Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 339 (2004) 2433–2440
Carbohydrate RESEARCH

Note

Glycosylation of 1,4:3,6-dianhydro-D-glucitol (isosorbide)

David J. Claffey, Mary F. Casey and Patrick A. Finan*

Chemistry Department, National University of Ireland, Galway, Ireland

Received 14 July 2003; received in revised form 13 March 2004; accepted 8 July 2004
Available online 24 August 2004

Abstract—Condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-, 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl- and of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromides with 1,4:3,6-dianhydro-D-glucitol under Koenigs–Knorr conditions, and using the Helferich modification of the reaction showed regioselectivity in glysosylation at C-5 of isosorbide.

Keywords: 2,5-Di-*O*-,2-*O*-, and 5-*O*-β-D-glucopyranosyl derivatives; β-D-Xylopyranosyl derivatives; β-D-Galactopyranosyl derivatives; Regioselective glycosylation

1,4:3,6-Dianhydro-D-glucitol (isosorbide) (**1**) consists of two fused tetrahydrofuran rings having the *cis*-arrangement at the ring junctions, giving a V-shaped molecule.[1] The compound has two hydroxyl groups, one at C-2 having the *exo*-orientation with respect to the V-shaped molecule, and the other at C-5 having the *endo*-orientation and involved in intramolecular hydrogen bonding with the oxygen atom of the neighbouring tetrahydrofuran ring. We have investigated possible regioselectivity in the chemical glycosyl- ation of the hydroxyl groups of **1** using traditional Koenigs–Knorr reaction conditions[2] and using the Helferich modification[3] of the reaction.

Isosorbide (**1**) was treated with 1 M equiv of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in dichloromethane in the presence of silver oxide. A portion of the resulting syrup was kept for HPLC analysis, while column chromatography gave the crystalline di-*O*-glucosylated product **2** and the mono-*O*-glucosylated isomers **3** and **4**. Compound **3** was eluted before the 5-*O*-glucosylated **4**, as an intramolecular hydrogen bond between OH-5 and the ring oxygen atom O-4 rendered it less polar than **4**. Product yields were low, but no attempts were made to improve or to optimise them since interest centred on the ratio of the mono-*O*-glucosylated isomers produced.

The ^{1}H NMR spectrum of **2** showed a triplet signal at δ 4.51 for H-4 (coupled with H-3 and H-5), and a doublet at δ 4.40 for H-3 (coupled with H-4 and not significantly with H-2) of the isosorbide moiety, and these signals provided verification[1c] for its presence in all the isosorbide derivatives reported in this paper. The ^{13}C NMR spectrum of compound **2** showed the expected signals[4,5] at δ 86.0 for C-3 and at δ 83.7 for C-4 of the isosorbide group, while the anomeric carbon atoms C-1′ and C-1″ gave separate signals at δ 100.2 and δ 100.1. Glucosylation caused a downfield shift of the signals for C-2 (δ 76.5–80.6) and C-5 (δ 72.2–78.1) compared to C-2 and C-5 in isosorbide, in accordance with published data for ^{13}C signals at glycosylated sites in oligosaccharide derivatives.[6] All our glycosylated products had the expected β-D-configuration as shown by the ^{1}H NMR signal for the anomeric proton H-1′ (and H-1″) as a doublet having $J_{1,2}$ value of ~8 Hz for D-glucopyranosyl and D-galactopyranosyl compounds, and $J_{1,2} \sim 6.5$ for the D-xylopyranosyl compounds.

In the glucosylation of **1** under Koenigs–Knorr conditions, twice the yield of compound **4** (the 5-*O*-glucosylated product) was obtained compared to isomer **3**, and this regioselectivity was confirmed by HPLC analysis of the reaction mixture. When isosorbide (**1**) was glucosylated in the presence of mercuric cyanide, the 5-*O*-glucosylated compound **4** was also obtained in excess over

* Corresponding author. Tel.: +353-91-512037; fax: +353-91-525700; e-mail: karen.costello@nuigalway.ie

0008-6215/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2004.07.007

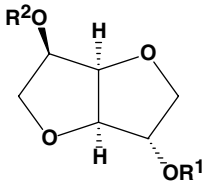
isomer **3**, with nitromethane or acetonitrile used as solvent.

In elaboration of the glucosylated derivatives obtained, octaacetate **2** was deacetylated to give solid 2,5-di-*O*-(β-D-glucopyranosyl)isosorbide (**5**), which was then reacetylated to give **2**. Benzoylation of compound **5** gave the crystalline octa-*O*-benzoyl derivative **6**. The 2-*O*-glucosylated tetraacetate **3** was acetylated to give the crystalline pentaacetate **7** and deacetylation of the latter gave 2-*O*-β-D-glucopyranosylisosorbide (**8**) as a glassy solid. Reacetylation of **8** gave **7**, and benzoylation of **8** gave the crystalline penta-*O*-benzoyl product **9**. The 5-*O*-glucoside tetraacetate **4** was acetylated to give the crystalline pentaacetate **10**, and the latter was also prepared by glucosylation of 2-*O*-acetylisosorbide[7] (**11**). Deacetylation of **4** gave 5-*O*-β-D-glucopyranosylisosorbide (**12**) as a glassy solid, which was readily reacetylated to the pentaacetate **10**. Benzoylation of **12** gave the crystalline penta-*O*-benzoyl product **13**. All structures were fully characterised using ^{1}H and ^{13}C NMR spectra, details of which have been summarised in Tables 3 and 4.

