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Syntheses of spacer-armed carbohydrate model compounds [1,2]

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Abstract

Commercially available chemicals, such as diethylene glycol, 1,9-nonanediol, 9-decen-1-ol, 1,2,6-hexanetriol, and *p*-nitrophenol were used to prepare spacer-armed carbohydrate derivatives. Glycosides of D-glucose, *N*-acetyl-D-glucosamine and 3-*O*-methyl-D-glucose have been synthesized, carrying reactive groups at the end of the spacer-arms. These glycosides are capable of forming neoglycoproteins. When bromo sugars were reacted with highly apolar aglycones in the presence of mercuric cyanide or mercuric bromide, a considerable amount of '2-OH-compounds' (such as 9-hydroxynonyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside) were formed. Some spacer-armed derivatives (such as 9,10-epoxydecyl β-D-glucopyranoside) are theoretically a mixture of diastereomers, but this fact does not mirror in the ^{1}H and ^{13}C NMR spectra. © 1997 Elsevier Science Ltd.

Keywords: Spacer-armed glycosides; Novel bridge molecules

1. Introduction

Spacer-armed carbohydrate derivatives capable of forming neoglycoconjugates have been found to be useful in biological research and in the last few decades a great number of neoglycoproteins have been prepared for immunological studies [1–12]. Carbohydrate-specific antibodies raised against these semi-artificial antigens have been investigated [13,14]. Purification of antibodies and lectins were possible by means of affinity chromatography after incorporating spacer-armed glycosides into solid matrixes [15]. The chemical syntheses of oligosaccharides related to different bacteria is one of the ongoing research projects in this laboratory [16–19]. Oligosaccharides which are only haptens must be attached to suitable immunogens, in most cases to proteins to prepare 'artificial' antigens.

In order to create covalent linkages the spacers must have two functional groups. The carbohydrate moiety can be easily attached to the bridge molecule as a glycoside and the other end of the spacer must contain a reactive group. There are many methods in the literature [1] for the preparation of neoglycoproteins, but in the case of complex oligosaccharides the number of methodologies is limited. In the past twenty years the 8-methoxycarbonyloctyl [3] and the *p*-iso-

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[1] Dedicated to Professor András Lipták on the occasion of his 60th birthday.

[2] A part of this work was presented at the XVIth International Carbohydrate Symposium, Paris, France, 1992, Abstract A055, p 90.

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thiocyanatophenyl glycosides [2] were the most popular for attaching oligosaccharide components of bacterial cell-wall or blood group substances. The first one has the ideal length and can react with amino groups via the corresponding acyl-azide and the latter can form a thiocarbamide linkage between the spacer and the protein. Bridge molecules bearing aldehydo terminal-groups seem to be the most useful. Reductive alkylation of amino groups is a rather simple procedure but the syntheses of suitable aldehydo derivatives are difficult [4,5]. The reducing end of an oligosaccharide can serve itself as a spacer by losing one monosaccharide unit [7].

Various reactive groups can be formed by applying short spacer-arms (e.g. 2-bromoethyl [20] or 2-azidoethyl [21] glycosides) which may be elongated in a later stage of the reaction sequence. Over the last decade it has been demonstrated that 'oxa' or 'dioxa' spacers prepared from diethylene or triethylene glycols [8,9,22–24] are very useful for the preparation of neoglycoproteins.

In this paper we report on the syntheses of a series of interesting spacer-armed glycosides related to D-glucose, *N*-acetyl-D-glucosamine, and 3-*O*-methyl-D-glucose.

2. Results and discussion

Commercially available chemicals, such as diethylene glycol (**1**), 1,9-nonanediol (**2**), 9-decen-1-ol (**3**), 1,2,6-hexanetriol (**4**), and *p*-nitrophenol (**5**) were used to prepare spacer-armed carbohydrate derivatives. Using **1**–**5**, various reactive end-groups, such as methoxycarbonyl, carboxyl, carbonyl, epoxide, and *p*-isothiocyanate, have been developed in order to produce neoglycoproteins. Monoglycosylation of **1** and **2**, followed by Jones oxidation would give methoxycarbonyl-alkyl spacers, respectively. After glycosylation of **3** and removal of the protecting groups, the double bond can be ozonolyzed [5] to give an aldehyde. In an alternative route an epoxide may be formed and used directly in the neoglycoprotein synthesis. The reaction of the appropriately protected **4** with a suitable glycosyl donor, followed by deprotection may give a derivative bearing a *vicinal* diol portion. Oxidation with sodium periodate then may produce an aldehyde for the reductive alkylation reaction with proteins [1,4,5]. Conversion of *p*-nitrophenyl glycosides to neoglycoproteins via *p*-isothiocyanatophenyl derivatives are well-documented [2,25].

