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C-Glycosylidene derivatives (*exo*-glycals): their synthesis by reaction of protected sugar lactones with tributylphosphonium ylids, conformational analysis and stereoselective reduction

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Abstract—Stabilised tributylphosphonium ylids $Bu_3PCH{=}CH(EWG)$, where EWG is CO_2Me, CO_2^tBu or CN, react with protected sugar lactones under mild conditions to give high yields of glycosylidene derivatives (**4** and **5**) with good *Z*/*E* selectivity. X-Ray crystallography shows that in the solid state the tetra-*O*-benzyl protected (*Z*)-glucosylideneacetonitrile (*Z*)-**4c** adopts a conformation intermediate between a boat and a twist-boat, whereas the isomeric galactose derivative (*Z*)-**5c** exists as a distorted chair. NMR data suggest that in solution chair-like conformations are again more favoured for galactosylidene derivatives than for their glucosylidene analogues. Solution phase NMR studies and molecular modelling show that the (*E*)-double bond geometry disfavours the chair-like geometry of the ring, even in the galactose series; this is consistent with the avoidance of allylic 1,3-strain. Reduction of the glycosylidene double bond to give stereoselective formation of β-*C*-glycoside derivatives may be achieved by using $Et_3SiH-CF_3CO_2H$ or $Et_3SiH-BF_3{\cdot}Et_2O$.

1. Introduction

A growing awareness of the importance of carbohydrate residues as recognition elements in biology has been coupled with impressive progress in the development of methodology for the synthesis of natural oligosaccharides and glycopeptides. However, such substances are generally less straightforward to prepare than simple peptides and the presence of relatively labile *O*- or *N*-glycosidic linkages can be a source of particular difficulty. Consequently several research groups have investigated the attachment of amino acid functionality through robust *C*-glycosidic linkages, thus allowing the use of established methods in peptide synthesis to construct unnatural compounds which display multiple carbohydrate residues.[1]

There are many possible ways to create the key *C*-glycosidic bond, including the use of transition metals and free radicals. Elegant work by Taylor et al. has shown the versatility of the Ramberg–Bäcklund rearrangement in preparing carbohydrate analogues with an exocyclic carbon–carbon double bond,[2] which are usually referred to as glycosylidenes or *exo*-glycals. Arguably the most common approach to *C*-glycosides is by attack of a carbon nucleophile at the anomeric position of a sugar derivative. For example, protected sugars such as 2,3,4,6-tetra-*O*-benzylglucopyranose can undergo a one pot Wittig-conjugate addition sequence on treatment with tributylphosphine, methyl bromoacetate and zinc metal, leading to stereoselective formation of β-*C*-glycosides.[3] Kishi has shown that addition of lithium enolates to protected sugar lactones, followed by deoxygenation of the resultant lactols using triethylsilane–boron trifluoride can give glycopyranosylacetic acid derivatives with high selectivity for the β-anomer.[4] Dehydration of these same lactols also provides a route to *exo*-glycals.[5] The groups of Chapleur[6] and Xie[7] have prepared glycosylidenes directly from protected sugar lactones by means of non-classical Wittig reactions[8] with stabilised triphenylphosphorane ylids; stereoselective reduction of the resultant exocyclic double bond, e.g. by catalytic hydrogenation, may give a predominance of either the α- or β-anomeric *C*-glycoside depending on the particular substrate and reaction conditions.[7]

Recently there has been renewed interest in the use of stabilised ylids derived from trialkylphosphines rather than the traditional triarylphosphines. Thus, Tsunoda et al. found that cyanomethylenetrimethylphosphorane reacted with simple lactones under particularly mild conditions;[9] Harcken and Martin reported that the reagent

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$MeO_2CCH{=}PBu_3$ gave enhanced yields and *E*/*Z* selectivities in Wittig reactions with α-hydroxyaldehydes and with sugar lactols,[10] whereas Stoodley and co-workers favoured the use of alkoxycarbonylmethylenetributylphosphoranes for Wittig reactions with 3-(glucopyranosyloxy)propenal derivatives that may be regarded as being vinylogous esters.[11]

We now wish to report that the Wittig reactions of stabilised tributylphosphorane ylids with sugar lactones occur under mild conditions and give high yields of glycosylidenes with excellent stereoselectivity. We have investigated the preferred conformations of these glycosylidene products both in the crystalline state and in solution. We also describe the stereoselective reduction of these products to form *C*-glycosides and compare 'ionic hydrogenation' procedures using triethylsilane in combination with either trifluoroacetic acid or boron trifluoride. This leads to usefully protected *C*-glycoside building blocks, suitable for the preparation of neoglycoconjugates.

2. Results and discussion

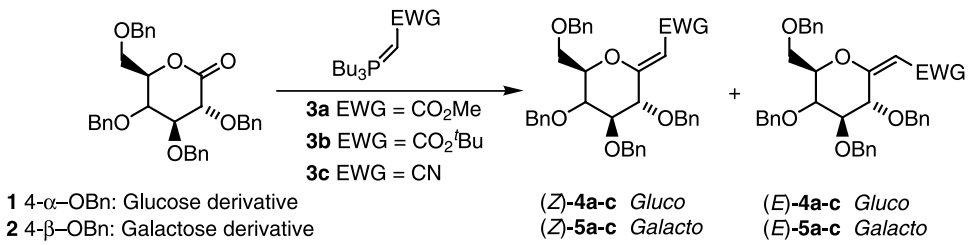
2.1. Wittig reactions

The known[12] 2,3,4,6-tetra-*O*-benzyl protected lactones **1** and **2**, derived from glucose and galactose, respectively, were found to react smoothly with stabilised tributylphosphorane ylids to provide good yields of glycosylidene derivatives as summarised in Scheme 1 and Table 1. These reactions occurred under somewhat milder conditions than had previously been employed for analogous reactions of triphenylphosphorane ylids. For example the lactone **1** has been reported to be recovered unchanged after heating in a steel bomb with $MeO_2CCH{=}PPh_3$ in toluene at 140°C;[6a] a subsequent report of a successful Wittig reaction between **1** and $EtO_2CCH{=}PPh_3$ involved 15 h reflux in toluene.[7a]

Our Wittig reactions showed excellent stereoselectivity, but in most cases we were able to isolate small amounts of minor stereoisomeric products following straightforward flash chromatography. In each case we considered our predominant product to have the (*Z*)-configuration at the newly created double bond and the minor stereoisomer, where present, to be of the (*E*)-configuration. Thus in the ^1H NMR spectra of the glucose derivatives **4a**-**c** the vinylic protons typically appeared at ca. 0.5 ppm higher field in the major isomer, as expected for the (*Z*)-geometry.[6a] However, the corresponding chemical shift differences were only of the order of 0.1 ppm for the isomers of the galactose derivative **5a** and vanished altogether in the case of **5c**. Further evidence for the double bond geometry included the observation of a nuclear Overhauser effect between the vinylic and allylic protons of the ester (*Z*)-**4b**, but not (*E*)-**4b**, and X-ray crystal structures of the major nitrile stereoisomers (*Z*)-**4c** and (*Z*)-**5c**.

In addition we found that pairs of geometrical isomers underwent reduction of the C=C double bond to form the same *C*-glycosides (Scheme 2). For example, reduction of the geometrically isomeric *C*-galactosylidenes (*Z*)-**5a** and (*E*)-**5a** generated a common β-*C*-galactoside β-**7a**. This shows that the major and minor stereoisomers differ only in double bond geometry and it excludes the possibility that one of these products could arise by base-induced epimerisation, as happened in the reaction of a mannose-derived lactone with $Ph_3P{=}CHCO_2Et$.[5] However, we did obtain NMR evidence for the formation of ca. 1% of a third glycosylidene product in the reaction of glucose-derived lactone **1** with the ylid **3a**; this product could not be isolated but might have arisen by a small amount of epimerisation into the mannose series.

The strong preference for forming α,β-unsaturated esters of (*Z*)-configuration is consistent with the avoidance of repulsion between the ester group and the adjacent

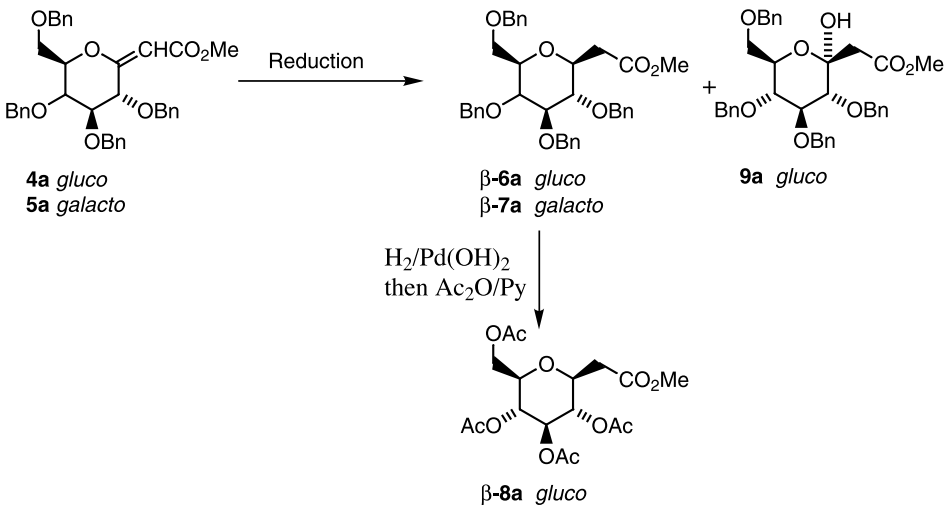


Scheme 1. Wittig reactions of sugar lactones with tributylphosphonium ylids.

Table 1. Wittig reactions of tributylphosphoranes with protected sugar lactones

Lactone	Phosphorane	Conditions	Yield of (*Z*)-glycosylidene **4** or **5** (%)	Yield of (*E*)-glycosylidene **4** or **5**
1	**3a**	Toluene, 80°C, 17 h	92	4%
1	**3b**	Toluene, 80°C, 12 h	92	3%
1	**3c**	CH_2Cl_2, 40°C, 20 h	75	10%[a,b]
2	**3a**	Toluene, 80°C, 24 h	76	4%
2	**3b**	Toluene, 80°C, 12 h	75	Not isolated
2	**3c**	CH_2Cl_2, 40°C, 20 h	68	10%[c]

[a] ^1H NMR shows *Z*/*E* ratio 6.5:1 in crude product.
[b] Reaction of **1** with $Ph_3P{=}CHCN$ (4 equiv., toluene, 16 h reflux) gave a 6:1 ratio of (*Z*)-**4c** and (*E*)-**4c** and after chromatography these two compounds were isolated in 83 and 3% yields, respectively.
[c] ^1H NMR shows *Z*/*E* ratio 4.7:1 in crude product.



