.15 g, 4.68 mmol) were treated according to the procedure used in compound **12l** to give the title compound **15b**, after column chromatography on silica gel (0.29 g, 59.3%) as a colorless gum. R_f = 0.3 (EtOAc/hexanes, 1:1); $[\alpha]^{27}_D$= -68.2 (c 0.6,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$); δ = 3.14 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.53-3.62 (m, 2 H), 3.64-3.70 (m, 1 H), 3.77-3.87 (m, 2 H), 3.91 (s, 6 H, 2xOMe), 3.92 (s, 3 H, OMe), 4.01 (t, J = 11.5 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.61 (s, 2 H), 4.63 (d, J = 7.5 Hz, 1 H), 4.68 (d, J = 7.5 Hz, 1 H), 4.75 (d, J = 8.5 Hz, 1 H), 4.85-4.91 (m, 3 H),7.37 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$); δ = 55.2 (CH_3, OMe), 56.2 (CH_3, OMe), 56.3(2 x CH_3, OMe), 56.5 (2 x CH_3, OMe), 60.9 (CH_3, OMe), 66.6 (CH_2), 76.5 (CH), 77.3 (CH), 79.3 (CH), 79.8 (CH), 83.2 (CH), 96.6 (CH_2), 97.9 (CH_2), 98.5 (CH_2), 106.7 (CH), 130.7 (C), 142.9 (C), 152.9 (2 x C), 192.8 (CO) ppm. IR ($CHCl_3$):1112, 1556, 1701, 2987, 3110 cm^{-1}. HRMS: Calcd for $C_{24}H_{39}O_{13}$ $[M+H]^+$ 535.2390, found 535.2390.

2,6-Anhydro-3,4,5,7-tetra-*O*-methoxymethyl-1-*C*-(3,5-(dimethoxy)-4-benzyloxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose15c:

Building block **14** (0.6 g, 1.40 mmol), magnesium turnings (0.112 g, 4.68 mmol), 1-bromo-3,5-dimethoxy-4-benzyloxybenzene (1.51 g, 4.68 mmol) were treated according to the procedure used in compound **12l** to give the title compound **15c**, after column chromatography on silica gel (0.66 g, 77.3%) as a colorless gum. R_f = 0.3 (EtOAc/hexanes, 2:3); $[\alpha]^{27}_D$=-136.2 (c 0.6, $CHCl_3$); ^1H NMR (400 MHz,$CDCl_3$); δ = 3.09 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 3.37-3.39 (m, 1 H), 3.43 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.53-3.62 (m, 2 H), 3.65-3.69 (m, 1 H), 3.79 (t, J = 8.8 Hz, 1 H), 3.87 (s, 6 H), 3.89-3.92 (m, 1 H), 4.00 (t, J = 9.2 Hz, 1 H), 4.52 (d, J = 9.2 Hz, 1 H), 4.60-4.62 (m, 2 H), 4.65 (d, J = 6.0 Hz, 1 H), 4.75 (d, J = 6.8 Hz, 1 H), 4.85-4.91 (m, 3 H), 5.11 (s, 2 H), 7.26-7.28 (m, 1 H), 7.30-733 (m, 2 H), 7.34 (s, 2H), 7.45 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 55.2 (CH_3, OMe), 56.2 (CH_3, OMe), 56.3 (2 x CH_3, OMe), 56.5 (CH_3, OMe), 66.6 (CH_2), 74.9 (CH), 76.6 (CH), 79.3 (CH), 79.6 (CH), 83.2 (CH), 96.6 (CH_2), 98.0 (CH_2), 98.6 (2 x CH_2), 106.7 (CH), 128.0 (CH), 128.1 (CH), 130.9(C), 137.2 (C), 141.7 (C), 153.2 (2 x C), 192.9 (CO) ppm. IR ($CHCl_3$):1216, 1557, 1698, 2987, 3017 cm^{-1}. HRMS: Calcd for $C_{30}H_{43}O_{13}$ $[M+H]^+$ 611.2703, found 611.2698.

