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Note

Synthesis of poly-*O*-sulfated glycosides of 2,5-anhydro-D-mannitol☆

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Dedicated to András Lipták on the occasion of his 70th birthday

Abstract—2,5-Anhydro-3-*O*-β-D-glucopyranosyl-; -3-*O*-α-L-idopyranosyl-; -3-*O*-α-D-arabinopyranosyl-; -3-*O*-α-L-arabinopyranosyl-; -3-*O*-β-D-maltopyranosyl-; -3-*O*-β-D-gentiobiopyranosyl-; -1,6-di-*O*-β-D-glucopyranosyl-; -1,6-di-*O*-α-L-idopyranosyl-; -1-*O*-β-D-maltopyranosyl-; -1,3,6-tri-*O*-β-D-glucopyranosyl-; -1,6-di-*O*-β-maltopyranosyl- and -1,6-di-*O*-β-D-gentiobiopyranosyl-2,5-anhydro-D-mannitol as well as their poly-*O*-sulfated derivatives were synthesized. The IP_3–IC_{50} values of their sodium and/or potassium salts were determined for structure–activity studies aiming at the synthesis of new, orally active antiasthmatic compounds.

Keywords: 2,5-Anhydro-D-mannitol derivatives; Mono-, di-, tri-, tetra- and pentasaccharides; Poly-*O*-sulfated saccharides; Antiasthmatic compounds

Heparin, well known as an anticoagulant,[1] possesses other very important and significant biological activities too, among others antiinflammatory, antiallergic and even antiasthmatic properties.[2–5] These activities are however independent from the anticoagulant activity of native heparin, and are displayed by low, and even ultralow molecular weight heparin fragments, obtained by degradation of the original GAGs.[6,7] Recently, it was claimed by Ahmed and Smith[8] that a mixture of poly-*O*-sulfated disaccharides, obtained by degradation of heparin with HNO_2 and subsequent reduction with $NaBH_4$ followed by O-sulfation, possesses pronounced antiasthmatic activity. As the separation of the two main components of this mixture, that is, the hepta sodium salt of 2,5-anhydro-3-*O*-(β-D-glucopyranosyluronate)- and (α-L-idopyranosyluronate)-D-mannitol hexa-*O*-sulfate **1** and **2** (Fig. 1), represented a very difficult problem, both were synthesized[9] and differed significantly in their biological activity. For establishing the structure–activity relationship of this type of polysulfated glycosides, further analogues were synthesized and tested for their biological activity. These compounds inhibit the binding of inositol-1,4,5-triphosphate (IP_3) to its receptor in microsomal membrane preparations. As IP_3 is a messenger molecule playing distinguished role in the activation of different cells, interfering with this function can explain the antiasthmatic effect of these glycosides. The IP_3 antagonist effect was determined using rat cerebellum membrane preparations,[10] and the obtained IC_{50} data are given in parenthesis for each polysulfated new compound.

First, we decided to investigate the role of the carboxylate group of the uronic acid glycosides **1** and **2** on the biological activity, therefore their D-glucopyranose **7** and L-idopyranose analogues **10**—containing an *O*-sulfate instead of the carboxylate group at the terminal position—were synthesized using the pathway in Scheme 1. Glycosidation of 2,5-anhydro-1,6-di-*O*-benzyl-D-mannitol **4**[9,11,12] with acetobromoglucose **3** using mercury cyanide as promoter afforded after column chromatography glycoside **5** in modest yield (30%). This mixed ester was submitted to Zemplén deacylation and the obtained crystalline disaccharide **6** was converted with $DMF{\cdot}SO_3$ into its hepta-*O*-sulfate, which after treatment with sodium acetate afforded the corresponding hepta sodium salt **7**. The corresponding L-idopyranoside

☆ Poly-*O*-sulfated saccharides as IP_3 receptor antagonists. Part I.

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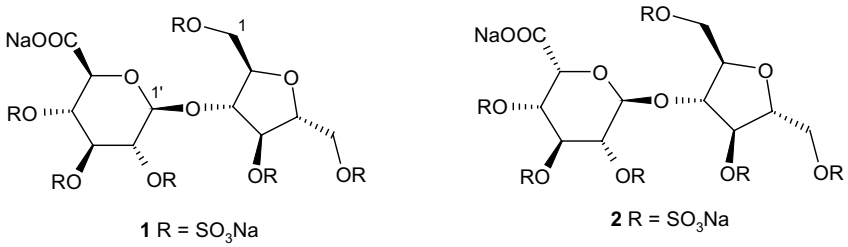
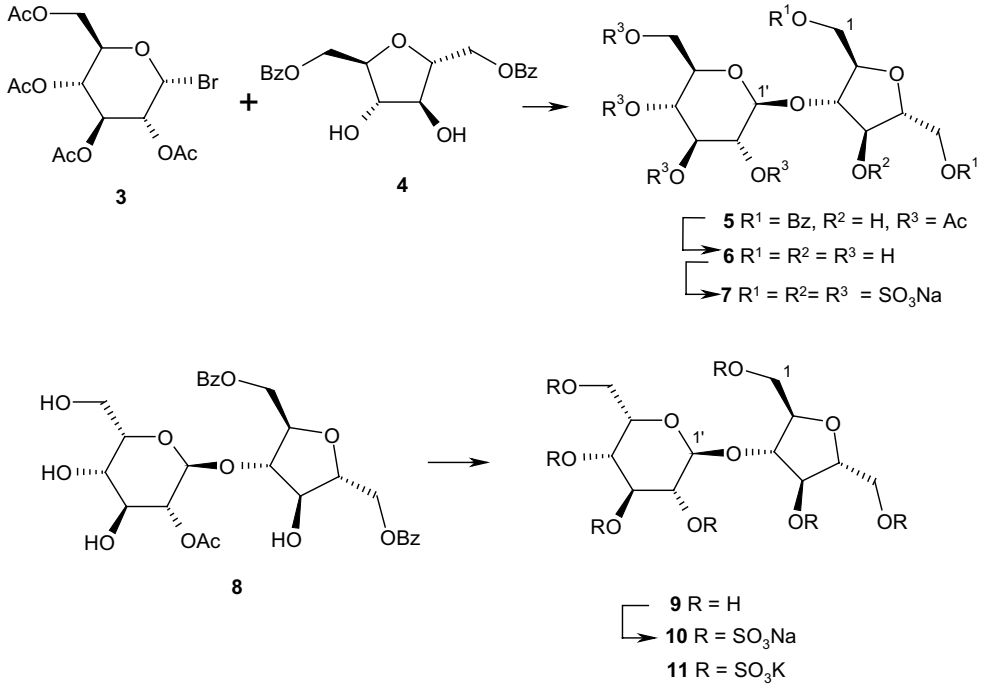


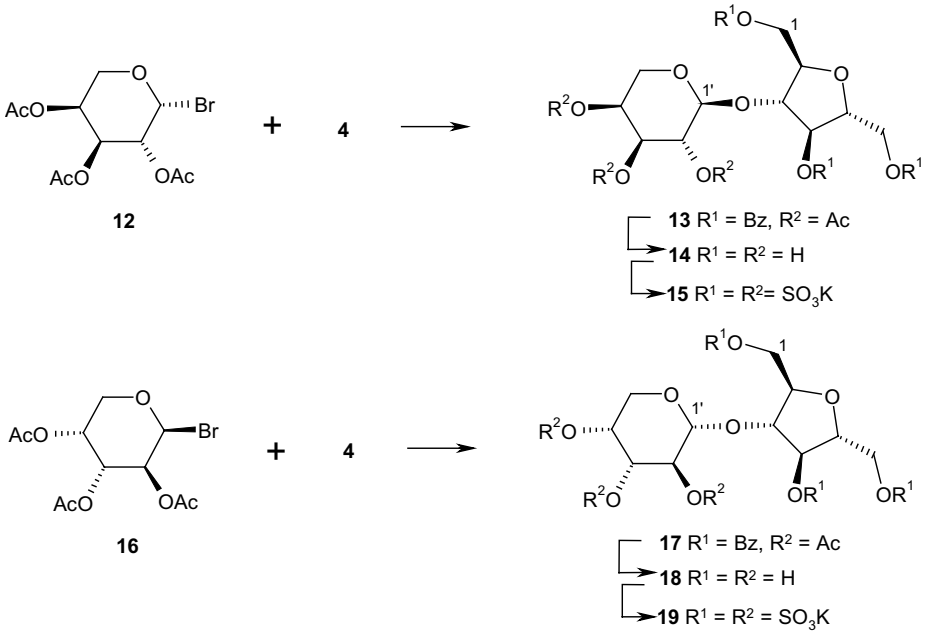
Figure 1.