Scheme 2. Reduction of *exo*-glycals.

benzyloxy substituent during the Wittig reaction.[7] The cyano group is so small that the preparation of glycosylidene nitriles is a particularly demanding test of the attainable levels of stereoselectivity. Ref. 6b reports a *Z*/*E* ratio of 1:2.8 for the reaction of **1** with NCCH=PPh_3 (toluene, 16 h reflux); however, these authors do not present detailed evidence for the assignment of geometry and upon repetition of their experiment in our laboratory we observed a 6:1 *Z*/*E* ratio by NMR integration and comparison with the crystallographically characterised (*Z*)-**4c**. We found that a change to the tributylphosphorane allowed the reaction to be performed at a lower temperature (CH_2Cl_2, 20 h, reflux) whilst still providing an excellent yield. However, the stereoselectivity (6.5:1 *Z*/*E* ratio) was similar to that which we had observed in our experiment with NCCH=PPh_3.

2.2. Conformational studies of glycosylidene derivatives

In order to prepare for future work on the diastereoselectivity of addition reactions to the glycosylidenes, the conformations of these compounds were examined by crystallographic, NMR and molecular modelling techniques.

2.2.1. Crystallography. The X-ray crystal structure of the glucosylidene nitrile (*Z*)-**4c** (Fig. 1) shows that the C=C unit and the atoms directly attached to it are completely coplanar. Experimental and calculated torsion angles for this and related compounds are detailed in Table 2. In the solid state the tetrahydropyran ring adopts a conformation which is intermediate between a boat and a twist-boat, as assessed by analysis of the endocyclic torsion angles using the method of Bérces et al.[13] To a first approximation this conformation can be designated as $^{O}S_2$. The bond between the ring oxygen and the adjacent tetrahedral carbon atom approaches coplanarity with the unsaturated grouping [C(4)–C(3)–O(3)–C(7) torsion angle=−13.5°], thus allowing the possibility for a substantial $n-\pi^*$ interaction involving a lone pair in a p-orbital of an sp^2-hybridised oxygen atom. The benzyloxymethyl substituent (C-8) has a pseudoequatorial orientation relative to the heterocyclic ring whilst two of the benzyloxy substituents (at C-4 and C-5) assume pseudoaxial positions and consequently have an antiperiplanar relationship [O(4)–C(4)–C(5)–O(5) torsion angle=178.6°]. Such an arrangement at first sight seems remarkable for a glucose derivative and is in stark contrast to the representations found for similar compounds

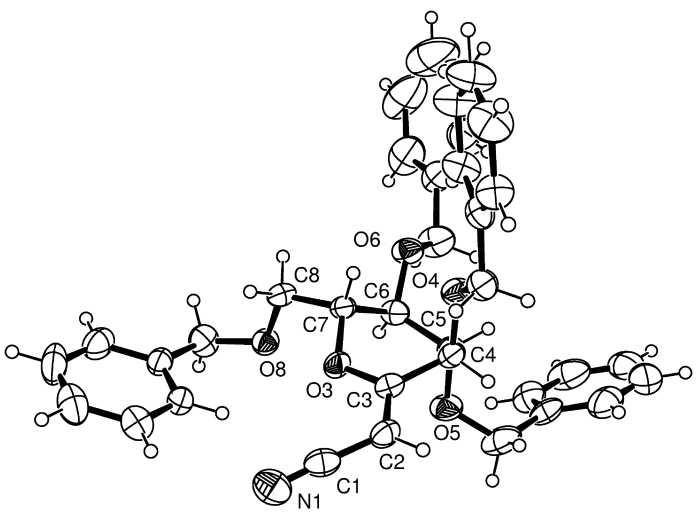


Figure 1. X-Ray crystal structure of (*Z*)-**4c**.

Table 2. Experimental and calculated values of selected torsion angles (degrees) for the glycosylidene nitriles; calculated (gas phase) enthalpies of formation

	X-Ray		Calc			
	(*Z*)-**4c**	(*Z*)-**5c**	(*Z*)-**4c**	(*Z*)-**5c**	(*E*)-**4c**	(*E*)-**5c**
C(4)–C(3)–O(3)–C(7)	−13.5	−42.6	−13.9	−42.5	−14.3	−6.6
C(3)–O(3)–C(7)–C(6)	+54.8	+53.5	+55.6	+53.8	+56.4	+38.3
O(3)–C(7)–C(6)–C(5)	−36.0	−62.4	−37.8	−64.1	−38.7	−65.6
C(7)–C(6)–C(5)–C(4)	−17.6	+61.6	−16.4	+63.6	−16.2	+61.0
C(6)–C(5)–C(4)–C(3)	+56.5	−49.3	+54.6	−51.4	+55.2	−32.4
C(5)–C(4)–C(3)–O(3)	−42.8	+40.4	−41.7	+40.9	−42.1	+3.9
C(5)–C(4)–C(3)–C(2)	+136.3	−146.4	+134.4	−146.2	+135.2	−179.2
C(7)–O(3)–C(3)–C(2)	+167.3	+143.9	+169.9	+149.4	+168.4	+176.1
H(4)–C(4)–C(5)–H(5)	−61.6	−171.8	−58.7	−165.9	−58.2	−149.2
H(5)–C(5)–C(6)–H(6)	+99.4	+63.0	+94.9	+66.2	+95.5	+62.6
H(6)–C(6)–C(7)–H(7)	−156.7	−63.5	−159.3	−69.3	−159.0	−71.5
ΔH_f (calc) (kJ mol^{-1})			−188.2	−177.8	−193.8	−173.3

in recent publications, where the substituents are shown as pseudoequatorial.[2,5,7a] However, the situation is analogous to that in 2-substituted methylenecyclohexene derivatives,[14] where adoption of an axial orientation by the substituent at C-2 can reduce 1,3-allylic strain, i.e. the steric repulsions with an atom or group directly attached to the C=C bond; the minimisation of such strain has already been used to account for the selective formation of the *Z*-geometrical isomer when *exo*-glycals are formed by dehydration.[5] Finally, it should be noted that H(6) and H(7) of the tetrahydropyran ring are antiperiplanar to one another [H(6)–C(6)–C(7)–H(7) torsion angle=−156.7°].

In contrast to the above results, the crystal structure of the galactosylidene nitrile (*Z*)-**5c** (Fig. 2 and Table 2) presents a $^4C_1$ chair-like arrangement.[15] Planarity around the C=C unit is preserved but it does not extend to the bond between C(7) and the ring oxygen atom [C(7)–O(3)–C(3)–C(4) torsion angle=−42.6°]. The benzyloxy groups at C(4) and C(5) occupy pseudoequatorial positions, so that H(4) and H(5) are antiperiplanar to one another [H(4)–C(4)–C(5)–H(5) torsion angle=−171.8°]. Previously Molina et al. have used X-ray crystallography to determine the double bond geometry in the galactosylidene derivative (*Z*)-**5d**, an analogue of (*Z*)-**5c** which has a CO_2Et group in place of the CN function.[7b] The view of the ethyl ester (*Z*)-**5d** provided in Ref. 7b again shows a chair-like arrangement, but as the atomic co-ordinates of this structure are not available from the Cambridge Crystallographic Data Centre a quantitative analysis of this structure is not possible here.

2.2.2. NMR studies. The solution phase conformations of known glycosylidenes were examined using NMR data available from our own work or reported in the literature.[2,5] In particular the three-bond coupling constants between the protons of the heterocyclic rings were sought. Unfortunately the presence of overlapping signals prevents a complete analysis of every spectrum but the most complete data are given in Table 3 (glucosylidenes) and Table 4 (galactosylidenes). In some cases the use of C_6D_6 as NMR solvent, rather than $CDCl_3$, was necessary in order to assist the analysis: this led to substantial movements in chemical shift, thus helping to resolve overlapping peaks. However, the available data indicate similar coupling constants in the two solvents, thus suggesting that similar conformations are adopted in these two solvents. Since the numbering of atoms in the ring depends on the nature of the R^1 and R^2 groups, as well as the preferences of the original authors, these results have been presented using the Greek letters H(α)–H(δ) to denote the four key hydrogen atoms as shown in Figure 3.

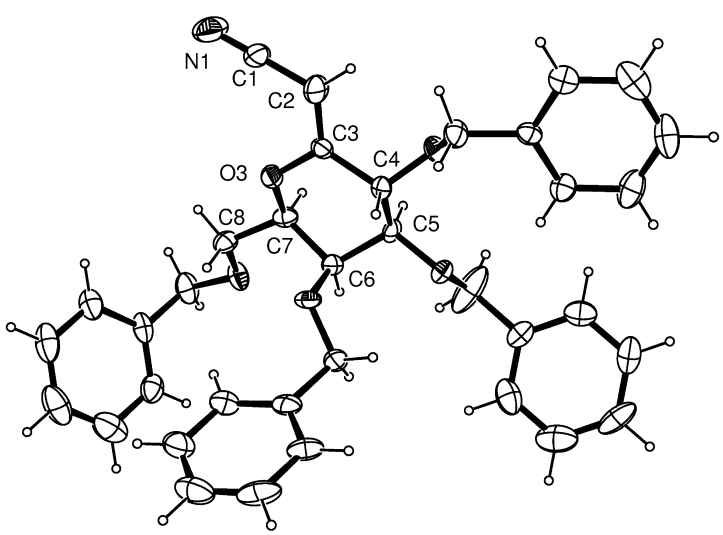


Figure 2. X-Ray crystal structure of (*Z*)-**5c**.

