Tandem cyclization and acetalization of a homologated D-glucose delivers \textit{D-glycero-D-gulo-septanosides}

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\textbf{Dedicated to Professor William Bailey on the occasion of his 65\textsuperscript{th} birthday}

\section*{Abstract}
A synthesis of methyl-\textit{D-glycero-D-gulo-septanoside} and allyl \textit{D-glycero-D-gulo-septanoside} from a D-glucose derived heptenitol is reported. Key steps in the synthesis include the diastereoselective dihydroxylation of the heptenitol, regioselective opening of the benzylidene protected diol and the tandem cyclization-acetalization that delivers the guloseptanosides. The facility in formation of the alkyl septanosides suggests that the cyclic hemi-acetal \ref{2} is favored over the acyclic hydroxy-aldehyde \ref{3} when they are able to equilibrate. The results here set the groundwork for the preparation of more complex septanosides by this route.

\textbf{Keywords:} Septanose carbohydrate, glycosylation, dihydroxylation

\section*{Introduction}
Septanose glycosides (e.g., \ref{1} in Figure 1) are carbohydrates that adopt a seven-membered ring form rather than the more common five (furanose) or six-membered (pyranose) rings. In their reducing form, septanoses such as \ref{2} are known to be less stable than pyranoses by 3-8 kcal/mol.\textsuperscript{1} The thermodynamic preference for pyranose formation was demonstrated when, upon hydrolysis of methyl septanosides, the corresponding pyranoses were observed by \textsuperscript{1}H NMR spectroscopy.\textsuperscript{2} Nonetheless, in examples where the hydroxyl groups that give rise to furanoses or pyranoses are blocked with protecting groups, the septanose ring form may be significantly populated.\textsuperscript{3} For example, under acidic conditions in methanol, 2-deoxy hydroxy-aldehydes yielded a mixture of the methyl septanosides and their corresponding dimethyl acetals in a roughly 1:1 ratio.\textsuperscript{4} We became interested in developing conditions where the equilibrium between a septanose such as \ref{2} in the cyclic, hemi-acetal form and its acyclic hydroxy-aldehyde form \ref{3} would favor the cyclic species. If septanose \ref{2} was significantly populated, we speculated that it could be trapped as its
corresponding septanoside 1, and thus allow access to various septanosides.\(^5\) Here we report the successful preparation of \(\text{D-glycero-D-gulo-septanosides} \ 1\) by trapping cyclic hemiacetals such as 2 under acidic conditions.

![Figure 1](image1.png)

**Figure 1.** Retrosyntheses of septanosides.

Recent efforts toward the synthesis of septanosides have utilized oxepines 5 as key intermediates.\(^6,7,8,9,10\) Carbohydrate based oxepines can be epoxidized to give 1,2-anhydrosugars such as 4 in a manner akin to glycalcs.\(^11\) Addition of an appropriate nucleophile then gives the corresponding glycoside. If a thiol is used, the resulting thioseptanoside may be used for subsequent glycosylation reactions.\(^12,13\) Our access to oxepines has been through the ring closing methathesis (RCM) of 6-\(\text{O-vinyl heptenitols}\).\(^7\) The RCM route accommodates a wide scope of starting materials, but scale-up is hindered by the cost (20-25 mol% Schrock catalyst is used in the RCM reaction) and inconvenience of doing dilute reactions (5 mM reactions for RCM) in a glove box. Variable yields for glycosylation, based on the nature of the glycosyl acceptor, prompted us to investigate routes to septanosides that did not require the intermediacy of oxepines. The new route required the preparation of a homologated pyranose such as 3 (Figure 1) to test the hypothesis.

