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Formation of and glycosylation with per-*O*-acetyl septanosyl halides: Rationalizing complex reactivity en route to *p*-nitrophenyl septanosides

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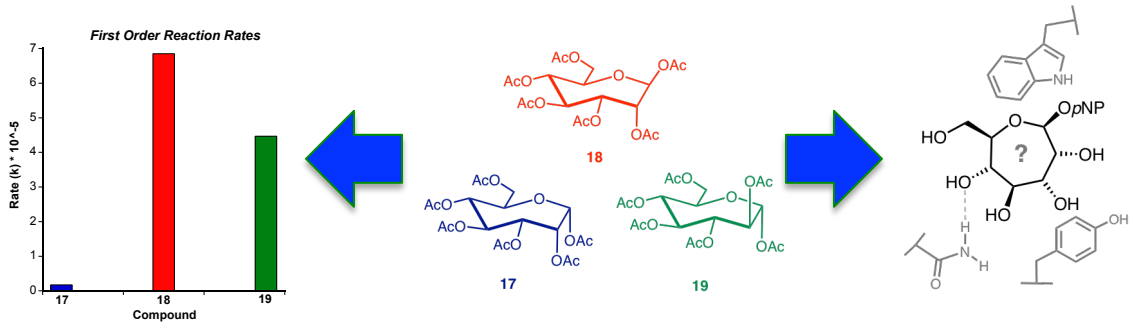
TOC Graphic



Key Topic

Carbohydrate Synthesis

Short Text

Glycosylation in the new old-fashioned way. A synthetic method to attach ring-expanded, septanose sugars to other compounds has been developed. Septanosyl halides were the key donors the glycosylations. The *p*-nitrophenyl septanoside products will be particularly useful tool compounds to evaluate septanose-glycosidase interactions.

Abstract

Protein-carbohydrate interactions are at the heart of many biological processes. For lectins, those interactions result simply in the association of two species, whereas for enzymes like glycosidases, association ultimately leads to cleavage and formation of covalent bonds. We have investigated lectin-septanose interactions in the past. Here we report on a route to synthesize *p*-nitrophenyl septanosides *via* the corresponding setpanosyl halides. During the investigation we observed differential rates of glycosyl halide formation of the per-*O*-acetyl septanoses based on the stereochemistry at C1 and C2. Further, we observed unexpected stereoselectivities in glycoside bond formation that depended on a number of factors including the electrophilic sugar species, the incoming nucleophile, and reaction conditions. The results provided new parameters to consider when approaching septanose glycosylations. Even more importantly, the synthesis of *p*-nitrophenyl septanosides will enable them to be used to interrogate septanose-glycosidase binding and hydrolysis.

Keywords

septanose carbohydrate; glycosylation; Koenigs-Knorr; kinetics;

Introduction

Homologated nucleosides, amino acids, and monosaccharides are related by the manner in which they mimic the corresponding naturally-occurring metabolites. The addition of another atom into their monomer structures sets up a situation where new, unique properties are manifested in addition to the original properties.[1] We have applied the homologation approach to pyranose sugars by investigating the synthesis and properties of seven membered-ring septanose carbohydrates.[2,3] An early question addressed was, "Can septanoses act as proxies for pyranoses in protein-carbohydrate interactions?" As shown in Figure 1, the question gets at how proteins may or may not be able to recognize the larger ring septanose sugars. An investigation on the binding of septanosides by the model lectin Concanavalin A provided interesting details on the interaction and confirmed that they can, in fact, act as ligands.[4] Key observations made in that study were that β- configured septanosides were bound instead of α- ones (opposite to the preference observed for pyranosides), affinity was approximately one order of magnitude lower than pyranosides, and that septanosides were binding competitively at the pyranoside binding site. Computational models of the complexes supported a binding mode with a similar set of hydrogen bonds between the protein and the monosaccharides and that binding was primarily enthalpy driven. Modeling also suggested that the orientation of septanosides in the monosaccharide binding pocket were ratcheted relative to pyranosides. That is, the C7 exocyclic hydroxymethyl group of septanoses was equivalent to C6 of pyranoses, C5 of septanoses was the cognate of pyranose C4, and so on. These principles were recently applied to the design and synthesis of septanose ligands of the *E. coli* lectin FimH, which is implicated in a majority of urinary tract infections.[5]

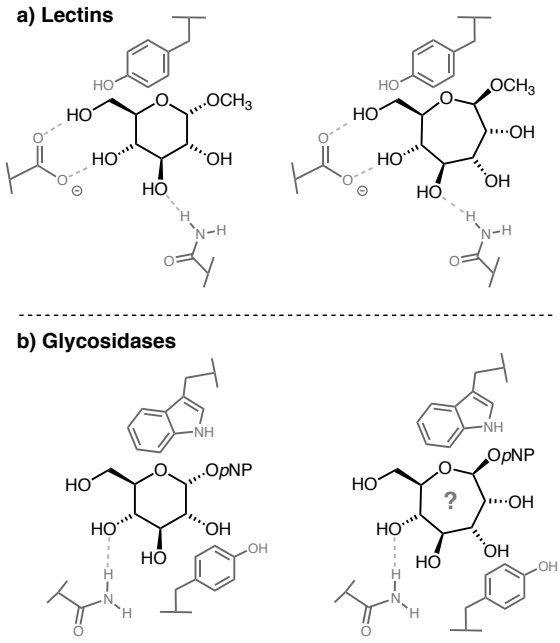
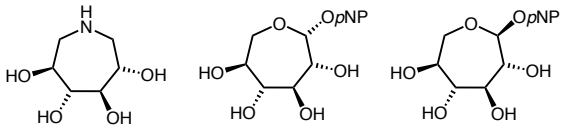


Figure. 1. Modes of protein-carbohydrates interaction, organized by class of protein: a) typical interactions in a lectin-ligand interaction; b) typical glycosidase-substrate interactions.

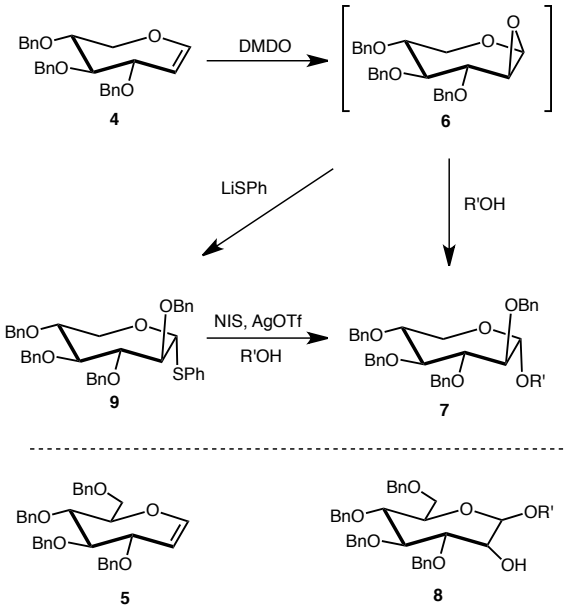
Another broad class of proteins that bind pyranosides is composed of glycoside hydrolase enzymes (glycosidases).[6] A logical extension of our investigation of protein-septanose interactions, therefore, is to inquire whether septanosides can act as substrates for transformations by glycosidases (Fig. 1). Stütz and coworkers previously reported on this question.[7] Their approach was rooted in the fact that 1,6-dideoxy-1,6-imino-iditol **1** is an inhibitor of glycosidases, so structurally related glycosides should be substrates. Their results showed that glycosides such as **2** and **3** were, in fact, weak substrates of glycosidases and that there was a selectivity for the configuration of the C1 anomeric position. Alpha configured septanoside **2** was preferred over β- septanoside **3** as a substrate for an α-glucosidase from *Saccharomyces*, for example. The aglycon of the septanosides was important to the investigation; the UV-vis activity of *p*-nitrophenol and its conjugate base, the *p*-nitrophenyate anion provide clear and quantifiable evidence of hydrolysis. To explore the possibility that the D-*glycero*- septanosides that had been previously investigated by us (that contain an exocyclic hydroxymethyl group) would also be substrates of glycosidases, the development of a new method to prepare *p*-nitrophenyl (pNP) septanoside substrates was required.



