Tandem cyclization and acetalization of a homologated D-glucose delivers D-*glycero*-D-gulo-septanosides

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Dedicated to Professor William Bailey on the occasion of his 65th birthday

Abstract
A synthesis of methyl-D-*glycero*-D-gulo-septanoside and allyl D-*glycero*-D-gulo-septanoside from a D-glucose derived heptenitol is reported. Key steps in the synthesis include the diasteroselective 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 **2** is favored over the acyclic hydroxy-aldehyde **3** when they are able to equilibrate. The results here set the groundwork for the preparation of more complex septanosides by this route.

Keywords: Septanose carbohydrate, glycosylation, dihydroxylation

Introduction

Septanose glycosides (e.g., **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 **2** are known to be less stable than pyranoses by 3-8 kcal/mol.[1] The thermodynamic preference for pyranose formation was demonstrated when, upon hydrolysis of methyl septanosides, the corresponding pyranoses were observed by ^{1}H NMR spectroscopy.[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.[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.[4] We became interested in developing conditions where the equilibrium between a septanose such as **2** in the cyclic, hemi-acetal form and its acyclic hydroxy-aldehyde form **3** would favor the cyclic species. If septanose **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 D-*glycero*-D-gulo-septanosides **1** by trapping cyclic hemiacetals such as **2** under acidic conditions.

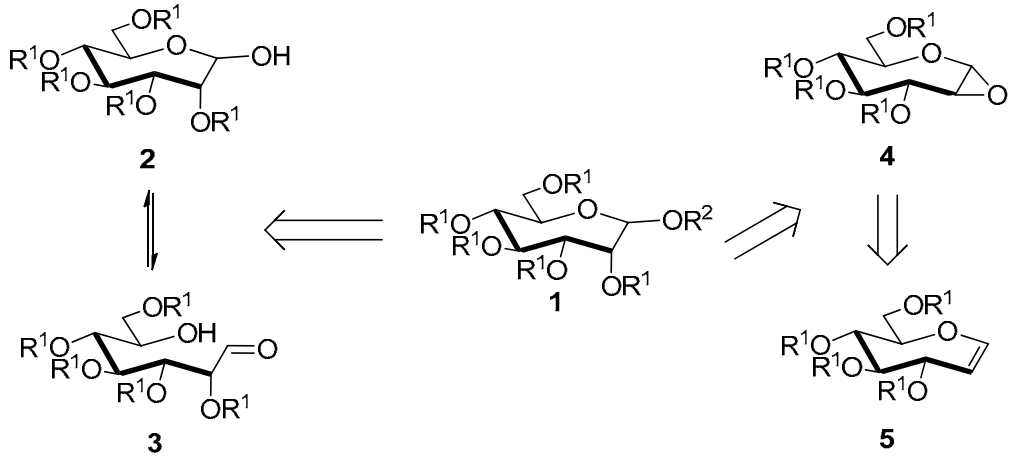


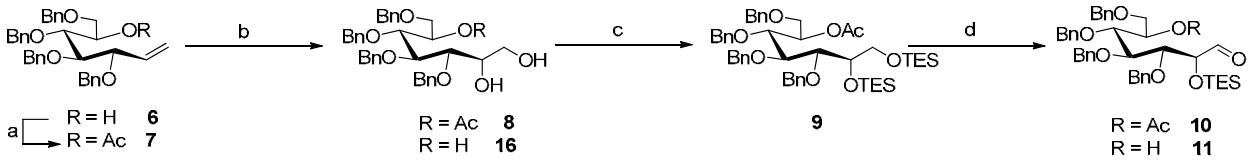
Figure 1. Retrosyntheses of septanosides.

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 glycals.[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-*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-*O*-acetyl derivative **7** (73%). Dihydroxylation of **7** using catalytic 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 determind by ^{1}H NMR.



Scheme 1. First generation approach. a: Ac_2O, py., 73%. b: OsO_4, NMO, acetone:H_2O (4:1), 50% (60% for conversion of **6** to **16**). c: TESCl, imid. DMF, 63%. d: $(COCl)_2$, DMF, DCM, then Et_3N, 64%.

Rather than delivering **11**, the methoxide reaction presumably gave **12**. We surmised that the NH_4Cl 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.