Diols **1** and **2** were reacted, separately, with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**). The mercuric bromide-promoted reaction [26] of **1** gave the crystalline monoglucoside **8** in an acceptable yield (61%). Compound **2** was not soluble in dichloromethane, so the reaction was performed under Helferich conditions at 50 °C. It should be noted that during our investigations Japanese authors also used 1,9-nonanediol to form an 8-methoxycarbonyl-octyl spacer [27]. Column chromatography of the crude product gave **9** (62%) and an unexpected by-product which turned out to be 9-hydroxynonyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (**10**). It is known from the literature that under Koenigs–Knorr condi-

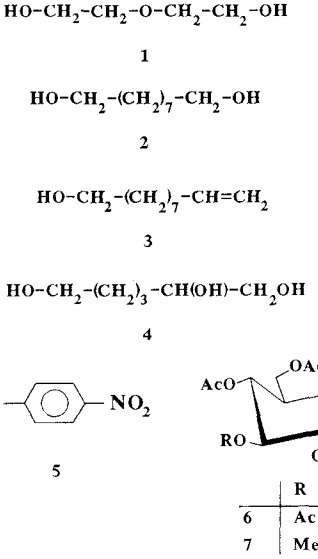
Table 1
^{13}C NMR data for spacered D-glucose derivatives in CD_3OD

Carbon	Compound			
	18	**19**	**20**	**21**
C-1	104.37	104.49	104.43	104.32
C-2	74.98	75.24	75.14	75.08
C-3	77.86	78.24	78.14	78.09
C-4	71.78	71.79	71.67	71.64
C-5	77.86	78.00	77.90	77.85
C-6	62.71	62.96	62.88	62.76
$-COOCH_3$	52.26	52.28		
C=O	172.77	176.14		
$-OCH_2-$	71.53	71.04	71.06	70.85
	69.68			
	69.04			
$-CH_2-$		35.01–26.21	35.07–27.27	33.54–27.02
$-CH=$			140.21	
$=CH_2$			115.05	
$-CH(O)-$				53.48

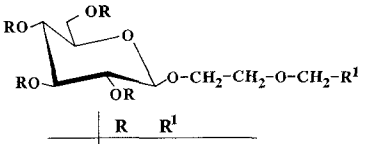
tions the '2-OH' compounds may be formed [28] because of the rearrangement of the corresponding orthoesters [29]. When **3** was coupled with **6** in the presence of mercuric bromide in dichloromethane, the expected product **11** and the 'by-product' **12** were isolated in almost equal amounts (32 and 29.9%). It is noteworthy that under the same conditions 2,4,6-tri-*O*-acetyl-3-*O*-allyl-α-D-glucopyranosyl bromide [30] and octanol yielded octyl 4,6-di-*O*-acetyl-3-*O*-allyl-α-D-glucopyranoside as the side-product [31].

The free hydroxyl group at the end of a spacer (e.g. in **8** and **9**) can be converted into different reactive groups. Tosylation, azide displacement and reduction to amine is a well-known reaction sequence (the first 'dioxa-spacers' were prepared by Lipták in Munich, 1971 [8,9]). Oxidation seems to be a very simple way to generate an aldehyde function, but before deprotection of the sugar unit the reactive function has to be masked [10]. Jones oxidation of **8** and **9** gave 4-methoxycarbonyl-3-oxa-butyl and 8-methoxycarbonyloctyl glycosides **13** and **14**, respectively. The double bond in **11** was converted into the corresponding epoxide (**15**) with *m*-chloroperbenzoic acid. The β-anomeric configuration in compounds **8–15** was determined from their ^{1}H NMR data; all $J_{1,2}$ coupling constants were in the range of 7.4–8 Hz. Compound **15** is theoretically a mixture of diastereoisomers, but this fact is not mirrored in the ^{1}H NMR spectrum. Conversion of the allyl glucoside **16** [32] with *m*-chloroperbenzoic acid to the epoxide **17** yielded the mixture of the 2′*S* and 2′*R* diastereoisomers [33] in a molar ratio of 4:1, as determined from the ^{1}H NMR spectrum. The 'extra' chiral carbon (2′) is so close to the sugar part that the isomers gave different spectra. *Zemplén* deacylation of **13**, **14**, and **11** yielded **18**, **19**, and **20**, respectively. In the case of the epoxides **15** and **17** *O*-deacylation, yielding **21** and **22**, respectively, was performed with magnesium oxide in methanol [34]. For the ^{13}C NMR data of **18–21**, see Table 1.

