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Formation and Selective Rupture of 1,4-Anhydroseptanoses

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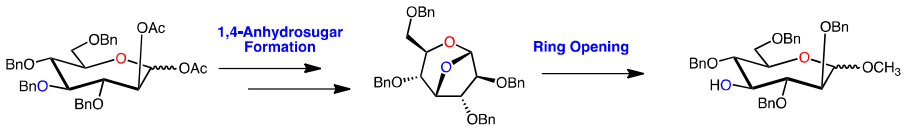
ABSTRACT



Formation 1,4-anhydroseptanose sugars via intramolecular attack of a benzyl ether oxygen onto an anomeric electrophile is reported. The regioselectivity of the cyclization was confirmed by NMR spectroscopy and an X-ray structure of a glucose-derived 1,4-anhydroseptanose. The transformation is relatively general and was applied to septanoses derived from glucose, mannose, xylose, and galactose. Regioselective opening of the 1,4-anhydro species to give septanose glycosides in preference to furanoses is also demonstrated.

Keywords: cyclization, acetal, septanose, anyhdro sugar, benzyl ether

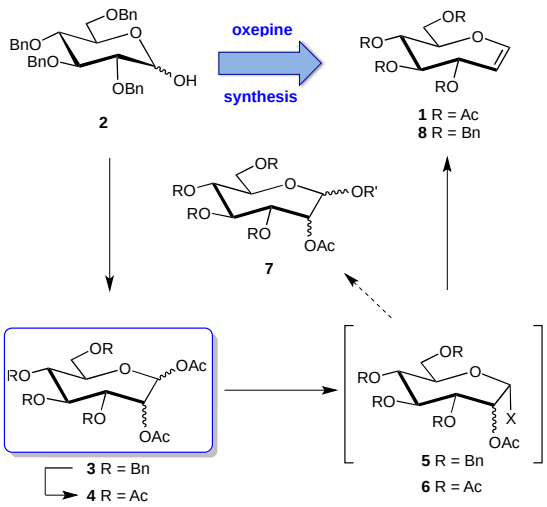
1. Introduction

The continuing search for biological and therapeutic applications of seven membered ring – septanose – carbohydrates requires the development of methods to synthesize these types of compounds.[1,2,3,4] To date, methods used to prepare septanoses can be grouped into two general categories.[5] In the first, 1,2-cyclopropanated sugars are expanded using acidic or basic conditions. In this approach, glycosylation is concomitant with ring expansion. The alternative approach is where glycosylation reactions utilize starting materials akin to those used in the synthesis of pyranose glycoconjugates.[6,7] Our group has been particularly interested in methods in this second category. The synthesis of carbohydrate based oxepines and their utilization as precursors of 1,2-anhydroseptanoses, which are intermediates in glycosylation reactions, have been one thrust of the program. Another has

been the preparation of septanosyl glycosides with a moiety on the anomeric carbon (e.g., -SPh, -F) that acts as a leaving group to create an electrophilic species, which is attacked by nucleophiles to form a new glycosidic bond. Further investigation and development of synthetic methods is required so that more complex targets can be prepared.

We recently reported a strategy for the synthesis of per-*O*-acetyl oxepines such as **1** (Scheme 1).[8] In it, benzyl protected pyranoses (e.g., **2**) were first converted into their corresponding per-*O*-acetyl septanoses (**4**) and, from there, the oxepines (**1**) themselves *via* halogenation and reductive elimination. The per-*O*-acetyl septanoses, analogous to per-*O*-acetyl pyranoses, were key intermediate species in those syntheses. We consider them, along with oxepines, to be useful starting materials for carbohydrate and target molecule synthesis (e.g., conversion of anomeric halides like **5** and **6** into septanosyl glycosides **7**). Conversion of a per-*O*-acetyl septanose to an oxepine required formation of the anomeric halide **6** followed by reductive elimination under Fischer-Zach conditions. The possibility of intercepting an earlier intermediate in the synthesis, like tetra-*O*-benzyl diacetate species **3**, for the preparation of benzyl protected oxepines did not escape our attention. The idea was to convert **3** to its anomeric halide (**5**) and then proceed to oxepines like **8** via reductive elimination. Septanose derivative **3** would potentially serve, therefore, as a common starting material in the preparation of both oxepines and septanosyl glycosides.

Scheme 1. Conversion of pyranose lactols to carbohydrate based oxepines and septanosyl glycosides



When di-*O*-acetyl septanose **3** was subjected to reaction conditions for formation of an anomeric halide (HBr/AcOH), no septanosyl bromide was observed; rather, analysis of the reaction mixture revealed the formation of a different, unexpected product. Here we report the discovery of the reaction by characterization of the new product 1,4-anhydrospetanose by NMR spectroscopy and X-ray crystallography. We further detail the scope of the cyclization reaction using other substrates and provide insight into the possibility that the product 1,4-anhydroseptanoses to serve as glycosyl donors in the formation of septanose glycosides.

