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Stereoselective synthesis and structure elucidation of spiro-ketodisaccharides

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Abstract—Cycloglycosylation of 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranoses (**2a**–**c**) was carried out stereoselectively under the catalysis of Lewis acid to afford two spiro-cyclodisaccharides **3a**–**c** and **4a**–**c** in good yields. The reaction provided the kinetic products **3a**–**c** or the thermodynamic products **4a**–**c** as the predominant products under different conditions, respectively. The unprotected disaccharides **5a**–**c** and **6a**–**c** and the acetylated derivatives **7a**–**c** and **8a**–**c** were prepared by catalytic hydrogenation and followed by acetylation. The structures of compounds **4a**–**c**, **6a**–**c** and **8a**–**c** were confirmed to be α,β-anomeric configuration with chair–chair–chair form for the tri-cycles based on the X-ray crystallographic analysis of **6a**–**c**. The α,α-anomeric configurations of compounds **3a**–**c**, **5a**–**c** and **7a**–**c** were determined based on the measurements of the three bond coupling constants $^3J_{C,H}$ between the C-1 and the H-3 of **7a**–**c**.

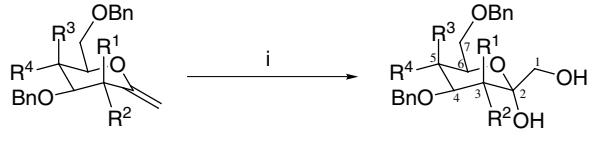
1. Introduction

The interesting properties that the various kinds of cyclodextrin inclusion complexes often exhibit enzymatic reactivity have attracted great attention to the chemical synthesis of cyclodextrins and their analogues.[1] For example, the total syntheses of natural and unnatural cyclodextrins, and some cyclic macroethers containing or with pendent aldose moieties have been reported in recent years.[2] However, stereoselective and efficient synthesis of their analogues involving different size of cycles or different kind of glycosyl linkage is still an exciting challenge.

We have previously reported the efficient glycosidations of methylenesugars and ketopyranoses under mild conditions, in which the glycosidations took place α-stereoselectively and afforded α-ketodisaccharides in excellent yields.[3,4] Taking advantage of the α-stereoselective glycosidation, we assumed that the application of this α-stereoselective reaction in the tandem manner of iterative glycosylation and intramolecular cyclo-glycosylation using 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranose **2a**–**c** would produce α-1,2-glycosyl-linked cyclic ketosaccharides, providing a convergent synthesis of cyclo-macroethers connecting glycosyl residues.[5] However, the reaction was found to give two isomers of spiro-ketodisaccharides, not only α,α-isomer **3a**–**c**, but also α,β-isomer **4a**–**c** as the major product under the theromdynamic conditions.[6] The formation of the unexpected α,β-isomer prompted us to investigate the glycosylation reaction in details and to confirm the structures of the products. We now report the stereoselective synthesis of the spiro heptulopyrano-disaccharides and their structural elucidation by X-ray crystallographic and NMR analyses.

2. Results and discussion

The requisite starting materials, 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranoses (**2a**–**c**) were prepared as shown in



1a~c **2a~c**

	R^1	R^2	R^3	R^4	Yield of **2** (%)
a	H	OBn	H	OBn	91.4%
b	H	OBn	OBn	H	93.8%
c	OBn	H	H	OBn	89.4%

Scheme 1. *Reagents and conditions*: (i) *N*-Methylmorpholine *N*-oxide (NMO) (2.0 equiv.), OsO_4 (5% mol), acetone/H_2O (5:2), rt, overnight.

Keywords: cycloglycosylation; spiro-ketodisaccharide; α-D-hept-2-ulopyranose; three-bond carbon–proton coupling constant $^3J_{C,H}$; X-ray crystallographic structure.

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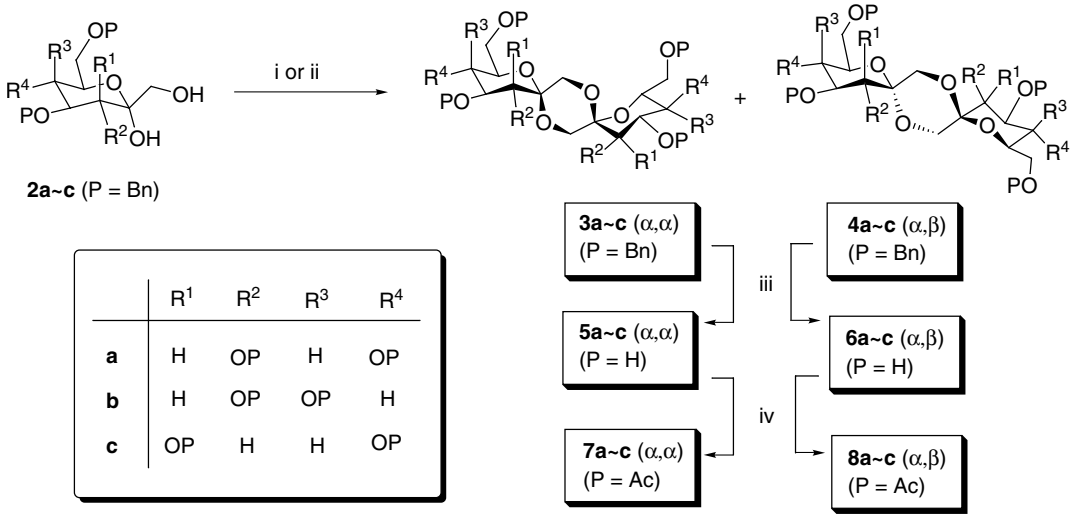


	R^1	R^2	R^3	R^4
a	H	OP	H	OP
b	H	OP	OP	H
c	OP	H	H	OP

Scheme 2. *Reagents and conditions*: (i) (Method A): TfOH (1.5 equiv.), $CaSO_4$, CH_2Cl_2, −78°C→rt; (ii) (Method B): TsOH (1.0 equiv.), TfONa (1.0 equiv.), Et_2O, reflux; (iii) $Pd(OH)_2$/C, CH_3OH, H_2 (1 atm), rt; (iv) Ac_2O, pyridine, rt.

Scheme 1 by the oxidation of the corresponding 1-methylenesugars (**1a**–**c**) using the combination of *N*-methylmorpholine *N*-oxide (NMO) and OsO_4 as the oxidant.[7,8] The reaction proceeded in high α-stereoselectivity with producing trace β-isomer.

Treatment of 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranoses (**2a**–**c**) with Lewis acid afforded two spiro ketodisaccharides **3a**–**c** and **4a**–**c**, respectively (Scheme 2). This self-condensation reaction might involve the tandem two steps of glycosylation of **2a**–**c** in which a disaccharide is formed initially, and then intramolecular cycloglycosylation takes place to give the products **3a**–**c** and **4a**–**c**. The structures of the compounds **3a**–**c** and **4a**–**c** were confirmed to be of α,α- and α,β-anomeric conformations by the instrumental analysis.

While various anomeric activation methods have been used in the glycosylation of ketoses,[9] there are a few reports on the direct glycosylation of ketoses like **2a**,[6,10] excluding the treatment of D-fructose and L-sorbose by strong protonic acids.[11,12] Thus, the reaction conditions were examined with **2a** as shown in Table 1. Although TMSOTf was a very efficient catalyst for the glycosidation of 1-deoxy-hept-2-ulopyranoses,[4] it seemed not effective for this reaction (entry 1). Furthermore, in the presence of a TMS-containing reagent, the primary 1-hydroxy group of **2a** was silylated to give the compound **A**[13] (entries 2 and 3). After

Table 1. Reaction conditions of **2a** under the catalysis of a Lewis acid

Entry	Lewis acid (equiv.)	Solvents	Conditions	Yield (%)[a]	**3a**: **4a**[b]
1	TMSOTf (1.0)	CH_2Cl_2	rt, 12 h	28.0[c,d]	1.0:1.4
2	TMSOTf (1.0), CSA (1.0)	CH_2Cl_2	−78°C, 1 h→rt, 1 h	**A** (39.8%)[d]	
3	$Yb(OTf)_3$ (0.2),TMSCl (1.5)	CH_2Cl_2	rt, 2 days	**A** (48.8%)[d]	
4	$BF_3{\cdot}Et_2O$ (1.5)	CH_2Cl_2	−78°C, 1 h→rt, 2 h	Trace[d]	
5	CSA (1.0)	CH_2Cl_2	0°C, 4 h	19.9[d]	1.0:1.0
6	$TiCl_4$ (1.0)	CH_2Cl_2	−78°C, 1 h→rt, 2 h	43.2	1.0:1.1
7	$SnCl_4$ (1.0)	CH_2Cl_2	−78°C, 1 h→rt, 2 h	40.6	1.0:1.0
8	TfOH (1.0)	CH_2Cl_2	−78°C, 1 h→rt, 2 h	58.4	1.0:1.1
9	TfOH (1.5)	CH_2Cl_2	−78°C, 1 h→rt, 1 h	68.9	1.1:1.0
10	TfOH (1.5)	CH_2Cl_2	−78°C, 3 h	58.2	1.5:1.0
11	TfOH (1.5)	Et_2O	−78°C, 1 h→rt, 2 h	No reaction	
12	TfOH (1.5)	THF	0°C, 1 h→rt, 2 h	No reaction	
13	TfOH (1.5), TfONa (2.0)	CH_2Cl_2	−78°C, 3 h→0°C, 2 h	48.9	1.2:1.0
14	TfOH (1.5), TfOK (2.0)	CH_2Cl_2	−78°C, 3 h→0°C, 2 h	54.3	1.2:1.0
15	TsOH (1.0)	CH_2Cl_2	Reflux, 10 h	25.4[d]	1.0:6.9
16	$Yb(OTf)_3$ (0.25)	CH_2Cl_2	Reflux, 10 h	29.0	1.0:6.3
17	TsOH (1.0), TfONa (1.0)	CH_2Cl_2	Reflux, 1 h	38.0	1.0:5.8
18	TsOH (1.0), TfONa (1.0)	Et_2O	Reflux, 3 h	51.6	1.0:6.5
19	TsOH (1.0), TfONa (1.0)	Et_2O	Reflux, 5 h	72.7	1.0:7.0
20	TsOH (1.0), TfONa (1.0)	THF	Reflux, 2 h	Many spots on TLC	
21	TsOH (1.0), TfOK (1.0)	CH_2Cl_2	Reflux, 1 h	47.1	1.0:1.6
22	TsOH (1.0), TfOK (1.0)	Et_2O	Reflux, 3 h	59.8	1.0:6.7
23	TsOH (1.0), TsONa (1.0)	Et_2O	Reflux, 10 h	27.2[d]	1.0:7.1

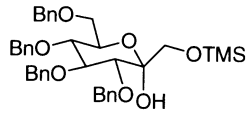
[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] 10% of **A** was obtained.
[d] **2a** was partially recovered.

