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Carbasugar analogues of galactofuranosides: β-O-linked derivatives and towards β-S-linked derivatives ☆

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ABSTRACT

A selectively protected carbasugar analogue of β-galactofuranose was synthesised from glucose using ring-closing metathesis as the key step. The carbasugar was converted into an α-*galacto* configured 1,2-epoxide, which was an effective electrophile in Lewis acid catalysed coupling reactions with alcohols. The epoxide was opened with regioselective attack at C-1 to give β-*galacto* configured C-1 ethers. Using carbohydrates as nucleophiles, we synthesised a number of pseudodisaccharides. The epoxide was also regioselectively opened at C-1 with a sulfur nucleophile under basic conditions to give a β-*galacto* configured C-1 thioether.

1. Introduction

Carbohydrates are found in nature as components of glycoconjugates: poly- or oligosaccharides linked to proteins, lipids and other molecules.[3] The carbohydrate structures are species-dependent: some structures, such as galactofuranose (the subject of this work), are not found in mammals, but they are widespread in numerous other organisms. Galactofuranose is found as a component of oligo- or polysaccharides in some bacteria, fungi and protozoa.[4,5] It has been proposed that interfering with the biosynthesis of galactofuranose and galactofuranose-containing structures could be a potential route to antimicrobial therapies.[6] Hydrolytically stable analogues of galactofuranose, including C-glycosides,[7] thioglycosides,[8] thiosugars,[9] iminosugars[10] and glycosyl amides,[11] have been synthesised before (Fig. 1). We considered the carbasugar **1** and its derivatives, in which the endocyclic oxygen is replaced by methylene.[12,13] Carbasugars have the attractive feature that other moieties may be linked to the carbasugar by carbon–heteroatom bond formation at C-1 to give hydrolytically stable carbaglycoconjugates.

Carba-aldohexofuranoses have not been extensively described in the literature.[†] Vasella and Huber synthesised a protected carbahexofuranose from mannose by Horner–Wadsworth–Emmons chemistry.[14] The Lundt group has synthesised some carbahexofuranoses, including 4a-carba-β-D-glucofuranose and 4a-carba-α-L-glucofuranose.[15,16] Ghosh et al. reported the synthesis of a number of diastereomers by using ring-closing metathesis to form the C-2–C-3 bond;[17] only the β-D-*allo* compound was obtained deprotected. Meanwhile, very recently, two syntheses of C-4=C-4a unsaturated carbahexofuranoses have been achieved starting from carbohydrates: Nguyen van Nhien et al. used an alkylidenecarbene to close the ring,[18] and Schneller et al. used an ene-yne metathesis strategy.[19] The synthesis of a modified carbagalactofuranose with a fused cyclopropane ring has also recently been reported.[20] Carbadisaccharides containing carba-(hexo or pento)-furanosides do not appear to have been described before.[2,21,22] Considering the scarce results in the carbahexofuranose field and the great biological significance of galactofuranose, both the synthesis and potential biological applications are of interest.

One possible disconnection for the synthesis of carbadisaccharides is shown in Scheme 1: the carbasugar ether linkage (in **I**) is put in place by attack of carbohydrate alcohol nucleophiles on an electrophilic carbasugar C-1 (**II**). This approach is versatile in that

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† Whereas all but two of the 16 possible carbapentofuranose stereoisomers have been synthesised: 4a-carba-α-D-ribofuranose and 4a-carba-α-L-lyxofuranose have not been described, see Ref. 13.

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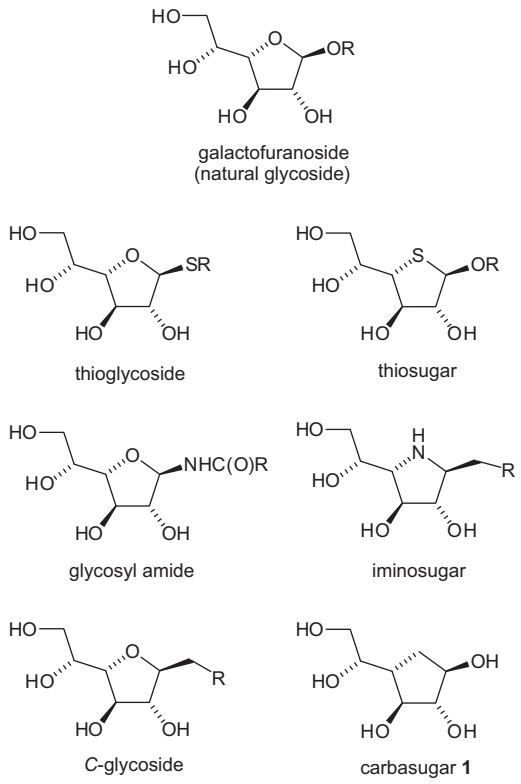


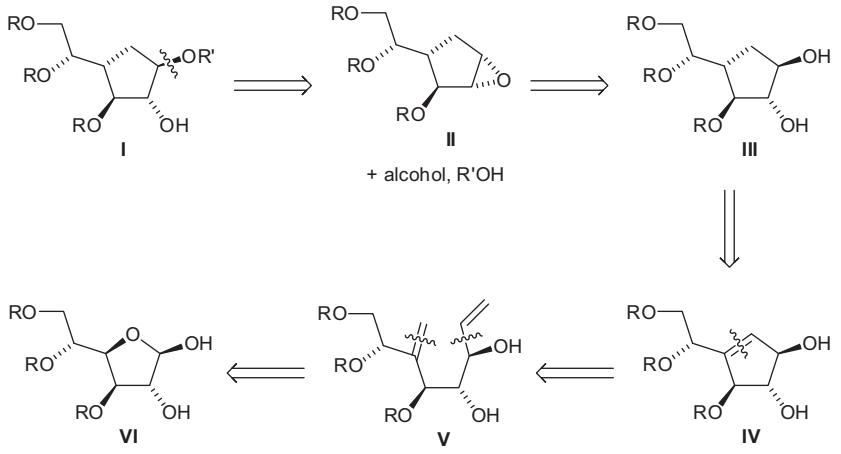
Figure 1. Galactofuranose and modified synthetic analogues.

many readily accessible carbohydrate alcohols, or indeed other nucleophiles, could be used to attack a single carbasugar C-1 electrophile. Galactofuranose is found in microorganisms glycosidically linked to miscellaneous saccharides,[4] so a more general route to carbagalactofuranose-containing carbadisaccharides would be advantageous. Ether- or amine-linked carbadisaccharides derived from carbapyranoses have been synthesised by nucleophilic ring-opening of 1,2-epoxides under Lewis acidic or basic conditions.[23–25]

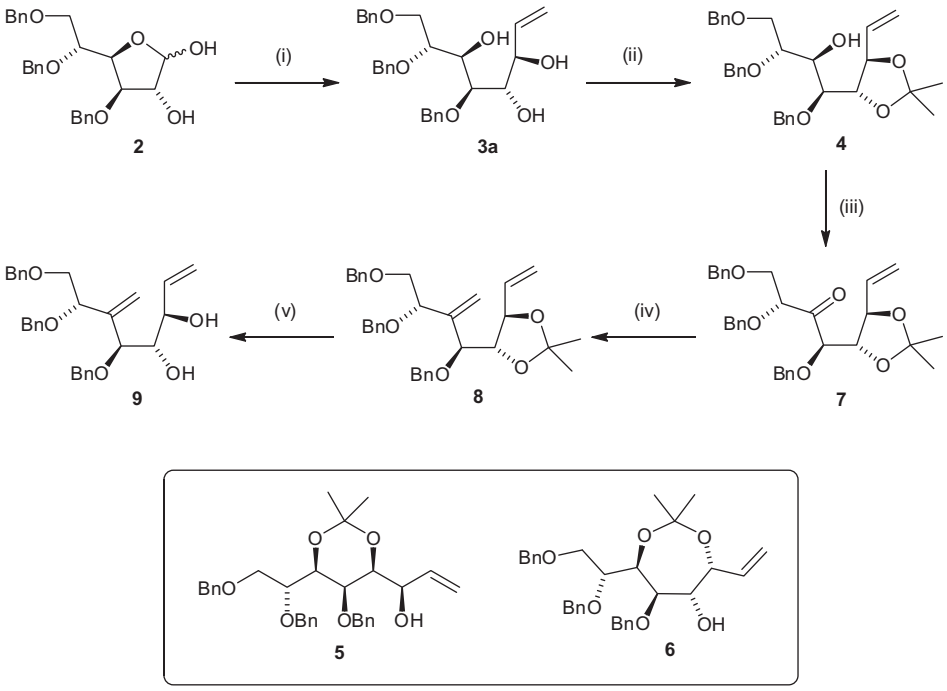
We required a partially protected carbagalactofuranose derivative with OH-1 and OH-2 free (**III**), and planned to synthesise this from a carbohydrate starting material.[1] Protected carbagalactofuranose **III** should be accessible by diastereoselective reduction of a C-4═C-4a unsaturated precursor **IV**, which would be made by ring-closing metathesis.[26] The required diene precursor **V** would be obtained in a few steps from a *gluco* hemiacetal **VI** via Grignard addition, regioselective protection, Swern oxidation and Wittig methylenation. Using the hemiacetal with OH-2 free (**IV**) should give a carbocycle with the correct protecting group pattern to allow 1,2-epoxide formation; we might also expect good diastereoselectivity in a 1,2-chelation-controlled Grignard reaction, and also be able to take advantage of regioselective protection of the resulting triol to give only OH-4 free. We may use glucose as the starting material, despite the fact that the target molecule has the *galacto* configuration, as the configuration at C-4 is lost during the synthesis. Related approaches to carbapentofuranose derivatives have been described before.[27–35]

2. Results and discussion

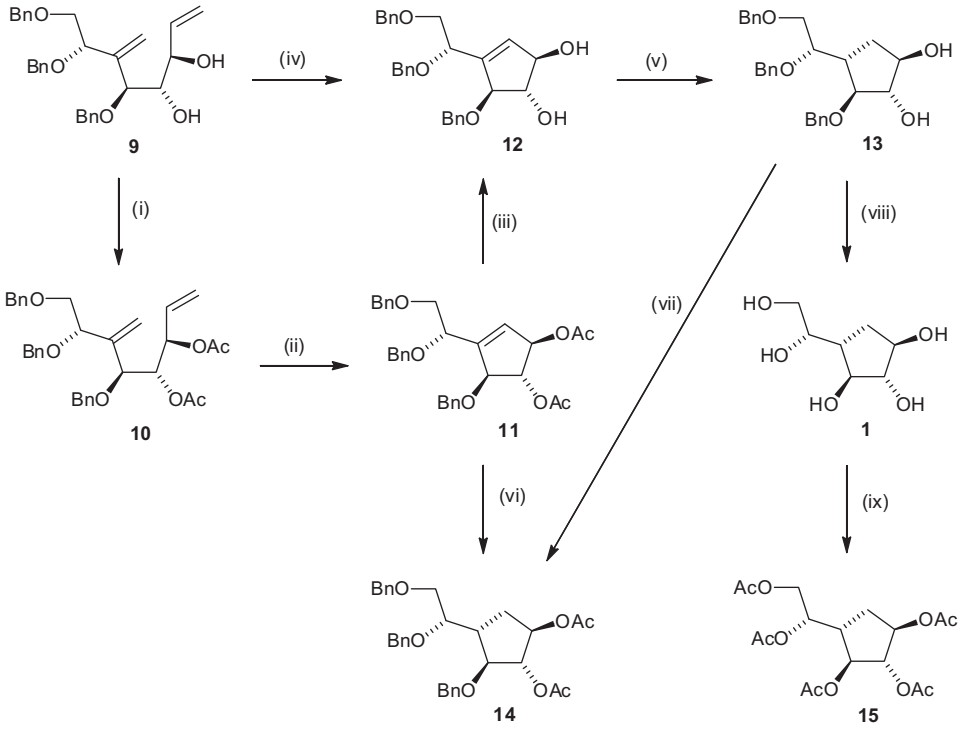
The hemiacetal **2** was synthesised in three steps from diacetone glucose according to literature procedures.[36–38] Addition of vinylmagnesium bromide to the hemiacetal **2** in THF gave a mixture (6:1) of epimers **3a** and **3b**, separable by column chromatography, in 87% yield (Scheme 2). When vinylmagnesium chloride in THF was used instead, the stereoselectivity improved to ca. 20:1. The C-1 configuration of the products was not assigned at this stage, but we later confirmed that triol **3a** was indeed the major product (see below). A 1,2-chelation model[39] accounts for the formation of the major diastereomer. The reason why the chloride reagent gives better selectivity than the bromide reagent is unclear, but similar behaviour has been observed before in related systems.[40] Triol **3a** was treated with 2,2-dimethoxypropane and catalytic camphorsulfonic acid, giving the five-membered ring acetonide **4** in a poor 33% yield along with two more products, which were identified as the six-membered (**5**) and seven-membered (**6**) ring isomers, respectively (**4**:**5**:**6**; 10:2:5). The regiochemical assignment of **4–6** was made based on ^{13}C NMR chemical shifts of the acetonide methyl groups and quaternary carbons.[41] When we ran the reaction under kinetic control, treating triol **3a** with 2-methoxypropene and pyridinium tosylate in dichloromethane, the five-ring acetonide **4** was formed as essentially the only product after 15 min, and isolated in 94% yield. The remaining free alcohol in **4** was oxidised under Swern conditions to give ketone **7** in 80% yield. Wittig methylenation of ketone **7** using the ylid derived from Ph_3PMeBr and *t*-BuOK gave diene **8** in a moderate 49% yield. The low yield was due to competing elimination. Ylid formation using *n*-BuLi gave much better results, and yields of diene **8** of up to 81% were obtained.



