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Carbohydrate Research 268 (1995) 47–56

CARBOHYDRATE RESEARCH

The reaction between epichlorohydrin and polysaccharides ☆: Part 2, synthesis of some model substances, with cyclic substituents

Lars Holmberg [a], Bengt Lindberg [b,*], Bengt Lindqvist [c]

[a] *Pharmacia LKB Biotechnology AB, S-75182 Uppsala, Sweden*
[b] *Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-10691 Stockholm, Sweden*
[c] *Kabi Pharmacia AB, Ophthalmics, S-75182 Uppsala, Sweden*

Received 9 May 1994; accepted 8 September 1994

Abstract

Eight derivatives of methyl α-D-glucopyranoside, in which the substituents are part of cyclic structures, have been prepared as model substances for possible structural elements formed on reaction of polysaccharides with epichlorohydrin. The substances were converted into the permethylated alditol-*1-d* acetates and characterised by CIMS and EIMS.

Keywords: Cross-linked polysaccharides; Epichorohydrin

1. Introduction

Polysaccharides form insoluble gels on reaction with epichlorohydrin. As part of our studies of this reaction, we have synthesised derivatives of methyl α-D-glucopyranoside, representative of different possible types of substitution, to be used as model substances in the structural studies. The syntheses of some model substances with non-cyclic substituents have been reported [1], and we now describe the syntheses of eight derivatives of methyl α-D-glucopyranoside, in which the substituents form part of cyclic structures. Since we are mainly interested in cross-linked dextran (Sephadex®), the model substances are not substituted in the 6-position.

* Corresponding author.

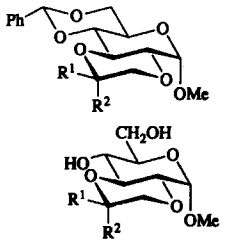
☆ Taken from the Ph.D. thesis of L.H., Swedish University of Agricultural Sciences, Uppsala, Sweden, 1983. For Part 1, see [1].

SSDI 0008-6215(94)00293-2

2. Results and discussion

Two different types of cyclic structures may be formed on reaction of epichlorohydrin with a polysaccharide. A 2,3-epoxypropyl group linked to a sugar residue may react with a hydroxyl group in the same residue, giving a bicyclic structure in which a 1,4-dioxane ring is fused to the sugar residue, as in model substance **3**. A 3-(2,3-epoxypropyl)-2-hydroxypropyl ether may be formed on reaction of epichlorohydrin with an initially formed 2,3-dihydroxypropyl ether, and then undergo internal cyclisation to a 6-hydroxymethyl-1,4-dioxan-2-ylmethyl ether, as in model substance **13**. Formation of seven-membered rings is considered less likely. Model substances containing these types of structural elements have now been prepared.

Methyl 2-*O*-allyl-4,6-*O*-benzylidene-α-D-glucopyranoside [2] was converted into the epoxide by treatment with hydrogen peroxide and benzonitrile in methanol [3]. Treatment of the resulting methyl 4,6-*O*-benzylidene-2-*O*-(2,3-epoxypropyl)-α-D-glucopyranoside with sodium hydroxide yielded a mixture of methyl 4,6-*O*-benzylidene-2,3-*O*-[(2*R*)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**1**) and the corresponding (2*S*)-isomer (**2**), which were separated by chromatography on silica gel. In the ^{13}C NMR spectrum the signals for Ć-2 and Ć-3 appeared at δ 75.6 and 61.9 (**1**) and at δ 73.2 and 59.4 (**2**), respectively, indicating that the hydroxymethyl group is equatorial in **1** and axial in **2**. Removal of the benzylidene groups in **1** and **2** by hydrolysis with acid yielded methyl 2,3-*O*-[(2*R*)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**3**) and the corresponding (2*S*)-isomer (**4**), respectively. The ^{13}C NMR spectra, and in particular the signals for Ć-2 and Ć-3, confirmed the structures and the assigned absolute configurations at Ć-2 (Table 1). In the preparation of other model substances containing this ring system, the (*R*)-forms (**1** and **3**) were used as starting materials, and the diastereomeric products formed were not separated.

