Tetrahedron 68 (2012) 7386–7399

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of the non-reducing end trisaccharide of the antithrombin-binding domain of heparin and its bioisosteric sulfonic acid analogues

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ARTICLE INFO

Article history:
Received 9 February 2012
Received in revised form 5 June 2012
Accepted 20 June 2012
Available online 4 July 2012

Keywords:
Blood coagulation
Heparinoid trisaccharides
D-Glucuronic acid
Sulfonatomethyl analogues
Glycosylation

ABSTRACT

A glucoronic acid-containing trisaccharide related to the antithrombin-binding DEFGH domain of heparin and its methanesulfonic acid analogues were synthesized. Trisaccharides without sulfonic acid content or possessing a sulfonatomethyl moiety at position 2 or 6 of unit F were prepared in high yields by [DE+F] couplings using the same disaccharide uronate donor, respectively. Synthesis of the trisaccharide with a 3-deoxy-3-sulfonatomethyl function was accomplished in three different pathways, from which a [D+EF] coupling and applying a non-oxidized precursor of the glucuronic acid afforded the trisaccharide in the highest yield.

1. Introduction

Heparin is a well-known blood anticoagulant employed extensively in medical practice.[1] Heparin and its fractionated derivatives (low molecular weight heparins, LMWHs) exert their anticoagulant activity by binding to the enzyme inhibitor antithrombin III (AT-III), which results in the inactivation of thrombin and factor Xa in the blood-coagulation cascade.[2] Heparin therapy is limited to intravenous administration and can be associated to cases of bleeding, liver toxicity and heparin induced thrombocytopaenia (HIT) due to the highly polyanionic and heterogeneous nature of the polysaccharide obtained from animal organs.[3]

After the AT-III-binding DEFGH pentasaccharide domain of heparin (**1**) was identified,[4] its closely related synthetic analogue, completely free of HIT activation has been developed into a novel antithrombotic (Arixtra, **2**).[5,6] This pentasaccharide selectively inhibits factor Xa and minimizes the bleeding risk and many other unfavourable factors in anticoagulant therapy. However, its synthesis was accomplished through a multistep and low-yielding procedure. Further research efforts directed at development of selective factor Xa inhibitors with simplified structure resulted in idraparinux[7] (**3**), a non-glycosaminoglycan derivative, possessing increased anticoagulant activity than Arixtra. It turned out, however, that the extremely long elimination half-life of idraparinux (~60 days) may lead to serious bleeding complications, therefore its development was terminated in the last phase of clinical trials.[8] Thus, the need for new synthetic anticoagulants with fewer adverse effects and feasible synthesis persists (Fig. 1).

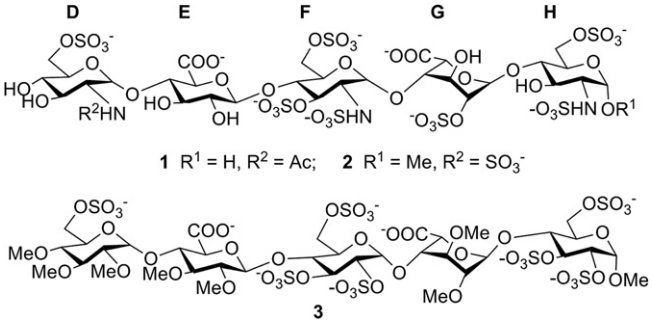

Fig. 1. Structures of the antithrombin-binding domain of heparin (**1**), the synthetic antithrombotic drug Arixtra (**2**) and the non-glycosaminoglycan anticoagulant pentasaccharide idraparinux (**3**).

Structure–activity relationship studies of synthetic analogues of the heparin pentasaccharide revealed that the type of the charged groups is crucial for the activation of AT-III, an essential sulfate group cannot be replaced by a phosphate, and the carboxylate

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0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.06.081

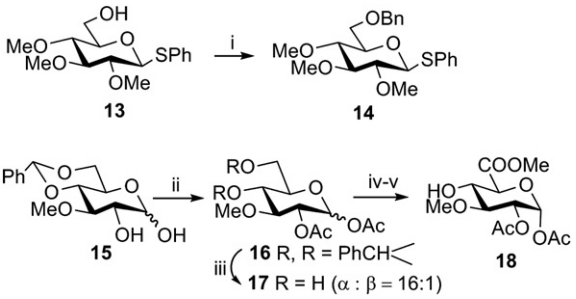
groups may not be exchanged for CH_2OSO_3-residues.[9] Replacement of the sulfate groups with isosteric sulfonatomethyl moieties has not been investigated previously.