Scheme 1. A retrosynthesis of carbagalactofuranosides.



Scheme 2. Reagents and conditions: (i) vinylmagnesium chloride (4 equiv), THF, rt, 17 h, 87% (**3a**:**3b**, ca. 20:1); (ii) 2-methoxypropene (2.8 equiv), PPTS (0.1 equiv), CH_2Cl_2, rt, 15 min, 94%; (iii) DMSO (2 equiv), oxalyl chloride (2 equiv), CH_2Cl_2, −60 °C; then Et_3N (5 equiv), rt, 80%; (iv) Ph_3PMeBr (5 equiv), *n*-BuLi (4.5 equiv), toluene, rt, then **7**, −78 °C, 81%; (v) AcOH, H_2O, (2:1), 75 °C, 2 h, quant.



Scheme 3. Reagents and conditions: (i) Ac_2O, py, 14 h, quant.; (ii) Grubbs' 2nd complex (0.035 equiv), toluene, 60 °C, 48 h; then DMSO (1.75 equiv), 24 h, 87%; (iii) NaOMe, MeOH, rt, 90 min, quant.; (iv) Hoveyda–Grubbs 2nd complex (0.05 equiv), toluene, 60 °C, 1 h, 43%; (v) H_2, Pd/C, Et_3N (4 equiv), EtOAc, rt, 1.5 h, 91%; (vi) H_2, Pd/C, Et_3N (5 equiv), EtOAc, rt, 1.5 h, 49%; (vii) Ac_2O, py, 72%; (viii) H_2, Pd/C, EtOAc, EtOH, rt, 1.5 h, quant.; (ix) Ac_2O, py, rt, 2 h, 69%.

We found that to get the best results in the ring-closing metathesis reaction, a protecting group swap at C-1 and C-2 was necessary. Thus, the acetonide of **8** was removed by acidic hydrolysis to give diol **9**, which was then acetylated to give diacetate **10** in excellent yield (Scheme 3). This compound underwent the ring-closing reaction with Grubbs' 2nd generation complex in toluene at 60 °C to give cyclopentene **11** in 87% yield. As the reaction rate dropped considerably after a few hours, the catalyst was added portionwise over 18 h. A total of 3.5 mol % catalyst was added to ensure complete consumption of the starting material.

Attempts to induce ring-closure of acetonide **8** (Grubbs' 2nd generation complex (5 mol %), toluene, 60 °C, 21 h) resulted in no reaction, which is not unexpected as the product from this reaction would contain a trans-fused 5,5-ring system. Attempted ring-closure of diol **9** did give cyclopentene **12** in 43% yield with the Hoveyda–Grubbs 2nd generation complex in toluene at 60 °C, and in lower yield (24–36%) when Grubbs' 2nd generation complex was used. These reactions with 1,2-diol **9** gave rapid consumption of starting material and formation of unidentified by-products in addition to the ring-closed product **12**.

The acetate protection was removed from the cyclopentene **11** by methanolysis to give diol **12** in quantitative yield. The C=C bond in **12** was reduced diastereoselectively by catalytic hydrogenation over palladium on carbon in the presence of Et_3N to preserve the benzyl ether protection,[42] and the saturated diol **13** was formed in 91% yield as a single diastereomer (see below for stereochemical assignment). The benzyl ethers were removed from **13** by catalytic hydrogenolysis over palladium on carbon gave the deprotected carbasugar **1**, which was also characterised as its peracetate **15**.

The diastereoselectivity of the C=C reduction is possibly counterintuitive, as hydrogen adds cis to both neighbouring ring substituents (i.e., at C-1 and C-3). Similarly good diastereoselectivity was observed by Lowary in a pseudoenantiomeric system, resulting in exclusive formation of an α-L-arabinoside from hydrogenation of the corresponding C-4=C-4a unsaturated carbapentofuranose,[30] but the catalyst used in that reaction (viz. Wilkinson's catalyst) should not necessarily show the same behaviour as palladium on carbon as used by us. We also investigated the reduction of C=C bonds in some related compounds, all of which appeared to give similarly good diastereoselectivity: Firstly, hydrogenation of the cyclopentene diacetate **11** over palladium on carbon in the presence of Et_3N gave the saturated diacetate **14** also with excellent diastereoselectivity (only one diastereomer was observed) but in a disappointing isolated yield of 49%. The diastereoselectivity in the hydrogenation of diacetate **11** had the same sense as in the hydrogenation of diol **12**, which was proved by acetylation of the saturated diol **13** to give the saturated diacetate **14**. The low yield in the hydrogenation of diacetate **11** can be rationalised as we saw a by-product formed in 46% yield that showed *m/z* 497 ($M+Na^+$) in its mass spectrum, and that had five high-field protons and only one acetate singlet in its ^1H NMR spectrum. This would be consistent with reduction of the C–O bond at C-1, resulting in the nett loss of acetate. Secondly, removal of the benzyl ethers from **12** by Birch reduction gave the unsaturated pentaol, which was hydrogenated over palladium on carbon to give the same β-*galacto* carbasugar **1** with excellent diastereoselectivity; the alternative β-*gluco* diastereomer was not detected. Thirdly, an attempted one-pot reduction–deprotection reaction of diol **12** by hydrogenation over palladium on carbon without Et_3N was not a clean reaction, giving a low yield of **1** along with many by-products. Possibly this was due to concomitant hydrogenolysis of allylic C–O bonds: it has been shown that addition of Et_3N to the palladium-catalysed hydrogenation of acarbose suppresses allylic C–N bond cleavage.[43] Regarding the diastereoselectivity of the reduction–deprotection of **12**, we only isolated and characterised the β-*galacto* carbasugar **1** but the possibility that some of the by-products had β-*gluco* stereochemistry (or the corresponding C-4 configuration) cannot be ruled out.

During the synthesis of carbasugar **1**, two new stereogenic centres are formed; one from the Grignard addition to give triol **3a** (C-1 configuration) and the other from the C=C reduction to form saturated compound **13** (C-4 configuration). Assuming fixed configurations at the remaining stereogenic centres, C-2, C-3 and C-5, the carbasugar products should have one of the four possible α or β D-*gluco* or D-*galacto* configurations. The inherent flexibility of five-membered rings means that it is more difficult to determine the configuration of stereogenic centres in five-membered rings than in six-membered rings using ^1H NMR spectroscopy. It has been observed empirically for cyclopentanes that ^3J $^1H,^1H$ coupling constants less than 5 Hz are indicative of a trans relationship between the protons, whereas higher coupling constants are non-diagnostic.[44] A similar observation for furanosides (for coupling constants below 2 Hz) has been rationalised by evaluating the dihedral angles in accessible ring-conformational trajectories in the context of the Karplus equation.[45] For the saturated carbahexofuranosides discussed in this paper,[‡] the values of $J_{1,2}$ were quite diverse, ranging from 3.1 to 7.1 Hz, whereas $J_{3,4}$ values were in the range 7.5–9.0 Hz, which was not helpful in determining the relative configuration.

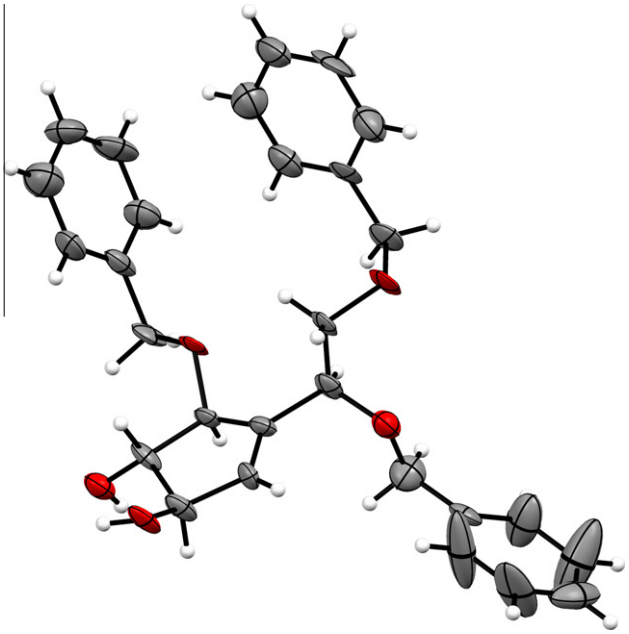
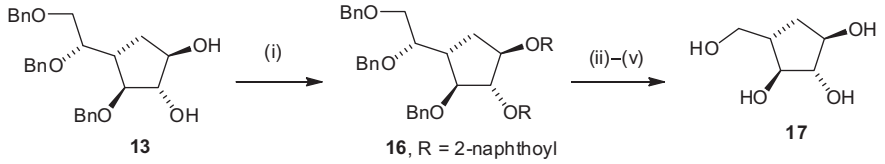


Figure 2. Crystal structure of **12**. Ellipsoids are shown at 50% probability.

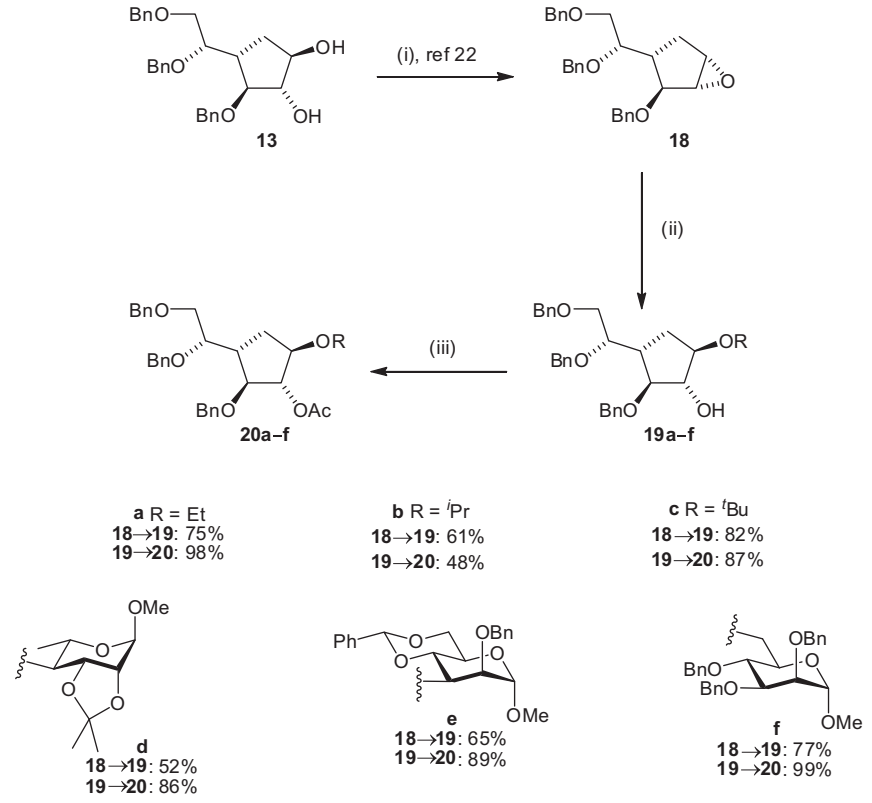
Lundt has reported the synthesis of carba-α-L-glucofuranose and carba-β-D-glucofuranose.[15,16] The non-identity of the reported ^1H NMR and ^{13}C NMR spectral data of either of these two compounds with NMR data from carbasugar **1** suggested that **1** was not a carbaglucofuranose and hence must be a carbagalactofuranose. We solved the crystal structure of the unsaturated diol **12** (Fig. 2), which was thus proved to have a β-D-*xylo* configuration, corresponding to a β-configuration at C-1 of **1**. Taken together, this suggested that carbasugar **1** had the β-*galacto* configuration, but we planned to prove the relative configuration of **1** by degradation, cleaving the C-5–C-6 bond of our carbasugar to form a carbapentose;[15] all four possible carbapentose diastereomers have been synthesised previously.[†]

We protected OH-1 and OH-2 of diol **13** as 2-naphthoate esters, giving the fully protected compound **16** (Scheme 4). The benzyl ethers of **16** were removed by catalytic hydrogenation, which was followed by oxidative cleavage of the C-5–C-6 bond and reduction of the resulting C-5 aldehyde in situ with sodium borohydride. The naphthoate protecting groups were then removed using sodium methoxide to give carbapentose **17** in 80% yield over three steps. The carbapentose **17** was unambiguously identified as 4a-carba-α-L-arabinofuranose[46,47] by comparison of the ^1H NMR and ^{13}C NMR spectra with those of the known carbapentoses (and bearing in mind the known absolute stereochemistry at C-2 and C-3);

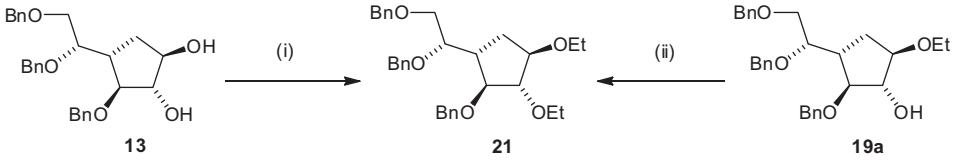
[‡] Based on assigned NMR data from 27 carba-β-D-galactofuranoses from this paper, and also from derivatives in Refs. 21,22.