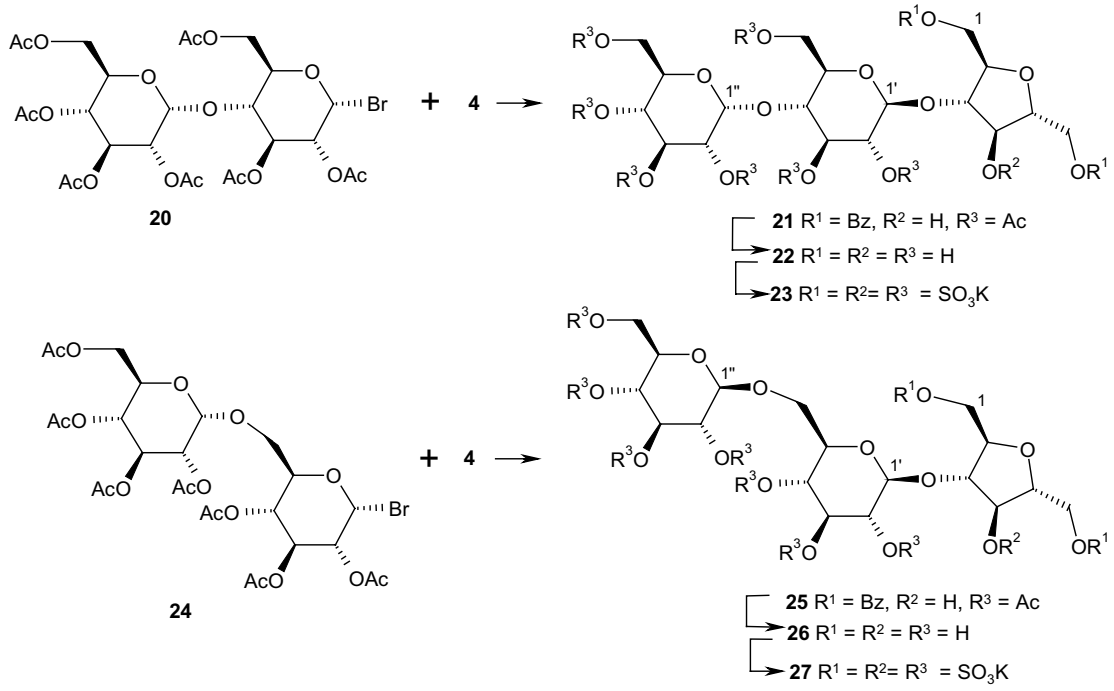
Scheme 1.

isomer **10** was synthesized starting from the mixed ester **8**[9] by deacylation and subsequent sulfation of the obtained amorphous disaccharide **9** (Scheme 1). It is worth mentioning that while the IP_3 antagonist activity decreased in the case of the D-gluco derivatives by changing the carboxylate for an *O*-sulfonate group (IC_{50}: 1.28 μM (**1**) → 4.81 μM (**7**)), a reversed tendency could be observed in the L-ido isomers (IC_{50}: 2.35 μM (**2**) → 1.49 μM (**10**)). As the potassium salts of polysulfated saccharides are usually easier to handle than the sodium salts,[13] the polysulfated idopyranoside was converted into the hepta potassium salt **11** too. As this change did not influence the biological activity (IC_{50}: 1.39 μM), all further derivatives were isolated as their potassium salts.

Next, we used pentopyranoside derivatives, that is, acetobromo L- (**12**) and D-arabinopyranose (**16**), as glycosylating agents. In both cases, multicomponent mixtures were obtained from which the needed glycosides could only be separated in modest yields, by column chromatography, after further O-benzoylation. The so obtained tri-*O*-benzoates **13** and **17** were converted after deacylation (**14** and **18**) into the potassium salts of their hexa-*O*-sulfates **15** and **19**, respectively (Scheme 2). These isomers showed very weak biological activity (IC_{50}: 20.33 μM (**15**) and 26.53 μM (**19**)), which led to the conclusion that at least seven negative charges are needed for a molecule to act as a potent IP_3 antagonist. For proving this hypothesis, the number of the *O*-sulfate groups was increased by attaching a disaccharide to the aglycon, using acetobromomaltose **20** as glycosylating agent. The obtained glycoside **21** was converted via deacylation (**22**) and subsequent sulfation into the deca potassium salt **23**, which showed a substantially increased biological activity (IC_{50}: 0.22 μM). A trisaccharide derivative **27** with similar activity (IC_{50}: 0.24 μM) was obtained when the same reaction sequence (**24** → **25** → **26** → **27**) was repeated using gentiobiopyranosyl bromide **24** as glycosylating agent. (Scheme 3). That means that the stereochemistry as well as the place

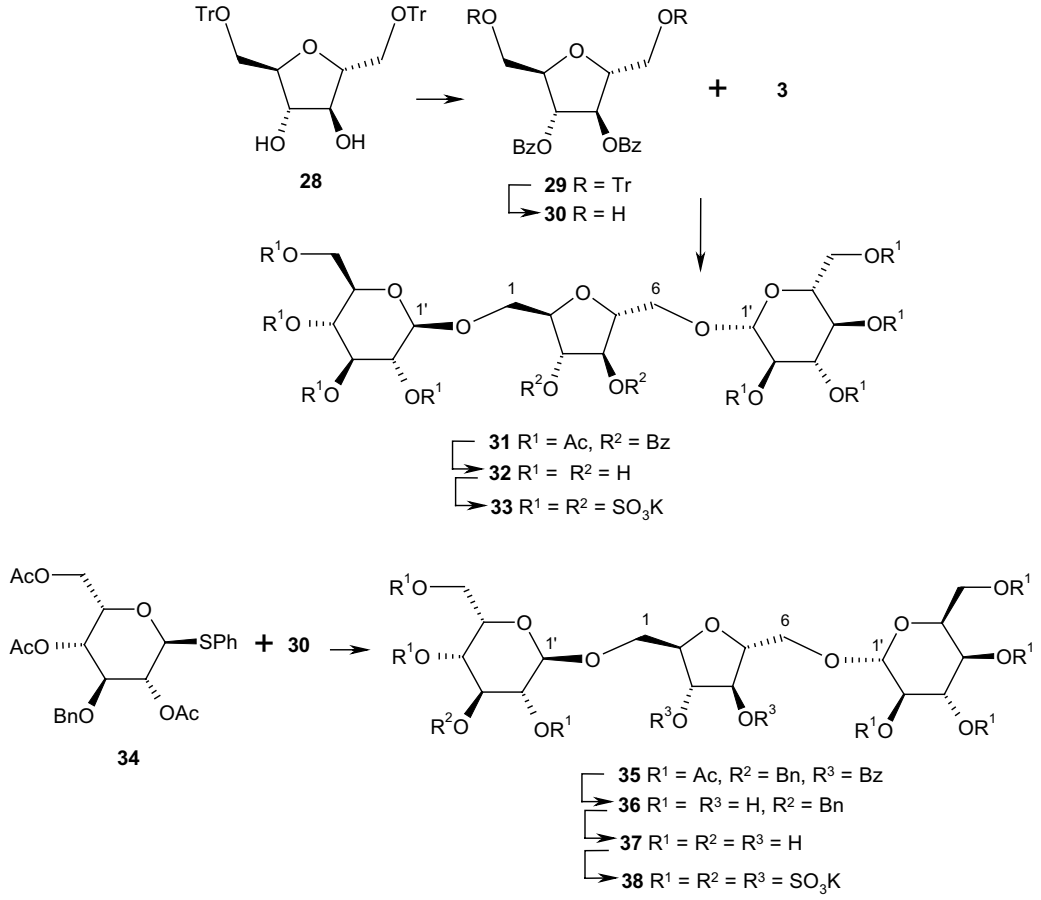


Scheme 2.