Table 3. $^{3}J_{HH}$ values (Hz) for ring protons of glucosylidene derivatives **4**

Compound	R^1	R^2	$J_{\alpha\beta}$	$J_{\beta\gamma}$	$J_{\gamma\delta}$	Source[a]
(*Z*)-**4a**	CO_2Me	H	3.2	ND[b]	9.7	
(*Z*)-**4a**	CO_2Me	H	3.6[c]	5.7[c]	10.2[c]	
(*E*)-**4a**	H	CO_2Me	1.8	3.9	10.2	
(*Z*)-**4b**	CO_2^tBu	H	4.1	ND	10.0	
(*E*)-**4b**	H	CO_2^tBu	1.7	4.1	10.4	
(*E*)-**4b**	H	CO_2^tBu	1.6[c]	4.2[c]	10.3[c]	
(*Z*)-**4c**	CN	H	ND	ND	9.1	
(*Z*)-**4c**	CN	H	5.0[c]	6.3[c]	9.9[c]	
(*E*)-**4c**	H	CN	2.0	3.7	10	
(*Z*)-**4d**	CO_2Et	H	ND	ND	9.6	Ref. 5
4e	H	H	7.2	ND	ND	Ref. 5
(*Z*)-**4f**	Br	H	5.3	ND	9.7	Ref. 2
(*Z*)-**4g**	Ph	H	4.6	ND	9.7	Ref. 2
4h	Me	Me	2.2	5.3	9.9	Ref. 2
4i	$-[CH_2]_5-$		2.2	5.6	9.9	Ref. 2

[a] Where no source is given data are from the present work.
[b] ND indicates that the coupling constant could not be determined as the relevant protons gave rise to overlapping multiplets.
[c] Value obtained from spectrum in C_6D_6: all other data not so indicated refer to spectra in $CDCl_3$.

Table 4. $^{3}J_{HH}$ values for ring protons of galactosylidene derivatives **5**

Compound	R^1	R^2	$J_{\alpha\beta}$	$J_{\beta\gamma}$	$J_{\gamma\delta}$	Source
(*Z*)-**5a**	CO_2Me	H	9.4	2.6	1.5	
(*E*)-**5a**	H	CO_2Me	3.4	3.4	4.6	
(*Z*)-**5b**	CO_2^tBu	H	9.2	2.6	1.4	
(*Z*)-**5c**	CN	H	9.8[a]	2.5[a]	1.2[a]	
(*E*)-**5c**	H	CN	5.2	3.2	3.2	
(*Z*)-**5d**	CO_2Et	H	9.3	2.8	1.0	Ref. 5
5e	H	H	9.0	2.7	2.3	Ref. 5
(*Z*)-**5j**	Et	H	8.1	2.7	2.5	Ref. 5

[a] Indicates value obtained from spectrum in C_6D_6: all data not so indicated refer to spectra in $CDCl_3$.

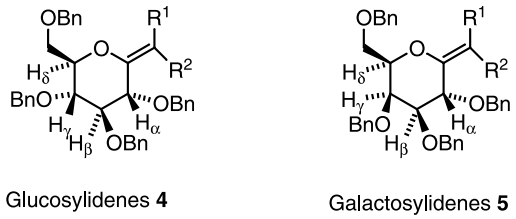


Figure 3. Designation of ring protons for use with Tables 3 and 4.

For the glucosylidene derivatives **4**, the available values of $J_{\gamma\delta}$ are generally large (9.1–10.4 Hz) and it appears probable that all of these compounds adopt solution phase conformations in which H(γ) and H(δ) are antiperiplanar to one another. Taken in isolation these data are consistent not only with twist conformations of the type seen in the crystal structure of (*Z*)-**4c**, but also with a $^{4}C_1$ chair arrangement. $^{1}C_4$ Inverted chairs, with equatorial hydrogen atoms, can be ruled by the large values of $J_{\gamma\delta}$.

The values of $J_{\alpha\beta}$ span a range from 1.6 to 7.2 Hz and thus it seems that in solution these diverse compounds cannot be described by a single type of conformation and may very well exist as equilibrium mixtures of conformers with similar energies. A $^{4}C_1$ conformation is most likely when $J_{\alpha\beta}$ is large, as in the case of the methylene derivative **4e**; conversely this type of arrangement can be excluded for the three (*E*)-configured Wittig products (*E*)-**4a-c**, all of which have $J_{\alpha\beta}\leq 2$ Hz and where the double bond geometry would impose excessive 1,3-allylic repulsion on such a conformation. In cases where the C=C bond is fully substituted, chair-like arrangements should be similarly disfavoured: this assertion is supported by the values of $J_{\alpha\beta}=2.2$ Hz, reported in the literature for both the isopropylidene derivative **4h** and the cyclohexylidene derivative **4i**.[2]

The NMR data for the galactosylidene derivatives **5** (Table 4) show large values of $J_{\alpha\beta}$ and relatively small $J_{\beta\gamma}$ and $J_{\gamma\delta}$, consistent with chair-like conformations for the (*Z*)-geometrical isomers and for the methylene derivative **5e**. Lower values of $J_{\alpha\beta}$ are observed for (*E*)-**5a** and (*E*)-**5c**, again suggesting that the *E*-geometry destabilises the chair conformation.

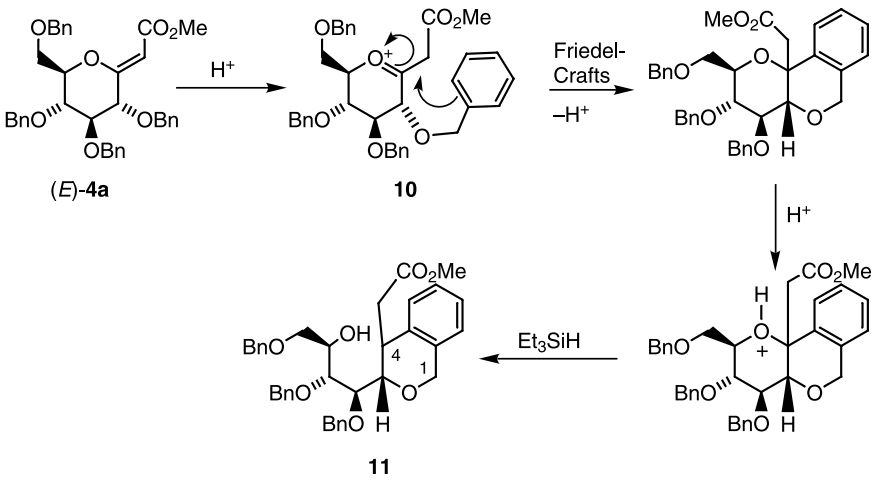
Another notable trend in the ^{1}H NMR data is the observation of ^{4}J couplings between the allylic and olefinic protons of between 1.0 and 1.8 Hz only in the cases of the *Z*-configured galactosylidene derivatives (*Z*)-**5a**, (*Z*)-**5b**, (*Z*)-**5c**, (*Z*)-**5d**, (*Z*)-**5j** and of the methylene *C*-galactoside **5e**. For the *E*-geometrical isomers and for the glucose derivatives the analogous four-bond allylic couplings could not be detected. Again this suggests that the *Z*-galactosylidenes and *Z*-glucosylidenes adopt two distinct types of ring conformation. A Karplus-like variation of allylic coupling constants with conformation has previously been observed: the *cisoid* allylic coupling is close to zero (as is seen for the glucose derivatives) when the allylic C–H and the C=C double bond are synperiplanar to one another.[16] Examination of the crystal structures of the nitriles (*Z*)-**4c** and (*Z*)-**5c** from the two series reveals that such a relationship is indeed present for the glucose derivative, but not for the galactose derivative [the respective H(4)–C(4)–C(3)=C(2) torsion angles are 15.7 and 94.5°].

2.2.3. Molecular modelling calculations. The glycosylidene nitriles (*E*)- and (*Z*)- **4c** and **5c** were subjected to further conformational analysis using MOPAC-6 semi-empirical calculations (Table 2). The crystal structures of (*Z*)-**4c** and (*Z*)-**5c** were used as starting points. It is to be expected that differences might be observed between these structures and the (gas phase) results of structure optimization using MOPAC-6. Nevertheless, when the crystallographically determined conformations were subjected to energy minimisation the conformational changes which occurred were relatively minor, suggesting that crystal packing effects are not important in establishing a preference for the observed conformations.

The structures (*E*)-**4c** and (*E*)-**5c** for which crystallographic data were not available were modelled by first reversing the *cis–trans* isomerism of the available structures. The program INTERCHEM (Interprobe Chemical Services, Lenzie) was used for this purpose. Before submission of the structures to MOPAC for optimization, simple molecular mechanics optimizations were performed. This step served to remove possible bad contacts, which might not have been acceptable to MOPAC. In the case of the glucosylidene derivative (*E*)-**4c** the calculated minimum energy conformation had similar ring torsion angles to those of (*Z*)-**4c** so that it could again be described as a $^{O}S_2$ form.

Table 5. Reductions of glycosylidene methyl esters **4a** and **5a**

Glycosylidene methyl ester	Conditions	% Yield β-*C*-glycoside	Other isolated products
(*Z*)-**4a**	Et_3SiH (2.5 equiv.), CF_3CO_2H (2.5 equiv.), CH_2Cl_2, 2 h, room temperature	–	**9a** (25%)
(*Z*)-**4a**	Et_3SiH (24 equiv.), CF_3CO_2H (100 equiv.), 2 h, CH_2Cl_2, room temperature	50	**11** (3%)
(*Z*)-**4a**	Et_3SiH (32 equiv.), $BF_3{\cdot}Et_2O$ (7.8 equiv.), CH_2Cl_2, 23 h, room temperature	80	
(*Z*)-**5a**	Et_3SiH (24 equiv.), CF_3CO_2H (100 equiv.), CH_2Cl_2, 2 h, room temperature	41	β-**12a** (15%)
(*Z*)-**5a**	Et_3SiH (32 equiv.), $BF_3{\cdot}Et_2O$ (7.8 equiv.), CH_2Cl_2, 23 h, room temperature	72	
(*E*)-**5a**	Et_3SiH (31 equiv.), $BF_3{\cdot}Et_2O$ (7.1 equiv.), CH_2Cl_2, 14 h, room temperature	50	



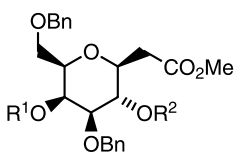
Scheme 3. Proposed mechanism for formation of **11**.

