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Synthesis of methyl α-D-glucopyranosyl-(1→4)-α-D-galactopyranoside and methyl α-D-*xylo*-hex-4-ulopyranosyl-(1→4)-α-D-galactopyranoside

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Abstract

The syntheses of methyl α-D-glucopyranosyl-(1→4)-α-D-galactopyranoside (**1**) and methyl α-D-*xylo*-hex-4-ulopyranosyl-(1→4)-α-D-galactopyranoside (**4**) are reported. The keto-disaccharide **4** is of interest in our design, synthesis, and study of pectate lyase inhibitors. The key step in the syntheses was the high-yielding, stereospecific formation of methyl 4,6-*O*-benzylidene-2′,3′-di-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**15**), which was accomplished by reacting 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranosyl trichloroacetimidate (**10**) with methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**14**) in the presence of a catalytic amount of *tert*-butyldimethylsilyl trifluoromethane sulfonate (TMSOTF). Compound **15** was either hydrogenolyzed to yield disaccharide **1** or treated with $NaBH_3CN$–HCl in 1:1 tetrahydrofuran–ether to yield methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**2**). The free 4′-OH of compound **2** was oxidized to a carbonyl group by a Swern oxidation, and the protecting groups were removed by hydrogenolysis to yield keto-disaccharide **4**. These synthetic pathways were simple, yet high yielding.

Keywords: α-D-Glucopyranosides; Trichloroacetimidate in α-glycoside formation; Keto-disaccharides

1. Introduction

Pectate lyases are a family of isoenzymes that constitute the major component of a complex mixture of cell-wall degrading enzymes produced and secreted by plant pathogens that cause diseases involving maceration and killing of parenchymatous tissues in many plants.[1–3] These enzymes cleave internal glycosidic bonds in polygalacturonic acid or low-methylesterified pectins by a β-elimination reaction to yield oligomers that contain 4,5-unsaturated sugars at their nonreducing ends. Using this β-elimination mechanism as a guide, we are currently in the process of designing and synthesizing compounds that will specifically inhibit pectate lyases. As part of our study, we synthesized methyl α-D-glucopyranosyl-(1→4)-α-D-galactopyranoside (**1**), and the selectively deprotected derivative of **1**,

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methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**2**), as well as the corresponding 4′-ketoderivatives **3** and **4**.

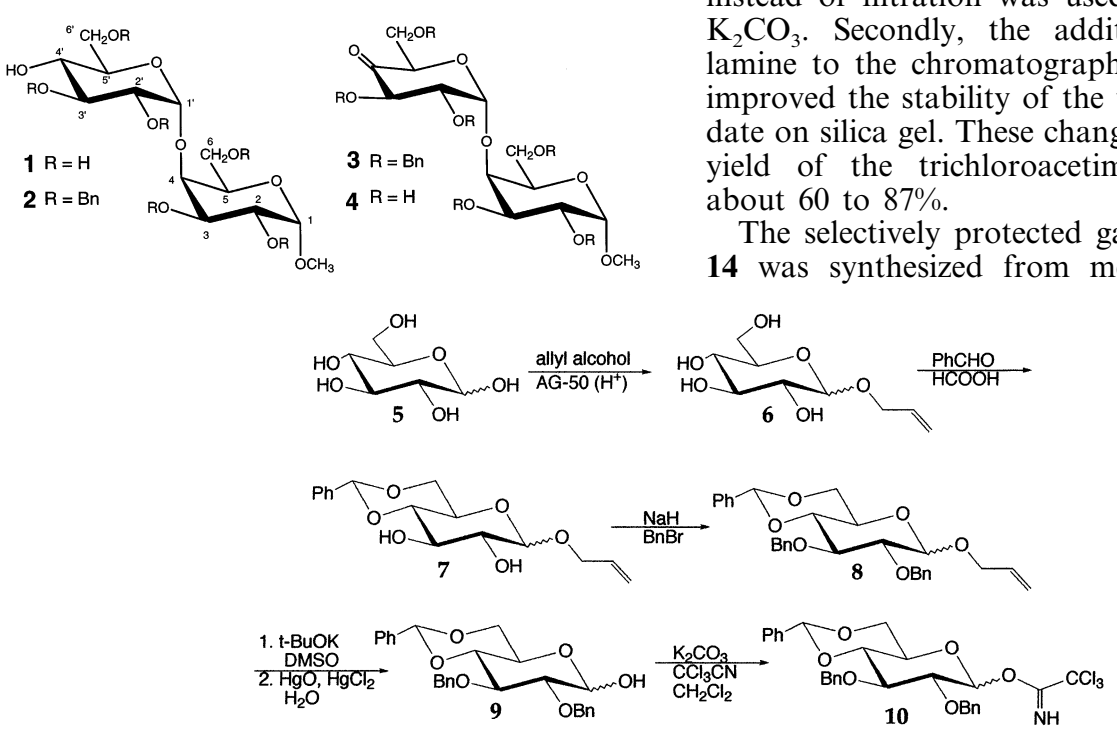
An earlier synthesis of **1** using a thioglycoside coupling has been reported. In this method the glycosidic bond formation gave 37% of the α isomer and 32% of the β isomer.[4] In addition the synthesis of the selectively protected galactoside required the use of environmentally toxic mercuric chloride in the formation of a metal chelate.[5] More recently an enzymatic synthesis of **1** using dextransucrase was reported.[6] However, this study indicated that methyl galactopyranoside was an inefficient glucose acceptor for reactions catalyzed by this enzyme.