Scheme 3.

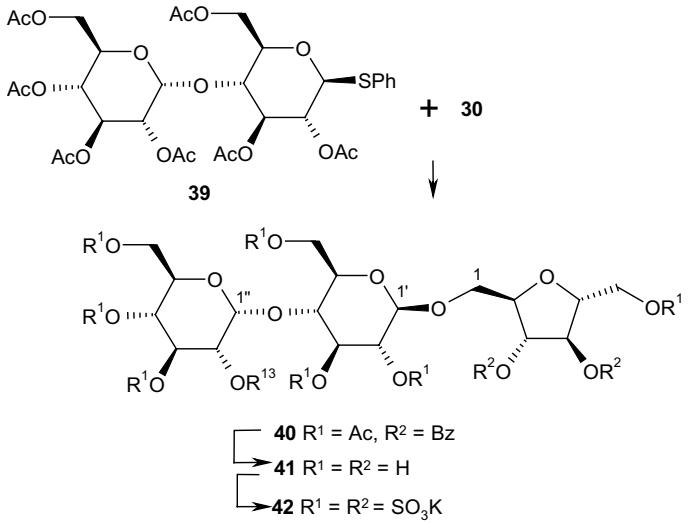
of the glycosidic bond of the disaccharide unit attached to 2,5-anhydro-D-mannnitol (α-(1→4) in **23** vs β-(1→6) in **27**) has practically no influence on the activity. This rose the question of whether the number of the charges, or the place of the attachment of the glycosylating unit to the 2,5-anhydro-D-mannitol residue is more important for the biological activity. Accordingly, the synthesis of a trisaccharide, containing two glucopyranosyl units attached to the two primary OH groups of the central 2,5-anhydro-mannitol moiety, was carried out in the following way. 2,5-Anhydro-D-mannitol was converted via its 1,6-di-*O*-trityl derivative **28** into the corresponding dibenzoate **29**, the trityl groups of which were split off yielding **30** and the latter was glycosylated using acetobromoglucose **3** as donor. The obtained trisaccharide **31** gave after deacylation (**32**) and subsequent sulfation the



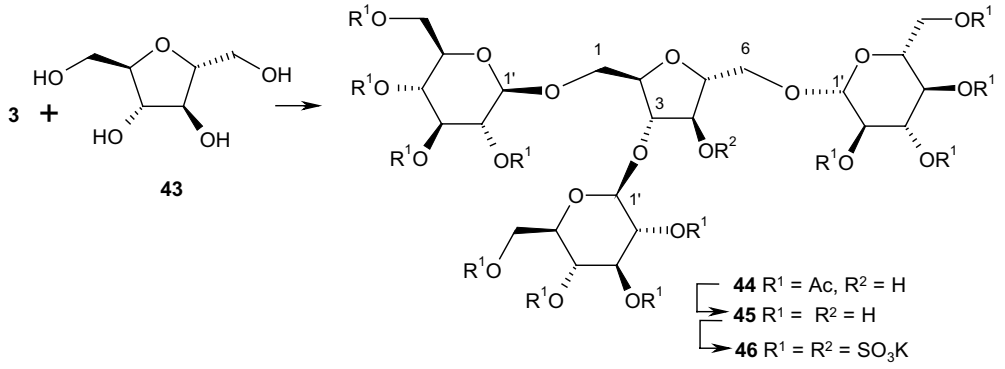
Scheme 4.

deca potassium salt **33**, which was only half as active (IC_{50}: 0.54 μM) as the isomeric trisaccharides **23** and **27**. The activity decreased further (IC_{50}: 1.40 μM), when instead of D-glucopyranose L-idopyranose was attached to the primary OH groups of 2,5-anhydro-D-mannitol (**38**) (Scheme 4). This led to the conclusion that, besides the number of the negative charges, the shape of the molecule is also strongly influencing the biological activity. For proving this assumption a molecule, with identical number of charges but differing in the sequence of the sugar units, was synthesized attaching maltose to one of the primary OH groups of the anhydro-mannitol moiety. This derivative was synthesized using thiophenylglycoside **39** as donor and the 3,4-di-*O*-benzoate **30** as acceptor. During the glycosidation reaction, a partial *O*-acetyl migration from the donor molecule to the acceptor took place, therefore the disaccharide **40**, which could be isolated after column chromatography in a very modest yield only (33%), contained a 6-*O*-acetyl group on the 2,5-anhydro moiety. The disaccharide **40** was converted the usual way into the deca potassium salt **42** of the polysulfated compound (Scheme 5). This polysulfated trisaccharide possessed a remarkable biological activity (IC_{50}: 0.11 μM).

For increasing further the number of the *O*-sulfate groups, a 'branched-chain' tetrasaccharide **46** was synthesized by glycosylating the unprotected 2,5-anhydro-D-mannitol **43** with acetobromoglucose **3** followed by the usual processing (Scheme 6). As expected, this compound showed a very strong biological activity (IC_{50}: 0.14 μM). Finally, two linear polysulfated pentasaccharides were synthesized, using the 3,4-dibenzoate **30** as acceptor and maltosyl bromide **20** as well as gentiobiosyl bromide **24** as donors. The formed two isomeric penta- saccharide derivatives **47** and **50** were converted after deprotection (**48** and **51**) and subsequent sulfation into the corresponding hexadeca potassium salts **49** and **52** (Scheme 7). Both proved to be strong IP_3 antagonists (IC_{50}: 0.11 and 0.18 μM, respectively), but they possessed some antithrombotic activities too, which is an unfavourable side effect in the case of antiasthmatic compounds. From these biological results, the conclusion can be drawn that at least seven negative charges/molecule are needed for the IP_3 antagonist activity, which becomes stronger when the number of the charges is increased. However, there seems to be threshold to this process, as when a certain molecule-size is reached, the antithrombotic activity becomes dominant.



Scheme 5.



Scheme 6.