Table 2. The cyclo-glycosylation of **2a–c** under different conditions

Entry	2	Method[a] (reaction time)	Total yield[b] (%)	3 (%)	4 (%)	3:4[c]
1	**2a**	A	65.9			1.1:1[d]
2	**2b**	A	56.4	29.9	26.5	1.1:1
3	**2c**	A	68.9	43.5	25.4	1.7:1
4	**2a**	B (5 h)	72.7			1:7.0[d]
5	**2b**	B (3 h)	75.9	12.5	63.4	1:5.1
6	**2c**	B (5 h)	78.0	30.5	47.5	1:1.6
7	**2c**	B (5 h)[e]	84.1	27.3	56.8	1:2.1

[a] Method A: TfOH (1.5 equiv.), $CaSO_4$, CH_2Cl_2, −78°C→rt; Method B: TsOH (1.0 equiv.), TfONa (1.0 equiv.), Et_2O, reflux.
[b] Isolated yields.
[c] Calculated according to the isolated yields except in the case of **2a** (entries 1 and 4).
[d] The ratio was estimated according to ^1H NMR spectrum.
[e] KOTf (1.0 equiv.) was used instead of NaOTf (1.0 equiv.).

scanning with various Lewis acids such as $SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$, and TfOH (entries 4–8), it was found that under the mild conditions of −78°C, a strong Lewis acid was necessary for promoting the reaction (entries 7–10), and the formation of **3a** and **4a** in good yield was achieved with 1.5 equiv. of TfOH in CH_2Cl_2 solution (entry 9). Moreover, the solvent was also important in the reaction. For example, the reaction did not proceed in Et_2O or THF (entries 11 and 12) probably due to weakening the acidity of the Lewis acid by solvation.



Compound **A**

An attempt to prepare cyclic macroethers with tri-, tetra- or pentasaccharide oligomers by the metallic cation Na^+ or K^+ which facilitates to coordinate with **2a** for the cyclic macroether formation was also unsuccessful (entries 13 and 14).

The relative ratio of **3a** and **4a** was affected by the reaction temperature, and **4a** became the major product as the reaction temperature increased (entries 9 and 10). This was evidently supported by the experiments at reflux temperature (entries 15–23). As shown in entry 19, the reaction provided **3a** and **4a** in 72.7% with the ratio of 1:7 after refluxing the Et_2O solution for 5 h catalyzed by the combination of TsOH (1.0 equiv.) and TfONa (1.0 equiv.) which might generate a proper amount of strong Lewis acid (TfOH) in situ, promoting the reaction going well. Comparatively, the combination of TsOH and TsONa seemed not strong enough for completing the reaction (entry 23).

As described above, the glycosylation of **2a** proceeded stereoselectively under the promotion of a Lewis acid. The mild conditions at low temperature (−78°C) with TfOH (Method A) was benefit to the formation of **3a**, called kinetic control product, and the thermodynamic product **4a** was predominant in refluxing Et_2O solution with TsOH–TfONa or TfOK (Method B). Similarly, the reactions of **2b** and **2c** were performed under the same conditions of Method A or Method B. Thus, the corresponding spiro-keto-disaccharides **3b**, **4b** and **3c**, **4c** were afforded respectively, and the results are shown in Table 2.

It was found that the reaction of **2a–c** showed the similar stereoselectivity under the conditions of Method A or Method B. However, the α,α-stereoselectivity (**3c**) for **2c** was higher than that in the cases of **2a** and **2b** (entries 3, 6 and 7 in Table 2), probably owing to the axial 3-benzyloxy group.

In addition, the isomerization test as exemplified by **3b** showed a partial inversion from **3b** to **4b** under the thermodynamic conditions of Method B, indicating that the α,β-isomers (**4a–c**) were more stable than the α,α-isomers (**3a–c**).

The compounds **3a–c** and **4a–c** were debenzylated by hydrogenolysis under the catalysis of $Pd(OH)_2/C$ to give the corresponding unprotected disaccharides **5a–c** and **6a–c** quantitatively. Sequentially, the compounds **5a–c** and **6a–c** were acetylated with acetic anhydride in pyridine to afford the acetylated derivatives **7a–c** and **8a–c**, respectively, as shown in Table 3.

Although the mixture of **3a** and **4a** could not be separated by silica gel column chromatography, the pure **4a** was obtained as a white solid by repeated recrystallization of the mixture of **3a** and **4a** (ratio 1:7) from ethyl acetate and hexane. Debenzylation of the mixture of **3a** and **4a**, and then acetylation followed by chromatography gave the acetylated derivatives **7a** and **8a**. The unprotected disaccharide **5a** was obtained by the deacetylation of **7a**.

The compounds **3a–c** and **4a–c** were proved to be spiro ketodisaccharides by mass spectral (FAB^+) and NMR analyses. The conformation of **4a–c** and their derivatives (**6a–c** and **8a–c**) were confirmed by the instrumental analysis based on the X-ray crystallographic and NMR analyses. The structures of **3a–c**, **5a–c** and **7a–c** were elucidated according to the three-bond carbon–proton coupling constants $^3J_{C,H}$ analyses. The X-ray crystallographic structures of **6a–c** are shown in Fig. 1.

Table 3. The yields of the acetylated derivatives **7a–c** and **8a–c**

Compounds	7 (%)	8 (%)
a (Glc)	82.1	
b (Gal)	83.7	80.5
c (Man)	80.6	75.2

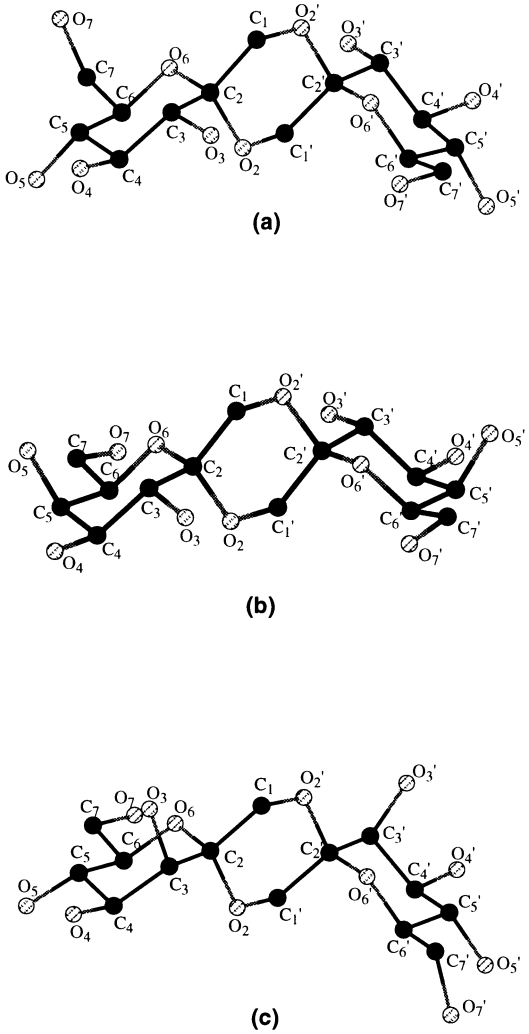


Figure 1. X-Ray crystallographic structures of the unprotected products **6a–c** represented with ball and sticks model (a) **6a**, (b) **6b**, and (c) **6c**. (Hydrogen atoms were omitted for clarity.)

The X-ray crystallographic structures of **6a–c** revealed that all of the three compounds have the same α,β-anomeric conformation with the chair–chair–chair form in the tricycles, a thermodynamically stable conformation. In this conformation, the two pyranose rings as well as the dioxane ring adopt the normal $^4C_1$ forms and are perpendicular to the dioxane ring planar. The aglyconic C_2–O_2 bond for the α-anomeric pyranose ring takes axial position, consisting with the expectation of anomeric effect. But for the β-anomeric pyranose ring, the aglyconic $C_{2'}$–$O_{2'}$ bond is equatorial, which seems inappropriate to the anomeric effect.[14] On the other hand, in the special case of the diheptulopyranose dianhydrides containing spiro tricycles, there is a alternative reference (pyranose ring or dioxane ring) for considering the anomeric effect in each anomeric center of C_2 and $C_{2'}$. Thus, taken the dioxane ring as the reference, this ring adopts the configuration of orienting both pyranonic C_2–O_6 and $C_{2'}$–$O_{6'}$ bonds axially, which responds to the anomeric effects in the two anomeric centers.[12]

In the crystals of **6a** and **6b**, water is included, and two kinds of hydrogen bonding interactions exist between the molecules. One is a direct interaction between hydroxy groups in two molecules, and the other is through the included water molecule. In the crystal of **6c**, only the direct hydrogen bonding interaction exists in multiple positions between two molecules, making the crystal arrange compactly.

Although X-ray analysis can provide the most accurate data on the conformation of carbohydrate compounds, it is not a common method due to the difficulty for preparing suitable single crystals of saccharides. So far only one of di-hexulopyranose dianhydrides, di-β-D-fructopyranose dianhydride[15] and its strontium complex[16] were reported with X-ray crystallographic analyses. Moreover, to determine the anomeric configuration of ketosaccharides by NMR was not so easy as that of aldosaccharides, because ketosaccharide does not have the anomeric proton (1-H), which is commonly used to determine the anomeric configuration of the aldosaccharide according to the vicinal coupling constant between 1-H and 2-H. In virtue of the rigid spiro tricyclic structure and molecular models, the configurations of several di-hexulopyranose dianhydrides could be estimated by ^{1}H- and ^{13}C NMR, and NOE analyses.[11,12,17]

In recent years, the three-bond carbon–proton coupling constant $^3J_{C,H}$ which related to the orientation of the 3-H and the 1-C (Fig. 2) has been successfully used for the determination of anomeric configuration of keto-glycosides in solution.[3,4,18] The structures of **3a–c**, **5a–c** and **7a–c** were established by the comparison of the coupling constants $^3J_{C\text{-}1,H\text{-}3}$ of **7a–c** with those of **8a–c** and the analysis of NOE.

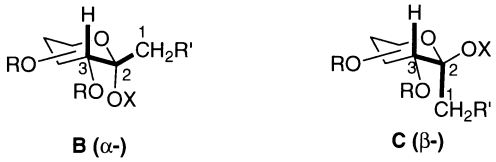
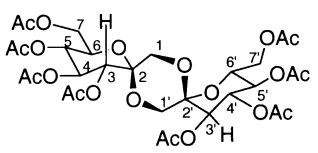


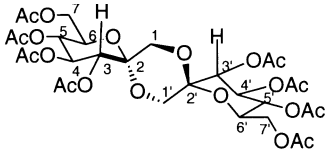
Figure 2.

The structures of the compounds **6a–c** deduced from ^{1}H- and ^{13}C NMR spectral analysis were identical to the X-ray crystallographic structures as shown in Fig. 1, indicating that the compounds **6a–c** had the same conformation in crystal and in solution. Furthermore, the compounds **4a–c** and **8a–c** gave similar sugar proton signals, that is, each corresponding sugar proton in the compounds **4a–c**, **6a–c**, and **8a–c** showed similar split pattern. Consequently, the compounds **4a–c**, and **8a–c** were proved to possess the similar sugar skeleton of α,β-configuration with chair–chair–chair form the same as the compounds **6a–c**. This indicated that the alterations of the protection groups and the polarity of solvent did not remarkably change the rigid conformation of the spiro-ketodisaccharides, which was further supported by the similar observation to the spectra of the compounds **3a–c**, **5a–c** and **7a–c**.