In order to obtain novel selective factor Xa inhibitors and to acquire further information on the structure–activity relationship of the antithrombotic action of heparin we decided to prepare sulfonatomethyl-containing analogues of the heparin pentasaccharide by systematic replacement of the sulfate esters with a sodium sulfonatomethyl moiety. Idraparinux (**3**) was chosen as a reference compound, due to its high anticoagulant activity and feasible synthesis. In the frame of this work EF- and GH-disaccharide fragments of compound **3**, and their sulfonic acid analogues possessing a primary or a secondary sulfonatomethyl function have been prepared.[10] Two pentasaccharide sulfonic acids, in which two or three primary sulfate esters of **3** were replaced with a sodium sulfonatomethyl group have also been prepared recently.[11] Both inhibited the blood coagulation proteinase factor Xa, and the disulfonate analogue displayed outstanding inhibitory activity, providing the evidence, for the first time, that sulfate esters could be replaced by an isosteric sulfonic acid moiety without detriment to the anticoagulant activity.

Preliminary results on the synthesis of sulfonic acid analogues of the DEF trisaccharide, carrying the sulfonatomethyl group at primary or secondary position, were also published recently.[12] Here, we describe the preparation of the DEF unit and its three sulfonic acid analogues in detail.

2. Results and discussion

The synthesis of the targeted DEF trisaccharide **9** and its three regioisomeric sulfonatomethyl analogues **10**–**12** was planned by coupling reactions of the common DE disaccharide **4** with acceptors **5**–**8**, respectively. To ensure the stereoselective formation of the 1,2-*trans*-interglycosidic linkage between the units E and F, the donor was equipped temporarily with a 2-*O*-acetyl group. Hydroxyl groups, which have to be sulfated were protected in form of benzyl ethers (Scheme 1).

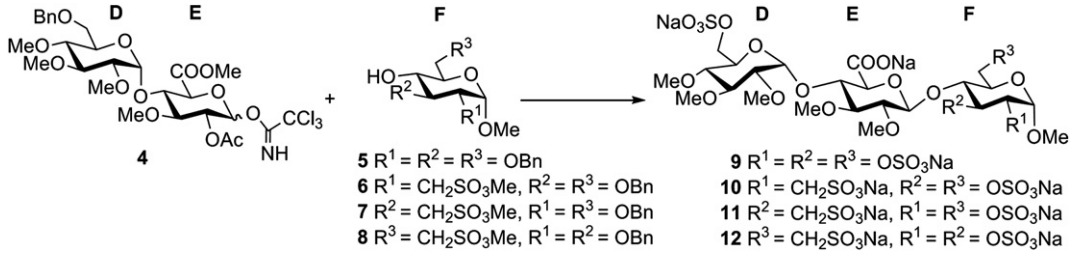


Scheme 2. Synthesis of the monosaccharide building blocks. Reagents and conditions: (i) BnBr, NaH in DMF (96%); (ii) Ac_2O, pyridine (93%); (iii) AcOH 80%, 70 °C (88%); (iv) TEMPO, $Ca(ClO)_2$, CH_2Cl_2, $NaHCO_3$, KBr, Bu_4NBr; (v) CH_2N_2 (Et_2O), THF (59%).

The stereoisomeric disaccharide **19**β formed as a minor product was also isolated in a yield of 4%. Selective deacetylation of the anomeric position of **19**α with benzylamine furnished the hemiacetal **20**, treatment of which with trichloroacetonitrile and DBU resulted in the corresponding imidate **4** in high yield (Scheme 3).[17]

The coupling reaction of compound **4** and acceptor **5**[18] upon TMSOTf activation afforded trisaccharide **21**, exclusively in the β-coupled form due to the presence of the 2-*O*-acetyl participating group of the donor. Unmasking of the 2′-OH group of **21** under Zemplén conditions furnished **22**. Attempted standard methylation using methyl iodide and sodium hydride led to complete loss of the ultimate glucose unit due to β-elimination of the base-sensitive uronic acid residue, thus resulting in a mixture of **23** and **24**.[10b] The elimination side reaction could be avoided by silver(I) oxide assisted methylation[19] affording the desired **25** in 79% yield (Scheme 4).