1. Experimental

1.1. General methods

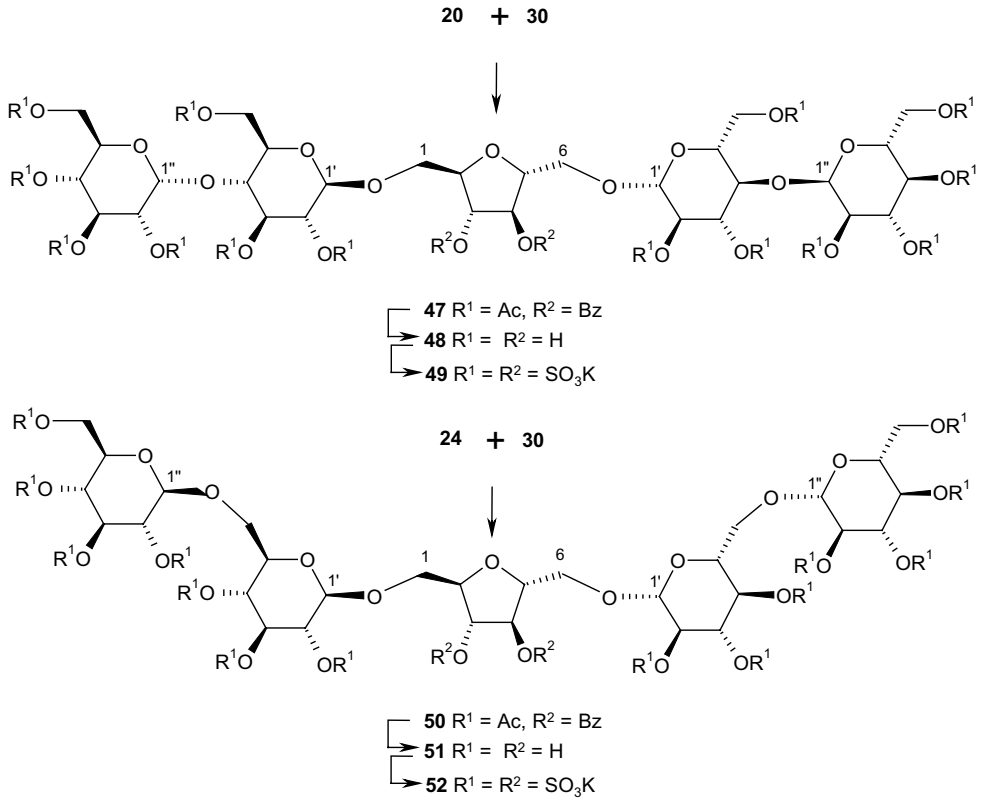
Organic solns were dried over $MgSO_4$ and concentrated under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F_{254} plates, with EtOAc (A), EtOAc–hexane mixtures (B, 1:1; C, 1:2; D, 1:5; E, 2:1; F, 5:1) and EtOAc–MeOH 1:5 (G); detection by spraying the plates with a 0.02 M soln of I_2 and a 0.3 M soln of KI in 10% aq H_2SO_4 soln followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. The mp are uncorrected. Optical rotations were determined on 1.0% solns in $CHCl_3$ at 20 °C unless stated otherwise. The NMR spectra were recorded on a Bruker Avance 500 spectrometer at 500 (^{1}H) and 125 (^{13}C) MHz, respectively, at ambient temperature. The chemical shifts were referenced to $\delta_{TMS} = 0$ ppm. The solvent is indicated at the ^{1}H NMR spectral data. For structure determination, ^{1}H,^{1}H COSY, TOCSY, HMQC, HMBC as well as selective 1D TOCSY and NOESY spectra were recorded.

1.2. General procedure A for the glycosidation reaction

A soln of the acceptor molecule (10 mmol) in dry MeCN (100 mL) was stirred in the presence of molecular sieves (4 Å) (7 g) for 30 min. Thereafter, the acetobromo donor (12 mmol) and $Hg(CN)_2$ (13 mmol) were added and stirring was continued at rt for 20 h. The filtered mixture was diluted with 3-fold $CHCl_3$, washed with 5% $NaHCO_3$ soln and a 10% aq soln of KBr, dried and concentrated.

1.3. General procedure B for the deacylation

To a soln of the glycoside (10 mmol) obtained according to procedure A in dry MeOH (100 mL), 2 M methanolic MeONa (1 mL) was added. When according to TLC the deacylation was complete, the sodium ions were removed with an ion-exchange resin and the residue



Scheme 7.

obtained on concentration was dissolved in water (50 mL) and freeze-dried.

1.4. General procedure C for the O-sulfation

To a stirred and cooled (−20 °C) suspension of SO_3·DMF (15 mmol) in DMF (5 mL), a soln of the saccharide to be sulfated (containing 10 mmol free OH groups) in DMF (4 mL) was added at such a rate to keep the temperature below −15 °C. Thereafter, the temperature was raised to 0 °C, after 1 h the mixture was cooled again to −15 °C and EtOH (1 mL) was added while keeping the temperature below −10 °C. The obtained mixture was processed according to the following general procedures.

1.5. General procedure D for the preparation of the sodium salts

The mixture obtained according to procedure C was poured into a vigorously stirred and cooled (0 °C) soln of NaOAc (4 g) in MeOH (40 mL). The formed precipitate was filtered off, washed with MeOH (3 × 40 mL) and dissolved in water (60 mL). The pH of the soln was adjusted to 8 with M NaOH, and M $Sr(OAc)_2$ was added. The formed precipitate was filtered off and the filtrate was submitted to a column of CHELX 100 ion-exchange resin (Na^+). The obtained soln was concentrated and the residue filtered with MeOH. The solid material was stirred with MeOH (20 mL) overnight, filtered, washed with MeOH and dried over P_2O_5.

1.6. General procedure E for the preparation of the potassium salts

The mixture obtained according to procedure C was poured into a vigorously stirred and cooled (0 °C) soln of KOAc (4 g) in MeOH (40 mL). The formed precipitate was filtered off, washed with MeOH (3 × 40 mL) and dissolved in water (60 mL). The pH of the soln was adjusted to 8 with M KOH, and M $Sr(OAc)_2$ was added. The formed precipitate was filtered off and the filtrate was submitted to a column of CHELX 100 ion-exchange resin (K^+). The obtained soln was concentrated to a volume of 10 mL and kept overnight at +4 °C. The precipitated material was filtered, washed with cold (0 °C) water and dried over P_2O_5.

1.7. 2,5-Anhydro-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,6-di-*O*-benzoyl-D-mannitol (5)

Prepared according to the general procedure A from **4** (9.0 g, 24 mmol) and **3** (10.5 g, 25.5 mmol) to yield after column chromatography (B) **5** (5.4 g, 30%) as syrup:

$[\alpha]_D$ +46 (*c* 1, $CHCl_3$); R_f 0.4. Anal. Calcd for $C_{34}H_{38}O_{16}$: C, 58.12; H, 5.45. Found: C, 58.01; H, 5.56.

1.8. 2,5-Anhydro-3-*O*-(-β-D-glucopyranosyl)-D-mannitol (6)

Prepared according to the general procedure B from **5** (5.2 g, 7.4 mmol) to yield **6** (1.7 g, 71%); mp 181–183 °C (MeOH), $[\alpha]_D$ +20 (*c* 1, water). Anal. Calcd for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 43.89; H, 6.92.

1.9. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-(2,3,4,6-tetra-*O*-sulfato-β-D-glucopyranosyl)-D-mannitol hepta sodium salt (7)

Prepared according to the general procedure C and D from **6** (0.65 g, 2 mmol) to give **7** (1.93 g, 93%); $[\alpha]_D$ +15 (*c* 1, water); ^{1}H NMR: δ 4.94–4.89 (m, 2H, H-4,1′), 4.69 (m, 1H, H-3′), 4.55–4.33 (m, 6H, H-2,3,5,2′,4′,6a′), 4.27–4.12 (m, 5H, H-1a,1b,6a,6b,6b′), 4.07 (m, 1H, H-5′); ^{13}C NMR: δ 102.9 (C-1′), 86.7, 84.5, 84.4, 83.6 (C-2,3,4,5), 79.5, 79.2 (C-2′,3′), 76.4, 75.4 (C-4′,5′), 70.1, 69.7, 69.7 (C-1,6,6′). Anal. Calcd for $C_{12}H_{15}O_{31}S_7Na_7$: C, 13.85; H, 1.45; Na, 15.47; S, 21.57. Found: C, 13.99; H, 1.65; Na, 15.39; S, 21.40.