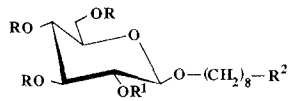
Chemical syntheses of oligosaccharide components of mycobacterial antigens is one of the ongoing research projects in this laboratory. 3-*O*-Methyl-D-glucose is a frequent building block in the surface antigens of different mycobacteria. In this context, spacer-armed derivatives of this sugar have also been prepared. Reaction of 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyl bromide (**7**) [35] with 3,6-dioxa-7-ethoxycarbonylheptan-1-ol (**23**) [8,9] under *Helferich* conditions gave the corresponding β-glycoside (**24**). Subsequent deacylation with sodium methoxide (0.35 equiv) in methanol [16] yielded 3,6-dioxa-7-methoxycarbonylheptyl 3-*O*-methyl-β-D-glucopyranoside (**25**). Saponification of **25** (0.05 M NaOH), followed by neutralization with Amberlite IR 120 H^+ resin resulted in compound **26**. The ^{13}C NMR spectra of **25** and **26** verified the structures: the chemical shifts of the anomeric carbons clearly demonstrated the β-anomeric configurations (103.3 and 102.1 ppm, respectively). Both **25** and **26** can be coupled to proteins by the acyl-azide [3] or one of the active-ester methods [6]. In parallel experiments, *p*-nitrophenyl 3-*O*-methyl-β-D-glucopyranoside (**27**) [17] was hydrogenated over palladium on carbon, and converted into the crystalline *p*-isothiocyanatophenyl compound **28** with thiophosgene [25]. The conjugation of this type of glycoside to proteins is well-documented [2,11].



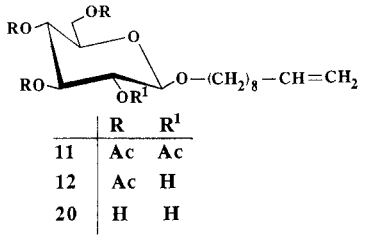
	R
6	Ac
7	Me



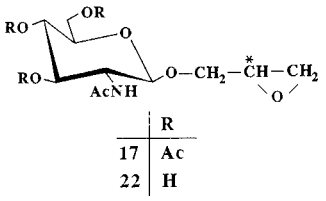
	R	R^1
8	Ac	CH_2OH
13	Ac	COOMe
18	H	COOMe



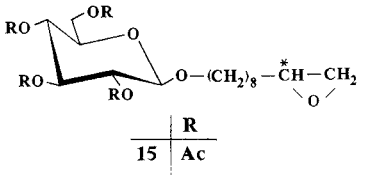
	R	R^1	R^2
9	Ac	Ac	CH_2OH
10	Ac	H	CH_2OH
14	Ac	Ac	COOMe
19	H	H	COOMe



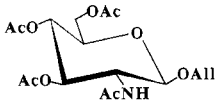
	R	R^1
11	Ac	Ac
12	Ac	H
20	H	H



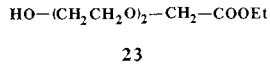
	R
17	Ac
22	H



	R
15	Ac
21	H



16



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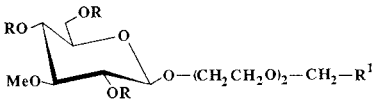
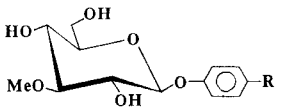


	R	R^1
24	Ac	COOEt
25	H	COOMe
26	H	COOH

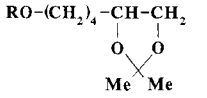
For the preparation of the glucoside **33** the hexanetriol **4** was converted into 5,6-diacetoxy-hexanol (**31**) as follows: compound **4** was reacted with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid and after the workup procedure TLC showed two spots. One (**29**) had the same chromatographic mobility as the reference compound (5*S*)-5,6-isopropylidene-dioxyhexanol, prepared according to [36]. It was obvious that the by-product was the mixed acetal **29a**. The mixture of **29** and **29a** was treated with acetic acid in dichloromethane to yield **29** (77%). Conventional benzylation, hydrolysis and then acetylation gave 1,2-diacetoxy-6-benzyloxy-hexane (**30**) which was hydrogenated (Pd–C, H_2) to afford 1,2-diacetoxy-hexanol **31**. Compounds **30** and **31** were purified by column chromatography. 2,4,6-Tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyl bromide (**7**) was coupled with **31** and the product (**32**) was deacylated to yield **33** (for ^{13}C NMR data, see Table 2). Oxidation of the *vicinal* diol into the *aldehydo* derivative **34** allows to prepare neoglycoproteins by the reductive alkylation method [1]. The structures of the deprotected compounds **18–21**, **25**, **26**, and **33** were confirmed by ^{13}C NMR spectroscopy.

