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Carbasugar Analogues of Galactofuranosides: Pseudodisaccharide Mimics of Fragments of Mycobacterial Arabinogalactan

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A partially protected carbasugar analogue of β-galactofuranose was converted into an α-*galacto*-configured 1,2-epoxide, which was opened by alcohols under Lewis acid catalysis with regioselective attack at C-1 to give β-*galacto*-configured C-1 ethers. Using OH-5 and OH-6 carbagalactofuranose derivatives as nucleophiles, we synthesised pseudodisaccharide analogues of substructures of the arabinogalactan from *M. tuberculosis*. The dicarba analogue of the disaccharide Gal*f*(β1→5)Gal*f* was found to moderately inhibit the action of GlfT2 galactofuranosyl transferase from *M. tuberculosis*.

Introduction

Carbagalactofuranose (**1**, Figure 1), a member of the carbasugar family of glycomimetics,[1] is the result of formal replacement of the ring oxygen (O-4) of galactofuranose by a methylene group. This modification means that substituents at O-1 become ether-linked and so become much more stable towards hydrolysis by glycosidases or acid than their glycosidic counterparts.

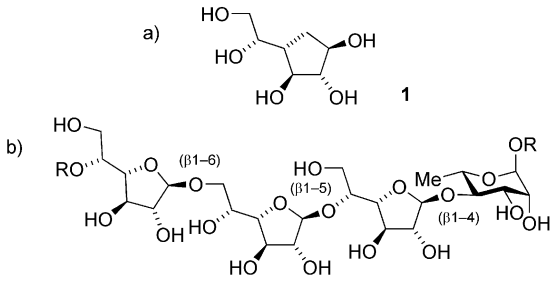

Figure 1. a) Carbasugar analogue of β-D-galactofuranose; b) fragment of mycobacterial arabinogalactan showing the Gal*f*(β1→6)-Gal*f*, Gal*f*(β1→5)Gal*f* and Gal*f*(β1→4)Rha*p* linkages.

One area that hydrolytically stable analogues of galactofuranose could find an application would be as potential agents against *M. tuberculosis*. This mycobacterium, the causative agent of tuberculosis, uses galactofuranose as a significant component of a cell-wall structure, arabinogalactan.[2] In the biosynthesis, a galactofuranosyl donor (UDP-Gal*f*) is formed from its pyranose isomer by UDP-Gal mutase. This donor is then the substrate for two bifunctional galactofuranosyl transferases, the first of which (GlfT1) adds galactofuranose onto a lipid-linked Rha(α1→3) GlcNAc disaccharide, forming first a Gal*f*(β1→4)Rha*p* linkage, and then a Gal*f*(β1→5)Gal*f* linkage.[3] The digalactosylated compound is subjected to the attention of the second galactofuranosyl transferase (GlfT2, previously GlfT), which adds galactofuranose to the non-reducing end of the growing polymer with alternating (1→5) and (1→6) linkages.[3,4] Recent studies indicate that GlfT2 also binds to the lipid anchor, and that this interaction is important in governing the chain length.[5,6] Arabinofuranose is then added stepwise to the galactan to complete the arabinogalactan macromolecule. The absence of galactofuranose from mammalian metabolism makes each of the enzymes involved in galactofuranoside biosynthesis a potential therapeutic target.[7] A carbasugar monomer could mimic the donor or acceptor substrates of a galactofuranosyl transferase, or the intermediates or products in UDP-Gal mutase. Larger galactofuranoside-mimicking structures, such as carbadisaccharides, could mimic the glycosyl acceptor parts of the growing arabinogalactan, or alternatively mimic the reaction product, incorporating both donor *and* acceptor moieties. This could lead to the development of inhibitors of these enzymes.

Some efforts to synthesise enzyme inhibitors based on mimicry of galactofuranose have been published.[8–15] Two reports of moderately potent inhibitors of galactofuranosyl transferases exist in the literature. Of these, an inhibitor of GlfT2 was described this year;[16] an inhibitor of the enzyme from *M. smegmatis* was reported earlier.[17] It is also important to note that carbasugar mimics of pyranosides have

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been shown to act as substrates for glycosyl transferases.[18]

We planned to synthesise carbadisaccharides mimicking the Gal*f*(β1→5)Gal*f* and Gal*f*(β1→6)Gal*f* substructures of mycobacterial arabinogalactan to investigate the interaction of these hydrolytically stable disaccharide analogues with the enzyme GlfT2. We have recently developed a synthetic route to a carbagalactofuranose building-block,[19] and to construct the ether linkages in a stereocontrolled manner we considered S_N2-type processes. 1,2-Epoxides derived from carbapyranoses have been used before as electrophiles for the synthesis of carbadisaccharides with nitrogen or oxygen nucleophiles under Lewis acidic or basic conditions.[20–22] In this paper, we describe the realisation of this concept in a carbafuranose system,[23] and its application to the synthesis of carbadisaccharide analogues of arabinogalactan fragments.

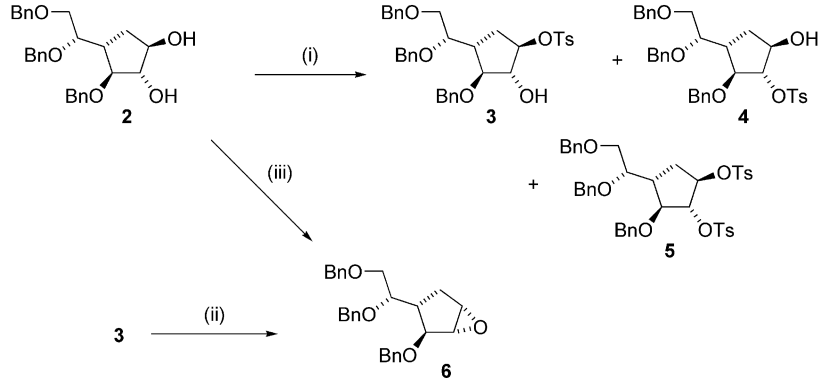
Results and Discussion

Carbasugar 1,2-diol **2**[19] was converted into a 1,2-epoxide electrophile **6** and OH-5 (**13**) and OH-6 (**9**) nucleophiles for use in the synthesis of carbadisaccharides. Attempted monotosylation of diol **2** using tosyl chloride in pyridine resulted in the formation of the desired 1-tosylate **3** in 42% isolated yield, along with the regioisomeric 2-tosylate **4** (14%), the 1,2-ditosylate **5** (5%) and recovered starting material **2** (16%; Scheme 1). The identities of the regioisomeric monotosylates were determined by 2D-COSY NMR experiments where we observed a coupling between the OH-2 proton and the H-2 proton in **3**, and OH-1 proton and the H-1 proton in **4**. Subsequent treatment of the major regioisomer **3** with NaH resulted in ring-closure to give α-*galacto* epoxide **6** in 87% yield. Mitsunobu conditions provided a superior alternative to the tosylation route: treatment of diol **2** with DIAD and triphenylphosphane at 0 °C gave epoxide **6** in a single step in 87% yield; only a single diastereomer was seen.

To synthesise the OH-6 nucleophile **9**, diol **2** was perbenzylated using benzyl bromide and NaH in DMF to give the pentabenzyl compound **7** in 92% yield (Scheme 2). The primary benzyl ether at C-6 was regioselectively removed[24] by acetolysis to give the acetate **8** in 76% yield, which was deacetylated to give the primary alcohol **9** in excellent yield. To synthesise an OH-5 nucleophile **13**, the fully deprotected carbasugar **1**[19] was regioselectively protected as its 5,6-acetonide **10** by treatment with 2-methoxypropene and catalytic CSA. Triol **10** was benzylated using benzyl bromide and NaH in DMF to give the fully protected derivative **11**, then the acetonide was removed by acidic hydrolysis to give the 5,6-diol **12**. Regioselective protection of the primary alcohol was achieved using the tin acetal method, giving the required OH-5 alcohol **13** with only small amounts (2–7%) of its regioisomer (**9**) being formed.

Using carbasugar alcohols **9** and **13** as nucleophiles, the epoxide **6** was opened under $BF_3{\cdot}Et_2O$ catalysis to give the carbadisaccharides **14** and **15**, respectively. Unreacted excess alcohol starting materials could be recovered. The regioselectivity of the reaction was excellent, and the products of nucleophilic attack at C-2 were not observed. The sense of regioselectivity was proved by acetylation of the coupling products to give the C-2^{II} acetates **16** and **17**. The carbadisaccharides **14** and **15** were smoothly completely deprotected by catalytic hydrogenolysis to give carbadisaccharides **18** and **19** (Scheme 3).