The work described herein not only provides an efficient, stereoselective synthesis of disaccharide **1**, but would allow also for this disaccharide to be incorporated into more complex molecules. By using the selectively deprotected disaccharide **2**, the larger oligosaccharide-containing substructure **1** attached by its 4′-hydroxyl group could be synthesized. Likewise the keto groups of structures **3** and **4** allow for a wide range of selective chemistry at the 4′-position, including reductive amination and nucleophilic addition.

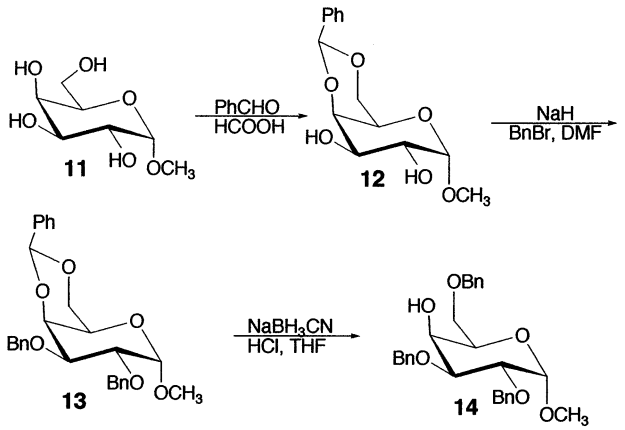
2. Results and discussion

The most challenging aspect of this synthesis was creating the (1→4)-α-D-glycosidic linkage with high selectivity. For this glycosidic bond formation we employed a trichloroacetimidate coupling between 2,3-di-*O*-benzyl-4,6-*O*-benzylidiene-D-glucopyranosyl trichloroacetimidate (**10**) and methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**14**).[7] The trichloroacetimidate **10** was synthesized in five steps from glucose in 31% overall yield as illustrated in Scheme 1. The synthesis of 2,3-di-*O*-benzyl-4.6-*O*-benzylidene-D-glucopyranose (**9**) was as previously described,[8] with the only improvement being the use of anhydrous formic acid as the catalyst for benzylidene acetal formation[9] as opposed to the more common anhydrous $ZnCl_2$. The conversion of glucopyranose derivative **9** into the trichloroacetimidate **10** was based on a procedure for similar glucopyaranoses.[7] Improvements to the literature procedure were in the area of purification of the trichloroacetimidate. Firstly, centrifugation of the reaction instead of filtration was used to remove the K_2CO_3. Secondly, the addition of triethylamine to the chromatography solvent vastly improved the stability of the trichloroacetimidate on silica gel. These changes improved the yield of the trichloroacetimidate **10** from about 60 to 87%.

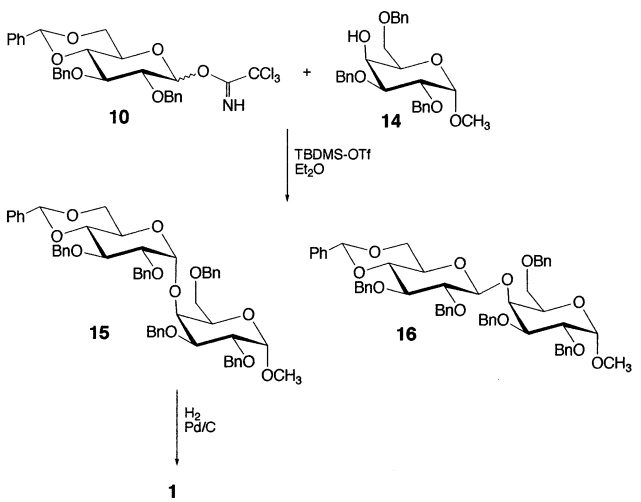
The selectively protected galactopyranoside **14** was synthesized from methyl α-D-galac-