Isosorbide (**1**) was treated with 1 M equiv of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide in the presence of silver oxide and also using mercuric cyanide in both nitromethane and acetonitrile as solvent. The crystalline di-*O*-xyloside hexaacetate **14**, the solid 2-*O*-xyloside triacetate **15** and the crystalline 5-*O*-xyloside triacetate **16** were obtained in each case, with xylosylation at C-5 predominating. Deacetylation of **15** gave 2-*O*-β-D-xylopyranosylisosorbide (**17**) as a syrup, while acetylation of **15** gave the crystalline tetraacetate **18**. Deacetylation of **16** gave 5-*O*-β-D-xylopyranosylisosorbide (**19**) as a syrup; acetylation of **16** gave the crystalline tetraacetate **20**. The latter was also prepared by treatment of 2-*O*-acetylisosorbide (**11**) with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide.

Isosorbide (**1**) was condensed with 1 M equiv of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in the presence of silver oxide, and also using mercuric cyanide in both nitromethane and acetonitrile as solvent. Crystalline di-*O*-galactoside octaacetate **21**, crystalline 2-*O*-galactoside tetraacetate **22** and syrupy 5-*O*-galactoside tetraacetate **23** were obtained, with the latter predominating in each case. Tetraacetate **22** was acetylated to give the pentaacetate **24** as a syrup, and was benzoylated to give the tetra-*O*-acetyl-mono-*O*-benzoyl galactoside **25** as a syrup. The latter was also prepared by treatment of 5-*O*-benzoylisosorbide[8] (**26**) with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in the presence of silver oxide. Acetylation of the 5-*O*-galactoside tetraacetate **23** gave the syrupy pentaacetate **27**, which was also prepared by treatment of 2-*O*-acetylisosorbide (**11**) with 2,3,4,6-tetra-*O*-acetyl-α-D-galctopyranosyl bromide (Scheme 1).

The above results showed that glycosylation of isosorbide (**1**) occurred with considerable regioselectivity for



1 $R^1 = R^2 = H$

2 $R^1 = R^2$ = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

3 R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl, $R^2 = H$

4 $R^1 = H$, R^2 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

5 $R^1 = R^2$ = β-D-glucopyranosyl

6 $R^1 = R^2$ = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl

7 R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl, R^2 = Ac

8 R^1 = β-D-glucopyranosyl, $R^2 = H$

9 R^1 = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl, R^2 = Bz

10 R^1 = Ac, R^2 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

11 R^1 = Ac, $R^2 = H$

12 $R^1 = H$, R^2 = β-D-glucopyranosyl

13 $R^1 = B_Z$, R^2 = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl

14 $R^1 = R^2$ = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl

15 R^1 = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl, $R^2 = H$

16 $R^1 = H$, R^2 = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl

17 R^1 = β-D-xylopyranosyl, $R^2 = H$

18 R^1 = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl, R^2 = Ac

19 $R^1 = H$, R^2 = β-D-xylopyranosyl

20 R^1 = Ac, R^2 = 2,3,4-tri-O-acetyl-β-D-xylopyranosyl

21 $R^1 = R^2$ = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

22 R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl, $R^2 = H$

23 $R^1 = H$, R^2, 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

24 R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl, R^2 = Ac

25 R^1 = 2,3,4,6-tetra-*O*-acetyl-β-galactopyranosyl, $R^2 = B_Z$

26 $R^1 = H$, $R^2 = B_Z$

27 R^1 = Ac, R^2 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl

Scheme 1.

C-5 over C-2. In order to ensure that the product ratios obtained were not reflecting the ease of isolation of the compounds, HPLC analysis was carried out on samples of the product mixture taken directly after each condensation reaction. The HPLC results have been summarised in Table 1. It is noteworthy that Lemieux and McInnes[9] had reported a predominance of the 5-ester in the unimolar tosylation of isosorbide. Also, Foster and co-workers[7] had shown that treatment of isosorbide with *p*-phenylazobenzoyl chloride gave mainly the 5-ester. In these cases the authors[7,9] concluded that engagement of the 5-hydroxyl group in intramolecular hydrogen bonding was a factor in the regioselectivity reported. When we consider the shape of the isosorbide molecule (see Fig. 1), HO-2 has the *exo*-orientation, and would be expected to be more accessible than the

Table 1. HPLC analysis of the mono-*O*-glycosylated products from the condensation of poly-*O*-acetyl-α-D-glycosyl bromides with isosorbide

Reaction conditions	Retention time (min)		Isomer ratios
Glucosylation	5-*O*-Glc **4**	2-*O*-Glc **3**	**4**:**3**
Ag_2O	6.7	5.2	2.06:1.00
$Hg(CN)_2/CH_3NO_2$	8.2	6.6	2.00:1.00
$Hg(CN)_2/CH_3CN$	5.8	4.7	1.06:1.00
Xylosylation	5-*O*-Xyl **16**	2-*O*-Xyl **15**	**16**:**15**
Ag_2O	13.6	17.5	4.18:1.00
$Hg(CN)_2/CH_3NO_2$	13.1	17.0	6.18:1.00
$Hg(CN)_2/CH_3CN$	13.4	17.0	5.18:1.00
Galactosylation	5-*O*-Gal **23**	2-*O*-Gal **22**	**23**:**22**
Ag_2O	15.9	20.2	5.71:1.00
$Hg(CN)_2/CH_3NO_2$	16.5	21.6	9.50:1.00
$Hg(CN)_2/CH_3CN$	16.8	21.5	6.58:1.00