It is conceivable that the pseudodisaccharides **18** and **19** could bind to the galactofuranosyl transferase GlfT2 either as acceptor mimics (as substrates or inhibitors)[25] or as bisubstrate inhibitors.[26] The behaviour of the (1→5)- and (1→6)-linked pseudodisaccharides **19** and **18** as acceptor substrates and as inhibitors of GlfT2 was tested.[27] Neither pseudodisaccharide was recognised as a substrate. Although the enzyme has been reported to glycosylate disaccharide acceptors, trisaccharides are better substrates.[4] Presumably, replacement of the ring-oxygens of the disaccharides by methylene groups further reduces availability as substrates. The (1→5)-linked pseudodisaccharide **19** was found to have some inhibitory activity on galactofuranosyl transfer; it gave 53% inhibition at 2 mM [Gal*f*(β1→5)Gal*f*(β1→6)Gal*f*βoctyl acceptor at 0.5 mM and UDP-Gal*f* donor at 1.5 mM]. The (1→6)-linked pseudodisaccharide **18** failed to show inhibitory activity under the same condi-



Scheme 1. (i) TsCl (6 equiv.), pyridine, room temp., 6 h, 42%; (ii) NaH (3 equiv.), DMF, room temp., 20 min, 87%; (iii) DIAD (2.3 equiv.), PPh_3 (2.1 equiv.), THF, 0 °C, 2 h, 87%.

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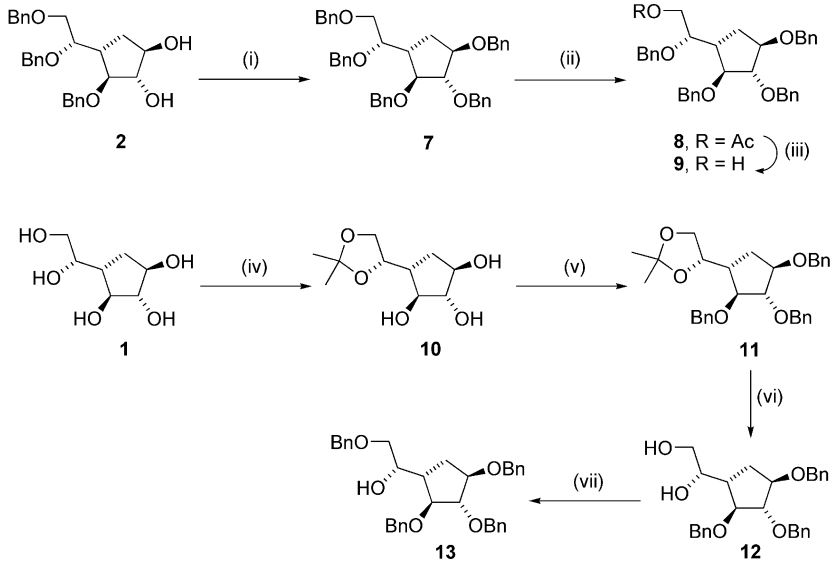
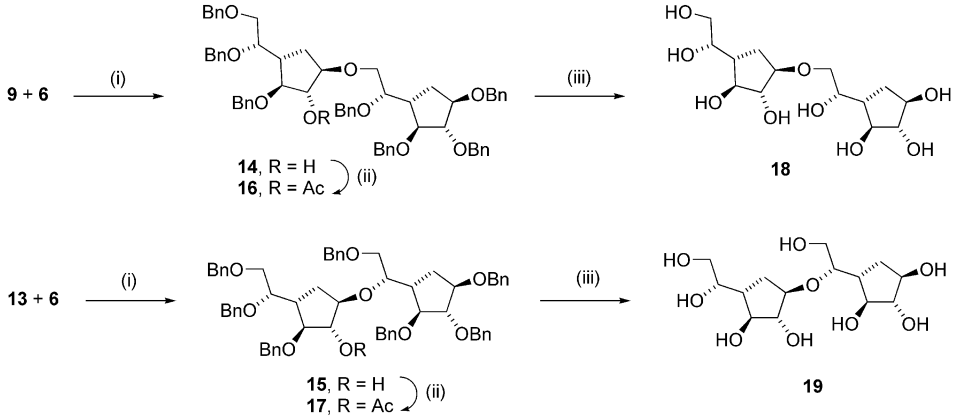


Scheme 2. (i) BnBr (3 equiv.), NaH (5 equiv.), DMF, room temp., 3 h, 92%; (ii) $ZnCl_2$ (5 equiv.), AcOH, Ac_2O, room temp., 3 h, 76%; (iii) NaOMe, MeOH, room temp., 2 h, 99%; (iv) 2-methoxypropene (2.8 equiv.), CSA (0.3 equiv.), DMF, acetone, room temp., 30 min, 60%; (v) BnBr (6 equiv.), NaH (8 equiv.), DMF, room temp., 2 h, 65%; (vi) AcOH, H_2O, 60 °C, 45 min, 86%; (vii) (a) Bu_2SnO (1.3 equiv.), MeOH, 60 °C; (b) BnBr (1.5 equiv.), CsF (1.5 equiv.), DMF, room temp., 88%.



Scheme 3. (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2; **14**, 69%; **15**, 52%; (ii) Ac_2O, py; **14**→**16**, 84%; **15**→**17**, 99%; (iii) H_2, Pd/C, MeOH, HCl (1 M); **14**→**18**, 57%; **15**→**19**, 91%.

tions. It was shown recently that the OH-5 and OH-6 acceptors bind to the same binding site in the transferase,[28] so a specific inhibition of each of the 1→5 and 1→6 glycosylations by different inhibitors is not expected.

The structures of the two earlier reported inhibitors of galactofuranosyl transferases are shown in Figure 2. Their inhibitory activity is of the same order of magnitude as that of compound **19**. While no structural studies on the binding have been carried out, both of these molecules can be said to superficially resemble all or part of the glycosyl donor substrate of the enzyme (UDP-Gal*f*), but not the acceptor (the growing galactan), which must be invoked to a greater or lesser extent to rationalise the binding of compound **19**.

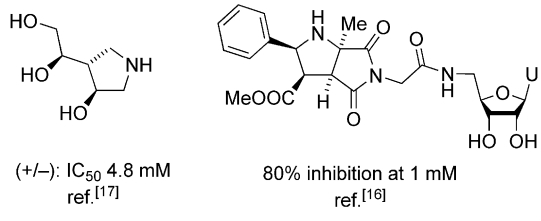


Figure 2. Previously reported galactofuranosyltransferase inhibitors.

Conclusions

While the formal substitution of the ring-oxygen for methylene was found to have a detrimental effect on the ability of galactofuranose (pseudo)disaccharides to act as substrates for mycobacterial galactofuranosyl transferase GlfT2, one pseudodisaccharide consisting of two carbagalactofuranose units linked (β1→5) was found to act as a moderate inhibitor of the enzyme. The mode of binding is unknown, and the level of inhibitory activity of this

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pseudodisaccharide is fairly low compared to the state of the art for glycosyl transferase inhibition.[29–31] Nevertheless, this result demonstrates that inhibition of this medically relevant enzyme by carbasugar derivatives is possible, and in fact, significantly better inhibitors for *galactofuranosyl* transferases have not been reported.

Experimental Section

General Methods: Proton nuclear magnetic resonance (^{1}H) spectra were recorded on Bruker Avance II 500 (500 MHz), Bruker Avance II 400 (400 MHz), Varian Mercury 400 (400 MHz) or Varian Mercury 300 (300 MHz) spectrometers; multiplicities are quoted as singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of doublet of doublets (dddd), triplet (t), apparent triplet (at), doublet of apparent triplets (dat), doublet of doublet of apparent triplets (ddat), quartet (q), apparent quartet (aq), apparent quartet of doublets (aqd) and multiplet (m). Carbon nuclear magnetic resonance (^{13}C) spectra were recorded on Bruker Avance II 500 (125 MHz), Bruker Avance II 400 (100 MHz) or Varian Mercury 400 (100 MHz) spectrometers. ^{1}H and ^{13}C spectra and ^{13}C multiplicities were assigned using COSY, HSQC, and DEPT experiments. All chemical shifts are quoted on the δ-scale in parts per million (ppm). Residual solvent signals or TMS were used as an internal reference. High-resolution (HRMS) electrospray (ESI^+) mass spectra were recorded using a Bruker Microtof instrument. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer using the thin film method on NaCl plates. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a path length of 1 dm; concentrations are given in g/100 mL. Thin-layer chromatography (TLC) was carried out on Merck Kieselgel sheets, pre-coated with $60F_{254}$ silica. Plates were visualized with UV light and developed using 10% sulfuric acid, or an ammonium molybdate (10% w/v) and cerium (IV) sulfate (2% w/v) solution in 10% sulfuric acid. Flash column chromatography was carried out on silica gel (35–70 μm, Grace). Dichloromethane was distilled from calcium hydride. Diethyl ether and THF were dried and dispensed from Vacuum Atmospheres solvent purification columns. Toluene was distilled from sodium. Reactions performed under an atmosphere of hydrogen or nitrogen were maintained by an inflated balloon.