Table 2
^{13}C NMR data for spacered 3-*O*-methyl-D-glucose derivatives

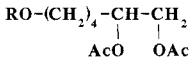
Carbon	Compound			
	25 $CDCl_3$	**26** $CDCl_3$–CD_3OD 1:1	**28** CD_3OD	**33** CD_3OD
C-1	103.27	102.09	102.37	104.30
C-2	73.77	72.66	74.68	74.91
C-3	85.67	85.56	87.72	87.84
C-4	70.21	69.26	70.97	71.16
C-5	75.64	75.91	78.14	77.74
C-6	62.03	60.76	62.49	62.60
$-OCH_3$	60.36	59.61	61.08	61.04
$-COOCH_3$	51.67			
$-OCH_2-$	70.75–68.72	69.26–67.75		70.72
$-CH_2-$				34.04–23.06
$-CH_2OH$				67.31
$-CH(OH)-$				73.15
Aromatic			127.74	
			119.08	



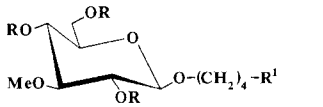
	R
27	NO_2
28	NCS



	R
29	H
29a	CH_3-C(OMe)-CH_3



	R
30	Bzl
31	H



	R	R^1
32	Ac	CH(OAc)-CH_2OAc
33	H	CH(OH)-CH_2OH
34	H	CHO

Preparation of neoglycoproteins using glycosides described in this paper will be published elsewhere.

3. Experimental

General.—Melting points (uncorrected) were determined on a Kofler hot-stage apparatus. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. NMR spectra were recorded with a Bruker WP-200 SY spectrometer for solutions in $CDCl_3$ (internal Me_4Si) or in CD_3OD. The reactions were monitored by TLC on Kieselgel 60 F_{254} (Merck, Darmstadt) with detection by charring with sulfuric acid. Kieselgel 60 (Merck) was used for short-column chromatography. 1,9-Nonanediol (**2**), 9-decen-1-ol (**3**), and 1,2,6-hexanetriol (**4**) were ordered from Aldrich.

5-Hydroxy-3-oxa-pentyl 2,3,4,6-tetra-O-*acetyl-β*-D-*glucopyranoside* (**8**).—A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**6**; 4.11 g, 10 mmol) and diethylene glycol (**1**; 10.6 g, 100 mmol) in dry CH_2Cl_2 (50 mL), containing activated powdered 4 Å molecular sieves (5 g), was stirred under Ar for 15 min. Then, $HgBr_2$ (3.60 g, 10 mmol) was added and stirring was continued at room temperature overnight. The mixture was diluted with CH_2Cl_2 (300 mL), filtered through Celite, and the filtrate was washed with aq 5% KI (3 × 30 mL) and water (3 × 30 mL), dried, and concentrated. The obtained crystalline mass was recrystallized from a mixture of EtOAc and cyclohexane to give **8** (2.68 g, 61%); mp 86–88 °C; lit. mp 87–88 °C [8,9]; $[\alpha]_D$ −13.5° (*c* 0.8, $CHCl_3$); lit. $[\alpha]_D$ −14° ($CHCl_3$) [8,9].

9-Hydroxynonyl 2,3,4,6-tetra-O-*acetyl-β*-D-*glucopyranoside* (**9**).—A mixture of 1,9-nonanediol (**2**; 16 g, 100 mmol), $Hg(CN)_2$ (6.3 g, 25 mmol), and $HgBr_2$ (0.90 g, 2.5 mmol) in 1:1 dry toluene–nitromethane (300 mL) was concentrated to half its volume at atmospheric pressure. After cooling to 50 °C under Ar, compound **6** (8.22 g, 20 mmol) was added and the mixture was stirred for 2 h. After cooling, the solution was diluted with CH_2Cl_2 (150 mL), filtered, and concentrated. The residue was taken up in CH_2Cl_2 (300 mL) and the solution was filtered, washed with aq 5% KI (2 × 50 mL) and water (2 × 50 mL), dried, and concentrated. The product was subjected to column chromatography using 8:2 CH_2Cl_2–acetone as the eluent. The first product that eluted was **9** (6.12 g, 62.4%); $[\alpha]_D$ −7° (*c* 0.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.26–4.90 (m, 3 H, H-2,3,4), 4.48 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.32–4.03 (m, 2 H, H-6a,6b), 3.94–3.40 (m, 5 H, H-5 and 2 $-CH_2-O-$), 2.10 (s, 3 H, Ac), 2.06 (bs, 1 H, OH, deuterable), 2.04, 2.03, and 2.01 (3 s, each 3 H, 3 Ac), 1.68–1.20 (m, 14 H, 7 $-CH_2-$). Compound **9** was used for the next step without further characterization. After mixed fractions (1.74 g), the next compound that eluted was 9-hydroxynonyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (**10**) (501 mg, 5.6%); mp 75–76 °C (from EtOH); $[\alpha]_D$ +5° (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.11 and 5.02 (2 t, 2 H, H-3,4), 4.36 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.32–4.03 (m, 2 H, H-6a,6b), 3.97–3.49 (m, 6 H, H-2,5 and 2 $-CH_2-O-$), 2.10 and 2.03 (2 s, 6,3 H, 3 Ac), 1.73–1.22 (m, 14 H, 7 $-CH_2-$). Anal. Calcd for $C_{21}H_{36}O_{10}$: C, 56.23; H, 8.09. Found: C, 56.35; H, 8.11.