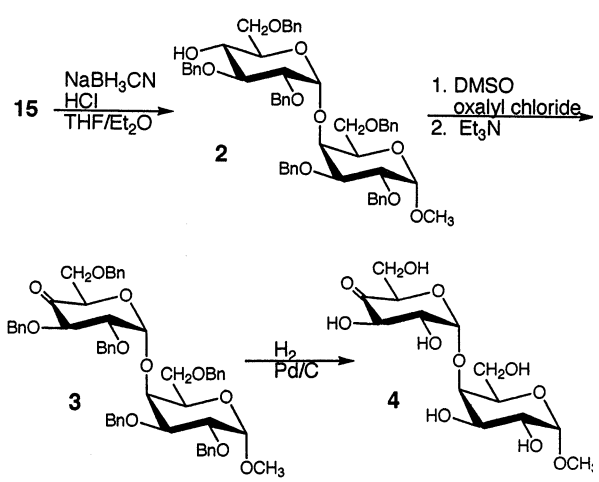
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

topyranoside (**11**) in three steps in 56% overall yield as illustrated in Scheme 2. This synthesis was as previously described[10] except anhydrous formic acid was used instead of $ZnCl_2$ as the catalyst for the benzylidene acetal formation. In both this synthesis and the synthesis of **10** above, using anhydrous formic as the catalyst for benzylidene acetal formation gave much higher yields than the traditional catalyst. In addition, the reactions with formic acid were faster (30 min compared to 2 days) and more easily purified.

The *t*-butyldimethylsilyl trifluoromethanesulfonate catalyzed coupling of **10** and **14** gave the protected α-disaccharide **15** in 90% yield and its β isomer **16** in 9% yield (Scheme 3). As described by Wegmann and Schmidt,[7] the high yield and stereoselectivity are as expected for a glycosidic bond formation taking place in ether as opposed to the more common dichloromethane, particularly with a weakly reactive glycosyl acceptor such as galactopyranoside **14**. The α isomer was verified by the presence of a doublet in the ^{1}H NMR at 4.94 ppm with a coupling constant of 4.2 Hz, corresponding to the anomeric hydrogen on the glucopyranoside. In addition, the ^{13}C NMR had a peak at 100.39 ppm corresponding to the anomeric carbon of the α configuration.[11] The β isomer was verified by the presence of a ^{13}C NMR peak at 103.49 ppm for the anomeric carbon[11] and the absence of a peak corresponding to the anomeric proton of the α isomer, since the anomeric proton of the β isomer was obscured by the benzyl protons.

Disaccharide **15** was deprotected by hydrogenolysis (H_2, Pd/C) to give the desired methyl α-D-glucopyranosyl-(1→4)-α-D-galactopyranoside (**1**) in 91% yield. Disaccharide **1** had identical physical and spectral characteristics as those previously reported.[11] Alternatively, treatment of disaccharide **15** with $NaBH_3CN$ and HCl in THF–ether resulted in the selectively deprotected derivative **2** in 63% yield (Scheme 4). The selective deprotection was verified by the loss of the benzylidene proton peak at 5.52 ppm and the appearance of two doublets at 4.38 and 4.22 ppm corresponding to the hydrogens of the 6′-*O*-benzyl ether. The structure of compound **2** was also supported by the disappearance of the benzylidene peak at 99.0 ppm in the ^{13}C NMR spectrum and the appearance of an O–H stretch at 3350–3600 cm^{-1} in the IR spectrum.

The 4-hydroxyl group of compound **2** was oxidized under Swern conditions (DMSO, oxalyl chloride, Et_3N) giving ketone **3** in 87% yield (Scheme 4).[12] Both the IR spectrum (C=O stretch at 1730 cm^{-1}) and the ^{13}C NMR spectrum (new C=O carbon at 205.0 ppm) verified the success of this reaction. In addition, the H-4′ proton of compound **2** was no longer observed, and the H-3′ and H-5′ peaks both shifted downfield. H-3′ was observed as a doublet at 4.35 ppm, while H-5′ was part of a multiplet at $\sim$4.7 ppm. A small amount of material ($\sim$11%), which has tentatively been identified as the compounds resulting from isomerization α to the carbonyl group, has also been isolated. The benzyl protecting groups were removed from compound **3** by catalytic hydrogenolysis (H_2, Pd/C) giving the desired keto-disaccharide **4** in quantitative yield. Preliminary proton NMR studies indicated that over time, isomerization occurs at C-3′ and C-5′ and that H-3′ and H-5′ exchange with deuterium (75% exchange in 2.5 days).