**Results and Discussion**

Scheme 1 illustrates the initial attempt at preparing septanosides via the new approach. Heptenitol 6, derived by the known Wittig methylenation of D-glucose,\(^14,15\) was protected as the 6-\(\text{O-acetyl derivative} \ 7\) (73%). Dihydroxylation of 7 using catalytic \(\text{OsO}_4\) gave diol 8 in 50% yield. Only one diastereomer of the diol was isolated after work-up and purification. We tentatively assigned the C2 stereocenter based on literature precedents that showed that the erythro diastereomer dominated.\(^16,17\) The allylic benzyloxy group at C3 in 7 directs the facial
selectivity of the dihydroxylation reaction. Protection of both hydroxyls in diol 8 gave the bis-silyl ether 9 in 63% yield. Under Swern reaction conditions, the TES group on the primary hydroxyl is selectively removed and subsequently oxidized to give 10 (64%). Next, we intended to remove the 6-O-acetyl group to give 11 followed by ring-closure/glycosylation (Figure 2). Unfortunately, when 10 was exposed to dilute sodium methoxide in methanol, we observed deprotection of both the 6-O-acetyl group and the 2-O-triethylsilyl group as determined by $^1$H NMR.

Scheme 1. First generation approach. a: Ac$_2$O, py., 73%. b: OsO$_4$, NMO, acetone:H$_2$O (4:1), 50% (60% for conversion of 6 to 16). c: TESCl, imid. DMF, 63%. d: (COCl)$_2$, DMF, DCM, then Et$_3$N, 64%.

Rather than delivering 11, the methoxide reaction presumably gave 12. We surmised that the NH$_4$Cl used in the work up was sufficiently acidic to facilitate equilibration of the product diol aldehyde 12. Ring closure between the C6 hydroxyl and the aldehyde could give septanose 13. Although cyclization to form 13 was the desired reaction course, we assumed that this path was unlikely. Rather, enolization of the α-hydroxy aldehyde functionality of 12 could form ene-diol 14. Ultimately, this ene-diol could then equilibrate to hemi-ketal 15. This route seemed especially likely to us because of the relative stability of hemi-ketal 15 compared to 13. The mere possibility of equilibration to 15 gave us sufficient pause such that we reconsidered the protecting group scheme that should be used, especially with regard to the C2 hydroxyl group. Preventing the formation of an α-hydroxy aldehyde such as 12 was the primary concern.

Figure 2. Equilibria available to hydroxy-aldehydes.

A new approach to hydroxy aldehyde intermediate 3 was subsequently implemented. Triol 16, prepared from heptenitol 6 (Scheme 1) in 60% yield, served as the starting material for the synthesis. Similar to the conversion of 7 to 8, only one diastereomer of the product was isolated upon dihydroxylation of 6; it was assigned with the same stereochemistry as the previous
reaction. As shown in Scheme 2, the 1,2-diol of 16 was selectively converted to the corresponding benzylidene 17 (61%). The material was collected as a mixture of diastereomers; the isomers were epimeric at the benzylidene carbon. Following literature precedent, the benzylidene of 17 was then opened to give 18 as the major product (60%).\textsuperscript{18} We anticipated that the benzyl ether at C2 would be stable to the acidic cyclization conditions. Protection of the diol as the bis-TES ether was followed by Swern oxidation to give 20 in 46% over two steps. Exposure of 20 to acidic methanol or acidic allyl alcohol solutions resulted in the isolation of the corresponding methyl 21 (\(\alpha:\beta 2:1 54\%\)) or allyl 22 (\(\alpha:\beta 6:1, 50\%\)) septanosides. Silyl ether deprotection at C6, followed by tandem cyclization and acetalization/glycosylation was the likely sequence leading to 21 and 22.

**Scheme 2.** Synthesis of D-glycero-D-gulo-septanosides via cyclization and acetalization. (a) PhCH(OCH\textsubscript{3})\textsubscript{2}, \(p\)TSA, DMF 61%; (b) Cu(OTf)\textsubscript{2}, BH\textsubscript{3}•THF, THF, 60%; (c) TESCl, imid. DMF, 67%; (d) (COCl)\textsubscript{2}, DMF, DCM, then Et\textsubscript{3}N, 68%; (e) \(p\)TSA, CH\textsubscript{3}OH 54% (2:1 \(\alpha:\beta\)); (f) \(p\)TSA, allyl alcohol 50% (5:1 \(\alpha:\beta\)).