1.10. 2,5-Anhydro-3-*O*-(α-L-idopyranosyl)-D-mannitol (9)

Prepared according to the general procedure B from **8**[9] (1.65 g, 3.97 mmol) to yield **9** (1.06 g, 82%); mp 162–164 °C (*c* 1, MeOH), $[\alpha]_D$ −40 (*c* 1, water). Anal. Calcd for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 44.00; H, 6.85.

1.11. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-(2,3,4,6-tetra-*O*-sulfato-α-L-idopyranosyl)-D-mannitol hepta sodium salt (10)

Prepared according to the general procedure C and D from **9** (0.65 g, 2 mmol) to give **10** (1.8 g, 87%); $[\alpha]_D$ −3 (*c* 1, water); ^{1}H NMR: δ 5.23 (s, 1H, H-1′), 5.03 (s, 1H, H-3′), 4.86 (t, 1H, $J_{2,3} = J_{3,4} = 2.5$ Hz, H-4), 4.60–4.46 (m, 6H, H-2,3,5,2′,4′,5′), 4.31 (dd, 1H, $J_{6a',6b'} = 11.2$, $J_{6a',5'} = 3.4$ Hz, H-6a′), 4.25–4.14 (m, 5H, H-1a,1b,6a,6b,6b′); ^{13}C NMR: δ 100.1 (C-1′), 84.5, 84.4, 84.4, 83.2 (C-2,3,4,5), 73.4, 72.9, 72.8, 66.7 (C-2′,3′,4′,5′), 70.0, 69.8, 69.3 (C-1,6,6′). Anal. Calcd for $C_{12}H_{15}O_{31}S_7Na_7$: C, 13.85; H, 1.45; Na, 15.47; S, 21.57. Found: C, 14.03; H, 1.69; Na, 15.32; S, 21.32.

1.12. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-(2,3,4,6-tetra-*O*-sulfato-α-L-idopyranosyl)-D-mannitol hepta potassium salt (11)

Prepared according to the general procedure C and E from **9** (0.65 g, 2 mmol) to give **11** (2.05 g, 89%); $[\alpha]_D$ −4 (*c* 1, H_2O); ^{1}H NMR and ^{13}C NMR identical with **10**; Anal. Calcd for $C_{12}H_{15}O_{31}S_7K_7$: C, 12.50; H, 1.31; S, 16.46; K 23.73. Found: C, 12.38; H, 1.82; S, 18.50; K, 22.90.

1.13. 2,5-Anhydro-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-arabino-pyranosyl)-1,4,6-tri-*O*-benzoyl-D-mannitol (13)

Prepared according to the general procedure A from **12** (12 g, 35.4 mmol) and **4** (13.0 g, 35 mmol) as starting materials. The residue of the concentrated $CHCl_3$ soln was dissolved in pyridine (100 mL) and benzoyl chloride (15 mL) was added. The mixture was stirred at rt for 2 h, then poured into ice-water. The precipitated oil was dissolved in CH_2Cl_2 to give after usual processing a syrup, which was purified by column chromatography (C). Concentration of the fractions having R_f 0.4 gave **13** (11 g, 39%) as syrup; $[\alpha]_D$ +12 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{38}H_{38}O_{15}$: C, 62.12; H, 5.21. Found: C, 62.34; H, 5.32.

1.14. 2,5-Anhydro-3-*O*-(-α-L-arabinopyranosyl)-D-mannitol (14)

Prepared according to the general procedure B from **13** (10.9 g, 14.8 mmol) to give **14** as hygroscopic amorphous powder (4.1 g, 94%), $[\alpha]_D$ +67 (*c* 1, water). Anal. Calcd for $C_{11}H_{20}O_9$: C, 44.59; H, 6.80. Found: C, 44.62; H, 6.95.

1.15. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-(2,3,4-tri-*O*-sulfato-α-L-arabinopyranosyl)-D-mannitol hexa potassium salt (15)

Prepared according to the general procedure C and D from **14** (0.59 g, 2 mmol) to give **15** (1.6 g, 80%); $[\alpha]_D$ +33 (*c* 1, water); ^{1}H NMR: δ 4.88 (t, 1H, $J_{3,4} = J_{4,5} = 3$ Hz, H-4), 4.87–4.81 (m, 2H, H-1′,4′), 4.68 (m, 1H, H-2′), 4.58–4.43 (m, 3H, H-3,5,3′), 4.41 (m, 1H, H-2), 4.30–4.15 (m, 5H, H-1a,1b,6a,6b,5a′), 3.76 (dd, 1H, $J_{5a',5b'} = 12.7$, $J_{5b',4'} = 2.5$ Hz, H-5b′); ^{13}C NMR: δ 102.6 (C-1′), 86.2 (C-3), 84.7 (C-4), 84.0 (C-5), 82.9 (C-2), 77.0 (C-3′), 76.6 (C-2′), 74.4 (C-4′), 70.0 (C-1), 69.4 (C-6), 63.2 (C-5′). Anal. Calcd for $C_{11}H_{14}O_{27}S_6K_6$: C, 13.14; H, 1.40; S, 19.14; K 23.34. Found: C, 13.05; H, 1.78; S, 18.55; K, 23.30.

1.16. 2,5-Anhydro-3-*O*-(2,3,4-tri-*O*-acetyl-α-D-arabino-pyranosyl)-1,4,6-tri-*O*-benzoyl-D-mannitol (17)

Acetobromo D-arabinose (**16**) was coupled with **4** as described for the L-isomer **13** to give **17** (10.6 g, 38%); $[\alpha]_D$ 0 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{38}H_{38}O_{15}$: C, 62.12; H, 5.21. Found: C, 62.28; H, 5.41.

1.17. 2,5-Anhydro-3-*O*-(-α-D-arabinopyranosyl)-D-mannitol (18)

Deacylation of **17** (8.4 g, 11.5 mmol) was carried out as described for the L-isomer **14** to give **18** (3.1 g, 91%) as an amorphous powder; $[\alpha]_D$ +7 (*c* 1, water). Anal. Calcd for $C_{11}H_{20}O_9$: C, 44.59; H, 6.80. Found: C, 44.42; H, 6.95.

1.18. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-(2,3,4-tri-*O*-sulfato-α-D-arabinopyranosyl)-D-mannitol hexa potassium salt (19)

Sulfation of **18** (0.59 g, 0.3 mmol) was carried out as described for the L-isomer **15** to give **19** (1.8 g, 90%); $[\alpha]_D$ +21 (*c* 1, water); ^{1}H NMR: δ 5.02 (m, 1H, H-1′), 4.90–4.78 (m, 2H, H-4′,4′), 4.75 (m, 1H, H-2′), 4.60–4.55 (m, 2H, H-5,3′), 4.52 (m, 1H, H-3), 4.42 (m, 1H H-2′), 4.32–4.15 (m, 4H, H-1a,1b,6a,6b), 4.12 (m, 1H, H-5a′), 3.78 (m, 1H, H-5b′); ^{13}C NMR: δ 100.8 (C-1′), 84.8 (C-4), 84.2 (C-5), 84.1 (C-3), 82.8 (C-2), 76.6 (C-3′), 76.3 (C-2′), 74.2 (C-4′), 69.7 (C-6), 69.3 (C-1), 62.5 (C-5′). Anal. Calcd for $C_{11}H_{14}O_{27}S_6K_6$: C, 13.14; H, 1.40; S, 19.14; K, 23.34. Found: C, 13.00; H, 1.69; S, 18.63; K, 23.21.

1.19. 2,5-Anhydro-1,6-di-*O*-benzoyl-3-*O*-(hepta-*O*-acetyl-β-D-maltosyl)-D-mannitol (21)

Prepared according to the general procedure A from **4** (6.5 g, 17.5 mmol) and **20** (12.5 g, 18.4 mmol) to yield after column chromatography (B) **21** as a syrup (5.6 g, 30%), R_f 0.4; $[\alpha]_D$ +65 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{46}H_{54}O_{240}$: C, 55.76; H, 5.49. Found: C, 55.89; H, 5.62.