The overall yield of disaccharide **1** was 51% from the starting methyl galactopyranoside **11**, while that of the keto-disaccharide **4** was 31%. Compounds **2** and **3**, the potential intermediates to more elaborate compounds, were produced in 35 and 31% overall yields, respectively. Thus, the described work provides a high-yielding synthesis of these biochemically important compounds.

3. Experimental

General methods.—Optical rotations were measured with a Perkin–Elmer 141 polarimeter. NMR spectra were recorded with a Bruker 300 MHz Aspect 3000 spectrometer. NMR spectra were run in either $CDCl_3$ using tetramethylsilane (TMS) as an internal standard or in D_2O using 3-(trimethylsilyl)propanoate (TSP) as the internal standard. Column chromatography was performed on KP-Sil™ silica gel (32–63 μm, 60 Å) using Biotage prepacked columns and the Biotage Flash 12i + 40i™ chromatography system. IR spectra were obtained on a Perkin–Elmer 1310 IR spectrometer. Diethyl ether was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from CaH_2. Trichloroacetonitrile was distilled from P_2O_5. Anhyd K_2CO_3 was dried at 60 °C for 2 days in a vacuum oven before use. All other solvents and reagents were used without further purification. The 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (**9**) was prepared as previously described.[8] Likewise, the methyl-2,3,6-tri-*O*-benzyl-α,D-galactopyranoside (**14**) was prepared as previously described.[10] In both syntheses, the 4,6-benzylidene acetal derivatives were prepared using anhyd formic acid as the catalyst.

2,3-Di-O-benzyl-4,6-O-benzylidene-D-glucopyranosyl trichloroacetimidate (**10**).—To a stirring solution of glucopyranose **9** (3.0 g, 6.70 mmol) in CH_2Cl_2 (225 mL) were added sequentially anhyd K_2CO_3 (33 g, 23 mmol) and CCl_3CN (33 mL, 329 mmol). The reaction was stirred under N_2 for 16 h at rt. The reaction mixture was centrifuged to remove the K_2CO_3. The K_2CO_3 pellet was washed with CH_2Cl_2 (2 × 100 mL). The washes were combined with the original CH_2Cl_2 supernatant and evaporated to an oil. This oil was purified by chromatography eluting the column with 100:5:1 CH_2Cl_2–CH_3CN–triethylamine to give trichloroacetimidate **10** (3.44 g, 87%) and recovered starting material **9** (332 mg, 11%). **10**: R_f 0.8 (100:5:1 CH_2Cl_2–CH_3CN–triethylamine); IR (neat): 3330 cm^{-1} (N–H stretch), 3000–3100 cm^{-1} (ar C–H stretch), 2850–2990 cm^{-1} (satd C–H stretch), 1670 cm^{-1} (C=N stretch); ^1H NMR ($CDCl_3$): δ 8.72 (s, 0.5 H, β-NH), 8.61 (s, 0.5 H, α-NH), 7.53–7.21 (m, 15 H, Ar), 6.43 (d, 0.5 H, $J_{1,2}$ 3.7 Hz, α-H-1), 5.93 (d, 1 H, $J_{1,2}$ 7.4 Hz, β-H-1), 5.57 (s, 1 H, PhCH), 4.96–4.73 (m, 4 H, 2 × $PhCH_2O$), 4.41 (dd, 0.5 H, $J_{5,6a}$ 5.0, $J_{6b,6a}$ 10.3 Hz, β-H-6a), 4.31 (dd, 0.5 H, $J_{5,6a}$ 5.0, $J_{6b,6a}$ 10.3 Hz, α-H-6a), 4.12 (t, 0.5 H, $J_{2,3,4}$ 9.3 Hz, β-H-3), 4.03 (dt, 0.5 H, $J_{4,5,6b}$ 10.0 Hz, β-H-5), 3.88–3.61 (m, 4 H, H-2, α-H-3, H-4, α-H-5, H-6b). ^{13}C NMR ($CDCl_3$): δ 161.7, 161.4, 138.9, 138.7, 138.3, 138.2, 137.5, 137.5, 129.4, 128.7, 128.7, 138.6, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 126.4, 126.4, 101.6, 98.6, 95.0, 81.8, 81.5, 81.3, 81.0, 79.0, 78.4, 75.6, 75.6, 75.4, 73.7, 69.1, 69.0, 67.0, 65.4; Anal. Calcd for $C_{29}H_{28}Cl_3NO_6$: C, 58.75; H, 4.76; N, 2.36. Found: C, 59.13; H, 4.65; N, 2.25.

Methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D-galactopyranoside (**15**).—Glucosyl-trichloroacetimidate **10** (2.76 g, 4.65 mmol) and the 4-O-deprotected galactoside **14** (1.34 g, 2.88 mmol) were dissolved in Et_2O (63 mL). While the reaction was stirred at rt under N_2, *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.355 mL, 1.55 mmol) was added by syringe. After stirring for 2.5 h at rt, the reaction was quenched by adding excess solid $NaHCO_3$. The reaction was washed with satd aq $NaHCO_3$ (65 mL). The $NaHCO_3$ layer was subsequently extracted with Et_2O (3 × 75 mL). The ether layers were combined, dried over Na_2SO_4, decanted, and evaporated to an oil. The oil was chromatographed through silica gel eluting with a solvent gradient of 40:30:1–40:30:4 CH_2Cl_2–hexane–EtOAc resulting in the α-disaccharide **15** (2.32 g, 90%) and the β-disaccharide **16** (0.23 g, 9%). **15**: $[\alpha]_D^{28}$ +49.6° (*c* 2.7, CH_2Cl_2); R_f 0.33 (40:30:3 CH_2Cl_2–hexane–EtOAc); IR (neat): 3000–3100 cm^{-1} (Ar C–H stretch), 2850–2990 cm^{-1} (satd C–H stretch); ^1H NMR ($CDCl_3$): δ 7.37–7.17 (m, 30 H, Ar), 5.52 (s, 1 H, PhCH), 4.95 (d, 1 H, *J* 10.7 Hz, 0.5 × $PhCH_2O$), 4.94 (d, 1 H, $J_{1',2'}$ 4.2 Hz, H-1′), 4.88 (d, 1 H, *J* 12.2 Hz, 0.5 × $PhCH_2O$), 4.87 (d, 1 H, *J* 11.8 Hz, 0.5 × $PhCH_2O$), 4.79 (s, 2 H, $PhCH_2O$), 4.76 (non-first order AB_q, 2 H, $PhCH_2O$), 4.69 (d, 1 H, *J* 11.8 Hz, 0.5 × $PhCH_2O$), 4.69 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.32 (dd, 1 H, $J_{5',6e'}$ 4.8, $J_{6e',6a'}$ 9.9 Hz, H-6e′), 4.25 (non-first order AB_q, 2 H, $PhCH_2O$), 4.07 (m, 1 H, H-4), 4.01 (t, 1 H, $J_{2',3',4'}$ 9.3 Hz, H-3′), 3.95 (dd, 1 H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.92–3.82 (m, 2 H, H-5, H-5′), 3.81 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, H-6b), 3.61 (t, 1 H, $J_{3',4',5'}$ 9.5 Hz, H-4′), 3.57 (dd, 1 H, $J_{5',6b'}$ 3.7 Hz, H-6b), 3.53–3.46 (m, 3 H, H-3, H-2, H-2′), 3.36 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 138.8, 138.5, 138.3, 138.2, 137.7, 128.7, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.5, 127.5, 127.3, 126.0, 101.0, 100.4, 99.0, 82.8, 79.6, 79.1, 77.7, 77.2, 75.1, 74.3, 74.2, 73.4, 72.9, 72.8, 69.2, 68.9, 68.0, 63.0, 55.3; Anal. Calcd for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53. Found: C, 73.73; H, 6.54.