Methyl septanoside 21 was used to verify the stereochemical configuration of the C2 hydroxyl group. Based on the knowledge that \(\alpha\)-septanosides prefer to adopt a \(3,4\text{TC}_{5,6}\) conformation, the \(J_{H,H}\) values for H2 were expected to be of low (H1, H2 and H2, H3) magnitude.\textsuperscript{19} The H2 signal of 21\(\alpha\) (in the \(\alpha:\beta\) mixture) was identified by a combination of HSQC and COSY experiments. The \(^1\)H signal for H1, which was in a section of the spectrum with many other overlapping signals, was located in the HSQC experiment. With this information, the H1-H2 correlation was collected from a COSY spectrum (Figure 3). The signal for H2 was clearly correlated with H1 (\(J_{H1,H2} 4.3\text{ Hz}\)) although correlation to H3 was not observed; this was consistent with the model where coupling between H1 and H2 would be weak and even weaker between H2 and H3. This result confirmed the C2 stereochemistry and reported on the diastereoselectivity of the dihydroxylation reaction.
Figure 3. H2 as a diagnostic for determining the stereochemistry of the C2 hydroxyl group of 21α. Left is the structure assigned to 21α; on the right is a detail of a COSY spectrum of 21 with inset showing signal for H2.

Conclusions

In summary, we defined a new route to D-glycero-D-gulo-septanosides that does not involve the intermediacy of carbohydrate based oxepines. The ability to efficiently trap the cyclic acetal in preference to the acyclic di-O-alkyl acetal suggests that the hemi-acetal form is largely favored in the hemi-acetal – hydroxy-aldehyde equilibrium. This result is consistent with our recent report of a protected 2-amino septanose where only the cyclic hemi-acetal was observed.5 The advancement made here should allow the preparation of more complex septanosides via the tandem cyclization-acetalization procedure or via new donors (e.g., septanosyl fluorides) that can be accessed by this route. Progress on these investigations will be reported in due course.

Experimental Section

General. Unless stated otherwise, all reactions were conducted at room temperature (rt) under N₂ atmosphere. Reactions were monitored by TLC (silica gel, 60 Å, F₂₅₄, 250 µm). Visualization was conducted either under UV light or by charring with 2.5% p-anisaldehyde in H₂SO₄, acetic acid, and ethanol solution. Preparative chromatography was conducted on silica gel (60 Å, 32-63 µm). ¹H NMR spectra were collected at 300 and 400 MHz with chemical shifts
referenced to (CH$_3$)$_4$Si (δ$_H$ 0.00 ppm) or CHCl$_3$ (δ$_H$ 7.27 ppm). $^{13}$C NMR were collected at 75 and 100 MHz and referenced to CDCl$_3$ (δ$_C$ 77.2 ppm).

3,4,5,7-Tetra-O-benzyl-6-O-acetyl-1,2-dideoxy-d-glucohept-1-ene (7). Alcohol 6 (1.85 g, 3.44 mmol) was dissolved in pyridine (9 mL). Acetic anhydride (0.488 mL, 5.16 mmol) was then added to the reaction under N$_2$ at rt. The reaction was stirred at rt for 12 h, then water (3 mL) was added. Solvents were removed under reduced pressure and the mixture was dissolved in 25 mL DCM, washing with sat. NaHCO$_3$ (1 x 10 mL) and water (1 x 20 mL). The organic layer was dried with Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The material was then purified by column chromatography using 85:15 hexanes:EtOAc as eluent to give 7 (1.45 g, 73%) as a clear colorless syrup. $^1$H NMR (CDCl$_3$) 300 MHz δ = 7.37-7.33 (m, 20H), 4.78 (d, 1H, J = 11.2 Hz), 4.73 (d, 1H, J = 11.2 Hz), 4.69-4.61 (m, 4H), 4.57 (d, 1H, J = 12.3 Hz), 4.51 (d, 1H, J = 12.1 Hz), 3.99 (m, 1H), 3.92-3.77 (m, 4H), 3.72 (dd, 1H, J = 11.8, 4.4 Hz), 3.67 (m, 1H), 3.37 (s, br, 1H), 2.53 (s, 1H), 2.07 (s, 3H) $^{13}$C NMR (CDCl$_3$) 100 MHz δ = 174.1, 141.8 (2), 141.7, 141.4, 132.3 (2), 132.2 (3), 132.0, 131.9, 131.8, 131.7, 131.5 (2), 82.9, 82.3, 81.4, 81.0, 80.6, 80.4, 78.3, 78.2, 75.6, 72.2, 67.3, 24.9; HRMS m/z calcd for C$_{37}$H$_{43}$O$_8$ 615.2958, found 615.2960.