9-Decen-1-yl 2,3,4,6-tetra-O-*acetyl-β*-D-*glucopyranoside* (**11**).—Compound **6** (2.06 g, 5 mmol) was coupled with 9-decen-1-ol (**3**; 1.09 g, 7 mmol) in the presence of $HgBr_2$ as described for the preparation of **8**. The products were separated by means of

column chromatography. The first compound that eluted as a syrup was **11** (778 mg, 32%); $[\alpha]_D$ −15.7° (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.72 (m, 1 H, –CH=), 5.18–4.78 (m, 5 H, H-2,3,4 and $=CH_2$), 4.49 (d, 1 H, $J_{1,2}$ 7.4 Hz, H-1), 4.24–4.00 (m, 2 H, H-6a,6b), 3.78 (m, 1 H, –O–CH_2–), 3.61 (m, 1 H, H-5), 3.38 (m, 1 H, –O–CH_2–), 1.98, 1.95, 1.92, and 1.90 (4 s, each 3 H, 4 Ac), 1.56–1.12 (m, 14 H, 7 –CH_2–). Anal. Calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.35; H, 7.97. The second product that eluted was 9-decen-1-yl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (**12**) (665 mg, 29.9%); mp 58–60 °C (from EtOH); $[\alpha]_D$ +12.7° (*c* 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.82 (m, 1 H, –CH=), 5.23–4.88 (m, 4 H, H-3,4 and CH_2=), 4.36 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.33–4.07 (m, 2 H, H-6a,6b), 3.92 (m, 1 H, –O–CH_2–), 3.68 (m, 1 H, H-5), 3.63–3.48 (m, 2 H, H-2 and –O–CH_2–), 2.39 (bs, 1 H, OH, deuterable), 2.09 and 2.03 (2 s, 6,3 H, 3 Ac), 1.71–1.22 (m, 14 H, 7 –CH_2–). Anal. Calcd for $C_{22}H_{36}O_9$: C, 59.44; H, 8.16. Found: C, 59.48; H, 8.20.

*4-Methoxycarbonyl-3-oxa-butyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**13**).—To a solution of **8** (873 mg, 2 mmol) in 1:1 CH_2Cl_2-acetone (40 mL) was added dropwise a solution of CrO_3 (500 mg, 5 mmol) in 3.5 M H_2SO_4 (2.5 mL) during 30 min at 0 °C. After an additional 30 min, the chilling was terminated and the mixture stirred for 2 h (TLC, 8:2 CH_2Cl_2-acetone). EtOH (10 mL) was then added at 0 °C and, after 30 min the solid separated was filtered off and washed with acetone. $NaHCO_3$ (1 g) was added to the combined organic phases in small portions, and the suspension was concentrated. The residue was partitionated between CH_2Cl_2 (30 mL) and water (30 mL), and Bu_4NBr (1 g) and MeI (5 mL) were added. The mixture was vigorously stirred for 48 h, diluted with CH_2Cl_2 (30 mL), and the organic layer was separated, washed with water (3 × 15 mL), dried, and concentrated. The residue was purified by column chromatography to yield **13** (643 mg, 69.2%); mp 69–70 °C (from EtOH); $[\alpha]_D$ −25.2° (*c* 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.27–4.97 (m, 3 H, H-2,3,4), 4.61 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.31–3.63 (m, 9 H, H-5,6a,6b, 3 –CH_2–), 3.74 (s, 3 H, $COOCH_3$), 2.08, 2.04, 2.02, and 2.00 (4 s, each 3 H, 4 Ac). Anal. Calcd for $C_{19}H_{28}O_{13}$: C, 49.14; H, 6.08. Found: C, 49.04; H, 6.02.

*8-Methoxycarbonyloctyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**14**).—Compound **9** (981 mg, 2 mmol) was converted into **14** (736 mg, 71%) as described for the preparation of **13**; mp 61–63 °C (from EtOH); $[\alpha]_D$ −14° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.22–4.83 (m, 3 H, H-2,3,4), 4.40 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 4.24–3.99 (m, 2 H, H-6a,6b) 3.87–3.30 (m, 3 H, H-5 and –O–CH_2–), 3.58 (s, 3 H, $COOCH_3$), 2.21 (t, 2 H, –CH_2–COOMe), 2.03, 1.99, 1.98, and 1.94 (4 s, each 3 H, 4 Ac), 1.60–1.11 (m, 12 H, 6 –CH_2–). Anal. Calcd for $C_{24}H_{38}O_{12}$: C, 55.59; H, 7.39. Found: C, 55.47; H, 7.42.