Deprotection of the carboxylic ester function by saponification (→**26**) and subsequent removal of the benzyl ethers by catalytic hydrogenolysis afforded the tetrahydroxy derivative **27** in high yield. O-Sulfation was achieved using SO_3·pyridine to give compound **9**, the non-reducing end trisaccharide fragment of the AT-III-binding pentasaccharide (Scheme 5).



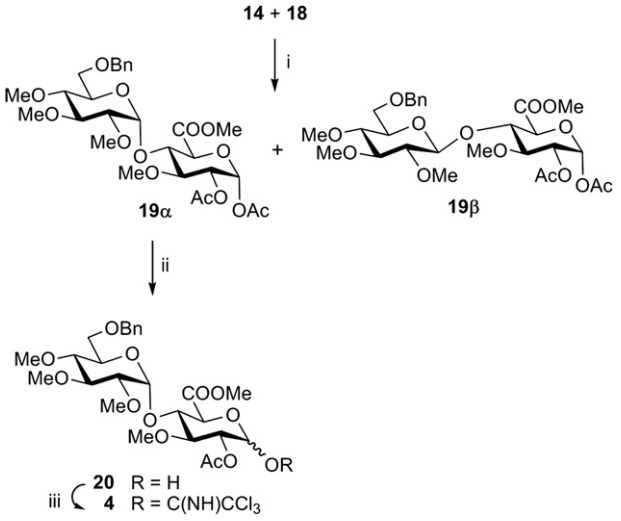
Scheme 1. Synthetic plan for **9**–**12**.

The non-reducing end building block **14**[12] was prepared from phenyl 2,3,4-tri-*O*-methyl-1-thio-β-D-glucopyranoside (**13**)[13] by benzylation. Synthesis of the uronate acceptor **18** started from the known crystalline **15**.[14] Acetylation and subsequent deacetalation of **15** afforded the 4,6-diol derivative **17**. (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO)-based selective oxidation[15] of **17** using calcium hypochlorite as co-oxidant[16] afforded the intermediate glucuronate which, after acidic work-up procedure, was treated with ethereal diazomethane to result in the methyl ester **18**. The product could be isolated in pure α-anomeric form by chromatographic purification (Scheme 2).

Condensation of the D-glucuronate acceptor **18** with phenylthioglucoside **14** in the presence of NIS and AgOTf at −45 °C gave the desired disaccharide **19**α with high stereoselectivity, probably due to the low reactivity of the uronic acid acceptor, that benefits the formation of the more thermodynamically favoured α-coupled product.

The synthesis of the methylsulfonatomethyl-containing acceptors (**6**–**8**) was described recently,[10] the key step in their preparation being the regio- and stereoselective addition of sulfate radical anion onto the exomethylene moiety of the appropriate glycoside derivatives.[20]

Glycosylation of the 2-deoxy-2-methylsulfonatomethyl-containing acceptor **6** with disaccharide imidate **4** upon trimethylsilyl triflate activation afforded trisaccharide **28** in a stereoselective manner. The fully protected trisaccharide was deacetylated under Zemplén conditions to give **29** with a free hydroxyl group on the uronic acid residue. Recent work from this laboratory showed that the sulfonatomethyl-containing uronate derivatives proved to be significantly more stable under the basic conditions of methylation than the non-sulfonic acid uronates.[10b] Thus, **29** was subjected to standard methylation using methyl iodide and sodium hydride. The reaction resulted in exclusively the desired 2′-*O*-methyl derivative