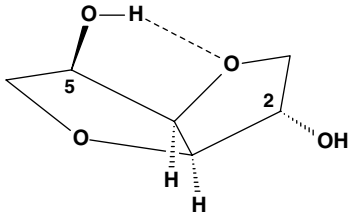


Figure 1. Structure of 1,4:3,6-dianhydro-D-glucitol (isosorbide) (**1**).

endo-HO-5 in a sterically demanding reaction. Our results for glycosylation using Koenigs–Knorr reaction conditions showed clear preference for HO-5 of isosorbide with glucosylation, with xylosylation and with galactosylation. The same regioselectivity was found when the glycosylations were carried out in homogeneous solution that is Helferich conditions.[3] Under the latter, steric factors might be expected to be less important than in the case of heterogeneous or surface catalysis, which is considered to be involved in the Koenigs–Knorr reaction using silver salts.[10] The involvement of HO-5 of isosorbide (**1**) in intramolecular hydrogen bonding is suggested as the major factor in its preferential glycosylation under the conditions used.

1. Experimental

1.1. General methods

Solid products were recrystallised from EtOH. Melting points are uncorrected. Optical rotations were determined at 15 °C with a Perkin–Elmer 241 polarimeter (1% solutions in 1 dm cell). Physiochemical data for products have been presented in Table 2. NMR spectra were recorded using a Jeol JNM-GX270 FT instrument at 67.8 MHz for ^{13}C NMR and at 270 MHz for ^{1}H NMR with Me_4Si as internal standard. NMR spectra data have been given in Tables 3 and 4. Evaporation of organic solutions was carried out on a rotary evaporator using a water vacuum pump and a water bath at 50 °C. Light petroleum used had bp 60–80 °C.

Table 2. Physiochemical data for compounds **2**–**27**

Compound	Mp (°C)	$[\alpha]_D$ ($CHCl_3$) (°)	Formula	Elemental analysis	
				Calcd	Found
2	192	+8	$C_{34}H_{46}O_{22}$	C, 50.6; H, 5.75	C, 50.7; H, 6.04
3	145	+2.9	$C_{20}H_{28}O_{13}$	C, 50.4; H, 5.92	C, 50.8; H, 6.04
4	165–166	+20	$C_{20}H_{28}O_{13}$	C, 50.4; H, 5.92	C, 50.6; H, 6.04
5	130–140	+6.2 (pyridine)	$C_{18}H_{30}O_{14}$	C, 45.9; H, 6.43	C, 45.6; H, 6.40
6	210	+10.25	$C_{74}H_{62}O_{22}$	C, 68.2; H, 4.80	C, 67.8; H, 5.01
7	135–136	+29.4	$C_{22}H_{30}O_{14}$	C, 51.0; H, 5.83	C, 51.1; H, 6.23
8	70–80	+12.4 (pyridine)	$C_{12}H_{20}O_9$	C, 46.8; H, 6.54	C, 46.5; H, 6.52
9	160–161	+20.2	$C_{47}H_{40}O_{14}$	C, 68.1; H, 4.86	C, 68.0; H, 4.89
10	115–116	+30	$C_{22}H_{30}O_{14}$	C, 51.0; H, 5.83	C, 51.0; H, 5.96
12	80–90	+24 (pyridine)	$C_{12}H_{20}O_9$	C, 46.8; H, 6.54	C, 46.6; H, 6.51
13	147	+44	$C_{47}H_{40}O_{14}$	C, 68.1; H, 4.86	C, 68.3; H, 5.15
14	181	−53	$C_{28}H_{38}O_{18}$	C, 50.7; H, 5.78	C, 50.4; H, 5.88
15	125–126	−5	$C_{17}H_{24}O_{11}$	C, 50.5; H, 5.98	C, 50.2; H, 5.97
16	154–155	−15	$C_{17}H_{24}O_{11}$	C, 50.5; H, 5.98	C, 50.8; H, 6.14
17	Syrup	−4 (pyridine)	$C_{11}H_{18}O_8$	C, 47.5; H, 6.52	C, 47.2; H, 6.47
18	143–144	+2	$C_{19}H_{26}O_{12}$	C, 51.1; H, 5.87	C, 51.3; H, 5.80
19	Syrup	−10 (pyridine)	$C_{11}H_{18}O_8$	C, 47.5; H, 6.52	C, 47.3; H, 6.52
20	143–144	+5	$C_{19}H_{26}O_{12}$	C, 51.1; H, 5.87	C, 50.9; H, 5.71
21	143–144	+14	$C_{34}H_{46}O_{22}$	C, 50.6; H, 5.75	C, 50.4; H, 5.75
22	133–134	+9	$C_{20}H_{28}O_{13}$	C, 50.4; H, 5.92	C, 50.4; H, 5.75
23	Syrup	+25	$C_{20}H_{28}O_{13}$	C, 50.4; H, 5.92	C, 50.3; H, 6.22
24	Syrup	+33	$C_{22}H_{30}O_{14}$	C, 51.0; H, 5.83	C, 51.3; H, 5.61
25	Syrup	+12	$C_{27}H_{32}O_{14}$	C, 55.9; H, 5.56	C, 55.9; H, 5.77
27	Syrup	+34	$C_{22}H_{30}O_{14}$	C, 51.0; H, 5.83	C, 50.8; H, 5.68