General procedure D for the MOM deprotection:

The methoxy methyl ether protected compound **15a-c** was dissolved in methanol (2 mL) in a round bottom flask with magnetic stir bar and kept the stirring at room temperature. To the reaction mixture, 6N HCl was added and stirring was continued until the starting material was disappear on TLC. The wine-red colored solution was concentrated in vacuum. The black colored residual material was purified by column chromatography on silica gel to give the title compounds **4k,4l** and**16**.

2,6-Anhydro-1-*C*-(3,4-(dimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4k):

Compound **15b** (0.3 g, 0.544 mmol), 6 N HCl (30 mL), methanol (3 mL) were treated according to the general procedure D, to give the title compound **4k**, after column chromatography on silica gel as a colorless solid (0.11 g, 67%).

2,6-Anhydro-1-*C*-(3,4,5-(trimethoxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose (4l):

Compound **15b** (0.23 g, 0.544 mmol), 6 N HCl (20 mL), methanol (3 mL) were treated according to the general procedure D, to give the title compound **4l**, after column chromatography on silica gel as a colorless solid (0.11 g, 71.4%).

2,6-Anhydro-1-*C*-(3,5-(dimethoxy)-4-hydroxy)phenyl)-aldehydo-D-glycero-D-gulo-heptose(16):

Compound **15c** (0.66 g, 1.08 mmol), 6 N HCl (50 mL), methanol (6 mL) were treated according to the general procedure D, to give the title compound **16**, after column chromatography on silica gel (0.29 g, 78.4%) as a colorless solid. R_f = 0.4 (MeOH/CH_2Cl_2, 1:4); m.p = 178-180 °C; $[\alpha]^{27}_D$ = -168.2 (c 0.3, MeOH); ^1H NMR (500 MHz, CD_3OD); δ = 3.42 (d, J = 9.5 Hz, 1 H), 3.50-3.53 (m, 1 H), 3.56 (t, J = 9.0 Hz, 1 H), 3.68-3.70 (m, 1 H), 3.71-3.74 (m, 1 H), 3.88-3.89 (m, 1 H), 3.92 (s, 6 H), 4.65 (d, J = 9.5 Hz, 1 H, anomeric proton), 7.46 (s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 56.9 (2xCH_3), 62.8 (CH_2), 71.4 (CH), 73.2 (CH), 79.6 (CH), 80.7 (CH), 82.7 (CH), 108.6 (CH), 128.2 (C), 143.1 (C), 149.0 (C), 196.6 (CO) ppm. IR (KBr): 1568, 1682, 2896, 3264, 3420 cm^{-1}. Elemental analysis:calcd (%) for $C_{15}H_{20}O_9$ (344.32): C 52.33, H 5.86; found: C 51.98, H 5.54.

General procedure E for the synthesis of benzyl-*C*-β-glucosides:

To obtained benzyl ether protected compound (1 eq.) in MeOH (5 mL) was added Pd/C (0.1 eq., 10 mol%) followed by catalytic amount of con.c HCl at rt. The reaction mixture was stirred under H_2 atmosphere (balloon pressure) for 24-36 h. The solution was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 1:9) to give the title compound **5a-e** as a colorless solids.

2,6-anhydro-1-deoxy-1-*C*-(4-(methoxy)phenyl)-D-glycero-D-gulo-heptitol (5a):

Compound **12i** (0.16 g, 0.536 mmol), Pd-C (0.058 g, 0.0536) and MeOH (3 mL) were treated according to the general procedure E, to give the title compound **5a** (0.05 g, 79.7%) as a colorless solid. R_f = 0.4 (MeOH/CH_2Cl_2, 1:9); m.p = 94-96 °C; $[\alpha]^{27}_D$ =-98.2 (c 0.7, MeOH);^1H NMR (400 MHz, CD_3OD); δ = 2.66 (dd, J = 14.4, 8.4 Hz, 1 H), 3.09-3.10 (m, 1 H), 3.13-3.17 (m, 1 H), 3.27-3.29 (m, 1 H), 3.32-3.37 (m, 3 H), 3.64 (dd, J = 12.0, 5.6 Hz, 1 H), 3.75-3.81 (m, 4 H), 6.81 (d, J = 7.2 Hz, 2 H), 7.23 (s, J = 8.4 Hz, 2 H). ^{13}C NMR (100 MHz, CD_3OD); δ = 36.3 (CH_2), 54.2 (CH_3, OMe), 61.6 (CH2), 70.5 (CH), 73.4 (CH), 78.5 (CH), 79.9 (CH), 80.4 (CH), 113.0 (CH), 130.2 (CH), 130.9 (C), 158.1 (C). IR (KBr):1213, 1571, 1696, 2896, 3264 cm^{-1}. Elemental analysis:calcd (%) for$C_{14}H_{20}O_6$(284.13): C 59.15, H 7.09; found: C 59.55, H 7.39.