3,5,6-Tri-*O*-benzyl-1-*O*-(p-tolylsulfonyl)-4a-carba-β-D-galactofuranose (3), 3,5,6-Tri-*O*-benzyl-2-*O*-(*p*-tolylsulfonyl)-4a-carba-β-D-galactofuranose (4) and 3,5,6-Tri-*O*-benzyl-1,2-di-*O*-(*p*-tolylsulfonyl)-4a-carba-β-D-galactofuranose (5): Diol **2** (369 mg, 0.823 mmol) was dissolved in pyridine (20 mL) at room temp. TsCl (706 mg, 3.70 mmol) was added and the reaction was stirred under N_2. TLC (toluene/EtOAc, 10:1) indicated a steady conversion of the starting material (R_f = 0) into three products; a ditosylated compound (R_f = 0.8) and two monotosylated compounds (R_f = 0.4 and 0.3). After 6 h, the reaction was quenched by H_2O (20 mL) to avoid excessive ditosylation. EtOAc (20 mL) was added and the mixture was washed with H_2O (2 × 20 mL) and NH_4Cl (satd. aq., 20 mL). The combined aqueous phases were extracted with EtOAc (3 × 30 mL) and the organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (toluene/EtOAc, 9:1) to give first the ditosylate **5** (33 mg, 5%). $[\alpha]_D^{25}$ = –28.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.86 (m, 1 H, 4a-H), 1.99 (ddd, $J_{1,4a'}$ = 5.9, $J_{4,4a'}$ = 10.4, $J_{4a,4a'}$ = 14.4 Hz, 1 H, 4a′-H), 2.32 (ddat, J_{at} = 7.7, $J_{4,5}$ = 3.1, $J_{4,4a'}$ = 10.5 Hz, 1 H, 4-H), 2.42 (s, 6 H, 2 × CH_3), 3.36 (dd, $J_{5,6}$ = 4.9, $J_{6,6'}$ = 10.0 Hz, 1 H, 6-H), 3.45 (dd, $J_{5,6'}$ = 6.0, $J_{6,6'}$ = 10.0 Hz, 1 H, 6′-H), 3.57 (m, 1 H, 5-H), 3.77 (dd, $J_{3,4}$ = 7.5, $J_{2,3}$ = 3.9 Hz, 1 H, 3-H), 4.00, 4.21 (2 × d, J = 11.6 Hz, 2 H, PhCH_2), 4.21, 4.60 (2 × d, J = 11.7 Hz, 2 H, PhCH_2), 4.42, 4.47 (2 × d, J = 12.0 Hz, 2 H, PhCH_2), 4.76 (dat, J_{at} = 3.1, $J_{1,4a'}$ = 5.8 Hz, 1 H, 1-H), 4.83 (m, 1 H, 2-H), 7.11 (d, J = 7.9 Hz, 2 H, Ar-H), 7.20 (d, J = 7.9 Hz, 2 H, Ar-H), 7.24–7.34 (m, 15 H, Ar-H), 7.71 (d, J = 8.3 Hz, 2 H, Ar-H), 7.75 (d, J = 8.3 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.8 (q, 2 × CH_3), 29.1 (t, C-4a), 44.4 (d, C-4), 71.9 (t, C-6), 72.2, 72.7, 73.5 (3 × t, 3 × PhCH_2), 76.1 (d, C-5), 82.8 (d, C-1), 83.6 (d, C-3), 87.5 (d, C-2), 127.7, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.5, 128.6, 129.9, 130.1 (13 × d, Ar-CH), 133.3, 133.6 (2 × s, 2 × Ar-CSO_2), 137.6, 138.1, 138.5 (3 × s, 3 × Ar-C), 145.0, 145.4 (2 × s, 2 × Ar-CCH_3) ppm. HRMS calcd. for $C_{42}H_{44}O_9S_2Na$ [MNa^+] 779.2319; found 779.2288.

Then the major product, monotosylate **3** (208 mg, 42%) as an oil. $[\alpha]_D^{25}$ = –25.8 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3435 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.76 (ddd, $J_{1,4a}$ = 4.9, $J_{4,4a}$ = 9.7, $J_{4a,4a'}$ = 14.5 Hz, 1 H, 4a-H), 2.06 (dat, J_{at} = 8.4, $J_{4a,4a'}$ = 14.5 Hz, 1 H, 4a′-H), 2.32 (m, 1 H, 4-H), 2.43 (s, 3 H, CH_3), 2.79 (d, $J_{OH,2}$ = 3.6 Hz, 1 H, OH-2), 3.40 (dd, $J_{5,6}$ = 5.0, $J_{6,6'}$ = 10.0 Hz, 1 H, 6-H), 3.50 (dd, $J_{5,6'}$ = 6.0, $J_{6,6'}$ = 10.0 Hz, 1 H, 6′-H), 3.68 (m, 2 H, 3-H, 5-H), 4.26 (m, 1 H, 2-H), 4.28, 4.63 (2 × d, J = 11.5 Hz, 2 H, PhCH_2), 4.45, 4.49 (2 × d, J = 11.8 Hz, 2 H, PhCH_2), 4.44–4.54 (m, 3 H, 1-H, PhCH_2), 7.20–7.21 (m, 2 H, Ar-H), 7.24–7.36 (m, 15 H, Ar-H), 7.75 (d, J = 8.3 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.8 (q, CH_3), 27.2 (t, C-4a), 43.1 (d, C-4), 71.8 (t, C-6), 72.3, 73.0, 73.5 (3 × t, 3 × PhCH_2), 76.4 (d, C-5), 82.2 (d, C-2), 83.6 (d, C-3), 86.0 (d, C-1), 127.7, 127.8, 128.1, 128.1, 128.2, 128.5, 128.5, 128.6, 130.0 (9 × d, Ar-CH), 133.3 (s, Ar-CSO_2), 145.1 (s, Ar-CCH_3), 138.2, 138.5, 138.5 (3 × s, 3 × Ar-C) ppm. HRMS calcd. for $C_{35}H_{38}O_7SNa$ [MNa^+] 625.2230; found 625.2207.

Then the regioisomeric monotosylate **4** (70 mg, 14%). $[\alpha]_D^{25}$ = –40.5 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3435 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.66 (ddd, $J_{1,4a}$ = 4.6, $J_{4,4a}$ = 9.2, $J_{4a,4a'}$ = 13.9 Hz, 1 H, 4a-H), 2.13 (dat, J_{at} = 8.9, $J_{4a,4a'}$ = 14.0 Hz, 1 H, 4a′-H), 2.29 (aqd, J_{aq} = 9.1, $J_{4,5}$ = 2.8 Hz, 1 H, 4-H), 2.42 (s, 3 H, CH_3), 2.84 (s, 1 H, OH-1), 3.43 (dd, $J_{5,6}$ = 5.0, $J_{6,6'}$ = 9.9 Hz, 1 H, 6-H), 3.54 (dd, $J_{5,6'}$ = 6.1, $J_{6,6'}$ = 9.9 Hz, 1 H, 6′-H), 3.65 (m, 1 H, 5-H), 3.87 (dd, $J_{3,4}$ = 8.6, $J_{2,3}$ = 6.6 Hz, 1 H, 3-H), 4.08, 4.24 (2 × d, J = 11.4 Hz, 2 H, PhCH_2), 4.26 (m, 1 H, 1-H), 4.29, 4.66 (2 × d, J = 11.7 Hz, 2 H, PhCH_2), 4.45, 4.50 (2 × d, J = 12.0 Hz, 2 H, PhCH_2), 4.53 (m, 1 H, 2-H), 7.04 (d, J = 7.6 Hz, 2 H, Ar-H), 7.23–7.33 (m, 15 H, Ar-H), 7.83 (d, J = 8.0 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.8 (q, CH_3), 28.8 (t, C-4a), 42.6 (d, C-4), 72.0 (t, C-6), 72.4, 72.8, 73.5 (3 × t, 3 × PhCH_2), 73.8 (d, C-1), 75.9 (d, C-5), 82.2 (d, C-3), 93.6 (d, C-2), 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.3, 128.4, 128.5, 128.5, 130.2 (11 × d, Ar-CH), 132.9 (s, Ar-CSO_2), 145.5 (s, Ar-CCH_3), 137.2, 138.2, 138.7 (3 × s, 3 × Ar-C) ppm. HRMS calcd. for $C_{35}H_{38}O_7SNa$ [MNa^+] 625.2230; found 625.2209.

And finally starting material **2** (58 mg, 16%).