*9,10-Epoxydecyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside* (**15**).—To a solution of **11** (973 mg, 2 mmol) in CH_2Cl_2 (20 mL) was added 3-chloroperbenzoic acid (800 mg). The mixture was stirred at room temperature for 3 days, then it was diluted with CH_2Cl_2 (100 mL), washed with aq 5% $NaHCO_3$ (2 × 20 mL) and water (3 × 20 mL), dried, and concentrated. The residue was subjected to column chromatography to give syrupy **15** (862 mg, 72%); $[\alpha]_D$ −15° (*c* 1.36, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.18–4.82 (m, 3 H, H-2,3,4), 4.39 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.23–3.98 (m, 2 H, H-6a,6b), 3.78 (m, 1 H, –O–CH_2–), 3.60 (m, 1 H, H-5), 3.38 (m, 1 H, –O–CH_2–), 2.82 (m, 1 H, –CH–O–), 2.68 and 2.38 (2 dd, each 1 H, –CH_2–O–), 2.00, 1.98, 1.96, and 1.93 (4 s, each 3 H, 4 Ac), 1.52–1.12 (m, 14 H, 7 –CH_2–). Anal. Calcd for $C_{24}H_{38}O_{11}$: C, 57.36; H, 7.62. Found: C, 57.56; H, 7.57.

*2,3-Epoxypropyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside* (**17**).—Allyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside [32] (**16**; 775 mg, 2 mmol) was converted into **17** (600 mg, 74.4%) as described for the preparation of **15**; mp 167–168 °C (from EtOAc–hexane); lit. mp 162–163 °C (from MeOH–Et_2O) [37]; ^1H NMR ($CDCl_3$): the product was a 1:4 mixture of the 2′*R* and 2′*S* diastereoisomers [33]. Characteristic data: δ 5.61 (d, 1 H, NH), 5.30–4.99 (m, 2 H, H-3,4), 4.76 (d, 0.2 H, $J_{1,2}$ 9 Hz, H-1 of the 2′*R* isomer), 4.62 (d, 0.8 H, $J_{1,2}$ 9 Hz, H-1 of the 2′*S* isomer), 4.33–4.08 (m, 2 H, H-6a,6b), 2.10, 2.04, and 1.98 (3 s, 3,6,3 H, 4 Ac). Anal. Calcd for $C_{17}H_{25}NO_{10}$: C, 50.62; H, 6.25. Found: C, 50.45; H, 6.30.

4-Methoxycarbonyl-3-oxa-butyl β-D-glucopyranoside (**18**).—To a solution of **13** (232 mg, 0.5 mmol) in dry MeOH (10 mL) was added a catalytic amount of NaOMe. After standing overnight (TLC, 85:15 CH_2Cl_2–MeOH) the solution was neutralized with Amberlite IR 120 (H^+) resin, filtered, and concentrated, to yield syrupy **18** (139 mg, 94%); $[\alpha]_D$ −25.6° (*c* 0.52, $CHCl_3$); for ^{13}C NMR data, see Table 1. Anal. Calcd for $C_{11}H_{20}O_9$: C, 44.59; H, 6.80. Found: C, 44.75; H, 6.88.

8-Methoxycarbonyloctyl β-D-glucopyranoside (**19**).—Zemplén *O*-deacylation of **14** (259 mg, 0.5

mmol) as described for the preparation of **18** gave crystalline **19** (169 mg, 96%); mp 71–73 °C (from EtOAc–hexane); $[\alpha]_D$ −24.1° (*c* 1.14, MeOH); for ^{13}C NMR data, see Table 1; Anal. Calcd for $C_{16}H_{30}O_8$: C, 54.84; H, 8.63. Found: C, 54.77; H, 8.59.

9-Decen-1-yl β-D-glucopyranoside (**20**).—Zemplén *O*-deacylation of compound **11** (122 mg, 0.25 mmol), followed by column chromatography (85:15 CH_2Cl_2–MeOH) of the crude product yielded **20**, isolated as a syrup (72 mg, 90%); $[\alpha]_D$ −19.9° (*c* 0.98, MeOH); for ^{13}C NMR data, see Table 1. Before recording the spectrum the sample was co-concentrated with CD_3OD.

9,10-Epoxydecyl β-D-glucopyranoside (**21**).—To a solution of **15** (503 mg, 1 mmol) in dry MeOH (40 mL) was added MgO (500 mg) [34]. The mixture was stirred for 80 h at room temperature, then filtered, and the filtrate was concentrated to give crystalline **21** (302 mg, 90%); mp 80–84 °C (from EtOAc–hexane); $[\alpha]_D$ −24° (*c* 0.9, MeOH); for ^{13}C NMR data, see Table 1. Anal. Calcd for $C_{16}H_{30}O_7$: C, 57.46; H, 9.04. Found: C, 56.67; H, 9.18.