On the other hand, the minimum energy conformation of the galactosylidene derivative (*E*)-**5c** was calculated to be a ^4E envelope arrangement. Thus these calculations support the experimental observations that the chair form is more favoured for galactose than for glucose but that it is destabilised by the presence of a substituent on the C=C bond *trans* to the ring oxygen atom.

2.3. Reductions of glycosylidene derivatives

The hydrogenation of glycosylidene derivatives has previously been investigated by Xie and co-workers.[7a] These authors found that the glucosylidene derivative (*Z*)-**4d**, which bears a CO_2Et substituent on the C=C bond, could be reduced by the combination of nickel chloride and sodium borohydride ('nickel boride') in methanol to give predominantly the α-*C*-glucoside without cleavage of the *O*-benzyl protecting groups; the galactosylidene analogue (*Z*)-**5d** underwent reduction under these conditions to give mainly the β-*C*-galactoside. On the other hand, catalytic hydrogenation of either (*Z*)-**4d** or (*Z*)-**5d** (15 h, room temperature, Pd–C) was reported to remove all the benzyl groups and give exclusively the β-*C*-glycosides.[7]

We first attempted reductions of the glycosylidene methyl esters using the triethylsilane–trifluoroacetic acid system in dichloromethane (Scheme 2; Table 5). This gave modest yields of β-*C*-glycosides. The β-configuration of the galactose derivative **7a** was evident from the ^1H NMR coupling $J_{1,2}$=9.3 Hz in the pyranose ring; in the case of the glucose derivative **6a** overlapping peaks were present and so hydrogenolysis of the benzyl groups and protection as the known peracetyl derivative β-**8a** ($J_{1,2}$=9.9 Hz) was performed. Additionally a number of by-products were produced, including the alcohol **9a** arising from formal hydration of the C=C bond and an isochroman **11** which can be generated by an intramolecular Friedel–Crafts alkylation involving the oxonium intermediate **10** (Scheme 3). The isolated sample of isochroman **11** was a single stereoisomer by 600 MHz ^1H NMR, but the configuration at C-4 of the heterocyclic ring could not be established. From the reduction of (*Z*)-**5a** a minor β-*C*-glycosidic product β-**12a** was isolated (Fig. 4), wherein the reduction of the C=C bond had been accompanied by the cleavage of one of the four *O*-benzyl groups, leaving an exposed hydroxyl group: NMR studies showed $J_{1,2}$=9 Hz and indicated that the OH proton coupled to one or other of the overlapping signals due to H-2 and H-4 of the pyranose system. α-*C*-Glycosides were not observed, consistent with axial delivery of hydride to oxonium intermediates as originally proposed by Kishi in discussing the deoxygenation of sugar lactols.[4] Greatly improved yields of β-*C*-glycosides could be obtained by reducing the glycosylidenes using triethylsilane in combination with boron



β-**12a**

R^1 = Bn, R^2 = H

or R^1 = H, R^2 = Bn

Figure 4. By-product of Et_3SiH–CF_3CO_2H reduction of (*Z*)-**5a**.

trifluoride etherate and again complete stereoselectivity was observed (Table 5). Both the isomeric products (*E*)-**5a** and (*Z*)-**5a**, produced in the Wittig reaction of the galactose-derived lactone **2** with $Bu_3P{=}CHCO_2Me$, underwent reduction by $BF_3{\cdot}Et_2O{-}Et_3SiH$ to give the same β-*C*-galactoside β-**7a**: this shows that the pair of products formed in the Wittig reaction are geometrical isomers.

3. Conclusions

We have found that stabilised ylids **3** derived from tributylphosphine undergo clean and efficient couplings with carbohydrate-derived lactones **1** and **2** under mild conditions, yielding the (*Z*)-glycosylidenes **4** and **5** as the major products. Although some of these products, notably (*Z*)-**5c**, may exist in chair-like conformations both in the crystal and in solution, many of the glycosylidene derivatives adopt alternative arrangements, such as the twisted boat seen in the crystal structure of (*Z*)-**4c**. 1,3-Allylic repulsion is important in determining these conformational preferences, particularly when the exocyclic double bond carries a substituent *trans*- to the oxygen atom of the pyranose ring. We have investigated the reduction of the exocyclic double bond and have found that the combination of triethylsilane and boron trifluoride etherate gives excellent selectivity in favour of the β-configured esters and is compatible with the presence of benzyl ether and methyl ester protecting groups. The use of these products as intermediates in the synthesis of neoglycoconjugates is currently being investigated in our laboratories.

4. Experimental

4.1. X-Ray diffraction data of 3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enononitrile (*Z*)-4c

Crystals of (*Z*)-**4c** were obtained by slow evaporation of a solution of (*Z*)-**4c** in a mixture of diethyl ether and petroleum spirit.

Chemical formula: $C_{36}H_{35}NO_5$; formula weight 561.65; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: *a*: 9.902(7) Å; *b*: 10.524(9) Å; *c*: 14.585(12) Å; α: 90°; β: 90.63(7)°; γ: 90°; volume: 1520(2) Å^3; temperature 295(2) K; space group $P2_1$, no. of molecules in unit cell (*Z*): 2; wavelength of radiation λ: 0.71073 Å; linear absorption coefficient (μ): 0.081 mm^{-1}; number of reflections measured: 3103; number of independent reflections: 2841 [R_{int}=0.0127]; final *R* indices [$I>2\sigma(I)$]: *R*1=0.0489, *wR*2=0.1132.

4.2. X-Ray diffraction data of 3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enononitrile (*Z*)-5c

Crystals of (*Z*)-**5c** were obtained by slow evaporation of a solution of (*Z*)-**5c** in a mixture of diethyl ether and petroleum spirit.

Chemical formula: $C_{36}H_{35}NO_5$; formula weight 561.65; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: *a*: 17.723(8) Å; *b*: 7.534(4) Å; *c*: 111.689(7) Å; α: 90°; β: 107.30(6)°; γ: 90°; volume: 1490(1) Å^3; temperature 160(2) K; space group $P2_1$, no. of molecules in unit cell (*Z*): 2; wavelength of radiation λ: 0.71073 Å; linear absorption coefficient (μ): 0.083 mm^{-1}; number of reflections measured: 3004; number of independent reflections: 2829 [R_{int}=0.0147]; final *R* indices [$I>2\sigma(I)$]: *R*1=0.0528, *wR*2=0.1083.

Crystallographic data (excluding structure factors) for the structures **4c** and **5c** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 215129 and 215130, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit @ccdc.cam.ac.uk].

4.3. Materials and general experimental procedures

'Petrol' or 'petroleum spirit' refers to the fraction of bp 40–60°C. Toluene was distilled from sodium benzophenone ketyl before use. Flash chromatography was performed on BDH silica gel (33–70 μm). Protected sugar lactones **1** and **2** were prepared by DMSO-Ac_2O oxidation of the corresponding hemiacetals.[12] All new compounds were homogeneous as assessed by TLC and high field NMR. Melting points were determined using a Reichert hot stage microscope. Specific rotations were determined on an Optical Activity Ltd AA-1000 polarimeter with a path length of 0.5 or 2 dm. IR spectra of films and KBr discs were recorded using a Shimadzu FTIR 8300 and ATR spectra were recorded using a Perkin–Elmer 1720 instrument. X-Ray diffraction data were collected on a CAD4 diffractometer using $\omega{-}2\theta$ scans. NMR spectra were recorded on Jeol EX270 and Bruker AM250, AMX400 or AMX600 spectrometers. FAB mass spectra were recorded on a ZAB-SE4F machine at the School of Pharmacy, University of London; other mass spectra were provided by the EPSRC National Service in Swansea using a Finnigan MAT 900.

4.3.1. (*E*)- and (*Z*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester 4a. A solution of (methoxycarbonylmethylene)tri-*n*-butylphosphorane **3a** (3.22 g, 11.7 mmol) in dry toluene (5 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **1** (3.16 g, 5.87 mmol) in dry toluene (5 mL) at 80°C under N_2. The reaction mixture was stirred for 17 h and concentrated under reduced pressure. The yellow residue was subjected to flash chromatography using petroleum spirit/EtOAc (5:1).

Less polar product: (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester (*E*)-**4a** (146 mg, 4%), an oil, $[\alpha]_D^{32}$=+27.9 (*c* 0.50, $CHCl_3$); ν_{max} (film)/cm^{-1} 1705 (C=O) and 1645 (C=C); δ_H (600 MHz, $CDCl_3$) 3.68 (1H, dd, *J*=11.2, 4.8 Hz, H-8$_a$), 3.68 (3H, s, CO_2Me), 3.70 (1H, dd, *J*=10.1, 3.9 Hz, H-6), 3.76 (1H, dd, *J*=11.2, 1.8 Hz, H-8$_b$), 3.94 (1H, dd, *J*=3.9, 1.8 Hz, H-5), 4.40 (1H, d, *J*=11.6 Hz, 1/2×OCH_2Ph), 4.42 (1H, d, *J*=11.4 Hz, 1/2×OCH_2Ph), 4.53 (1H, d, *J*=11.4 Hz,

1/2×OCH_2Ph), 4.54 (1H, d, J=12.2 Hz, 1/2×OCH_2Ph), 4.60 (1H, d, J=12.2 Hz, 1/2×OCH_2Ph), 4.62 (1H, ddd, J=10.3, 4.7, 1.8 Hz, H-7), 4.61 (1H, d, J=11.7 Hz, 1/2×OCH_2Ph), 4.67 (1H, d, J=11.9 Hz, 1/2×OCH_2Ph), 4.69 (1H, d, J=11.9 Hz, 1/2×OCH_2Ph), 5.67 (1H, s, 2-H), 5.93 (1H, d, J=1.8 Hz, H-4), 7.14–7.16 (2H, m, Ph), and 7.24–7.36 (18H, m, Ph); δ_C (151.0 MHz, $CDCl_3$) 51.0, 68.7, 69.4, 70.8, 71.0, 72.3, 73.3, 74.9, 77.7, 80.5, 100.3, 127.5, 127.6, 127.79, 127.82, 127.87, 128.25, 128.36, 137.3, 137.7, 137.9, 138.0, 165.9 and 167.9; m/z (FAB) M^++H 595.2708 [$C_{37}H_{39}O_7$ requires 595.2696].