3,4,5,7-Tetra-O-benzyl-6-O-acetyl-D-glycero-D-gulitol (8). Acetate 7 (1.45 g, 2.51 mmol) was dissolved in 10 mL of a 4:1 acetone: water mixture. To the solution was added NMO (0.30 g, 2.53 mmol) and then 0.3 mL OsO$_4$ (4 wt% in water). The reaction was stirred 2d at rt and then quenched by addition of sat. NH$_4$Cl (5 mL) with stirring an additional 0.5 h. The product was extracted from the mixture using DCM (3 x 15 mL). The organic layer was dried with Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Purification by column chromatography eluting with 3:2 hexanes:EtoAc gave diol 8 (0.759 g, 50%) as a clear colorless oil. $^1$H NMR (CDCl$_3$) 300 MHz δ = 7.37-7.34 (m, 20H), 5.45 (ddd, 1H, J = 6.3, 3.9, 3.9 Hz), 4.78 (d, 1H, J = 11.2 Hz), 4.73 (d, 1H, J = 11.2 Hz), 4.69-4.61 (m, 4H), 4.57 (d, 1H, J = 12.3 Hz), 4.51 (d, 1H, J = 12.1 Hz), 3.99 (m, 1H), 3.92-3.77 (m, 4H), 3.72 (dd, 1H, J = 11.8, 4.4 Hz), 3.67 (m, 1H), 3.37 (s, br, 1H), 2.53 (s, 1H), 2.07 (s, 3H) $^{13}$C NMR (CDCl$_3$) 100 MHz δ = 174.1, 141.8 (2), 141.7, 141.4, 132.3 (2), 132.2 (3), 132.0, 131.9, 131.8, 131.7, 131.5 (2), 82.9, 82.3, 81.4, 81.0, 80.6, 80.4, 78.3, 78.2, 75.6, 72.2, 67.3, 24.9; HRMS m/z calcd for C$_{37}$H$_{45}$O$_8$ 581.2903, found 581.2881.

3,4,5,7-Tetra-O-benzyl-6-O-acetyl-1,2-di-O-triethylsilyl-D-glycero-D-gulitol (9). Diol 8 (0.759 g, 1.24 mmol) was dissolved in DMF (10 mL) under N$_2$. Triethylchlorosilane (TESCl) (0.448 g, 2.97 mmol) was then added to the reaction followed by imidazole (0.515 g, 7.416 mmol). The reaction was stirred 12h, then the solvent was removed under reduced pressure. The mixture was redissolved in 30 mL DCM and washed with water (3 x 20 mL). The organic layer was dried with Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Column chromatography of the resulting material using 85:15 hexanes:EtOAc as eluent gave TES protected material 9 (0.6574 g, 63%) as a clear slightly yellow oil. $^1$H NMR (CDCl$_3$) 300 MHz δ = 7.37-7.33 (m,
20H), 5.46 (ddd, 1H, J = 2.8, 5.6 Hz), 4.92 (d, 1H, J = 10.7 Hz), 4.87 (d, 1H, J = 11.55 Hz), 4.78 (d, 2H, J = 12.12 Hz), 4.73 (d, 1H, J = 11.6 Hz), 4.60 (ddd, 2H, J = 4.0, 10.7 Hz), 4.49 (d, 1H, J = 11.8 Hz), 4.10-3.83 (m, 7H), 3.68 (dd, 1H, J = 6.2, 10.4 Hz), 2.08 (s, 3H), 1.04 (m, 18H), 0.68 (m, 12H)

13C NMR (CDCl3) 100 MHz δ = 170.1, 139.4, 138.8, 138.6, 138.4, 128.4, 128.3(2), 128.2, 127.9 (2), 127.7, 127.6 (2), 127.5, 127.3, 81.0, 79.2, 79.1, 75.8, 75.4, 74.7, 74.0 73.3, 73.1, 68.8, 64.7, 21.3, 7.1, 7.0, 5.3, 4.5; HRMS m/z calcd for C49H71O8Si2 843.4688, found 843.4605.