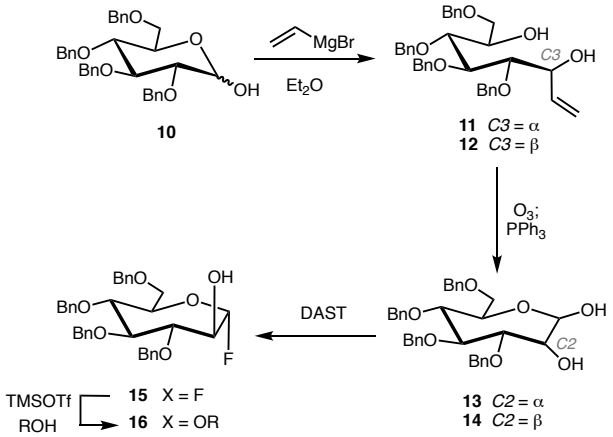
Reported methods for the synthesis of septanose glycosides have followed two main strategies, both of which ultimately rely on natural pyranoses as starting materials. [3] The first method directly adds a carbon to a glycal *via* a cyclopropanation reaction followed by a ring opening, which is concomitant with glycoside bond formation. In the other method, a pyranose ring is expanded by any of number of different routes to species containing functionality that enable glycosylation in subsequent steps. These "glycosyl donors" are analogs of their pyranose counterparts and glycosylations using them use similar reagents and conditions. For example, carbohydrate based oxepines **4** and **5** as in Scheme 1 contain cyclic enol ethers that can be converted to the 1,2-anhydroseptanose by epoxidation (e.g., **6**). The anhydroseptanose is then susceptible to regioselective (and diastereoselective) ring opening *via* attack by nucleophiles that set the glycosidic bond, giving septanosides such as **7** and **8**.[8,910,11] We have also shown that thioglycosides such as **9** and anomeric fluorides like **15** (Scheme 2) can be activated by

thiophilic reagents or Lewis acids, respectively, to generate electrophilic species that are trapped by nucleophiles to again give glycosides **7** and **16**.[12] It should be noted that, whereas thiophenyl glycoside **9** was itself prepared from an oxepine, glycosyl fluoride **13** arose by a longer sequence of steps. Vinyl Grignard addition on protected pyranose lactol **10** gave a diastereomeric mixture of allylic alcohols **11** and **12** (Scheme 2). After separation, ozonolysis of **11** yielded hemiacetals like **13** or **14**. The hemiacetal like **13** with a specific C2 configuration, was then converted to glycosyl fluoride **15**, and ultimately glycosides such as **16**. [13,14]

Scheme 1. Oxepine-Based Routes for the Synthesis of Septanosyl Glycosides



Scheme 2. Synthesis of and glycosylation with a septanosyl fluoride



The target *p*-nitrophenyl glycosides carried with them some considerations that had to be addressed as we embarked on their synthesis. Benzyl protected donors, for example, were incompatible with our approach. We reasoned that, during the deprotection of the benzyl groups *via* hydrogenolysis, the nitro-aryl moiety would also be reduced to the anilino glycoside. Further, because *p*-nitrophenol is a weak nucleophile, the benzyl ethers would compete as nucleophiles, potentially forming 1,4-anhydroseptanoses, which we had observed previously.[15] Also, anomeric fluorides such as **15** would likely be prone to formation of α-linked glycosides only.[13,14] Another consideration was the interplay between the C2 stereochemistry and mechanistic pathway of the glycosylation reactions. Specifically, we wanted to learn if groups at C2 would participate and how that would influence anomeric stereochemistry. With these considerations in mind, acyl protected sugars, like per-*O*-acetyl septanoses **17**-**20** in Figure 2 were chosen for the synthesis of the pNP septanosides. Inspiration for targeting per-*O*-acyl sugars as starting materials came from the known versatility of per-*O*-acetyl pyranoses in glycosylation reactions,[16,17,18] as well as from our recent synthesis of acetate protected carbohydrate based oxepines where per-O-acetyl septanoses were key intermediates.[19] Here we report the conversion of the glucose-derived per-*O*-acetyl septanoses to anomeric halides and their subsequent glycosylations, including formation of the pNP septanosides. We further report on the influence the stereochemistry at C1 (anomeric) and C2 has on the rate and distribution of products of these reactions.

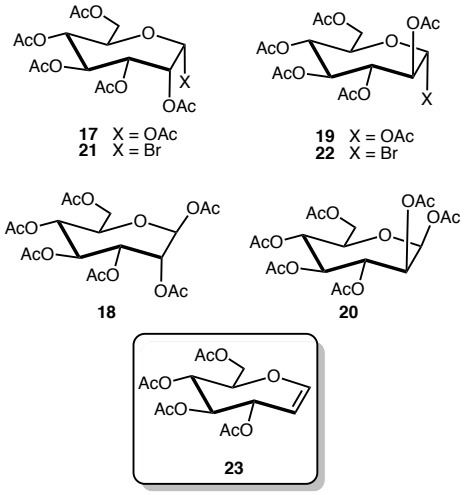


Figure 2. Per-*O*-acetyl septanoses, their corresponding α-anomeric bromides, and oxepine **23**.

Results and Discussion

Formation of Septanosyl Bromides

In our recent synthesis of oxepines, per-*O*-acetyl septanoses (i.e., **17**-**20**) were the key intermediates. They were prepared by vinyl Grignard addition to benzyl-protected pyranose lactols, followed by ozonolysis and protecting group manipulations.[19,20,21] Once in hand, the per-*O*-acetates were converted to their anomeric bromides (**21**, **22**) and then the cyclic enol ether (oxepine) **23** *via* reductive elimination of bromide and acetate across the C1-C2 bond. In that synthesis, the configurations of C1 and C2 were ultimately of no consequence because they were removed en route to the oxepine product. Anomeric mixtures of **17**-**20** (four diastereomers!) were therefore directly subjected to the sequence of bromination and reductive elimination in that process. Using a similar logic, we reasoned that anomeric mixtures of each of the C2 diastereomers could be used in the formation of the corresponding septanosyl bromides. The fact that the compounds were mixtures of two anomers was of little concern to us because we assumed that the C1 center would coalesce to the α-configuration upon formation of the anomeric bromide. Compounds **17** and **18** were the α- and β-anomers of one C2 series ("2*R* series") and **19** and **20** the other ("2*S* series").

The anomeric mixtures were transformed to the septanosyl bromides under standard reaction conditions: anhydrous HBr in acetic acid with methylene chloride as solvent at room temperature. Product anomeric bromides were characterized by ^{1}H and ^{13}C NMR spectroscopy after work up, but without extensive purification. Prolonged storage resulted in hydrolysis, forming the acetate protected lactols. Spectral data to support the assignment of α-configuration included the following. For **21,** H1 δ = 6.43 ppm, $^{3}J_{H1,H2}$ = 4.6 Hz, and δ ^{13}C of C1 = 84.5 ppm; for **22,** H1 δ = 6.12 ppm, $^{3}J_{H1,H2}$ = 8.2 Hz, and δ ^{13}C of C1= 87.1 ppm. The spectra for **21** and **22** were therefore consistent with the selective formation of only one anomer of relatively high purity (See Supplementary Information).

Synthesis of septanose glycoconjugates using bromides as donors

Having established a method to synthesize septanosyl bromides **21** and **22**, we next endeavored to use them in glycosylation reactions. Glycosyl bromides are venerable glycosyl donors, being the glycosylating agents used in Koenigs-Knorr reactions.[16,22] Activation of septanosyl bromide **21** or **22** with AgOTf in the presence of methanol yielded **24** and **25**, respectively, in 29% and 52% yields (Table 1 and Fig. 3). Glycosylation of *n*-octanol with **22** under the same reaction conditions yielded septanoside **26** in 38% yield, accompanied by 13% of the α-anomer (structure not shown). Finally, when diacetone D-galactose was then reacted with **22** under the Koenigs-Knorr conditions, α-septanoside **27** was the only product, albeit in modest yield (21%). Whereas the selective formation of β-septanoside **24** from **21**

can be rationalized by neighboring group participation, the trend for glycosylations involving **22** are less intuitive. It was noted, though, that with increased steric bulk of the acceptor, the formation of α-septanoside increased. The results were counterintuitive because the acetate protecting group at C2 in the donors was expected to be participatory.

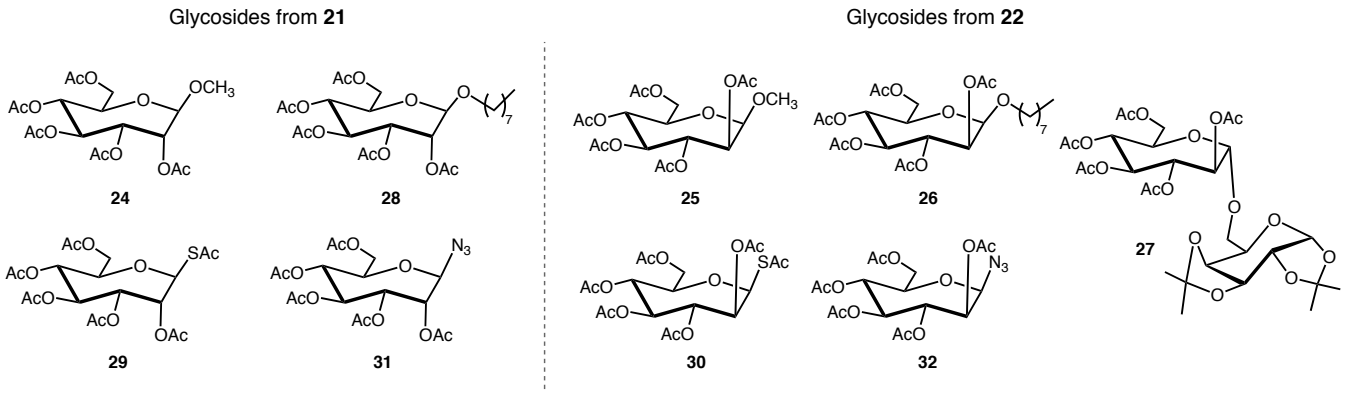


Figure 3. Products of glycosylation reactions using anomeric bromides **21** and **22**.