More polar product: (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester (*Z*)-**4a** (3.23 g, 92%), obtained as a waxy syrup; $[\alpha]_D^{25}$=+47.0 (*c* 2.85, $CHCl_3$); ν_{max} (film)/cm^{-1} 1720 (C=O), 1701, and 1651; δ_H (400 MHz, $CDCl_3$) 3.70 (3H, s, CO_2Me), 3.82 (1H, dd, J=11.5, 3.8 Hz, H-8$_a$), 3.82–3.84 (1H, m, H-5 or H-6), 3.84 (1H, d, J=3.2 Hz, H-4), 3.85–3.89 (1H, m, H-6 or H-5), 3.89 (1H, dd, J=11.5, 2.1 Hz, H-8$_b$), 4.34 (1H, ddd, J=9.7, 3.5, 2.0 Hz, H-7), 4.50 (1H, d, J=12.0 Hz, 1/2×OCH_2Ph), 4.53 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 4.53 (1H, d, J=12.8 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, J=11.7 Hz, 1/2×OCH_2Ph), 4.64 (1H, d, J=12.4 Hz, 1/2×OCH_2Ph), 4.65 (1H, d, J=11.1 Hz, 1/2×OCH_2Ph), 4.71 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.76 (1H, d, J=12.3 Hz, 1/2×OCH_2Ph), 5.19 (1H, s, H-2) and 7.11–7.39 (20H, m, 4×Ph); δ_H (400 MHz, C_6D_6) 3.56 (3H, s, CO_2Me), 3.83 (1H, dd, J=11.8, 3.6 Hz, H-8$_a$), 3.86 (1H, d, J=3.6 Hz, 4-H), 3.93 (1H, d, J=11.8, 1.9 Hz, H-8$_b$), 3.96 (1H, dd, J=5.7, 3.6 Hz, H-5), 4.10 (1H, dd, J=10.2, 5.7 Hz, H-6), 4.25 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.37 (1H, d, J=11.9 Hz, 1/2×OCH_2Ph), 4.45 (1H, d, J=11.9 Hz, 1/2×OCH_2Ph), 4.50 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.56 (1H, ddd, J=10.1, 3.5, 1.9 Hz, H-7), 4.59 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.70 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.71 (1H, d, J=12.3 Hz, 1/2×OCH_2Ph), 4.84 (1H, d, J=12.3 Hz, 1/2×OCH_2Ph), 5.44 (1H, s, H-2), 7.02–7.29 (18H, m, Ar-H) and 7.51–7.53 (2H, m, Ar-H); δ_C (62.9 MHz, $CDCl_3$) 50.9, 68.3, 71.4, 72.7, 73.4, 73.6, 77.4, 77.7, 82.7, 99.4 (C=*C*H), 127.4, 127.7, 127.8, 127.9, 128.3, 128.4, 128.5, 137.1 (C-*ipso*), 137.6 (C-*ipso*), 137.8 (C-*ipso*), 138.4 (C-*ipso*), 161.9 (*C*=CH) and 165.1 (C=O); m/z (FAB) M^++Na 617.2540 [$C_{37}H_{38}O_7$Na requires 617.2515].

4.3.2. (*E*)- and (*Z*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, *tert*-butyl ester 4b. A solution of (*tert*-butoxycarbonylmethylene)tri-*n*-butylphosphorane **3b** (1.29 g, 4.08 mmol) in dry toluene (10 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **1** (1.10 g, 2.04 mmol) in dry toluene (10 mL) at 80°C under N_2. The reaction mixture was stirred for 12 h and concentrated under reduced pressure. The yellow residue was subjected to flash chromatography using petroleum spirit/AcOEt (8:1) to give the following products.

Less polar product: (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, *tert*-butyl ester (*E*)-**4b** (45 mg, 3%), $[\alpha]_D^{24}$=+22.2 (*c* 0.95, $CHCl_3$); ν_{max} (film)/cm^{-1} 1695 (C=O) and 1645 (C=C); δ_H (600 MHz, $CDCl_3$) 1.49 (9H, s, ^{t}Bu), 3.70 (1H, dd, J=11.3, 4.6 Hz, H-8$_b$), 3.72 (1H, dd, J=10.4, 4.1 Hz, H-6), 3.78 (1H, dd, J=11.3, 1.8 Hz, H-8$_a$), 3.97 (1H, dd, J=4.1, 1.7 Hz, H-5), 4.43 (1H, d, J=11.3 Hz, 1/2×OCH_2Ph), 4.47 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 4.55 (1H, d, J=12.2 Hz, 1/2×OCH_2Ph), 4.58 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 4.60–4.63 (1H, m, H-7), 4.62 (1H, d, J=12.1 Hz, 1/2×OCH_2Ph), 4.64 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.70 (1H, d, J=11.3 Hz, 1/2×OCH_2Ph), 4.71 (1H, d, J=11.7 Hz, 1/2×OCH_2Ph), 5.63 (1H, s, H-2, irradiation of this signal gave no significant nOe at H-4), 5.96 (1H, d, J=1.7 Hz, H-4), 7.17–7.38 (20H, m, 4×Ph); δ_H (250 MHz, C_6D_6) 1.46 (9H, s, ^{t}Bu), 3.70 (2H, d, J=2.9 Hz, H-8a+H-8b), 4.06 (1H, dd, J=10.3, 4.2 Hz, H-6), 3.97 (1H, dd, J=4.2, 1.6 Hz, H-5), 4.31–4.86 (8H, m, 4×OCH_2Ph), 4.92 (1H, dt, J=10.3, 2.9 Hz, H-7), 6.04 (1H, s, H-2), 6.43 (1H, br s, H-4) and 7.09–7.44 (20H, m, 4×Ph); δ_C (62.9 MHz, $CDCl_3$) 28.3 (CH_3), 68.9, 69.5, 70.7, 71.1, 72.4, 73.4, 74.8, 77.9, 79.6, 80.9, 102.8 (C=*C*H), 127.5, 127.6, 127.8, 128.3, 128.4, 137.5 (C-*ipso*), 137.9 (C-*ipso*), 138.2 (C-*ipso*), 138.2 (C-*ipso*), 164.3 (*C*=CH) and 166.8 (C=O); m/z (FAB) M^++Na 659.2985 [$C_{40}H_{44}O_7$Na requires 659.2985].

More polar product: (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, *tert*-butyl ester (*Z*)-**4b** (1.20 g, 92%) as a waxy syrup; $[\alpha]_D^{25}$=+41.4 (*c* 5.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 1713 (C=O) and 1647 (C=C); δ_H (600 MHz, $CDCl_3$) 1.48 (9H, s, ^{t}Bu), 3.81–3.82 (1H, m, H-5 or H-6), 3.83 (1H, d, J=8.6, 3.5 Hz, H-8$_a$), 3.86 (1H, d, J=4.1 Hz, H-4), 3.86–3.88 (1 H, m, H-6 or H-5), 3.88 (1H, dd, J=11.1, 2.0 Hz, H-8$_b$), 4.26 (1H, ddd, J=10.0, 3.5, 2.0 Hz, H-7), 4.51 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.54 (1H, d, J=11.2 Hz, 1/2×OCH_2Ph), 4.55 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, J=12.3 Hz, 1/2×OCH_2Ph), 4.63 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.67 (1H, d, J=11.2 Hz, 1/2×OCH_2Ph), 4.72 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.73 (1H, d, J=12.3 Hz, 1/2×OCH_2Ph), 5.14 (1H, s, H-2, irradiation of this signal gave 6.1% nOe at H-4), 7.15–7.40 (20H, m, 4×Ph); δ_C (151.0 MHz, $CDCl_3$) 28.3 (CH_3), 68.4 (CH_2), 71.6 (CH_2), 73.0 (CH_2), 73.6 (CH_2), 76.7 (CH_2), 77.2 (CH), 77.4 (CH), 78.1 (CH), 79.7 (C), 83.2 (CH), 101.9 (C=*C*H), 127.5, 127.7, 127.8, 127.9, 128.0, 128.3, 128.5, 128.5, 137.3 (C-*ipso*), 137.7 (C-*ipso*), 138.0 (C-*ipso*), 138.4 (C-*ipso*), 160.7 (C=CH), and 164.2 (C=O); m/z (FAB) M^++Na 659.2985 [$C_{40}H_{44}O_7$Na requires 659.2985].

4.3.3. (*Z*)- and (*E*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enononitrile 4c. A solution of (cyanomethylene)tri-*n*-butylphosphorane **3c** (0.67 g, 2.77 mmol) in dry CH_2Cl_2 (3 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **1** (0.75 g, 1.39 mmol) in dry CH_2Cl_2 (2 mL) at 40°C under N_2. The reaction mixture was stirred 20 h and concentrated under reduced pressure. The *Z*/*E* isomer ratio of this crude product was 6.5:1 as determined by ^{1}H NMR. The yellow residue (1.56 g) was subjected to flash chromatography using petroleum spirit/Et_2O (5:2) to give firstly (*E*)-3,7-anhydro-2-deoxy-4,5,6,8-tetra-*O*-benzyl-D-gluco-oct-2-enononitrile (*E*)-**4c** (0.081 g, 10%) as a colourless oil and from the later fractions (*Z*)-3,7-anhydro-2-deoxy-4,5,6,8-tetra-*O*-benzyl-D-gluco-oct-2-enononitrile (*Z*)-**4c** (0.58 g, 1.04 mmol, 75%) as a white solid.

Less polar product: (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enononitrile (*E*)-**4c**; $[\alpha]_D^{20}$=+30.5 (*c*

0.65, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2218 (C≡N) and 1639 (C=C); δ_H (250 MHz, $CDCl_3$) 3.65 (1H, dd, J=11.3, 4.4 Hz, H-8$_a$), 3.70 (1 H, dd, J=10, 3 Hz, H-6), 3.74 (1 H, dd, J=11.3, 2.0 Hz, H-8$_b$), 3.92 (1H, dd, J=3.7, 2.1 Hz, H-5), 4.37 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 4.39 (1H, d, J=11.4 Hz, 1/2×OCH_2Ph), 4.48–4.61 (5 H, m, benzyl-H$_5$), 4.53–4.60 (1H, m, H-7), 4.68 (1H, d, J=1.8 Hz, H-4), 4.73 (1H, d, J=11.7 Hz, 1/2×OCH_2Ph), 5.01 (1H, s, H-2) and 7.16–7.39 (20H, m, 4×Ph); δ_C (62.9 MHz, $CDCl_3$) 68.5, 71.4, 71.8, 72.6, 72.9, 73.5, 76.0, 79.4, 80.3, 117.3 (*C*≡N), 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 136.8 (C-*ipso*), 137.5 (C-*ipso*), 137.8 (C-*ipso*), 168.8 (*C*=CH); *m*/*z* (FAB) M^++Na 562.2606 [$C_{36}H_{35}NO_5Na$ requires 562.2593].