The ^{1}H and ^{13}C NMR spectra of the compounds **3a–c** showed the simple eight sugar proton and seven sugar



7a



8a

Figure 3.

Table 4. The three-bond coupling constants $^3J_{C\text{-}1,H\text{-}3}$ of the compounds **7a** and **8a** (Hz)

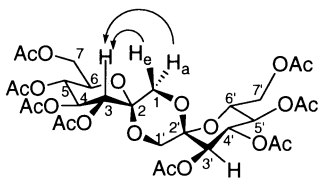
Compounds	**7**	**8** (Φ^H of **6**)[a]	
	H_3–C_1 (α)	H_3–C_1 (α)	$H_{3'}$–$C_{1'}$ (β)
a (Glc)	1.5	1.6 (46.7°)	2.7 (161.3°)
b (Gal)	1.5	1.9 (40.0°)	2.5 (158.7°)
c (Man)	1.7	1.1 (56.9°)	1.7 (55.6°)

[a] The dihedral angles Φ^H (C_1–C_2–C_3–H_3) of **6a**–**c** were approximately calculated from the dihedral angle of C_1–C_2–C_3–O_3 and the bond angle of H_3–C_3–O_3 according to their X-ray crystallographic data.

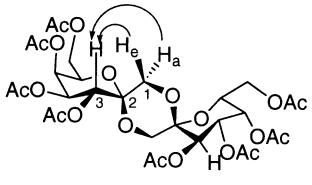
carbon signals corresponding to the monomeric unit of 3,4,5,7-tri-*O*-benzyl-D-*glyco*-hept-2-ulopyranose with the normal $^4C_1$ chair form, which implied that the two pyranose rings should have the same conformation and the molecule had C_2-symmetry. Therefore, the two anomeric carbons should possess the same configuration, namely, the compounds **3a**–**c** would be in either α,α- or β,β-anomeric configuration with $^4C_1$ chair form of pyranose rings.[17] Moreover, the compounds **5a**–**c** and **7a**–**c** gave rise to the similar NMR spectral signals for the sugar protons and carbons to the compounds **3a**–**c**, meaning that the compounds **3a**–**c**, **5a**–**c** and **7a**–**c** might be in the similar conformations for the spiro-tricycles. Thus, the anomeric configurations of the compounds **3a**–**c**, **5a**–**c** and **7a**–**c** were determined by the technique based on the measurement and comparison of the coupling constants $^3J_{C\text{-}1,H\text{-}3}$ as exemplified by **7a**–**c** and **8a**–**c** (For example, **7a** and **8a** in Fig. 3). The three-bond carbon–proton coupling constants $^3J_{C\text{-}1,H\text{-}3}$ of the compounds **7a**–**c** and **8a**–**c** are listed in Table 4.

As shown in Table 4, the coupling constants $^3J_{C\text{-}1,H\text{-}3}$ values for the α- and β-anomeric pyranose rings of **8a** and **8b** are interrelated to the theoretical expectations from the dihedral angles Φ^H of the corresponding **6a** and **6b**.[18b] It was found that the compounds **7a** and **7b** being of C_2-symmetry showed similar coupling constant $^3J_{C\text{-}1,H\text{-}3}$ values to that at the α-anomeric centers of the compounds **8a** and **8b**. Therefore, the compounds **7a** and **7b** were attested to be in α,α-anomeric configuration, not in β,β-one. However, in the case where **8c** was mannose moiety, since the dihedral angles Φ^H of C_1–C_2–C_3–H_3 for α-pyranose ring and $C_{1'}$–$C_{2'}$–$C_{3'}$–$H_{3'}$ for β-ring are similar due to the equatorial 3-proton, the coupling constants $^3J_{C\text{-}1,H\text{-}3}$ are not so much different and not suitable for distinguishing the anomeric configuration in the *manno*-ketosaccharides.

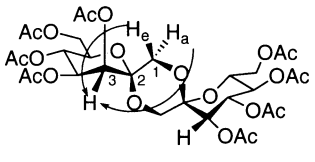
In order to establish the conformation of the α,α-isomers, NOE experiments of **7a**–**c** were performed by irradiating the dioxane protons 1-H_a and 1-H_e (Fig. 4). While no NOE interaction other than that with the geminate proton 1-H_e was observed when the 1-H_a was irradiated, the irradiation of 1-H_e resulted in NOE interactions with the axial 3-H and the *gem*-1-H_a. Thus, 1-H_e and 3-H should be in *cis*-orientation. By virtue of molecular model and taking account of the C_2-symmetric conformation and the NOE results, the compounds **7a**–**c** were confirmed to possess the α,α-anomeric configuration with chair–boat–chair form for the spiro-tricycles as shown in Fig. 4.



7a



7b



7c

	7a	**7b**	**7c**
1-H_a → 3-H	0	0	0
1-H_e → 3-H	5.49%	5.51%	5.09%
1-H_a → 1-H_e	19.57%	21.23%	16.62%
1-H_e → 1-H_a	14.87%	16.53%	18.19%

Figure 4.

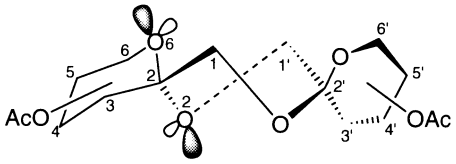


Figure 5. A lone pair of electrons on O-6 (or O-2) antiperiplanar to the bond between C-2 and O-2 (or O-6).

As concluded above that the spiro-tricyclic compounds **4a**–**c**, **6a**–**c** and **8a**–**c** with various protection groups had the same conformation and gave rise to similar NMR spectral signals on the sugar protons, the compounds **3a**–**c** and **5a**–**c** should have the same α,α-anomeric configuration with chair–boat–chair form for the spiro-tricycles as **7a**–**c** considering their similar NMR spectral signals for the sugar protons. The results were identical to the expectation of the literature.[12] Obviously, this conformation was operated by the *exo*-anomeric effects, placing a lone pair of electrons on O-6 (or O-2) antiperiplanar to the bond between C-2 and O-2 (or O-6) (as shown in Fig. 5).[12] As a result, the pyranoid C_2–O_6 bond and the O_2–$C_{1'}$ bond were kept in a *gauche* relationship when viewed on the aglyconic C_2–O_2 bond, which gave rise to a less thermodynamically favorable boat conformation for the dioxane ring.

The conformations and their corresponding energies (ΔE) of the unprotected compounds **5a**–**c** and **6a**–**c** in water were calculated[19] using MacroModel 6.0 with the mm2* force field[20] with LOMD (Low Mode) conformational search technique[21] and GB/SA solvation calculation.[22] It was shown that in all cases the two pyranoid rings were in energetically favored chair form. As for the dioxane ring, it adopted the favorable chair conformation in the α,β-isomer (**6a**–**c**), giving the chair–chair–chair conformation for the spiro-tricycles which was identical to the results of the X-ray crystallographic analysis. In the case of α,α-isomer (**5a**–**c**) the calculation could not suggest the energetically favorable conformation exactly. However, the calculated energies of the most stable conformers of the α,α-isomers (**5a**–**c**) were higher than those of the α,β-isomers (**6a**–**c**) as shown in Table 5. The result indicated that the α,β-isomers were stable than the α,α-isomers in the three series, and further supported the α,β-stereoselectivity of the cyclo-ketosylation under the thermodynamic reaction conditions.

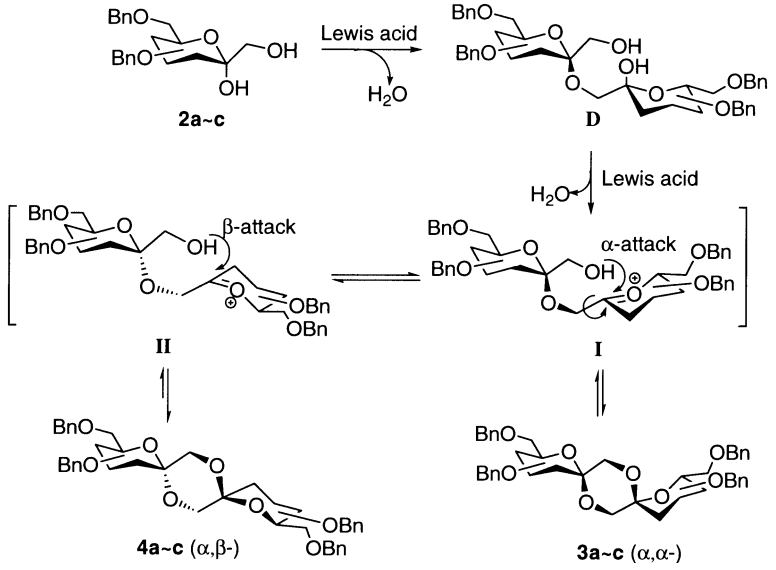
Mechanism for the formation of diketose dianhydrides by the action of protonic acids on unprotected ketose has been reported.[11a,11d] In view of the above discussion, the mechanism for the formation of the spiro-ketodisaccharides **3a**–**c** and **4a**–**c** from the corresponding α-D-hept-2-ulopyranoses (**2a**–**c**) was proposed as shown in Scheme 3.

According to this process, the reaction involved the two steps of glycosylation and cycloglycosylation of **2a**–**c**. The first step of glycosylation proceeded α-stereoselectively to afford the linear α-disaccharide (**D**).[3,4] In the second step, the disaccharides (**D**) initially generated the stable tertiary oxycarbenium ion intermediates (**I**) and (**II**) in the action of

Table 5. The differences of the calculated energy corresponding to the most stable conformation between the unprotected compounds **5a**–**c** and **6a**–**c** in water

	α,α-Isomer (**5**) $\Delta E_{\alpha,\alpha}$[a] (kcal/mol)	α,β-Isomer (**6**) $\Delta E_{\alpha,\beta}$[a] (kcal/mol)	$\Delta\Delta E(\Delta E_{\alpha,\beta}-\Delta E_{\alpha,\alpha})$ (kcal/mol)
a (Glc)	−205.83	−208.10	−2.27
b (Gal)	−208.39	−210.97	−2.58
c (Man)	−205.82	−209.05	−3.23

[a] The energy corresponding to the most stable conformation.



Scheme 3.