Table 1. Glycosylation reactions of anomeric bromides **21** and **22**

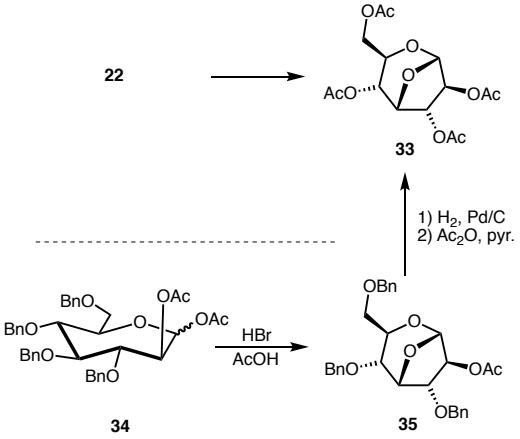
entry	donor	acceptor	con.	product	yield
1	**21**	methanol	A	**24**	29[a]
2	**22**		A	**25**	52[b]
3	**22**	*n*-octanol	A	**26**	38[c]
4	**22**	diacetone-D-galactose	A	**27**	21
4	**21**	methanol	B	**24**	46
5	**22**		B	**25**	56
6	**21**	*n*-octanol	C	**28**	32[a]
7	**22**		C	**26**	43
8	**21**	KSAc	D	**29**	47
9	**22**		D	**30**	51
10	**21**	NaN_3	E	**31**	60
11	**22**		E	**32**	33

Conditions: A: AgOTf, DCM, 0 °C-rt; B: I_2, DCM, 0 °C-rt; C: I_2, DDQ, DCM, 0 °C-rt; D: KSAc in acetone, rt; E: NaN_3 in DMF, 60 °C
a **17** was also recovered from this reaction: 9% (entry 1), 10% (entry 6).
b 1,4-Anhydro product **33** was also isolated from this reaction (23%).
c The α-product was also isolated in 13%. See Supplementary Information.

Notably, in the Koenigs-Knorr glycosylation of **22** to form methyl septanoside **25**, a side product was isolated in appreciable amounts (23%) from the reaction mixture. The other product proved to be, after spectroscopic characterization, 1,4-anhydro adduct **33** (Scheme 3), a compound we have previously characterized.[15] Similarly, attempted glycosylation of phenol[23] with **22** under these conditions, or activation of **22** in the absence of any acceptor at all, led only to isolation of the 1,4-anhydro product in 25% yield in both cases. We originally saw formation of the 1,4-anhydrosugar when we attempted to

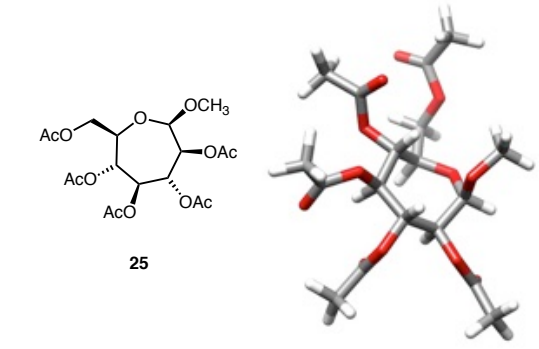
form the 3,4,5,7-tetra-*O*-benzyl-2-*O*-acetyl α-septanosyl bromide from its corresponding diacetate **34**; [15] instead, we isolated 1,4-anyhdroseptanose **35** from that reaction. The benzyl protecting groups were converted to acetates to facilitate its characterization. Because of the ample precedent of benzyl ethers acting as nucleophiles in cyclization reactions,[24] a mechanism that explained the conversion of **34** to **35** was readily apparent. A mechanism to describe the cyclization for the per-acetyl bromides such as **22**, on the other hand, escaped us. We decided, therefore, to explore related activation methods in an effort to gain more understanding about the initial observations made in these reactions.

Scheme 3. Routes to formation of 1,4-anhydroseptanose **33**



In an effort to avoid the formation of the 1,4-anhydro product, we decided to utilize a milder Lewis acid as activator. [25] Activation of septanosyl bromides **21** and **22** with iodine in the presence methanol afforded the corresponding β-septanosides **24** and **25** with a high degree stereocontrol, forming the β-septanosides in yields that were slightly better (46% and 56%, respectively) than the Koenigs-Knorr reactions (Table 1). Glycosylation of *n*-octanol similarly yielded **26** and **28** as the major products in moderate yields (36% and 43%) with the β-glycoside as a major product in both the cases.[26] In the case of the Koenigs-Knorr and iodine mediated glycosylations, reactions proceeded through some version of cyclic oxocarbenium intermediate formed due to removal of bromide anion. [27] The intermediate was then presumably trapped with the incoming nucleophile to deliver the products selectively. In the case of **24** and **28** (Fig. 3), the C2 acetate is likely participatory, therefore preventing nucleophilic attack on the α-face. This is not the case during glycosylations to form **25** and **26**; formation of β-products in glycosylation by **22** was unexpected, and we originally anticipated formation of α-septanosides using this donor.

We have struggled to compose a model that explains the formation of β-septanosides from donor **22** under the two glycosylation conditions used. Two observations support, but do not necessarily explain, the observed selectivity. First, DFT minimization of 2*S*-series methyl septanosides **25** and **36** in Figure 4, showed that β-anomer **25** was more stable than α-anomer **36** by 6.5 kcal/mol. In its lowest energy conformation, the ring of **25** adopted a $^{O,1}C_4$ conformation, where the aglycone was positioned pseudoaxially to optimize stereoelectronic stabilization.[28,29,30] This conformation is adjacent on the septanose conformational itinerary to those adopted by similar septanosides.[30,31] While it is speculative, it could be that the conformation of the oxocarbenium ion is such that it favors attack from the β-face. At some point, unfavorable interactions between bulkier nucleophiles and the C2 acetate group may favor formation of the α-septanoside. Take, for example, the series of Koenings-Knorr glycosylations of methanol, *n*-octanol, and diacetone-D-galactose using **22**. The distribution of isolated products goes from exclusively β-septanoside in the case of methanol (**25**) to exclusively α- in the case of galactose (**27**). Second, in the case of the mannose per-acetate pyranose system reported by Field and co-workers,[26] β-glycosides were the major product in the iodine mediated glycosylations involving per-*O*-acetyl mannose. We repeated the reaction reported there by converting per-*O*-acetyl mannose to its bromide and then activating it using iodine and DDQ with *n*-octanol as acceptor. Product analysis showed that only one product was formed in the reaction. Isolation and characterization of that product by NMR spectroscopy proved that it was the octyl per-*O*-acetyl-β-mannoside as reported.[26,32]



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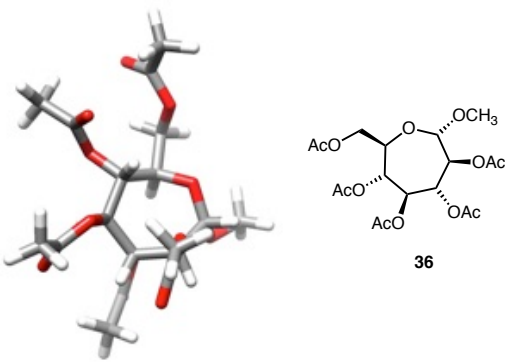

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Figure 4. DFT structures of the lowest energy conformers of methyl septanosides **25** and **36**.

The attack of anionic nucleophiles on **21** and **22** resulted in the formation of β-septanosides. Reactions using either sodium azide or potassium thioacetate and respective bromides cleanly gave β-septanosides **29, 30, 31** and **32** in good yields (Table 1 and Fig. 3).[33,34,35,36] Formation of β-septanosides in these cases strongly suggested S_N2-type substitution by the anionic nucleophiles to α-septanosyl bromides. Once deprotected, the anomeric azides may find use as surrogate substrates for glycosidases or glycosyl transferases. The assignment of the anomers of septanosides was done based on ^3J couplings between H1 and H2 as well as their chemical shifts in ^{13}C NMR spectra (See Supporting Information.). Septanoses, like their six-membered analogs, show multiple mechanisms (e.g., oxocarbenium ion formation, direct S_N2 displacement) to produce glycosidic bonds under different reaction conditions. The reactions that are involved in the septanose glycosides are generally easy to handle and scalable. The newly synthesized thio- and azido-septanosides will be tested for functionalization at the hetero-atom to prepare novel septanose glycoconjugates or nucleoside mimics.