Table 3. ^{1}H NMR data ($CDCl_3$) for the carbohydrate components of compounds **2**–**27**

Compound	H-1a,1b	H-2	H-3	H-4	H-5	H-6a,6b	H-1′,1″	H-2′,2″	H-3′,3″	H-4′,4″	H-5′,5″	H-5′a,5′b,-5″a,5″b	H-6′a,6′b,-6″a,6″b
2	4.00–3.99 (m)	4.29–4.12 (m)	4.40 (d)	4.51 (t)	4.29–4.12 (m)	4.00–3.99 (m)	4.68–4.62 (d)	5.02–4.92 (t)	5.25–5.16 (t)	5.12–5.06 (t)	3.73 (m)		4.29–4.12 (m)
	3.89–3.83 (dd)		*J* 4.4			3.60 (t)	*J* 8.1						
3	3.97–3.84 (m)	4.29–4.08 (m)	4.44 (d)	4.50 (t)	4.29–4.08 (m)	4.29–4.08 (m)	4.64 (d)	4.93 (t)	5.20 (t)	5.07 (t)	3.74–3.68 (m)		4.37–4.33 (m)
			J 4.5			3.50 (dd)	*J* 7.9						4.29–4.08 (m)
4	3.92–3.84 (m)	4.35–4.13 (m)	4.37 (d)	4.63–4.60 (m)	4.35–4.13 (m)	4.35–4.13 (m)	4.63–4.60 (m)	5.10 (t)	5.22 (t)	5.14 (t)	3.79–3.71 (m)		4.35–4.13 (m)
			J 4.0			3.51 (t)							
6	4.25–4.15 (m)	4.49–4.36 (m)	4.49–4.36 (m)	4.64 (m)	4.60 (m)	4.25–4.15 (m)	4.95–4.90 (d)	5.58–5.44 (t)	5.90–5.83 (t)	5.68–5.62 (t)	3.94–3.92 (m)		4.49–4.36 (m)
	3.75–3.69 (m)					3.48 (t)	*J* 7.7						4.25–4.15 (m)
7	4.20–4.16 (m)	4.20–4.16 (m)	4.41 (d)	4.72 (t)	5.06 (m)	4.00–3.92 (m)	4.65 (d)	4.95 (t)	5.15 (t)	5.11 (t)	4.00–3.92 (m)		4.33 (m)
	3.77–3.71 (m)		*J* 4.7			3.77–3.71 (m)	*J* 8.0						4.00–3.92 (m)
9	4.72–4.62 (m)	4.58–4.48 (dd)	4.46 (d)	5.20 (t)	5.57–5.53 (m)	4.08 (dd)	5.06 (d)	5.57–5.53 (m)	5.98 (t)	5.70 (t)	4.22 (m)		4.72–4.62 (m)
	3.99–3.87 (m)		*J* 4.2			3.99–3.87 (m)	*J* 7.9						3.99–3.87 (m)
10	4.01 (m)	5.14–5.07 (m)	4.48 (d)	4.65 (t)	4.32 (3d)	4.25 (dd)	4.68 (d)	5.14–5.07 (m)	5.23 (t)	5.14–5.07 (m)	3.66 (m)		4.18 (dd)
	3.84 (dd)		*J* 4.4			3.63 (dd)	*J* 7.7						3.95 (d)
13	4.58 (m)	5.67–5.62 (m)	4.64 (d)	5.33 (t)	3.90 (t)	4.32 (m)	5.05 (d)	5.67–5.62 (m)	5.94 (t)	5.70 (t)	4.10–4.06 (m)		4.76–4.65 (m)
	4.22 (m)		*J* 3.3			3.61 (t)	*J* 7.9						4.10–4.06 (m)
14	3.97 (m)	4.28–4.08 (m)	4.40 (d)	4.52 (t)	4.28–4.08 (m)	3.97 (m)	4.64–4.60 (2d)	5.02–4.83 (m)	5.17 (m)	5.02–4.83 (m)		4.28–4.08 (m)	
	3.86 (dd)		*J* 4.4			3.57 (t)	*J* 6.7 *J* 6.2					3.40 (m)	
15	4.09–4.06 (m)	4.32–4.27 (m)	4.40 (d)	4.55 (t)	4.32–4.27 (m)	3.97–3.86 (dd)	4.61 (d)	4.90 (m)	5.16 (t)	4.90 (m)		4.09–4.06 (m)	
	3.97–3.86 (dd)		*J* 4.5			3.57 (dd)	*J* 7.0					3.37 (dd)	
16	3.87 (m)	4.25 (m)	4.43 (d)	4.68 (t)	4.25 (m)	3.87 (m)	4.62 (d)	5.02–4.97 (m)	5.15 (t)	5.02–4.97 (m)		4.25 (m)	
			J 4.0			3.55 (t)	*J* 6.4					3.41 (dd)	
18	3.96–3.90 (m)	4.28 (m)	4.40 (d)	4.70 (t)	5.16–5.06 (m)	3.96–3.90 (m)	4.61 (d)	4.95–4.83 (m)	5.16–5.06 (m)	4.95–4.83 (m)		4.10 (dd)	
			J 4.6			3.72 (dd)	*J* 6.6					3.35 (dd)	
20	4.13–4.01 (m)	5.26–5.20 (m)	4.55 (d)	4.72 (t)	4.35–4.27 (m)	3.94 (dd)	4.70 (d)	5.09–4.98 (m)	5.26–5.20 (m)	5.09–4.98 (m)		4.35–4.27 (m)	
			J 4.2			3.67 (dd)	*J* 6.4					3.47 (dd)	