1,2-Anhydro-3,5,6-tri-*O*-benzyl-4a-carba-α-D-galactofuranose (6)

Method 1. Intramolecular Mitsunobu Reaction: PPh_3 (75 mg, 0.290 mmol) was dissolved in THF (5 mL) under N_2. The solution was cooled to 0 °C and DIAD (62 μL, 0.319 mmol) was added. The reaction temperature was maintained at 0 °C and after 30 min, a solution of diol **2** (62 mg, 0.138 mmol) in THF (5 mL) was added by cannula. The reaction was monitored by TLC (toluene/EtOAc, 4:1) and after 2 h, consumption of starting material (R_f = 0) and formation of a major product (R_f = 0.8) were seen. The reaction mixture was concentrated in vacuo. The crude product was purified

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by flash column chromatography (toluene/EtOAc, 6:1) to give epoxide **6** (52 mg, 87%) as an oil. $[\alpha]_D^{25} = -15.2$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.05$ (ddd, $J_{1,4a} = 1.6$, $J_{4,4a} = 9.8$, $J_{4a,4a'} = 14.9$ Hz, 1 H, 4a-H), 2.17 (dd, $J_{1,4a'} = 2.6$, $J_{4a,4a'} = 14.8$ Hz, 1 H, 4a′-H), 2.51 (at, $J = 9.7$ Hz, 1 H, 4-H), 3.39 (ddd, $J_{5,6'} = 3.2$, $J_{5,6} = 4.7$, $J_{4,5} = 9.8$ Hz, 1 H, 5-H), 3.51 (m, 1 H, 2-H), 3.52 (dd, $J_{5,6} = 4.7$, $J_{6,6'} = 10.8$ Hz, 1 H, 6-H), 3.56 (m, 1 H, 1-H), 3.61 (dd, $J_{6,6'} = 10.8$, $J_{5,6'} = 3.1$ Hz, 1 H, 6′-H), 3.92 (m, 1 H, 3-H), 4.46, 4.56 (2× d, $J = 11.8$ Hz, 2 H, PhCH_2), 4.50, 4.67 (2× d, $J = 11.5$ Hz, 2 H, PhCH_2), 4.52 (s, 2 H, PhCH_2), 7.26–7.35 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 28.4$ (t, C-4a), 46.6 (d, C-4), 58.9, 58.9 (2× d, C-1, C-2), 71.0 (t, C-6), 71.7, 72.7, 73.5 (3× t, 3× Ph*C*H_2), 80.5, 80.5 (2× d, C-3, C-5), 127.7, 127.8, 127.8, 127.9, 128.0, 128.5, 128.5, 128.6 (8× d, Ar-CH), 138.2, 138.4, 138.8 (3× s, 3× Ar-C) ppm. HRMS calcd. for $C_{28}H_{30}O_4Na$ [MNa^+] 453.2036; found 453.2046.

Method 2. Intramolecular Tosylate Displacement: 1-*O*-Tosylgalactofuranose **3** (208 mg, 0.345 mmol) was dissolved in DMF (30 mL) under N_2. The reaction mixture was cooled to 0 °C, and NaH (60% in oil, 42 mg, 1.05 mmol) was added. The mixture was stirred at room temp. and monitored by TLC (toluene/EtOAc, 9:1) and within 20 min, all starting material ($R_f = 0.4$) had been consumed and a major product ($R_f = 0.6$) could be seen. The reaction was quenched at 0 °C by the slow addition of MeOH (20 mL). All MeOH was then removed in vacuo. Et_2O (30 mL) was added, and the organic phase was washed with brine (3× 60 mL). The aqueous phase was extracted with Et_2O (3× 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (pentane/EtOAc, 8:1) to give epoxide **6** (129 mg, 87%) as an oil, identical to that described above.

1,2,3,5,6-Penta-*O*-benzyl-4a-carba-β-D-galactofuranose (7): NaH (60% in oil, 492 mg, 12.3 mmol) was added to DMF (25 mL) and cooled to 0 °C under N_2. Diol **2** (1.10 g, 2.46 mol) was dissolved in DMF (75 mL) and added slowly to the reaction vessel. Benzyl bromide (0.88 mL, 7.4 mmol) was added to the vessel and the reaction was stirred at room temp. for 2.5 h, after which time TLC (toluene/EtOAc, 9:1) showed complete consumption of starting material ($R_f = 0$) and formation of a major product ($R_f = 0.8$). The reaction was quenched by the addition of MeOH (20 mL) at 0 °C. The MeOH was removed in vacuo, then Et_2O (150 mL) was added, and the mixture washed with brine (3× 150 mL). The aqueous phases were extracted with Et_2O (2× 100 mL) and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (toluene/EtOAc, 9:1) to give perbenzylated carbasugar **7** (1.44 g, 92%) as an oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.82$ (ddd, $J_{1,4a} = 3.3$, $J_{4a,4} = 8.3$, $J_{4a,4a'} = 13.6$ Hz, 1 H, 4a-H), 2.02 (ddd, $J_{1,4a'} = 7.0$, $J_{4a',4} = 10.2$, $J_{4a,4a'} = 13.6$ Hz, 1 H, 4a′-H), 2.40 (ddat, $J_{at} = 8.7$, $J_{4,5} = 3.5$, $J_{4a',4} = 10.0$ Hz, 1 H, 4-H), 3.55 (dd, $J_{5,6} = 4.6$, $J_{6,6'} = 10.0$ Hz, 1 H, 6-H), 3.61 (dd, $J_{5,6'} = 6.3$, $J_{6,6'} = 10.0$ Hz, 1 H, 6′-H), 3.79 (dat, $J_{at} = 4.3$, $J_{5,6'} = 6.2$ Hz, 1 H, 5-H), 3.86 (dd, $J_{2,3} = 5.9$, $J_{3,4} = 8.8$ Hz, 1 H, 3-H), 3.92 (dat, $J_{at} = 3.8$, $J_{1,4a'} = 7.0$ Hz, 1 H, 1-H), 4.03 (m, 1 H, 2-H), 4.41, 4.74 (2× d, $J = 11.7$ Hz, 2 H, PhCH_2), 4.46 (d, $J = 11.7$ Hz, 1 H, PhC*H*H′), 4.48 (d, $J = 11.8$ Hz, 1 H, PhC*H*H′), 4.51 (d, $J = 12.0$ Hz, 1 H, PhC*H*H′), 4.54 (d, $J = 12.1$ Hz, 1 H, PhC*H*H′), 4.57 (d, $J = 12.1$ Hz, 1 H, PhCH*H*′), 4.61 (d, $J = 11.8$ Hz, 1 H, PhCH*H*′), 4.67 (d, $J = 11.7$ Hz, 1 H, PhCH*H*′), 4.69 (d, $J = 11.7$ Hz, 1 H, PhCH*H*′), 7.31–7.38 (m, 25 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 27.6$ (t, C-4a), 43.4 (d, C-4), 71.0, 72.1, 72.2, 72.7, 73.0, 73.5 (6× t, 5× Ph*C*H_2, C-6), 77.0 (d, C-5), 81.4 (d, C-1), 84.0 (d, C-3), 90.0 (d, C-2), 127.5, 127.7, 127.7, 127.8, 127.9, 128.1, 128.4, 128.4, 128.5 (9× d, Ar-CH), 138.5, 138.6, 138.8, 139.0 (4× s, 5× Ar-C) ppm. HRMS calcd. for $C_{42}H_{44}O_5Na$ [MNa^+] 651.3081; found 651.3099.

6-*O*-Acetyl-1,2,3,5-tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (8): $ZnCl_2$ (189 mg, 1.39 mmol) was suspended in a [5:1]-mixture of Ac_2O/AcOH (2.4 mL) and cooled to 0 °C. Perbenzylated carbasugar **7** (169 mg, 0.269 mmol) was dissolved in Ac_2O/AcOH (2.4 mL, [5:1]) and added to the zinc chloride solution dropwise at 0 °C. The reaction was allowed to reach room temp. TLC (toluene/EtOAc, 10:1) showed that the starting material ($R_f = 0.4$) was steadily consumed while a major product ($R_f = 0.3$) and a minor product ($R_f = 0.2$) emerged. To avoid any further deprotections, the reaction was quenched after 3 h at 0 °C by the addition of $NaHCO_3$ (satd. aq., 5 mL). The reaction mixture was extracted with EtOAc (3× 10 mL) washed with $NaHCO_3$ (satd. aq., 3× 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (toluene/EtOAc, 15:1) to give acetate **8** (118 mg, 76%) as an oil. $[\alpha]_D^{25} = -42.8$ ($c = 1.0$, $CHCl_3$). IR (film): $\tilde{\nu} = 1740$ (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.84$ (m, 1 H, 4a-H), 1.96 (ddd, $J_{1,4a'} = 6.9$, $J_{4a',4} = 10.5$, $J_{4a,4a'} = 13.6$ Hz, 1 H, 4a′-H), 2.02 (s, 3 H, CH_3), 2.34 (ddat, $J_{at} = 8.7$, $J_{4,5} = 3.7$, $J_{4a',4} = 10.6$ Hz, 1 H, 4-H), 3.71 (m, 1 H, 5-H), 3.80 (dd, $J_{2,3} = 5.8$, $J_{3,4} = 9.0$ Hz, 1 H, 3-H), 3.88 (dat, $J_{at} = 3.5$, $J_{1,4a'} = 7.0$ Hz, 1 H, 1-H), 3.99 (ddd, $J_{1,2} = 3.8$, $J_{2,3} = 5.5$, $J_{2,4a} = 1.1$ Hz, 1 H, 2-H), 4.11 (dd, $J_{5,6} = 6.0$, $J_{6,6'} = 11.6$ Hz, 1 H, 6-H), 4.16 (dd, $J_{5,6'} = 4.9$, $J_{6,6'} = 11.6$ Hz, 1 H, 6′-H), 4.32 (d, $J = 11.6$ Hz, 1 H, PhC*H*H′), 4.42 (d, $J = 11.8$ Hz, 1 H, PhC*H*H′), 4.45 (d, $J = 11.9$ Hz, 1 H, PhC*H*H′), 4.55–4.66 (m, 5 H, PhC*H*H′, 4× PhCH*H*′), 7.25–7.35 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 21.1$ (q, CH_3), 27.6 (t, C-4a), 43.3 (d, C-4), 65.5 (t, C-6), 71.0, 72.1, 72.2, 73.0 (4× t, 4× Ph*C*H_2), 75.7 (d, C-5), 81.2 (d, C-1), 83.7 (d, C-3), 89.9 (d, C-2), 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.5 (9× d, Ar-CH), 138.4, 138.5, 138.6 (3× s, 4× Ar-C), 170.1 (s, C=O) ppm. HRMS calcd. for $C_{37}H_{40}O_6Na$ [MNa^+] 603.2723; found 603.2746.