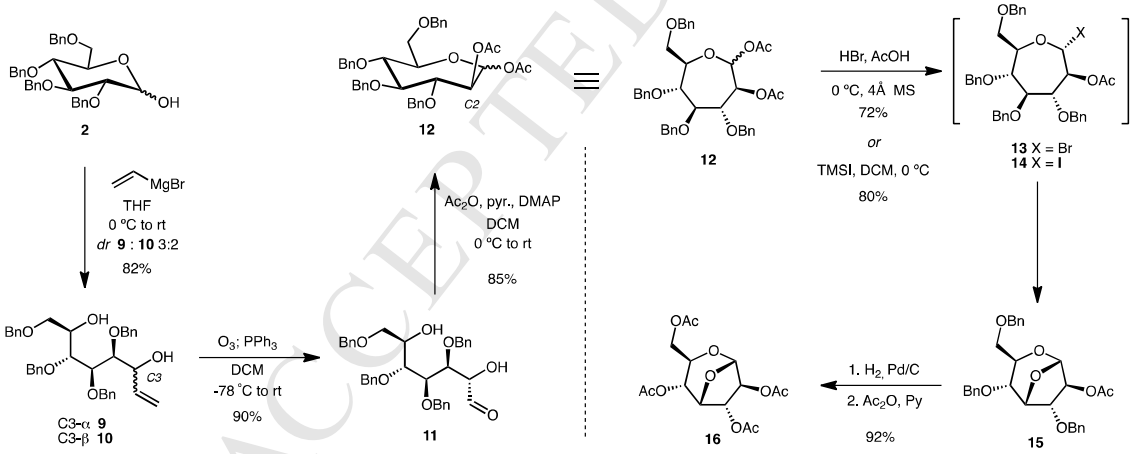
2. Results and discussion

2.1 Intramolecular cyclization and characterization of the 1,4-anhydro product

It was the attempted conversion of 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-idoseptanose **12**, having C2 in the β configuration as shown in Scheme 2, to its anomeric bromide where the 1,4-anhydro formation was first identified. The synthesis of **12** started with the addition of vinyl magnesium bromide to 2,3,4,6-tetra-*O*-benzyl D-glucose **2** to give allylic alcohols **9** and **10** (3:2 **9**:**10**).[9] The major isomer, **9**, was treated with ozone at -78 °C, followed by reduction of the ozonide *in situ* with triphenyl phosphine at the same temperature to provide hydroxy aldehyde **11** in 90% yield. This hydroxy

aldehyde was in equilibrium with the septanose lactol (not shown) as we have noted previously for related compounds.[9,10] Acetylation of the C1 and C2 hydroxyls sequestered the compound in its seven-membered ring configuration, providing exclusively 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-idoseptanose **12** in 85% yield. When **12** was treated with HBr in AcOH, we expected α-septanosyl bromide **13** to form. Rather, within 30 min, TLC analysis of the reaction mixture showed the disappearance of the starting material and the appearance of a new compound; its R_f, however, was lower than the starting material, which was inconsistent with earlier reactions where septanosyl halides (higher R_f) were formed. The ^{1}H NMR spectrum of the purified material (72% isolated yield) showed that a benzyl group had been lost in the reaction and the ^{13}C NMR spectrum of the new compound was inconsistent with the formation of an anomeric bromide. Additional NMR spectra, especially the DEPT spectrum and HRMS data, confirmed the loss of one benzyl group in going from starting material to the product. When **12** was reacted with iodotrimethylsilane, the same compound was isolated in 80% yield.

Scheme 2. Synthesis of di-*O*-acetyl septanose **12** and 1,4-anhydro septanose **16**



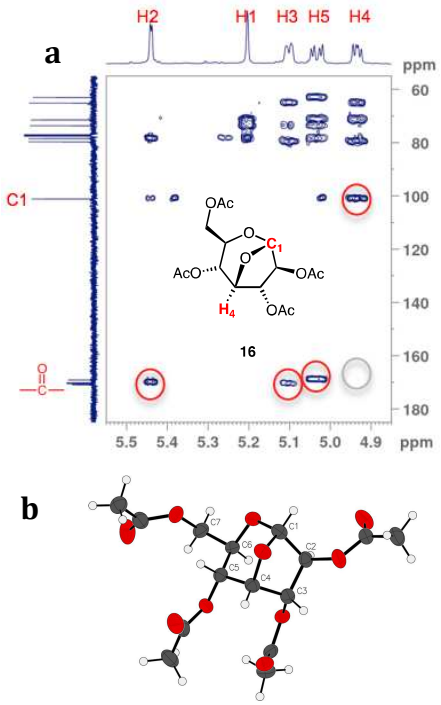


Figure 1. (a) HMBC data used in the structural assignment of **16**. Red circles show the presence of HMBC crosspeaks consistent with the proposed 1,4-anhydro structure. The gray circle identifies where an H4-carbonyl would have been present. (b) Structure of 1,4-anhydroseptanose **16** from the X-ray crystallographic data.

Having obtained preliminary information about the composition of the new compound, we set about collecting more details on its structure. At this stage, the key hurdle was determining which benzyl group had been involved in the intramolecular cyclization reaction.[4d,9,10] Conclusive assignment of the structure was not possible from the NMR spectra of **15** due to coincidental overlap of several NMR signals. Instead, to pinpoint the regiochemistry of the cyclization and the associated anomeric stereochemistry, we switched the protecting groups from benzyl ethers to acetate esters via hydrogenolysis and acetylation (92%, two steps). ^{1}H and ^{13}C NMR spectra of the new, per-*O*-acetyl protected compound were tractable and allowed for the interpretation of each proton and carbon. Analysis of the NMR data allowed the assignment of all of protons H1-H7 (carbohydrate numbering) and their corresponding carbons C1-C7 of 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-idoseptanose, **16**. HMBC data (Fig. 1a) showed correlations between acetyl carbonyl groups and hydrogens on C2, C3,

C5, and C7; no such correlations were observed for the hydrogens on C1, C4, or C6. Also, C1 had a correlation with H4. All of these observations supported the loss of the C4 benzyl group. Hence, we concluded that the compound was the 1,4-anhydroseptanose. Furthermore, a crystal structure of **16** (Fig. 1b) unequivocally supported the NMR structural assignment and absolute configurations at C1 and C2. The connectivity of C4 and C1 via an oxygen in the structure clearly proved that the 1,4-anhydroseptanose **15** was the product of the original cyclization reaction.

2.2 Scope: additional examples of 1,4-anhydroseptanose formation

With the product of the reaction established, its structure suggested that the cyclization was dependent on the ring substituents and the α-configuration of the anomeric halide. We subsequently expanded the investigation to other di-*O*-acetyl starting materials to understand the scope of the cyclization. 1,2-Di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-guloseptanose **17** (Fig. 2 and Table 1), the C2 epimer of **12**, was subjected to a sequence of three reactions: anomeric halide formation,[11] hydrogenolysis, and acetylation. This sequence mirrored the one we had just established in the preparation of **16** and facilitated product characterization. NMR spectroscopy of **18** showed an HMBC spectrum similar to **16** and a $^{3}J_{H1,H2}$ of 4.5 Hz, indicative of the *anti* relationship between the groups at C1 and C2.