More polar product: (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enononitrile (*Z*)-**4c**; mp 95–97°C (from Et_2O/petrol); $[\alpha]_D^{20}$=+74.6 (*c* 2.45, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2218 (C≡N) and 1639; δ_H (250 MHz, $CDCl_3$) 3.75–3.94 (5H, m, H-4, H-5, H-6, H-8$_a$, H-8$_b$), 4.20 (1H, ddd, J=9.1, 3.3, 2.1 Hz, H-7), 4.52–4.72 (8H, m, 4×OCH_2Ph), 4.70 (1H, s, H-2) and 7.16–7.39 (20H, m, 4×Ph); δ_H (400 MHz, C_6D_6) 3.56 (1H, dd, J=11.5, 3.2 Hz, H-8$_a$), 3.61 (1H, dd, J=11.5, 2.0 Hz, H-8$_b$), 3.63 (1H, d, J=5.0 Hz, H-4), 3.72 (1H, dd, J=6.3, 5.0 Hz, H-5), 3.91 (1 H, dd, J=9.9, 6.4 Hz, H-6), 4.09 (1H, ddd, J=10.0, 3.2, 2.0 Hz, H-7), 4.12 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.24 (1H, d, J=11.8 Hz, 1/2×OCH_2Ph), 4.34–4.38 (3H, m, H-2 and 2×benzylic H), 4.41 (1H, d, J=11.7 Hz, 1/2×OCH_2Ph), 4.46 (1H, d, J=12.2 Hz, 1/2×OCH_2Ph), 4.49 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, J=11.5 Hz, 1/2×OCH_2Ph), 7.05–7.24 (18H, m, Ar-H$_{18}$) and 7.34–7.37 (2H, m, Ar-H$_2$); δ_C (62.9 MHz, $CDCl_3$) 67.9, 72.5, 73.5, 73.6, 73.9, 76.9, 78.0, 78.7, 82.6, 115.2 (C≡N), 128.3, 128.4, 128.6, 128.7, 136.6 (C-*ipso*), 137.5 (C-*ipso*), 137.5 (C-*ipso*), 137.9 (C-*ipso*), 168.5 (*C*=CH); *m*/*z* (FAB) M^++Na 562.2580 [$C_{36}H_{35}NO_5Na$ requires 562.2593].

4.3.4. (*E*)- and (*Z*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester 5a. A solution of (methoxycarbonylmethylene)tri-*n*-butylphosphorane **3a** (0.401 g, 1.46 mmol) in dry toluene (3 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-galacto-1,5-lactone **2** (0.394 g, 0.73 mmol) in dry toluene (2 mL) at 80°C under N_2. The reaction mixture was stirred for 24 h and concentrated under reduced pressure. The yellow residue was subjected to flash chromatography with petroleum spirit/Et_2O (2:1) to give first (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*E*)-(**5a**) (18 mg, 4%) and then (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-D-galacto-oct-2-enonic acid, methyl ester (*Z*)-**5a** (330 mg, 76%).

Less polar product: (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*E*)-**5a** was a colourless oil; $[\alpha]_D^{30}$=−21.4 (*c* 1.27, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1711 (C=O) and 1645 (C=C); δ_H (600 MHz, $CDCl_3$) 3.68 (3H, s, CO_2Me), 3.75 (1 H, dd, J=11.0, 3.7 Hz, H-8$_a$), 3.82 (1 H, dd, J=11.0, 7.5 Hz, H-8$_b$), 3.90 (1H, t, J=3.4 Hz, H-5), 4.20, (1H, 't', J=4.3 Hz, H-6), 4.45–4.68 (8H, m, 4×PhCH_2O), 4.55–4.60 (1H, m, H-7), 5.69 (1H, d, J=3.1 Hz, H-4), 5.72 (1H, s, H-2), 7.23–7.34 (20H, m, 4×Ph); δ_C (67.9 MHz, $CDCl_3$) 51.1, 68.5, 70.5, 71.0, 71.6, 71.8, 72.4, 73.2, 76.1, 77.9, 105.2 (C=*C*H), 127.6, 127.65, 127.74, 127.77, 128.3, 137.8 (C-*ipso*), 138.0 (C-*ipso*), 138.1 (C-*ipso*), 138.1 (C-*ipso*), 165.0 (*C*=CH), 167.5 (C=O); *m*/*z* (FAB) M^++Na 617.2540 [$C_{37}H_{38}O_7Na$ requires 617.2515].

More polar product: (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*Z*)-**5a** was a waxy syrup; $[\alpha]_D^{24}$=+81.6 (*c* 1.03, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1724 (C=O) and 1653 (C=C); δ_H (270 MHz, $CDCl_3$) 3.64 (3H, s, CO_2Me), 3.73 (1H, dd, J=9.3, 2.6 Hz, H-5), 3.78 (2H, d, J=6.7 Hz, H-8$_a$, H-8$_b$), 4.01 (1H, td, J=6.9, 1.3 Hz, H-7), 4.13 (1H, dd, J=2.5, 1.5 Hz, H-6), 4.44 (1H, dd, J=9.4, 1.5 Hz, H-4), 4.46 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.55 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, J=11.4 Hz, 1/2×OCH_2Ph), 4.70 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 4.70 (2H, s, OCH_2Ph), 4.78 (1H, d, J=11.4 Hz, 1/2×OCH_2Ph), 4.94 (1H, d, J=11.6 Hz, 1/2×OCH_2Ph), 5.61 (1H, d, J=1.5 Hz, H-2), 7.23–7.35 (20H, m); δ_C (67.9 MHz, $CDCl_3$) 50.9, 68.0, 72.5, 73.5, 73.5, 74.4, 74.6, 76.3, 78.5, 81.6, 99.4 (C=*C*H), 127.5, 127.6, 127.7, 127.8, 127.9, 127.9, 128.2, 128.4, 137.5 (C-*ipso*), 137.7 (C-*ipso*), 137.9 (C-*ipso*), 138.2 (C-*ipso*), 165.1 (*C*=CH), 165.4 (C=O); *m*/*z* (FAB) M^++Na 617.2535 [$C_{37}H_{38}O_7Na$ requires 617.2515].

4.3.5. (*Z*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, *tert*-butyl ester (*Z*)-5b. A solution of (*tert*-butoxycarbonylmethylene)tri-*n*-butylphosphorane **3b** (310 mg, 0.98 mmol) in dry toluene (2 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-galacto-1,5-lactone **2** (264 mg, 0.49 mmol) in dry toluene (2 mL) at 80°C under N_2. The reaction mixture was stirred for 12 h and concentrated under reduced pressure. The yellow residue was subjected to flash chromatography using petroleum spirit/AcOEt (6:1) to give (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, *tert*-butyl ester (*Z*)-**5b** (234 mg, 0.37 mmol, 75%) as a waxy syrup; ν_{max} (film)/cm^{-1} 1713 (st, C=O), 1650; δ_H (270 MHz, $CDCl_3$) 1.43 (9H, s, ^{t}Bu), 3.69 (1H, dd, J=9.3, 2.6 Hz, H-5), 3.73–3.83 (2H, m, H-8$_a$, H-8$_b$), 3.95 (1H, td, J=7.2, 1.4 Hz, H-7), 4.12 (1H, dd, J=2.6, 1.4 Hz, H-6), 4.40 (1H, dd, J=9.2, 1.4 Hz, H-4), 4.47–4.97 (8H, m, 4×OCH_2Ph), 5.50 (1H, d, J=1.4 Hz, H-2) and 7.25–7.36 (20H, m, 4×Ph); δ_C (101 MHz, $CDCl_3$) 28.7, 68.3, 73.0, 74.0, 74.1, 74.7, 75.1, 76.9, 78.6, 80.0, 82.2, 102.3, 128.0, 128.12, 128.18, 128.23, 128.37, 128.38, 128.7, 128.8, 138.1, 138.2, 138.5, 138.9, 164.0 and 165.0; *m*/*z* (FAB) M^++Na 659.2971 [$C_{40}H_{44}O_7Na$ requires 659.2985].

4.3.6. (*Z*)- and (*E*)-3,7-Anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enononitrile 5c. A solution of (cyanomethylene)tri-*n*-butylphosphorane **3c** (269 mg, 1.11 mmol) in dry CH_2Cl_2 (1.5 mL) was added to a solution of 2,3,4,6-tetra-*O*-benzyl-D-galacto-1,5-lactone **2** (295 mg, 0.56 mmol) in dry CH_2Cl_2 (1.5 mL) at 40°C under N_2. The reaction mixture was stirred 20 h and concentrated under reduced pressure. The yellow residue (659 mg), which had a *Z*/*E* isomer ratio of 4.7:1 as determined by ^{1}H NMR, was subjected to flash chromatography using petroleum spirit/Et_2O (2:1) to give first (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enononitrile (*E*)-**5c** (45 mg, 10%) as a colourless oil. From the later fractions (*Z*)-3,7-anhydro-2-deoxy-4,5,6,8-tetra-*O*-benzyl-D-galacto-oct-2-enononitrile (*Z*)-**5c** (212 mg, 68%) was obtained as a white solid.

Less polar product: (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enononitrile (*E*)-**5c**; $[\alpha]_D^{21}=+13.4$ (*c* 0.81, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2216 (C≡N), 1632 (C=C); δ_H (270 MHz, $CDCl_3$) 3.65 (1H, dd, *J*=10.0, 5.2 Hz, H-8_a), 3.70 (1 H, dd, *J*=10.0, 6.4 Hz, H-8_b), 3.86 (1H, dd, *J*=5.2, 3.2 Hz, H-5), 4.11 (1H, t, *J*=3.2 Hz, H-6), 4.32 (1H, td, *J*=5.8, 3.2 Hz, H-7), 4.45–4.83 (9H, m, 4×OCH_2Ph and H-4), 5.02 (1H, s, H-2) and 7.17–7.36 (20H, m, 4×Ph); δ_C (62.9 MHz, $CDCl_3$) 68.2, 71.8, 72.3, 72.9, 73.4, 73.5, 74.6, 78.5, 78.6, 82.2, 116.9 (C≡N), 127.7, 127.8, 127.9, 128.0, 128.2, 128.4, 128.4, 128.5, 137.0 (C-*ipso*), 137.3 (C-*ipso*), 137.6 (C-*ipso*), 137.7 (C-*ipso*) and 169.9 (*C*=CH); *m*/*z* (FAB) M^++Na 562.2604 [$C_{36}H_{35}NO_5Na$ requires 562.2593].