Lewis acid, then intramolecular cycloglycosylation took place in α-attack or β- attack manner to give the kinetic products **3a–c** or the thermodynamic products **4a–c**, respectively. Because of the equilibrium between **I** and **II**, and the reversible cycloglycosylation, the reaction stereoselectivity was mainly determined by the stability of the product and the reaction conditions. Thus, under thermodynamic conditions (reflux temperature), the more stable products **4a–c** were predominant. Under kinetic conditions (low temperature), the kinetic control products **3a–c** were formed with the competition of forming **4a–c**. In addition, the kinetic products **3a–c** could isomerize to the thermodynamically stable products **4a–c** via the intermediates **I** and **II** under the thermodynamic conditions. On the other hand, it would be reasonably understood that the different stereoselectivity was observed in the formations of the cyclic spiro-ketodisaccharides (α,β-selectivity) and the linear ketodisaccharides (α-selectivity) due to the stable α,β- configuration in the spiro-tricyclic structure.[3,4]

In conclusion, the cycloglycosylation of 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranoses (**2a–c**) was carried out under the catalysis of Lewis acid to give two spiro-cyclodisaccharides **3a–c** and **4a–c**. While the reaction with strong Lewis acid at low temperature resulted in the major formation of the kinetic products **3a–c**, the thermodynamic products **4a–c** were predominant in the use of weak Lewis acid at higher temperature. Catalytic hydrogenation and followed by acetylation of the products provided the unprotected disaccharides **5a–c** and **6a–c**, and the acetylated derivatives **7a–c** and **8a–c**, respectively. X-Ray crystallographic analyses of **6a–c** showed that the compounds **4a–c**, **6a–c** and **8a–c** were of α,β-anomeric configurations with chair–chair–chair forms in the tri-cycles. The compounds **3a–c**, **5a–c** and **7a–c** were confirmed to possess α,α-anomeric configurations with chair–boat–chair forms for the tri-cycles by the comparison of the three-bond carbon–proton coupling constants $^{3}J_{C\text{-}1,C\text{-}3}$ between **7a–c** and **8a–c**, and by the NOE analyses of **7a–c**. The stable conformation of the spiro-ketodisaccharides resulted in the stereoselectivities of the cyclo-ketoglycosylation different from that of the ketoglycosylation.

3. Experimental

3.1. General methods

Melting points were measured on a YANACO Micro Melting Point Apparatus and were uncorrected. IR spectra were recorded on a Jasco FT/IR-800 Fourier-transform infrared spectrometer. ^{1}H- and ^{13}C NMR, 2D COSY, NOE and three bond carbon–proton coupling constants $^{3}J_{C,H}$ were measured on a JEOL ECP 600 (600 MHz) NMR spectrometer in $CDCl_3$ or D_2O solutions using tetramethylsilane (Me_4Si) or methanol (CH_3OH) as the internal standards, respectively. Mass spectra (MS) and high resolution mass spectra (HRMS) were carried out on a JEOL JMS-SX102A mass spectrometer with FAB (Fast Atomic Bombardment) using 3-Nitrobenzyl alcohol (NBA) as the matrix. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. X-Ray crystallographic measurements were made on a Rigaku RAXIS-RAPID Imaging Plate Diffractometer with graphite monochromated MoKα radiation at 123 K. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in EtOH/H_2O followed by heating. Column chromatography was performed using SiO_2 (Wakogel C-200, Wako).

3.2. Calculations

Low-mode searches (LOMD)[21] for compounds **5** and **6** in water were performed using MacroModel version 6.0[20] with the mm2* derivative of mm2 force field on a Silicon Graphics IRIS-Indigo workstation. LOMD for each compound was continued until around 5,000 conformers were generated. Solvation energies were established by GB/SA model[22] installed in the software.

3.3. General procedure of preparing 3,4,5,7-tetra-*O*-benzyl-α-D-hept-2-ulopyranose (2)[7,8]. 3,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-hept-2-ulopyranose (2a)

To a solution of 1.17 g (10.0 mmol) of *N*-methylmorpholine *N*-oxide (NMO) in 50 mL of acetone and 10 mL of water was added 1 mL (2.5% w) of osmium tetraoxide (OsO_4) (0.1 mmol, 0.02 equiv.) in *tert*-butanol solution at room temperature under argon atmosphere with stirring. The solution was stirred for 5 min, then 2.7 g (5.0 mmol) of 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*gluco*-hept-1-enitol (**1a**) was added. The reaction mixture was stirred overnight, a slurry of 1.0 g of sodium hydrosulfite and 5.0 g of Florisil® in 10 mL of water was added, the mixture was stirred for 30 min, and filtered through a Celite pad. The solid was washed thoroughly with acetone. The filtrate, combined with the acetone washing, was neutralized to pH≈7 with diluted H_2SO_4 (3 mol/L). The solution was concentrated in vacuo to remove acetone, the resulting aqueous solution was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, and solvent was removed under reduced pressure. The residue was applied on silica gel chromatographic column using AcOEt/hexane (1:1 v/v) as the eluent to afford a white solid product **2a**, 2.60 g (91.4%). Mp 116–117°C, $[\alpha]^{23}_{D}$=+42.5° (*c* 0.95, $CHCl_3$) (lit.[8] mp 112.5–113.5°C, $[\alpha]_{D}$=+14.7°).

Following the procedure of preparing **2a**, the diol **2b** and **2c** were prepared from **1b** and **1c**, respectively.

3.3.1. 3,4,5,7-Tetra-*O*-benzyl-α-D-*galacto*-hept-2-ulopyranose (2b). Colorless syrup; $[\alpha]^{25}_{D}$=+15.1°, (*c* 1.0, $CHCl_3$); IR (neat): 3433.71, 3088.41, 3064.30, 3030.54, 2922.51, 2874.29, 1954.15, 1876.85, 1809.45, 1720.71, 1604.97, 1585.68, 1496.94, 1454.50, 1400.49, 1363.84, 1207.59, 1097.63, 1028.18, 914.37, 881.58, 848.78, 819.85, 736.90, 689.32 cm^{-1}; ^{1}H NMR($CDCl_3$): δ (ppm) 1.86 (s, br, 2H, OH), 3.45 (d, 1H, *J*=10.99 Hz, 1-H), 3.51–3.53 (m, 3H, 1-H and two 7-H), 4.00 (s, br 3H, 3-H, 4-H and 5-H), 4.13 (t, br, 1H, *J*=6.60 Hz, 6-H), 4.43 (d, 1H, *J*=11.54 Hz, CH_2Ph), 4.46 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.59 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.68 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.72 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.76 (d, 1H, *J*=11.54 Hz, CH_2Ph), 4.94 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.95 (d, 1H, *J*=11.00 Hz, CH_2Ph),

7.27–7.38 (m, 20H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 65.85 (1-C), 68.80 (7-C), 70.19 (6-C), 72.54 (CH_2Ph), 73.38 (CH_2Ph), 74.41 (5-C), 74.51 (CH_2Ph), 75.42 (CH_2Ph), 75.57 (3-C), 80.69 (4-C), 97.63 (anomeric 2-C), 127.50 (Ar), 127.56 (Ar), 127.61 (Ar), 127.78 (Ar), 127.84 (Ar), 127.88 (Ar), 128.01 (Ar), 128.20 (Ar), 128.36 (Ar), 128.39 (Ar), 128.41 (Ar), 128.43 (Ar), 137.74 (Ar), 137.89 (Ar), 138.31 (Ar), 138.62 (Ar); HRMS (FAB): calcd for $C_{35}H_{38}O_7Na$ 593.2516, found 593.2511.

3.3.2. 3,4,5,7-Tetra-*O*-benzyl-α-D-*manno*-hept-2-ulopyranose (2c). White solid, mp 73–74°C; $[\alpha]^{25}_D$=+31.2°, (*c* 1.0, $CHCl_3$); IR (KBr): 3416.35, 3088.41, 3063.33, 3030.54, 2868.50, 1954.13, 1878.90, 1809.45, 1726.50, 1604.97, 1496.94, 1454.50, 1394.70, 1367.70, 1275.10, 1207.59, 1091.84, 1028.18, 902.80, 734.97, 698.32 cm^{-1}; ^{1}H NMR($CDCl_3$): δ (ppm) 1.78 (s, br, 1H, OH), 3.23 (d, 1H, *J*=11.55 Hz, 1-H), 3.56 (s, br, 1H, OH), 3.65–3.71 (m, 2H, 7-H), 3.82 (s, br, 1H, 3-H), 3.83 (d, 1H, *J*=11.00 Hz, 1-H), 3.89 (t, 1H, *J*=9.35 Hz, 5-H), 3.96–3.98 (m, 1H, 6-H), 4.12 (d, br, 1H, *J*=9.35 Hz, 4-H), 4.50 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.53 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.57 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.62 (d, 1H, *J*=11.54 Hz, CH_2Ph), 4.77 (s, 2H, CH_2Ph), 4.87 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.95 (d, 1H, *J*=11.55 Hz, CH_2Ph), 7.17–7.39 (m, 20H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 66.24 (1-C), 69.74 (7-C), 72.06 (6-C), 72.71 (CH_2Ph), 73.22 (CH_2Ph), 74.37 (CH_2Ph), 74.96 (CH_2Ph), 75.41 (5-C), 76.15 (3-C), 81.59 (4-C), 97.18 (anomeric 2-C), 127.55 (Ar), 127.59 (Ar), 127.70 (Ar), 127.74 (Ar), 127.97 (Ar), 128.21 (Ar), 128.23 (Ar), 128.28 (Ar), 128.31 (Ar), 128.35 (Ar), 128.40 (Ar), 128.45 (Ar), 137.77 (Ar), 138.19 (Ar), 138.27 (Ar), 138.40 (Ar); HRMS (FAB): calcd for $C_{35}H_{38}O_7Na$ 593.2516, found 593.2521.

3.4. Cycloglycosylation reactions of 3,4,5,7-tetra-*O*-benzyl-α-D-*gluco*-hept-2-ulopyranose (2a)

Method A (promoted by TfOH at low temperature). To a solution of **2a** (114 mg, 0.2 mmol) and calcium sulfate anhydrous (Drierite®) (500 mg) in 5.0 mL of dry dichloromethane were added 27 μL (0.3 mmol, 1.5 equiv.) of triflic acid (TfOH) at −78°C under argon atmosphere with stirring. The solution was stirred at the same temperature for 1 h, then warmed up to room temperature gradually, stirred at room temperature for 1 h. Three drops of triethylamine (Et_3N) were added to quench the reaction. The solvent was removed, and the residue was applied on silica gel column chromatography eluted with AcOEt/hexane (1:4) to afford 76.1 mg (68.9%) of a mixture of **3a** and **4a** (1.1:1.0, the ratio was determined according to the ^{1}H NMR of the mixture). Similarly, different conditions with various Lewis acids were examined and the results are summarized in Table 1.

Method B (promoted by the combination of TsOH and NaOTf or KOTf at reflux temperature). To a solution of **2a** (114 mg, 0.2 mmol) in 10 mL dry Et_2O was added 38.0 mg (0.2 mmol) of $TsOH{\cdot}H_2O$ and 34.4 mg (0.2 mmol) of NaOTf. The mixture was refluxed through a short molecular sieves 4 A (MS 4 A) column under the argon atmosphere for 5 h until the reactant **2a** disappeared (TLC AcOEt/hexane=1:2). After removing the solvent, the residue was submitted to silica gel column chromatography (AcOEt/hexane=1:4) to afford a mixture of **3a** and **4a** 80.3 mg (72.7%) (**3a/4a**=1.0:7.0). Recrystallization of the mixture from AcOEt/hexane three times gave the product **4a** as a white solid. Different reaction conditions were also explored, and the results are shown in Table 1.