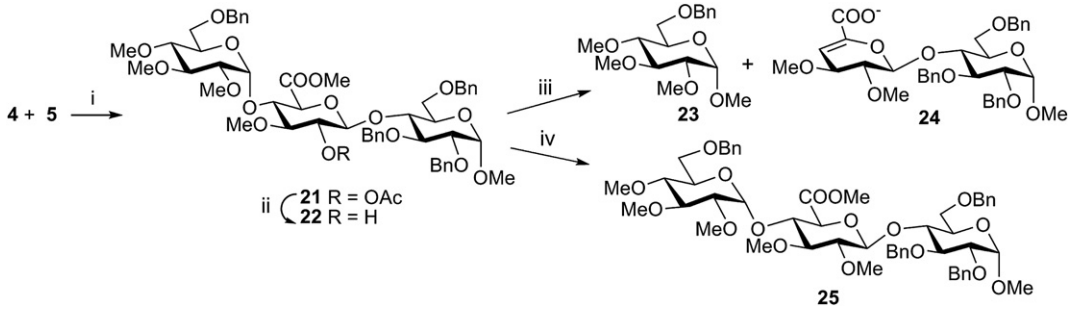


Scheme 3. Formation of the disaccharide uronate donor **4**. Reagents and conditions: (i) CH_2Cl_2, NIS, AgOTf, MS, −45 °C, 1 h (72% for **19**α, 4% for **19**β); (ii) THF, $BnNH_2$, rt, 5 h (92%); (iii) CH_2Cl_2, CCl_3CN, DBU, 0 °C, 30 min (85%).

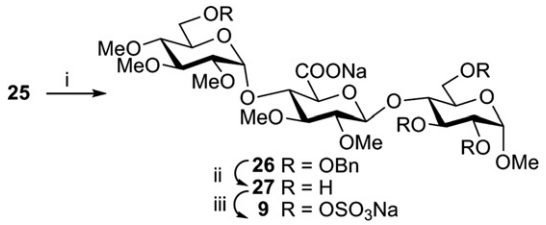
afforded the corresponding trisaccharide **36** as an inseparable 1:1 mixture of the α- and the β-coupled products, despite the presence of the *C*-2 participating group at the donor. The unexpected formation of the α-linkage could be explained by the steric mismatch between the acetoxonium ion intermediate formed from the donor and the sulfonatomethyl-containing acceptor, which disfavours the formation of the β-linkage that normally would be promoted by ester neighbouring group participation. Treatment of the stereoisomeric mixture with sodium methoxide under Zemplén conditions[21] resulted in chemoselective deacetylation of **36**α, and the desired **36**β could be separated by column chromatography in a yield of 30%. Although the following transformations leading to trisaccharide **11**[12] took place smoothly and with high yields, the overall yield of the synthesis depicted on Scheme 8 was only 14%.

In order to improve the yield of the desired trisaccharide **11**, two novel synthetic routes were elaborated based on the concept that a non-oxidized precursor of unit E could be coupled to **7**, and oxidation to a uronic acid would then carried out at an oligosaccharide level.

Our first approach was to keep the original [DE+F] coupling sequence applying the new disaccharide donor **44** and to create the carboxylic function of unit E at a trisaccharide level. The synthesis



Scheme 4. Construction of the model trisaccharide. Reagents and conditions: (i) CH_2Cl_2, TMSOTf, −30 °C to rt, 2 h (74%); (ii) MeOH, MeONa (86%); (iii) NaH, MeI, DMF (36% for **23**, 76% for **24**); (iv) Ag_2O, MeI, DMF, 48 h (79%).



Scheme 5. Synthesis of the model trisaccharide. Reagents and conditions: (i) 0.1 M NaOH, MeOH (94%); (ii) 10% Pd/C, H_2 (91%); (iii) SO_3·pyridine, DMF (61%).