More polar product: (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enononitrile (*Z*)-**5c**; mp 100–102°C; $[\alpha]_D^{21}=+88.7$ (*c* 1.04, $CHCl_3$); (found: C, 76.6; H, 6.5; N, 2.5. $C_{36}H_{35}NO_5$ requires C, 77.0; 6.3; N, 2.5%); ν_{max} (KBr)/cm^{-1} 2220 (C≡N) and 1633 (C=C); δ_H (400 MHz, C_6D_6) 3.31 (1H, dd, *J*=9.8, 2.5 Hz, H-5), 3.58–3.63 (2H, m, H-7, H-8_a), 3.74 (1H, dd, *J*=10.4, 9.9 Hz, H-8_b), 3.84 (1H, dd, *J*=2.5, 1.2 Hz, H-6), 4.18 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.20 (1H, d, *J*=11.3 Hz, 1/2×OCH_2Ph), 4.25 (1H, d, *J*=11.9 Hz, 1/2×OCH_2Ph), 4.30 (1H, d, *J*=11.8 Hz, 1/2×OCH_2Ph), 4.32 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.37 (1H, dd, *J*=9.8, 1.8 Hz, H-4), 4.47 (1H, d, *J*=11.4 Hz, 1/2×OCH_2Ph), 4.49 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph), 4.81 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph), 4.93 (1H, d, *J*=1.8 Hz, H-2) and 7.06–7.27 (20H, m, 4×Ph); δ_H (270 MHz, $CDCl_3$) 3.67–3.76 (3H, m), 4.00 (1H, dd, *J*=6.9, 6.4 Hz), 4.14 (1H, s, 2-H), 4.46 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.54 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph), 4.68 (1H, d, *J*=11.4 Hz, 1/2×OCH_2Ph), 4.71 (2H, s, OCH_2Ph), 4.71–4.79 (1H, m), 4.85 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph), 4.93 (1H, d, *J*=11.4 Hz, 1/2×OCH_2Ph), 5.02 (1H, d, *J*=1.5 Hz, H-2) and 7.22–7.33 (20H, m, 4×Ph); *m*/*z* (FAB) M^++Na 562.2610 [$C_{36}H_{35}NO_5Na$ requires 562.2593].

4.3.7. Attempted reduction of (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester (*Z*)-4a using a modest excess of Et_3SiH–CF_3CO_2H. Trifluoroacetic acid (151 mg, 0.32 mmol) was added to a solution of triethylsilane (37 mg, 0.32 mmol) and (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid methyl ester (*Z*)-**4a** (79 mg, 0.13 mmol) in dry CH_2Cl_2 (5 mL) at 18°C. The reaction mixture was stirred for 2 h and concentrated under reduced pressure. $CHCl_3$ (3×3 mL) was repeatedly added to the residue and evaporated in order to eliminate traces of volatile reagents and by-products. The crude product was subjected to flash chromatography using a gradient from petroleum spirit/AcOEt (5:1) to CH_2Cl_2 and then Et_2O to give methyl (2,3,4,6-tetra-*O*-benzyl-1-hydroxy-D-glucopyranosyl)-acetate **9a** (20 mg, 25%) as an oil; ν_{max} (film)/cm^{-1} 3433 (O–H), 1720 (C=O); δ_H (270 MHz, $CDCl_3$) 2.30 (1H, d, *J*=15.5 Hz, 1/2×CH_2CO_2), 2.74 (1H, d, *J*=15.5 Hz, 1/2×CH_2CO_2), 3.32 (1H, dd, *J*=9.5, 1.4 Hz), 3.59–3.76 (4H, m), 3.66 (1H, s, CO_2Me), 4.00 (1H, ddd, *J*=10.1, 3.6, 1.9 Hz, H-7), 4.13 (1H, dd, *J*=9.3, 8.7 Hz), 4.48, 4.58, 4.62, 4.65, 4.84, 4.97 (6H, 6×d, *J*=10.9–12.3 Hz, 3×OCH_2Ph), 4.91 (2H, s, OCH_2Ph), 5.29 (1H, s, OH), 7.17–7.42 (20H, m, 4×Ph); δ_C (62.9 MHz, $CDCl_3$) 40.3 (CH_2), 52.0 (CH_3), 68.5, 71.5, 73.2, 74.9, 75.2, 75.6, 77.2, 78.5, 81.8, 83.2, 97.0, 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.3 (CH), 128.47 (CH), 128.52 (CH), 128.5 (CH), 137.8 (C-*ipso*), 138.3 (C-*ipso*), 138.6 (C-*ipso*), and 172.8 (C=O); *m*/*z* (FAB) M^++Na 635.2649 [$C_{37}H_{40}O_8Na$ requires 635.2621]; some of starting material (*Z*)-**4a** (3 mg, 4%) was recovered and several other products were formed but could not be isolated.

4.3.8. Methyl (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetate (β-6a) by reduction of (*Z*)-4a using a large excess of Et_3SiH–CF_3CO_2H. Trifluoroacetic acid (21.5 mL, 0.28 mol) was added to a solution of triethylsilane (10.7 mL, 67.3 mmol) and (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester (*Z*)-**4a** (1.67 g, 2.8 mmol) in dry CH_2Cl_2 (30 mL) at 18°C. The reaction mixture was stirred for 2 h and concentrated under reduced pressure. $CHCl_3$ (3×3 mL) was added to the residue and evaporated to eliminate traces of volatile reagents and by-products. The crude material was subjected to flash chromatography using a gradient from petroleum spirit/Et_2O (5:2) to CH_2Cl_2/Et_2O (10:1) to give the following products.

Less polar product: methyl (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetate (β-**6a**) (0.84 g, 50%) as a white solid; mp 65–67°C (lit.,[17] 65–66°C), $[\alpha]_D^{23}=-5.2$ (*c* 0.92, $CHCl_3$) (lit.,[17] $[\alpha]_D^{20}=-3.5$; *c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 1745 (C=O); δ_H (270 MHz, $CDCl_3$) 2.48 (1H, dd, *J*=15.3, 8.2 Hz, 1/2×CH_2CO_2), 2.74 (1H, dd, *J*=15.3, 4.0 Hz, 1/2×CH_2CO_2), 3.37 (1H, t, *J*=9.2 Hz, H-3), 3.47 (1H, ddd, *J*=9.5, 3.1, 2.9 Hz, H-5), 3.60 (1H, s, CO_2Me), 3.62–3.79 (5H, m, H-1, H-2, H-4, H-6_a, H-6_b), 4.50–4.92 (8H, m, 4×OCH_2Ph), 7.14–7.36 (20H, m, 4×Ph); δ_C (62.9 MHz, $CDCl_3$) 37.4 (CH_2), 51.6 (CH_3), 68.6, 73.3, 74.96, 75.01, 75.5, 75.8, 78.4, 79.1, 81.2, 87.1, 127.5 (CH), 127.67 (CH), 127.71 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.37 (CH), 128.40 (CH), 128.4 (CH), 137.9 (C-*ipso*), 138.06 (C-*ipso*), 138.13 (C-*ipso*), 138.4 (C-*ipso*) and 171.4 (C=O).

More polar product: 3-[1,2,4-tris(benzyloxy)-3-hydroxybutyl]isochroman-4-acetic acid, methyl ester **11** (55 mg, 3%) as a white solid; mp 65–66°C, $[\alpha]_D^{24}=+28.4$ (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 3518 (O–H), 1717 (C=O); δ_H (600 MHz, $CDCl_3$) 2.00 (1H, d, *J*=3.0 Hz, OH), 2.53 (1H, dd, *J*=15.6, 7.8 Hz, 1/2×CH_2CO_2), 2.77 (1H, dd, *J*=15.6, 3.6 Hz, 1/2×CH_2CO_2), 3.29 (1H, ddd, *J*=9.6, 9.3, 3.0 Hz, H-3′), 3.42–3.45 (2H, m, H-2′, H-3), 3.61 (1H, dd, *J*=9.0, 8.4 Hz, H-1′), 3.63–3.66 (1H, m, H-4), 3.67 (3H, s, OCH_3), 3.67–3.70 (2H, m, H-$4'_a$, H-$4'_b$), 4.02 (1H, d, *J*=15.6 Hz, 1/2×OCH_2Ph), 4.06 (1H, d, *J*=15.6 Hz, 1/2×OCH_2Ph), 4.51 (1H, d, *J*=12.6 Hz, 1/2×OCH_2Ph), 4.56 (1H, d, *J*=10.8 Hz, 1/2×OCH_2Ph), 4.60 (1H, d, *J*=12.6 Hz, 1/2×OCH_2Ph), 4.60 (1H, d, *J*=12.6 Hz, 1/2×OCH_2Ph), 4.73 (1H, d, *J*=10.8 Hz, 1/2×OCH_2Ph), 4.75 (1H, d, *J*=12.0 Hz, 1/2×OCH_2Ph), 4.92 (1H, d, *J*=12.0 Hz, 1/2×OCH_2Ph), 7.06–7.07 (2H, m, Ph), 7.13–7.18 (5H, m, Ph), 7.22–7.27 (7H, m, Ph), 7.30–7.33 (5H, m, Ph) and 7.40 (1H, dd, *J*=7.2, 1.2 Hz, Ph); δ_C (62.9 MHz, $CDCl_3$) 37.7

(CH_2), 38.4 (CH_2), 51.7 (CH_3), 68.8 (CH_2), 73.0 (CH_2), 73.5 (CH_2), 73.8 (CH), 74.7 (CH_2), 76.0 (CH), 78.3 (CH), 79.3 (CH), 86.7 (CH), 126.2 (CH), 126.8 (CH), 127.6 (CH), 127.78 (CH), 127.84 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 130.7 (CH), 136.9 (C-*ipso*), 138.1 (C-*ipso*), 138.2 (C-*ipso*), 138.7 (C-*ipso*), 140.4 (C-*ipso*) and 171.8 (C=O); *m/z* (FAB) M^++Na 619.2692 [$C_{37}H_{40}O_7Na$ requires 619.2672].