The cycloglycosylations of **2b** and **2c** were carried out under the same conditions of Method A and Method B to afford the corresponding spiro-ketodisaccharides **3b**, **4b** and **3c**, **4c**, respectively. The mixtures were separated by silica gel chromatographic column (AcOEt/hexane=1:4). The results are listed in the Table 2.

3.4.1. 3,4,5,7-Tetra-*O*-benzyl-α-D-*galacto*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*galacto*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (3b). Colorless syrup; $[\alpha]^{27}_D$=+72.4°, (*c* 1.0, $CHCl_3$); IR (neat): 3088.41, 3063.33, 3030.54, 2922.51, 2872.36, 1954.13, 1878.90, 1809.45, 1732.29, 1604.97, 1496.94, 1454.50, 1280.89, 1209.51, 1101.49, 1047.47, 912.44, 733.04, 696.39 cm^{-1}; ^{1}H NMR($CDCl_3$): δ (ppm) 3.49 (dd, 1H, *J*=9.35, 5.50 Hz, 7-H), 3.55 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 3.58 (dd, 1H, *J*=9.35, 7.70 Hz, 7-H), 3.73 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 3.91 (d, 1H, *J*=9.90 Hz, 3-H), 3.96–3.99 (m, 1H, 6-H), 3.99 (d, 1H, *J*=2.75 Hz, 5-H), 4.07 (dd, 1H, *J*=9.90, 2.75 Hz, 4-H), 4.38 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.43 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.60 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.74 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.76 (s, 1H, CH_2Ph), 4.77 (d, 1H, *J*=10.99 Hz, CH_2Ph), 4.92 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.95 (d, 1H, *J*=11.55 Hz, CH_2Ph), 7.14–7.16 (m, 3H, ArH), 7.24–7.36 (m, 15H, ArH), 7.40–7.42 (m, 2H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 63.93 (dioxane 1-C), 68.65 (7-C), 70.59 (6-C), 72.90 (CH_2Ph), 73.39 (CH_2Ph), 74.26 (CH_2Ph), 74.69, (CH_2Ph) 74.95 (5-C), 79.51 (3-C), 79.72 (4-C), 97.29 (anomeric 2-C), 127.11 (Ar), 127.46 (Ar), 127.49 (Ar), 127.51 (Ar), 127.52 (Ar), 128.16 (Ar), 128.17 (Ar), 128.31 (Ar), 128.33 (Ar), 128.35 (Ar), 137.98 (Ar), 138.65 (Ar), 138.80 (Ar), 138.83 (Ar); HRMS (FAB): calcd for $C_{70}H_{72}O_{12}Na$ 1127.4922, found 1127.4917.

3.4.2. 3,4,5,7-Tetra-*O*-benzyl-α-D-*manno*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (3c). Colorless syrup; $[\alpha]^{25}_D$=+78.70°, (*c* 1.0, $CHCl_3$); IR (neat): 3063.33, 3030.54, 2916.72, 2897.43, 2864.64, 1952.20, 1871.18, 1809.45, 1734.22, 1604.97, 1587.61, 1496.94, 1454.50, 1365.77, 1311.75, 1263.53, 1209.51, 1105.35, 1028.18, 908.58, 734.97, 698.32 cm^{-1}; ^{1}H NMR($CDCl_3$): δ (ppm) 3.57 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 3.70 (dd, 1H, *J*=11.00, 1.65 Hz, 7-H), 3.74 (d, 1H, *J*=2.75 Hz, 3-H), 3.79 (dd, 1H, *J*=11.00Hz, 4.65 Hz, 7-H), 3.84–3.87 (m, 2H, 6-H and dioxane 1-H) 4.02 (dd, 1H, *J*=9.35, 2.20 Hz, 4-H), 4.05 (t, 1H, *J*=9.35 Hz, 5-H), 4.48 (d, 1H, *J*=12.09 Hz, CH_2Ph), 4.54 (d, 1H, *J*=10.45 Hz, CH_2Ph), 4.63 (d, 1H, *J*=11. 54 Hz, CH_2Ph), 4.64 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.74 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.78 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.84 (d, 1H, *J*=10.45 Hz, CH_2Ph), 5.02 (d, 1H, *J*=11.55 Hz, CH_2Ph), 7.17–7.19 (m, 2H, ArH), 7.21–7.35 (m, 16H, ArH), 7.39–7.40 (m, 2H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 60.53 (dioxane 1-C), 69.08 (7-C), 72.79 (CH_2Ph), 73.29 (CH_2Ph), 73.32 (6-C), 74.60 (CH_2Ph), 74.83(two C, 5-C

and CH_2Ph), 75.39 (3-C), 81.13 (4-C), 98.18 (anomeric 2-C), 127.30 (Ar), 127.45 (Ar), 127.48 (Ar), 127.50 (Ar), 127.53 (Ar), 127.66 (Ar), 127.68 (Ar), 127.71 (Ar), 127.77 (Ar), 127.83 (Ar), 128.14 (Ar), 128.17 (Ar), 128.20 (Ar), 128.22 (Ar), 128.30 (Ar), 128.35 (Ar), 138.27 (Ar), 138.44 (Ar), 138.45 (Ar), 138.60 (Ar); HRMS: (FAB) calcd for $C_{70}H_{72}O_{12}Na$ 1127.4922, found 1127.4925.

3.4.3. 3,4,5,7-Tetra-*O*-benzyl-α-D-*gluco*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*gluco*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (4a). White solid, mp 151–152°C; $[\alpha]^{25}_D$=+47.60°, (*c* 1.0, $CHCl_3$); IR (KBr): 3088.41, 3063.33, 3030.54, 2907.08, 2864.64, 1950.27, 1871.18, 1811.38, 1747.72, 1604.97, 1496.94, 1454.50, 1369.63, 1359.98, 1280.89, 1209.51, 1155.50, 1097.63, 1070.62, 1028.18, 914.37, 736.90, 698.32 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 3.30 (d, 1H, *J*=9.35 Hz, 3-H), 3.40 (d, 1H, *J*=11.54 Hz, dioxane 1-H), 3.51–3.56 (m, 3H, 3-H, 5-H and 7-H), 3.64 (ddd, 1H, *J*=9.90, 2.75 Hz, *J*=2.20 Hz, 6-H), 3.69 (ddd, 1H, *J*=9.90, 2.75, 2.20 Hz, 6-H), 3.75–3.80 (m, 3H, 7-H, 4-H and 7-H), 3.83–3.87 (m, 3H, dioxane 1-H, 7-H and 5-H), 4.10 (t, 9.35 Hz, 4-H), 4.17 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 4.38 (d, 1H, *J*=12.65 Hz, CH_2Ph), 4.41 (d, 1H, *J*=11.00 Hz, dioxane 1-H), 4.49 (d, 1H, *J*=12.09 Hz, CH_2Ph), 4.55–4.59 (m, 3H, CH_2Ph), 4.68 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.69 (d, 1H, *J*=12.54 Hz, CH_2Ph), 4.73 (d, 1H, *J*=10.45 Hz, CH_2Ph), 4.80 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.81 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.86 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.87 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.90 (d, 1H, *J*=1.10 Hz, CH_2Ph), 5.01 (d, 1H, *J*=11.55 Hz, CH_2Ph), 7.13–7.15 (m, 4H, ArH), 7.22–7.36 (m, 36H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 55.62 (dioxane 1-C), 62.33 (dioxane 1-C), 68.37 (7-C), 68.84 (7-C), 71.25 (6-C), 73.34 (6-C), 73.51 (CH_2Ph), 73.74 (CH_2Ph), 74.16 (CH_2Ph), 74.93 (CH_2Ph), 75.06 (CH_2Ph), 75.45 (CH_2Ph), 75.63 (CH_2Ph), 75.66 (CH_2Ph), 77.50 (5-C), 78.16 (5-C), 79.73 (3-C), 82.69 (3-C), 83.01 (4-C), 83.62 (4-C), 95.38 (anomeric 2-C), 96.34 (anomeric 2-C), 127.46 (Ar), 127.57 (Ar), 127.59 (Ar), 127.62 (Ar), 127.65 (Ar), 127.68 (Ar), 127.71 (Ar), 127.80 (Ar), 127.81 (Ar), 127.85 (Ar), 127.88 (Ar), 127.92 (Ar), 127.97 (Ar), 128.24 (Ar), 128.31 (Ar), 128.34 (Ar), 128.37 (Ar), 128.43 (Ar), 137.67 (Ar), 138.02 (Ar), 138.17 (Ar), 138.31 (Ar), 138.54 (Ar), 138.58 (Ar), 138.60 (Ar); HRMS (FAB): calcd for $C_{70}H_{72}O_{12}Na$ 1127.4922, found 1127.4928.

3.4.4. 3,4,5,7-Tetra-*O*-benzyl-α-D-*galacto*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*galacto*-hept-2′-ulopyranose 1,2′: 2,1′-dianhydride (4b). White solid, mp 115–116 °C; $[\alpha]^{27}_D$=+37.7° (*c* 1.0, $CHCl_3$); IR (KBr): 3088.41, 3063.33, 3030.54, 2918.65, 2870.43, 1956.06, 1869.25, 1809.45, 1747.72, 1604.97, 1496.94, 1454.50, 1363.84, 1207.59, 1101.49, 1028.18, 937.52, 734.97, 698.32 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 3.41–3.45 (m, 3H, 7-H, dioxane 1-H and 4-H), 3.59 (dd, 1H, *J*=8.35, 3.88 Hz, 7-H), 3.69–3.80 (m, 5H, 7-H, 6-H, 3-H, dioxane 1-H and 7-H), 3.85 (dd, br, 1H, *J*=8.80, 5.50 Hz, 6-H), 3.93 (d, 1H, *J*=10.45 Hz, 3-H), 4.02–4.04 (m, 2H, 5-H and 4-H), 4.08 (d, 1H, *J*=1.65 Hz, 5-H), 4.22 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 4.28 (d, 1H, *J*=11.54 Hz, CH_2Ph), 4.33–4.37 (m, 3H, CH_2Ph), 4.46 (d, 1H, *J*=11.55 Hz, dioxane 1-H), 4.54 (d, 1H, *J*=11.00 Hz, CH_2Ph), 4.57 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.63 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.64 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.67–4.73 (m, 4H, CH_2Ph), 4.88–4.92 (m, 3H, CH_2Ph), 4.96 (d, 1H, *J*=10.99 Hz, CH_2Ph), 7.20–7.35 (m, 40H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 55.34 (dioxane 1-C), 62.40 (dioxane 1-C), 67.95 (7-C), 68.10 (7-C), 69.42 (6-C), 71.64 (6-C), 72.57 (CH_2Ph), 73.10 (5-C), 73.40 (CH_2Ph), 73.51 (CH_2Ph), 73.55 (5-C), 73.99 (CH_2Ph), 74.70 (CH_2Ph), 74.72 (CH_2Ph), 74.88 (CH_2Ph), 75.75 (CH_2Ph), 76.35 (3-C), 80.18 (4-C), 80.48 (4-C), 80.86 (3-C), 95.73 (anomeric 2-C), 96.96 (anomeric 2-C), 127.32 (Ar), 127.35 (Ar), 127.43 (Ar), 127.46 (Ar), 127.50 (Ar), 127.56 (Ar), 127.67 (Ar), 127.77 (Ar), 127.79 (Ar), 127.96 (Ar), 127.97 (Ar), 127.99 (Ar), 128.02 (Ar), 128.09 (Ar), 128.10 (Ar), 128.17 (Ar), 128.20 (Ar), 128.27 (Ar), 128.30 (Ar), 128.36 (Ar), 128.38 (Ar), 128.40 (Ar), 128.45 (Ar), 137.75 (Ar), 137.86 (Ar), 137.98 (Ar), 138.41 (Ar), 138.51 (Ar), 138.67 (Ar), 138.74 (Ar), 138.91 (Ar); HRMS: (FAB) calcd for $C_{70}H_{72}O_{12}Na$ 1127.4922, found 1127.4920.