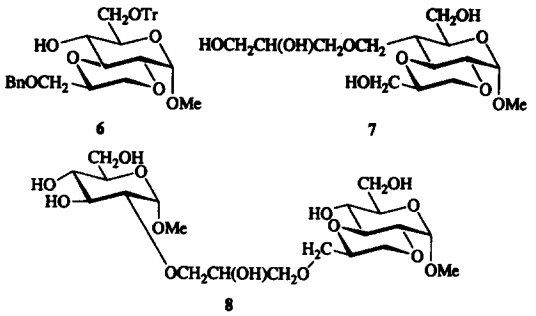


1 R^1 = $HOCH_2$-, R^2 = H
2 R^1 = H, R^2 = $HOCH_2$-
3 R^1 = $HOCH_2$-, R^2 = H
4 R^1 = H, R^2 = $HOCH_2$-
5 R^1 = $HOCH_2CH(OH)CH_2OCH_2$-, R^2 = H

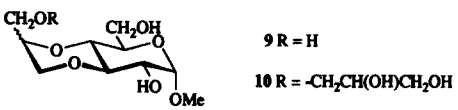
Alkylation of **1** with 2,3-epoxypropyl triflate gave the 3′-(2,3-epoxypropyl) ether, which on treatment with acid yielded methyl 2,3-*O*-[(2*R*)-6,7-dihydroxy-4-oxaheptane-1,2-diyl]-α-D-glucopyranoside (**5**).

Benzylation of **1**, removal of the benzylidene group, and tritylation yielded **6**, which on reaction with 2,3-epoxypropyl triflate, opening of the epoxide ring, and deblocking yielded methyl 4-*O*-(2,3-dihydroxypropyl)-2,3-*O*-[(2*R*)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**7**).

Alkylation of **1** with the triflate prepared from methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-benzyloxy-3-hydroxypropyl)-α-D-glucopyranoside [1], followed by catalytic hydrogenolysis, yielded the model substance **8**, representing a possible cross-linkage.



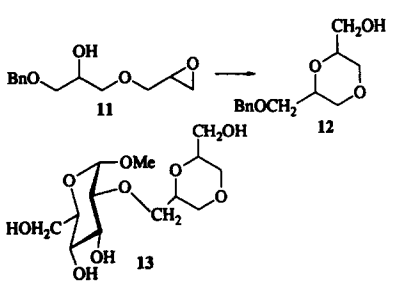
The bicyclic model substance methyl 3,4-*O*-(3-hydroxypropane-1,2-diyl)-α-D-glucopyranoside (**9**) was prepared from methyl 3-*O*-allyl-2-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside via epoxidation, ring closure to methyl 2-*O*-benzyl-3,4-*O*-(3-hydroxypropane-1,2-diyl)-6-*O*-trityl-α-D-glucopyranoside, and deblocking. The 3′-(2,3-dihydroxypropyl) ether (**10**) of this substance was prepared from the same intermediate by reaction with 2,3-epoxypropyl triflate, opening of the epoxide ring, and deblocking.



9 R = H

10 R = -$CH_2CH(OH)CH_2OH$

2-Benzyloxymethyl-6-hydroxymethyl-1,4-dioxane (**12**), as a mixture of diastereomers, was prepared from 1-*O*-allylglycerol by benzylation at the primary position, epoxidation of the double bond to give 1-*O*-benzyl-3-*O*-(2,3-epoxypropyl)glycerol (**11**), and treatment with base. The triflate of **12** on reaction with methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside, followed by catalytic hydrogenolysis, yielded methyl 2-*O*-(6-hydroxymethyl-1,4-dioxan-2-ylmethyl)-α-D-glucopyranoside (**13**), representative of the second type of possible cyclic substituents discussed above.



The ^{13}C NMR spectra of the model substances **3**, **4**, **5**, **7**, and **8**, with tentative assignments of the signals, are given in Table 1. For the other model substances, **9**, **10**, and **13**, which are mixtures of diastereoisomers with equatorial or axial substituents in a six-membered ring, significant differences in chemical shifts for the isomers are expected, and assignments of the signals were not attempted. The signals observed for these and the other substances, as given in the Experimental section, are, however, consistent with the proposed structures. Thus **9**, which is a mixture of two diastereomers, gives signals

Table 1
^{13}C NMR shifts for some model substances [a,b]