16: $[\alpha]_D^{28}$ +29.4° (*c* 2.3, CH_2Cl_2); R_f 0.20 (40:30:3 CH_2Cl_2–hexane–EtOAc); IR (neat): 3000–3100 cm^{-1} (ar C–H stretch), 2850–2990 cm^{-1} (satd C–H stretch); ^1H NMR ($CDCl_3$): δ 7.56–7.18 (m, 30 H, Ar), 5.59 (s, 1 H, PhCH), 5.10 (d, 1 H, *J* 9.6 Hz, 0.5 × $PhCH_2O$), 5.09 (d, 1 H, *J* 9.6 Hz, 0.5 × $PhCH_2O$), 4.93 (d, 1 H, *J* 12.0 Hz, 0.5 × $PhCH_2O$), 4.91 (d, 1 H, *J* 11.5 Hz, 0.5 × $PhCH_2O$), 4.83–4.72 (m, 4 H, $PhCH_2O$, H-1, H-1′), 4.66 (d, 1 H, *J* 11.8 Hz, 0.5 × $PhCH_2O$), 4.63 (d, 1 H, *J* 11.9 Hz, 0.5 × $PhCH_2O$), 4.56 (d, 1 H, *J* 11.9 Hz, 0.5 × $PhCH_2O$), 4.40 (d, 1 H, *J* 12.2 Hz, 0.5 × $PhCH_2O$), 4.27 (m, 1 H, H-4), 4.25 (dd, 1 H, $J_{5',6e'}$ 5.0, $J_{6e',6a'}$ 10.5 Hz, H-6e′), 4.01–3.97 (m, 3 H, H-5, H-6a, H-6b), 3.80–3.63 (m, 5 H, H-2, H-3, H-3′, H-4′, H-6a′), 3.50 (t, 1 H, $J_{1',2',3'}$ 8.0 Hz, H-2′), 3.45 (s, 3 H, OCH_3), 3.34 (ddd, $J_{4',5'}$ 10.0, $J_{5',6a'}$ 10.0 Hz, H-5′); ^{13}C NMR ($CDCl_3$): δ 139.2, 139.1, 139.0, 138.8, 138.7, 137.7, 129.3, 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 126.4, 103.5, 101.5, 99.0, 82.7, 81.9, 81.1, 78.9, 77.4, 75.3, 75.0, 74.0, 74.0, 73.8, 73.7, 70.3, 69.7, 69.1, 66.1, 55.7.

Preparation of methyl α-D-glucopyranosyl-(1→4)-α-D-galactopyranoside (**1**).—Protected disaccharide **15** (0.171 g, 0.191 mmol) was dissolved in reagent-grade alcohol (6 mL). Pd/C (ca. 20 mg, 10%) was added to the solution. The reaction was flushed with H_2, then stirred at rt under an H_2 atmosphere for 16 h. The mixture was filtered through a plug of Celite on glass wool. The residue was rinsed with EtOH (3 × 1.5 mL). The filtrate and rinses were combined and evaporated to dryness. The resulting white solid was dissolved in water (5 mL) and washed with CH_2Cl_2 (2 × 3 mL). The CH_2Cl_2 extracts were combined and extracted once with water (1 mL). The water fractions were combined and evaporated to dryness giving disaccharide **1** (62 mg, 91%) as an amorphous powder. **1**: $[\alpha]_D^{26}$ +195.6° (*c* 1.03, water), lit.[6] +116.1°; $[\alpha]_{578}^{26}$ +203.2° (*c* 1.03, water), lit.[4] +210°; R_f 0.55 (1:1 CH_2Cl_2–CH_3OH); IR (Nujol): 3100–3600 cm^{-1} (O–H stretch), 2850–2990 cm^{-1} (satd C–H stretch); ^1H NMR (D_2O): δ 4.93 (d, 1 H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.90 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 4.12 (dt, 1 H, $J_{4',5}$ 10.2, $J_{5',6'}$ 3.3 Hz, H-5′), 4.06 (m, 1 H, H-4), 4.03–3.79 (m, 7 H, H-2, H-3, H-5, H-6a, H-6b, H-6a′, H-6b′),

3.74 (t, 1 H, $J_{2',3',4'}$ 9.8 Hz, H-3′), 3.55 (dd, 1 H, H-2′), 3.46 (t, 1 H, H-4′), 3.43 (s, 3 H, OCH_3); ^{13}C NMR (D_2O): δ 103.0, 102.3, 81.4, 75.5, 74.8, 74.6, 74.0, 72.1, 71.8, 71.1, 63.3, 62.9, 58.0; Anal. Calcd for $C_{13}H_{24}O_{11}$: C, 43.82; H, 6.79. Found: C, 43.3; H, 6.36.