1,2,3,5-Tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (9): Acetate **8** (338 mg, 0.582 mmol) was dissolved in a pH 10 solution of NaOMe in MeOH (30 mL) at room temp. After 2 h, TLC (toluene/EtOAc, 6:1), showed that all starting material ($R_f = 0.7$) had been converted into a major product ($R_f = 0.2$). The reaction was quenched by the addition of acidic Dowex resin HCR-W2. The resin was filtered off and all the solvent was removed in vacuo to afford alcohol **9** (312 mg, 99%) as an oil. $[\alpha]_D^{25} = -37.8$ ($c = 1.0$, $CHCl_3$). IR (film): $\tilde{\nu} = 3417$ (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.83$ (ddd, $J_{1,4a} = 6.6$, $J_{4,4a} = 11.0$, $J_{4a,4a'} = 13.8$ Hz, 1 H, 4a-H), 2.05 (dddd, $J_{2,4a'} = 1.5$, $J_{1,4a'} = 2.5$, $J_{4,4a'} = 7.9$, $J_{4a,4a'} = 13.8$ Hz, 1 H, 4a′-H), 2.47 (m, 1 H, 4-H), 3.48 (dat, $J_{at} = 4.4$, $J = 5.6$ Hz, 1 H, 5-H), 3.59 (dd, $J_{5,6} = 4.7$, $J_{6,6'} = 12.0$ Hz, 1 H, 6-H), 3.72 (dd, $J_{5,6'} = 3.8$, $J_{6,6'} = 12.1$ Hz, 1 H, 6′-H), 3.77 (dd, $J_{2,3} = 5.3$, $J_{3,4} = 9.1$ Hz, 1 H, 3-H), 3.89 (dat, $J_{at} = 3.0$, $J_{1,4a} = 6.5$ Hz, 1 H, 1-H), 4.02 (ddd, $J_{1,2} = 3.2$, $J_{2,3} = 5.0$, $J_{2,4a} = 1.4$ Hz, 1 H, 2-H), 4.43 (d, $J = 11.7$ Hz, 1 H, PhC*H*H′), 4.47 (d, $J = 11.9$ Hz, 1 H, PhC*H*H′), 4.48 (d, $J = 11.6$ Hz, 1 H, PhC*H*H′), 4.55 (d, $J = 11.6$ Hz, 1 H, PhC*H*H′), 4.58 (d, $J = 11.8$ Hz, 1 H, PhCH*H*′), 4.58 (d, $J = 11.8$ Hz, 1 H, PhCH*H*′), 4.64 (d, $J = 11.6$ Hz, 1 H, PhCH*H*′), 4.68 (d, $J = 11.6$ Hz, 1 H, PhCH*H*′), 7.28–7.37 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 29.7$ (t, C-4a), 43.4 (d, C-4), 63.3 (d, C-6), 70.9, 72.1, 72.2, 72.5 (4× t, 4× Ph*C*H_2), 80.4 (d, C-5), 81.0 (d, C-1), 84.7 (d, C-3), 89.9 (d, C-2), 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 128.5 (8× d, Ar-CH), 138.1, 138.2, 138.4, 138.6 (4× s, 4× Ar-C) ppm. HRMS calcd. for $C_{35}H_{38}O_5Na$ [MNa^+] 561.2611; found 561.2607.

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5,6-*O*-Isopropylidene-4a-carba-β-D-galactofuranose (10): Fully deprotected carbasugar **1** (73 mg, 0.410 mmol) was suspended in a mixture of acetone (3 mL) and DMF (3 mL) at room temp. 2-Methoxypropene (350 μL, 3.74 mmol) and CSA (53 mg, 0.23 mmol) were added in portions. TLC (CMAW) indicated that once the pH was below 5, the reaction was completed after 30 min as no starting material (R_f = 0.3) remained and formation of a major product could be seen (R_f = 0.9). The reaction was quenched by Et_3N (1 mL) and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/MeOH, 6:1 + 3% Et_3N) to give acetonide **10** (53 mg, 60%). IR (film): $\tilde{\nu}$ = 3390 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.32, 1.37 [2× s, 6 H, $C(CH_3)_2$], 1.69 (ddd, $J_{1,4a}$ = 6.0, $J_{4,4a}$ = 9.6, $J_{4a,4a'}$ = 13.3 Hz, 1 H, 4a-H), 1.91–2.01 (m, 2 H, 4a′-H, 4-H), 3.55 (at, J = 7.9 Hz, 1 H, 3-H), 3.60–3.64 (m, 2 H, 2-H, 6-H), 3.80 (dat, J_{at} = 6.3, J = 7.7 Hz, 1 H, 1-H), 4.03 (dd, $J_{5,6'}$ = 6.3, $J_{6,6'}$ = 8.2 Hz, 1 H, 6′-H), 4.13 (dat, J_{at} = 6.1, J = 7.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 25.8, 27.0 [2× q, $C(CH_3)_2$], 31.7 (t, C-4a), 45.1 (d, C-4), 69.0 (t, C-6), 75.4 (d, C-1), 78.6 (d, C-5), 78.9 (d, C-3), 85.6 (d, C-2), 109.8 [s, $C(CH_3)_2$] ppm. HRMS calcd. for $C_{10}H_{18}O_5Na$ [MNa^+] 241.1046; found 241.1040.

1,2,3-Tri-*O*-benzyl-5,6-*O*-isopropylidene-4a-carba-β-D-galactofuranose (11): NaH (60% in oil, 49 mg, 1.23 mmol) was suspended in DMF (5 mL) under N_2. Triol **10** (33 mg, 0.151 mmol) was dissolved in DMF (5 mL) and slowly added to the suspension at 0 °C. Benzyl bromide (109 μL, 0.91 mmol) was added dropwise at 0 °C. TLC (toluene/EtOAc, 3:1) showed the formation of a major product (R_f = 0.8) and the consumption of the starting material (R_f = 0). After 2 h, the reaction was quenched by the addition of MeOH at 0 °C. The MeOH was then removed in vacuo and the remaining solution was diluted with EtOAc (10 mL) and washed with brine (3× 10 mL). The combined aqueous phases were extracted with EtOAc (3× 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (pentane/EtOAc, 6:1) to give acetonide **11** (48 mg, 65%) as an oil. $[\alpha]_D^{25}$ = –28.4 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.33, 1.38 [2× s, 6 H, $C(CH_3)_2$], 1.88 (ddd, $J_{1,4a}$ = 6.7, $J_{4,4a}$ = 10.0, $J_{4a,4a'}$ = 13.7 Hz, 1 H, 4a-H), 2.00 (dddd, $J_{2,4a'}$ = 1.0, $J_{1,4a'}$ = 3.6, $J_{4,4a'}$ = 8.2, $J_{4a,4a'}$ = 13.7 Hz, 1 H, 4a′-H), 2.29 (ddat, J_{at} = 8.3, $J_{4,5}$ = 6.5, $J_{4,4a}$ = 9.8 Hz, 1 H, 4-H), 3.65 (at, J = 7.5 Hz, 1 H, 6-H), 3.71 (dd, $J_{2,3}$ = 5.6, $J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 3.91 (dat, J_{at} = 3.6, $J_{1,4a}$ = 6.8 Hz, 1 H, 1-H), 3.95 (dd, $J_{5,6'}$ = 6.1, $J_{6,6'}$ = 8.2 Hz, 1 H, 6′-H), 4.01 (ddd, $J_{1,2}$ = 3.8, $J_{2,3}$ = 5.4, $J_{2,4a'}$ = 1.1 Hz, 1 H, 2-H), 4.06 (dat, J_{at} = 6.2, $J_{5,6}$ = 7.4 Hz, 1 H, 5-H), 4.48, 4.60 (2× d, J = 11.9 Hz, 2 H, PhCH_2), 4.53, 4.68 (2× d, J = 11.6 Hz, 2 H, PhCH_2), 4.57, 4.66 (2× d, J = 11.7 Hz, 2 H, PhCH_2), 7.27–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 25.7, 26.7 [2× q, $C(CH_3)_2$], 29.5 (t, C-4a), 43.9 (d, C-4), 68.2 (t, C-6), 71.0, 72.2, 72.4 (3× t, 3× PhCH_2), 77.4 (d, C-5), 81.2 (d, C-1), 85.1 (d, C-3), 90.0 (d, C-2), 108.7 [s, $C(CH_3)_2$], 127.8, 127.8, 127.8, 127.9, 128.0, 128.5, 128.5, 128.6 (8× d, Ar-CH), 138.4, 138.4, 138.5 (3× s, 3× Ar-C) ppm. HRMS calcd. for $C_{31}H_{36}O_5Na$ [MNa^+] 511.2455; found 511.2453.