Kinetics study on the conversion of per-O-acetyl septanoses to their anomeric iodides

When purifying reaction mixtures where **21** was the glycosyl donor, unreacted per-*O*-acetate, **17**, was also isolated (Table 1). Considering this observation, we speculated that the individual anomers, **17** and **18**, might react at different rates during glycosyl bromide formation. To investigate this and to better understand the yields of **24** and **28** with Lewis acid activation, we set out to quantitate the rate of septanosyl halide formation for each of the per-*O*-acetate isomers **17**-**20**. One of the isomers, **20**, was present in such small quantities that it could not be isolated. We therefore investigated only compounds **17**-**19** in the kinetics studies. Following a similar kinetics study reported by Gervay-Hague and co-workers, we opted to characterize the rates by ^1H NMR integrations.[37] Disappearance of the starting material was monitored with 1.5 eq. of TMSX in CD_2Cl_2 over a period of seven hours at 273 K. We began by attempting to monitor per-*O*-acetyl septanose **18** with bromotrimethyl silane (TMSBr). The TMSBr reaction proceeded very slowly, however, with low conversion over the timeframe of the experiment. The more reactive iodotrimethyl silane (TMSI) was utilized, therefore, to study the relative reactivities. Diminution of the integral value for the H1 protons of each anomeric acetate was measured at ten-minute intervals over the course of the experiment. The integration was then converted to concentration using the eretic quantitation module in Bruker Topspin 3.5pl7.

Macroscopic rate constants were calculated by fitting plots of the decrease in the natural logarithm of starting material concentration as a function time. The experiments confirmed that **17** was consumed at a significantly slower (40 times) pace than both **18** or **19** (Fig. 5 and Table 2). It (**17**) is also unique in being the only 1,2-*cis* anomeric acetate, whereas **18** and **19** are both *trans*. The data were fit linearly, approximating a mechanism where the rate determining step was unimolecular (Fig. 5 a-c). Formation of an oxocarbenium ion from a silylated anomeric acetate is likely the key step in the mechanism (See Supplementary Information). As depicted in Figure 6, anchimeric assistance by the C2 acetate likely accelerated oxocarbenium ion formation for species like **18** and **19** (not shown), whereas there was no such participation in the case of **17**. The first order (linear) fits for **18** and **19** showed excellent correlation with the model, but less so for **17**, and suggested that competing processes are likely at play.[37] With per-*O*-acetyl septanose **17** being the least reactive, it explains the fact that it was isolated from glycosylations. It presumably did not completely react during activation *via* HBr in acetic acid, and decreased the isolated yields for glycosylation as a consequence.

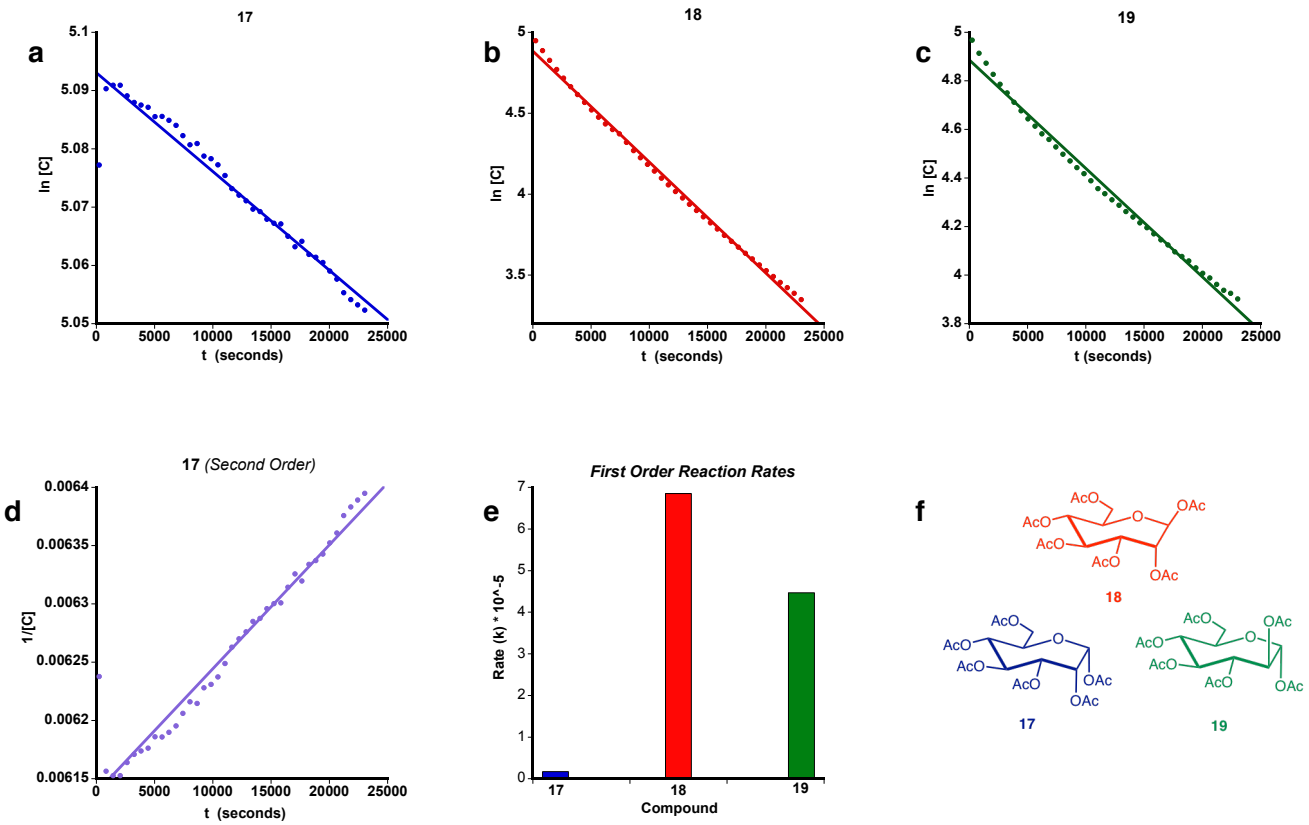


Figure 5. Kinetics of septanosyl iodide formation for per-*O*-acetyl septanoses **17**, **18**, and **19**. Plots in **a**, **b**, and **c** show first order fits, plot **d** shows a second order fit for **17**; **e** compares rates and **f** shows structures of the compounds.

Table 2. Kinetics data of septanosyl iodide formation

entry	cmpd	k_{obs} (sec^{-1})	$t_{1/2}$ (sec)	R^2
1	**17**	1.70×10^{-6}	4.09×10^{5}	0.944
2	**18**	6.85×10^{-5}	1.01×10^{4}	0.997
3	**19**	4.47×10^{-5}	1.56×10^{4}	0.990
4	**17**	1.06×10^{-8} *a*	ND	0.944

a Units for the second order fit should be M^{-1}•sec^{-1}.

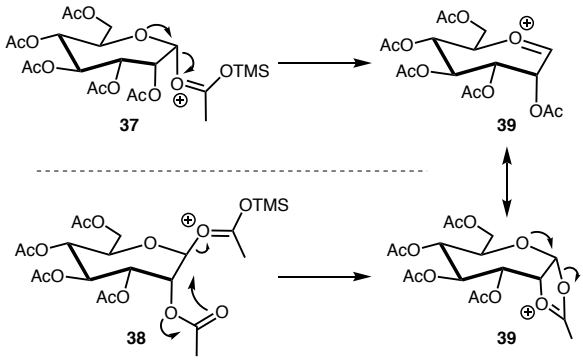
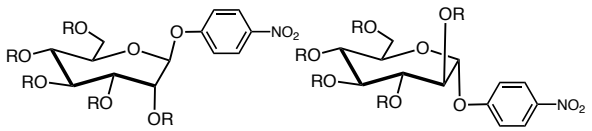


Figure 6. Depiction of oxocarbenium ion formation from **17** and **18**.