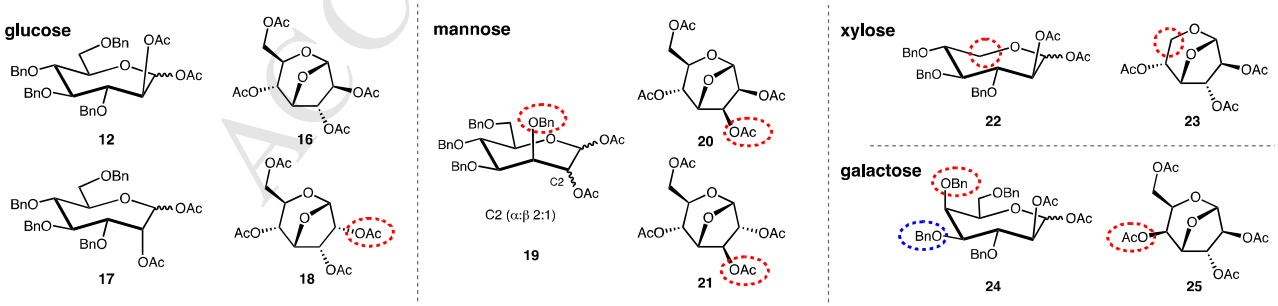


Figure 2. 1,2-Di-*O*-acetyl septanoses and their corresponding 1,4-anhydroseptanse derivatives.

Using the same set of reactions, 1,2-di-*O*-acetyl septanoses **19**, **22**, and **24**, derived from D-mannose, D-xylose, and D-galactose respectively, were converted to their corresponding 1,4-anhydroseptanoses (Fig. 2). We resorted to use of iodotrimethyl silane exclusively for formation of the anomeric halides to avoid side reactions during the cyclization.[11,12] Mannose configured septanose **19**, epimeric at C3 relative to **12** and **17**, was used as a mixture of C1 and C2 isomers because they were inseparable by chromatography. When **19** was subjected to the three-step sequence of reactions, 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-altroseptanose **20** and 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-alloseptanose **21** were isolated in 3:2 ratio at 38% overall yield. Vinyl Grignard addition to tetra-*O*-benzyl xylose is selective and gives only primarily one C2 isomer that can be converted to diacetate **22**. This diacetate species, which lacks an exocyclic alkoxymethyl group, was cleanly converted to 2,3,5-tri-*O*-acetyl-1,4-anhydro-D-idoseptanose **23** (45%, three steps). Galactose analog **24** is distinct from the other derivatives because it gives insight into the strength of the nucleophilicity of the equatorial and axial benzyloxy groups (red and blue circles in Fig. 2). Sequential halogenation, debenzylation and per-acetylation of **24** gave 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-L-glucoseptanose **25** (45%, three steps). Characterization of **25** confirmed that the benzyloxy group at C4 was the only one involved in the cyclization reaction. These results were also consistent with the literature that the equatorial benzyloxy group is more nucleophilic than axial benzyloxy group.[13] The structures of all the per-*O*-acetyl 1,4-anhydroseptanoses **20**, **21** and **25** were characterized by coupling constant analysis. (See Table S1 in Supplementary Data). Overall, the results indicated that the configuration of other ring carbons did not affect the cyclizations en route to the formation of the 1,4-anhydroseptanoses.

Table 1. Yields for conversion of 1,2-di-O-acetyl-tetra-benzyl septanoses to 1,4-anhydro-per-*O*-acetyl septanoses

Entry	**1,2-di-acetyl**	**1,4- anhydro**	**Yield(%)**[a]

1	**12**	**16**	66[b]
2	**12**	**16**	74[c]
3	**17**	**18**	40[b]
4	**17**	**18**	58[c]
5	**19 (2:1 C2 α:β)**	**20:21 (3:2)**	38 [c]
6	**22**	**23**	45 [c]
7	**24**	**25**	45 [c]

[a] three step yield; [b] via the anomeric bromide; [c] via the anomeric iodide

The cyclization reaction forming 1,4-anhydroseptanoses can be explained by a mechanism that has become somewhat familiar to us.[1,9,10] Nucleophilic attack by a benzyl ether oxygen onto a septanosyl electrophile is a central feature of our proposed mechanism. To start, conversion of the 1,2-di-*O*-acetate to its anomeric halide should prefer formation of the α-configured anomeric halides. The oxygen of the C4 benzyloxy group then attacks the C1 halide in an intramolecular fashion yielding a benzyloxonium ion. Whether the attack is S_N2-like on the anomeric halide or onto an oxocarbenium ion is uncertain. It is of little consequence, though, because the configuration of the developing C1 stereocenter is dictated by the attack of the nucleophile. The liberated halide then attacks the benzyl carbon to deliver the 1,4-anhydro product. Both the regioselectivity (formation of 1,4-anhydroseptanoses) and stereoselectivity (the β-configuration at C1) support the proposed mechanism. Moreover, this is another example of a transannular reaction that occurs with septanoses; a five membered ring is formed in the reaction, which is kinetically favored.[14] These types of cyclizations commonly appear in the literature when the two reacting groups are in 1,4-relationship.[15,16] A few examples are debenzylative cycloetherifications in epoxides,[17] allylic systems,[18] and iodoetherification reactions.[19]

The transannular cyclization we report here suggests that septanosyl halide reactivity is different than that of the corresponding pyranosyl halides.[20] In particular, the relatively mild conditions used for the cyclization (halo-trimethylsilane, low temperature) to form 1,4-anhydroseptanoses is in contrast to the formation of 1,4-anhydropyranoses from the corresponding glycosides.[21] One contributing factor to

this difference may be lower barriers to the interconversion of conformers for septanoses.[22] The bifurcated reactivity (i.e. cyclization versus anomeric halide formation) is dependent on the nature of the protecting groups on the ring because both septanoses and pyranoses form stable anomeric halides in the per-*O*-acetyl systems. It is worth noting that, similarly, the efficiency of cyclization for formation of 1,4-anhydrogalactopyranose was higher for a benzyl-protected glycoside compared to a benzoyl-protected one.[21]

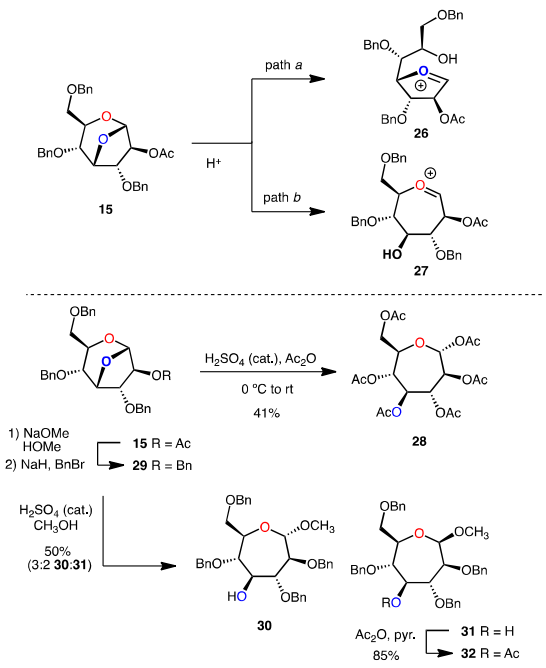
2.3 Selective opening of 1,4-anhydroseptanoses