21	4.01 (d)	4.31–4.25 (m)	4.40 (d) *J* 3.5	4.52 (t)	4.31–4.25 (m)	3.84 (dd)	4.59 (d)	5.28 (dd)	5.02 (dd)	5.38–5.37 (m)	3.94–3.91 (m)	4.22–4.07 (m)
						3.60 (t)	*J* 8.1	5.16 (dd)	4.98 (dd)			
							4.57 (d) *J* 7.9					
22	3.98–3.85 (m)	4.35 (br s)	4.40 (d) *J* 4.4	4.57 (t)	4.29–4.27 (m)	3.98–3.85 (m)	4.62 (d) *J* 7.9	5.19 (dd)	5.02 (dd)	5.40 (d)	4.15–4.11 (m)	4.15–4.11 (m)
						3.56 (dd)						
23	3.98–3.92 (m)	4.28 (t)	4.42 (d) *J* 4.0	4.67 (t)	4.33 (q)	3.85 (dd)	4.61 (d) *J* 8.1	5.29 (dd)	5.00 (dd)	5.39 (dd)	3.98–3.92 (m)	4.20 (dd)
						3.58 (dd)						4.12 (dd)
24	4.15–3.92 (m)	4.34 (br s)	4.43 (d) *J* 4.4	4.71 (t)	5.21–5.10 (m)	4.15–3.92 (m)	4.61 (d) *J* 7.7	5.21–2.10 (m)	5.02 (dd)	5.39 (d)	4.15–3.92 (m)	4.15–3.92 (m)
						3.74 (dd)						
25	4.07–3.86 (m)	4.31 (br s)	4.42 (d) *J* 4.8	4.81 (t)	5.32 (m)	4.07–3.86 (m)	4.57 (d) *J* 7.8	5.11 (t)	4.97 (m)	5.32 (m)	4.07–3.86 (m)	4.07–3.86 (m)
27	4.05–3.90 (m)	5.08 (d)	4.43 (d) *J* 4.4	4.60 (t)	4.31 (q)	3.81 (dd)	4.57 (d) *J* 8.1	5.25 (t)	5.00 (dd)	5.35 (d)	4.05–3.90 (m)	4.12 (m)
						3.59 (t)						

1.2. Condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with isosorbide (1)

1.2.1. Using Ag_2O. A mixture of isosorbide (1.46 g, 0.01 mol), Ag_2O (6.3 g, 0.03 mol), Drierite (10/20 mesh, 8.3 g) and CH_2Cl_2 (100 mL) was stirred for 1 h. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.11 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added dropwise over 1 h, and the mixture was stirred at rt with the exclusion of light and with TLC monitoring (EtOAc). After 25 h the mixture was filtered twice through Celite and the filtrate was evaporated. A portion (0.15 g) of the resulting syrup was kept for HPLC analysis. The remainder (4.76 g) was chromatographed on a column of silica gel (150 g). Elution (10:1 EtOAc–light petroleum) gave 2,5-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)isosorbide (**2**) as white plates (44 mg, 0.6%). Continued elution gave 2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)isosorbide (**3**), as white plates (0.4 g, 8.4%), followed by 5-*O*-(2,3,4,6,tetra-*O*-acetyl-β-D-glucopyranosyl)isosorbide (**4**), as white plates (0.75 g, 16%).

1.2.2. Using $Hg(CN)_2$. To a stirred mixture of isosorbide (1.46 g, 0.01 mol) and Drierite (9 g) in CH_3NO_2 (100 mL), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.21 g, 0.01 mol) was added, followed by $Hg(CN)_2$ (2.4 g, 0.01 mol). After 25 h the mixture was processed as in Section 1.2.1 above to give **2** (89 mg, 1.0%), **3** (0.22 g, 4.6%) and **4** (0.59 g, 12%). Condensation using CH_3CN (100 mL) as solvent instead of CH_3NO_2 gave **2** (45 mg, 0.6%), **3** (0.22 g, 4.6%) and **4** (0.32 g, 6.7%).

1.3. 2.5-Di-*O*-(β-D-glucopyranosyl)isosorbide (5)

To **2** (0.18 g, 1.6 mmol) in anhydrous MeOH (20 mL), NaOMe (from 0.2 g Na) in MeOH (10 mL) was added and the mixture was stirred at rt for 24 h. After deionisation (Zerolit 236 H^+ form), the solution was evaporated to give **5** as a glassy solid (0.07 g, 67%).

Compound **5** (0.03 g, 0.06 mmol) in pyridine (3 mL) was treated with Ac_2O (1 mL, 11 mmol) at rt for 18 h. The mixture was poured into ice-water (50 mL) and the product was extracted with $CHCl_3$. The extract was washed (H_2O, brine), dried (Na_2SO_4) and evaporated. Recrystallisation of the resulting solid gave **2** (0.035 g, 68%).