2,6-anhydro-1-deoxy-1-*C*-(4-(hydroxy)phenyl)-D-glycero-D-gulo-heptitol (5b):

Compound **12j** (0.22 g, 0.298 mmol), Pd-C (0.03 g, 0.0298) and MeOH (4 mL) were treated according to the general procedure E, to give the title compound **5b (**0.08 g, 93%) as a colorless solid. R_f = 0.4 (MeOH/CH_2Cl_2, 1:4); $[\alpha]^{27}_D$ **=** 95.2 (c 0.3, MeOH); ^1H NMR (500 MHz, CD_3OD); δ = 2.62-2.67 (m, 1 H), 3.09-3.17 (m, 1 H), 3.29-3.38 (m, 5 H), 3.64-3.66 (m, 1 H), 3.67-3.80 (m, 1 H), 6.01 (d, J = 7.5 Hz, 2 H), 7.16 (d, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 36.4 (CH_2), 61.6 (CH_2), 70.5 (CH), 73.4 (CH), 78.5 (CH), 79.9 (CH), 80.5 (CH), 114.3 (CH), 129.7 (C), 130.2 (CH), 155.2 (C) ppm. IR (KBr): 1568, 1682, 2896, 3264, 3420 cm^{-1}. HRMS**:** Calcd for $C_{13}H_{18}O_6Na$ $[M+Na]^+$ 293.1001, found 293.1001.

2,6-anhydro-1-deoxy-1-*C*-(3,4-(dimethoxy)phenyl)-D-glycero-D-gulo-heptitol (5c):

Compound **12k** (0.22 g, 0.298 mmol), Pd-C (0.03 g, 0.0298) and MeOH (4 mL) were treated according to the general procedure E, to give the title compound **5c (**0.055 g, 68%) as a light brown color solid. R_f=0.4 (MeOH/CH_2Cl_2, 1:4); $[\alpha]^{27}_D$ = 95.2 (c 0.3, MeOH); ^1H NMR (500 MHz, CD_3OD); δ = 2.56 (dd, J = 15.5,8.0 Hz, 1 H), 2.97-2.99 (m, 1 H), 3.04-3.07 (m, 1 H), 3.13-3.17 (m, 1 H), 3.22-3.23 (s, 1 H), 3.53 (dd, J = 12.0, 6.0 Hz, 1H), 3.69 (s, 3 H), 3.71(s, 3 H), 3.73 (m, 1 H), 4.47 (s, 2 H), 6.73 (s, 2 H),

6.89 (s, 1 H) ppm.^{13}C NMR (125 MHz, CD_3OD); δ = 36.7 (CH_2), 55.0 (CH_3, OMe), 55.1 (CH_3, OMe), 61.7 (CH_2), 70.5 (CH), 73.4 (CH), 78.5 (CH), 80.0 (CH), 80.4 (CH), 111.3 (CH), 113.4 (CH), 121.6 (CH), 132.0 (C), 147.4 (C), 148.5 (C) ppm. IR (KBr):1568, 1682, 2896, 3264, 3420 cm^{-1}. HRMS: Calcd for $C_{15}H_{22}O_7K$ $[M+K]^+$ 353.1002, found 353.1007.