2,3-Epoxypropyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**22**).—Compound **17** (202 mg, 0.5 mmol) was deacylated with MgO as described for the preparation of **21**. The crude product was subjected to column chromatography (7:3 CH_2Cl_2–MeOH) to yield crystalline **22** (72 mg, 52%); mp 152–155 °C (from EtOAc–MeOH); $[\alpha]_D$ −32° (*c* 0.70, MeOH); lit. mp 175–178 °C (acetone–H_2O); $[\alpha]_D$ −37.4° (H_2O) [37].

3,6-Dioxa-7-ethoxycarbonylheptyl 2,4,6-tri-O-acetyl-3-O-methyl-β-D-glucopyranoside (**24**).—A mixture of 3,6-dioxa-7-ethoxycarbonylheptan-1-ol [8,9] (**23**; 1.92 g, 10 mmol) and $Hg(CN)_2$ (2.53 g, 10 mmol) in 1:1 dry toluene–nitromethane (60 mL) was concentrated to half its volume at atmospheric pressure. After cooling, 2,4,6-tri-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyl bromide (**7**) (1.92 g, 5 mmol) [35] was added, and the mixture was stirred overnight at room temperature, then diluted with CH_2Cl_2 (150 mL), filtered, and the filtrate was washed with aq 5% KI (2 × 20 mL) and water (3 × 20 mL), dried ($MgSO_4$), and concentrated. Column chromatography (9:1 CH_2Cl_2–acetone) of the residue gave **24**, isolated as a syrup (1.89 g, 76.4%); $[\alpha]_D$ −15.3° (*c* 1.35; $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.15–4.97 (m, 2 H, H-2,4), 4.56 (d, 1 H, H-1), 4.35–4.13 (m, 6 H, CH_2–COOEt, O–CH_2–CH_3, and H-6a,6b), 4.03–3.90 (m, 1 H, H-5), 3.85–3.47 (m, 9 H, 4 –CH_2– and H-3), 3.43 (s, 3 H, OMe), 2.13, 2.11, and 2.10 (3 s, each 3 H, 3 Ac), 1.31 (t, 3 H, O–CH_2–CH_3). Anal. Calcd for $C_{21}H_{34}O_{13}$: C, 51.01; H, 6.93. Found: C, 51.23; H, 6.96.

3,6-Dioxa-7-methoxycarbonylheptyl 3-O-methyl-β-D-glucopyranoside (**25**).—To a solution of **24** (1.30 g) in dry MeOH (50 mL) was added NaOMe (50 mg) [16], and the mixture was stored for 3 days at room temperature, then neutralized with HOAc, and concentrated. The residue was purified by column chromatography (85:15 CH_2Cl_2–MeOH) to give **25**, isolated as a syrup (656 mg, 70.4%); $[\alpha]_D$ −14.9° (*c* 1.03, MeOH); for ^{13}C NMR data, see Table 2. Anal. Calcd for $C_{14}H_{26}O_{10}$: C, 47.45; H, 7.40. Found: C, 47.30; H, 7.38.

7-Carboxyl-3,6-dioxa-heptyl 3-O-methyl-β-D-glucopyranoside (**26**).—Compound **25** (177 mg, 0.5 mmol) was dissolved in 0.05 M NaOH (5 mL), and the solution was kept for 2 h at 60 °C. After cooling, the solution was neutralized with Amberlite IR 120 (H^+) resin, concentrated, and the residue (121 mg, 71%) was purified by column chromatography (1:1 CH_2Cl_2–MeOH) to yield **26**, isolated as a syrup (60 mg, 35%); $[\alpha]_D$ −13° (*c* 0.44, MeOH); for ^{13}C NMR data, see Table 2.

p-Isothiocyanatophenyl 3-O-methyl-β-D-glucopyranoside (**28**).—*p*-Nitrophenyl 3-*O*-methyl-β-D-glucopyranoside [17] (**27**; 63 mg, 0.2 mmol) was hydrogenated over Pd–C (20 mg) in aq 80% EtOH (10 mL) for 2 h, then the catalyst was filtered off. The pH of the filtrate was adjusted to 8 with $BaCO_3$ and maintained by adding $BaCO_3$ whilst thiophosgene (0.2 mL) was added, and the mixture was stirred for 1 h at room temperature. Filtration and concentration yielded a slightly coloured syrup which was purified by column chromatography (9:1 CH_2Cl_2–MeOH) to give **28** (49 mg, 75%); mp 153–156 °C; $[\alpha]_D$ −63.6° (*c* 0.50, MeOH); for ^{13}C NMR data, see Table 2. Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.36; H, 5.24. Found: C, 51.50; H, 5.29.