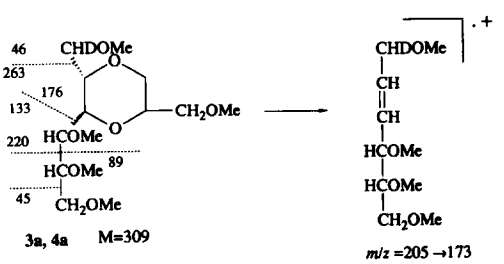
Substance	Chemical shift (δ)												
	C-1	C-2	C-3	C-4	C-5	C-6	Ć-1	Ć-2	Ć-3	Ć-5	Ć-6	Ć-7	OCH_3
3	97.2	75.0	76.6	67.0	72.3	60.2	67.6	75.9	60.7				54.9
4	97.3	76.1	73.0	67.3	72.7	60.5	66.0	69.7	58.4				55.0
5	97.3	75.0	76.7	67.0	72.2	60.3	67.6	74.6	70.0	72.0	70.3	62.5	54.9
7	97.2	75.0	75.4	76.9	70.7	0.2	67.7 [c]	75.9 [c]	60.8 [c]	72.9 [d]	71.2 [d]	62.5 [d]	55.0
			75.5	77.0	70.8					73.1	71.3		
8 [e]	97.4	75.2	76.9	67.2	71.8	60.8	67.8	74.8	70.2	72.6	69.4	67.7	55.0
8 [f]	97.2	80.1	72.3	69.7	71.6	60.5							55.1

[a] The substances, except **3** and **4**, are mixtures of diastereoisomers, and some signals given by the different forms are resolved.
[b] The assignments of some signals with similar chemical shifts may be reversed.
[c] Substituent on O-2 and O-3.
[d] C″-1, C″-2, and C″-3, respectively, of the substituent on O-4.
[e] Sugar residue with a fused 1,4-dioxane ring. Numbering of the carbon atoms in the substituent starts from that linked to O-2 of this residue.
[f] Monocyclic sugar residue.

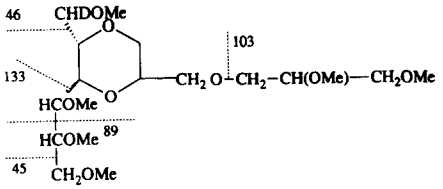
at δ 60.8 and 58.5, assigned, respectively, to the equatorial and axial hydroxymethyl group linked to the dioxane ring.

Mass spectrometry of the permethylated alditol-1-d *derivatives obtained from the model substances.*—The model substances were subjected to hydrolysis with acid, reduction with sodium borodeuteride, and permethylation. The products were characterised by chemical ionisation GLC–MS, using ammonia as the ionisation gas, which gave $[M + H]^+$ and $[M + NH_4]^+$, and by electron impact GLC–MS, which should give fragmentation patterns in agreement with established principles [4].

The permethylated alditol-*1-d* derivatives **3a** and **4a**, prepared from **3** and **4**, respectively, each gave a single peak on GLC, and had a molecular mass of 309. In addition to the ions formed on fission of the alditol chain, elimination of the 2,3-substituent from the molecular ion gave an ion of m/z 205, as indicated below. The primary, unsaturated fragment formed from this type of substance is often weak, but the secondary fragment formed from it by elimination of methanol is considerably stronger.

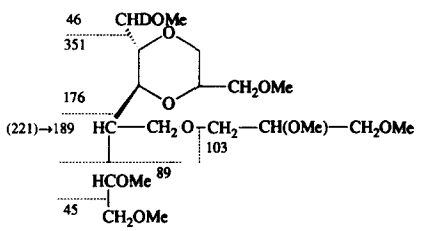


The product prepared from **5** gave a single peak on GLC, and had a molecular mass of 397. Only small primary fragments were observed on EIMS, but these were all in agreement with the postulated structure, **5a**.



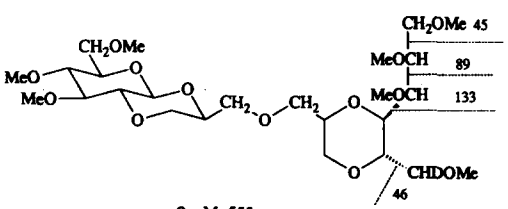
5a M=397

The product prepared from **7** gave two peaks on GLC, both with a molecular mass of 397. The primary fragments indicated in **7a** are in agreement with the postulated structure. Elimination of the 2,3-substituent and then of methanol gave the secondary fragment m/z 261.