Scheme 4. Reagents and conditions: (i) 2-naphthoyl chloride, DMAP (0.06 equiv), pyridine, 50 °C, 24 h, 90%; (ii) H_2, Pd/C, 1 M HCl, EtOAc, 5 days, 50%; (iii) $NaIO_4$, H_2O, 0 °C, 1 h; (iv) $NaBH_4$, H_2O, rt, 2 h; (v) NaOMe, MeOH, 3 h, 50 °C, 80% (three steps).



Scheme 5. Reagents: (i) see Ref. 22; (ii) ROH (equiv: **a–c**, 10; **d**, 3.2; **e**,**f**, 5.0), $BF_3{\cdot}Et_2O$ (0.1–0.2 equiv), CH_2Cl_2; (iii) Ac_2O, py, DMAP.



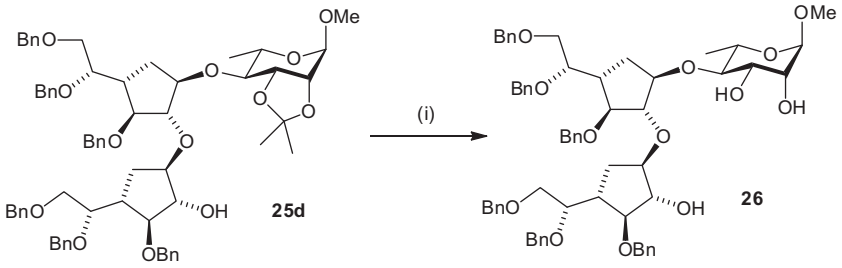
Scheme 6. Reagents and conditions: (i) EtBr (10 equiv), NaH, DMF, rt, 5 d, 45%; (ii) EtBr (10 equiv), NaH, DMF, rt, 4 h, 46%.

the optical rotation confirmed the assignment. This means that diol **13** can indeed be assigned the β-D-*galacto* stereochemistry.

We then turned to the synthesis of pseudodisaccharides based on carbagalactofuranose. Treatment of diol **13** with DIAD and triphenylphosphine resulted in 1,2-epoxide **18**, formed as a single diastereomer by intramolecular Mitsunobu type reaction.[22] The stereochemistry of epoxide **18** was apparent as a two-step procedure from diol **13** via an isolated C-1 tosylate gave the same product **18**.[22]

We investigated the epoxide-opening reaction with simple model alcohol nucleophiles (10 equiv) in the presence of $BF_3{\cdot}Et_2O$ as a Lewis acid catalyst (Scheme 5). Opening with primary (ethanol), secondary (isopropanol), or tertiary (*tert*-butanol) alcohols gave the respective ethers **19a–c** in high yields. In all three reactions, epoxide **18** suffered nucleophilic attack at C-1 exclusively, giving the product ethers with OH-2 free. The regiochemistry of substitution was proved by acetylation of the coupling products **19a–c**; 2D-COSY $^1H,^1H$ NMR spectroscopy showed a large downfield shift for H-2 in the acetates **20a–c**, proving that OH-2 had been acetylated.

To unambiguously prove the stereochemistry of the products **19**, diol **13**, with known relative configuration, was alkylated with ethyl bromide to give diethyl derivative **21**. Ether **19a**, resulting from epoxide opening by ethanol, was also alkylated with ethyl bromide and gave the same product **21**, showing that the product of epoxide opening has the β-*galacto* stereochemistry, consistent



Scheme 7. Reagents and conditions: (i) AcOH, H_2O, 70 °C, 54%.

with C-1 attack with inversion of configuration in the epoxide-opening reaction (Scheme 6).

Epoxide **18** was also opened using primary and secondary carbohydrate alcohols (3–5 equiv) as nucleophiles (viz. Rha OH-4 **22**,[48a] Man OH-3 **23**,[48b] Man OH-6 **24**[48c]) under $BF_3{\cdot}Et_2O$ catalysis, resulting in the formation of carbadisaccharides **19d–f**. Unreacted excess alcohol starting materials were recovered. The regioselectivity of the reaction was again excellent in all cases, and the products of nucleophilic attack at C-2 were not observed. Again, the sense of regioselectivity was proved by acetylation of the coupling products to give C-2^{II} acetates **20d–f**.

The reaction products **19** contain a secondary alcohol (OH-2^{II}), which could feasibly act as a nucleophile, consuming epoxide and product and forming pseudotrisaccharides (where the original alcohol was a carbohydrate) or pseudodisaccharides (where it was not).[49] This scenario is to be avoided not only because the valuable starting materials and products are consumed to form undesired by-products, but also because separation of the desired carbasugar ether from its homologue by chromatography may not be straightforward. For example, in the reaction forming pseudodisaccharide **19d**, we did observe formation of a pseudotrisaccharide (**25d**) whose identity was suggested by MS, with a peak seen at *m/z* 1101 ($M+Na^+$). However, removal of impurities from this compound by flash chromatography was difficult. The isopropylidene group was cleaved from **25d** by acidic hydrolysis to give a triol that was purified and characterised as pseudotrisaccharide **26** (Scheme 7).

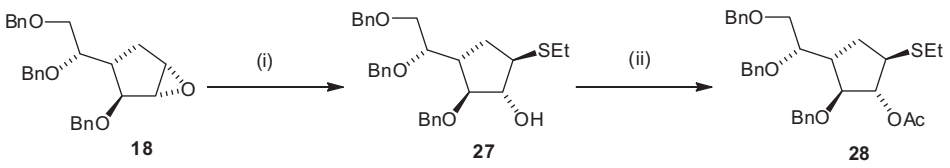
Hence the best results in the coupling reactions were obtained by using an excess of the alcohol (which should be recovered after the consumption of the epoxide). Using excess epoxide with an alcohol of low nucleophilicity such as a secondary carbohydrate alcohol can only result in low yields of the monocoupled product.

Ogawa has described ring-opening of carbapyranose 1,2-epoxides by alcohol nucleophiles to give α-carbamannopyranosides. He found that while a primary carbohydrate alcohol coupled with the epoxide under Lewis acid catalysis, more hindered secondary alcohol nucleophiles failed to give coupling products under these conditions, and he instead used basic conditions.[50] We tried to open carbafuranose epoxide **18** under basic conditions (NaH, 15-crown-5, DMF, 70–100 °C) without success; no reaction was seen with alcohols Rha OH-4 (**22**) and Man OH-3 (**23**), even after several days.

We then examined the reactivity of the epoxide **18** towards a sulfur nucleophile for the synthesis of carbagalactofuranose C-1 thioethers. When the epoxide **18** was treated with excess ethanethiol in MeOH under basic conditions, a thioether product **27** was formed as a single regioisomer (Scheme 8). The identity of thioether **27** was confirmed by acetylation of the free hydroxyl group. Examination of the ^1H NMR spectra of acetate **28** indicated that O-2 had been acetylated, and that, therefore, nucleophilic attack had occurred at C-1 during the epoxide-opening reaction in this case also. The assignment of β-*galacto* stereochemistry to **27** is based on the assumption that nucleophilic attack at C-1 by EtS^- will occur with inversion of configuration. In the epoxide-opening reaction, we used excess base (15 equiv NaOMe, 10 equiv EtSH), meaning that both MeO^- and EtS^- were present as potential nucleophiles in the reaction mixture. Only attack by the sulfur nucleophile was observed.

Some issues regarding regioselectivity in epoxide formation and opening are worthy of comment. In the epoxide-opening reactions of **18**, the fact that C-1 has an unsubstituted neighbour (C-4a), while C-2 is linked to a carbon bearing a bulky substituent (the benzyl ether on C-3) provides a steric argument for the preferential nucleophilic attack at C-1 over C-2 that applies both in Lewis acidic (O-nucleophile) and basic (S-nucleophile) conditions. In Lewis acid mediated epoxide-opening reactions, an electronic influence on regioselectivity can be explained in terms of the relative stability of partial positive charges on the two epoxide carbons. A build-up of positive charge would be less favourable at C-2 than at C-1 due to the proximity of the electron-withdrawing benzyl ether at C-3; the carbon flanking C-1, i.e., C-4a, does not bear any electron-withdrawing functionality, so the electronic argument would also favour attack at C-1 over C-2. Under basic conditions, the β-oxygen effect that defines the low reactivity of carbohydrate electrophiles in S_N2 reactions applies. Hence, C-2 (which has a β-oxygen at C-3) is less electrophilic than C-1 (which has no β-oxygen at C-4a). The Fürst–Plattner guideline (or the principle of microscopic reversibility) predicting trans-diaxial opening in six-membered rings may be used to explain the good regioselectivity observed by Ogawa in related carbapyranose pseudodisaccharide formation,[50,51] but it is not useful to explain our results, this difference being due to the more flexible nature of five-membered rings.[21] Indeed, we have found that the diastereomeric β-*talo* epoxide **29** (Fig. 3) was also opened with very good regioselectivity for attack at C-1 under Lewis acidic conditions.[21]

Two possible explanations for the excellent regioselectivity in the Mitsunobu (epoxidation) reaction are considered. The higher nucleophilicity of OH-1 than OH-2 could explain the outcome if formation of the activated alcohol ($RO–P^+Ph_3$) is rate-determining. Alternatively, if there is a rapid equilibrium between the two reg-



Scheme 8. Reagents and conditions: (i) EtSH (10 equiv), NaOMe (15 equiv), MeOH, 68%; (ii) Ac_2O, pyridine, 92%.

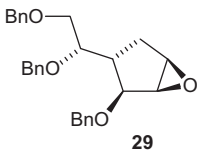


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Figure 3.

ioisomeric activated alcohols (RO^1–P^+Ph_3 and $R'O^2$–P^+Ph_3), possibly via a discrete five-membered ring intermediate,[52] before rate-determining ring-closure, the regioselectivity may be explained by the higher electrophilicity of C-1 than C-2. Bearing in mind our other results on the relative nucleophilicity of OH-1 and OH-2 in **13** (moderate–good regioselectivity with TsCl as electrophile)[22,21] and epoxide-opening of **18** (excellent regioselectivity), the latter explanation seems more likely.

To conclude, we have synthesised 4a-carba-β-D-galactofuranose from glucose in 13 steps via a diastereoselective Grignard addition to hemiacetal **3**, ring-closing metathesis for carbocycle formation, and highly diastereoselective hydrogenation of the double bond in cyclopentene **15**. Carbagalactofuranosides have been formed by Lewis acid catalysed opening of a carbasugar 1,2-epoxide **18** using carbohydrate-derived and non-carbohydrate alcohols as nucleophiles, with excellent regioselectivity for attack at C-1 in all cases. The reaction appears to be generally applicable. The use of excess nucleophile minimises competitive attack on the epoxide by the secondary alcohol in the coupling product. Attempted ring-opening under basic conditions failed to give any reaction with oxygen nucleophiles, but this approach seems to hold some promise with sulfur nucleophiles, as a thiolate opened the epoxide with excellent regioselectivity for attack at C-1.

3. Experimental

3.1. General methods

Melting points were measured using a Gallenkamp melting point apparatus and are uncorrected. 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), 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, 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. Low- and high-resolution (HRESIMS) 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 visualised 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). CMAW means $CHCl_3$–MeOH–AcOH–H_2O, 60:30:3:5. Grubbs' second generation complex (CAS No.: 246047-72-3) was bought from Sigma–Aldrich and coated in wax (complex 12% by weight) before use. Hoveyda–Grubbs second generation complex (CAS No.: 301224-40-8) was bought from Sigma–Aldrich and used as supplied. Dichloromethane was distilled from calcium hydride. Diethyl ether and THF were dried over molecular sieves and dispensed from a solvent purifier by VAC. Toluene was distilled from sodium. Reactions performed under an atmosphere of hydrogen, nitrogen or argon were maintained by an inflated balloon.

3.2. (2*R*,3*R*,4*R*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-1,2,3,4,5,6-hexahydroxy-oct-7-ene (3a)

Hemiacetal **2** (11.0 g, 24.4 mmol) was dissolved in THF (45 mL) and cooled to 0 °C under N_2. Vinylmagnesium chloride (1.6 M in THF, 62.6 mL, 100.2 mmol) was added at 0 °C and the reaction mixture was stirred at rt for 17 h. The reaction was then quenched by slow addition of NH_4Cl (satd aq) at 0 °C until a neutral pH was obtained. Et_2O (45 mL) was added and the reaction mixture was washed with water (45 mL) and brine (2 × 45 mL). The combined aqueous phases were extracted with Et_2O (3 × 45 mL). The organic phases were combined and dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash column chromatography to give triol **3a** (10.1 g, 87%) as a yellow oil (R_f 0.3, CH_2Cl_2–Et_2O, 4:1); $[\alpha]_D^{25}$ −28.3 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 3400 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.67–3.73 (2H, m, H-2, H-5), 3.75 (1H, dd, $J_{1,2}$ 4.7 Hz, $J_{1,1'}$ 10.2 Hz, H-1), 3.86 (1H, dd, $J_{1',2}$ 3.9 Hz, $J_{1,1'}$ 10.2 Hz, H-1′), 3.91 (1H, dd, $J_{3,4}$ 1.9 Hz, $J_{4,5}$ 4.7 Hz, H-4), 3.99 (1H, m, H-3), 4.35 (1H, m, H-6), 4.47, 4.74 (2H, 2 × d, *J* 11.5 Hz, PhC*H*$_2$), 4.52 (2H, s, PhC*H*$_2$), 4.58 (2H, s, PhC*H*$_2$), 5.21 (1H, dat, J_{cis} 10.6 Hz, *J* 1.6 Hz, H-8$_{cis}$), 5.33 (1H, dat, J_{trans} 17.3 Hz, *J* 1.6 Hz, H-8$_{trans}$), 5.84 (1H, ddd, $J_{6,7}$ 5.5 Hz, J_{cis} 10.6 Hz, J_{trans} 17.3 Hz, H-7), 7.22–7.37 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 69.9 (t, C-1), 70.8 (d, C-3), 70.9 (d, C-6), 72.0, 73.7, 74.1 (3 × t, 3 × PhCH$_2$), 73.3, 77.8 (2 × d, C-2, C-5), 77.2 (d, C-4), 116.8 (t, C-8), 127.8, 127.9, 128.1, 128.1, 128.5, 128.5, 128.6 (7 × d, Ar-CH), 137.7, 137.9, 138.2 (d, 2 × s, C-7, 3 × Ar-C); HRESIMS calcd for $C_{29}H_{34}O_6Na$ (MNa^+) 501.2248; found 501.2239.