1.4. 2,5-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)isosorbide (6)

To **5** (0.035 g, 0.07 mmol) in pyridine (2 mL), PhCOCl (0.16 mL, 1 mmol) in benzene (1 mL) was added at 0 °C and the mixture was stirred at rt for 15 h. After pouring

Table 4. ^{13}C NMR data ($CDCl_3$) for the carbohydrate components of compounds **2**–**27**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1′,1″	C-2′,2″	C-3′, 3″	C-4′, 4″	C-5′, 5″	C-6′,6″
2	73.8	80.6	86.0	83.7	78.1	69.0	100.2	70.9	72.4	68.0	71.9	61.6
							100.1	70.1	72.3	67.9	71.7	
3	74.1	81.6	86.2	83.6	72.2	73.4	100.1	71.2	72.7	68.2	72.0	61.9
4	76.0	77.6	88.0	80.9	79.2	69.3	100.2	70.7	72.7	68.4	72.2	62.0
6	74.2	81.0	86.6	84.4	78.9	69.6	100.6	71.8	72.9	69.1	71.3	63.2
									72.6			
7	74.1	80.5	86.4	83.3	73.9	69.9	99.9	71.2	72.8	68.3	72.1	62.0
9	74.0	80.3	86.7	83.4	74.3	70.5	100.4	71.7	72.8	69.6	72.5	63.1
10	73.8	78.5	85.8	81.4	78.7	70.6	100.1	69.6	72.1	68.4	72.7	62.0
13	73.8	79.0	85.8	81.5	79.3	69.3	100.8	71.5	72.7	69.8	72.9	63.3
14	74.2	81.0	86.4	84.4	79.2	69.3	100.4	71.2	70.6	68.6	62.0	
							99.9	70.9	70.0			
15	74.2	81.6	86.2	83.2	72.2	73.6	100.2	70.8	71.4	68.7	62.3	
16	76.0	79.6	88.2	80.9	79.6	69.4	100.6	71.1	70.3	68.7	62.2	
18	73.9	80.5	86.3	82.7	74.0	69.8	99.8	71.2	70.6	68.6	62.1	
20	73.8	78.5	85.8	81.4	79.4	69.6	100.6	71.0	70.1	68.7	62.2	
21	74.3	81.0	86.4	84.2	78.4	69.4	100.8	68.7	70.8	66.9	71.2	61.3
							100.6	67.9				
22	74.2	81.7	86.3	83.8	72.2	73.5	100.8	68.7	70.8	67.0	71.0	61.4
23	76.0	76.4	88.0	80.9	78.9	69.4	100.6	68.1	70.8	66.9	71.0	61.3
24	74.0	80.4	86.5	83.3	73.8	69.8	100.4	68.7	70.8	67.0	71.0	61.4
25	73.9	80.7	86.5	83.2	74.2	70.3	100.3	68.7	70.8	67.0	70.9	61.3
27	73.7	78.5	85.5	81.3	78.2	69.5	100.4	97.9	70.6	66.8	71.0	61.1

into ice-water (50 mL) the mixture was extracted with $CHCl_3$. The extract was washed (H_2O, aq $NaHCO_3$, H_2O and brine), dried (Na_2SO_4) and evaporated to a syrup, which was chromatographed on a column of silica gel (30 g). Elution (1:1 EtOAc–light petroleum) gave **6** as plates (0.065 g, 67%).

1.5. 5-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)isosorbide (7)

To **3** (0.5 g, 1 mmol) in pyridine (5 mL), Ac_2O (1.4 mL, 15 mmol) was added at 0 °C and the mixture was stirred at rt for 20 h. Working up as in Section 1.3 gave **7** as fine needles (0.4 g, 74%).

1.6. 2-*O*-β-D-Glucopyranosylisosorbide (8)

Compound **7** (0.28 g, 0.5 mmol) in anhydrous MeOH (15 mL) was treated with NaOMe (from 0.2 g Na) in MeOH (30 mL) at rt for 24 h. After deionisation the solution gave **8** as a glassy solid (0.15 g, 90%).

Reacetylation of **8** (0.1 g, 0.33 mmol) in pyridine (3 mL) with Ac_2O (1 mL, 10 mmol) at rt for 18 h gave **7** (0.14 g, 83%).

1.7. 5-*O*-Benzoyl-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)isosorbide (9)

Compound **8** (0.15 g, 0.5 mmol) in pyridine (3 mL) was treated with PhCOCl (0.6 mL, 5 mmol) in benzene (2 mL) at 0 °C for 20 h, as in the preparation of **6** above, to give **9** as plates (0.32 g, 79%).

1.8. 2-*O*-Acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)isosorbide (10)

1.8.1. By acetylation of 4. To **4** (0.5 g, 0.9 mmol) in pyridine (5 mL), Ac_2O (1.4 mL, 15 mmol) was added at 0 °C and the mixture was stirred at rt for 22 h. Working up as usual gave **10** as needles (0.37 g, 68%).

1.8.2. By glucosylation of 2-*O*-acetylisosorbide (11). A mixture of **11** (1 g, 5 mmol, mp 78–80 °C, lit.[7] mp 77.5–78.5 °C), Ag_2O (4.17 g), Drierite (5.5 g) and CH_2Cl_2 (100 mL) was stirred at rt for 1 h. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (3.5 g, 8.5 mmol) in CH_2Cl_2 (30 mL) was added dropwise over 0.5 h, and the mixture was stirred at rt for 36 h. Working up as in Section 1.2.1 gave **10** (1.46 g, 53%).

1.9. 5-*O*-β-D-Glucopyranosylisosorbide (12)

Compound **4** (1 g, 2 mmol) in anhydrous MeOH (30 mL) was treated with NaOMe (from 0.2 g Na) in MeOH (30 mL) at rt for 17 h to give **12** as a glassy solid (0.52 g, 81%).

Reacetylation of **12** (0.15 g, 0.5 mmol) in pyridine (4 mL) with Ac_2O (1 mL, 11 mmol) at rt for 15 h gave **10** (0.16 g, 64%).