4.3.9. Methyl (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetate (β-6a) by reduction of (*Z*)-4a using Et_3SiH–$BF_3{\cdot}Et_2O$. $BF_3{\cdot}Et_2O$ (1.69 mL, 13.43 mmol) was added to a solution of triethylsilane (8.84 mL, 55.40 mmol) and (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-gluco-oct-2-enonic acid, methyl ester (*Z*)-**4a** (1.025 g, 1.72 mmol) in dry CH_2Cl_2 (5 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 23 h at room temperature and quenched with a saturated solution of $NaHCO_3$ (10 mL). After the addition of H_2O (50 mL), the reaction mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a colourless oil; this was recrystallised using ether and petroleum spirit to give β-**6a** as white crystals (808 mg, 80%), identical by ^1H NMR with material from the previous experiment.

4.3.10. Methyl (2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)acetate (β-7a) and methyl (tri-*O*-benzyl-β-D-galactopyranosyl)acetate (β-12a) by reduction with (*Z*)-5a with excess Et_3SiH–CF_3CO_2H. Trifluoroacetic acid (4.10 mL, 53.55 mmol) was added to a solution of (*Z*)-3,7-anhydro-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*Z*)-**5a** (319 mg, 0.54 mmol) and triethylsilane (1.494 g, 12.85 mmol) in dry CH_2Cl_2 (6 mL) at 18°C under nitrogen. The reaction mixture was stirred for 2 h and concentrated under reduced pressure. The waxy residue (317 mg) was subjected to flash chromatography using gradients from CH_2Cl_2 to petroleum spirit/Et_2O (1:1) to CH_2Cl_2/Et_2O (20:1) to give the following products.

Less polar product: methyl (2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)acetate β-**7a** (132 mg, 41%) as a colourless oil; $[\alpha]_D^{23}$=+1.3 (*c* 0.93, $CHCl_3$) lit.[3] $[\alpha]_D^{20}$=+8.6 (*c* 1.3, $CHCl_3$); ν_{max} (film)/cm^{-1} 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 2.49 (1H, dd, *J*=15.3, 7.9 Hz, 1/2×CH_2CO_2), 2.76 (1H, dd, *J*=15.3, 3.4 Hz, 1/2×CH_2CO_2), 3.53–3.60 (6H, m, H-5, H-6_a, H-6_b, CO_2Me), 3.63 (1H, dd, *J*=9.3, 2.6 Hz, H-3), 3.72 (1H, dd, *J*=9.3, 9.3 Hz, H-2), 3.76 (1H, td, *J*=9.3, 3.7 Hz, H-1, homonuclear decoupling confirms coupling to CH_2CO_2), 4.00 (1H, d, *J*=2.5 Hz, H-4), 4.40 (1H, d, *J*=11.8 Hz, 1/2×OCH_2Ph), 4.45 (1H, d, *J*=11.8 Hz, 1/2×OCH_2Ph), 4.60 (1H, d, *J*=11.6 Hz, 1/2×OCH_2Ph), 4.61 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph), 4.65 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.74 (1H, d, *J*=11.7 Hz, 1/2×OCH_2Ph), 4.92 (1H, d, *J*=11.6 Hz, 1/2×OCH_2Ph), 4.97 (1H, d, *J*=11.1 Hz, 1/2×OCH_2Ph) and 7.22–7.35 (20H, m, 4×Ph); δ_C (100.6 MHz, $CDCl_3$) 37.8 (CH_2), 51.6 (CH_3), 68.7 (CH_2), 72.2 (CH_2), 73.5 (CH_2), 73.9 (CH), 74.6 (CH_2), 75.2 (CH_2), 76.4 (CH), 77.2 (CH), 78.2 (CH), 84.8 (CH), 127.6 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 138.0 (C-*ipso*), 138.2 (C-*ipso*), 138.3 (C-*ipso*), 138.8 (C-*ipso*) and 171.6 (C=O); *m/z* (FAB) M^++Na 619.2690 [$C_{37}H_{40}O_7Na$ requires 619.2672].

The more polar product was considered to be substantially one regioisomer of methyl (tri-*O*-benzyl-β-D-galactopyranosyl)acetate β-**12a** (38 mg, 15%), which was obtained as a colourless, viscous oil, $[\alpha]_D^{32}$=+30.4 (*c* 1.03, $CHCl_3$); ν_{max} (film)/cm^{-1} 3450 (br, O–H) and 1738 (C=O); δ_H (250 MHz, C_6D_6) 2.09 (1H, br, OH), 2.64 (1H, dd, *J*=15.7, 8.6 Hz, CHCO_2Me), 2.99 (1H, dd, *J*=15.7, 2.5 Hz, CHCO_2Me), 3.19 (1H, dd, *J*=8.8, 2.8 Hz, H-3), 3.39 (3H, s, CO_2Me), 3.59–3.68 (2H, m, H-6_a and H-6_b), 3.78–3.84 (1H, m, H-5), 3.87–3.96 (2H, m, H-2 and H-4, appearance changes on irradiation of OH or H-3), 4.02 (1H, td, *J*=ca. 9, 3 Hz, 1-H, collapses on irradiation of either CHCO_2Me proton), 4.16–4.42 (4H, m, 2×OCH_2Ph), 4.59 (1H, d, *J*=11.3 Hz, 1/2×OCH_2Ph), 4.90 (1H, d, *J*=11.3 Hz, 1/2×OCH_2Ph), 7.10–7.41 (15H, m, 3×Ph); δ_C (101 MHz, $CDCl_3$) 37.7, 51.7, 68.5, 70.2, 71.7, 72.7, 73.5, 74.5, 76.5, 77.3, 83.9, 127.6, 127.77, 127.82, 127.9, 128.1, 128.3, 128.4, 128.7, 137.7, 137.9, 138.5 and 172.0; *m/z* (ES) 524.2650 [M+NH_4^+ requires 524.2643].

4.3.11. Reduction of (*E*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*E*)-5a using Et_3SiH–$BF_3{\cdot}Et_2O$: formation of β-7a. Boron trifluoride diethyl ether complex (20 μL, 0.16 mmol) was added to a mixture of triethylsilane (0.11 mL, 0.66 mmol) and (*E*)-**5a** (12 mg, 0.021 mmol) in dry CH_2Cl_2 (0.5 mL) under N_2 at 0°C. The reaction mixture was stirred overnight at room temperature and quenched with a saturated solution of $NaHCO_3$ (5 mL). After the addition of H_2O (10 mL), the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow waxy product, which was subjected to flash chromatography using petroleum spirit/Et_2O (1:1) to give β-**7a** (6 mg, 50%) identical by ^1H and ^{13}C NMR to β-**7a** prepared in the preceding experiment.

4.3.12. Methyl (2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)acetate (β-7a) by reduction of (*Z*)-5a using Et_3SiH–$BF_3{\cdot}Et_2O$. $BF_3{\cdot}Et_2O$ (0.345 mL, 2.72 mmol) was added to a mixture of Et_3SiH (1.8 mL, 11.2 mmol) and (*Z*)-3,7-anhydro-4,5,6,8-tetra-*O*-benzyl-2-deoxy-D-galacto-oct-2-enonic acid, methyl ester (*Z*)-**5a** (206.7 mg, 0.348 mmol) in dry CH_2Cl_2 (1 mL) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 23 h at room temperature, then diluted with CH_2Cl_2 (10 mL) and added to a stirred, saturated, ice-cold aqueous solution of $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried ($MgSO_4$), evaporated and subjected to flash chromatography (2:1 petrol/Et_2O) to give β-**7a** (149 mg, 72%), identical by ^1H NMR to the samples prepared in the two preceding experiments.

4.3.13. Methyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)ethanoate (β-8a). A solution of methyl (2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)acetate (β-**6a**) (100 mg, 0.168 mmol) in MeOH/THF (2 mL/0.3 mL) was stirred

under hydrogen at atmospheric pressure over 20% $Pd(OH)_2$ on charcoal (25 mg) for 20 h. The reaction mixture was filtered through Celite® and concentrated under reduced pressure to a waxy residue, which was dissolved in a mixture of pyridine (1 mL) and acetic anhydride (0.5 mL). The reaction mixture was stirred overnight at room temperature under N_2 and concentrated under reduced pressure to give a white residue, which was subjected to flash chromatography using petroleum spirit/AcOEt (3:2) to give methyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-ethanoate (β-**8a**) (59 mg, 0.25 mmol, 87%) as a white solid; mp 110–112°C (lit.[18] 108°C); ν_{max} (film)/cm^{-1} 1742 (st C=O), 1729 (st, C=O); δ_H (600 MHz, $CDCl_3$) 2.00 (3H, s, OAc), 2.02 (3H, s, OAc), 2.03 (3H, s, OAc), 2.11 (3H, s, OAc), 2.49 (1H, dd, J=16.0, 4.4 Hz, 1/2×CH_2CO$_2$), 2.58 (1H, dd, J=16.0, 7.7 Hz, 1/2×CH_2CO$_2$), 3.67–3.73 (1H, m, H-5), 3.70 (3H, s, CO$_2$*Me*), 3.96 (1H, ddd, J=9.9, 7.7, 4.4 Hz, H-1), 4.06 (1H, dd J=12.4, 2.2 Hz, H-6$_a$), 4.25 (1H, dd, J=12.4, 4.7 Hz, H-6$_b$), 4.93 (1H, dd, J=9.9, 9.4 Hz, H-2), 5.07 (1H, dd, J=9.6, 9.6 Hz, H-4), and 5.20 (1H, dd, J=9.4, 9.4 Hz, H-3); δ_C (62.9 MHz, $CDCl_3$) 20.6, 37.0, 51.9, 62.0, 68.4, 71.4, 74.1, 74.4, 75.7, 169.4, 169.6, 170.2, 170.4, and 170.6; *m/z* (FAB) M^++H 405.1408. [$C_{37}H_{40}O_7Na$ requires 405.1397].

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