Seeking to leverage the serendipitous formation of the 1,4-anhydro species to our advantage, we next endeavored to rupture the 1,4-anhydro linkage to expose an electrophile which could be trapped by other nucleophiles. If so, the 1,4-anhydrosugars might eventually be used as building blocks in the synthesis of septanose glycosides. We have shown previously that 1,2-anhydroseptanoses are donors in the synthesis of septanose glycosides. These donors had similar reactivities in comparison to the corresponding 1,2-anhydropyranose analogs. In the pyranose series, 1,4-anhydrosugars are well known to give furanose derivatives in ring-opening reactions under acidic conditions with nucleophiles.[21,23] Additionally access to 1,4-anhydroseptanoses offered the opportunity to explore their fundamental reactivity. For example, **15** can undergo ring opening via two different manifolds (Scheme 3). In one case (path *a*), five-membered ring oxocarbenium **26** forms; the other (path *b*) would give a seven-membered ring oxocarbeium, **27**. Activation under acidic conditions would, therefore, give insight into the relative stabilities of furanoses and septanoses.[24] Moreover, inspection of the crystal structure of **16** lent support to the likelihood for selective ring opening. For **16**, the C1-O4 bond is 1.431 Å whereas the C1-O6 bond is 1.406 Å. It is probable that the bond lengths/bond strengths for C1-O4 and C1-O6 for **15** are also significantly different, favoring the rupture of the weaker C1-O4 bond, which would give **27**.[21]

Reaction of 2-*O*-acetyl-3,5,7-tri-*O*-benzyl-1,4-anhydro-D-*glycero*-D-idoseptanose **15** with Ac_2O and catalytic H_2SO_4 gave hexa-*O*-acetyl-α-D-*glycero*-D-idoseptanose **28** exclusively in 41% yield.

Structural analysis of **28** showed that, in addition to opening of the five-membered ring, the benzyl groups had been cleaved and subsequently acetylated *in situ*. The α-selectivity of the reaction was confirmed by a $^{3}J_{H1,H2}$ coupling constant of 6.8 Hz, a value akin to those observed for 1,2-*trans* disposed protons in septanoses. Also, a ^{13}C NMR chemical shift of 93.1 ppm for C1 is consistent with other α-disposed septanoses. Other conditions aimed at selectively opening **15** resulted in loss of the C2 acetyl group or no observed reaction (Table S3 in the Supplementary Data). Switching the C2 protecting group from an acetyl to a benzyl group (i.e., **15** to **29**, Scheme 3) allowed us to evaluate its donor capabilities. We were delighted to find that catalytic H_2SO_4 in methanol also selectively opened the five membered ring, leading to methyl 2,3,5,7-tetra-*O*-benzyl-α-D-*glycero*-D-idoseptanoside **30** and methyl 2,3,5,7-tetra-*O*-benzyl-β-D-*glycero*-D-idoseptanoside **31** in a combined yield of 50%, based on recovered starting material. Formation of the seven membered ring products was confirmed by acetylation of C4 on β-anomer **31** (to give **32**) and analysis of its HMBC spectrum. While these initial reactions have secured that the five-membered ring of 1,4-anhydroseptanoses ruptures selectively, considerable challenges remain to be overcome in their use as glycosyl donors. Mechanistic studies and more efficient conditions for ring opening will be pursued and reported in due course.

Scheme 3. Ring openings of 1,4-anhydroseptanoses



3. Conclusions

In conclusion, we report the serendipitous formation of 1,4-anhydroseptanoses via intramolecular attack of a benzyloxy ether on an anomeric septanosyl halide. The process is relatively general; we have demonstrated that 1,4-anhydroseptanoses arise in the glucose, mannose, galactose, and xylose series. Moreover, we provide preliminary results that indicate the 1,4-anhydro species can be selectively opened to deliver septanosyl glycosides. This may ultimately open the door to an iterative process for oligomerizing septanose carbohydrates. As such, 1,4-anhydro derivatives will be valuable intermediates towards the synthesis of variety of septanosides.

4. Experimental

4.1. General All the reactions were performed under nitrogen (N_2) atmosphere, unless otherwise noted. All the bromination or iodination reactions were carried out in dark conditions. All commercially available reagents and solvents were used without repurification. All reactions were monitored by TLC (silica gel HL, w/UV254, 250μm) and visualized either under UV lamp or by charring with 2.5% *p*-

anisaldehyde in H_2SO_4, AcOH and EtOH solutions. Flash chromatography was performed on silica gel (60 Å, 40-63 μm). Optical rotations were measured at 22±2 °C, ^{1}HNMR spectra were collected at 400 and 500 MHz with chemical shift referenced to $(CH_3)_4Si$ (δ_H 0.00 ppm) or the residual peak in $CDCl_3$ (δ_H 7.24 ppm).^{13}C NMR spectra were collected at 100 MHz and referenced to residual peak in $CDCl_3$ (δ_C 77.2 ppm).

4.2. General procedure for the ozonolysis and diacetylation of allylic alcohols: Preparation of 3,4,5,7-tetra-*O*-benzyl-1,2-di-*O*-acetyl septanoses. *Ozonolysis*: To a solution of 4,5,7,8-tetra-*O*-benzyl-oct-1-ene-3,6-di-itol (2.0 g, 3.5 mmol, 1 eq.) in DCM (60 mL) cooled to -78 °C on a dry ice-acetone bath was bubbled ozone gas by using a WELSBACH ozone generator until a dark blue color persisted. Upon the appearance of the blue color, ozone generation was ceased and the reaction mixture was purged with oxygen gas until the reaction mixture became clear and colorless once again. With the mixture still at -78 °C, a solution of triphenylphosphine (PPh_3) (4.0 g, 15.3 mmol) in DCM (8 mL) was added drop-wise to the reaction mixture. It was allowed to stir as it warmed to rt over 14 h. After, the solvents were concentrated under reduced pressure and the residue was purified by column chromatography using hexanes: ethyl acetate as a solvent system to give the hydroxyaldehyde as a colorless oil (75 - 91%). *Diacetylation*: To a solution of hydroxyaldehyde (3.0 g, 5.2 mmol, 1 eq.) in DCM (30 mL) was added pyridine (12 mL) and N,N-dimethylaminopyridine (DMAP) (0.063 g, 0.52 mmol, 10 mol%). To this mixture acetic anhydride (21 mL) was added drop by drop at 0 °C. After completion of the reaction (~12 h), ice-cold water was added into the flask and the reaction mixture was extracted with DCM (2 x 90 mL). The combined organic layers were evaporated under reduced pressure and purified by column chromatography using hexane:ethyl acetate as a solvent system to give the respective 3,4,5,7-tetra-*O*-benzyl-1,2-di-*O*-acetylseptanoses (80 - 90%).