1.20. 2,5-Anhydro-3-*O*-(β-D-maltosyl)-D-mannitol (22)

Prepared according to the general procedure B from **21** (1.6 g, 1.6 mmol) to give **22** (0.75 g, 95%) as an amorphous powder, $[\alpha]_D$ +96 (*c* 1, water). Anal. Calcd for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.08; H, 6.82.

1.21. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-[4-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-2,3,6-tri-*O*-sulfato-β-D-glucopyranosyl]-D-mannitol deca potassium salt (23)

Prepared according to the general procedure C and D from **22** (0.6 g, 1.2 mmol) to give **23** (1.95 g, 95%), $[\alpha]_D$ +33 (*c* 1, water); ^{1}H NMR: δ 5.59 (d, 1H, $J_{1'',2''}$ = 3.1 Hz, H-1″), 5.04 (d, 1H, $J_{1',2'}$ = 5.3 Hz, H-1′), 4.95 (s, 1H, H-4), 4.86 (t, 1H, $J_{2'',3''} = J_{3'',4''}$ = 8 Hz, H-3″) 4.75 (t, $J_{2',3'}$ = 5 Hz, H-2′), 4.58 (s, 1H, H-3), 4.56–4.03 (m, 16H); ^{13}C NMR: δ 103.7 (C-1′), 97.3 (C-1″), 86.8 (C-3), 84.8 (C-4), 84.5, 83.5 (C-2,5), 79.9 (C-2′), 79.4 (C-2″), 77.7, 76.5, 76.2, 76.1, 74.9 (C-4′, C-5′, C-3″, C-4″, C-5″), 70.2, 70.0, 69.8, 68.9 (C-1,6,6′,6″). Anal. Calcd for $C_{18}H_{22}O_{35}S_{10}K_{10}$: C, 12.95; H, 1.33; S, 19.20; K, 23.41. Found: C, 12.48; H, 1.65; S, 18.95; K, 23.08.

1.22. 2,5-Anhydro-1,6-di-*O*-benzoyl-3-*O*-(heptaacetyl-β-gentiobiosyl)-D-mannitol (25)

Prepared according to the general procedure A from **4** (2.6 g, 7 mmol) and **24** (4.7 g, 6.5 mmol) to give **25** (2.2 g, 32%); mp 166–168 °C (EtOH), $[\alpha]_D$ +9 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{46}H_{54}O_{240}$: C, 55.76; H, 5.49. Found: C, 55.79; H, 5.51.

1.23. 2,5-Anhydro-3-*O*-(β-gentiobiosyl)-D-mannitol (26)

Prepared according to the general procedure B from **25** (2.0 g, 1.87 mmol) to give **26** (0.95 g, ~100%) as amorphous powder, $[\alpha]_D$ +7 (*c* 1, water). Anal. Calcd for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.14; H, 6.85.

1.24. 2,5-Anhydro-1,4,6-tri-*O*-sulfato-3-*O*-[6-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-2,3,4-tri-*O*-sulfato-β-D-glucopyranosyl]-D-mannitol deca potassium salt (27)

Prepared according to the general procedure C and D from **26** (0.54 g, 1.1 mmol) to give **27** (1.75 g, 95%), $[\alpha]_D$ +7 (*c* 1, water); ^{1}H NMR: δ 4.97 (d, 1H, $J_{1'',2''}$ = 7.4 Hz, H-1″), 4.91 (t, 1H, $J_{3,4} = J_{4,5}$ = 4 Hz, H-4), 4.83 (d, 1H $J_{1',2'}$ = 6.3, H-1′), 4.76 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 8.7 Hz, H-4′) 4.69 (t, 1H, $J_{2'',3''} = J_{3'',4''}$ = 8.3 Hz, H-3″), 4.61 (t, 1H, $J_{2,3}$ = 4 Hz, H-3), 4.59 (t, 1H, $J_{2,3}$ = 4 Hz, H-3′) 4.53 (m, 2H, H-5,6″) 4.47–4.00 (m, 11H), 3.90 (m, 1H, H-5′); ^{13}C NMR: δ 104.1 (C-1″), 103.1 (C-1′), 86.4 (C-3), 84.6 (C-4), 83.2 (C-5), 82.6 (C-2), 80.7 (C-3′), 79.9 (C-3″), 79.6 (C-2″), 79.3 (C-2′), 76.7 (C-5′), 76.4 (C-4″), 76.0 (C-4′) 75.5 (C-5″), 71.1 (C-6′), 70.4 (C-6), 70.0 (C-1), 70.1 (C-6″). Anal. Calcd for $C_{18}H_{22}O_{45}S_{10}K_{10}$: C, 12.90; H, 1.32; S, 19.18; K, 23.38. Found: C, 12.59; H, 1.89; S, 18.33; K, 21.08.

1.25. 2,5-Anhydro-1,6-di-*O*-trityl-D-mannitol (28)

To a stirred soln of crude 2,5-anhydro-D-mannitol[11,14] (4.6 g, 28 mmol) in pyridine (50 mL), TrCl (23 g, 70 mmol) was added and the mixture was stirred for 2 days at 20 °C. Thereafter, it was poured into water, extracted with CH_2Cl_2, washed with M H_2SO_4, water, 5% $NaHCO_3$ and water, dried and concentrated. The semicrystalline residue (26 g) was purified by column chromatography using first 1:5 EtOAc–hexane for removing the by-products (R_f 0.9; 0.7 and 0.5) and then EtOAc for eluting the product. Concentration of this latter fraction gave **28** (13.2 g, 74%), R_f 0.5 (B); $[\alpha]_D$ +14 (*c* 1, pyridine) as solid foam, which was used without further

purification in the next step. Lit.[15] mp 78–85 °C, $[\alpha]_D$ +18 (c 1, pyridine), yield 15.5%.

1.26. 2,5-Anhydro-3,4-di-*O*-benzoyl-D-mannitol (30)

To a stirred soln of **28** (13.0 g, 20 mmol) in pyridine (60 mL), benzoyl chloride (6.0 mL, 50 mmol) was added gradually with cooling below 10 °C. The mixture was kept at rt for 3 h, then poured into water and extracted with CH_2Cl_2. The organic soln was processed the usual way to give on concentration crude **29** (17.0 g, ~100%). This was dissolved in AcOH (100 mL) at 80 °C and water (25 mL) was added gradually. The soln was kept at this temperature for 1 h, and TrOH, which precipitated on cooling, was filtered off. The filtrate was diluted with CH_2Cl_2, washed with water, 5% $NaHCO_3$ soln and water, dried and concentrated. The semisolid residue was filtered with toluene, to give after recrystallization from 3-fold toluene **30** (2.6 g, 35%), mp 120–122 °C. Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 54.50; H, 5.44.

1.27. 2,5-Anhydro-3,4-di-*O*-benzoyl-1,6-bis-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol (31)

Prepared according to the general procedure A from **30** (2.6 g, 7 mmol) and **3** (10.5 g, 25.5 mmol) to yield after column chromatography (E) **31** (2.0 g, 28%); mp 132–134 °C (EtOH), $[\alpha]_D$ −28 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{46}H_{54}O_{24}$: C, 55.76; H, 5.49. Found: C, 55.81; H, 5.52.

1.28. 2,5-Anhydro-1,6-bis-*O*-(β-D-glucopyranosyl)-D-mannitol (32)

Prepared according to the general procedure B from **31** (1.6 g, 1.55 mmol) to give **32** (0.75 g, ~100%) as amorphous powder, $[\alpha]_D$ −3 (*c* 1, water). Anal. Calcd for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.15; H, 6.72.