1.10. 2-*O*-Benzoyl-5-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)isosorbide (13)

Compound **12** (0.2 g, 6 mmol) in pyridine (3 mL) was treated with PhCOCl (1.5 mL, 13 mmol) in benzene

(2 mL) as described above in Section 1.4 to give **13** as plates (0.35 g, 65%).

1.11. Condensation of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide with isosorbide (1)

1.11.1. Using Ag_2O. Isosorbide (1.46 g, 0.01 mol) was treated with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (3.4 g, 0.01 mol) as in Section 1.2.1. Column chromatography gave 2,5-di-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)isosorbide (**14**) as white needles (17 mg, 0.26%), followed by 2-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)isosorbide (**15**) as a white solid (0.11 g, 2.7%) and 5-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)isosorbide (**16**) as white prisms (0.25 g, 6.2%).

1.11.2. Using $Hg(CN)_2$. To a mixture of isosorbide (1.46 g, 0.01 mol) and Drierite (9 g) in CH_3NO_2 (80 mL), 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (3.4 g, 0.01 mol) was added, followed by $Hg(CN)_2$ (2.4 g, 0.01 mol). The mixture was stirred at rt for 24 h and was processed as in Section 1.2.1 to give **14** (21 mg, 0.32%), **15** (0.06 g, 15%) and **16** (0.39 g, 9.7%). Condensation using CH_3CN as solvent in place of CH_3NO_2 gave **14** (16 mg, 0.24%), **15** (0.07 g, 1.7%) and **16** (0.38 g, 9.4%).

1.12. 2-*O*-β-D-Xylopyranosylisosorbide (17)

Compound **15** (0.24 g, 0.6 mmol) in anhydrous MeOH (15 mL) was treated with NaOMe (from 0.2 g Na) in MeOH (30 mL) at rt for 24 h to give **17** as a colourless syrup (90 mg, 55%).

1.13. 5-*O*-Acetyl-2-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)isosorbide (18)

To **15** (3 g, 7.4 mmol) in pyridine (10 mL), Ac_2O (2 mL, 21 mmol) was added dropwise at O °C and the mixture was stirred at rt for 24 h. Working up as usual gave **18** as white plates (2.72 g, 82%).

1.14. 5-*O*-β-D-Xylopyranosylisosorbide (19)

Compound **16** (0.24 g, 0.6 mmol) in anhydrous MeOH (15 mL) was treated with NaOMe (from 0.2 g Na) in MeOH (30 mL) at rt for 24 h to give **19** as a colourless syrup (0.1 g, 61%).

1.15. 2-*O*-Acetyl-5-*O*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)isosorbide (20)

1.15.1. By acetylation of 16. To **16** (1.5 g, 3.7 mmol) in pyridine (10 mL), Ac_2O (1 mL, 11 mmol) was added at 0 °C and the mixture was stirred at rt for 24 h. Working up as usual gave **20** as plates (1.29 g, 78%).

1.15.2. By glycosylation of 2-*O*-acetylisosorbide (11). A mixture of **11** (4 g, 21 mmol), Ag_2O (25 g), Drierite (20 g) and CH_2Cl_2 (250 mL) was stirred at rt for 1 h. 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide (13.6 g, 0.04 mol) in CH_2Cl_2 (50 mL) was added dropwise over 0.5 h and the mixture was stirred at rt for 36 h. Working up as in Section 1.2.1 gave compound **20** (4.56 g, 48%).

1.16. Condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with isosorbide (1)

1.16.1. Using Ag_2O. A mixture of isosorbide (2.92 g, 0.02 mol), Ag_2O (14 g) and Drierite (8 g) in CH_2Cl_2 (200 mL) was treated with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (8.2 g, 0.02 mol, mp 83–84 °C, lit.[11] mp 83–84 °C) in CH_2Cl_2 (75 mL) as in Section 1.2.1 above. Column chromatography on silica gel gave 2,5-di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-isosorbide (**21**) as white prisms (63 mg, 0.4%), followed by 2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-isosorbide (**22**) as white prisms (0.31 g, 3.3%) and 5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)isosorbide (**23**) as a clear syrup (1.18 g, 12%).

1.16.2. Using $Hg(CN)_2$. To a stirred mixture of isosorbide (1.46 g, 0.01 mol) and Drierite (9 g) in CH_3NO_2 (80 mL), 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (4.1 g, 0.01 mol) was added, followed by $Hg(CN)_2$ (2.4 g, 0.01 mol). After 24 h the mixture was processed as in Section 1.2.2 above to give **21** (94 mg, 1.2%), **22** (0.06 g, 1.3%) and **23** (0.54 g, 11%). Condensation using CH_3CN as solvent instead of CH_3NO_2 gave **21** (42 mg, 0.5%), **22** (0.07 g, 1.5%) and **23** (0.47 g, 9.9%).

1.17. 5-*O*-Acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)isosorbide (24)

To compound **22** (0.2 g, 0.42 mmol) in pyridine (1 mL), Ac_2O (1 mL, 11 mmol) was added at 0 °C and the mixture was stirred at rt with TLC monitoring (10:1 $CHCl_3$–MeOH). After 12 h the reaction was worked up as usual to give **24** as a clear syrup (0.19 g, 87%).