3,4,5,7-Tetra-O-benzyl-6-O-acetyl-2-O-triethylsilyl-D-glycero-D-gulose (10). Oxalyl chloride (0.296 mL, 3.44 mmol) in DCM (2 mL) was cooled to -70 °C. To this was slowly added a solution of DMSO (0.451 mL, 6.35 mmol) in DCM (2 mL) over 10 min. Then a solution of 9 (0.657 g, 0.781 mmol) in DCM (2 mL) was added and the mixture was stirred for 20 min at –70 °C, then additional 20 min at -40 °C. TEA (1.63 mL, 11.7 mmol) was added and the reaction was allowed to warm to rt over 1h. Water (10 mL) and DCM (10 mL) were added to the reaction. The organic layer was washed with sat. NaCl (2 x 10 mL) and the organic layer was dried with Na2SO4 and the solvent was removed under reduced pressure. Purification via column chromatography which used 9:1 hexanes:EtOAc as eluent gave aldehyde 10 (0.365 g, 64%) as a clear colorless oil.

1H NMR (CDCl3) 300 MHz δ = 9.69 (d, 1H, J = 1.2 Hz), 7.37-7.31 (m, 20H), 5.44 (ddd, 1H, J = 10.0, 4.4 Hz), 4.79-4.64 (m, 6H), 4.57 (d, 1H, J = 12.1 Hz), 4.47 (d, 1H, J = 12.1 Hz) 4.23 (m, 1H), 4.12 (dd, 1H, J = 5.1, 5.1 Hz), 3.99 (dd, 1H, J = 5.7, 2.8 Hz), 3.95-3.87 (m, 2H), 3.78 (dd, 1H, J = 10.5, 5.9 Hz), 2.05 (s, 3H), 0.98 (t, 9H, J = 7.7 Hz), 0.62 (q, 6H, J = 7.7 Hz)

13C NMR (CDCl3) 100 MHz δ = 201.7, 170.1, 138.5, 138.3, 138.1 (2), 128.6, 128.5, 128.4 (2), 128.3, 128.0, 127.8 (2), 127.7 (2), 82.1, 79.4, 79.2, 79.0, 75.2, 74.3, 74.2, 73.2, 72.8, 68.5, 21.3, 6.9, 4.9.

3,4,5,7-Tetra-O-benzyl-D-glycero-D-gulitol (16). Alcohol 6 (2.00 g, 3.72 mmol) was dissolved in 10 mL of a 4:1 acetone: water mixture. NMO was added (0.440 g, 3.76 mmol) to the mixture followed by OsO4 (0.8 mL of a 4 wt% solution in water). The reaction was stirred 2d at rt and then quenched by addition of sat. NH4Cl (5 mL) with stirring an additional 0.5 h. The product was extracted from the mixture using DCM (3 x 15 mL). The organic layer was dried with Na2SO4 and the solvent was removed under reduced pressure. Purification of the residue by column using 6:4 hexanes:EtOAc as eluent gave triol 16 (1.26 g, 60%) as a clear, slightly gray oil. 1H NMR (CDCl3) 400MHz δ = 7.40-7.26 (m, 20H), 4.65 (s, br, 1H), 4.67-4.64 (m, 2H), 4.62 (s, br, 4H) 4.57-4.54 (m, 2H), 4.12-4.04 (m, 1H), 3.98-3.94 (m, 1H), 3.90 (dd, 1H, J = 6.7, 3.3 Hz) 3.86-3.80 (m, 1H), 3.70-3.64 (m, 3H), 3.40 (d, 1H, J = 2.7Hz), 2.89 (d, 1H, J = 5.0 Hz), 2.16 (m, br, 1H) 13C NMR (CDCl3) 100 MHz δ 138.1, 137.9, 137.6, 128.7 (3), 128.4, 128.3 (2), 128.2, 128.1 (2), 79.1, 77.1, 74.2, 73.8, 73.7, 72.2, 71.3, 71.0 63.9; HRMS m/z calcd for C35H41O7 573.2852, found 573.2857.