2,6-anhydro-1-deoxy-1-*C*-(3,4,5-(trimethoxy)phenyl)-D-glycero-D-gulo-heptitol (5d):

Compound **12l** (0.23 g, 0.326 mmol), Pd-C (0.035 g, 0.032) and MeOH (5 mL) were treated according to the general procedure E, to give the title compound **5d** (0.097 g, 86.6%) as a colorless solid. R_f = 0.4 ($MeOH/CH_2Cl_2$, 1:9); m.p = 128-130 °C; $[\alpha]^{27}_D$=102.2 (c 0.3, MeOH);^{1}H NMR (500 MHz, CD_3OD); δ = 2.57 (dd, *J* = 16.0, 8.5 Hz, 1 H), 2.98-3.02 (m, 2 H), 3.07-3.10 (m, 1 H), 3.14-3.17 (m, 1 H), 3.21-3.23 (m, 1 H), 3.53 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.63 (s, 3 H, OMe), 3.71 (s, 6 H, 2 x OMe), 4.48 (s, 2H), 6.55 (s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 37.4 (CH_2), 55.1 (2 x CH_3, OMe), 59.7 (CH_3, OMe), 61.7 (CH2), 70.5 (CH), 73.3 (CH), 78.5 (CH), 80.0 (CH), 80.3 (CH), 106.6 (CH), 135.3 (CH), 135.8 (C), 152.5 (C) ppm. IR (KBr):1566, 1689, 2896, 3214, 3410 cm^{-1}. HRMS: Calcd for $C_{16}H_{24}O_8K$ $[M+K]^+$ 383.1108, found 383.1107.

2,6-anhydro-1-deoxy-1-*C*-(3,5-(dimethoxy)-4-(hydroxy)phenyl)-D-glycero-D-gulo-heptitol (5e):

Compound **7d** (0.47 g, 0.589 mmol), Pd-C (0.05 g, 0.048), aq. HCl (1 mL) and MeOH (8 mL) were treated according to the general procedure E, to give the title compound **5e (**0.06 g, 64 %) as a colorless solid. R_f **=** 0.4 ($MeOH/CH_2Cl_2$, 1:4); $[\alpha]^{27}_D$ = 95.2 (c 0.3, MeOH);^{1}H NMR (500 MHz, CD_3OD); δ = 2.54 (dd, *J* = 15.5, 8.5 Hz, 1 H), 2.96-2.99 (m, 1 H), 3.00-3.02 (m, 1 H), 3.06-3.09 (m, 1 H), 3.13-3.17 (m, 1 H), 3.24-3.25 (m, 2 H), 3.53 (dd, *J* = 12.0, 5.5 Hz, 1 H), 3.72 (s, 7H), 6.53 (s, 2 H) ppm. ^{13}C NMR (125 MHz, CD_3OD); δ = 37.0 (CH_2), 55.3 (2 x CH_3, OMe), 61.7 (CH2), 70.6 (CH), 73.3 (CH), 78.5 (CH), 80.0 (CH), 80.5 (CH), 106.5 (CH), 129.6 (C), 129.7 (C), 133.2 (C), 147.3 (C) ppm. IR (KBr):1572, 1676, 2886, 3281, 3320 cm^{-1}**.**HRMS: Calcd for $C_{15}H_{22}O_8Na$ $[M+Na]^+$ 353.1212, found 353.1214.

Cell cytotoxicity

C2C12 myoblasts were procured from NCCS, Pune and maintained in Minimum Eagles Medium (MEM) containing essential antibiotics, fetal bovine serum (10% of FBS) and maintained with 5% CO2 at 37°C. The compatibility of the compounds and the commercial drugs (Pioglitazone and Metformin) was tested against C2C12 myoblast by MTT assay. The cells were seeded at 10^4 cells/well into 96 well plate and cultured overnight. The cells were treated with pioglitazone (5 µM), metformin (600 µM) and acyl and benzyl-*C*-β-D-glucosides (5 and 10 µM) for 24 hrs. MTT (1 mg/ml) was added to the wells and incubated for 4 hrs. The formazan precipitates formed were dissolved in DMSO and the absorbance was measured at 570 nm using a microplate reader (EnSpire, Perkin Elmer, Singapore). The percentage cytotoxic cells were calculated relative to the untreated control cells.