1,2,3-Tri-*O*-benzyl-4a-carba-β-D-galactofuranose (12)

Method 1. From 11: Primary acetonide **11** (238 mg, 0.49 mmol) was dissolved in a 11:4 mixture of AcOH and H_2O (15 mL) and the reaction was left to stir at 60 °C for 30 min, after which time TLC (toluene/EtOAc, 4:1) showed complete consumption of starting material (R_f = 0.9) and formation of a major product (R_f = 0.2). All solvent was co-evaporated with toluene (2× 10 mL). Purification by flash column chromatography (toluene/EtOAc, 1:1) gave diol **12** (189 mg, 86%) as an oil. IR (film): $\tilde{\nu}$ = 3402 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.85 (ddd, $J_{1,4a}$ = 6.5, $J_{4,4a}$ = 10.8, $J_{4a,4a'}$ = 13.8 Hz, 1 H, 4a-H), 2.05 (dddd, $J_{2,4a'}$ = 1.4, $J_{1,4a'}$ = 2.6, $J_{4,4a'}$ = 7.9, $J_{4a,4a'}$ = 13.7 Hz, 1 H, 4a′-H), 2.30 (ddat, J_{at} = 8.3, $J_{4,5}$ = 6.3, $J_{4,4a}$ = 10.8 Hz, 1 H, 4-H), 3.51 (dd, $J_{5,6}$ = 6.1, $J_{6,6'}$ = 11.7 Hz, 1 H, 6-H), 3.59 (dd, $J_{5,6'}$ = 3.0, $J_{6,6'}$ = 11.7 Hz, 1 H, 6′-H), 3.63 (dat, J_{at} = 6.3, $J_{5,6'}$ = 3.0 Hz, 1 H, 5-H), 3.74 (dd, $J_{2,3}$ = 5.1, $J_{3,4}$ = 8.9 Hz, 1 H, 3-H), 3.91 (dat, J_{at} = 2.9, $J_{1,4a}$ = 6.5 Hz, 1 H, 1-H), 4.02 (ddd, $J_{1,2}$ = 3.1, $J_{2,3}$ = 4.8, $J_{2,4a'}$ = 1.2 Hz, 1 H, 2-H), 4.47, 4.58 (2× d, J = 11.8 Hz, 2 H, PhCH_2), 4.52, 4.68 (2× d, J = 11.5 Hz, 2 H, PhCH_2), 4.53, 4.63 (2× d, J = 11.6 Hz, 2 H, PhCH_2), 7.27–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 29.8 (t, C-4a), 44.1 (d, C-4), 65.7 (t, C-6), 70.9, 72.2, 72.4 (3× t, 3× PhCH_2), 73.7 (d, C-5), 81.1 (d, C-1), 84.9 (d, C-3), 89.7 (d, C-2), 127.9, 127.9, 128.0, 128.0, 128.1, 128.3, 128.6, 128.6 (8× d, Ar-CH), 138.0, 138.1, 138.3 (3× s, 3× Ar-C) ppm. HRMS calcd. for $C_{28}H_{32}O_5Na$ [MNa^+] 471.2142; found 471.2139.

Method 2. From 1, Isolation Only After 3 Steps: Carbasugar **1** (179 mg, 1.00 mmol) was suspended in acetone (3 mL) at room temp. CSA (47 mg, 0.20 mmol) was added. After 18 h, the reaction was quenched by the addition of Et_3N (0.5 mL, 3.6 mmol) and all solvents were removed in vacuo.

The crude triol **10** was dissolved in DMF, and NaH (60% in oil, 400 mg, 10 mmol) was added at 0 °C under N_2. BnBr (717 μL, 6.0 mmol) was slowly added to the reaction mixture, which was then allowed to reach room temp. After 2 h, TLC (toluene/EtOAc, 3:1) showed the formation of a major product (R_f = 0.8) and the consumption of the starting material (R_f = 0). The reaction was quenched by the addition of MeOH at 0 °C. The MeOH was then removed in vacuo and the remaining solution was diluted with EtOAc (10 mL) and washed with brine (3× 10 mL). The combined aqueous phases were extracted with EtOAc (3× 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo.

The crude acetonide **11** was dissolved in a 11:4 mixture of AcOH and H_2O (10 mL) and the reaction was left to stir at 60 °C for 6 h, after which TLC (toluene/EtOAc, 4:1) showed complete consumption of starting material (R_f = 0.9) and formation of a major product (R_f = 0.2). All solvent was co-evaporated with toluene (2× 10 mL). Purification by flash column chromatography (toluene/EtOAc, 1:1) gave diol **12** (256 mg, 57% over three steps), identical to that described above.

1,2,3,6-Tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (13): Diol **12** (253 mg, 0.565 mmol) was dissolved in MeOH (5 mL). Bu_2SnO (183 mg, 0.735 mmol) was added, and the mixture was put under N_2 and refluxed at 60 °C. After 1 h, all MeOH was removed in vacuo and the residue was dissolved in DMF (5 mL). CsF (129 mg, 0.849 mmol) and BnBr (101 μL, 0.845 mmol) were added and the mixture was stirred under N_2. After 18 h, TLC (toluene/EtOAc, 3:1) showed complete consumption of starting material (R_f = 0), and the formation of minor (R_f = 0.5) and major (R_f = 0.6) products. The reaction mixture was diluted by addition of toluene (5 mL) and the mixture was washed with KF (satd. aq., 3× 15 mL). The aqueous phase was extracted with diethyl ether (3× 15 mL). The organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (toluene/EtOAc, 5:1) to give alcohol **13** (266 mg, 88%) as a colourless oil. $[\alpha]_D^{25}$ = –24.2 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3419 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.86 (ddd, $J_{1,4a}$ = 2.8, $J_{4,4a}$ = 8.3, $J_{4a,4a'}$ = 13.6 Hz, 1 H, 4a-H), 1.97 (ddd, $J_{1,4a'}$ = 6.8, $J_{4,4a'}$ = 10.1, $J_{4a,4a'}$ = 13.7 Hz, 1 H, 4a′-H), 2.25 (ddat, J_{at} = 8.5, $J_{4,5}$ = 4.8, $J_{4,4a'}$ = 10.0 Hz, 1 H, 4-H), 2.40 (d, $J_{OH,5}$ = 2.9 Hz, 1 H, OH-5), 3.37 (dd, $J_{5,6}$ = 8.4, $J_{6,6'}$ = 9.5 Hz, 1 H, 6-H), 3.52 (dd, $J_{5,6'}$ = 3.2, $J_{6,6'}$ = 9.6 Hz, 1 H, 6′-H), 3.86 (dd, $J_{2,3}$ = 5.6,

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$J_{3,4}$ = 8.6 Hz, 1 H, 3-H), 3.90–3.96 (m, 2 H, 1-H, 5-H), 4.01 (ddd, $J_{2,3}$ = 5.2, $J_{1,2}$ = 3.7, $J_{2,4a}$ = 1.0 Hz, 1 H, 2-H), 4.48, 4.58 (2× d, J = 11.8 Hz, 2 H, PhCH_2), 4.51, 4.55 (2× d, J = 12.0 Hz, 2 H, PhCH_2), 4.54, 4.69 (2× d, J = 11.7 Hz, 2 H, PhCH_2), 4.58, 4.67 (2× d, J = 11.7 Hz, 2 H, PhCH_2), 7.27–7.38 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 28.2 (t, C-4a), 43.5 (d, C-4), 70.3 (d, C-5), 70.8, 72.0, 72.3, 73.4 (4× t, 4× PhCH_2), 73.5 (t, C-6), 81.2 (d, C-1), 84.5 (d, C-3), 89.5 (d, C-2), 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.4, 128.4, 128.5 (11× d, Ar-CH), 138.0, 138.3, 138.4 (3× s, Ar-C) ppm. HRMS calcd. for $C_{35}H_{38}O_5Na$ [MNa^+] 561.2611; found 561.2595.

The regioisomeric alcohol **9** was also isolated (7 mg, 2%) as an oil.