4.2.1. 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-idoseptanose **12**

Obtained as colorless oil in 77% yield after two steps using **9** as starting material. R_f 0.4 (5:1 Hex: EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30-7.16 (m, 20H), 5.99 (d, *J* = 7.1 Hz, 1H), 5.38-5.34 (dd, *J* = 9.5, 7.7 Hz, 1H), 4.96-4.73 (m, 4H), 4.66-4.55 (m, 2H), 4.49-4.42 (dd, *J* = 14.5, 11.5 Hz, 2H), 4.02-3.98 (m, 1H), 3.83-3.72 (m, 2H), 3.67-3.59 (m, 2H), 3.52-3.48 (d, *J* = 10.2, 6.6 Hz, 1H), 1.85 (s, 3H), 1.82 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.9, 169.4, 138.4, 138.2, 138.0, 137.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7(2), 127.6, 127.5, 127.4, 126.9, 93.4, 87.9, 79.7, 78.6, 76.4, 75.8, 75.1, 73.5, 72.3, 71.4, 70.2, 20.8, 20.7; TOF HRMS (DART) m/z calcd for $C_{39}H_{46}O_9N$ $(M+NH_4)^+$ 672.3173, found 672.3170.

4.2.2. 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-D-guloseptanose **17**

Obtained as colorless oil in 68% yield after two steps using **10** as starting material. R_f 0.4 (5:1 Hex: EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ; 7.37- 7.19 (m, 40H), 6.07 (d, *J* = 5 Hz, 1H), 5.99 (d, *J* = 8.1 Hz, 1H), 5.73 (d, *J* = 4.8 Hz, 1H), 5.46 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.03-4.32 (m, overlapping signals, 17H), 4.24-4.09 (m, 3H), 3.99 (m, 1H), 3.88 (m, 2H), 3.76-3.62 (m, 5H), 2.23-2.06 (m, 10H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 169.7, 169.1, 138.8, 138.5, 138.2, 138.1, 137.9, 137.8, 137.5, 128.6, 128.4 (2), 128.4, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6,95.3, 89.6, 80.8, 80.2, 78.2, 77.9, 76.6, 75.5, 73.7, 73.3, 73.3, 73.2, 72.5, 72.4, 72.1, 71.3, 70.5, 70.1, 60.5, 21.2, 21.1, 21.0, 20.9; TOF HRMS (DART) m/z calcd for $C_{39}H_{46}O_9N$ $(M+NH_4)^+$ 672.3173, found 672.3170.

4.2.3. 1,2-di-*O*-acetyl-3,4,5,7-tetra-*O*-benzyl-D-*glycero*-L-glucoseptanose **24**

Obtained as colorless oil in 66% yield after two steps using the galactose-derived oct-1-ene-itol **S6** as starting material. R_f 0.4 (5:1 Hex: EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.43-7.33 (m, 40H), 6.21 (d, *J* = 8.1 Hz, 1H), 5.78 (d, *J* = 2 Hz, 1H), 5.37-5.26 (m, 2H), 5.10-5.06 (m, 2H), 4.99-4.68 (overlapping signals, 9H), 4.60-4.46 (m, 4H), 4.32 (dd, *J* = 9.3, 4.2 Hz, 1H), 4.21-4.17 (m, 3H), 4.11-4.01 (m, 3H), 3.89-3.85 (m, 1H), 3.80-3.68 (m, 3H), 2.21-1.97 (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.4, 169.5 (2), 169.2, 138.5, 138.3, 138.2, 138.1, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 93.6, 90.2, 83.5, 83.1, 79.7, 79.2, 78.8, 78.1, 77.8, 76.0, 75.0, 74.9, 74.8, 74.7, 74.5, 74.3,

74.2, 74.0, 73.4 (2), 68.4, 68.3, 21.0, 20.9, 20.8; TOF HRMS (DART) m/z calcd for $C_{39}H_{42}O_9Na$ $(M+Na)^+$ 677.2727, found 677.2710.

4.3 General procedure for conversion of 3,4,5,7-tetra-*O*-benzyl-1,2-di-*O*-acetyl septanoses and to 1,4-anhydroseptanoses: Preparation of 2-*O*-acetyl-3,5,7-tri-*O*-benzyl-1,4-anhydroseptanoses. *Using HBr in Acetic Acid:* To a solution of di-*O*-acetyl-tetra-*O*-benzyl septanose (0.25 g, 0.38 mmol, 1 eq.) containing 4 Å molecular sieves in dry DCM (5 mL) was added 33% HBr in AcOH (0.22 mL, 1.1 mmol, 5 eq.) dropwise at 0 °C. TLC was used to analyze the progress of the reaction. Upon complete disappearance of starting material (R_f 0.4 in 4:1 hexane:ethylacetate), the reaction mixture was then filtered using frit to remove the molecular sieves and poured over ice (~30 g) in a beaker. The resulting mixture was extracted with DCM (3 x 20 mL). The organic layer was then washed with sat'd $NaHCO_3$ (1 x 30 mL), H_2O (1 x 30 mL), sat'd NaCl (1 x 30 mL) and dried with Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by column chromatography using a gradient elution with hexanes:ethyl acetate to give respective the 1,4-anhydroseptanoses (50 - 72%). *Using Iodotrimethylsilane:* To a solution of di-*O*-acetyl-tetra-*O*-benzyl-septanose (0.740 g, 1.13 mmol, 1eq.) in DCM (18 mL) was added TMSI (0.161 mL, 1.13 mmol, 1 eq.) at 0 °C. The reaction mixture was stirred at rt for 0.5 h. The reaction mixture was then diluted with more DCM (20 mL) and the organic layers were washed with $Na_2S_2O_3$ (2 x 15 mL), H_2O (1 x 15 mL), sat'd NaCl (1 x 15 mL) and dried with Na_2SO_4. The solvents were removed under reduced pressure and the residue was purified by column chromatography using a gradient solvent system with hexane:ethyl acetate to give respective 1,4-anhydroseptanoses (60 - 80%).