3,4,5,7-Tetra-O-benzyl-1,2-O-benzylidene-D-glycero-D-gulitol (17). Triol 16 (1.26 g, 2.20 mmol) was dissolved in DMF (10 mL). Benzaldehyde dimethyl acetal (0.995 mL, 6.61 mmol) and p toluenesulfonic acid (0.420 g, 2.20 mmol) were added to the mixture. It was then put on a rotoevaporator under house vacuum for 3h with the bath temp set to 70 °C. After, the reaction was then quenched with TEA and solvent was removed under reduced pressure. The residue was
dissolved in 25 mL DCM and washed with water (3 x 20 mL). The organic layer was dried with Na2SO4 and the solvent was removed under reduced pressure. Column chromatography of the resulting material using 4:1 hexane:EtOAc as eluent gave 17 (0.888 g, 61%, clear colorless oil) as a mixture of diastereomers based on epimers at the benzylidene carbon. 1H NMR (CDCl3) 300 MHz δ = 7.65-7.32 (m, 25H), 5.98 (s, 1H), 5.80 (s, 1H), 4.95-4.90 (m, 2H), 4.88-4.73 (m, 2H), 4.7 (d, 2H, J = 5.0 Hz), 4.67-4.55 (m, 2H), 4.52-4.41 (m, 1H), 4.37-4.29 (m, 1H), 4.29-4.22 (m, 1H), 4.22-4.11 (m, 1H), 4.11-4.04 (m, 1H), 4.02-3.86 (m, 2H), 3.77-3.69 (m, 1H), 13C NMR (CDCl3) 100 MHz δ = 138.5, 138.3, 138.2, 138.1, 129.7, 129.3, 129.2, 129.0, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8 (2), 127.7 (2), 127.6, 126.7, 126.5, 103.6, 103.5, 80.2, 79.4, 78.7, 78.2, 77.7, 74.9, 74.8, 74.7, 74.5, 73.7, 73.6, 73.5 (2), 71.2 (2), 67.3, 66.8; HRMS m/z calcd for C42H45O7 661.3165, found 661.3215.

2,3,4,5,7-Penta-O-benzyl-D-glycero-D-gulitol (18). 3,4,5,7-Tetra-O-benzyl-1,2-O-benzyldiene-D-glycero-D-gulitol 17 (0.759 g, 1.15 mmol) was dissolved in dry THF (2 mL) and a solution of BH3•THF (0.75 mL, 1.0 M) was added to the reaction. After stirring 10 min at rt, Cu(OTf)2 (0.008 g, 0.023 mmol) was added to the reaction and it was stirred at rt for 3 h. The reaction was quenched using Et3N (100 µL), followed by MeOH (1 mL). Solvents were removed under reduced pressure. The residue was dissolved in DCM (30 mL) and washed with H2O (1 x 15 mL) and brine (1 x 15 mL). The organic layer was dried with Na2SO4 and the solvent was removed under reduced pressure. The material was then purified by column chromatography using 7:3 hexane:EtOAc as eluent to give 18 (0.458 g, 60%) as a clear colorless oil. 1H NMR (CDCl3) 300 MHz δ = 7.49-7.30 (m, 25H), 4.90 (d, 1H, J = 11.1 Hz), 4.82 (d, 1H, J = 11.1 Hz), 4.75 (s, br, 2H), 4.68-4.54 (m, 5H), 4.48(d, 1H, J = 11.8 Hz), 4.16 (dd, 1H, J = 5.2 Hz), 4.11 (m, 1H), 3.86 (dd, 1H, J = 4.4 Hz), 3.10 (d, 1H, J = 4.4 Hz) 1.402-3.89 (m, 3H), 3.79-3.66 (m, 3H), 2.48 (m, 1H) 13C NMR (CDCl3) 100 MHz δ = 138.3, 138.2 (2), 138.1, 128.5 (2), 128.4, 128.3, 128.2, 128.1, 127.8 (2), 80.1, 79.4, 79.0, 77.7, 74.7, 74.6, 73.5, 73.4, 71.6, 71.3, 71.1, 61.0; HRMS m/z calcd for C42H47O7 663.3322, found 663.3358.