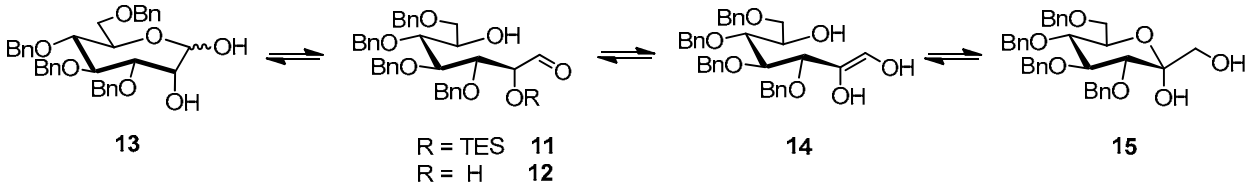
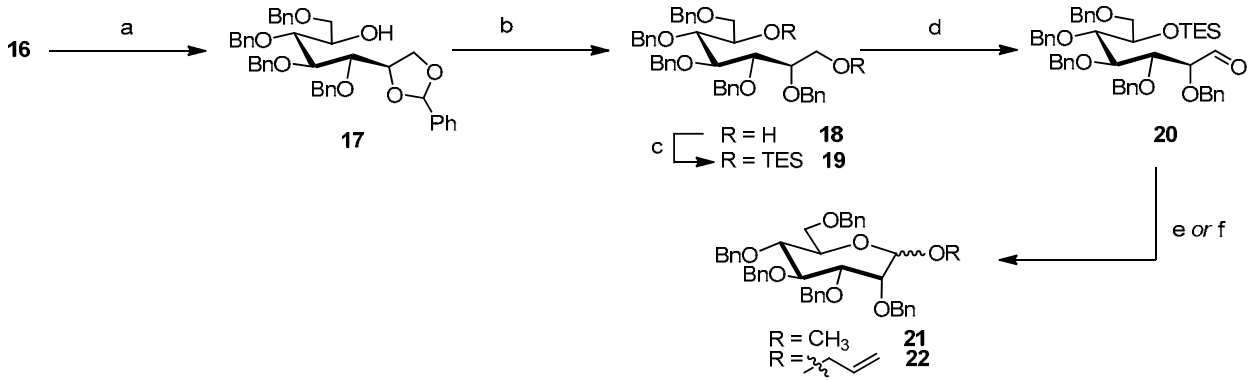


Figure 2. Equilibria available to hydroxy-aldehydes.

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%).[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** (α:β 2:1 54%) or allyl **22** (α:β 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) $PhCH(OCH_3)_2$, *p*TSA, DMF 61%; (b) $Cu(OTf)_2$, BH_3•THF, THF, 60%; (c) TESCl, imid. DMF, 67%; (d) $(COCl)_2$, DMF, DCM, then Et_3N, 68%; (e) *p*TSA, CH_3OH 54% (2:1 α:β); (f) pTSA, allyl alcohol 50% (5:1 α:β).

Methyl septanoside **21** was used to verify the stereochemical configuration of the C2 hydroxyl group. Based on the knowledge that α-septanosides prefer to adopt a $^{3,4}TC_{5,6}$ conformation, the $^3J_{H,H}$ values for H2 were expected to be of low (H1, H2 and H2, H3) magnitude.[19] The H2 signal of **21α** (in the α:β mixture) was identified by a combination of HSQC and COSY experiments. The ^1H 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 ($^3J_{H1,H2}$ 4.3 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 dihyroxylation reaction.