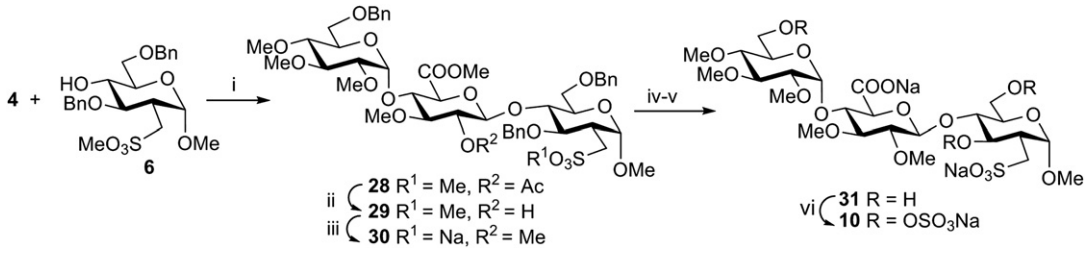
30 and β-elimination did not occur. In addition, transformation of the sulfonic acid methyl ester into sodium sulfonate moiety also took place as a result of nucleophilic attack of the in situ formed sodium iodide. Then, hydrolysis of the uronic ester with sodium hydroxide, followed by catalytic hydrogenation of the benzyl groups resulted in **31**. O-Sulfation of the triol derivative using SO_3·pyridine afforded trisaccharide **10**,[12] as the first isosteric sulfonatomethyl analogue of the DEF fragment of Idraparinux (Scheme 6).

Synthesis of trisaccharide **12** was accomplished in an analogous fashion, using acceptor **8**[10] possessing the sulfonic acid moiety at position 6. Coupling of **4** and **8** gave the desired trisaccharide **32**. Its transformation through a five-step procedure via **33**–**35** furnished the target trisaccharide sulfonic acid **12**[12] (Scheme 7).

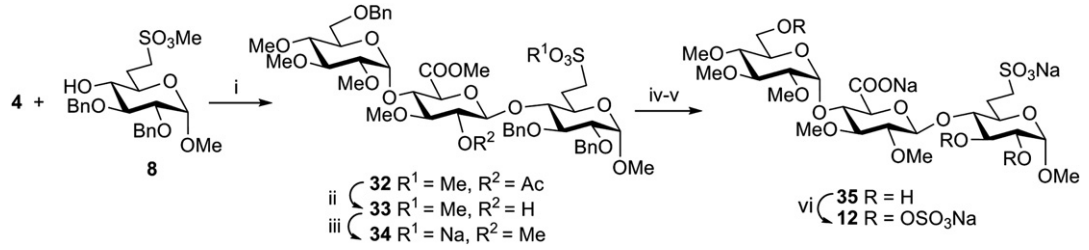
Preparation of trisaccharide **11** was also attempted by a [DE+F] coupling using donor **4** and acceptor **7**.[10] However, glycosylation of compound **7** possessing the sulfonatomethyl moiety at position 3 of the new building block started from phenyl 1-thio-β-D-glucopyranoside **40**, whose (2-naphthyl)methylenation (**41**) and subsequent acetylation afforded the fully protected **42**. Regioselective cleavage of the 4,6-*O*-acetal ring using Et_3SiH and $BF_3 \cdot Et_2O$ resulted in the acceptor **43** in 82% yield. The coupling reaction of the thioglucosides **43** and **14** in the presence of NIS and AgOTf furnished, chemoselectively, the new DE donor **44** (Scheme 9).

Glycosylation of acceptor **7** with the thioglycoside donor **44** upon NIS–AgOTf activation gave rise to the stereoselective formation of **45** with the required β-linkage between units E and F. The 6′-position, which has to be oxidized was unmasked using DDQ as a reagent,[22] and the product **46** was transformed by TEMPO–[bis(acetoxy)iodo]benzene (BAIB) oxidation[23] and subsequent treatment with ethereal diazomethane into the fully protected trisaccharide **47** possessing both the uronic and sulfonic acid functions. This synthesis route provided **47** with 19% overall yield from the monosaccharide building blocks **40**, **14** and **7** (Scheme 10).