4.3.1. 2-*O*-acetyl-3,5,7-tri-*O*-benzyl-1,4-anhydro-D-*glycero*-D-idoseptanose **15**

Obtained as colorless oil in 72% yield from **12** using HBr in acetic acid. Using iodotrimethylsilane gave the same compound in 80% yield from **12**. R_f 0.3 (10:3 Hex: EtOAc); $[\alpha]_D$ +26.7 (c 10, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.26-7.17 (m, 15H), 5.24 (s, 1H), 5.04 (s, 1H), 4.60- 4.41 (m, 8H), 4.23-4.17 (m,

2H), 3.85-3.82 (dd, *J* = 3.1 Hz, 1H), 3.67-3.60 (m, 2H), 2.00 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.0, 138.2, 138.0, 137.8, 128.5, 128.4, 128.1 (2), 128.0, 127.8, 101.7, 84.6, 81.3, 74.8, 74.6, 73.7, 73.3, 73.2, 72.6, 68.9, 21.1; TOF HRMS (DART) m/z calcd for $C_{30}H_{33}O_7$ $(M+H)^+$ 505.2226, found 505.2209.

4.4 General procedure for debenzylation and per-*O*-acetylation of 2-O-acetyl-3,5,7-tri-*O*-benzyl-1,4-anhydroseptanoses. *Debenzylation*: To a solution of tri-O-benzyl-1,4-anhydroseptanose (0.1 g, 0.2 mmol, 1 eq.) in THF (2 mL), was added 25 weight percent of 10% of Pd/C (0.025 g) and the mixture was stirred for 12 h at rt under an atmosphere of hydrogen gas. The mixture was then filtered through celite and the filter was washed with additional MeOH (~25 mL). The combined solvents were removed under reduced pressure to give the 1,4-anhydrosugar as colorless oil. This material was carried on to the next step directly. *Per-acetylation*: The crude, deprotected 1,4-anhydrosugar was dissolved in pyridine (3.2 mL), and acetic anhydride (1.5 mL) was added at 0 °C and stirred it for 12 h at rt. The mixture was concentrated under reduced pressure and purified by column chromatography using gradient Hex: EtOAc as solvent system to give respective 1,4-anhydro-per-*O*-acetyl septanoses (50 - 92%).

4.4.1. 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-idoseptanose **16**

Obtained as white solid in 92% yield from **15** after two steps. m.p. 140.7-141.3 °C; R_f 0.4 (1:1 Hex: EtOAc); $[\alpha]_D$ -16.2 (c 1.6, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.40 (d, *J* = 2 Hz, 1H), 5.17 (s, 1H), 5.06 (m, 1H), 5.00 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.90 (dd, *J* = 6.3, 4.0 Hz, 1H), 4.25- 4.21 (m, 1H), 4.19-4.11 (m, 2H), 2.10-2.08 (m, 9H), 1.97 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 170.1, 169.1, 101.1, 79.6, 78.4, 73.5, 71.4, 65.0, 62.9, 20.9 (2), 20.7, 20.6; TOF HRMS (DART) m/z calcd for $C_{15}H_{21}O_{10}$ $(M+H)^+$ 361.1135, found 361.1151.

4.4.2. 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-guloseptanose **18**

Obtained as colorless oil in 40% overall yield from **17** after three steps using HBr for formation of the anomeric halide and 58% overall yield from **17** using iodotrimethylsilane. R_f 0.4 (1:1 Hex: EtOAc); $[\alpha]_D$

-47.9 (c 0.6, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.41 (d, *J* = 4.5 Hz, 1H), 5.29-5.26 (dd, *J* = 10.2, 6.7 Hz, 1H), 5.13-5.10 (dd, *J* = 9.6, 4.6 Hz, 1H), 5.04-5.01 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.81-4.79 (dd, *J* = 6.2, 3.9 Hz, 1H), 4.48-4.45 (ddd, *J* = 10.3, 4.8, 2.1 Hz, 1H), 4.24-4.21 (dd, *J* = 12.2, 2.2 Hz, 1H), 4.16-4.12 (dd, *J* = 12.2, 4.8 Hz, 1H), 2.18 (s, 3H), 2.11 (m, 6H), 2.01 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.0, 170.1, 169.7, 169.3, 96.2, 72.8, 70.8, 68.8, 67.4, 65.2, 63.0, 21.0, 20.7 (2), 20.6; TOF HRMS (DART) m/z calcd for $C_{15}H_{21}O_{10}$ $(M+H)^+$ 361.1135, found 361.1106.

4.4.3. 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-altroseptanose **20**

Obtained as colorless oil in 14% yield from **19** after three steps using iodotrimethylsilane to form the anomeric halide. R_f 0.4 (1:1 Hex: EtOAc); $[\alpha]_D$ +74.1 (c 4.5, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.41 (m, 2H), 4.89-4.84 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.63 (d, *J* = 4.4 Hz, 1H), 4.25-4.21(dd, *J* = 12.0, 2.2 Hz, 1H), 4.14-4.10 (m, 1H), 3.79-3.74 (m, 1H), 2.13-2.06 (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.8, 170.0, 169.7 (2), 102.0, 79.8, 74.6, 71.1, 70.5, 63.9, 63.0, 20.9, 20.8, 20.6, 20.4 ; TOF HRMS (DART) m/z calcd for $C_{15}H_{20}O_{10}$ $(M+H)^+$ 361.1135, found 361.1150

4.4.4. 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-alloseptanose **21**

Obtained as colorless oil in 24% yield from **19** after three steps using the iodotrimethylsilane to form the anomeric halide. R_f 0.3 (1:1 Hex: EtOAc); $[\alpha]_D$ +100.2 (c 2.2, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.58 (d, *J* = 4.4 Hz, 1H), 5.25 (d, *J* = 2.4 Hz, 1H), 5.15-5.14 (m, 1H), 4.89-4.85 (dd, *J* = 10.1, 4.5 Hz, 1H), 4.48 (d, *J* = 4.4 Hz, 1H), 4.28-4.24 (dd, *J* = 2.2, 11.9 Hz, 1H), 4.15-4.10 (dd, *J* = 4.9, 11.9 Hz, 1H), 4.08-4.04 (m, 1H), 2.14-2.10 (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.9, 170.7, 169.9, 168.8, 96.9, 78.7, 78.5, 75.6, 70.7, 64.4, 63.0, 21.0, 20.9, 20.8, 20.6; TOF HRMS (DART) m/z calcd for $C_{15}H_{21}O_{10}$ $(M+H)^+$ 361.1135, found 361.1152.