1.29. 2,5-Anhydro-3,4-di-*O*-sulfato-1,6-bis-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-D-mannitol deca potassium salt (33)

Prepared according to the general procedure C and E from **32** (0.54 g, 1.1 mmol) to give **33** (1.5 g, 83%), $[\alpha]_D$ +33 (*c* 1, water); ^{1}H NMR: δ 5.03 (m, 2H, H-3,4), 4.93 (d, 2H, $J_{1',2'}$ = 5.5 Hz, H-1′), 4.73 (t, $J_{2',3'}$ = $J_{3',4'}$ = 6.4 Hz, 2H, H-3′), 4.52 (m, 2H, H-4′) 4.50–4.38 (m, 6H, H-2,5,2′,6a′), 4.26–4.15 (m, 4H, H-1a,6a,6b′), 4.10 (m, 2H, H-5′), 3.96–3.87 (m, 2H, H-1b,6b); ^{13}C NMR: δ 103.7 (C-1′), 83.2 (C-3,4), 83.0 (C-2,5), 78.9 (C-2′,3′), 76.2 (C-5′), 75.6 (C-4′), 71.6 (C-1,6), 70.3 (C-6′). Anal. Calcd for $C_{18}H_{22}O_{45}S_{10}K_{10}$: C, 12.90; H, 1.32; S, 19.18; K, 23.38. Found: C, 11.66; H, 1.67; S, 18.68; K, 22.92.

1.30. 2,5-Anhydro-1,6-bis-*O*-(3-*O*-benzyl-α-L-ido-pyranosyl)-D-mannitol (36)

To a stirred soln of 2,5-anhydro-3,4-di-*O*-benzoyl-D-mannitol **30** (4.46 g, 12 mmol) in CH_2Cl_2 (150 mL), molecular sieve 4 Å (18 g) and the thiophenyl glycoside **34**[9] (13 g, 27 mmol) were added. After 30 min the mixture was cooled to −40 °C, NIS (9 g, 40 mmol) and TfOH (0.5 mL) were added and stirring was continued at −40 °C for 15 min. Thereafter, Et_3N (9 mL) was added and the temperature was raised to 20 °C. The filtered mixture was washed with aq $Na_2S_2O_3$ and subsequently with $NaHCO_3$ soln and water. The dried organic soln was concentrated and the residue purified by column chromatography (B). Concentration of the fractions having R_f 0.35 gave crude 2,5-anhydro-3,4-di-*O*-benzoyl-1,6-bis-*O*-(2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-L-idopyranosyl)-D-mannitol **35** (8 g, 59%) as syrup, $[\alpha]_D$ −75 (*c* 1, $CHCl_3$) the purity of which was ~60% according to NMR. This was dissolved in MeOH (80 mL), and 2 M NaOMe in MeOH (0.3 mL) was added. After 2 h, when according to TLC the deacylation was complete the sodium ions were removed with an ion-exchange resin and the filtered soln was concentrated. The residue was partitioned between water and CH_2Cl_2 for removing the methyl benzoate. The aq soln was freeze-dried to give after column chromatography (ethyl acetate–ethanol 5:1) **36** (1.7 g, 36%), $[\alpha]_D$ −41 (*c* 1, water).

1.31. 2,5-Anhydro-1,6-bis-*O*-α-L-idopyranosyl-D-mannitol (37)

A soln of **36** (1.7 g) in MeOH (50 mL) and water (5 mL) was hydrogenated in the presence of 10% Pd/C (1 g) at normal pressure for 6 h when according to TLC both benzyl groups were removed. The filtered soln was concentrated, the residue dissolved in water (10 mL) and freeze-dried to yield **37** (1.2 g, 96%) as amorphous powder; $[\alpha]_D$ 0 (*c* 1, water). Anal. Calcd for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.11; H, 6.80.

1.32. 2,5-Anhydro-3,4-di-*O*-sulfato-1,6-bis-*O*-(2,3,4,6-tetra-*O*-sulfato-α-L-idopyranosyl)-D-mannitol deca potassium salt (38)

Prepared according to the general procedure C and E from **37** (0.97 g, 2 mmol) to give **38** (2.5 g, 75%), $[\alpha]_D$ −13 (*c* 1, water); ^{1}H NMR: δ 5.18 (s, 2H, H-1′), 5.07 (s, 2H, H-3′), 4.99 (s, 2H, H-3,4), 4.63 (s, 2H, H-4′) 4.59 (s, 2H, H-2′), 4.54 (m, 4H, H-2,5,5′), 4.31–4.21 (m, 4H, H-6′), 4.05 (d, 2H, $J_{1a,1b,6a,6b}$ = 11.3 Hz, H-1a,6a), 3.82 (dd, 2H, $J_{1b,2,5,6b}$ = 6.5 Hz, H-1b,6b); ^{13}C

NMR: δ 101.5 (C-1′), 84.0 (C-3,4), 83.8 (C-2,5), 73.4 (C-2′,3′), 73.0 (C-4′), 70.2 (C-6′), 70.1 (C1,6), 66.7 (C-5′). Anal. Calcd for $C_{18}H_{22}O_{45}S_{10}K_{10}$: C, 12.95; H, 1.33; S, 19.20; K, 23.41. Found: C, 12.48; H, 1.62; S, 18.89; K, 22.71.

1.33. Phenyl 1-thio-β-maltopyranosyl-peracetate (39)

Acetobromomaltose, obtained from octaacetyl-maltose (11.5 g, 17 mmol) according to the lit.,[16] was dissolved in 1,2-dichloroethane (60 mL) and thiophenol (2 mL) was added followed by Et_3N (5 mL). The mixture was stirred at rt for 2 h, washed with water, concentrated and the residue submitted to column chromatography (B). Concentration of the fractions having R_f 0.5 afforded **39** (7 g, 56%) as syrup; $[\alpha]_D$ +57 (*c* 1, $CHCl_3$). Lit.[17] $[\alpha]_D$ +47 (c 1, $CHCl_3$).

1.34. 6-*O*-Acetyl-2,5-anhydro-3,4-di-*O*-benzoyl-1-*O*-[2′,3′,4′,6′,2,3,6-hepta-*O*-acetyl-β-maltopyranosyl]-D-mannitol (40)

Prepared as described for **36**, starting from **30** (1.6 g, 4.3 mmol) and **39** (7 g, 9.6 mmol), to give after separation by column chromatography (C) **40** (1.5 g, 33%) as a syrup, R_f 0.7; $[\alpha]_D$ +10 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{46}H_{54}O_{240}$: C, 55.76; H, 5.49. Found: C, 55.859; H, 5.66.

1.35. 2,5-Anhydro-1-*O*-β-maltopyranosyl-D-mannitol (41)

Prepared according to the general procedure B from **40** (1.3 g, 1.2 mmol). The residue obtained on concentration of the methanolic soln was partitioned between water and CH_2Cl_2 for removing the methyl benzoate. The aq soln was freeze-dried to give **41** (0.6 g, 60%) as amorphous powder, $[\alpha]_D$ +86 (*c* 1, water). Anal. Calcd for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.18; H, 6.79.