NBDG uptake

For differentiation of C2C12 myoblast into myotubes, the cells were cultured in MEM with 2% FBS (differentiation medium) for 6 days. The C2C12 cells (10^4 to 10^5 cells /ml) were seeded in 24 well plate, after the cells reached 70% confluency, the differentiation media was added and maintained in 5% CO2 incubator at 37˚C for 6 days. Once the elongated myotubes were formed the cells were serum starved in low glucose (1%) MEM without serum for 16 hrs. The differentiated mytotubes were then treated with pioglitazone (5 µM), metformin (600 µM) and acyl and benzyl-*C*- β -D-glucosides (5 and 10 µM) for 16 hrs followed by addition of insulin (100nM) and incubated for 30 minutes. After insulin stimulation the mytotubes were washed once with PBS. 2-NBDG, a fluorescent glucose analogue (50µM) in no glucose medium was added to each well and the plates were further incubated for 1 hour. The cells were thoroughly washed thrice with ice cold 1X PBS and 200 µl lysis buffer was added to each well and incubated for 10 mins.[33] The lysate was added to 96 black well microtitre plate and fluorescence (λex = 467 nm, λem = 542 nm) was measured for NBDG uptake using Perkin Elmer multimode plate reader. Results were expressed as mean±SD. Data was analysed using one way ANOVA (GraphPad Prism 6 software).

Real time PCR quantification

The differentiated C2C12 cells were serum starved for 16 hrs and treated with pioglitazone (5 µM), metformin (600 µM) and acyl and benzyl-*C*- β -D-glucosides (5 and 10 µM) for 16hrs. This was followed by insulin (100 nM) for 30 min. The cells were harvested and the total RNA was isolated using RNAiso Plus(Total RNA extraction reagent, Takara Bio Inc., Japan). RNA (1 µg) was transcribed using cDNA Reverese Transcription Kit(Applied Biosystems, Thermo Fischer Scientific, USA) with Applied Biosystems Veriti™ Dx Thermal Cycler (Thermo Fischer Scientific, USA). The mRNA expressions of PI3K, GLUT4 and PPARγ genes were quantified using a SYBR® Premix Ex Taq™ II kit (Takara Bio, USA) with a Mastercycler ep realplex PCR system (Eppendorf, Australia). The primer sequences GLUT4 (Forward: 5´-CCAGCCTACGCCACCATAG-3´, Reverse: 5´-TTCCAGCAGCAGCAGAGC-3´), PPAR-γ (Forward: 5´-AGGGCCCTGTCTGCTCTGTG-3´, Reverse: 5´-TACCAGCTTGAGCAGCACAAGTCG-3´) and PI3K (Forward: 5´-TGACGCTTTCAAACGCTATC-3´, Reverse: 5´-CAGAGAGTACTCTTGCATTC-3´). The PCR cycle was set as follows: 95°C for 30s, followed by 40 cycles at 95°C for 5s and at 60°C for 35 s. The expression levels were normalized to the house keeping β-actin mRNA and the fold change were determined using ΔΔCt method.

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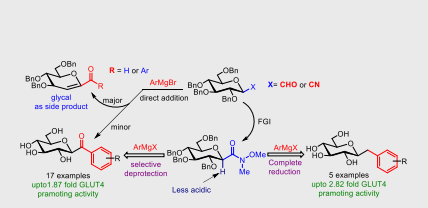

A convenient and scalable approach was developed for the synthesis of acyl-*C*-β-D-glucosides and benzyl-*C*-β-D-glucosides using Weinreb amide (WA) functionality. Addition of organometallic reagents followed by chemo selective deprotection afford the acyl-C-β-D-glucoside and complete reduction of the same could resulted the benzyl-C-β-D-glucosides. The synthesis and biostudies of envisaged *C*-glucosides are presented in this paper.

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Acyl and benzyl-C-β-D-glucosides*

Dr. Mannem Rajeswara Reddy, Dr. Shanmugam Hemaiswarya, Dr. Harikrishna Kommidi, Prof. Indrapal Singh Aidhen, Prof. Mukesh Doble **

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Acyl and Benzyl-*C*-β-*D*-Glucosides: Synthesis and Biostudies for Glucose-Uptake Promoting Activity in C2C12 Mytotubes