3.4.5. 3,4,5,7-Tetra-*O*-benzyl-α-D-*manno*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-benzyl-α-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (4c). Colorless syrup; $[\alpha]^{25}_D$=+0.68° (*c* 5.0, $CHCl_3$); IR (neat): 3088.41, 3063.33, 3030.54, 2918.65, 2868.50, 1952.20, 1876.97, 1811.38, 1728.43, 1604.97, 1587.61, 1496.94, 1454.50, 1365.77, 1286.68, 1211.44, 1095.70, 1028.18, 910.51, 734.97, 696.39 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 3.47 (dd, 1H, *J*=8.35, 3.30 Hz, 4-H), 3.57 (d, 1H, *J*=3.30 Hz, 3-H), 3.59 (d, 1H, *J*=11.55 Hz, dioxane 1-H), 3.62 (d, 1H, *J*=11.55 Hz, dioxane 1-H), 3.69–3.72 (m, 1H, 6-H), 3.76–3.83 (m, 5H, three 7-H, 6-H and 3-H), 3.86 (dd, 1H, *J*=9.90, 2.20 Hz, 7-H), 3.91–3.96 (m, 4H, two dioxane 1-H and two 5-H), 4.02 (dd, 1H, *J*=9.35, 2.75 Hz, 4-H), 4.41 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.44 (d, 1H, *J*=11.55 Hz, CH_2Ph), 4.51–4.60 (m, 5H, CH_2Ph), 4.63–4.70 (m, 5H, CH_2Ph), 4.76 (d, 1H, *J*=10.99 Hz, CH_2Ph), 4.85 (d, 1H, *J*=10.45 Hz, CH_2Ph), 4.86 (d, 1H, *J*=12.10 Hz, CH_2Ph), 4.91 (d, 1H, *J*=11.55 Hz, CH_2Ph), 7.19–7.36 (m, 38H, ArH), 7.39–7.40 (m, 2H, ArH); ^{13}C NMR($CDCl_3$): δ (ppm) 58.77 (dioxane 1-C), 64.18 (dioxane 1-C), 69.35 (7-C), 69.98 (7-C), 71.73 (CH_2Ph), 72.60 (CH_2Ph), 73.22 (CH_2Ph), 73.83 (6-C), 74.27 (CH_2Ph), 74.55 (CH_2Ph), 74.65 (3-C), 74.68 (6-C), 74.80 (5-C), 75.10 (5-C), 75.11 (CH_2Ph), 75.13 (CH_2Ph), 75.14 (CH_2Ph), 75.15 (3-C), 79.05 (4-C), 81.30 (4-C), 94.87 (anomeric 2-C), 95.38 (anomeric 2-C), 127.32 (Ar), 127.40 (Ar), 127.47 (Ar), 127.54 (Ar), 127.56 (Ar), 127.61 (Ar), 127.62 (Ar), 127.64 (Ar), 127.65 (Ar), 127.72 (Ar), 127.96 (Ar), 128.01 (Ar), 128.08 (Ar), 128.28 (Ar), 128.31 (Ar), 128.38 (Ar), 137.91 (Ar), 138.15 (Ar), 138.17 (Ar), 138.30 (Ar), 138.38 (Ar), 138.59 (Ar), 138.64 (Ar), 138.65 (Ar); HRMS: (FAB) calcd for $C_{70}H_{72}O_{12}Na$ 1127.4922, found 1127.4919.

3.5. Debenzylation of 3a and 4a

The mixture of **3a** and **4a** (220 mg, 0.2 mmol) was dissolved in 10 mL of methanol. To the solution 40 mg of $Pd(OH)_2/C$ (20 wt%) was added, and the mixture was stirred vigorously under H_2 atmosphere at room temperature for 12 h. The reaction was monitored by TLC detection (AcOEt/*i*-PrOH/H_2O=5:3:1). After the reaction completed, the catalyst was

removed by filtration through a Celite pad and the solvent was evaporated in vacuum to give the mixture of the unprotected products **5a** and **6a** quantitatively.

Following the above procedure, the compounds **3b–c** and **4a–c** were debenzylated and quantitatively afforded the compounds **5b–c** and **6a–c**, respectively.

3.5.1. α-D-*galacto*-Hept-2-ulopyranose α-D-*galacto*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (5b). White solid, mp 155–156°C; $[\alpha]^{25}_{D}$=+201.4° (*c* 0.5, H_2O); ^{1}H NMR (D_2O): δ (ppm): 3.55 (d, 1H, *J*=10.45 Hz, 3-H), 3.57–3.62 (m, 2H, two 7-H), 3.62 (d, 1H, *J*=12.65 Hz, dioxane 1-H, overlapped with 7-H), 3.74 (dd, 1H, *J*=9.90, 3.30 Hz, 4-H), 3.80 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 3.83 (d, br, 1H, *J*=3.30 Hz, 5-H), 3.86 (dd, br, 1H, *J*=7.70, 4.40 Hz, 6-H); ^{13}C NMR (D_2O): δ (ppm): 61.34 (7-C), 63.49 (dioxane 1-C), 69.27 (5-C), 70.10 (4-C), 72.62 (3-C), 72.68 (6-C), 96.68 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1165.

3.5.2. α-D-*manno*-Hept-2-ulopyranose α-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (5c). Amorphous solid; $[\alpha]^{25}_{D}$=+99.2° (*c* 0.5, H_2O); ^{1}H NMR (D_2O): δ (ppm) 3.38 (t, 1H, *J*=9.35 Hz, 5-H), 3.41 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 3.46–3.51 (m, 2H, 6-H and 7-H), 3.63 (dd, 2H, *J*=9.35 Hz, *J*=2.20 Hz, 4-H and 7-H, overlapped), 3.76 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 3.77 (d, 1H, *J*=3.85 Hz, 3-H); ^{13}C NMR (D_2O): δ (ppm) 60.98 (dioxane 1-C), 61.04 (7-C), 66.46 (5-C), 69.12 (3-C), 70.59 (4-C), 73.82 (6-C), 97.35 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1160.

3.5.3. α-D-*gluco*-Hept-2-ulopyranose β-D-*gluco*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (6a). White solid, mp>250°C; $[\alpha]^{25}_{D}$=+42.00° (*c* 0.6, $CHCl_3$); ^{1}H NMR(D_2O): δ (ppm) 3.13 (d, 1H, *J*=9.35 Hz, 3-H), 3.22 (d, 1H, *J*=9.90 Hz, 3-H), 3.28 (t, br, 2H, *J*=9.90 Hz, two 5-H, overlapped), 3.35 (t, 1H, *J*=9.35 Hz, 4-H), 3.39 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 3.44 (ddd, 1H, *J*=9.90, 4.40, 2.20 Hz, 6-H), 3.46 (ddd, 1H, *J*=9.90, 4.40, *J*=2.20 Hz, 6-H), 3.56 (t, 1H, *J*=9.35 Hz, 4-H), 3.61 (dd, 1H, *J*=12.09, 6.05 Hz, 7-H), 3.63 (dd, 1H, *J*=12.09, 6.05 Hz, 7-H), 3.76 (dd, 1H, *J*=12.09, 2.20 Hz, 7-H), 3.79 (dd, 1H, *J*=12.65, 2.20 Hz, 7-H), 3.83 (d, 1H, *J*=13.19 Hz, dioxane 1-H), 3.93 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 4.26 (d, 1H, *J*=11.55 Hz, dioxane 1-H); ^{13}CNMR($CHCl_3$): δ (ppm) 55.40 (dioxane 1-C), 61.65 (7-C), 62.00 (7-C), 63.43 (dioxane 1-C), 70.46 (5-C), 70.92 (5-C), 72.65 (3-C), 73.53 (6-C), 74.27 (4-C), 74.34 (4-C), 75.57 (6-C), 75.98 (3-C), 95.84 (anomeric 2-C), 96.96 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1162.

3.5.4. α-D-*galacto*-Hept-2-ulopyranose β-D-*galacto*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (6b). White solid, mp 185–188°C; $[\alpha]^{25}_{D}$=+86.0° (*c* 0.5, H_2O); ^{1}H NMR (D_2O) δ (ppm) 3.36 (d, 1H, *J*=9.90 Hz, 3-H), 3.40 (d, 1H, *J*=11.54 Hz, dioxane 1-H), 3.52 (s, 2H, 6-H and 6-H), 3.59 (dd, 1H, *J*=11.54, 3.84 Hz, 7-H), 3.62–3.66 (m, 2H, 7-H and 7-H), 3.67–3.74 (m, 4H, 7-H, 3-H, 4-H and 4-H), 3.81 (d, 1H, *J*=12.64 Hz, dioxane 1-H, overlapped with 5-H), 3.81 (s, br, 1H, 5-H, oerlapped with dioxane 1-H), 3.96 (d, *J*=13.20 Hz, dioxane 1-H), 4.29 (d, 1H, *J*=12.10 Hz, dioxane 1-H); ^{13}C NMR(D_2O) δ (ppm) 54.17 (dioxane 1-C), 61.37 (7-C), 61.42 (7-C), 62.41 (dioxane 1-C), 68.76 (3-C), 68.89 (5-C), 69.30 (5-C), 69.94 (4-C), 70.43 (6-C), 71.85 (4-C), 72.39 (6-C), 73.87 (3-C), 95.17 (anomeric 2-C), 96.62 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1168.