2,3,4,5,7-Penta-O-benzyl-1,6-Bis-O-triethylsilyl-D-glycero-D-gulitol (19). Diol 18 (0.278 g, 0.420 mmol) was dissolved in DMF (8 mL) and TESCl (0.180 g, 1.05 mmol) was then added followed by imidazole (0.172 g, 2.52 mmol). The mixture was stirred at rt under N2 for 12 h H2O (20 mL) was added to the mixture, and the product was extracted using DCM (3 x 10 mL). The organic layers were combined and dried with Na2SO4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography using 85:15 hexanes:EtOAc as eluent. The reaction gave 19 (0.249 g, 67%) as a clear, slightly yellow oil. 1H NMR (CDCl3) 300 MHz δ = 7.49-7.35 (m, 25H), 4.91 (d, 1H, J = 11.0 Hz), 4.82 (d, 1H, J = 11.1 Hz), 4.75 (s, br, 2H), 4.68-4.54 (m, 5H), 4.48(d, 1H, J = 11.8 Hz), 4.16 (dd, 1H, J = 5.2 Hz), 4.11 (m, 1H), 3.86 (dd, 1H, J = 4.4 Hz), 3.10 (d, 1H, J = 4.4 Hz) 1.402-3.89 (m, 3H), 3.79-3.66 (m, 3H), 2.48 (m, 1H) 13C NMR (CDCl3) 100 MHz δ = 139.4, 139.3, 139.2 (2), 138.6, 128.4, 128.3 (2), 128.0, 127.9, 127.8, 127.6, 127.5, 127.4 (2), 127.3 (2), 82.0, 80.9, 79.8, 79.6, 75.2, 74.6, 74.0, 73.4, 72.6, 72.4, 62.9, 7.1, 7.0, 5.3, 4.6; HRMS m/z calcd for C54H75O7Si2 891.5051, found 891.5081.
2,3,4,5,7-Penta-O-benzyl-6-O-triethylsilyl-D-glycero-D-gulose (20). A solution of oxalyl chloride (0.296 ml, 0.344) in DCM (2 mL) was added to a solution of DMSO (0.18 mL, 2.46 mmol) in DCM (2 mL) with stirring at -70 °C. After 15 min, 2,3,4,5,7-Penta-O-benzyl-1,6-Bis-O-triethylsilyl-D-glycero-D-gulitol 19 (2.49 g, 0.280 mmol) in DCM (2 mL) was added and stirring was continued for 20 min at -70 °C followed by 20 min at -40 °C. After, Et3N (0.59 mL, 4.2 mmol) was added at -70 °C. The reaction was allowed to warm to rt. Additional DCM (20 mL) was added and the solution was washed with H2O (3 x 10 mL) and brine (1 x 10 mL). The DCM was dried with Na2SO4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography which used 9:1 hexanes:EtOAc as eluent to give 20 (0.150 g, 68%) as a clear colorless oil. ¹H NMR (CDCl₃) 400 MHz  δ = 9.79 (d, 1H,  J = 1.6 Hz), 7.36-7.30 (m, 25H), 4.84 (d, 1H,  J = 11.3 Hz), 8.80 (d, 1H,  J = 3.8, 2.1 Hz), 4.77-4.72 (m, 2H), 4.62-4.61 (m, 1H), 4.59-4.58 (m, 1H) 4.48 (s, br, 2H), 4.01 (dd, 1H,  J = 3.8, 2.1 Hz), 4.31 (d, 1H,  J = 11.7 Hz), 4.16-4.09 (m, 2H), 3.98-3.97 (m, 2H), 3.82 (dd, 1H,  J = 9.7, 4.4 Hz), 2.34 (dd, 1H,  J = 9.7, 5.6 Hz), 1.12-0.93 (m, 9H), 0.79-0.55 (m, 6H).