Synthesis of p-nitrophenyl septanosides

Colorimetric assays have been widely used to monitor glycosidase activity *in vitro*.[38] Saccharide substrates containing a pro-chromogenic aglycone absorb more strongly upon cleavage of the glycosidic bond. Drawing on inspiration from pyranose glycoside substrates, we chose to synthesize *p*-nitrophenyl (pNP) septanosides. Glycosylations of *p*-nitrophenol with glycosyl bromides are well established in pyranose systems including a wide variety of glycosylation protocols. We investigated these protocols with septanose donors **21** and **22**. [39] The glycosylation reaction of septanosyl bromide **21** using BF_3 as a promoter resulted in no product formation,[40] whereas activation with Ag_2CO_3 delivered the glycoside **40** in only 20% yield.[41] The low yield of the reaction may be attributed to lower nucleophilicity of the *p*-nitrophenol. Hence, glycosylations of *p*-nitrophenol under basic conditions were also explored in the presence of phase-transfer-catalysts. Using tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst in a two-phase system consisting of aqueous sodium hydroxide and dichloromethane gave 15% of β-pNP-septanoside **40**.[42] Alternatively, glycosylations using tetrabutylammonium hydrogensulfate (TBAS) gave the β-pNP-septanoside **40** in 33% yield at room temperature. A mixture of products were observed if the reaction temperature was elevated to 35 °C. [43]



40 R = OAc
42 R = H

41 R = OAc
43 R = H

While modest, the glycosylation protocol with tetrabutylammonium hydrogensulfate (TBAS) was the best amongst the methods tested and, hence, was utilized to synthesize the 2*S* series pNP septanoside. When starting from anomeric bromide **22**, the product formed was the 1,2-trans, α-configured glycoside, **41** in 35% yield. The preference for α-glycoside formation might be explained by one of two conditions, or even a combination of them. First, it may reflect the size and nucleophilicity of the *p*-nitrophenol acceptor, akin to the observed trend in the Koenigs-Knorr glycosylations. On the other hand, a double-displacement mechanism that invokes a reactive, β-glycosyl sulfate could also be operative. In the case of the acetate protected pNP septanosides **40** and **41**, the H1 chemical shift is not resolved, but amongst other signals of the product. Hence, the stereochemistry at the anomeric carbon was assigned after the deprotection because the H1 signals were visible and coupling constants could be assigned.[44] The pNP septanosides **42** and **43** were characterized extensively using NMR spectroscopy for the assignment of the stereochemistry at C1. We are currently investigating protocols to optimize the reaction conditions and yields for pNP septanosides by directly utilizing per-*O*-acetyl septanoses **17**, **18** and **19** as donors under Lewis acidic conditions.[45,46]

Conclusion

Here we have developed a glycosylation method that uses septanosyl bromides as donors in reactions to prepare new *p*-nitrophenyl septanosides. The method also enabled the synthesis of septanosides using various hetereoatom acceptors, which had been difficult *via* previous glycosylation methods. We observed differential rates of conversion of the per-*O*-acetyl septanose precursors to the anomeric bromides based on the relative stereochemistry at C1 and C2. Specifically, 1,2-*trans* relationships resulted in faster activation whereas 1,2-*cis* was slower; we invoked a kinetic rationale for this based on the mechanism of the reaction. Another key finding related to the stereoselectivity of glycoside formation. Considerations that were included in the explanation of selectivity were the reaction mechanism, which could be either S_N2-like or involve an oxocarbenium intermediate, and the nature (e.g., size, reactivity) of the acceptor. Importantly, we used product conformational optimization to help support our argument for selectivity. Ultimately, the method has delivered *p*-nitrophenyl septanosides that can be utilized as substrates to evaluate glycosidase activity. As such, it will allow the exploration

of protein septanose interactions in the context of a new class of proteins. Results of these investigations will be reported in due course.

Experimental Section

General procedure for the formation per-acetylated glycosyl iodides (NMR Kinetics experiment). Three isomers of per-*O*-acetyl septanoses (1 eq.) were dissolved in CD_2Cl_2 (0.6 mL) and placed in an NMR tube. Iodotrimethylsilane (1.5 eq.) was added directly into the NMR tube at ~0 °C, mixed well and the reaction was followed by NMR spectroscopy at 273.2K using a Bruker 400 spectrometer. ^{1}H NMR spectra was taken at every 10 minutes for next 8 hours. Concentration of products for the kinetic plots were calculated using the eretic quantitative module in Bruker Topspin 3.5pl7. The integration region for H1 of the per-*O*-acetyl septanose at each time point was imported from $t = 0$ forward, and calculated against one of the acetate methyl integrations or a proton other than the anomeric proton signal; these reference signals served as internal standards.[47]

Minimization and conformational optimization of methyl septanosides. Starting structures for methyl α-septanoside **25** and methyl β-septanoside **36** were adapted from our previous conformational analysis of 5-*O*-methyl septanosides[31a] by using the Maestro GUI included in the Schrodinger software suite.[48] Modifications of the preexisting -OH moieties were converted to -OAc groups manually. The respective septanoside structures were minimized by Density Functional Theory (DFT) using the functional B3LYP and basis set 6-31G**. Conformational searches were accomplished on each minimized septanoside to identify the existence of any lower-energy conformations by the MacroModel program within the Schrodinger software suite. Conformations were systematically searched for by mixed torsional and low-mode sampling, a hybrid technique where specific torsions may vary outside a standard low mode search. Any redundant conformers are removed from the data set. This resulted in 192 unique conformers for α-septanoside **25** and 193 β-septanoside **36**. The top ranked (lowest energy) conformers were re-minimized by DFT at the same level of theory, B3LYP/ 6-31G**, to acquire each septanoside conformers' energy (See Supplementary Information for Cartesian coordinates of the DFT structures.)

General procedure for debenzylation and per-O-acetylation. To di-*O*-acetyl-tetra-*O*-benzyl septanoses (1.00 g, 1.50 mmol, 1 eq.) dissolved in THF (20 mL per g starting material), was added 20% weight of 10% Pd/C (0.20 g) and the mixture was stirred for 12 h at rt under an atmosphere of hydrogen gas. The solution was then filtered through celite, washed with excess methanol and the combined filtrates were concentrated under reduced pressure. After TLC analysis showing the absence of starting material and no UV active spots, the crude reaction mixture was then dissolved in pyridine (5 mL g^{-1} starting material), and acetic anhydride (7.2 mL g^{-1}) was added at 0 °C and stirred it for 6-8 h at rt. The mixture was concentrated under reduced pressure and purified by column chromatography using hexane: ethyl acetate as solvent system to give the respective per-*O*-acetyl septanoses.

1,2,3,4,5,7-hexa-O-acetyl-α-D-glycero-D-guloseptanose (**17**). Obtained after column chromatography as a colorless oil (407 mg, 42%) using the general two-step procedure described above; note that β-anomer **18** (below) was also isolated from the same reaction. R_f 0.4 (1:1 Hex: EtOAc); $[\alpha]_D$ +75.8 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (d, *J* = 4.9 Hz, 1H), 5.64–5.59 (dd, *J* = 10.1, 8.5 Hz, 1H), 5.57–5.55 (dd, *J* = 4.9, 0.9 Hz), 5.27–5.24 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.08–5.03 (dd, *J* = 10.4, 8.5 Hz, 1H), 4.54–4.49 (ddd, (*J* = 8.4, 5.8, 2.5 Hz, 1H), 4.20–4.15 (dd, *J* = 12.0, 5.9 Hz, 1H), 3.98–3.95 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.26 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 169.6, 169.5, 169.3, 168.1, 89.0, 71.9, 71.5, 71.3, 69.5, 69.2, 63.6, 20.9, 20.8, 20.7; HRMS (DART-TOF) *m/z* calcd. for $C_{19}H_{30}NO_{13}$ $[M+NH_4]^+$ 480.1717, obs. 480.1718.

1,2,3,4,5,7-hexa-O-acetyl-β-D-glycero-D-guloseptanose (**18**). Obtained as a colorless oil (498 mg, 52%). R_f 0.5 (1:1 Hex: EtOAc); $[\alpha]_D$ +3.1 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, *J* = 6.9 Hz, 1H), 5.43–5.41 (dd, *J* = 7.9, 2.4 Hz, 1H), 5.33–5.29 (m, 2H), 5.03–4.99 (dd, *J* = 9.5, 3.9 Hz, 1H), 4.18–4.12 (m, 2H), 4.06–4.00 (m, 1H), 2.09 (broad s, 9H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.4, 169.2 (2), 169.1 (2), 95.4, 75.5, 71.7, 70.6, 70.3, 69.1, 63.7, 21.0, 20.9, 20.8 (2); HRMS (DART-TOF) *m/z* calcd. for $C_{19}H_{30}NO_{13}$ $[M+NH_4]^+$ 480.1717, obs. 480.1720.

1,2,3,4,5,7-hexa-O-acetyl-α-D-glycero-D-idoseptanose (**19**). Obtained as colorless oil in 83% yield (440 mg) after two steps using the general procedure. R_f 0.3 (3:2 Hex: EtOAc); $[\alpha]_D$ +39.2 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (d, *J* = 6.7 Hz, 1H), 5.39–5.29 (m, 3H), 5.03–4.98 (ddd, *J* = 8.3, 8.3, 3.9 Hz, 1H), 4.26–4.20 (ddd, *J* = 8.8, 6.2, 2.5 Hz, 1H), 4.14–4.09 (dd, *J* = 12.0, 6.2 Hz, 1H), 3.93–3.88 (dd, *J* = 12.0, 2.5 Hz, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.6, 169.3, 169.0, 168.9, 168.8, 92.9, 74.8, 70.5, 69.3, 69.2, 67.8, 63.6, 21.0, 20.7(2), 20.5, 20.4(2); HRMS (DART-TOF) *m/z* calcd. for $C_{19}H_{30}NO_{13}$ $[M+NH_4]^+$ 480.1717, obs. 480.1724.