5,6-Isopropylidene-dioxyhexanol (**29**).—A mixture of 1,2,6-hexanetriol (**4**; 1.34 g, 10 mmol), 2,2-dimethoxypropane (8 mL, 65 mmol) and *p*-toluenesulfonic acid (50 mg) was stirred at room temperature for 3 h. The reaction was terminated with aq 5% $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (100 mL), and the organic phase was washed with water (3 × 15 mL), dried, and concentrated. After this workup procedure, TLC (9:1 CH_2Cl_2–MeOH) of the product showed two spots, but only one had the same chromatographic mobility as the reference compound (5*S*)-5,6-isopropylidene-dioxyhexanol, prepared according to [36]. The product

was dissolved in CH_2Cl_2 (30 mL), aq 60% HOAc was added, and the mixture was stirred at room temperature until the mixed acetal (**29a**) had been converted into **29**. The solution was then neutralized as described above, dried, and concentrated to give **29**, isolated as a syrup (1.35 g, 77.5%); ^{1}H NMR ($CDCl_3$): δ 4.18–3.98 (m, 2 H, H-1a,1b), 3.68–3.44 (m, 3 H, H-5,6a,6b), 2.75 (bs, 1 H, OH, deuterable), 1.77–1.43 (m, 6 H, 3 $-CH_2-$), 1.42 and 1.36 (2 s, each 3 H, CMe_2).

1,2-Diacetoxy-6-benzyloxy-hexane (**30**).—A mixture of **29** (3.48 g, 20 mmol), dry DMF (15 mL), powdered KOH (2.8 g), and benzyl bromide (2.85 mL, 24 mmol) was stirred vigorously at room temperature for 3 h, then diluted with CH_2Cl_2 (150 mL). Inorganics were filtered off, and the filtrate was washed with water (3 × 40 mL), dried, and concentrated. The residue (5.1 g) was suspended in aq 60% HOAc (30 mL) and kept for 30 min at 60 °C (TLC, 8:2 CH_2Cl_2–acetone). After concentration and co-concentration with toluene (3 × 20 mL), the crude product was conventionally acetylated in 1:1 pyridine–Ac_2O (60 mL) at room temperature. After standing overnight, the mixture was concentrated and co-concentrated with toluene (3 × 20 mL), and the crude product was purified by column chromatography (97:3 CH_2Cl_2–EtOAc) to yield syrupy **30** (2.53 g, 41%); ^{1}H NMR ($CDCl_3$): δ 7.38–7.22 (m, 5 H, Ph), 5.05 (m, 1 H, –CH–OAc), 4.48 (s, 2 H, PhCH_2), 4.27–3.96 (m, 2 H, $-CH_2-$OAc), 3.47 (t, 2 H, O–CH_2-), 2.04 (s, 6 H, 2 Ac), 1.70–1.32 (m, 6 H, 3 $-CH_2-$).

1,2-Diacetoxyhexan-6-ol (**31**).—A mixture of **30** (617 mg, 2 mmol), EtOH (10 mL), HOAc (1 mL), and Pd–C (50 mg) was stirred in an H_2 atmosphere overnight. The mixture was filtered through Celite, the filtrate was concentrated and co-concentrated with toluene (3 × 10 mL), and the residue was purified by column chromatography (97:3 CH_2Cl_2–EtOAc) to give syrupy **31** (360 mg, 82%); ^{1}H NMR ($CDCl_3$): δ 5.08 (m, 1 H, –CH–OAc), 4.28–3.97 (m, 2 H, $-CH_2-$OAc), 3.64 (t, 2 H, $-CH_2-$O–), 2.08 (s, 6 H, 2 Ac), 1.70–1.30 (m, 7 H, 3 $-CH_2-$ and OH, deuterable).

*5,6-Diacetoxyhexyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-β-*D*-glucopyranoside* (**32**).—Compound **7** (383 mg, 1 mmol) was reacted with **31** (327 mg, 1.5 mmol) as described for the preparation of **8**. Column chromatography of the crude product gave **32**, isolated as a syrup (162 mg, 31%); $[\alpha]_D$ −11° (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.15–4.91 (m, 3 H, H-2,4 and –CH–OAc), 4.38 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 3.39 (s, 3 H, OMe), 2.14–2.04 (m, 15 H, 5 Ac), 1.70–1.22 (m, 6 H, 3 $-CH_2-$). Anal. Calcd for $C_{23}H_{36}O_{13}$: C, 53.07; H, 6.97. Found: C, 52.80; H, 6.93.

*5,6-Dihydroxyhexyl 3-*O*-methyl-β-*D*-glucopyranoside* (**33**).—To a solution of **32** (104 mg, 0.2 mmol) in dry MeOH (10 mL) was added NaOMe (27 mg, 0.5 mmol). The mixture was kept at room temperature for 2 days, then neutralized with Amberlite IR 120 (H^+) resin, filtered, and concentrated. Column chromatography of the crude product gave **33** (49 mg, 79%); $[\alpha]_D$ −10.5° (*c* 1.6, MeOH); for ^{13}C NMR data, see Table 2. Anal. Calcd for $C_{13}H_{26}O_8$: C, 50.31; H, 8.45. Found: C, 50.52; H, 8.41.

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