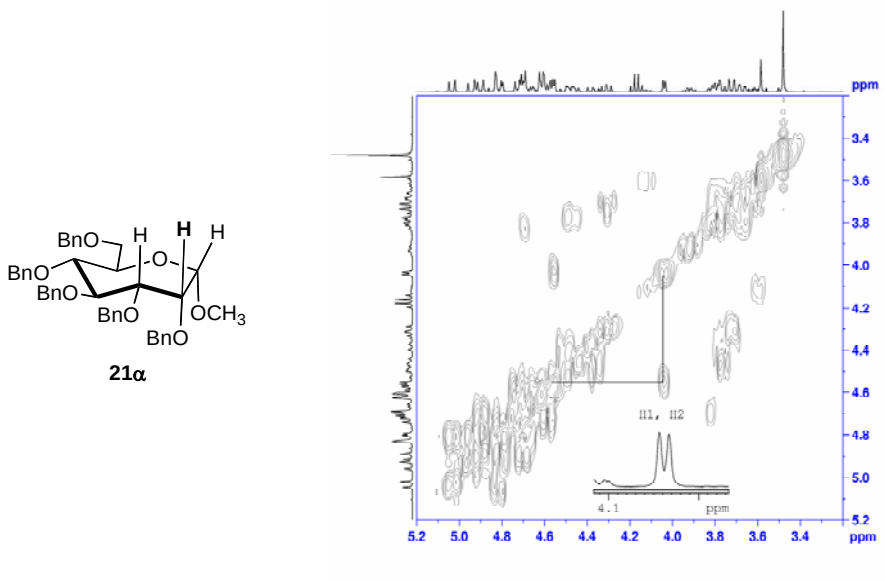


Figure 3. H2 as a diagnostic for determining the stereochemistry of the C2 hydroxyl group of **21α**. Left is the structure assigned to **21α**; on the right is a detail of a COSY spectrum of **21** with inset showing signal for H2.

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 N_2 atmosphere. Reactions were monitored by TLC (silica gel, 60 Å, F_{254}, 250 μm). Visualization was conducted either under UV light or by charring with 2.5% *p*-anisaldehyde in H_2SO_4, acetic acid, and ethanol solution. Preparative chromatography was conducted on silica gel (60 Å, 32-63 μm). ^{1}H NMR spectra were collected at 300 and 400 MHz with chemical shifts