1.36. 2,5-Anhydro-3,4,6-tri-*O*-sulfato-1-*O*-[4-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-2,3,6-tri-*O*-sulfato-β-D-glucopyranosyl]-D-mannitol deca potassium salt (42)

Prepared according to the general procedure C and E from **41** (0.44 g, 0.9 mmol) to give **42** (1.35 g, 90%), $[\alpha]_D$ +31 (*c* 1, water); ^{1}H NMR: δ 5.56 (s, 2H, H-1″), 5.02 (s, 1H, H-1′), 4.99 (s, 1H, H-3), 4.96 (s, 1H, H-4), 4.80 (m, 2H, H-3′,3″) 4.55 (s, 1H, H-2′), 4.50 (m, 2H, H-5,2″), 4.48–4.05 (m, 13H), 3.93–3.85 (m, 1H, H-1a); ^{13}C NMR: δ 104.0 (C-1′), 97.4 (C-1″), 84.1 (C-2), 84.0 (C-3), 83.8 (C-4), 83.0 (C-5), 79.1 (C-3′), 78.7 (C-2′), 77.8 (C-3″), 76.6 (C-2″), 76.2 (C-4″), 75.9 (C-5′), 74.9 (C-4′), 72.7 (C-5″), 71.3 (C-1), 70.4 (C-6′), 70.0 (C-6), 69.0 (C-6″). Anal. Calcd for $C_{18}H_{22}O_{45}S_{10}K_{10}$: C, 12.95; H, 1.33; S, 19.20; K, 23.41. Found: C, 12.63; H, 1.68; S, 18.30; K, 22.96.

1.37. 2,5-Anhydro-1,3,6-tri-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-D-mannitol (44)

Prepared according to the general procedure A from **43** (1.64 g, 10 mmol) and **3** (14.8 g, 36 mmol) to give after column chromatography (F) **44** (3.9 g, 34%), R_f 0.4; $[\alpha]_D$ +4 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{48}H_{66}O_{32}$: C, 49.91; H, 5.76. Found: C, 49.65; H, 5.83.

1.38. 2,5-Anhydro-1,3,6-tri-*O*-β-D-glucopyranosyl-D-mannitol (45)

Prepared according to the general procedure B from **44** (3.70 g, 3.2 mmol) to give **45** (1.80 g, 97%), $[\alpha]_D$ +8 (*c* 1, water). Anal. Calcd for $C_{24}H_{42}O_{20}$: C, 44.31; H, 6.51. Found: C, 44.44; H, 6.65.

1.39. 2,5-Anhydro-4-*O*-sulfato-1,3,6-tri-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-D-mannitol trideca potassium salt (46)

Prepared according to the general procedure C and E from **45** to yield **46** (1.5 g, 69%), $[\alpha]_D$ +4 (*c* 1, water); ^{1}H NMR: δ 5.05–4.88 (m, 4H, H-4,1′,1″,1‴), 4.84–3.87 (m, 25H); ^{13}C NMR: δ 103.8 (C-1′), 85.9, 84.2, 84.2, 82.0 (C-2,3,4,5) 79.4, 79.4, 79.3, 79.1, 78.9, 78.9 (D-gluco-2,3), 76.3, 76.2, 76.0, 75.9, 75.8, 75.5 (D-gluco-C-4,5), 72.5, 70.7, 70.2, 70.2, 69.8 (C-1,6,6′,6″,6‴). Anal. Calcd for $C_{24}H_{29}O_{59}S_{13}K_{13}$: C, 13.18; H, 1.34; S, 19.06; K, 23.25. Found: C, 12.38; H, 1.77; S, 18.68; K, 21.85.

1.40. 2,5-Anhydro-3,4-di-*O*-benzoyl-1,6-bis-*O*-(hepta-*O*-acetyl-β-maltosyl)-D-mannitol (47)

Prepared according to the general procedure A from **20** (14 g, 20 mmol) and **30** (2.75 g, 7.4 mmol) to yield after column chromatography (E) **47** as a syrup (6.3 g, 53%), R_f 0.35; $[\alpha]_D$ +38 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{72}H_{88}O_{41}$: C, 53.73; H, 5.51. Found: C, 53.99; H, 5.82.

1.41. 2,5-Anhydro-1,6-bis-*O*-β-maltosyl-D-mannitol (48)

Prepared according to the general procedure B from **47** (2.1 g) to give after column chromatography (G) **48** (0.7 g, 66%) as a solid foam; R_f 0.4; $[\alpha]_D$ +92 (*c* 1, water). Anal. Calcd for $C_{30}H_{52}O_{25}$: C, 44.34; H, 6.45. Found: C, 44.55; H, 6.56.

1.42. 2,5-Anhydro-3,4-di-*O*-sulfato-1,6-bis-*O*-[4-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-2,3,6-tri-*O*-sulfato-β-D-glucopyranosyl]-D-mannitol hexadeca potassium salt (49)

Prepared according to the general procedure C and E from **48** (0.63 g, 0.78 mmol) to give **49** (1.5 g, 71%), $[\alpha]_D$

+35 (*c* 1, water); ^{1}H NMR: δ 5.56 (s, 2H, H-1″), 5.01 (m, 4H, H-1′,3,4), 4.84 (t, 2H, $J_{2'',3''} = J_{3'',4''} = 8.3$ Hz, H-3″), 4.80 (m, 2H, H-3′), 4.58–3.86 (m, 26H); ^{13}C NMR: δ 104.1 (C-1′), 97.5 (C-1″), 83.2 (C-3,4), 83.0 (C-2,5), 79.4 (C-3′), 78.9 (C-2′), 77.7 (C-3″), 76.5 (C-2″), 76.2, 76.1 (C-5′,4″), 75.1 (C-4′), 72.7 (C-5″), 71.4 (C-1,6), 70.3 (C-6′), 69.0 (C-6″). Anal. Calcd for $C_{30}H_{36}O_{73}S_{16}K_{16}$: C, 13.33; H, 1.33; S, 18.96; K, 23.10. Found: C, 12.85; H, 1.72; S, 18.56; K, 22.88.

1.43. 2,5-Anhydro-3,4-di-*O*-benzoyl-1,6-bis-*O*-[6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl]-D-mannitol (50)

Prepared according to the general procedure A from **24** (4.16 g, 6 mmol) and **30** (1.0 g, 2.7 mmol) to give after column chromatography (E) **50** (2.1 g, 48%) as syrup, R_f 0.4; $[\alpha]_D$ −17 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{72}H_{88}O_{41}$: C, 53.73; H, 5.51. Found: C, 54.06; H, 5.80.

1.44. 2,5-Anhydro-1,6-bis-*O*-[6-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl]-D-mannitol (51)

Prepared according to the general procedure B from **50** (2.0 g, 1.24 mmol). The residue obtained on concentration of the methanolic soln was partitioned between water and CH_2Cl_2 for removing the methyl benzoate. The aq soln was freeze-dried to give after column chromatography (G) **51** (0.80 g, 80%) as solid foam, $[\alpha]_D$ −8 (*c* 1, water). Anal. Calcd for $C_{30}H_{52}O_{25}$: C, 44.34; H, 6.45. Found: C, 44.62; H, 6.59.

1.45. 2,5-Anhydro-1,6-bis-*O*-[6-*O*-(2,3,4,6-tetra-*O*-sulfato-α-D-glucopyranosyl)-2,3,4-tri-*O*-sulfato-β-D-glucopyranosyl]-D-mannitol hexadeca-*O*-sulfate hexadeca potassium salt (52)

Prepared according to the general procedure C and E from **51** (0.7 g, 0.86 mmol) to give **52** (1.9 g, 82%), $[\alpha]_D$ 0 (*c* 1, water); ^{1}H NMR: δ 5.00 (m, 2H, H-3,4), 4.90–4.81 (m, 4H, H-1′,1″), 4.70–4.13 (m, 22H), 4.03–3.89 (m, 8H); ^{13}C NMR: δ 104.0, 103.9 (C-1,1′), 83.0 (C-3,4), 82.3 (C-2,5), 80.3, 79.9, 79.1, 79.1 (C-2′,3′,2″,3″), 76.2, 76.2, 76.0, 75.6 (C-4′,5′,4″,5″), 72.2 (C-1,6), 71.6, 70.4 (C-6′,6″). Anal. Calcd for $C_{30}H_{36}O_{73}S_{16}K_{16}$: C, 13.33; H, 1.33; S, 18.96; K, 23.10. Found: C, 12.62; H, 1.82; S, 17.48; K, 21.41.

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