7a M=397

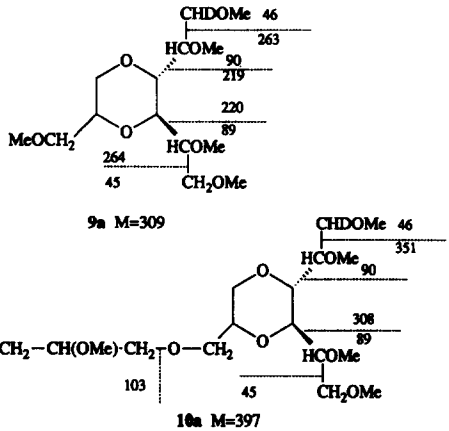
The product prepared from **8** gave some minor peaks on GLC in addition to a major peak with a molecular mass of 555, indicating that it was an internal glycoside, exemplified by the β-pyranoside **8a**. On EIMS it gave, *inter alia*, the fragments from the alditol part indicated in the formula, m/z 88 $[MeO–CH=CH–OMe]^+$, which is a typical fragment from the glycoside moiety, and m/z 173, formed by consecutive eliminations of the 2,3-substituent and methanol from the alditol moiety.



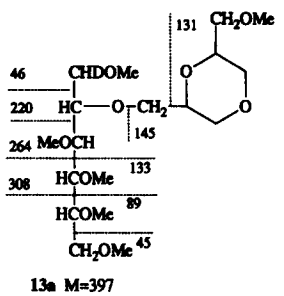
8a M=555

The product prepared from **9** gave two peaks on GLC, both having the molecular mass 309, and giving almost identical EI mass spectra. In addition to the fragments indicated in **9a**, they gave m/z 205 by elimination of the 3,4-substituent.

The product prepared from **10** gave three peaks on GLC, all having a molecular mass of 397, and giving similar EI mass spectra. In addition to the primary fragments indicated in **10a**, they gave m/z 173 by consecutive eliminations of the 3,4-substituent and methanol.



The product prepared from **13** gave four peaks on GLC, all having a molecular mass of 397, and giving similar EI mass spectra. The formation of some primary fragments is indicated in **13a**.



3. Experimental

General methods and general procedure for the preparation of triflates.—Reactions were followed by TLC on silica gel; lipophilic substances were purified by chromatography on silica gel, using toluene–EtOAc mixtures as irrigants, and hydrophilic by chromatography on Sephadex® G15. Solutions were concentrated to dryness under reduced pressure. Also, in other respects, general methods and procedures were the same as in [1]. Signals in the ^{13}C NMR spectra were assigned by off-resonance or INEPT spectra. In the spectra given below, signals given by aromatic carbons, and also some minor signals which may derive from impurities, are omitted.

Methyl 4,6-O-benzylidene-2-O-(2,3-epoxypropyl)-α-D-glucopyranoside.—Hydrogen peroxide (30%, 4 mL) was added dropwise to a stirred mixture of methyl 2-*O*-allyl-4,6-*O*-benzylidene-α-D-glucopyranoside [3] (5 g, 15 mmol), K_2CO_3 (400 mg), and benzonitrile (3.4 mL, 50 mmol) in MeOH (50 mL), the temperature being kept at 25°C by external cooling. After addition, stirring was continued for 1 h, and then Pd–C (10%, 250 mg) was added in order to destroy the excess of H_2O_2. The solution was filtered, neu-

tralised with AcOH, and diluted with CH_2Cl_2 (200 mL). This solution was washed with water (3 × 25 mL), dried over $MgSO_4$, concentrated, and purified by chromatography, to give the title compound (4.4 g, 84%). ^{13}C NMR: δ 44.3, 50.9, 51.3, 55.3, 62.0, 69.0, 70.1, 70.3, 71.3, 72.5, 80.9, 81.3, 82.0, 98.4, 98.8, 101.9.

Methyl 4,6-O-benzylidene-2,3-O-[(2R)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**1**) *and the corresponding (2S)-derivative* (**2**).—A solution of the epoxide above (1.0 g, 2.7 mmol) in a mixture of THF (10 mL) and 2 M NaOH (1 mL) was refluxed for 30 min, concentrated, and purified by chromatography to give **1** (460 mg, 46%) and **2** (350 mg, 35%) as syrups. ^{13}C NMR, **1**: δ 55.1, 61.5, 62.7, 68.3, 68.6, 73.4, 75.2, 76.2, 78.6, 98.0, 101.6; **2**: δ 55.4, 59.4, 63.4, 66.9, 67.2, 68.9, 73.2, 77.5, 79.5, 98.5, 102.0.