3.5.5. α-D-*manno*-Hept-2-ulopyranose β-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (6c). White solid, mp 246–250°; $[\alpha]^{25}_{D}$=+26.6° (*c* 0.5, H_2O); ^{1}H NMR (D_2O): δ (ppm) 3.27 (ddd, 1H, *J*=9.35, 6.35, 2.20 Hz, 6-H), 3.33 (ddd, 1H, *J*=9.90, 6.05, 2.20 Hz, 6-H), 3.38 (dd, 1H, *J*=9.35, 3.30 Hz, 4-H), 3.40 (t, 1H, *J*=9.90 Hz, 5-H), 3.45 (t, 1H, *J*=9.90 Hz, 5-H), 3.49–3.56 (m, 4H, 7-H, 7-H, two dioxane 1-H), 3.61 (dd, 1H, *J*=8.80, 3.30 Hz, 4-H), 3.62 (d, 1H, *J*=3.30 Hz, 3-H), 3.63 (d, 1H, *J*=3.30 Hz, 3-H), 3.68 (d, br, 2H, *J*=12.65 Hz, 7-H and 7-H), 3.81 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 3.90 (d, 1H, *J*=12.65 Hz, dioxane 1-H); ^{13}C NMR (D_2O) δ (ppm) 57.38 (dioxane 1-C), 60.92 (7-C), 61.29 (7-C), 63.67 (dioxane 1-C), 66.59 (5-C), 66.71 (5-C), 70.35 (3-C), 70.47 (3-C), 71.00 (4-C), 71.25 (4-C), 73.61 (6-C), 74.99 (6-C), 94.58 (anomeric 2-C), 94.99 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1163.

3.6. Acetylation of 5a and 6a

The mixture of **5a** and **6a** (76.8 mg, 0.2 mmol) was dissolved in 5.0 mL of dry pyridine. The solution was cooled with ice bath and 3.0 mL of acetic anhydride was added, then the solution was stirred at room temperature overnight. After completion of the reaction, the solution was poured into 50 g ice water, and the mixture was extracted with AcOEt (20 mL×3). The organic phase was washed with water (30 mL) four times and dried over $MgSO_4$. After removing solvent, the residue was submitted to silica gel column chromatography (AcOEt/hexane 1:1) to afford the acetylated derivatives **7a** (31.1 mg, 21.6%) and **8a** (87.1 mg, 60.5%), (total: 118.2 mg, 82.1%).

Under the same conditions, the acetylations of the compounds **5b–c** and **6a–c** were carried out and provided the corresponding compounds **7b–c** and **8a–c**, respectively. The results are shown in Table 3.

3.6.1. 3,4,5,7-Tetra-*O*-acetyl-α-D-*gluco*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-α-D-*gluco*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (7a). Colorless amorphous solid; $[\alpha]^{25}_{D}$=+112.99° (*c* 1.0, $CHCl_3$); IR (KBr): 2959.16, 1749.65 (st), 1649.34, 1456.43, 1435.21, 1371.55, 1226.88, 1097.63, 1041.69, 978.03, 900.87, 798.63 cm^{-1}; ^{1}H NMR($CDCl_3$): δ (ppm) 1.99 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.17 (s, 3H, CH_3CO), 3.60 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 4.00 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 4.06 (dd, br, 2H, *J*=10.45 Hz, 6-H and 7-H, overlapped), 4.21 (dd, 1H, *J*=12.64, 4.40 Hz, 7-H), 5.09 (t, 1H, *J*=9.89 Hz, 5-H), 5.09 (d, 1H, *J*=10.45 Hz, 3-H), 5.48 (t, 1H, *J*=9.90 Hz, 4-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.55 (two C, CH_3), 20.60 (CH_3), 20.73 (CH_3), 61.64 (7-C), 62.68 (dioxane

1-C), 68.11 (3-C), 69.32 (6-C), 69.65 (4-C), 72.46 (5-C), 96.30 (anomeric 2-C), 169.42 (C═O), 170.02 (C═O), 170.62 (C═O), 170.86 (C═O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2018.

3.6.2. 3,4,5,7-Tetra-*O*-acetyl-α-D-*galacto*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-α-D-*galacto*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (7b). Colorless amorphous solid; $[\alpha]^{25}_D$=+111.49° (c 1.0, $CHCl_3$); IR (KBr): 2968.02, 1752.79 (st), 1649.34, 1434.45, 1371.55, 1225.66, 1088.62, 1053.09, 959.06, 911.01 cm^{-1}; ^1H NMR(CDCl3): δ (ppm) 2.02 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.19 (s, 3H, CH_3CO), 2.20 (s, 3H, CH_3CO), 3.61 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 4.08 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 4.12 (dd, 1H, *J*=11.00, 6.60 Hz, 7-H), 4.15 (dd, 1H, *J*=10.99, 7.15 Hz, 7-H), 4.35 (t, *J*=6.60 Hz, 4-H), 5.39–5.41 (m, 1H, 6-H), 5.44–5.46 (m, 2H, 3-H and 5-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.59 (CH_3), 20.62 (CH_3), 20.64 (CH_3), 20.70 (CH_3), 61.27 (7-C), 63.01 (dioxane 1-C), 67.23 (3-C), 67.81 (5-C), 68.28 (4-C), 70.06 (6-C), 96.82 (anomeric 2-C), 169.87 (C═O), 170.09 (C═O), 170.30 (C═O), 170.94 (C═O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2010.

3.6.3. 3,4,5,7-Tetra-*O*-acetyl-α-D-*manno*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-α-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (7c). Colorless amorphous solid; $[\alpha]^{28}_D$=+102.0° (c 1.0, $CHCl_3$); IR (KBr): 2991.96, 2963.02, 1749.65 (st), 1649.34, 1433.28, 1371.55, 1226.88, 1147.79, 1091.84, 1053.26, 964.53, 900.87, 736.90 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 1.97 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.18 (s, 3H, CH_3CO), 3.59 (d, 1H, *J*=12.19 Hz, dioxane 1-H), 3.70 (d, 1H, *J*=12.65 Hz, dioxane 1-H), 4.04 (ddd, 1H, *J*=9.90, 5.50, 2.20 Hz, 6-H), 4.12 (dd, 1H, *J*=12.10, 2.20 Hz, 7-H), 4.25 (dd, 1H, *J*=12.10, 5.50 Hz, 7-H), 5.23 (t, 1H, *J*=9.90 Hz, 5-H), 5.38 (dd, 1H, *J*=9.90, 3.30 Hz, 4-H), 5.41 (d, 1H, *J*=3.30 Hz, 3-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.34 (CH_3), 20.63 (CH_3), 20.67 (CH_3), 20.70 (CH_3), 60.59 (dioxane 1-C), 62.36 (7-C), 65.74 (5-C), 68.45 (3-C), 69.26 (4-C), 69.92 (6-C), 96.44 (anomeric 2-C), 169.42 (C═O), 169.64 (C═O), 169.71 (C═O), 170.56 (C═O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2006.

3.6.4. 3,4,5,7-Tetra-*O*-acetyl-α-D-*gluco*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-β-D-*gluco*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (8a). White solid, mp 186–186.5°C; $[\alpha]^{25}_D$=+46.30° (c 1.0, $CHCl_3$); IR (KBr): 2955.31, 2910.94, 1747.72 (st), 1435.21, 1371.55, 1226.81, 1099.56, 1057.12, 1037.83, 993.46, 920.16, 900.87 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 1.99 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.09 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3CO), 2.11 (s, 3H, CH_3CO), 3.53 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 3.78 (d, 1H, *J*=11.55 Hz, dioxane 1-H), 3.85 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 3.93 (ddd, 1H, *J*=9.89, 4.39, 2.20 Hz, 6-H), 3.99 (dt, 1H, *J*=11.00, 2.20 Hz, 6-H), 4.07 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 4.15 (dd, 1H, *J*=12.64, 2.20 Hz, 7-H), 4.20 (dd, 1H, *J*=12.10, 2.20 Hz, 7-H), 4.25 (dd, 1H, *J*=12.10, 4.40 Hz, 7-H), 4.30 (dd, 1H, *J*=12.65, 2.75 Hz, 7-H), 4.91 (d, 1H, *J*=10.44 Hz, 3-H), 5.02–5.06 (m, 2H, 3-H and 5-H), 5.10 (t, 1H, *J*=10.44 Hz, 5-H), 5.42 (dd, 1H, *J*=10.45, 8.25 Hz, 4-H), 5.50 (t, 1H, *J*=9.89 Hz, 4-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.45 (CH_3), 20.55 (CH_3), 20.58 (CH_3), 20.63 (CH_3), 20.64 (two C, CH_3), 20.68 (CH_3), 20.73 (CH_3), 59.16 (dioxane 1-C), 61.29 (dioxane 1-C), 61.55 (7-C), 61.87 (7-C), 67.48 (4-C), 68.41 (5-C), 68.52 (6-C), 69.52 (3-C), 70.48 (4-C), 70.76 (6-C), 72.85 (two C, 5-C and 3-C), 94.14 (anomeric 2-C), 94.28 (anomeric 2-C), 168.76 (C═O), 169.36 (C═O), 169.48 (C═O), 169.95 (C═O), 170.00 (C═O), 170.21 (C═O), 170.59 (C═O), 170.65 (C═O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2013.

3.6.5. 3,4,5,7-Tetra-*O*-acetyl-α-D-*galacto*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-β-D-*galacto*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (8b). White solid, mp 120–121°C; $[\alpha]^{25}_D$=+70.37° (c 0.8, $CHCl_3$); IR (KBr): 2968.81, 1755.44 (st), 1649.34, 1435.21, 1373.48, 1223.02, 1060.98, 958.74, 925.84, 902.80 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 1.95 (s, 3H, CH_3CO), 1.96 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.13 (s, 3H, CH_3CO), 2.14 (s, 3H, CH_3CO), 3.54 (d, 1H, *J*=12.09 Hz, dioxane 1-H), 3.88 (d, 1H, *J*=12.64 Hz, dioxane 1-H), 3.96 (d, 1H, *J*=12.10 Hz, dioxane 1-H), 4.01 (d, 1H, *J*=12.09 Hz, dioxane 1-H), 4.04–4.13 (m, 4H, 6-H, 7-H, 7-H and 6-H), 4.16 (dd, 1H, *J*=10.45, 6.60 Hz, 7-H), 4.27 (dd, 1H, *J*=10.45, 7.15 Hz, 7-H), 4.93 (dd, 1H, *J*=11.00, 3.30 Hz, 4-H), 5.09 (d, 1H, *J*=10.45 Hz, 3-H), 5.33 (dd, 1H, *J*=10.45, 3.30 Hz, 4-H), 5.34 (d, 1H, *J*=11.00 Hz, 3-H), 5.43 (dd, 1H, *J*=3.30, 1.10 Hz, 5-H), 5.46 (dd, 1H, *J*=3.30, 1.65 Hz, 5-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.49 (CH_3), 20.50 (CH_3), 20.59 (two C, CH_3), 20.62 (CH_3), 20.69 (three C, CH_3), 55.37 (dioxane 1-C), 60.97 (7-C), 61.50 (7-C), 61.85 (dioxane 1-C), 66.67 (5-C), 66.87 (3-C), 67.52 (6-C), 67.85 (5-C), 67.94 (3-C), 68.71 (4-C), 69.49 (4-C), 69.58 (6-C), 94.76 (anomeric 2-C), 95.34 (anomeric 2-C), 168.82 (C═O), 169.84 (C═O), 169.99 (two C, C═O), 170.10 (C═O), 170.12 (C═O), 170.20 (C═O), 170.27 (C═O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2009.