4.4.5. 2,3,5-tri-*O*-acetyl-1,4-anhydro-D-idoseptanose **23**

Obtained as colorless oil in 45% yield from **22** after three steps using iodotrimethylsilane to form the anomeric halide. R_f 0.5 (1:1 Hex: EtOAc); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.46 (d, *J* = 2.1 Hz, 1H), 5.21 (m, 1H), 5.17 (m, 2H), 4.94 (dd, *J* = 4.8, 4.8Hz, 1H), 4.15 (m, 1H), 3.95 (dd, *J* = 10.7, 10.7 Hz, 1H),

2.16 (s, 6H), 2.03 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.5, 170.2, 169.2, 100.9, 79.9, 78.3, 73.3, 64.9, 62.8, 20.9, 20.7; TOF HRMS (DART) m/z calcd for $C_{12}H_{17}O_8$ $(M+H)^+$ 289.0923, found 289.0905.

4.4.6. 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-L-glucoseptanose **25**

Obtained as colorless oil in 45% yield from **24** using iodotrimethylsilane to form the anomeric halide. R_f 0.3 (1:1 Hex: EtOAc); $[\alpha]_D$ -12.3 (c 1.7, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.40 (d, *J* = 1.7 Hz, 1H), 5.29 (m, 1H), 5.23 (s, 1H), 4.81 (m, 1H), 4.67 (dd, *J* = 6.8, 1.2 Hz, 1H), 4.42 (m, 1H), 4.21-4.08 (m, 2H), 2.16-2.06 (m, 12H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.8, 170.4, 170.0, 169.7, 101.8, 79.4, 76.5 (2), 69.5, 65.5, 63.3, 21.0, 20.9(2), 20.8; TOF HRMS (DART) m/z calcd for $C_{15}H_{21}O_{10}$ $(M+H)^+$ 361.1135, found 361.1143.

4.5. Hexa-*O*-acetyl-α-D-*glycero*-D-idoseptanose 28

To a solution of 1,4-Anhydroseptanose **15** (0.056 g, 0.111 mmol) in Ac_2O (1 mL) was added H_2SO_4 (0.062 mL, 1.11 mmol) at 0 °C. The reaction mixture was stirred for 1.5h and allowed to warm to rt over that time; progress was monitored by TLC. After completion of the reaction as determined by disappearance of the SM, the mixture was diluted with DCM (10 mL). The organic layer was washed sequentially with H_2O (15 mL), sat'd. $NaHCO_3$ (15mL), and sat'd. NaCl (15 mL), then dried with Na_2SO_4. The solvents were removed under reduced pressure and the crude material was purified by column chromatography using 1:1 Hex: EtOAc as eluent to give 41% of **28** as a clear, colorless oil. R_f 0.31 (1:1 Hex: EtOAc); $[\alpha]_D$ +39.4 (c 1.87, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.03 (d, *J* = 6.7 Hz, 1H), 5.41 (m, 3H), 5.08 (dd, *J* = 10.2, 8.0 Hz, 1H), 4.29 (ddd, *J* = 9.9, 6.1, 2.5 Hz, 1H), 4.19 (dd, *J* = 11.9, 6.3 Hz, 1H), 3.98 (dd, *J* = 11.9, 2.5 Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H); ^{13}CNMR (125.7 MHz, $CDCl_3$) δ 170.6, 169.6, 169.4, 169.1, 168.8, 93.1, 74.4, 70.6, 69.5, 69.3, 67.7, 63.5, 21.1, 20.8, 20.8, 20.6, 20.5, 20.4. TOF HRMS (DART) m/z calcd. for $C_{19}H_{26}O_{13}$ $(M+NH_4)^+$ 480.1717, found 480.1713.

4.6. 2,3,5,7-tetra-*O*-benzyl-1,4-anhydro-D-*glycero*-D-idoseptanose 29

To a solution of 1,4-anhydroseptanose **15** (0.060 g, 0.119 mmol) in MeOH (1.2 mL) was added a catalytic amount of NaOMe (0.004 g, 0.07 mmol). The progress of the reaction was monitored by TLC. When the SM had been consumed, the solvent was evaporated under vacuum and the crude material was dissolved in dry DMF (3 mL). To this solution was added NaH (0.007 g, 0.162 mmol) and benzyl bromide (0.1 mL, 0.14 mmol) and TBAI (0.005 g, 0.02 mmol) at 0 ^{o}C. The reaction mixture was monitored by TLC and quenched with addition of ice-cold water (1 mL). The product was extracted from the mixture with DCM (30 mL) and the organic layer was then washed sequentially with H_2O (20 mL) and sat'd. NaCl (20 mL) and then dried with Na_2SO_4. The solvents were removed under reduced pressure and the crude material was purified by the column chromatography using 7:3 Hex: EtOAc as eluent to give 79% (2 steps) of **29** as colorless oil. R_f 0.73 (7:3 Hex: EtOAc); $[\alpha]_D$ +42.54 (c 0.65, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (m, 20H), 5.21 (m, 1H), 4.65-4.37 (m, 9H), 4.28 (m, 1H), 4.24-4.19 (m, 2H), 3.85-3.80 (dd, J = 9.6, 3.5 Hz, 1H), 3.65 (m, 2H); ^{13}CNMR (75 MHz, $CDCl_3$) 138.2, 137.9, 137.8, 137.5, 129.1, 128.7, 128.6 (2), 128.5 (2), 128.4, 128.2, 128.1, 128 (2), 127.8 (2), 127.1, 101.6, 86.5, 85.6, 74.6, 74.3, 73.6, 73.3, 73.1, 72.9, 69.4. TOF HRMS (DART) m/z for $C_{35}H_{36}O_6$ $(M+H)^+$ calc. 553.2590, obs. 553.2565.