Methyl 2,3-O-[(2R)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**3**).—A solution of compound **1** (142 mg, 0.42 mmol) in a mixture of acetone (5 mL) and 0.25 M HCl (1 mL) was refluxed until no starting material was left (TLC), concentrated, dissolved in water (3 × 5 mL), and concentrated again. Chromatography yielded pure **3** (96 mg, 91%).

Methyl 2,3-O-[(2S)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**4**).—This substance was prepared from **2** analogously as **3** from **1**, and in comparable yield.

Methyl 4,6-O-benzylidene-2,3-O-[(2R)-6,7-epoxy-4-oxaheptane-1,2-diyl]-α-D-glucopyranoside.—Sodium hydride (200 mg, 8.3 mmol) was added in portions to a stirred solution of **1** (200 mg, 0.59 mmol) in THF (5 mL), and stirring continued for 30 min at room temperature. The mixture was then cooled to −10°C, and a solution of 2,3-epoxypropyl triflate (206 mg, 1.21 mmol) in CH_2Cl_2 (3 mL) added dropwise. The mixture was allowed to reach room temperature and, after 30 min, the excess of sodium hydride was destroyed with MeOH (3 mL). The mixture was concentrated, dissolved in CH_2Cl_2 (15 mL), washed with water (3 × 5 mL), concentrated, and purified by chromatography to give the title compound (77 mg, 31%). ^{13}C NMR: δ 44.0, 50.5, 55.3, 63.1, 68.9, 69.4, 70.8, 72.1, 73.8, 74.0, 76.7, 79.0, 98.5, 101.7.

Methyl 2,3-O-[(2R)-6,7-dihydroxy-4-oxaheptane-1,2-diyl]-α-D-glucopyranoside (**5**).—A solution of the epoxide above (77 mg, 0.20 mmol) in a mixture of acetone (5 mL), water (5 mL), and 0.5 M CF_3CO_2H (0.5 mL) was refluxed until no starting material was left (TLC), concentrated, dissolved in water (5 mL), washed with CH_2Cl_2 (3 × 3 mL), concentrated, and chromatographed to give pure **5** (52 mg, 82%).

Methyl 4,6-O-benzylidene-2,3-O-[(2R)-3-benzyloxypropane-1,2-diyl] -α-D-glucopyranoside.—Sodium hydride (550 mg, 23 mmol) was added in portions to a stirred solution of **1** (1.7 g, 5.0 mmol) in DMF (50 mL). After 30 min at room temperature, benzyl bromide (3.1 g, 18 mmol) was added and, after 2 h, the excess of NaH was destroyed with MeOH (5 mL). The mixture was concentrated, dissolved in CH_2Cl_2 (250 mL), washed with water (3 × 50 mL), dried over $MgSO_4$, filtered, concentrated, and purified by chromatography, to yield the title compound (1.9 g, 89%). ^{13}C NMR: δ 55.1, 63.0, 68.7, 69.3, 69.5, 73.1, 73.7, 73.9, 76.6, 78.9, 98.4, 101.5.

Methyl 2,3-O-[(2R)-3-benzyloxypropane-1,2-diyl]-α-D-glucopyranoside.—A solution of the benzylidene compound above (1.8 g, 4.2 mmol) in acetone (50 mL) and 0.1 M HCl (10 mL) was refluxed for 4 h, then concentrated, and the benzaldehyde removed by distillations with water (3 × 10 mL). A solution of the product in toluene was con-

centrated and purified by chromatography to give the title compound (1.4 g, 98%). ^{13}C NMR: δ 54.8, 61.1, 67.6, 68.5, 69.3, 72.2, 73.1, 73.9, 75.6, 76.8, 97.6.

Methyl 2,3-O-[(2R)-3-benzyloxypropane-1,2-diyl]-6-O-trityl-α-D-glucopyranoside (**6**).—A solution of the compound above (1.4 g, 4.1 mmol) and chlorotriphenylmethane (1.7 g, 6.1 mmol) in pyridine (25 mL) was stirred at room temperature overnight, poured into ice–water (200 mL), and stirred for 1 h. The insoluble material was collected, washed with water (100 mL), and dissolved in toluene (100 mL). The solution was concentrated and purified by chromatography, to yield **6** (1.4 g, 60%). ^{13}C NMR: δ 54.8, 63.5, 68.9, 69.4, 71.1, 73.1, 74.0, 75.7, 77.2, 86.6, 97.6.