General procedure for septanosyl bromide formation. To a solution of per-*O*-acetyl septanose (0.50 g, 1.1 mmol, 1 eq.) in DCM (5 mL) was added a 30% HBr in acetic acid (2.5 mL) solution at 0 °C. After complete consumption of the starting material (usually ∼12 h) as observed by TLC, the reaction mixture was poured directly into a 100-mL beaker half full of ice. Additional DCM was added to this mixture and it was then transferred to a separatory funnel. The water was removed and the organic phase was washed with cold, sat'd $NaHCO_3$ (2 × 40 mL), water (40 mL) and brine (40 mL) and dried with Na_2SO_4. The solvents were removed under reduced pressure to give the respective septanosyl bromides.

1-Bromo-2,3,4,5,7-hexa-O-acetyl-α-D-glycero-D-guloseptanose (**21**). Obtained as yellow oil in 93% yield [83 mg obtained from 86 mg (0.186 mmol) of the starting material] using the general procedure for bromide formation. The product was further utilized for glycosylation reactions without purification. R_f 0.6 (1:1 Hex: EtOAc); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 6.49 (d, *J* = 4.7 Hz, 1H), 5.60-5.57 (dd, *J* = 7.6, 2.1 Hz, 1H), 5.19-5.12 (m, 2H), 4.58-4.53 (ddd, *J* = 10.5, 7.6, 2.5 Hz, 1H), 4.27-4.23 (dd, *J* = 12.2, 5.2 Hz, 1H), 4.13-4.10 (dd, *J* = 14.2, 7.2 Hz), 4.05-4.01 (dd, *J* = 12.2, 2.3 Hz), 2.31 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.0, 169.5, 168.9, 84.5, 73.1, 71.8, 71.4, 70.1 (2), 62.5, 21.0 (2), 20.9, 20.8.

1-Bromo-2,3,4,5,7-penta-O-acetyl-α-D-glycero-D-idoseptanose **(22)**. Obtained as yellow oil in 95% yield [117 mg obtained from 118 mg (0.255 mmol) of the starting material] using the general procedure for bromide formation. R_f 0.6 (1:1 Hex: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, *J* = 8.2 Hz, 1H), 5.69-5.62 (dd, *J* = 10.0, 8.3 Hz, 1H), 5.39-5.34 (dd, *J* = 9.4, 8.5 Hz, 1H), 5.25-5.18 (dd, *J* = 6.1, 6.1 Hz, 1H), 5.18-5.13 (dd, *J* = 9.9, 8.6 Hz, 1H), 4.40-4.35 (ddd, *J* = 10.1, 5.0, 2.4 Hz, 1H), 4.28-4.22 (dd, *J* = 12.2, 5.0 Hz, 1H), 4.10-4.05 (dd, *J* = 12.2, 2.5 Hz, 1H), 2.06 (s, 6H), 2.01 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 169.4, 169.0, 168.3, 87.1, 74.4, 73.5, 72.0, 69.5, 68.6, 62.3, 20.9, 20.7, 20.6, 20.4; HRMS (DART-TOF) *m/z* calcd. for $C_{17}H_{23}BrNaO_{11}$ $[M+Na]^+$ 505.0321, found 505.0258.

Methyl-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-guloseptanose **(24)**. *Method A*. To a solution of **21** (46 mg, 0.095 mmol) in DCM (2 mL), was added 4Å mol. sieves (0.2 g) and MeOH (0.2 mL, 5.712 mmol), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. AgOTf (37 mg, 0.144 mmol) was added to the resulting solution and was stirred allowing the reaction mixture to come to the room temperature. The reaction progress was monitored by TLC. The reaction mixture was then quenched, filtered and extracted with DCM (3 x 15 mL), washed with sat. $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellowish oil (29% yield). R_f 0.4 (1:1 Hex: EtOAc). *Method B*. To a solution of **21** (50 mg, 0.103 mmol) in DCM (3 mL), was added 4Å mol. sieves (0.1 g) and I_2 crystals (26 mg, 0.103 mmol), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. MeOH (0.8 mL) was added to the resulting solution and was stirred overnight allowing the reaction mixture to come to the room temperature. The reaction mixture was then quenched with ice, extracted with DCM (3 x 20 mL), washed with sat. $Na_2S_2O_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellowish oil. (46% yield) R_f 0.4 (1:1 Hex: EtOAc); $[\alpha]_D$ +1.6 (c 0.2, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.43-5.39 (dd, *J*= 8.2, 2.3 Hz, 1H), 5.37-5.33 (dd, *J*= 8.3, 4.5 Hz, 1 H), 5.24-5.21 (dd, *J*= 5.7, 2.3 Hz, 1 H), 5.08-5.03 (dd, *J*= 9.9, 4.4 Hz, 1H), 4.57 (d, *J*=5.7 Hz, 1 H), 4.17- 4.13 (m, 2H), 4.05- 4.01 (m, 1H), 3.51 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.7, 169.6, 169.4, 169.2 (2), 104.9, 73.7, 72.6, 71.9, 70.7, 69.4, 64.4, 56.6, 21.1, 20.9 (2); HRMS (DART-TOF) *m/z* calcd. for

$C_{12}H_{27}O_{12}$ $[M+H]^+$ 435.1503, obs. 435.1505.

Methyl-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-idoseptanose **(25)**. *Method A*. To a solution of **22** (47 mg, 0.097 mmol) in DCM (2 mL), was added 4Å mol. sieves (0.2 g) and MeOH (0.24 mL, 5.835 mmol), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. AgOTf (37.5 mg, 0.146 mmol) was added to the resulting solution and was stirred allowing the reaction mixture to come to the room temperature. The reaction progress was monitored by TLC. The reaction mixture was then quenched, filtered and extracted with DCM (3 x 15 mL), washed with sat. $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellowish oil. (52% yield) R_f 0.3 (13:7 Hex: EtOAc). *Method B.* To a solution of **22** (94 mg, 0.194 mmol) in DCM (3 mL), was added 4Å mol. sieves (0.25 g) and I_2 crystals (49 mg, 0.194 mmol), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. MeOH (0.8 mL) was added to the resulting solution and was stirred overnight allowing the reaction mixture to come to the room temperature. The reaction mixture was then quenched with ice, extracted with DCM (3 x 20 mL), washed with sat. $Na_2S_2O_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellowish oil. (56% yield) R_f 0.3 (13:7 Hex: EtOAc); $[\alpha]_D$ -15.5 (c 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40-5.36 (m, 1H), 5.28–5.25 (m, 3H), 4.68 (d, *J* = 2.3 Hz, 1H), 4.24–4.20 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.16–4.12 (dd, *J* = 12.0 Hz, 2.6 Hz, 1H), 3.93–3.90 (m, 1H), 3.47 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 169.4, 169.2, 169.0, 102.3, 76.2, 72.2, 71.7, 70.6, 70.4, 64.0, 56.5, 20.9, 20.8, 20.7, 20.6; HRMS (DART-TOF) *m/z* calcd. for $C_{12}H_{30}NO_{12}$ $[M+NH_4]^+$ 452.1768, obs. 452.1762.

Octyl-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-idoseptanose **(26)**. *Method A*. To a solution of **22** (29 mg, 0.060 mmol) in DCM (2.5 mL), was added 4 Å mol. sieves (0.2 g) and 1-Octanol (29 µL, 0.180 mmol), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. AgOTf (23 mg, 0.090 mmol) was added to the resulting solution and was stirred allowing the reaction mixture to come to the room temperature. The reaction progress was monitored by TLC. The reaction mixture was then quenched, filtered and extracted with DCM (3 x 15 mL), washed with sat. $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless oil. (38% yield) R_f 0.4 (3:2 Hex: EtOAc). *Method B*. To a solution of I_2 crystals (40 mg, 0.153 mmol) and *n*-octanol (72 µL,

0.459 mmol) in DCM (2 mL), was added DDQ (18 mg, 0.077 mmol), stirred at 0 °C under inert atmosphere for 10 minutes under dark conditions. To this solution, was added **22** (74mg, 0.153mmol) dissolved in DCM (2 mL) and the resulting solution was allowed to come to room temperature slowly. The reaction progress was monitored by TLC. The reaction mixture was then quenched with ice cold water, extracted with DCM (3 x 15 mL), washed with sat. $Na_2S_2O_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless oil. (43% yield) R_f 0.3 (7:3 Hex: EtOAc); $[\alpha]_D$ -91.3 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42–5.38 (m, 1H), 5.30–5.24 (m, 3H), 4.76 (d, *J* = 2.4 Hz, 1H) 4.23–4.19 (dd, *J* = 12, 6 Hz, 1H), 4.15–4.12 (dd, *J* = 12, 2.6 Hz, 1H), 3.91–3.82 Hz (m, 2H), 3.44–3.39 (app dt, *J* = 9, 6.8 Hz), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2. 00 (m, 6H), 1.61–1.56 (m, 2H), 1.26 (m, 10H), 0.89–0.86 (t, *J* = 6.7Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.0, 169.5, 169.2, 169.0, 101.1, 76.3, 72.6, 71.6, 70.7, 70.5, 69.5, 64.2, 31.9, 29.5, 29.4(2), 26.1, 22.8, 20.9, 20.8, 20,7, 20.6, 14.3; HRMS (DART-TOF) *m/z* calcd. for $C_{25}H_{44}NO_{12}$ $[M+NH_4]^+$ 550.2864, obs. 550.2848.