3.3. (2*R*,3*R*,4*S*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-1,2,3,4,5,6-hexahydroxy-oct-7-ene (4)

Triol **3a** (4.93 g, 10.3 mmol) was dissolved in CH_2Cl_2 (100 mL) at rt, and 2-methoxypropene (2.70 mL, 28.9 mmol) and PPTS (259 mg, 1.03 mmol) were added. The reaction mixture was stirred at rt for 15 min, after which time TLC (pentane–EtOAc, 2:1) showed complete consumption of starting material (R_f 0.2) and the formation of a product (R_f 0.9). The reaction was quenched by addition of Et_3N (5 mL) and then concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2–Et_2O, 10:1 + 0.5% Et_3N) to afford acetonide **4** (5.04 g, 94%) as a colourless oil; $[\alpha]_D^{25}$ −15.1 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 3468 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.45 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$), 2.75 (1H, br s, 3-OH), 3.65–3.74 (2H, m, H-1, H-2), 3.81 (1H, d, *J* 7.6 Hz, H-3), 3.87–3.90 (2H, m, H-1′, H-4), 4.06 (1H, dd, $J_{4,5}$ 5.7 Hz, $J_{5,6}$ 8.2 Hz, H-5), 4.35 (1H, at, *J* 7.4 Hz, H-6), 4.39, 4.77 (2H, 2 × d, *J* 11.3 Hz, PhC*H*$_2$), 4.42, 4.73 (2H, 2 × d, *J* 11.7 Hz, PhC*H*$_2$), 4.58 (2H, s, PhC*H*$_2$), 5.26 (1H, dat, J_{cis} 10.3 Hz, *J* 1.3 Hz, H-8$_{cis}$), 5.37 (1H, dat, J_{trans} 17.2 Hz, *J* 1.2 Hz, H-8$_{trans}$), 5.85 (1H, ddd, J_{cis} 10.3 Hz J_{trans} 17.3 Hz, $J_{6,7}$ 7.3 Hz, H-7), 7.24–7.36 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 27.1, 27.1 (2 × q, C(*C*H$_3$)$_2$), 69.7 (t, C-1), 70.9, 78.0 (2 × d, C-4, C-5), 72.0, 73.6, 74.2 (3 × t, 3 × PhCH$_2$), 76.6 (d, C-2), 79.0 (d, C-3), 82.5 (d, C-6), 109.3 (s, *C*(CH$_3$)$_2$), 119.4 (t, C-8), 127.7, 127.8, 127.9, 127.9, 128.1, 128.1, 128.5, 128.5, 128.5 (9 × d, Ar-CH), 135.6 (d, C-7), 138.4, 138.5 (2 × s, 3 × Ar-C); HRESIMS calcd for $C_{32}H_{38}O_6Na$ (MNa^+) 541.2561; found 541.2549.

NMR data for regioisomeric acetonides **5** and **6**. The six-membered ring acetonide **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.43, 1.47 (6H, 2 × s, 2 × CH_3), 2.84 (1H, d, *J* 0.9 Hz, OH), 3.64–3.69 (3H, m, H-5), 3.83–3.87 (2H, m), 4.06 (1H, d, *J* 9.0 Hz), 4.35–4.40 (2H, m, PhC*H*H′, H-6), 4.51–4.79 (5H, m, 2 × PhC*H*$_2$, PhCH*H*′), 5.25 (1H, dat, J_{cis} 10.6 Hz, J_{at} 1.3 Hz, H-8$_{cis}$), 5.37 (1H, dat, J_{trans} 17.2 Hz, J_{at} 1.5 Hz, H-8$_{trans}$), 5.76 (1H, ddd, $J_{6,7}$ 6.5 Hz, H-7), 7.24–7.36 (15H, m, Ar-H); ^{1}H NMR (100 MHz, $CDCl_3$) δ_C 19.4, 29.7 (2 × q, C(*C*H$_3$)$_2$), 67.5, 70.3, 71.2, 71.3, 72.0, 73.6, 73.8, 76.4, 76.5 (4 × t, 5 × d, 3 × PhCH$_2$, C-1, C-2, C-3, C-4, C-5, C-6), 99.7 (s, O$_2$*C*(CH$_3$)$_2$), 118.9 (t, C-8), 127.2, 127.5, 127.7, 127.8, 127.9, 127.9, 128.4, 128.5, 128.5 (9 × d, 9 × Ar-CH), 135.5 (d, C-7), 138.4, 138.5, 138.7 (3 × s, 3 × Ar-C). The seven-membered ring acetonide **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.34, 1.37 (6H, 2 × s, 2 × CH_3), 2.38 (1H, d, *J* 9.4 Hz, OH-5), 3.59–4.09 (6H, m, H-1, H-1′, H-2, H-3, H-4, H-5), 4.30–4.77 (7H, m, 3 × PhCH_2, H-6), 5.18 (1H, dat, J_{at} 1.7 Hz, J_{cis} 10.6 Hz, C-8$_{cis}$), 5.29 (1H, dat, J_{at} 1.7 Hz, J_{trans} 17.2 Hz, H-8$_{trans}$), 5.80 (1H, m, H-7), 7.24–7.35 (15H, m, Ar-H); ^{1}H NMR (100 MHz, $CDCl_3$) δ_C 24.4, 25.2 (2 × q, C(*C*H$_3$)$_2$), 68.2, 68.6, 69.1, 71.0, 71.9, 72.9, 73.5, 76.3, 78.3 (4 × t, 5 × d, 3 × PhCH_2, C-1, C-2, C-3, C-4, C-5, C-6), 101.5 (s, O$_2$*C*(CH$_3$)$_2$), 116.3 (t, C-8), 127.6, 127.7, 127.8, 127.9, 127.9, 128.4, 128.5, 128.5, 128.5 (9 × d, 9 × Ar-CH), 136.7 (d, C-7), 138.4, 138.6, 138.8 (3 × s, 3 × Ar-C).

3.4. (2*R*,4*R*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-1,2,4,5,6-pentahydroxy-oct-7-en-3-one (7)

A cold (−60 °C) solution of DMSO (362 μL, 5.10 mmol) in CH_2Cl_2 (5 mL) was transferred to a solution of oxalyl chloride (217 μL, 2.53 mmol) in CH_2Cl_2 (5 mL) under N_2 at −60 °C. The reaction mixture was stirred for 30 min. Alcohol **4** (600 mg, 1.16 mmol) was dissolved in CH_2Cl_2 (15 mL) and transferred to the reaction vessel. The reaction was left to stir for 45 min at −60 °C. Et_3N (806 μL, 5.79 mmol) was then added, and the reaction was allowed to reach rt and was left to stir for another 30 min. CH_2Cl_2 (20 mL) was added and the reaction mixture was washed with water (25 mL) and brine (2 × 25 mL) and the aqueous phases were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried on Na_2SO_4 and concentrated in vacuo. The crude product (R_f 0.4, toluene–EtOAc, 9:1) was purified by flash column chromatography (toluene–EtOAc, 9:1) to give ketone **7** (481 mg, 80%) as an oil; $[\alpha]_D^{25}$ +19.8 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 1729 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.32 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 3.76 (1H, dd, $J_{1,1'}$ 10.7 Hz, $J_{1,2}$ 6.0 Hz, H-1), 3.83 (1H, dd, $J_{1',2}$ 3.8 Hz, $J_{1,1'}$ 10.7 Hz, H-1′), 4.10 (1H, dd, $J_{4,5}$ 2.6 Hz, $J_{5,6}$ 8.3 Hz, H-5), 4.20 (1H, d, $J_{4,5}$ 2.7 Hz, H-4), 4.25, 4.69 (2H, 2 × d, *J* 11.9 Hz, PhC*H*$_2$), 4.40–4.44 (2H, m, H-2, H-6), 4.52 (2H, s, PhC*H*$_2$), 4.58, 4.63 (2H, 2 × d, *J* 11.9 Hz, PhC*H*$_2$), 5.02 (1H, dd, J_{trans} 17.0 Hz, *J* 1.0 Hz, H-8$_{trans}$), 5.09 (1H, dd, J_{cis} 10.3 Hz, *J* 0.8 Hz, H-8$_{cis}$), 5.66 (1H, ddd, $J_{6,7}$ 7.3 Hz, J_{cis} 10.4 Hz, J_{trans} 17.2 Hz, H-7), 7.24–7.33 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.7, 27.1 (2 × q, 2 × *C*H$_3$), 70.6 (t, C-1), 72.8, 73.2, 73.6 (3 × t, 3 × PhCH$_2$), 78.0, 82.0 (2 × d, C-2, C-6), 79.3 (d, C-4), 80.0 (d, C-5), 109.8 (s, *C*(O)$_2$(CH$_3$)$_2$), 119.3 (t, C-8), 127.3, 127.8, 128.1, 128.2, 128.2, 128.3, 128.5, 128.6, 128.6 (9 × d, Ar-CH), 134.8 (d, C-7), 137.2, 137.6, 137.9 (3 × s, 3 × Ar-C), 207.1 (s, *C*=O); HRESIMS calcd for $C_{32}H_{36}O_6Na$ (MNa^+) 539.2404; found 539.2397.

3.5. (2*S*,4*S*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-3-methylene-oct-7-ene-1,2,4,5,6-pentaol (8)

CH_3PPh_3Br (6.89 mg, 19.3 mmol) was suspended at 0 °C in toluene and *n*-BuLi (1.6 M in hexane, 10.8 mL, 17.3 mmol) was added, after which the mixture was allowed to reach rt and stirred for 1 h. The reaction mixture was cooled to −78 °C, after which ketone **7** (1.99 g, 3.85 mmol) was added by cannula under N_2. After 2 h, the reaction was allowed to reach rt, and after an additional 1 h, TLC (pentane–EtOAc, 4:1) showed product formation (R_f 0.5) and no remaining starting material (R_f 0.4). The reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was then purified by flash column chromatography (toluene–EtOAc, 12:1→8:1), giving alkene **8** (1.60 g, 81%) as a yellowish oil; $[\alpha]_D^{30}$ +53.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.40 (3H, s, CH_3), 1.40 (3H, s, CH_3), 3.62 (1H, dd, $J_{1,2}$ 4.4 Hz, $J_{1,1'}$ 10.6 Hz, H-1), 3.65 (1H, dd, $J_{1',2}$ 6.4 Hz, $J_{1,1'}$ 10.7 Hz, H-1′), 3.74 (1H, dd, $J_{4,5}$ 2.7 Hz, $J_{5,6}$ 8.1 Hz, H-5), 3.84 (1H, d, $J_{4,5}$ 2.6 Hz, H-4), 4.22 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{1',2}$ 6.4 Hz, H-2), 4.30, 4.61 (2H, 2 × d, *J* 12.1 Hz, PhC*H*$_2$), 4.42 (1H, at, *J* 7.7 Hz, H-6), 4.53, 4.68 (2H, 2 × d, *J* 11.9 Hz, PhC*H*$_2$), 4.55, 4.69 (2H, 2 × d, *J* 12.1 Hz, PhC*H*$_2$), 5.01 (1H, dat, J_{trans} 17.2 Hz, *J* 1.3 Hz, H-8$_{trans}$), 5.10 (1H, dat, J_{cis} 10.3 Hz, *J* 1.4 Hz, H-8$_{cis}$), 5.50 (1H, s, H-3a), 5.60 (1H, s, H-3a′), 5.68 (1H, ddd, $J_{6,7}$ 7.4 Hz, J_{trans} 17.4 Hz, J_{cis} 10.4 Hz, H-7), 7.26–7.39 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.9, 27.2 (2 × q, 2 × *C*H$_3$), 70.9, 71.2, 73.4 (3 × t, 3 × PhCH$_2$), 73.8 (t, C-1), 76.0 (d, C-4), 78.1 (d, C-2), 78.4 (d, C-6), 81.8 (d, C-5), 109.4 (s, *C*(O)$_2$(CH$_3$)$_2$), 116.3 (t, C-3a), 118.8 (t, C-8), 127.6, 127.7, 127.8, 127.8, 128.1, 128.4, 128.5, 128.5, 128.7 (9 × d, Ar-CH), 135.7 (d, C-7), 138.2, 138.5, 138.8 (3 × s, Ar-C), 144.0 (s, C-3); HRESIMS calcd for $C_{33}H_{38}O_5Na$ (MNa^+) 537.2611; found 537.2632.