Methyl 2,3-O-[(2R)-3-benzyloxypropane-1,2-diyl]-4-O-(2,3-epoxypropyl)-6-O-trityl-α-D-glucopyranoside.—Sodium hydride (300 mg, 12.5 mmol) was added in portions to a stirred solution of **6** (400 mg, 0.71 mmol) in THF (10 mL). The solution was kept at room temperature and stirred for 30 min, then cooled to −10°C, and freshly prepared 2,3-epoxypropyl triflate (515 mg, 3.0 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was allowed to reach room temperature, and after 30 min the excess of NaH was destroyed with MeOH (3 mL). The solution was concentrated, dissolved in CH_2Cl_2 (25 mL), washed with water (3 × 20 mL), dried over $MgSO_4$, and purified by chromatography to give the title compound (320 mg, 72%). ^{13}C NMR: δ 44.1, 44.2, 50.2, 54.8, 62.2, 69.0, 69.5, 70.4, 72.7, 72.8, 73.1, 74.0, 75.9, 76.1, 76.2, 77.7, 86.1, 97.5.

Methyl 2,3-O-[(2R)-3-benzyloxypropane-1,2-diyl]-4-O-(2,3-dihydroxypropyl)-α-D-glucopyranoside.—A solution of the epoxide above (320 mg, 0.52 mmol) in a mixture of acetone (10 mL), water (5 mL), and 0.5 M H_2SO_4 (1 mL) was refluxed until no starting material remained, neutralised with M NaOH, concentrated, and purified by chromatography, to give the title compound (173 mg, 84%). ^{13}C NMR: δ 55.0, 61.1, 63.1, 68.7, 69.2, 71.2, 73.2, 74.0, 75.7, 76.9, 97.4.

Methyl 4-O-(2,3-dihydroxypropyl)-2,3-O-[(2R)-3-hydroxypropane-1,2-diyl]-α-D-glucopyranoside (**7**).—A solution of the benzyl ether above (173 mg, 0.42 mmol) in EtOH (7 mL) and AcOH (0.2 mL) was hydrogenolysed over Pd–C (10%, 100 mg), filtered, concentrated, and purified by chromatography on silica gel, to give **7** (56 mg, 41%).

Methyl 4,6-O-benzylidene-2,3-O-[(2R)-6-benzyloxy-7-(methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosid-2-O-yl)-4-oxaheptane-1,2-diyl]-α-D-glucopyranoside.—Sodium hydride (200 mg, 8.3 mmol) was added in portions to a stirred solution of **1** (159 mg, 0.47 mmol) in THF (10 mL). The mixture was stirred for 30 min at room temperature, cooled to −10°C, and the triflate of methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-benzyloxy-3-hydroxypropyl)-α-D-glucopyranoside [1] (380 mg, 0.68 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was allowed to reach room temperature and, after 1 h, the excess of NaH was destroyed by addition of MeOH (3 mL). The solution was concentrated, dissolved in CH_2Cl_2 (50 mL), washed with water (3 × 10 mL), concentrated, and purified by chromatography, to give the title compound (314 mg, 70%). ^{13}C NMR: δ 55.1, 55.5, 63.1, 68.6, 69.0, 69.7, 70.2, 70.6, 71.0, 71.7, 72.2, 73.5, 74.1, 75.0, 75.5, 76.4, 76.7, 77.0, 77.2, 77.7, 77.8, 79.1, 81.4, 81.9, 97.8, 98.6, 101.8.

Methyl 2,3-O-[(2R)-6-hydroxy-7-(methyl α-D-glucopyranosid-2-O-yl)-4-oxaheptane-1,2-diyl]-α-D-glucopyranoside (**8**).—A solution of the substance above (250 mg, 0.27 mmol) in EtOH (5 mL) and AcOH (0.2 mL) was hydrogenolysed over Pd–C (10%, 200 mg), filtered, and purified by chromatography on Sephadex® G15 to give **8** (90 mg, 68%).

Methyl 3-O-allyl-2-O-benzyl-6-O-trityl-α-D-glucopyranoside.—A solution of methyl 3-*O*-allyl-2-*O*-benzyl-α-D-glucoyranoside [2] (4 g, 12 mmol) and chlorotriphenylmethane (3.8 g, 14 mmol) in pyridine (50 mL) was kept at room temperature overnight, then poured into ice–water (500 mL), and stirred for 1 h. The insoluble material was collected, washed with water (300 mL), and dissolved in toluene (40 mL). The solution was concentrated and purified by chromatography, to give the title compound (3.7 g, 53%). ^{13}C NMR: δ 55.2, 64.2, 70.2, 71.8, 73.3, 74.5, 79.8, 81.4, 87.1, 98.2, 117.1, 135.5.