(1,2,3,4-Di-O-isopropylidene-D-galactopyranosyl)-2,3,4,5,7-penta-O-acetyl-α-D-glycero-D-idoseptanose **(27)**. To a solution of **22** (57 mg, 0.118 mmol) in DCM (2 mL), was added 4Å mol. sieves (0.25 g) and Di-acetone-D-galactose (92 mg, 0.354 mmol) dissolved in DCM (1 mL), stirred for 10 minutes in an ice bath under N_2 atmosphere in dark conditions. AgOTf (45 mg, 0.177 mmol) was added to the resulting solution and was stirred allowing the reaction mixture to come to the room temperature. The reaction progress was monitored by TLC. The reaction mixture was then quenched, filtered and extracted with DCM (3 x 15 mL), washed with sat. $NaHCO_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless oil. (21% yield) R_f 0.4 (3:2 Hex: EtOAc); $[\alpha]_D$ +8.2 (c 0.1, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.48 (d, *J* = 5.1 Hz, 1H), 5.33-5.25 (m, 3H), 5.13-5.09 (dd, *J* = 10.2, 7.9 Hz, 1H), 4.88-4.85 (m, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.60-4.57 (dd, *J* = 7.7, 2.5 Hz, 1H), 4.31-4.29 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.24-4.20 (m, 2H), 4.14-4.12 (m, 1H), 3.92-3.89 (m, 1H), 3.63-3.60 (m, 1H), 2.08 (m, 1H), 2.03 (m, 1H), 1.99 (m, 1H), 1.98 (m, 3H), 1.97 (m, 3H), 1.52 (m, 1H), 1.41 (m, 3H), 1.32 (m, 3H), 1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.7, 169.6, 169.3, 168.8, 109.5, 108.8, 100.8, 96.5, 74.9, 71.0, 70.8, 70.7, 70.5, 67.7, 67.3, 67.2, 66.1, 63.6, 62.9, 26.3, 26.2, 25.1, 24.8, 21.0, 20.9, 20.7, 20.6; HRMS (DART-TOF) *m/z* calcd. for $C_{29}H_{42}NaO_{17}$ $[M+Na]^+$ 685.2309, found 685.2354.

Octyl-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-guloseptanose **(28)**. To a solution of I_2 crystals (25 mg, 0.097 mmol) and 1–Octanol (46 μL, 0.291 mmol) in DCM (1.5 mL), was added DDQ (11 mg, 0.049 mmol), stirred at 0°C under inert atmosphere for 10 minutes under dark conditions. To this solution, was added **21** (47 mg, 0.097 mmol) dissolved in DCM (1.5 mL) and the resulting solution was allowed to come to room temperature slowly. The reaction progress was monitored by TLC. The reaction mixture was then quenched with ice cold water, extracted with DCM (3 x 15 mL), washed with sat. $Na_2S_2O_3$ solution, water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless oil. (32% yield) R_f 0.4 (3:2 Hex: EtOAc); $[\alpha]_D$ +8.1 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43–5.41 (dd, *J* = 8.3, 2.7 Hz, 1H), 5.36–5.33 (dd, *J* = 8.3, 4.5 Hz, 1H), 5.23–5.21 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.07–5.04 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.63 (d, *J* = 5.8 Hz, 1H), 4.14–4.12 (m, 2H), 4.04–3.99 (ddd, *J* = 9.6, 5.9, 3.6 Hz, 1H), 3.90–3.85 (app dt, *J* = 9.4, 6.5 Hz, 1H), 3.47–3.41 (app dt, *J* = 9.7, 6.8 Hz, 1H), 2.1 (s, 3H), 2.09 (s, 3H) 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.61–1.57 (m, 2H) 1.27 (m, 10 H), 0.9–0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.3, 169.2, 169.0, 168.9, 103.7, 73.5, 72.5, 71.8, 70.6, 69.4, 69.2, 64.3, 31.8, 29.3 (2), 29.2, 25.9, 22.6, 20.8, 20.7 (2), 20.6, 14.1; HRMS (DART-TOF) *m/z* calcd. for $C_{25}H_{40}KO_{12}$ $[M+K]^+$, calc. 571.2157, obs. 571.5152.

(1-S-Acetyl)-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-guloseptanose **(29)**. To a solution of **21** (100 mg, 0.2 mmol) in Acetone (2 mL), was added KSAc (35 mg, 0.31 mmol). Resulting solution was stirred overnight at room temperature under inert atmosphere in dark conditions. The reaction mixture was then quenched with ice cold water, extracted with EtOAc (3 x 15 mL) and washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as brownish oil. (47% yield) R_f 0.48 (1:1 Hex: EtOAc); $[\alpha]_D$ +1.7 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48-5.44 (d, *J* = 7.7 Hz, 1H), 5.41-5.37 (m, 3H), 5.07-5.02 (m, 1H), 4.22-4.17 (m, 1H), 4.13-4.04 (m, 2H), 2.38 (s, 3H), 2.11 (s, 3H), 2.09 (s, 6H), 2.07 (s, 3H), 2.03 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 192.7, 170.9, 169.4, 169.3, 169.2, 83.9, 79.2, 71.8, 70.6, 70.4, 69.9, 63.9,31.0, 20.9, 20.8 (2); HRMS (DART-TOF) *m/z* calcd for $C_{19}H_{26}O_{12}S$ $(M+NH_4)^+$ 496.1462, found 496.1489; ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 143.1, 126.8, 117.3, 94.5, 78.4, 74.3, 71.1, 70.8, 70.6, 65.0; HRMS (DART-TOF) *m/z* calcd. for $C_{19}H_{26}NaO_{12}S$ $[M+Na]^+$ 354.0801, found 354.0769.

(1-S-Acetyl)-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-idoseptanose **(30)**. To a solution of **22** (121 mg, 0.25 mmol) in Acetone (4 mL), was added KSAc (57 mg, 0.5 mmol). Resulting solution was stirred overnight

at room temperature under inert atmosphere in dark conditions. The reaction mixture was then quenched with ice cold water, extracted with EtOAc (3 x 15 mL) and washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as brownish liquid. (51% yield) R_f 0.39 (3:2 Hex: EtOAc); $[\alpha]_D$ -26.2 (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (d, J = 2.6 Hz, 1H), 5.42–5.40 (m, 1H), 5.39–5.35 (m, 2H), 5.23–5.18 (app t, J = 9.2 Hz, 1H), 4.14–4.09 (m, 3H), 1.36 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 170.8, 169.5, 169.2, 169.1, 84., 81.0, 74.9, 71.7, 70.7, 70.2, 63.4, 30.8, 20.9, 20.7(2), 20.6, 20.5; HRMS (DART-TOF) *m/z* calcd. for $C_{19}H_{27}O_{12}S$ $[M+H]^+$ 479.1223, obs. 479.1244.

Azido-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-guloseptanose (**31**). To a solution of **21** (90 mg, 0.186 mmol) in DMF (1.5 mL), was added NaN_3 (35 mg, 0.46 mmol). Resulting solution was stirred overnight at 70 °C under inert atmosphere in dark conditions. Solvent was removed under reduced pressure, crude mixture was taken up with water, extracted with EtOAc (3 x 15 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless liquid. (60% yield) R_f 0.3 (1:1 Hex: EtOAc); $[\alpha]_D$ +8.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40-5.37 (dd, J = 8.0, 1.7 Hz, 1H), 5.35-5.32 (dd, J = 8.0, 3.8 Hz, 1 H), 5.10-5.08 (dd, J = 6.5, 1.7 Hz, 1H), 5.05 (d, J = 6.6 Hz, 1H), 5.03-4.99 (m, 1H), 4.17- 4.12 (m, 3H), 2.11 (s, 3H), 2.10 (broad s, 6H) 2.08 (s, 3H), 2.04 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.8, 169.2, 169.1 (2), 91.3, 76.0, 72.1, 71.7, 70.6, 69.3, 64.3, 20.9, 20.8 (2); HRMS (DART-TOF) *m/z* calcd. for $C_{17}H_{27}N_4O_{11}$ $[M+NH_4]^+$ 463.1676, found 463.1645.