Methyl-2,3,4,5,7-penta-O-benzyl-D-glycero-D-gulosaptanoside (21). 2,3,4,5,7-Penta-O-benzyl-6-O-triethylsilyl-D-glycero-D-gulose 20 (0.150 g, 0.194 mmol) was dissolved in CH₃OH (3 mL) and p–toluenesulfonic acid (0.50 g, 0.253 mmol) was added. The reaction was stirred at rt for 5 h. The reaction solvent was removed and the residue was redissolved in DCM (20 mL). The DCM was washed with sat. NaHCO₃ (2 x 10 mL) and H₂O (2 x 10 mL). The organic layer was dried with Na₂SO₄ and the solvent was removed under reduced pressure. The material was then purified by column chromatography using 8:2 hexanes:EtOAc as eluent to give 21 (0.071 g, 54%, clear glass) as a 2:1 α:β mixture of anomers based on the ¹H integration of the methyl peak of the aglycone. ¹H NMR (CDCl₃) 300 MHz  δ = 7.46-7.43 (m, 1H), 7.36-7.26 (m, 21H), 7.21-7.14 (m, 3H), 5.01 (d, 1H,  J = 10.7 Hz), 4.94-4.77 (m, 4H), 4.73-4.64 (m, 3H), 4.61-4.41 (m, 1H), 4.38-4.23 (m, 3H), 4.15-3.97 (m, 1H), 3.96-3.85 (m, 1H), 3.83-3.56 (m, 4H), 3.56 (s, 1H), 3.53 (s, 2H); ¹³C NMR (CDCl₃) 100 MHz  δ = 139.3, 139.1, 138.5, 138.1, 137.6, 128.6, 128.5, 128.4 (3), 128.3, 128.1 (2), 128.0, 127.8, 127.7 (2), 127.5, 84.7, 81.6, 81.1, 79.7, 75.2, 74.6, 73.8, 73.7, 73.5, 72.6, 72.3, 7.1, 5.2.

Allyl-2,3,4,5,7-penta-O-benzyl-D-glycero-D-gulo-septanoside (22). 2,3,4,5,7-Penta-O-benzyl-6-O-triethylsilyl-D-glycero-D-gulose 20 (0.050 g, 0.065 mmol) was dissolved in allyl alcohol (3 mL) to which p–toluenesulfonic acid (0.50 g, 0.253 mmol) was added. The reaction was stirred at rt for 5 h. After, the solvent was removed and the residue was redissolved in DCM (20 mL). The DCM was washes with sat. NaHCO₃ (2 x 10 mL) and H₂O (2 x 10 mL). The organic layer was dried with Na₂SO₄ and the solvent was removed under reduced pressure. The material was then purified by column chromatography using 85:15 hexanes:EtOAc as eluent to give 22 (0.023 g, 50%, clear colorless oil) as a 5:1 α:β mixture of anomers based on the ¹H integration of the vinyl signal of the aglycone. ¹H NMR (CDCl₃) 400 MHz  δ = 7.37-7.28 (m, 25H), 6.01-5.85 (m,
1H), 5.29-5.15 (m, 2H), 5.02 (d, 1H, J = 10.9 Hz), 4.97 (d, 1H, J = 12.2 Hz), 4.88 (d, 1H, J = 10.9 Hz), 4.85-4.78 (m, 2H), 4.72-4.67 (m, 3H), 4.64-4.56 (m, 3H), 4.53-4.29 (m, 3H), 4.07-4.02 (m, 2H), 3.94-3.83 (m, 1H), 3.78-3.69 (m, 2H), 3.65-3.55 (m, 1H); 13C NMR (CDCl3) 100 MHz δ = 139.4, 139.0 (2), 138.7, 138.4, 134.7, 128.5 (2), 128.4, 128.3, 128.1 (2), 128.0, 127.9, 1237.7, 127.6 (2), 127.5 (2), 116.5, 98.2, 84.6, 81.2, 80.7, 80.2, 76.2, 75.2, 75.1, 73.5, 73.6, 73.5, 70.7, 70.3, 68.3; HRMS m/z calcd for C45H49O7 701.3478, found 701.3411.

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References