Methyl 2-O-benzyl-3,4-O-(3-hydroxypropane-1,2-diyl)-6-O-trityl-α- D-glucopyranoside.—Hydrogen peroxide (30%, 1.5 mL) was added dropwise to a stirred mixture of the compound above (3.5 g, 6.2 mmol), MeOH (50 mL), benzonitrile (1.2 mL, 18 mmol), and K_2CO_3 (300 mg). After 2 h the solution was concentrated and the residue dissolved in THF (50 mL). 5 M NaOH (20 mL) was added and the mixture refluxed overnight, neutralised with AcOH, concentrated, dissolved in CH_2Cl_2 (200 mL), washed with water (3 × 50 mL), dried over $MgSO_4$, concentrated, and purified by chromatography, to give the title compound (0.5 g, 14%). ^{13}C NMR: δ 55.2, 59.5, 62.3, 66.2, 68.2, 69.2, 72.4, 73.3, 77.0, 78.5, 86.6, 98.9.

Methyl 3,4-O-(3-hydroxypropane-1,2-diyl)-α-D-glucopyranoside (**9**).—A solution of the compound above (100 mg, 0.18 mmol) in EtOH (5 mL) and AcOH (0.2 mL) was hydrogenolysed at room temperature over Pd–C (10%, 100 mg), filtered, concentrated, and purified by chromatography on Sephadex® G15 to give **9** (24 mg, 51%). ^{13}C NMR: δ 55.2, 58.5, 59.7, 60.8, 66.1, 67.2, 67.7, 68.7, 69.0, 69.6, 69.9, 72.9, 73.7, 76.2, 76.9, 77.8, 99.6.

Methyl 2-O-benzyl-3,4-O-(6,7-epoxy-4-oxaheptane-1,2-diyl)-6-O-trityl-α-D-glucopyranoside.—Sodium hydride (150 mg, 6.3 mmol) was added in portions to a stirred solution of methyl 2-*O*-benzyl-3,4-*O*-(3-hydroxypropane-1,2-diyl)-6-*O*-trityl-α-D-glucopyranoside (400 mg, 0.67 mmol) in THF (10 mL), the mixture was stirred at room temperature for 30 min, then cooled to −10°C, and a solution of 2,3-epoxypropyl triflate (412 mg, 2.7 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The mixture was allowed to reach room temperature, and after 30 min the excess of NaH was destroyed with MeOH (3 mL). The mixture was concentrated, dissolved in CH_2Cl_2 (50 mL), washed with water (3 × 10 mL), dried over $MgSO_4$, and purified by chromatography, to give the title compound (168 mg, 38%). ^{13}C NMR: δ 44.2, 50.5, 55.3, 62.8, 66.9, 68.8, 68.9, 69.2, 69.5, 71.3, 72.0, 72.4, 73.3, 75.0, 75.3, 77.0, 77.9, 78.7, 81.7, 86.6, 98.9.

Methyl 2-O-benzyl-3,4-O-(6,7-dihydroxy-4-oxaheptane-1,2-diyl)-α-D-glucopyranoside.—A solution of the substance above (160 mg, 0.25 mmol) in a mixture of acetone (10 mL), water (5 mL), and 0.5 M H_2SO_4 (1 mL) was refluxed and the reaction followed by TLC. When all starting material had reacted, the solution was neutralised with M NaOH, concentrated, and purified by chromatography, to give the title compound (78 mg, 76%). ^{13}C NMR: δ 55.3, 60.4, 60.9, 63.6, 66.5, 67.1, 68.2, 69.5, 69.5, 70.6, 70.9, 73.1, 73.6, 74.4, 74.8, 76.4, 77.1, 77.3, 78.0, 98.9.

Methyl 3,4-O-(6,7-dihydroxy-4-oxaheptane-1,2-diyl)-α-D-glucopyranoside (**10**).—A solution of the compound above (78 mg, 0.19 mmol) in a mixture of EtOH (5 mL) and AcOH (0.2 mL) was hydrogenolysed over Pd–C (10%, 100 mg) and worked up as described for **9**, to give **10** (48 mg, 79%). ^{13}C NMR: δ 55.2, 59.7, 59.8, 62.6, 62.7, 66.3, 67.4, 67.7, 68.8, 68.9, 69.5, 69.9, 70.0, 70.3, 70.4, 70.8, 71.9, 72.2, 73.7, 74.8, 76.8, 77.8, 99.6.