Azido-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-idoseptanose (**32**). To a solution of **22** (140 mg, 0.289 mmol) in DMF (2 mL), was added NaN_3 (57 mg, 0.869 mmol). Resulting solution was stirred overnight at 70 °C under inert atmosphere in dark conditions. Solvent was removed under reduced pressure, crude mixture was taken up with water, extracted with EtOAc (3 x 15 mL), washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless liquid. (32% yield) R_f 0.19 (3:1 Hex: EtOAc); $[\alpha]_D$ -33.0 (c 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35–5.5.27 (m, 2H), 5.25–5.19 (m, 2H), 5.10 (d, J = 2.5 Hz, 1H), 4.28–4.24 (dd, J = 12.0, 6.7 Hz, 1H), 4.17–4.13 (dd, J = 12.0, 2.3Hz, 1H), 4.07–4.02 (ddd, J = 9.2, 6.7, 2.5 Hz, 1H), 2.14 (s ,3H), 2.08 (s, 3H), 2.05 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.7, 169.3, 169.1, 168.8, 88.8, 77.7, 72.3, 71.9, 71.5, 70.2, 63.7, 20.9, 20.7, 20.6; HRMS (DART-TOF) *m/z* calcd. for $C_{17}H_{27}N_4O_{11}$ $[M+NH_4]^+$ 463.1676, obs. 463.1689.

2,3,5,7-Tetra-O-acetyl-1,4-anhydro-D-glycero-D-idoseptanose (**33**). To a solution of phenol (40 mg, 0.422 mmol) in DCM (3 mL), was added AgOTf (65 mg, 0.253 mmol) in presence of 4Å mol. sieves (0.5g), stirred at 0 °C under inert atmosphere for 10 minutes under dark conditions. To this solution, was added **22** (102 mg, 0.211mmol) dissolved in DCM (3 mL) and the resulting solution was allowed to come to room temperature slowly and kept overnight. The reaction mixture was then quenched with DIEA (0.8 mL), diluted with 5 mL of DCM and the residue was filtered off. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as colorless oil/semisolid. (25% yield) R_f 0.35 (3:2 Hex: EtOAc); $[\alpha]_D$ -77.9 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, *J* = 2.1Hz, 1H), 5.19 (s, 1H), 5.10–5.08 (m, 1H), 5.04–5.01 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.94–4.91 (dd, *J* = 6.2, 3.9 Hz, 1H), 4.28–4.23 (m,1H), 4.19–4.13 (m,2H), 2.12 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.00 (s,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.6, 170.1, 169.1, 101.1, 79.7, 78.4, 73.6, 71.4, 65.1, 62.9, 20.9(2), 20.8, 20.6; HRMS (DART-TOF) *m/z* calcd. for $C_{15}H_{21}O_{10}$ $[M+H]^+$ 361.1135, obs. 361.1107.

(4-Nitrophenyl)-2,3,4,5,7-penta-O-acetyl-β-D-glycero-D-guloseptanose (**40**). To a solution of **21** (130 mg, 0.274 mmol) in DCM (4 mL), was added *p*–nitrophenol (75 mg, 0.54 mmol), TBAS (93 mg, 0.274 mmol), stirred for 15 minutes under dark condition. To the resulting solution/suspension, was added 1M aq. NaOH solution (4 mL), stirred vigorously, and monitored by TLC. The organic phase was washed with cold 1M aq. NaOH solution (2 x 10 mL), water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellow liquid. (33% yield) R_f 0.3 (1:1 Hex: EtOAc); $[\alpha]_D$ -43.6 (c 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J*= 9.1 Hz, 2H), 7.10 (d, *J* = 9.1 Hz, 2H), 5.52- 5.48 (m, 2H), 5.42-5.38 (m, 2H), 5.04-5.01 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.28- 4.23 (ddd, *J* = 9.6, 7.3, 2.1 Hz, 1H), 4.20-4.17 (dd, *J* = 12.2, 2.1 Hz, 1H), 4.07-4.02 (m ,1H) 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.3, 169.3, 169.2, 169.1, 169.0, 161.3, 143.2, 125.8, 116.8, 100.5, 74.2, 72.0, 71.6, 70.3, 69.1, 64.4, 20.9, 20.9, 20.8 (2), 20,7; HRMS (DART-TOF) *m/z* calcd. for $C_{23}H_{31}N_2O_{14}$ $[M+NH_4]^+$ 559.1778, found 559.1778.

4-Nitrophenyl-β-D-glycero-D-guloseptanose (**41**). To a solution of **40** (100 mg, 0.185 mmol) in Methanol (5 mL), was added NaOMe (6 mg, 0.11 mmol), stirred overnight under N_2 atmosphere in dark conditions. The progress of a reaction was monitored by TLC. After the completion, the reaction mixture was neutralized using Amberlite® 120 resin. Residue was filtered and the solvent was removed under

reduced pressure and residue was purified by column chromatography, then dissolved in minimum amount of water and subjected to lyophilization to obtain the desired product as yellowish powder. (74% yield) R_f 0.42 (1:4 MeOH: DCM); 1H NMR (400 MHz, CD3OD) δ 8.21-8.19 (dd, J = 7.2, 2.1 Hz, 2H), 7.28-7.26 (dd, J = 7.1, 2.1 Hz, 2H), 5.35 (d, *J* = 4.7 Hz, 1H), 4.84 (s, 5H), 4.20-4.18 (dd, *J* = 4.7, 2.3 Hz, 1H), 3.95-3.88 (m, 4H), 3.60-3.55 (dd, *J* = 11.9, 7.2 Hz, 1H), 3.43-3.39 (dd, *J* = 9.9, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.7, 143.8, 126.7, 117.9, 105.2, 81.0, 75.6, 75.4, 74.9, 72.7, 64.4; HRMS (DART-TOF) *m/z* calcd. for $C_{13}H_{17}NNaO_9$ $[M+Na]^+$ 354.0801, found 354.0975.

(4-Nitrophenyl)-2,3,4,5,7-penta-O-acetyl-α-D-glycero-D-idoseptanose (**42**). To a solution of **22** (183 mg, 0.379 mmol) in DCM (5 mL), was added *p*–Nitrophenol (116 mg, 0.834 mmol), TBAS (154 mg, 0.454mmol), stirred for 15 minutes under dark condition. To the resulting solution/suspension, was added 1M aq. NaOH solution (3 mL), stirred vigorously, and monitored by TLC. The organic phase was washed with cold 1M aq. NaOH solution (2 x 10 mL), water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography to obtain the desired product as yellow liquid. (35% yield) R_f 0.28 (3:2 Hex: EtOAc); $[\alpha]_D$ -68.9 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.20 (d, *J* = 9.2 Hz, 2H), 7.16–7.13 (d, *J* = 9.2Hz, 2H), 5.61–5.57 (m, 2H), 5.43-5.41 (dd, *J* = 8.1, 1.9 Hz, 1H) 5.38–5.32 (m, 2H), 4.25–4.17 (m, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.7, 169.5, 169.1, 168.9, 161.1, 143.4, 125.9, 117.1, 97.9, 75.2, 73.1, 71.2, 69.9, 69.7, 63.7, 20.8, 20.7, 20.6; HRMS (DART-TOF) *m/z* calcd. for $C_{23}H_{28}NO_{14}$ $[M+H]^+$ 559.1775, obs. 559.1788.

4-Nitrophenyl-α-D-glycero-D-idoseptanose (**43**). To a solution of **42** (44 mg, 0.081 mmol) in Methanol (4 mL), was added NaOMe (5 mg, 0.09 mmol), stirred overnight under N_2 atmosphere in dark conditions. The progress of a reaction was monitored by TLC. After the completion, the reaction mixture was neutralized using Amberlite® 120 resin. Residue was filtered and the solvent was removed under reduced pressure and residue was purified by column chromatography, then dissolved in minimum amount of water and subjected to lyophilization to obtain the desired product as yellowish powder. (73% yield) R_f 0.4 (1:4 MeOH: DCM); ^{1}H NMR (400 MHz, CD_3OD) δ 8.21-8.19 (dd, *J* = 7.3, 2.0 Hz, 2H), 7.21-7.19 (dd, *J* = 7.3, 1.9 Hz, 2H), 5.13 (d, *J* = 8.0 Hz, 1H), 4.84 (s, 5H), 4.55-4.53 (dd, *J* = 7.9, 3.0 Hz, 1H), 4.25-4.24 (app t, *J* = 3.5 Hz, 1H), 4.00-3.99 (dd, *J* = 3.8, 0 Hz, 1H), 3.94-3.93 (dd, *J* = 8.4, 0.7 Hz, 1H), 3.90-3.88 (dd, *J* = 5.4, 3.2 Hz, 1H), 3.83-3.80 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.66-3.64 (dd, *J* = 11.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 140.1, 126.8, 117.3, 94.5, 78.4, 74.3, 71.1, 70.8, 70.6, 65.0; HRMS (DART-TOF) *m/z* calcd. for $C_{13}H_{17}NNaO_9$ $[M+Na]^+$ 354.0801, found 354.0792.

Supplementary Information

Supplementary information for this article is given *via* a link at the end of the document.

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