3.6. (2*S*,4*S*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-3-methylene-oct-7-ene-1,2,4,5,6-pentaol (9)

Alkene **8** (3.64 g, 7.08 mmol) was suspended in acetic acid/water 7:4 (220 mL). 1 M HCl (20 mL) was added, and the reaction was left to stir at 80 °C. After 2.5 h, TLC (pentane–EtOAc, 10:1) showed formation of a product (R_f 0.1) and complete consumption of starting material (R_f 0.5). The reaction mixture was co-evaporated with toluene to give diol **9** (3.46 g, quantitative) as a colourless oil; $[\alpha]_D^{25}$ +65.6 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 3437 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.83 (1H, d, $J_{OH,6}$ 3.8 Hz, OH-6), 2.88 (1H, d, $J_{OH,5}$ 5.5 Hz, OH-5), 3.45 (1H, dat, $J_{4,5}$ 3.8 Hz, J_{at} 5.5 Hz, H-5), 3.61 (1H, dd, $J_{1,2}$ 4.9 Hz, $J_{1,1'}$ 10.2 Hz, H-1), 3.72 (1H, dd, $J_{1',2}$ 6.6 Hz, $J_{1,1'}$ 10.2 Hz, H-1′), 4.02 (1H, d, $J_{4,5}$ 3.7 Hz, H-4), 4.13 (2H, m, H-2, H-6), 4.24, 4.61 (2H, 2 × d, *J* 11.5 PhC*H*$_2$), 4.52, 4.53 (2H, 2 × d, *J* 11.8 Hz, PhC*H*$_2$), 4.59, 4.67 (2H, 2 × d, *J* 12.1 Hz, PhC*H*$_2$), 5.11–5.18 (2H, m, H-8$_{cis}$, H-8$_{trans}$), 5.51 (1H, s, H-3a), 5.59 (1H, s, H-3a′), 5.70 (1H, ddd, $J_{6,7}$ 7.1 Hz, J_{cis} 10.3 Hz, J_{trans} 17.2, H-7), 7.25–7.37 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 71.1, 71.3, 73.6 (3 × t, 3 × PhCH$_2$), 73.2, 78.5 (2 × d, C-2, C-4), 73.2 (t, C-1), 74.5 (d, C-5), 79.6 (d, C-6), 117.4 (t, C-8), 117.5 (t, C-3a), 127.8, 127.9, 127.9, 128.2, 128.3, 128.5, 128.7 (7 × d, Ar-CH), 136.1 (d, C-7), 137.2, 137.6, 138.1 (3 × s, Ar-C), 143.5 (s, C-3); HRESIMS calcd for $C_{30}H_{34}O_5Na$ (MNa^+) 497.2298; found 497.2282.

3.7. (2*S*,4*S*,5*S*,6*R*)-1,2,4-Tri-*O*-benzyl-5,6-di-*O*-acetyl-3-methylene-oct-7-ene-1,2,4,5,6-pentaol (10)

Diol **9** (3.28 g, 6.92 mmol) was dissolved in a 1:1 mixture of Ac_2O and pyridine (200 mL) and stirred for 18 h. TLC (toluene–EtOAc, 7:1) showed complete consumption of starting material (R_f 0) and the formation of a product (R_f 0.4). The solvents were removed in vacuo and co-evaporated with toluene (2 × 100 mL). The crude product was filtered through a plug of silica (EtOAc) to give diacetate **10** (3.86 g, quant.) as a yellowish oil; $[\alpha]_D^{25}$ +39.2 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 1747 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.00 (3H, s, C*H*$_3$), 2.04 (3H, s, C*H*$_3$), 3.60 (1H, dd, $J_{1,1'}$ 10.4 Hz, $J_{1,2}$ 4.4 Hz, H-1), 3.69 (1H, dd, $J_{1',2}$ 6.2 Hz, $J_{1,1'}$ 10.3 Hz, H-1′), 4.05 (1H, dd, $J_{1,2}$ 4.3 Hz, $J_{1',2}$ 6.0 Hz, H-2), 4.10 (1H, d, $J_{4,5}$ 3.5 Hz, H-4), 4.13, 4.60 (2H, 2 × d, *J* 11.7 Hz, PhC*H*$_2$), 4.54–4.56 (4H, m, 2 × PhC*H*$_2$), 5.09–5.17 (2H, m, H-8$_{cis}$, H-8$_{trans}$), 5.20 (1H, dd, $J_{4,5}$

3.5 Hz, $J_{5,6}$ 7.3 Hz, H-5), 5.43–5.52 (3H, m, H-7, H-3a, H-3a′), 5.61 (1H, m, H-6), 7.26–7.38 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.9, 21.1 (2 × q, 2 × *C*H$_3$), 70.9, 71.5, 73.6 (3 × t, 3 × PhCH$_2$), 73.3, 73.4 (t, d, C-1, C-5), 73.9 (d, C-6), 76.8 (d, C-4), 79.2 (d, C-2), 116.9 (t, C-3a), 120.0 (t, C-8), 127.6, 127.8, 127.8, 127.9, 128.0, 128.4, 128.5, 128.5 (8 × d, Ar-CH), 132.3 (d, C-7), 137.9, 138.2, 138.6 (3 × s, 3 × Ar-C), 142.8 (s, C-3), 169.8, 170.4 (2 × s, 2 × *C*=O); HRESIMS calcd for $C_{34}H_{38}O_7Na$ (MNa^+) 581.2510; found 581.2503.

3.8. 1,2-Di-*O*-acetyl-3,5,6-tri-*O*-benzyl-4a-carba-β-D-*xylo*-hex-4(4a)-enofuranose (11)

Diacetate **10** (2.99 g, 5.36 mmol) was dissolved in toluene (225 mL) under N_2 at 60 °C. Grubbs′ 2nd generation complex (23 mg, 0.027 mmol) was added and the reaction mixture was stirred at 60 °C. The formation of product (R_f 0.3) and consumption of starting material (R_f 0.4) was followed by TLC (pentane–EtOAc, 9:1). Further catalyst was added, a total amount of 161 mg (0.19 mmol) was added in seven portions (including the initial addition) over 47 h. The problem of coloured ruthenium residues co-eluting with the product was solved by adding DMSO after completion of the reaction. The complex formed between DMSO and ruthenium was immobile on silica during the normal chromatographic purification.[53] DMSO (670 μL, 9.4 mmol) was added to the solution and stirred for 24 h. The mixture was then concentrated in vacuo, and the residue purified by flash column chromatography (pentane–EtOAc, 8:1) to give cyclopentene **11** (2.46 g, 87%) as an oil; IR (Film) *ν* 1732 (C=O), 1739 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.09 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.71 (1H, dd, $J_{6,6'}$ 10.5 Hz, $J_{5,6}$ 6.9 Hz, H-6), 3.85 (1H, dd, $J_{6,6'}$ 10.5 Hz, $J_{5,6'}$ 3.6 Hz, H-6′), 4.32 (1H, m, H-5), 4.43 (1H, d, $J_{2,3}$ 2.9 Hz, H-3), 4.52, 4.68 (2H, 2 × d, *J* 11.7 Hz, PhC*H*$_2$), 4.54–4.63 (4H, m, 2 × PhC*H*$_2$), 5.35 (1H, at, *J* 2.9 Hz, H-2), 5.54 (1H, br s, H-1), 5.91 (1H, br s, H-4a), 7.26–7.39 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.1 (q, 2 × *C*H$_3$), 72.1, 72.3, 73.5 (3 × t, 3 × PhCH$_2$), 72.2 (t, C-6), 75.0 (d, C-5), 80.0 (d, C-1), 83.4 (d, C-2), 85.7 (d, C-3), 127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.5, 128.5, 128.6 (9 × d, Ar-CH, C-4a), 137.9, 138.4, 138.5 (3 × s, 3 × Ar-C), 146.2 (s, C-4), 170.2, 170.7 (2 × s, 2 × *C*=O); HRESIMS calcd for $C_{32}H_{34}O_7Na$ (MNa^+) 553.2197; found 553.2182.

3.9. 3,5,6-Tri-*O*-benzyl-4a-carba-β-D-*xylo*-hex-4(4a)-enofuranose (12)

3.9.1. Method 1: deprotection of diacetate 11

Diacetate **11** (604 mg, 1.14 mmol) was dissolved in MeOH (25 mL). A solution of NaOMe made from Na (20 mg, 0.87 mmol) and MeOH (20 mL) was added, and the reaction was left to stir at rt for 1 h. Dowex resin HCR-W2 was added until pH 4 was reached, after which the solution was filtered and concentrated in vacuo. The crude product was filtered through silica (EtOAc) to give diol **12** (514 mg, quant.) as white crystals; mp 74–76 °C (EtOAc–pentane); IR (Film) *ν* 3380, 3305 (OH) cm^{-1}; $[\alpha]_D^{25}$ +9.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.03 (2H, br s, OH-1, OH-2), 3.66 (1H, dd, $J_{6,6'}$ 10.7 Hz, $J_{5,6}$ 7.1 Hz, H-6), 3.79 (1H, dd, $J_{6,6'}$ 10.6 Hz, $J_{5,6'}$ 3.6 Hz, H-6′), 4.07 (1H, br s, H-2), 4.25 (1H, m, H-3), 4.29 (1H, m, H-5), 4.39 (1H, br s, H-1), 4.52, 4.66 (2H, 2 × d, *J* 12.2 Hz, PhC*H*$_2$), 4.56–4.61 (4H, m, 2 × PhC*H*$_2$), 5.84 (1H, s, H-4a), 7.23–7.33 (15H, m, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 71.9, 72.3, 73.5 (3 × t, 3 × PhCH$_2$), 72.3 (t, C-6), 75.0 (d, C-5), 79.8 (d, C-1), 87.0 (d, C-3), 87.4 (d, C-2), 127.8, 127.9, 127.9, 128.0, 128.4, 128.5, 128.6 (7 × d, Ar-CH), 130.5 (d, C-4a), 138.3, 138.4, 138.5 (3 × s, 3 × Ar-C), 142.9 (s, C-4); HRESIMS calcd for $C_{28}H_{30}O_5Na$ (MNa^+) 469.1985; found 469.1988.

3.9.2. Method 2: ring-closing metathesis of diene 9

Diene **9** (94 mg, 0.198 mmol) and Hoveyda–Grubbs 2nd generation complex (6 mg, 0.01 mmol) were dissolved in toluene (5 mL) under N_2 at 60 °C. After 1 h, TLC (pentane–EtOAc, 2:1) showed that all the starting material (R_f 0.5) had been consumed and that a major product was formed (R_f 0.3). The reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography (toluene–EtOAc, 3:2) to give unsaturated carbasugar **12** (38 mg, 43%) as white crystals identical to those described above.

3.10. 3,5,6-Tri-*O*-benzyl-4a-carba-β-D-galactofuranose (13)

Unsaturated cyclopentene diol **12** (510 mg, 1.14 mmol) was dissolved in EtOAc (13 mL), and Et_3N (90 μL, 0.65 mmol) and Pd/C (10%, 56 mg, 0.053 mmol) were added. The mixture was degassed and stirred under H_2. The reaction was followed by TLC (pentane–EtOAc, 4:5), but starting material and product had similar R_f values (0.4). After 2 h, the reaction mixture was filtered through Celite and concentrated in vacuo to give the saturated cyclopentadiol **13** (467 mg, 91%) as an oil; $[\alpha]_D^{25}$ −24.2 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 3401 (OH) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.78 (1H, m, H-4a), 2.04 (1H, ddd, *J* 6.0 Hz, *J* 7.8 Hz, $J_{4a,4a'}$ 13.7 Hz, H-4a′), 2.48 (1H, m, H-4), 3.48 (1H, dd, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 9.9 Hz, H-6), 3.62 (1H, dd, $J_{6,6'}$ 10.0 Hz, $J_{5,6'}$ 6.0 Hz, H-6′), 3.65 (1H, m, H-3), 3.78 (1H, m, H-5), 3.97–4.00 (2H, m, H-1, H-2), 4.45, 4.75 (2H, 2 × d, *J* 11.4 Hz, PhC*H*$_2$), 4.48, 4.52 (2H, 2 × d, *J* 11.8 Hz, PhC*H*$_2$), 4.53, 4.59 (2H, 2 × d, *J* 11.9 Hz, PhC*H*$_2$), 7.26–7.37 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 30.4 (t, C-4a), 44.4 (d, C-4), 71.8 (t, C-6), 72.2, 73.0, 73.6 (3 × t, 3 × PhCH$_2$), 77.5, 80.5 (2 × d, C-1, C-2), 77.8 (d, C-5), 87.0 (d, C-3), 127.7, 127.9, 128.0, 128.0, 128.1, 128.4, 128.6, 128.6 (8 × d, Ar-CH), 137.9, 138.1, 138.1 (3 × s, 3 × Ar-C); HRESIMS calcd for $C_{28}H_{32}O_5Na$ (MNa^+) 471.2142; found 471.2134.