referenced to $(CH_3)_4Si$ (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 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_2SO_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. ^1H NMR ($CDCl_3$) 300 MHz δ 7.3= 7-7.30 (m, 20H), 5.91 (ddd, 1H, *J* = 17.5, 10.5, 7.8 Hz) 5.35-5.31(m, 2H), 5.26 (d, 1H, *J* = 17.8 Hz), 4.79 (d, 1H, *J* = 11.1 Hz), 4.70 (d, 1H, *J*= 11.6 Hz), 4.65-4.60 (m, 3H) 4.49 (d, 1H, *J* = 12.0 Hz), 4.44-4.30 (m, 2H), 4.15 (m, 1H), 3.95 (dd, 1H, *J* = 5.0, 5.0 Hz) 3.88 (dd, 1H, *J* = 10.9, 3.5,Hz), 3.76 (dd, 1H,*J* = 6.2, 10.7 Hz), 3.69 (dd, 1H, *J* = 5.6, 5.6 Hz), 2.04 (s, 3H) ^{13}C NMR ($CDCl_3$) 100 MHz δ = 170.2, 138.6, 138.4, 138.3, 138.1, 135.0, 128.3, 128.2, 128.2, 128.0, 127.8, 127.6 (2), 127.5(3), 119.5, 81.7, 81.3, 79.2, 75.0, 74.4, 73.2, 73.0, 70.8, 68.3, 21.2; 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_4Cl (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_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography eluting with 3:2 hexanes:EtOAc and gave diol **8** (0.759 g, 50%) as a clear colorless oil.^1H 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, 11.2 Hz), 4.69-4.61 (m, 4H), 4.57 (d, 1H, *J* = 12.3 Hz), 4.51 (d, 1H, 12.1 Hz), 4.21-4.14 (m, 1H) 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 $C_{37}H_{41}O_8$ 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 reducted pressure. The mixture was redissolved in 30 mL DCM and washed with water (3 x 20 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography of the resulting material using 85:15 hexanes:EtOAc as eluent gave bis-TES protected material **9** (0.6574 g, 63%) as a clear slightly yellow oil. ^1H 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 (dd, 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) ^{13}C NMR ($CDCl_3$) 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 $C_{49}H_{71}O_8Si_2$ 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. ^{1}H NMR ($CDCl_3$) 300 MHz δ = 9.69 (d, 1H, *J* = 1.2 Hz), 7.37-7.31 (m, 20H), 5.44 (dd, 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) ^{13}C NMR ($CDCl_3$) 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 OsO_4 (0.8 mL of a 4 wt% solution in water). The reaction was stirred 2d at rt and then quenched by addition of sat. NH_4Cl (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_2SO_4 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. ^{1}H NMR ($CDCl_3$) 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) ^{13}C NMR ($CDCl_3$) 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 $C_{35}H_{41}O_7$ 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 thre 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. ^{1}H NMR ($CDCl_3$) 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, 1 H), 4.22-4.11 (m, 1H), 4.11-4.04 (m, 1H), 4.02-3.86 (m, 2H), 3.77-3.69 (m, 1H), ^{13}C NMR ($CDCl_3$) 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 $C_{42}H_{45}O_7$ 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*-benzylidene-D-*glycero*-D-gulitol **17** (0.759 g, 1.15 mmol) was dissolved in dry THF (2 mL) and a solution of BH_3•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 Et_3N (100 μL), followed by MeOH (1 mL). Solvents were removed under reduced pressure. The residue was dissolved in DCM (30 mL) and washed with H_2O (1 x 15 mL) and brine (1 x 15 mL). The organic layer was dried with Na_2SO_4 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. ^{1}H NMR ($CDCl_3$) 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* = 7.1, 4.2 Hz), 3.10 (d, 1H, *J* = 4.4 Hz) 1 4.02-3.89 (m, 3H), 3.79-3.66 (m, 3H), 2.48 (m, 1H) ^{13}C NMR ($CDCl_3$) 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 $C_{42}H_{47}O_7$ 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 N_2 for 12 h H_2O (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. ^{1}H NMR ($CDCl_3$) 300 MHz δ = 7.42-7.35 (m, 25H), 4.93 (d, 1H, *J* = 11.0 Hz), 4.85-4.74 (m, 5H), 4.57-4.56 (m, 2H), 4.49 (d, 1H, *J* = 11.6 Hz), 4.26 (m, 2H), 4.19 (dd, 1H, *J* = 10.8, 2.4 Hz), 4.12 (dd, 1H, *J* = 6.0, 4.6 Hz), 4.06 (dd, 1H, *J* = 5.5, 5.5 Hz),4.02-3.95 (m, 2H), 3.95-3.85 (m, 2H), 3.65 (dd, 1H, *J* = 9.9, 5.8 Hz), 1.10-1.00 (m, 18H), 0.81-0.60 (m, 12H) ^{13}C NMR ($CDCl_3$) 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 $C_{54}H_{75}O_7Si_2$ 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, 0.3.44) 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, Et_3N (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 H_2O (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. ^{1}H NMR ($CDCl_3$) 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* = 11.3 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) ^{13}C NMR ($CDCl_3$) 100 MHz δ = 201.6, 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.

Methyl-2,3,4,5,7-penta-*O*-benzyl-D-*glycero*-D-gulo-septanoside (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 CH_3OH (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. $NaHCO_3$ (2 x 10 mL) and H_2O (2 x 10 mL). The organic layer was dried with Na_2SO_4 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 ^{1}H integration of the methyl peak of the aglycone. ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 100 MHz δ = 139.3, 139.1, 139.0 (2), 138.9, 138.8, 138.7, 138.4 (2), 128.6, 128.5 (2), 128.4, 128.3, 128.2, 128.1 (2), 128.0 (2), 127.9, 127.8, 127.7 (2), 127.6, 106.7, 100.4, 84.5, 81.3, 81.1, 80.6, 80.0, 78.8, 76.1, 75.0, 73.7 (2), 73.6, 73.5, 73.4, 72.8, 72.7, 71.7, 70.7, 70.2, 56.4, 55.8; HRMS *m/z* calcd for $C_{43}H_{47}O_7$ 675.3322, found 675.3327.

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 washed with sat. $NaHCO_3$ (2 x 10 mL) and H_2O (2 x 10 mL). The organic layer was dried with Na_2SO_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 **22** (0.023 g, 50%, clear colorless oil) as a 5:1 α:β mixture of anomers based on the ^{1}H integration of the vinyl signal of the aglycone. ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{45}H_{49}O_7$ 701.3478, found 701.3411.

Ackowledgements

M.W.P. thanks NSF for a CAREER award (CHE-0546311).

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