1-O-Allyl-3-O-benzylglycerol.—A mixture of aq NaOH (M, 65 mL), 1-*O*-allylglycerol (6.7 g, 51 mmol), $(Bu_4N)_4SO_4$ (3.4 g, 10 mmol), benzyl bromide (8.6 g, 50 mmol), and CH_2Cl_2 (300 mL) was refluxed overnight. The organic phase was collected, washed with water (3 × 50 mL), dried over $MgSO_4$, and purified by chromatography, to yield the title compound(2.5 g, 22%). ^{13}C NMR: δ 69.2, 71.2, 71.3, 71.9, 73.1, 116.7, 134.4.

1-O-Benzyl-3-O-(2,3-epoxypropyl)glycerol (**11**).—Hydrogen peroxide (30%, 3.5 mL) was added dropwise to a stirred mixture of 1-*O*-allyl-3-*O*-benzylglycerol (2 g, 9.7 mmol), K_2CO_3 (350 mg), and benzonitrile (2.8 mL, 41 mmol) in MeOH (25 mL). After 2 h the excess of H_2O_2 was decomposed with Pd–C (10%, 100 mg), and the solution filtered, neutralised with aq AcOH, concentrated, and purified by chromatography, to yield the title compound (0.9 g, 42%). ^{13}C NMR: δ 43.4, 50.5, 69.2, 71.2, 71.6, 71.7, 72.5, 72.6, 72.9.

2-Benzyloxymethyl-6-hydroxymethyl-1,4-dioxane (**12**).—A solution of **11** (0.8 g, 3.6 mmol) in a mixture of THF (5 mL), water (2 mL), and 0.1 M NaOH (0.5 mL) was refluxed for 48 h, neutralised with aq AcOH, and concentrated. The product was dissolved in CH_2Cl_2 (100 mL), washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, concentrated, and purified by chromatography, to yield **12** (200 mg, 25%). ^{13}C NMR: δ 61.5, 62.9, 68.2, 68.4, 69.0, 69.1, 69.7, 70.5, 71.0, 72.2, 74.3, 75.3, 75.5, 75.6, 75.8.

Methyl 3,4,6-tri-O-benzyl-2-O-(6-benzyloxymethyl-1,4-dioxan-2-ylmethyl)-α-D-glucopyranoside.—Sodium hydride (75 mg, 3.1 mmol) was added in portions to a stirred solution of methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside [2] (130 mg, 0.28 mmol) in THF (10 mL), the solution was stirred for 30 min, then cooled to −10°C, and a freshly prepared solution of the triflate of **12** (133 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) added dropwise. The mixture was allowed to reach room temperature and, after 30 min, the excess of NaH was decomposed with MeOH (3 mL). The solution was concentrated, dissolved in CH_2Cl_2 (50 mL), washed with water (3 × 10 mL), dried over $MgSO_4$, filtered, concentrated, and purified by chromatography, to yield the title compound (108 mg, 57%).^{13}C NMR : δ 55.5, 68.9, 69.0, 70.6, 73.9, 75.4, 75.9, 78.1, 82.2, 82.4, 98.3.

Methyl 2-O-(6-hydroxymethyl-1,4-dioxan-2-ylmethyl)-α-D-glucopyranoside (**13**).—The compound above (108 mg, 0.17 mmol) in a mixture of EtOH (5 mL) and AcOH (0.2 mL) was hydrogenolysed over Pd–C (10%, 100 mg). The solution was filtered, concentrated, and purified by chromatography on Sephadex® G15, to yield **13** (21 mg, 41%). ^{13}C NMR: δ 55.0, 59.9, 60.7, 61.1, 66.7, 67.0, 68.9, 69.0, 69.4, 69.7, 70.1, 70.2, 70.9, 71.6, 72.5, 73.3, 73.5, 73.6, 73.8, 74.9, 76.0, 76.1, 80.0, 80.1, 97.2. The underlined signals derive from the methyl α-D-glucopyranoside residue.

Preparation of permethylated alditol-1-d *derivatives.*—The model substances were transformed into alditol-*1-d* derivatives as previously described [1].

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