3.11. 1,2-Di-*O*-acetyl-3,5,6-tri-*O*-benzyl-4a-carba-β-D-galactofuranose (14)

3.11.1. Method 1: acetylation of diol 13

Diol **13** (14 mg, 0.031 mmol) was dissolved in a 1:1 mixture of Ac_2O and pyridine (1 mL), and stirred at rt for 3 h. TLC (pentane–EtOAc, 1:1) showed complete consumption of starting material (R_f 0.2). The reaction mixture was co-evaporated with toluene and filtered through a plug of silica to give diacetate **14** (12 mg, 72%) as an oil; IR (Film) *ν* 1741 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.76 (1H, m, H-4a), 2.01, 2.05 (6H, 2 × s, 2 × C(O)CH$_3$), 2.13 (1H, ddd, $J_{1,4a'}$ 6.8 Hz, $J_{4,4a'}$ 11.0 Hz, $J_{4a,4a'}$ 14.2 Hz, H-4a′), 2.42 (1H, ddat, J_{at} 8.1 Hz, $J_{4,5}$ 3.4 Hz, $J_{4a',4}$ 11.3 Hz, H-4), 3.51 (1H, dd, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 10.0 Hz, H-6), 3.59 (1H, dd, $J_{5,6'}$ 6.2 Hz, $J_{6,6'}$ 10.0 Hz, H-6′), 3.75 (1H, m, H-5), 3.83 (1H, dd, $J_{2,3}$ 4.8 Hz, $J_{3,4}$ 8.2 Hz, H-3), 4.31, 4.71 (2H, 2 × d, *J* 11.6 Hz, PhC*H*$_2$), 4.33, 4.56 (2H, 2 × d, *J* 11.7 Hz, PhC*H*$_2$), 4.48, 4.53 (2H, 2 × d, *J* 12.1 Hz, PhC*H*$_2$), 5.00 (1H, dat, J_{at} 3.0 Hz, $J_{1,4a'}$ 6.8 Hz, H-1), 5.22 (1H, ddd, $J_{1,2}$ 3.2 Hz, $J_{2,3}$ 4.7 Hz, $J_{4a,2}$ 1.3 Hz, H-2), 7.27–7.38 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.2, 21.3 (2 × q, 2 × *C*H$_3$), 28.7 (t, C-4a), 44.7 (d, C-4), 72.3, 72.4, 73.0, 73.5 (4 × t, 3 × PhCH$_2$, C-6), 76.5 (d, C-5), 76.8 (d, C-1), 82.3 (d, C-2), 83.6 (d, C-3), 127.7, 127.7, 127.8, 127.9, 127.9, 128.2, 128.4, 128.5, 128.6 (9 × d, Ar-CH), 138.2, 138.3, 138.9 (3 × s, 3 × Ar-C), 170.0, 170.5 (2 × s, 2 × OC=O); HRESIMS calcd for $C_{32}H_{36}O_7Na$ (MNa^+) 555.2353; found 555.2368.

3.11.2. Method 2: reduction of cyclopentene 11

Cyclopentene diacetate **11** (29 mg, 0.055 mmol) was dissolved in EtOAc (5 mL) and Et_3N (20 μL, 0.14 mmol) was added. Pd/C (10%, 5 mg, 0.005 mmol) was added and all air in the reaction

vessel was removed by evacuation using N_2 before adding H_2 via balloon. The reaction was followed by TLC (pentane–EtOAc, 7:1), but the starting material and the major product had similar R_f values (0.3). After 1.5 h, the reaction mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by flash column chromatography (CH_2Cl_2–Et_2O, 15:1) to give cyclopentane diacetate **14** (14 mg, 49%) as an oil, identical to that described above.

Also a reduced product (12 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.53–2.14 (5H, m), 1.97 (3H, s, C(O)CH_3), 3.52 (1H, dd, *J* 4.4 Hz, *J* 10.0 Hz), 3.58 (1H, dd, *J* 6.4 Hz, *J* 10.0 Hz), 3.70 (1H, m), 3.77 (1H, dd, *J* 3.3 Hz, *J* 7.1 Hz), 4.36, 4.74 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.40, 4.62 (2H, 2 × d, *J* 12.0 Hz, PhCH_2), 4.47, 4.53 (2H, 2 × d, *J* 12.1 Hz, PhCH_2), 5.08 (1H, dat, J_{at} 3.4 Hz, *J* 6.7 Hz), 7.24–7.36 (15H, m, Ar-H); HRESIMS calcd for $C_{30}H_{34}O_5Na$ (MNa^+) 497.2298; found 497.2305.

3.12. 4a-Carba-β-D-galactofuranose (1)

3.12.1. Method 1: debenzylation of cyclopentane 13

Cyclopentanediol **13** (432 mg, 0.963 mmol) was dissolved in MeOH (7 mL), and Pd/C (10%, 70 mg, 0.066 mmol) was added. The mixture was degassed and stirred under H_2. After 7 h, TLC (CMAW) showed formation of a single product (R_f 0.2), and the reaction mixture was filtered through Celite and purified by flash column chromatography (CMAW) to give 4a-carba-β-D-galactofuranose **1** (179 mg, quant.) as an oil; $[\alpha]_D^{25}$ −15.6 (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ_H 1.67 (1H, m, H-4a), 1.96–2.05 (2H, m, H-4, H-4a′), 3.51 (1H, dd, $J_{5,6}$ 7.8 Hz, $J_{6,6'}$ 11.7 Hz, H-6), 3.62 (1H, dd, $J_{5,6'}$ 4.2 Hz, $J_{6,6'}$ 11.7 Hz, H-6′), 3.71–3.79 (3H, m, H-2, H-3, H-5), 3.90 (1H, m, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ_C 30.5 (t, C-4a), 45.1 (d, C-4), 66.4 (t, C-6), 73.5, 78.4, 85.5 (3 × d, C-2, C-3, C-5), 75.5 (d, C-1); HRESIMS calcd for $C_7H_{14}O_5Na$ (MNa^+) 201.0733; found 201.0728.

3.12.2. Method 2: hydrogenation of cyclopentene 12

Unsaturated diol **12** (57 mg, 0.128 mmol) was dissolved in EtOH/EtOAc 1:1 (25 mL) and Pd/C (10%, 25 mg, 0.023 mmol) was added. The mixture was degassed and stirred under H_2. After 18 h, TLC (pentane–EtOAc, 1:2) showed complete consumption of starting material (R_f 0.25) and product formation (R_f 0). TLC (CMAW) also showed formation of several by-products (R_f 0.5–0.9) as well as product formation (R_f 0.4). The reaction mixture was filtered through Celite, concentrated in vacuo and purified by column chromatography (CMAW) to give 4a-carba-β-D-galactofuranose **1** (11 mg, 48%) identical to that described above.

3.12.3. Method 3: hydrogenation of the unsaturated pentaol

Unsaturated diol **12** (30 mg, 0.067 mmol) was dissolved in THF (1 mL) and the reaction was cooled to −78 °C. $NH_{3(l)}$ (10 mL) was condensed into the flask, after which Na (54 mg, 2.3 mmol) was added in portions until a sustained deep blue colour was seen. After 20 min, MeOH (110 μL) was added and after a further 30 min, the reaction was quenched by the addition of $NH_4Cl_{(s)}$ (186 mg, 3.45 mmol). The solvent was allowed to slowly evaporate by allowing the mixture to reach rt. The crude product was partitioned between EtOAc and water, and the aqueous phase was evaporated. In order to remove salts, the residue was dissolved in EtOH and filtered through a plug of cotton wool. The solvent was removed in vacuo and the residue dissolved in pyridine/Ac_2O [1:1] (1 mL) with a catalytic amount of DMAP. After 18 h, TLC (toluene–EtOAc 1:1) showed formation of a major product (R_f 0.8). The reaction mixture was washed with 1 M HCl (3 × 5 mL) and the combined aqueous phases were extracted with EtOAc (3 × 10 mL). The organic extracts were then dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (toluene–EtOAc 2:1) to give the unsaturated pentaacetate (18 mg, 69%) as an oil; $[\alpha]_D^{25}$ −17.9 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 1744 (s, C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.06, 2.07, 2.08, 2.08, 2.09 (15H, 5 × s, 5 × CH_3), 4.11 (1H, dd, $J_{5,6}$ 7.3 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 4.48 (1H, dd, $J_{5,6'}$ 3.3 Hz, $J_{6,6'}$ 12.0 Hz, H-6′), 5.30 (1H, at, J_{at} 3.9 Hz, H-2), 5.55 (2H, m, H-1, H-5), 5.83 (1H, m, H-3), 5.95 (1H, s, H-4a); ^{13}C NMR (100 MHz, D_2O) δ_C 20.9, 20.9, 20.9, 21.0 (4 × q, CH_3), 63.7 (t, C-6), 67.0, 78.2 (2 × d, C-1, C-5), 78.4 (d, C-3), 82.9 (d, C-2), 129.8 (d, C-4a), 141.4 (s, C-4), 170.0, 170.1, 170.3, 170.4, 170.7 (5 × s, 5 × C=O).

Na (2 mg, 0.09 mmol) was added to MeOH (2 mL), and a solution of the unsaturated pentaacetate (18 mg, 0.047 mmol) in MeOH (1 mL) was added. The mixture was stirred at rt. After 2 h, 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 the pentaol (8 mg, quantitative) as an oil.

The pentaol (8 mg, 0.045 mmol) was dissolved in EtOH/H_2O [3:1] (4 mL). Pd/C (10%, 5 mg, 0.005 mmol) was added to the solution. All air was evacuated and the reaction was put under H_2. After 1.5 h, the mixture was filtered through Celite and all solvent was removed in vacuo to give the unprotected carbasugar **1** (8 mg, quant.) identical to that described above.

3.13. 1,2,3,5,6-Penta-*O*-acetyl-4a-carba-β-D-galactofuranose (15)

Unprotected carbasugar **1** (2 mg, 0.011 mmol) was suspended in a 1:1 mixture of Ac_2O and pyridine (1 mL) and stirred for 2 h, after which TLC (pentane–EtOAc, 1:1) showed consumption of starting material (R_f 0) and formation of a major product (R_f 0.6). The reaction mixture was concentrated in vacuo and purified by flash column chromatography (pentane–EtOAc, 2:1) to give peracetate **15** (3 mg, 69%) as an oil; IR (Film) *ν* 1743 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.90 (1H, ddd, $J_{1,4a}$ 2.4 Hz, $J_{4,4a}$ 8.6 Hz, $J_{4a,4a'}$ 14.5 Hz, H-4a), 2.05, 2.06, 2.06, 2.07, 2.10 (15H, 5 × s, 5 × CH_3), 2.17 (1H, m, H-4a′), 2.54 (1H, ddat, *J* 4.6 Hz, J_{at} 8.6 Hz, *J* 11.2 Hz, H-4), 4.01 (1H, dd, $J_{5,6}$ 6.5 Hz, $J_{6,6'}$ 11.9 Hz, H-6), 4.21 (1H, dd, $J_{5,6'}$ 4.2 Hz, $J_{6,6'}$ 11.9 Hz, H-6′), 5.02 (1H, m, H-3), 5.04 (1H, m, H-1), 5.17 (1H, m, H-5), 5.20 (1H, m, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 20.9, 21.0, 21.0, 21.0, 21.2 (5 × q, 5 × CH_3), 29.5 (t, C-4a), 41.8 (d, C-4), 64.0 (t, C-6), 69.4 (d, C-5), 75.3 (d, C-1), 76.6 (d, C-3), 81.1 (d, C-2), 170.3, 170.5, 170.7 (3 × s, 5 × *C*=O); HRESIMS calcd for $C_{17}H_{24}O_{10}Na$ (MNa^+) 411.1262; found 411.1251.

3.14. 3,5,6-Tri-*O*-benzyl-1,2-di-*O*-(2-naphthoyl)-4a-carba-β-D-galactofuranose (16)

Cyclopentanediol **13** (183 mg, 0.408 mmol) was suspended in pyridine (10 mL) and 2-naphthoyl chloride (311 mg, 1.63 mmol) was added at rt. A catalytic amount of DMAP (3 mg, 0.024 mmol) was added and the reaction was heated to 50 °C. After 18 h, TLC (toluene–EtOAc, 10:1) showed formation of a major product (R_f 0.6) but no starting material (R_f 0). The reaction mixture was co-evaporated with toluene and purified by flash column chromatography (toluene–EtOAc, 10:1) to give dinaphthoate **16** (279 mg, 90%); IR (Film) *ν* 1717 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.07 (1H, dd, $J_{4,4a}$ 7.9 Hz, $J_{4a,4a'}$ 14.2 Hz, H-4a), 2.41 (1H, ddd, $J_{4,4a'}$ 11.3 Hz, $J_{4a',1}$ 6.1 Hz, $J_{4a,4a'}$ 14.2 Hz, H-4a′), 2.68 (1H, ddat, J_{at} 7.8 Hz, $J_{4,5}$ 3.4 Hz, $J_{4,4a'}$ 11.3 Hz, H-4), 3.57 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.0 Hz, H-6), 3.66 (1H, dd, $J_{5,6'}$ 6.2 Hz, $J_{6,6'}$ 10.0 Hz, H-6′), 3.87 (1H, m, H-5), 4.11 (1H, dd, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 7.7 Hz, H-3), 4.46, 4.85 (2H, 2 × d, *J* 11.6 Hz, PhCH_2), 4.53, 4.84 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.57, 4.63 (2H, 2 × d, *J* 12.1 Hz, PhCH_2), 5.50 (1H, dat, J_{at} 3.0 Hz, $J_{4a',1}$ 6.1 Hz, H-1), 5.75 (1H, m, H-2), 7.20–7.31 (15H, m, Ar-H), 7.52–7.64 (4H, m, Ar-H), 7.87–7.95 (6H, m, Ar-H), 8.06 (1H, dd, *J* 1.7 Hz, *J* 8.6 Hz, Ar-H), 8.08 (1H, dd, *J* 1.7 Hz, *J* 8.6 Hz, Ar-H), 8.60 (1H, s, Ar-H), 8.64 (1H, s, Ar-H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ_C 29.5 (t, C-4a), 45.6 (d, C-4), 72.3, 72.4 (2 × t, C-6, $PhCH_2$), 73.1, 73.5 (2 × t, 2 × $PhCH_2$), 76.7 (d, C-5), 77.8 (d, C-1), 82.4 (d, C-2), 84.2 (d, C-3), 125.4, 125.5, 126.2, 126.7, 126.8, 127.1, 127.2, 127.4, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.9, 129.1, 129.3, 129.5, 129.6, 129.7, 131.5, 132.5, 132.6 (30 × d, s, Ar-CH, Ar-C), 135.7, 135.7, 138.1, 138.2, 138.8 (5 × s, Ar-C), 165.6, 166.0 (2 × s, 2 × C=O); HRESIMS calcd for $C_{50}H_{44}O_7Na$ (MNa^+) 779.2979; found 779.2979.