3,5,6-Tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→6)-1,2,3,5-tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (14): Epoxide **6** (31 mg, 0.072 mmol) and alcohol **9** (150 mg, 0.279 mmol) were dissolved in CH_2Cl_2 (0.75 mL) under N_2 at room temp. $BF_3{\cdot}Et_2O$ (18 μL, 0.14 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) and 125 μL (7 μmol $BF_3{\cdot}Et_2O$) of this solution was transferred to the colourless reaction mixture, which instantly turned pale yellow. After 10 min, TLC (toluene/EtOAc, 5:1) showed complete consumption of epoxide (R_f = 0.8) and formation of a major product (R_f = 0.5) as well as remaining alcohol (R_f = 0.4). The reaction was quenched by addition of Et_3N (0.5 mL) and the mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (toluene/EtOAc, 4:1) to give the pseudodisaccharide **14** (48 mg, 69%) as a colourless oil. $[\alpha]_D^{25}$ = –55.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.58, 1.79 (2× m, 2 H, 4a^I-H, 4a^{II}-H), 1.90–2.03 (m, 2 H, 4a′^{I}-H, 4a′^{II}-H), 2.24, 2.36 (2× m, 2 H, 4^I-H, 4^{II}-H), 3.41–4.07 (m, 12 H, 1^I-H, 2^I-H, 3^I-H, 5^I-H, 6^I-H, 6′^{I}-H 1^{II}-H, 2^{II}-H, 3^{II}-H, 5^{II}-H, 6^{II}-H, 6′^{II}-H), 4.36–4.73 (m, 14 H, 7× PhCH_2), 7.25–7.34 (m, 35 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 26.8, 27.6 (2× t, C-4a^I, C-4a^{II}), 42.7, 43.0 (2× d, C-4^I, C-4^{II}), 71.0, 71.5, 72.1, 72.2, 72.5, 73.0, 73.0, 73.5 (8× t, C-6^I, C-6^{II}, 7× PhCH_2), 77.4, 81.3, 82.5, 83.8, 83.9, 84.0, 90.1 (7× d, C-1^I, C-2^I, C-3^I, C-5^I, C-1^{II}, C-2^{II}, C-3^{II}, C-5^{II}), 127.6, 127.7, 127.7, 127.7, 127.9, 127.9, 128.0, 128.1, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5 (16× d, Ar-CH), 138.4, 138.5, 138.5, 138.6, 138.9, 138.9, 138.9 (7× s, 7× Ar-C) ppm. HRMS calcd. for $C_{63}H_{68}O_9Na$ [MNa^+] 991.4756; found 991.4745.

Also formed was the pseudotrisaccharide resulting from attack of the pseudodisaccharide alcohol on a second molecule of epoxide (7 mg, ca. 14%), but this compound could not be obtained completely pure. HRMS calcd. for $C_{91}H_{98}O_{13}Na$ [MNa^+] 1421.7055; found 1421.6900.

3,5,6-Tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→5)-1,2,3,6-tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (15): Epoxide **6** (52 mg, 0.121 mmol) and alcohol **13** (261 mg, 0.485 mmol) were dissolved in CH_2Cl_2 (0.75 mL) at room temp. under N_2. $BF_3{\cdot}Et_2O$ (20 μL, 0.158 mmol) was dissolved in dry CH_2Cl_2 (4 mL), and 306 μL (12 μmol $BF_3{\cdot}Et_2O$) of this solution was transferred to the colourless reaction mixture, which instantly turned pale yellow. After 10 min, TLC (toluene/EtOAc, 5:1) showed complete consumption of epoxide (R_f = 0.8) and formation of a major product (R_f = 0.3) as well as remaining alcohol (R_f = 0.2). The reaction was quenched by addition of Et_3N (1 mL) and the mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (pentane/EtOAc, 3:1) to give pseudodisaccharide **15** (61 mg, 52%) as an oil. $[\alpha]_D^{25}$ = –44.8 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3436 (OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.58 (ddd, J = 7.7, J = 11.3, $J_{4a,4a'}$ = 13.3 Hz, 1 H, 4a^y-H), 1.71 (m, 1 H, 4a^x-H), 1.84 (ddd, J = 6.7, J = 10.7, $J_{4a,4a'}$ = 13.5 Hz, 1 H, 4a′^{x}-H), 2.03 (ddd, J = 6.5, J = 8.9, $J_{4a,4a'}$ = 13.6 Hz, 1 H, 4a′^{y}-H), 2.09–2.19 (m, 2 H, 4^I-H, 4^{II}-H), 3.44–4.02 (m, 12 H, 1^I-H, 2^I-H, 3^I-H, 5^I-H, 6^I-H, 6′^{I}-H, 1^{II}-H, 2^{II}-H, 3^{II}-H, 5^{II}-H, 6^{II}-H, 6′^{II}-H), 4.35 (d, J = 11.6 Hz, 1 H, PhCHH′), 4.41–4.69 (m, 12 H, 5× PhCH_2, PhCHH′, PhCHH′), 4.76 (d, J = 11.7 Hz, 1 H, PhCHH′), 7.25–7.37 (m, 35 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 27.2, 27.9 (2× t, C-4a^I, C-4a^{II}), 41.5, 44.0 (2× d, C-4^I, C-4^{II}), 70.9, 72.0, 72.1, 72.4, 72.6, 73.0, 73.4, 73.8, 74.0 (9× d, C-6^I, C-6^{II}, 7× PhCH_2), 77.3, 78.0, 81.2, 82.2, 83.9, 84.4, 86.2, 89.8 (8× d, C-1^I, C-2^I, C-3^I, C-5^I, C-1^{II}, C-2^{II}, C-3^{II}, C-5^{II}), 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.7 (18× d, Ar-CH), 137.2, 128.4, 138.4, 138.5, 138.5, 139.0, 139.1 (7× s, 7× Ar-C) ppm. HRMS calcd. for $C_{63}H_{68}O_9Na$ [MNa^+] 991.4756; found 991.4718.

The descriptor "x" refers to an unspecified one of the carbasugars "I" or "II"; "y" refers to the other one.

General Procedure for Acetylation: The alcohol was dissolved in a mixture of Ac_2O and pyridine, and stirred at room temp. After TLC (toluene/EtOAc, 8:1) showed complete consumption of starting material and formation of a single product (typically up to 3 h), the reaction mixture was concentrated by co-evaporating all solvent with toluene (2× 10 mL). The residue was purified by flash column chromatography to give the acetate.

2-*O*-Acetyl-3,5,6-tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→6)-1,2,3,5-tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (16): Pseudodisaccharide **14** (49 mg, 0.050 mmol) was converted with Ac_2O/pyridine [1:1] (2 mL) and DMAP (1 mg, 0.008 mmol) into its acetate **16** (42 mg, 84%), an oil (R_f = 0.3, pentane/EtOAc, 3:1), according to the general procedure. $[\alpha]_D^{25}$ = –38.1 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1733 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.79 (m, 2 H, 4a^I-H, 4a^{II}-H), 1.90 (ddd, $J_{1,4a'}$ = 5.8, $J_{4,4a}$ = 11.1, $J_{4a,4a'}$ = 13.5 Hz, 1 H, 4a′^{II}-H), 2.01 (s, 3 H, CH_3), 2.04 (m, 1 H, 4a′^{I}-H), 2.30 (ddat, J = 3.1, J = 9.5, J_{at} = 8.8 Hz, 1 H, 4^I-H), 2.44 (ddat, J = 3.4, J_{at} = 8.0, $J_{4,4a}$ = 11.2 Hz, 1 H, 4^{II}-H), 3.49 (dd, J = 3.7, J = 10.0 Hz, 1 H, 6-H), 3.52 (dd, J = 4.5, J = 10.0 Hz, 1 H, 6-H), 3.59 (dd, J = 6.5, J = 10.0 Hz, 1 H, 6′-H), 3.65 (m, 1 H, 1^{II}-H), 3.67 (dd, J = 6.9, J = 10.0 Hz, 1 H, 6′-H), 3.74 (m, 2 H, 5^I-H, 5^{II}-H), 3.81 (dd, J = 4.0, J = 8.1 Hz, 1 H, 3^{II}-H), 3.86 (dd, $J_{2,3}$ = 6.1, $J_{3,4}$ = 8.8 Hz, 1 H, 3^I-H), 3.91 (dat, J = 7.2, J_{at} = 3.9 Hz, 1 H, 1^I-H), 4.00 (at, J = 4.9 Hz, 1 H, 2^I-H), 4.33 (d, J = 11.8 Hz, 1 H, PhCHH′), 4.34 (d, J = 11.7 Hz, 1 H, PhCHH′), 4.38 (d, J = 11.7 Hz, 1 H, PhCHH′), 4.45 (d, J = 11.6 Hz, 1 H, PhCHH′), 4.46 (d, J = 11.8 Hz, 1 H, PhCHH′), 4.50 (d, J = 12.1 Hz, 1 H, PhCHH′), 4.52–4.56 (m, 2 H, PhCHH′, PhCHH′), 4.57 (d, J = 11.8 Hz, 1 H, PhCHH′), 4.58–4.64 (m, 2 H, 2× PhCHH′), 4.68 (d, J = 11.8 Hz, 1 H, PhCHH′), 4.75 (d, J = 11.7 Hz, 1 H, PhCHH′), 4.76 (d, J = 11.7 Hz, 1 H, PhCHH′), 5.22 (m, 1 H, 2^{II}-H), 7.25–7.36 (m, 35 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.3 (q, CH_3), 27.4 (t, C-4a^I), 29.0 (t, C-4a^{II}), 43.4 (d, C-4^I), 45.2 (d, C-4^{II}), 71.0, 72.1, 72.3, 73.1, 73.2, 73.5 (6× t, 7× PhCH_2, C-6^I, C-6^{II}), 77.0, 77.4 (2× d, C-5^I, C-5^{II}), 81.4, 81.8 (2× d, C-1^{II}, C-2^{II}), 82.7 (C-1^I), 83.9, 84.3 (2× d, C-3^I, C-3^{II}), 90.0 (d, C-2^I), 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5 (11× d, Ar-CH), 138.4, 138.4, 138.6, 138.7, 138.8, 139.1, 139.2 (7× s, 7× Ar-C), 170.0 (s, C=O) ppm. HRMS calcd. for $C_{65}H_{70}O_{10}Na$ [MNa^+] 1033.4861; found 1033.4838.