4.7. Methyl 2,3,5,7-tetra-*O*-benzyl-α-D-*glycero*-D-idoseptanoside 30

To a solution of 1,4-anhydroseptanose **29** (0.032 g, 0.058 mmol) in MeOH (2 mL) was added a catalytic amount of H_2SO_4 (4-5 drops) at RT. The reaction mixture was then refluxed at 70 ^{o}C for 48 h, with monitoring by TLC. The reaction mixture was then diluted with 10 mL DCM and the organic layer was washed with H_2O (20 mL), sat'd. $NaHCO_3$ (30mL), and sat'd. NaCl (20 mL), then dried with Na_2SO_4. The solvents were removed under reduced pressure and the crude material was purified by the column chromatography using 3:2 Hex: EtOAc as solvent system to give 51% (b.r.s.m.) of **30** and **31**, both as colorless oils. R_f 0.45 (3:2 Hex: EtOAc); $[\alpha]_D$ -37.63 (c 0.32, $CHCl_3$); ^{1}HNMR (400 MHz, CDCl3) δ

7.33 – 7.12 (m, 20 H), 4.79 (d, J = 11.7 Hz, 1 H), 4.72 (d, J = 4.4 Hz, 1 H), 4.67-4.56 (m, 4 H), 4.51 (m, 2 H), 4.49 (dd, J = 7.7, 1.8 Hz, 1 H), 4.42-4.39 (m, 2 H), 4.20 (dd, J = 7.4, 4.4 Hz, 1 H), 3.94 (quint, 1 H), 3.67 (dd, J = 7.0, 1.7 Hz, 1 H), 3.63 (m, 2 H), 3.34 (s, 3 H), 2.57 (d, J = 6.6 Hz, 1 H); ^{13}CNMR (100 MHz, CDCl3) δ 138.5, 138.1, 137.9, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 100.2, 82.6, 81.3, 77.1, 75.9, 73.3, 73.3, 73.2, 71.0, 70.3, 55.2. TOF HRMS (DART) m/z for $C_{36}H_{40}O_7$ $(M+NH_4)^+$ calc. 602.3118, obs. 602.3108.

4.8. Methyl 2,3,5,7-tetra-*O*-benzyl-β-D-*glycero*-D-idoseptanoside 31

R_f 0.58 (3:2 Hex: EtOAc); ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.34-7.24 (m, 20H), 4.94 (d, J=1.9 Hz, 1H), 4.9 (d, J=11.4 Hz, 1H), 4.58-4.53 (m, 3H), 4.49-4.43 (m, 4H), 4.38-4.36 (dd, J=5.3, 6.5Hz, 1H), 4.09-4.06 (m, 2H), 3.95 (app t, 1H) 3.86 (quint, 1H), 3.59-3.58 (m, 2H), 3.44 (s, 3H); ^{13}CNMR (125.7 MHz, CDCl3) 139.2, 138.3, 137.9, 137.8, 128.6 (2), 128.4, 128.3, 128.1, 128.0, 127.9 (2), 127.5, 108.6, 85.6, 81.9, 81,5, 78.9, 74.4, 73.5, 74.4, 73.5, 72.1 (2), 71.1 (2), 56.3. TOF HRMS (DART) m/z calcd. for $C_{36}H_{40}O_7$ $(M+NH_4)^+$ 602.3118, found 602.3159.

4.9. Methyl 4-O-acetyl-2,3,5,7-tetra-*O*-benzyl-β-D-*glycero*-D-idoseptanoside 32

To a solution of **31** (5mg, 0.01mmol) was added pyridine (0.309 mmol 0.025mL) and Ac_2O (0.206 mmol, 0.02 mL) at 0 ^oC. The reaction mixture was allowed to warm to RT and reaction progress was monitored by TLC. After the completion, the reaction mixture was diluted with 5 mL DCM. The organic layer was washed with H_2O (15 mL), sat'd. NaHCO3 (15mL), and sat'd. NaCl (15 mL), then dried with Na_2SO_4. The solvents were removed under reduced pressure and the crude material was purified by the preparative TLC using 7:3 Hex: EtOAc as solvent system to give 85% of **32** as colorless oil. R_f 0.62 (7:3 Hex: EtOAc); $[\alpha]_D$ -305.52 (c 0.25, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 20 H), 5.24 (dd, J=9.2,5.0 Hz, 1 H), 4.91 (d, J=1.9 Hz, 1 H), 4.83 (d, J=11.5 Hz, 1 H), 4.65 (d, J=11.6 Hz, 1 H), 4.58 – 4.46 (m, 4 H), 4.43-4.39 (dd, J=11.9,1.7 Hz, 2H) 4.35 (dd, J=6.2, 5.4 Hz, 1H), 4.05 – 4.01 (m, 3 H),

3.82-3.79 (dd, J=10.4, 4.9 Hz, 1H), 3.66-3.62 (dd, J=10.5, 5.5 Hz, 1H), 3.39 (s, 3 H), 1.99 (s, 3 H); ^{13}CNMR (100 MHz, CDCl3) δ 169.9, 139.1, 138.1, 137.7, 137.5, 128.4 (2), 128.3, 128.1, 127.8 (2), 127.7, 127.6 (2), 127.2, 108.3, 85.3, 81.0 (2), 78.6, 74.3, 73.0, 72.6, 72.2, 71.9, 68.0, 55.9, 29.7, 21.1; TOF HRMS (DART) m/z for $C_{38}H_{42}O_8$ $(M+NH_4)^+$ calc. 644.3223, obs. 644.3256.

Supplementary Data

Supplementary data associated with this article can be found in the online version at: URLXXX. Materials are available in two files: 1 –additional experimental details, physical characterization and NMR spectra of new compounds; 2 – a crystal information file (.cif) of 2,3,5,7-tetra-*O*-acetyl-1,4-anhydro-D-*glycero*-D-idoseptanose, **16.**

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11. Bromination of **17** gave two anhydro compounds. One was the C2 epimer of **15** (compound **S2**) and the other was the C5 de-benzylated analog (**S3**). Upon hydrogenolysis and acetylation, both of these compounds converged to give **18**. Debenzylation during the cyclization step was not observed when iodotrimethyl silane was used. See Supplementary data for details.

12. Additional information on the intermediates in the route to **20**, **21**, **23**, and **25** are in the Supplementary Data.

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