1.18. 2-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-5-*O*-benzoylisosorbide (25)

1.18.1. By benzoylation of 22. Compound **22** (0.2 g, 0.42 mmol) in pyridine (15 mL) was cooled to −5 °C. PhCOCl (0.1 mL, 0.86 mmol) was added dropwise and the mixture was stirred at rt with TLC monitoring (9:1 EtOAc–light petroleum). After 48 h the mixture was processed as in Section 1.4 to give **25** as a clear syrup (0.12 g, 50%).

1.18.2. From 5-*O*-benzoylisosorbide (26). A mixture of **26** (2.5 g, 0.01 mol, mp 118 °C, lit.[8] mp 117–117.5 °C), Ag_2O (10 g), Drierite (8.5 g) and CH_2Cl_2 (100 mL) was stirred at rt for 1 h. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (6.17 g, 0.015 mol) in CH_2Cl_2 (40 mL) was added dropwise over 0.5 h, and the mixture was stirred at rt with TLC monitoring (9:1 $CHCl_3$–MeOH). After 48 h the mixture was processed as in Section 1.2.1 to give **25** as a clear syrup (1.57 g, 27%).

1.19. 2-*O*-Acetyl-5-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)isosorbide (27)

1.19.1. By acetylation of 23. To **23** (0.35 g, 0.74 mmol) in pyridine (10 mL), Ac_2O (1 mL, 11 mmol) was added at 0 °C and the mixture was stirred at rt for 12 h. Working up as usual gave **27** as a colourless syrup (0.27 g, 71%).

1.19.2. From 2-*O*-acetylisosorbide (11). A mixture of **11** (4 g, 20 mmol), Ag_2O (25 g), Drierite (20 g) and CH_2Cl_2 (250 mL) was stirred at rt for 1 h. 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (10.5 g, 25.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 0.5 h and the mixture was stirred with TLC monitoring (9:1 EtOAc–light petroleum). Working up as in Section 1.2.1 gave **27** as a clear syrup (3.75 g, 34%).

1.20. HPLC analysis of the mono-glycosylated isosorbide products

Analyses were carried out using a Waters HPLC pump equipped with a Spectra-physics Chrom Jet integrator and a Waters 484 tunable detector set at wavelength 215 nm. A Techopad 10/c 18 reverse phase column 25 cm × 6.6 mm was used. Elution was carried out with 4:1 H_2O–MeOH at a flow rate of 1.5 mL/min. Purified samples of the 2-*O*- and 5-*O*-glucosides **3** and **4**, of the 2-*O*- and 5-*O*-xylosides **15** and **16**, and of the 2-*O*- and 5-*O*-galactosides **22** and **23** were used to standardise the R_t characteristics of the column. Satisfactory separation of the pairs of isomers was obtained in each case (see Table 1 for R_t values). Solutions were made of the individual compounds **3**, **4**, **15**, **16**, **22** and **23** in concentrations varying from 0.2 to 1.0 mol/L × 10^{-1} in 1:1 H_2O–MeOH. A portion (15 μL) of each solution was chromatographed in the HPLC system with 4:1 H_2O–MeOH as eluant. For each of the compounds, the relationship between the peak area and concentration was found to be linear. A sample of the syrup (0.15 g) from each of the condensation reactions 1.2, 1.11 and 1.16 was dissolved in 1:1 H_2O–MeOH (5 mL). A portion (15 μL) of the solution was injected onto the HPLC column, and elution was carried out with 4:1 H_2O–MeOH at a flow rate of 1.5 mL/min. Each analysis was repeated at least three times and the average of the measurement of the isomer ratios was taken. The results have been summarised in Table 1.

Acknowledgements

We are grateful to Dr. N. W. A. Geraghty for advice and assistance with the HPLC work, to Mr. P. Naughton for microanalyses and to Mr. S. Collier for NMR Spectra.

References and notes

1. (a) Soltzberg, S. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 229–283; (b) Stoss, P.; Hemmer, R. *Adv. Carbohydr. Chem. Biochem.* **1991**, *49*, 92–171; (c) Hopton, F. J.; Thomas, G. H. S. *Can. J. Chem.* **1969**, *47*, 2395–2401; (d) Camerman, A.; Camerman, M.; Trotter, J. *Acta Crystallogr.* **1965**, *19*, 449–456.
2. Koenigs, W.; Knorr, E. *Ber.* **1901**, *34*, 957–981.
3. Helferich, B.; Wedemeyer, K. *Liebigs Ann. Chem.* **1949**, *563*, 139–145; *Chem. Ber.* **1950**, *83*, 538–540.
4. Sohar, P.; Medgyes, G.; Kuszmann, J. *Org. Magn. Reson.* **1978**, *11*, 357–359.
5. Goodwin, J. C.; Hodge, J. E.; Weisleder, D. *Carbohydr. Res.* **1980**, *79*, 133–141.
6. Boch, K.; Pedersen, C.; Pedersen, H. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 193–224.
7. Buck, K. W.; Duxbury, J. M.; Foster, A. B.; Perry, A. R.; Weber, J. M. *Carbohydr. Res.* **1966**, *2*, 122–131.
8. Stoss, P.; Merrath, P.; Schluter, G. *Synthesis* **1987**, *6*, 174–176.
9. Lemieux, R. U.; McInnes, A. G. *Can. J. Chem.* **1960**, *38*, 136–140.
10. Wulff, G.; Rohle, G. *Angew. Chem. Int., Ed. Engl.* **1974**, *13*, 157–170.
11. Conchie, J.; Levvy, G. A. *Methods Carbohydr. Chem.* **1963**, *2*, 335–337.