2-*O*-Acetyl-3,5,6-tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→5)-1,2,3,6-tetra-*O*-benzyl-4a-carba-β-D-galactofuranose (17): Pseudodisaccharide **15** (29 mg, 0.030 mmol) was converted with Ac_2O/pyridine (3 mL) and DMAP (1 mg, 0.008 mmol) into its acetate **17** (31 mg, 99%), an oil (R_f = 0.7, toluene/EtOAc, 6:1), according to the general procedure. $[\alpha]_D^{25}$ = –61.2 (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1736 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H =

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1.66–1.96 (m, 7 H, 4a^{I}-H, 4a′^{I}-H, 4a^{II}-H, 4a′^{II}-H, CH_3), 2.33–2.42 (m, 2 H, C-4^{I}, C-4^{II}), 3.40–3.55 (m, 4 H, 6^{I}-H, 6′^{I}-H, 6^{II}-H, 6′^{II}-H), 3.69–4.01 (m, 7 H, 1^{I}-H, 2^{I}-H, 3^{I}-H, 5^{I}-H, 1^{II}-H, 3^{II}-H, 5^{II}-H), 4.29–4.76 (m, 14 H, 7× PhCH_2), 5.20 (m, 1 H, 2^{II}-H), 7.25–7.35 (m, 35 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.3 (q, CH_3), 27.2, 29.3 (2× t, C-4a^{I}, C-4a^{II}), 43.0, 45.3 (2× d, C-4^{I}, C-4^{II}), 71.0, 71.8, 72.0, 72.1, 72.4, 73.2, 73.3, 73.4, 73.5 (9× t, C-6^{I}, C-6^{II}, 7× PhCH$_2$), 75.9, 77.3, 81.4, 82.1, 84.0, 84.5, 90.0 (7× d, C-1^{I}, C-2^{I}, C-3^{I}, C-5^{I}, C-1^{II}, C-3^{II}, C-5^{II}), 82.7 (d, C-2^{II}), 127.5, 127.5, 127.6, 127.6, 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6 (19× d, Ar-CH), 138.5, 138.5, 138.6, 138.6, 138.9, 139.2 (6× s, Ar-C), 169.9 (s, C=O) ppm. HRMS calcd. for $C_{65}H_{70}O_{10}Na$ [MNa$^+$] 1033.4861; found 1033.4875.

4a-Carba-β-D-galactofuranosyl-(1→6)-4a-carba-β-D-galactofuranose (18): Pseudodisaccharide **14** (76 mg, 0.079 mmol) was dissolved in MeOH (10 mL). Pd/C (10%, 12 mg, 0.011 mmol) and 1 M HCl (0.1 mL) were added to the solution. All air was evacuated and the reaction was put under H_2. After 24 h, the reaction mixture was filtered through Celite and all solvent was removed in vacuo. The crude product (48 mg) was purified by flash column chromatography (CMAW) and freeze-dried to give the deprotected pseudodisaccharide **18** (15 mg, 57%) as a hygroscopic white powder. ^{1}H NMR (400 MHz, CD_3OD): δ_H = 1.55–1.64 (m, 2 H, 4a^{I}-H, 4a^{II}-H), 1.92–2.00 (m, 4 H, 4^{I}-H, 4^{II}-H, 4a′^{I}-H, 4a′^{II}-H), 3.34–3.81 (m, 12 H, 1^{I}-H, 2^{I}-H, 3^{I}-H, 5^{I}-H, 6^{I}-H, 6′^{I}-H, 1^{II}-H, 2^{II}-H, 3^{II}-H, 5^{II}-H, 6^{II}-H, 6′^{II}-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ_C = 28.2, 30.4 (2× t, C-4a^{I}, C-4a^{II}), 45.1, 45.4 (2× d, C-4^{I}, C-4^{II}), 66.4 (t, C-6^{II}), 71.6, 73.3, 75.5, 78.3, 78.4, 84.0, 84.1, 85.5 (8× d, C-1^{I}, C-2^{I}, C-3^{I}, C-5^{I}, C-1^{II}, C-2^{II}, C-3^{II}, C-5^{II}), 73.8 (t, C-6^{I}) ppm. HRMS calcd. for $C_{14}H_{26}O_9Na$ [MNa$^+$] 361.1469; found 361.1460.

4a-Carba-β-D-galactofuranosyl-(1→5)-4a-carba-β-D-galactofuranose (19): Pseudodisaccharide **15** (92 mg, 0.094 mmol) was dissolved in MeOH (3 mL). Pd/C (10%, 15 mg, 0.014 mmol) and 1 M HCl (0.03 mL) were added to the solution. All air was evacuated and the reaction was put under H_2. After 18 h, the reaction was filtered through Celite and all solvent was removed in vacuo. The crude product was purified by flash column chromatography (CMAW) and freeze dried to give the deprotected pseudodisaccharide **19** (29 mg, 91%) as a hygroscopic white powder. ^{1}H NMR (400 MHz, D_2O): δ_H = 1.53–1.71 (m, 2 H, 4a^{I}-H, 4a^{II}-H), 1.91–2.04 (m, 4 H, 4a′^{I}-H, 4a′^{II}-H, 4^{I}-H, 4^{II}-H), 3.47–3.81 (m, 12 H, 1^{I}-H, 2^{I}-H, 3^{I}-H, 5^{I}-H, 6^{I}-H, 6′^{I}-H, 1^{II}-H, 2^{II}-H, 3^{II}-H, 5^{II}-H, 6^{II}-H, 6′^{II}-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ_C = 28.4, 30.8 (2× t, C-4a^{I}, C-4a^{II}), 44.4, 44.8 (2× d, C-4^{I}, C-4^{II}), 64.7, 66.3 (2× t, C-6^{I}, C-6^{II}), 73.4, 75.5, 77.7, 78.2, 81.2, 83.7, 84.2, 85.5 (8× d, C-1^{I}, C-2^{I}, C-3^{I}, C-5^{I}, C-1^{II}, C-2^{II}, C-3^{II}, C-5^{II}) ppm. HRMS calcd. for $C_{14}H_{26}O_9Na$ [MNa$^+$] 361.1469; found 361.1482.

Galactofuranosyl transferase Assay: Spectrophotometric assays were performed as described previously[27] in 384-array microtitre plate wells that contained 100 mM MOPS, pH 7.6, 50 mM KCl, 20 mM $MgCl_2$, 1.1 mM NADH, 3.5 mM PEP, 3.75 U pyruvate kinase (PK, EC 2.7.1.40), and 8.4 U lactate dehydrogenase (LDH, EC 1.1.1.27). MOPS at pH 7.6, was added as a 20-fold stock solution. KCl, $MgCl_2$, acceptor and acceptor analogues were dissolved in deionised distilled water (MQ). All other assay components were prepared in 100 mM MOPS, pH 7.6, with the exception of PEP, which, owing to its acidity, was buffered in 250 mM MOPS, pH 7.6. In each assay, 0.75 μg GlfT2 was used. Stock solutions of NADH, PEP, PK, and LDH were made fresh on the day of use and all solutions were stored on ice. Compounds **18** and **19** were tested as potential GlfT2 substrates at 2 mM with the concentration of the donor, UDP-Gal*f*, at 1.5 mM. To determine the inhibitory potential of **18** and **19** against GlfT2, each compound was screened at 2 mM concentration with a standard acceptor trisaccharide substrate [β-D-Gal*f*-(1→5)-β-D-Gal*f*-(1→6)-β-D-Gal*f*-octyl] at 0.5 mM and UDP-Gal*f* at 1.5 mM.

Supporting Information (see footnote on the first page of this article): Copies of ^{13}C NMR spectra of new compounds.

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