3.6.6. 3,4,5,7-Tetra-*O*-acetyl-α-D-*manno*-hept-2-ulopyranose 3′,4′,5′,7′-tetra-*O*-acetyl-β-D-*manno*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (8c). Colorless amorphous solid; $[\alpha]^{25}_D$=+6.50° (c 1.0, $CHCl_3$); IR (KBr): 2959.12, 1751.86 (st), 1649.34, 1435.12, 1370.85, 1221.18, 1089.88, 1056.02, 978.05, 910.17, 741.21 cm^{-1}; ^1H NMR($CDCl_3$): δ (ppm) 1.95 (s, 3H, CH_3CO), 2.00 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.11 (2s, 6H, CH_3CO×2, overlapped), 2.12 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 3.60 (d, 1H, *J*=12.09 Hz, dioxane 1-H), 3.74 (d, 1H, *J*=12.09 Hz, dioxane 1-H), 3.89–3.93 (m, 2H, two 6-H), 3.91 (d, 1H, *J*=12.10 Hz, dioxane 1-H, overlapped with 6-H), 3.92 (d, 1H, *J*=12.10 Hz, dioxane 1-H, overlapped with 6-H), 4.11 (dd, 1H, *J*=12.10, 2.20 Hz, 7-H), 4.25 (dd, *J*=12.10, 2.20 Hz, 7-H), 4.31 (dd, *J*=12.10, 6.05 Hz, 7-H), 4.36 (dd, *J*=12.10, 6.60 Hz, 7-H), 5.00 (dd, *J*=9.35, 3.30 Hz, 4-H), 5.22 (t, 1H, *J*=8.80 Hz, 5-H), 5.23 (t, 1H, *J*=8.90 Hz, 5-H), 5.24 (d, 1H, *J*=3.30 Hz, 3-H), 5.29 (d, 1H, *J*=3.85 Hz, 3-H), 5.34 (dd, 1H, *J*=9.90, 3.30 Hz, 4-H); ^{13}C NMR($CDCl_3$): δ (ppm) 20.49 (CH_3), 20.55 (CH_3), 20.60 (CH_3), 20.66 (CH_3), 20.68 (two C,

CH_3), 20.71 (two C, CH_3), 58.59 (dioxane 1-C), 62.55 (7-C), 62.72 (7-C), 62.93 (dioxane 1-C), 65.84 (5-C), 66.45 (5-C), 67.89 (3-C), 69.11 (4-C), 69.15 (4-C), 69.56 (6-C), 69.84 (3-C), 71.93 (6-C), 93.19 (anomeric 2-C), 93.70 (anomeric 2-C), 169.51 (C=O), 169.65 (C=O), 169.68 (C=O), 169.78 (C=O), 169.96 (C=O), 170.01 (C=O), 170.68 (C=O), 170.74 (C=O); HRMS: (FAB) calcd for $C_{30}H_{40}O_{20}Na$ 743.2011, found 743.2015.

3.6.7. α-D-*gluco*-Hept-2-ulopyranose α-D-*gluco*-hept-2′-ulopyranose 1,2′:2,1′-dianhydride (5a). Deacetylation of 7a. To a solution of **7a** (72 mg, 0.5 mmol) in methanol (3 mL) was added KOH (3.0 mg, 0.05 mmol) at room temperature, and the mixture was stirred for 1.5 h. After the completion of the reaction, the mixture was concentrated in vacuo and the residue was applied on a short silica gel chromatographic column (AcOEt/*i*-PrOH/H_2O=5:3:1) to afford the unprotected product **7a** (16.9 mg, 88.0%), colorlessly amorphous solid, $[\alpha]^{25}_D$=+141.02° (*c* 0.9, H_2O); ^1H NMR (D_2O): δ (ppm): 3.35 (t, 1H, *J*=9.90 Hz, 5-H), 3.38 (d, 1H, *J*=9.90 Hz, 3-H), 3.66–3.70 (m, 4H, 7-H, 4-H, dioxane 1-H and 6-H, overlapped), 3.81 (d, br, 1H, *J*=8.89 Hz, 7-H), 3.89 (d, 1H, *J*=12.65 Hz, dioxane 1-H); ^{13}C NMR (D_2O): δ (ppm): 60.67 (7-C), 63.20 (dioxane 1-C), 69.64 (5-C), 73.45 (6-C), 73.53 (4-C), 75.44 (3-C), 96.56 (anomeric 2-C); HRMS: (FAB) calcd for $C_{14}H_{24}O_{12}Na$ 407.1166, found 407.1169.

3.7. X-Ray crystallographic measurements of single crystals of 6a–c at 123 K

The unprotected compounds **5a**–**c** and **6a**–**c** were tried to be recrystallized from the solution of H_2O/EtOH. It was found that **5a**–**c** could not crystallize from the solution. Single crystals of the compounds **6a**–**c** suitable for X-ray analysis were obtained from the solution.

6a: *Crystal data*. Colorless platelet crystal, dimensions 0.40×0.10×0.03 mm, $C_{14}H_{24}O_{12}\cdot H_2O$, *M*=402.34, orthorhomic, space group $P2_12_12_1$, lattice parameters: *a*=6.1538(2), *b*=11.5971(4), *c*=23.482(1) Å, *V*=1675.8(1)Å^3, *Z*=4, D_{calc}=1.523 g cm^{-3}, F_{000}=816.00, μ(MoKα)=1.35 cm^{-1}. *Data collection*. Rigaku RAXIS-RAPID Imaging Plate diffractometer, graphite monochromated MoKα radiation, *T*=123 K, $2\theta \leq 60.0°$. A total of 55 images, corresponding to 220.0° oscillation angles, were collected with two different goniometer settings. Exposure time was 3.50 min per degree. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Data were processed by the PROCESS-AUTO program package. Of the 17401 reflections which were collected, 2822 were unique (R_{int}=0.054). A symmetry-related absorption corrected using the program ABSCOR[23] was applied which resulted in transmission factors ranging from 0.90 to 1.00. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR97)[24] and expanded using Fourier techniques.[25] The non-hydrogen atoms were refined anisottropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-square refinement was based on 2819 observed reflections ($I > -3.00\sigma(I)$, $2\theta < 60.04$) and 244 variable parameters and converged with unweighted and weighted agreement factors. The crystallographic structure is shown in Fig. 1(a).

6b: *Crystal data*. Colorless block crystal, dimensions 0.35×0.20×0.15 mm, $C_{14}H_{24}O_{12}\cdot 3H_2O$, *M*=438.38, monoclinic, space group $P2_1$, lattice parameters: *a*=7.555(1), *b*=14.670(2), *c*=8.386(1) Å, β=92.467(3)°, *V*=928.6(2) Å^3, *Z*=2, D_{calc}=1.568 g cm^{-3}, F_{000}=468.00, μ(MoKα)=1.43 cm^{-1}. *Data collection*. Rigaku RAXIS-RAPID Imaging Plate diffractometer, graphite monochromated MoKα radiation, *T*=123 K, $2\theta \leq 60.1°$. A total of 44 images, corresponding to 220.0° oscillation angles, were collected with teo different goniometer settings. Exposure time was 0.10 min per degree. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Data were processed by the PROCESS-AUTO program package. Of the 10730 reflections which were collected, 2813 were unique (R_{int}=0.025). A symmetry-related absorption corrected using the program ABSCOR[23] was applied which resulted in transmission factors ranging from 0.87 to 0.98. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR97)[24] and expanded using Fourier techniques.[25] The non-hydrogen atoms were refined anisottropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-square refinement was based on 2813 observed reflections ($I > -3.00\sigma(I)$, $2\theta < 60.06$) and 262 variable parameters and converged with unweighted and weighted agreement factors. The crystallographic structure is shown in Fig. 1(b).

6c: *Crystal data*. Colorless block crystal, dimensions 0.30×0.20×0.10 mm, $C_{14}H_{24}O_{12}$, *M*=384.34, monoclinic, space group $P2_1$, lattice parameters: *a*=6.2435(9), *b*=8.857(1), *c*=14.290(2) Å, β=93.210(3)°, *V*=789.0(2) Å^3, *Z*=2, D_{calc}=1.618 g cm^{-3}, F_{000}=408.00, μ(MoKα)=1.43 cm^{-1}. *Data collection*. Rigaku RAXIS-RAPID Imaging Plate diffractometer, graphite monochromated MoKα radiation, *T*=123 K, $2\theta \leq 60.0°$. A total of 40 images, corresponding to 220.0° oscillation angles, were collected with two different goniometer settings. Exposure time was 0.20 min per degree. The camera radius was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. Data were processed by the PROCESS-AUTO program package. Of the 8072 reflections which were collected, 4214 were unique (R_{int}=0.031). A symmetry-related absorption corrected using the program ABSCOR[23] was applied which resulted in transmission factors ranging from 0.91 to 0.99. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR97)[24] and expanded using Fourier techniques.[25] The non-hydrogen atoms were refined anisottropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-square refinement was based on 2434 observed reflections ($I > -3.00\sigma(I)$, $2\theta < 60.01$) and 236 variable parameters and converged with unweighted and weighted agreement factors. The crystallographic structure is shown in Fig. 1(c).

The crystallographic data of **6a**–**c** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication, no. **6a**: CCDC-167645, **6b**: CCDC-

167646, and **6c**: CCDC-167647. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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13. Compound **A**: Colorless syrup, ^{1}H NMR ($CDCl_3$) δ (ppm): 0.09 (s, 9H, TMS), 3.38 (d, 1H, *J*=10.07 Hz, 1-H), 3.45 (d, 1H, *J*=9.46 Hz, 3-H), 3.51 (d, 1H, *J*=9.77 Hz, 1-H overlapped with 2-OH), 3.52 (s, br, 1H, 2-OH), 3.65 (d, br, 1H, *J*=11.29 Hz, 7-H), 3.69 (t, 1H, *J*=9.46 Hz, 5-H), 3.75 (dd, 1H, *J*=10.98, 3.66 Hz, 7-H), 3.97 (d, br, 1H, *J*=10.37 Hz, 6-H), 4.08 (t, 1H, *J*=9.46 Hz, 4-H), 4.51 (d, 1H, *J*=12.21 Hz, CH_2Ph), 4.59 (d, 1H, *J*=11.90 Hz, CH_2Ph), 4.60 (d, 1H, *J*=10.98 Hz, CH_2Ph), 4.65 (d, 1H, *J*=11.29 Hz, CH_2Ph), 4.84 (d, 1H, *J*=11.68 Hz, CH_2Ph), 4.90 (s, 2H, CH_2Ph), 4.91 (d, 1H, *J*=11.99 Hz, CH_2Ph), 7.18–7.33 (m, 20H, ArH); ^{13}C NMR ($CDCl_3$) δ (ppm): −0.37 (CH_3 of TMS), 65.08, 68.79, 71.39, 73.40, 74.87, 75.21, 75.67, 78.44, 78.98, 83.67, 97.05 (anomeric-C), 127.46, 127.52, 127.62, 127.80, 127.86, 127.88, 128.28, 128.35, 128.40, 128.44, 137.92, 138.27, 138.36, 138.66.
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