Methyl 2,3,6-tri-O-*benzyl*-α-D-*glucopyranosyl*-(1→4)-*2,3,6-tri*-O-*benzyl*-α-D-*galactopyranoside* (**2**).—To benzylidene-protected disaccharide **15** (2.02 g, 2.26 mmol) was added 3 Å molecular sieves, followed by 1 M $NaBH_3CN$ in THF (31 mL, 3.1 mmol, Aldrich). The mixture was stirred at rt under N_2 while 1 M HCl in ether (33 mL, 3.3 mmol, Aldrich) was added dropwise. When the addition was complete, the reaction mixture was decanted and the sieves and flask rinsed with 1:1 CH_2Cl_2–water (2 × 60 mL). The rinse and reaction solutions were combined, and the CH_2Cl_2 was removed. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined CH_2Cl_2 extracts were washed with satd aq $NaHCO_3$ (100 mL). The $NaHCO_3$ wash was subsequently extracted with CH_2Cl_2 (50 mL). The CH_2Cl_2 fractions were combined, dried over Na_2SO_4, decanted and evaporated to a yellow oil. The oil was chromatographed through silica gel, eluting with 5:9:2 CH_2Cl_2–hexane–EtOAc, yielding the desired disaccharide **2** (1.27 g, 63%). **2**: $[\alpha]_D^{29}$ +73.1° (*c* 2.86, CH_2Cl_2); R_f 0.38 (5:9:2 CH_2Cl_2–hexane–EtOAc); IR (neat): 3350–3600 cm^{-1} (O–H stretch), 3000–3100 cm^{-1} (ar C–H stretch), 2850–2990 cm^{-1} (satd C–H stretch); ^1H NMR ($CDCl_3$): δ 7.37–7.17 (m, 30 H, Ar), 4.99 (d, 1 H, $J_{1',2'}$ 3.3 Hz, H-1′), 4.92 (d, 1 H, *J* 11.2 Hz, 0.5 × $PhCH_2O$), 4.85 (d, 1 H, *J* 12.2 Hz, 0.5 × $PhCH_2O$), 4.78 (d, 1 H, *J* 11.3 Hz, 0.5 × $PhCH_2O$), 4.77 (d, 1 H, *J* 11.9 Hz, 0.5 × $PhCH_2O$), 4.75–4.64 (m, 5 H, 2 × $PhCH_2O$, H-1), 4.38 (d, 1 H, *J* 12.2 Hz, 0.5 × $PhCH_2O$), 4.25 (non-first order AB_q, 2 H, $PhCH_2O$), 4.22 (d, 1 H, *J* 12.3 Hz, 0.5 × $PhCH_2O$), 4.19–4.10 (m, 1 H, H-5′), 4.08 (m, 1 H, H-4), 3.98–3.73 (m, 6 H, H-2, H-3, H-5, H-6a, H-3′, H-6a′), 3.53–3.46 (m, 2 H, H-6b, H-6b′), 3.36 (s, 3 H, OCH_3), 3.33–3.27 (m, 1 H, H-4′), 3.16 (dd, 1 H, $J_{1',2'}$ 3.9, $J_{2',3'}$ 10.2 Hz, H-2′); ^{13}C NMR ($CDCl_3$): δ 138.9, 138.8, 138.7, 138.5, 138.1, 138.0, 128.3, 128.3, 128.2, 128.2, 127.8, 127.7, 127.7, 127.7, 127.6,127.5, 127.4, 127.3, 127.3, 99.5, 98.8, 81.6, 80.0, 77.7, 76.5, 75.1, 75.0, 73.6, 73.4, 73.3, 72.9, 72.7, 71.6, 70.2, 69.2, 69.0, 68.0, 55.2; Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.52; H, 6.62.