3.15. 4a-Carba-α-L-arabinofuranose (17)

Dinaphthoate **16** (270 mg, 0.357 mmol) was dissolved in EtOAc/EtOH (6:1, 7 mL) and Pd/C (10%, 60 mg, 0.056 mmol) was added. HCl (1 M, 0.1 mL) was added, and the mixture was degassed and stirred under H_2. The reaction mixture was allowed to stir at rt for 5 days as the deprotection was very slow. Product formation (R_f 0) was followed by TLC (toluene–EtOAc, 10:1). When all starting materials (R_f 0.8) had been fully debenzylated, the mixture was filtered through Celite and concentrated in vacuo to afford a crude product that was purified by flash column chromatography (toluene–EtOAc, 1:1) to give a triol (87 mg, 50%).

The triol (87 mg, 0.179 mmol) was dissolved in dioxane/H_2O (2:1) (6 mL) and cooled to 0 °C. The reaction mixture was protected from light by aluminium foil. A solution of $NaIO_4$ (76 mg, 0.357 mmol) in H_2O (0.5 mL) was added and the reaction was stirred for 1 h at 0 °C. TLC (EtOAc) showed formation of a possible aldehyde (R_f 0.9) and no starting material (R_f 0.2). $NaBH_4$ (27 mg, 0.72 mmol) in H_2O (0.5 mL) was added and the reaction was stirred at rt. After 2 h, TLC (EtOAc) showed formation of a new product (R_f 0.7). The white/grey reaction mixture was quenched at 0 °C by addition of AcOH (1 mL), after which the solution turned yellow then deep orange. All solvents were removed in vacuo to afford a white solid. The crude product was stirred with NaOMe (from MeOH (9 mL) and Na (82 mg, 3.6 mmol)) at 50 °C for 3 h to completely remove the naphthoates. The reaction was quenched by the addition of Dowex Resin HCR-W2 and the crude product (R_f 0.4, CMAW) was purified by flash column chromatography (CMAW) to afford 4a-carba-α-L-arabinofuranose **17** (21 mg, 80% over three steps; 40% from **16**); $[\alpha]_D^{25}$ −39.8 (*c* 1.0, MeOH), lit.[47] $[\alpha]_D^{16}$ −40.5 (*c* 0.84, MeOH); ^1H NMR (400 MHz, CD_3OD) δ_H 1.74 (1H, ddd, *J* 6.2 Hz, *J* 10.0 Hz, $J_{4a,4a'}$ 13.7 Hz, H-4a), 1.86 (1H, dat, J_{at} 7.8 Hz, $J_{4a,4a'}$ 13.7 Hz, H-4a′), 2.05 (1H, m, H-4), 3.52 (2H, m, H-3, H-5), 3.65 (2H, m, H-2, H-5′), 3.83 (1H, dat, J_{at} 6.3 Hz, $J_{1,4a'}$ 8.0 Hz, H-1); ^{13}C NMR (100 MHz, CD_3OD) δ_C 33.2 (C-4a), 45.1 (C-4), 64.7 (C-5), 75.6 (C-1), 78.8 (C-3), 85.7 (C-2).

3.16. 3,5,6-Tri-*O*-benzyl-1-*O*-ethyl-4a-carba-β-D-galactofuranose (19a)

Epoxide **18** (12 mg, 0.028 mmol) was dissolved in CH_2Cl_2 (2 mL), and EtOH (16 μL, 0.28 mmol) was added under N_2 at rt. $BF_3{\cdot}Et_2O$ (14 μL, 0.11 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and 0.5 mL (5.5 μmol $BF_3{\cdot}Et_2O$) of this solution was transferred to the colourless reaction mixture, which then immediately turned yellow and within minutes dark orange. The reaction was stirred under N_2 for 18 h, after which time TLC (toluene–EtOAc, 6:1) showed complete consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.2). The reaction was quenched by addition of $NaHCO_3$ (satd aq, 2 mL) and washed with $NaHCO_3$ (satd aq, 3 × 10 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (toluene–EtOAc, 10:1) to give ethyl ether **19a** (10 mg, 75%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.18 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.60 (1H, ddd, $J_{1,4a}$ 5.8 Hz, $J_{4,4a}$ 10.2 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a), 2.03 (1H, dat, J_{at} 7.8 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a′), 2.28 (1H, ddat, J_{at} 7.7 Hz, $J_{4,5}$ 3.1 Hz, $J_{4,4a}$ 10.4 Hz, H-4), 3.44–3.52 (3H, m, H-6, CH_2CH_3), 3.56–3.61 (2H, m, H-1, H-6′), 3.66 (1H, at, *J* 7.3 Hz, H-3), 3.74 (1H, ddd, *J* 4.7 Hz, $J_{4,5}$ 3.1 Hz, *J* 6.3 Hz, H-5), 4.00 (1H, at, *J* 6.4 Hz, H-2), 4.40, 4.73 (2H, 2 × d, *J* 11.6 Hz, $PhCH_2$), 4.49 (1H, d, *J* 12.1 Hz, PhCHH′), 4.51 (1H, d, *J* 12.1 Hz, PhCHH′), 4.54 (1H, d, *J* 12.7 Hz, PhCHH′), 4.62 (1H, d, *J* 11.9 Hz, PhCHH′), 7.27–7.35 (15H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.6 (q, CH_2CH_3), 26.9 (t, C-4a), 42.8 (d, C-4), 64.8 (t, CH_2CH_3), 72.4, 72.5 (2 × t, C-6, $PhCH_2$), 73.0, 73.5 (2 × t, 2 × $PhCH_2$), 77.1 (d, C-5), 82.3 (d, C-2), 82.7 (d, C-1), 84.4 (d, C-3), 127.7, 127.7, 127.7, 127.8, 128.0, 128.1, 128.5, 128.5, 128.5 (9 × d, Ar-CH), 138.4, 138.8, 138.9 (3 × s, 3 × Ar-C); HRESIMS calcd for $C_{30}H_{36}O_5Na$ (MNa^+) 499.2455; found 499.2461.

3.17. Methyl 3,5,6-tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (19d)

Epoxide **18** (133 mg, 0.309 mmol) and rhamnose alcohol **22** (217 mg, 0.994 mmol) were dissolved in CH_2Cl_2 (1.25 mL) at rt under N_2. $BF_3{\cdot}Et_2O$ (39 μL, 0.309 mmol) was dissolved in dry CH_2Cl_2 (1.25 mL) and 125 μL (30.9 μmol $BF_3{\cdot}Et_2O$) of this solution was transferred to the colourless reaction mixture. After 30 min, TLC (toluene–EtOAc, 3:1) showed complete consumption of the epoxide (R_f 0.9) and formation of a major product (R_f 0.5) as well as remaining alcohol (R_f 0.1). 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 (toluene–EtOAc, 4:1) to give pseudodisaccharide **19d** (105 mg, 52%) as an oil; $[\alpha]_D^{25}$ −48.9 (*c* 1.0, $CHCl_3$); IR (Film) *ν* 3455 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.23 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6), 1.37, 1.56 (6H, 2 × s, $C(CH_3)_2$), 1.62 (1H, ddd, $J_{1,4a}$ 7.0 Hz, $J_{4,4a}$ 10.5 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a^{II}), 2.10 (1H, ddd, *J* 6.9 Hz, *J* 8.5 Hz, $J_{4a,4a'}$ 13.6 Hz, H-4a′^{II}), 2.22 (1H, ddat, J_{at} 7.1 Hz, *J* 3.3 Hz, $J_{4,4a}$ 11.0 Hz, H-4^{II}), 3.11 (1H, dd, *J* 7.2 Hz, *J* 9.9 Hz, H-4^{I}), 3.36 (3H, s, OCH_3), 3.48 (1H, dd, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 10.0 Hz, H-6^{II}), 3.54–3.58 (2H, m, H-5^{I}, H-6′^{II}), 3.68–3.75 (3H, m, H-1^{II}, H-3^{II}, H-5^{II}), 4.07 (1H, at, *J* 7.1 Hz, H-2^{II}), 4.13–4.21 (2H, m, H-2^{I}, H-3^{I}), 4.37, 4.71 (2H, 2 × d, *J* 11.6 Hz, $PhCH_2$), 4.48, 4.53 (2H, 2 × d, *J* 12.1 Hz, $PhCH_2$), 4.50, 4.82 (2H, 2 × d, *J* 11.7 Hz, $PhCH_2$), 4.84 (1H, s, H-1^{I}), 7.24–7.26 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.5 (q, C-6^{I}), 26.2, 27.9 (2 × q, $C(CH_3)_2$), 27.6 (t, C-4a^{II}), 41.9 (d, C-4^{II}), 54.9 (q, OCH_3), 64.7 (d, C-5^{I}), 72.2, 72.5, 73.0, 73.5 (4 × t, 3 × $PhCH_2$, C-6^{II}), 76.1, 78.6 (2 × d, C-2^{I}, C-3^{I}), 77.4, 83.3, 87.1 (3 × d, C-1^{II}, C-3^{II}, C-5^{II}), 84.3, 84.5 (2 × d, C-4^{I}, C-2^{II}), 98.0 (d, C-1^{I}), 109.7 (s, $C(CH_3)_2$), 127.6, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.4, 128.5 (9 × d, Ar-CH), 138.4, 139.0, 139.0 (3 × s, Ar-C); HRESIMS calcd for $C_{38}H_{48}O_9Na$ (MNa^+) 671.3191; found 671.3166.

Also obtained was the pseudotrisaccharide **25d** (30 mg, ca. 18%), but this was not obtained completely pure; HRESIMS calcd for $C_{66}H_{78}O_{13}Na$ (MNa^+) 1101.5335; found 1101.5317.

Pseudotrisaccharide **25d** (25 mg, 0.023 mmol) was dissolved in 80% AcOH and heated to 70 °C. After 4 h, TLC (toluene–EtOAc, 3:1) showed complete consumption of starting material (R_f 0.6) and formation of a major product (R_f 0.1). The reaction mixture was co-evaporated with toluene to yield a residue that was purified by flash column chromatography (toluene–EtOAc, 1:1) to give pseudotrisaccharide triol **26** (13 mg, 54%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6^{I}), 1.62–1.70 (2H, m, H-4a^{x}, H-4a^{y}), 1.93 (1H, dat, J_{at} 6.4, $J_{4a,4a'}$ 13.4 Hz, H-4a′^{x}), 2.11 (1H, dat, J_{at} 7.8 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a′^{y}), 2.25 (1H, m, H-4^{y}), 2.34 (1H, m, H-4^{x}), 3.24 (1H, at, J_{at} 9.3 Hz, H-4^{I}), 3.33 (3H, s, OCH_3), 3.43–3.49 (2H, m, H-6^{x}, H-6′^{y}), 3.54–3.67 (5H, m, H-5^{I}, H-5^{x}, H-5^{y}, H-6′^{x}, H-6′^{y}), 3.69–3.98 (8H, m, H-2^{I}, H-3^{I}, H-1^{x}, H-1^{y}, H-2^{x}, H-2^{y}, H-3^{x}, H-3^{y}), 4.35–4.72 (12H, m, 6 × $PhCH_2$), 4.63 (1H, m (obs), H-1^{I}), 7.23–7.36 (30H, m, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 17.9 (q, C-6^{I}), 27.1 (t, C-4a^{y}), 28.8 (C-4a^{x}), 42.4 (d, C-4^{y}), 43.4 (d,

C-4^{x}), 54.9 (q, OCH_3), 66.8 (d, C-5^{I}), 71.1 (d, C-2^{I}), 71.5 (d, C-3^{I}), 71.8, 72.2, 72.4, 72.6, 72.6, 73.0, 73.5, 73.5 (8 × t, 6 × PhCH_2, C-6^{x}, C-6^{y}), 77.2, 78.0, 82.9, 83.3, 83.4, 83.5, 84.9, 87.2 (8 × d, C-1^{x}, C-1^{y}, C-2^{x}, C-2^{y}, C-3^{x}, C-3^{y}, C-5^{x}, C-5^{y}), 81.7 (d, C-4^{I}), 100.4 (d, C-1^{I}), 127.7, 127.7, 127.8, 128.1, 128.1, 128.2, 128.4, 128.5, 128.5, 128.6, 128.6, 129.2 (12 × d, Ar-CH), 137.5, 138.2, 138.4, 138.7, 138.8, 138.9 (6 × s, 6 × Ar-C); HRESIMS calcd for $C_{63}H_{74}O_{13}Na$ (MNa^+) 1061.5022; found 1061.4981.

The descriptor '*x*' refers arbitrarily to one of the carbasugars 'II' or 'III'; '*y*' refers to the other.

3.18. General procedure for acetylation

Alcohol **19** was dissolved in a mixture of Ac_2O and pyridine, and stirred at rt. 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 **20**.