Methyl 2,3,6-tri-O-*benzyl*-α-D-xylo-*hex*-4-*ulopyranosyl*-(1→4)-*2,3,6-tri*-O-*benzyl*-α-D-*galactopyranoside* (**3**).—A solution of dimethyl sulfoxide (410 μL, 5.77 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a solution of oxalyl chloride (193 μL, 2.21 mmol) in CH_2Cl_2 (6 mL) that had been precooled to −60 °C. The resulting reaction mixture was stirred under N_2 at −60 °C for 10 min. The 4-unprotected disaccharide **2** (1.088 g, 1.21 mmol) was dissolved in CH_2Cl_2 (3 mL). The resulting solution was added dropwise to the −60 °C reaction mixture. After 15 min at −60 °C, triethylamine (2 mL, 14.3 mmol) was added, and the reaction was allowed to warm to rt. The reaction mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (4 × 175 mL). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, decanted and evaporated to a viscous oil. The oil was chromatographed through silica gel eluting with 4:1 hexane–EtOAc, yielding the desired keto-disaccharide **3** (0.94 g, 87%). **3**: $[\alpha]_D^{29}$ +100.8° (*c* 3.70, CH_2Cl_2); R_f = 0.55 (2:1 hexane–EtOAc); IR (neat): 3000–3100 cm^{-1} (ar C–H stretch), 2850–2990 cm^{-1} (satd C–H stretch), 1730 cm^{-1} (C=O stretch); ^1H NMR ($CDCl_3$): δ 7.44–7.17 (m, 30 H, Ar), 5.21 (d, 1 H, $J_{1',2'}$ 3.1 Hz, H-1′), 5.03 (d, 1 H, *J* 10.9 Hz, 0.5 × $PhCH_2O$), 4.82 (d, 1 H, *J* 11.9 Hz, 0.5 × $PhCH_2O$), 4.79–4.67 (m, 6 H, 2 × $PhCH_2O$, H-1, H-5′), 4.64 (d, 1 H, *J* 11.9 Hz, 0.5 × $PhCH_2O$), 4.62 (d, 1 H, *J* 10.9 Hz, 0.5 × $PhCH_2O$), 4.40 (non-first order AB_q, 2 H, $PhCH_2O$), 4.35(d, 1 H, $J_{2',3'}$ 10.5 Hz, H-3′), 4.27 (s, 2 H, $PhCH_2O$), 4.21 (m, 1 H, H-4), 4.00–3.79 (m, 5 H, H-2, H-3, H-5, H-6a, H-6a′), 3.53–3.46 (m, 2 H, H-6b, H-6b′), 3.36 (s, 3 H, OCH_3), 3.26 (dd, 1 H, H-2′); ^{13}C NMR ($CDCl_3$): δ 205.0, 139.1, 138.8, 138.7, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 100.1, 99.2, 83.2, 80.3, 78.2, 77.9, 75.7, 75.6, 75.2, 74.7, 74.3, 73.8, 73.7, 73.5, 69.6, 68.2, 68.2, 56.0; Anal. Calcd for $C_{55}H_{58}O_{11}$: C, 73.81; H, 6.53. Found: C, 73.42; H, 6.52.

α-D-xylo-*Hex-4-ulopyranosyl-(1→4)*-α-D-*galactopyranoside* (**4**).—Protected keto-disaccharide **3** (0.163 g, 0.182 mmol) was dissolved in reagent alcohol (6 mL). Pd/C (ca. 40 mg, 10%) was added to the solution. The reaction was flushed with H_2, then stirred at rt under an H_2 atmosphere for 21 h. The mixture was filtered through a plug of Celite on glass wool. The residue was rinsed with EtOH (3×1.5 mL). The filtrate and rinses were combined and evaporated to dryness. The resulting white solid was dissolved in water (5 mL) and washed with CH_2Cl_2 (2×3 mL). The CH_2Cl_2 was combined and extracted once with water (1 mL). The water fractions were combined and evaporated to dryness giving disaccharide **4** (64 mg, 99.5%) as an amorphous powder. **4**: $[\alpha]_D^{26}$ +204.8° (*c* 1.07, water); $[\alpha]_{578}^{26}$ +212.7° (*c* 1.07, water); R_f 0.54 (1:1 CH_2Cl_2–CH_3OH); IR (Nujol): 3100–3600 cm^{-1} (O–H stretch), 2850–2990 cm^{-1} (satd C–H stretch), 1725 cm^{-1} (C=O stretch); ^1H NMR (D_2O): δ 5.17 (m, 1 H, H-5′) 4.97 (d, 1 H, $J_{1',2'}$ 3.7 Hz, H-1′), 4.90 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.61 (d, 1 H, $J_{2',3'}$ 10.8 Hz, H-3′), 4.20 (q, 1 H, $J_{4',5',6'}$3.2 Hz, H-5), 4.11 (m, 1 H, H-4), 4.08–3.67 (m, 7 H, H-2, H-2′, H-3, H-6a, H-6b, H-6a′, H-6b′), 3.43 (s, 3 H, OCH_3); ^{13}C NMR (D_2O): δ 208.1, 102.9, 102.3, 81.7, 75.6, 75.2, 73.9, 73.5, 72.0, 71.2, 63.4, 62.0, 58.0; Anal. Calcd for $C_{13}H_{22}O_{11}$: C, 44.07; H, 6.26. Found: C, 43.64; H, 6.02.

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