3.19. 2-*O*-Acetyl-3,5,6-tri-*O*-benzyl-1-*O*-ethyl-4a-carba-β-D-galactofuranose (20a)

Ethyl ether **19a** (24 mg, 0.050 mmol) was converted with Ac_2O/pyridine [1:1] (5 mL) into its acetate **20a** (23 mg, 89%), an oil (R_f 0.5, toluene–EtOAc, 8:1), according to the general procedure; IR (Film) ν 1724 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.18 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.75 (1H, ddat, J_{at} 1.8 Hz, $J_{4,4a}$ 7.8 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a), 1.90 (1H, ddd, $J_{1,4a'}$ 6.0 Hz, $J_{4,4a'}$ 11.4 Hz, $J_{4a,4a'}$ 13.5 Hz, H-4a′), 2.03 (3H, s, C(O)CH_3), 2.42 (1H, ddat, $J_{4,5}$ 3.4 Hz, J_{at} 7.9 Hz, $J_{4,4a'}$ 11.4 Hz, H-4), 3.40–3.61 (4H, m, CH_2CH_3, H-6, H-6′), 3.64 (1H, m, H-1), 3.75 (1H, dat, J_{at} 4.0 Hz, *J* 6.2 Hz, H-5), 3.79 (1H, dd, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 8.2 Hz, H-3), 4.32, 4.75 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.34, 4.56 (2H, 2 × d, *J* 11.8 Hz, PhCH_2), 4.49, 4.53 (2H, 2 × d, *J* 12.0 Hz, PhCH_2), 5.16 (1H, m, H-2), 7.24–7.35 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.6 (q, CH_2CH_3), 26.9 (t, C-4a), 42.8 (d, C-4), 64.8 (t, CH_2CH_3), 72.4, 72.5 (2 × t, C-6, PhCH_2), 73.0, 73.5 (2 × t, 2 × PhCH_2), 77.1 (d, C-5), 82.3 (d, C-2), 82.7 (d, C-1), 84.4 (d, C-3), 127.7, 127.7, 127.7, 127.8, 128.0, 128.1, 128.5, 128.5, 128.5 (9 × d, Ar-CH), 138.4, 138.8, 138.9 (3 × s, 3 × Ar-C); HRESIMS calcd for $C_{32}H_{38}O_6Na$ (MNa^+) 541.2561; found 541.2551.

3.20. Methyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-4a-carba-β-D-galactofuranosyl-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (20d)

Pseudodisaccharide **19d** (12 mg, 0.018 mmol) was converted with Ac_2O/pyridine (4 mL) and DMAP (1 mg, 0.008 mmol) into its acetate **20d** (11 mg, 86%), an oil (R_f 0.7, toluene–EtOAc, 6:1), according to the general procedure; $[\alpha]_D^{25}$ −56.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.24 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6^{I}), 1.30, 1.50 (6H, 2 × s, $C(CH_3)_2$), 1.81–1.90 (2H, m, H-4a^{II}, H-4a′^{II}), 2.05 (3H, s, C(O)CH_3), 2.39 (1H, ddat, J_{at} 7.9 Hz, *J* 3.7 Hz, *J* 11.1 Hz, H-4^{II}), 3.21 (1H, dd, *J* 6.9 Hz, *J* 9.8 Hz, H-4^{I}), 3.34 (3H, s, OCH_3), 3.50 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 10.0 Hz, H-6^{II}), 3.55–3.61 (2H, m, H-5^{I}, H-6′^{II}), 3.70–3.76 (2H, m, H-3^{II}, H-5^{II}), 4.07–4.13 (3H, m, H-2^{I}, H-3^{I}, H-1^{II}), 4.30, 4.72 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.33, 4.63 (2H, 2 × d, *J* 11.8 Hz, PhCH_2), 4.48, 4.53 (2H, 2 × d, *J* 12.1 Hz, PhCH_2), 4.83 (1H, s, H-1^{I}), 5.28 (1H, br s, H-2^{II}), 7.24–7.32 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 17.9 (q, C-6^{I}), 21.4 (q, C(O)CH_3), 26.4, 28.1 (2 × q, $C(CH_3)_2$), 28.5 (t, C-4a^{II}), 45.3 (d, C-4^{II}), 54.9 (q, OCH_3), 64.6 (d, C-5^{I}), 71.9, 73.1, 73.5 (3 × t, 3 × PhCH_2), 73.0 (t, C-6^{II}), 76.1, 78.3, 81.8 (3 × d, C-2^{I}, C-3^{I}, C-1^{II}), 77.4, 84.4 (2 × d, C-3^{II}, C-5^{II}), 79.9 (d, C-4^{I}), 82.2 (d, C-2^{II}), 98.2 (d, C-1^{I}), 109.2 (s, $C(CH_3)_2$), 127.5, 127.7, 127.7, 127.8, 128.3, 128.4, 128.5 (7 × d, Ar-CH), 138.4, 138.5, 139.1 (3 × s, 3 × Ar-C), 170.0 (s, C=O); HRESIMS calcd for $C_{40}H_{50}O_{10}Na$ (MNa^+) 713.3296; found 713.3274.

3.21. 3,5,6-Tri-*O*-benzyl-1,2-di-*O*-ethyl-4a-carba-β-D-galactofuranose (21)

3.21.1. Method 1: alkylation of alcohol 19a

Alcohol **19a** (35 mg, 0.073 mmol) was dissolved in DMF (2 mL) at rt under N_2. At 0 °C, NaH (60% in oil, 33 mg, 0.83 mmol) was added and stirred for a few minutes after which bromoethane (67 μL, 0.90 mmol) was added at rt. The reaction was left to stir under N_2 at rt. After 4 h, TLC (toluene–EtOAc, 7:1) showed complete consumption of alcohol (R_f 0.4) and the formation of a major product (R_f 0.8). The reaction was quenched by the addition of EtOH (5 mL) at 0 °C and the mixture was concentrated in vacuo until a slurry remained. The mixture was partitioned between Et_2O (10 mL) and brine (3 × 10 mL). The aqueous phases were extracted with Et_2O (2 × 10 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product (50 mg) was purified by flash column chromatography (toluene–EtOAc, 12:1) to give ether **21** (17 mg, 46%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.18 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.23 (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.66 (1H, ddd, $J_{1,4a}$ 3.6 Hz, $J_{4,4a}$ 8.5 Hz, $J_{4a,4a'}$ 13.6 Hz, H-4a), 1.92 (1H, ddd, $J_{1,4a'}$ 7.2 Hz, $J_{4,4a'}$ 10.2 Hz, $J_{4a,4a'}$ 13.6 Hz, H-4a′), 2.27 (1H, m, H-4), 3.43–3.74 (10H, m, 2 × CH_2CH_3, H-1, H-2, H-3, H-5, H-6, H-6′), 4.37, 4.70 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.45, 4.67 (2H, 2 × d, *J* 11.7 Hz, PhCH_2), 4.48, 4.53 (2H, 2 × d, *J* 12.1 Hz, PhCH_2), 7.25–7.32 (15H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 15.7, 15.9 (2 × q, 2 × CH_2CH_3), 27.8 (t, C-4a), 43.2 (d, C-4), 64.4, 65.6 (2 × t, 2 × CH_2CH_3), 72.1, 72.9, 73.1, 73.5 (4 × t, 3 × PhCH_2, C-6), 77.4, 81.8, 83.9, 90.4 (4 × d, C-1, C-2, C-3, C-5), 127.5, 127.6, 127.7, 127.7, 128.0, 128.1, 128.4, 128.4, 128.5 (9 × d, Ar-CH), 138.6, 139.0, 139.2 (3 × s, 3 × Ar-C); HRESIMS calcd for $C_{32}H_{40}O_5Na$ (MNa^+) 527.2768; found 527.2786.

3.21.2. Method 2: alkylation of diol 13

Diol **13** (14 mg, 0.031 mmol) was dissolved in DMF (2 mL) and NaH (60% in oil, 8 mg, 0.2 mmol) was added at 0 °C under N_2. Bromoethane (23 μL, 0.31 mmol) was added. The reaction was stirred at rt for 5 d, after which time TLC (toluene–EtOAc, 7:1) showed that all starting material (R_f 0) was consumed and that a major product (R_f 0.7) had been formed. The reaction was quenched by the addition of NH_4Cl (satd aq, 2 mL). Et_2O (10 mL) was added, and the organic phase was washed with brine (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. An impure crude product was purified by flash column chromatography (toluene–EtOAc, 7:1) to give ether **21** (7 mg, 45%) as an oil, identical to that described above.

3.22. 3,5,6-Tri-*O*-benzyl-1-deoxy-1-*S*-ethyl-1-thio-4a-carba-β-D-galactofuranose (27)

Na (80 mg, 3.49 mmol) was added to MeOH (4 mL) at rt under N_2. Ethanethiol (172 μL, 2.33 mmol) was added via syringe. Epoxide **18** (100 mg, 0.233 mmol) was dissolved in MeOH (2 mL) and added to the reaction mixture by syringe. After 5 days, TLC (toluene–EtOAc, 6:1) showed a complete consumption of epoxide (R_f 0.6) and formation of a major product (R_f 0.4). $NaHCO_3$ (satd aq, 5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with $NaHCO_3$ (satd aq 2 × 10 mL). The combined aqueous phases were acidified by addition of 1 M HCl (5 mL) and then once again extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (toluene–EtOAc, 12:1)

to give thioether **27** (78 mg, 68%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, t, *J* 7.3 Hz, C*H*$_3$), 1.72 (1H, m, H-4a), 2.19–2.28 (2H, m, H-4, H-4a′), 2.57 (2H, m, C*H*$_2$CH$_3$), 2.89 (1H, aq, *J* 8.3 Hz, H-1), 3.51 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 9.9 Hz, H-6), 3.61 (1H, dd, $J_{5,6}$ 6.2 Hz, $J_{6,6'}$ 9.8 Hz, H-6′), 3.71–3.76 (2H, m, H-3, H-5), 3.91 (1H, at, *J* 7.4 Hz, H-2), 4.41 (1H, d, *J* 11.6 Hz, PhC*H*H′), 4.50–4.58 (3H, m, PhC*H*$_2$, PhC*H*H′), 4.71–4.76 (2H, m, 2 × PhCH*H*′), 7.28–7.39 (15H, m, Ar-H); ^{1}H NMR (100 MHz, $CDCl_3$) δ_C 15.2 (q, CH$_3$), 25.1 (t, *C*H$_2$CH$_3$), 28.7 (t, C-4a), 43.2 (d, C-4), 48.1 (d, C-1), 72.2, 72.3, 72.9, 73.4 (4 × d, 3 × PhCH$_2$, C-6), 77.4, 85.4 (2 × d, C-3, C-5), 82.3 (d, C-2), 127.6, 127.7, 127.7, 128.0, 128.1, 128.4, 128.5, 128.5 (8 × d, Ar-CH), 138.3, 138.7, 138.7 (3 × s, 3 × Ar-C); HRE-SIMS calcd for $C_{30}H_{36}O_4NaS$ (MNa^+) 515.2227; found 515.2229.

Thioether **27** (3 mg, 6 mol) was dissolved in a mixture of Ac_2O (1 mL) and pyridine (1 mL) and the mixture was stirred for 3 h. After this time, TLC (toluene–EtOAc, 8:1) showed complete consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.7). The reaction was concentrated in vacuo and co-evaporated with toluene (2 × 10 mL). The residue was purified by column chromatography (toluene–EtOAc, 10:1) to give acetate **28** (3 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.24 (3H, t, *J* 7.5 Hz, CH$_2$C*H*$_3$), 1.74 (1H, ddd, $J_{1,4a}$ 5.0 Hz, $J_{4,4a}$ 8.4 Hz, $J_{4a,4a'}$ 13.3 Hz, H-4a), 2.02 (3H, s, C(O)CH$_3$), 2.17 (1H, m, H-4a′), 2.40 (1H, m, H-4), 2.60 (2H, m, C*H*$_2$CH$_3$), 3.05 (1H, br s, H-1), 3.49 (1H, dd, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 10.0 Hz, H-6), 3.56 (1H, dd, $J_{5,6'}$ 6.3 Hz, H-6′), 3.69 (1H, m, H-5), 3.80 (1H, dd, $J_{2,3}$ 4.2 Hz, $J_{3,4}$ 7.6 Hz, H-3), 4.28, 4.71 (2H, 2 × d, *J* 11.7 Hz, PhC*H*$_2$), 4.35, 4.57 (2H, 2 × d, *J* 11.9 Hz, PhC*H*$_2$), 4.47, 4.53 (2H, 2 × d, *J* 12.1 Hz, PhC*H*$_2$), 5.17 (1H, at, *J* 4.3 Hz, H-2), 7.24–7.36 (15H, m, Ar-H); ^{1}H NMR (100 MHz, $CDCl_3$) δ_C 21.4 (q, C(O)*C*H$_3$), 29.9 (t, C-4a), 45.6 (d, C-4), 72.1, 73.1, 73.5 (3 × t, 3 × PhCH$_2$), 72.7 (t, C-6), 77.4 (d, C-5), 82.5 (d, C-2), 84.8 (d, C-3), 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 128.5, 128.6 (8 × d, Ar-CH), 138.3, 138.4, 139.0 (3 × s, 3 × Ar-C), 170.2 (s, C=O).

3.23. Crystal structure of compound 12

CCDC-797053 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The crystals were measured at beamline I911-5 at Maxlab, Lund, Sweden with traditional data collection methods at 100 K. The tiny needle-shaped crystals did not diffract significantly above approximately 1 Å resolution. The structure crystallises in the monoclinic space group $P2_1$ and contains two molecules per asymmetric unit. The phenyl rings were refined as rigid bodies allowed to rotate around the pivot atoms. Considerable disorder was still left at T = 100 K, maybe of static character. The packing of the molecules is characterised by alternating regions of mainly hydrophobic interactions between phenyl groups and regions of considerably more hydrophilic character with interactions between the hydroxy groups and other oxygen atoms.

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Supplementary data

Supplementary data (experimental procedures and characterisation data for **19b,c,e,f** and **20b,c,e,f** and ^{1}H NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.04.032.

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