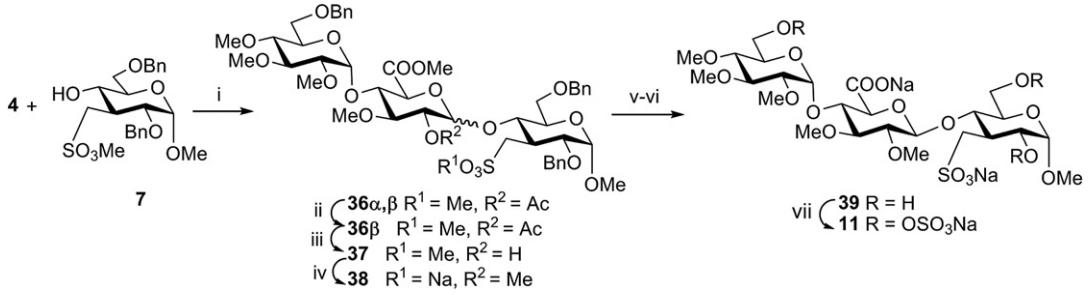
Using the same starting compounds the synthesis of **47** was also accomplished via another synthetic route involving a reverse sequence of glycosylations and oxidation to a carboxylate at the disaccharide level. Treatment of compound **40** with 4-methoxybenzaldehyde upon acid catalysis furnished the diol **48**,[24] whose acetylation gave **49**, as a new non-oxidized precursor of the uronic acid residue. Glycosylation of acceptor **7** with donor **49** in the presence of the NIS–AgOTf promoter system gave exclusively the β-coupled disaccharide **50** in good yield. This reaction demonstrated again, that it was not the 3-sulfonatomethyl moiety per se, but the interaction between the carboxylate and sulfonate



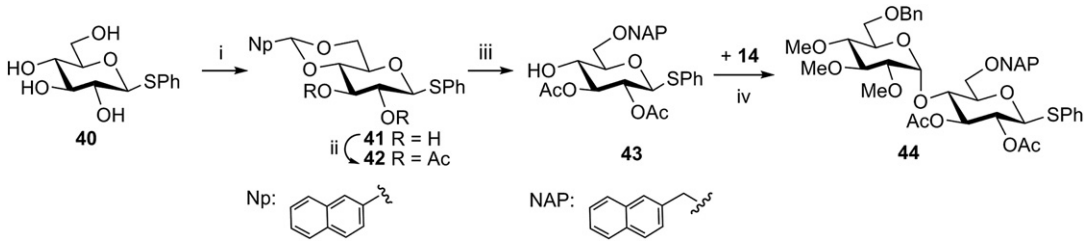
Scheme 6. Synthesis of trisaccharide sulfonic acid **10**. Reagents and conditions: (i) CH_2Cl_2, TMSOTf, −30 °C to rt, 12 h (67%); (ii) MeOH, MeONa (80%); (iii) NaH, MeI, DMF (90%); (iv) 0.1 M NaOH, MeOH (92%); (v) 10% Pd/C, H_2, EtOH (98%); (vi) SO_3·py, DMF (81%).



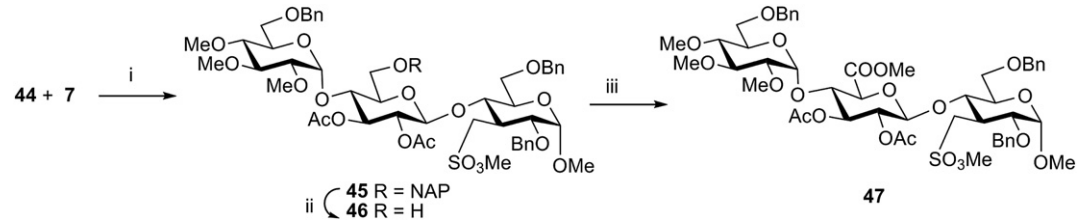
Scheme 7. Synthesis of trisaccharide sulfonic acid **12**. Reagents and conditions: (i) CH_2Cl_2, TMSOTf, −30 °C to rt, 12 h (61%); (ii) MeOH, MeONa (88%); (iii) NaH, MeI, DMF (89%); (iv) 0.1 M NaOH, MeOH (92%); (v) 10% Pd/C, H_2, EtOH (98%); (vi) SO_3·py, DMF (81%).



Scheme 8. Construction of trisaccharide **11** by using uronate donor **4**. Reagents and conditions: (i) CH_2Cl_2, TMSOTf, −30 °C to rt, 12 h (80%, α/β ~1:1); (ii) MeOH, MeONa, 1 h (chemoselective deacetylation of **36**α), then chromatographic separation (30% for **36**β); (iii) MeOH, MeONa (71%); (iv) NaH, MeI, DMF (82%); (v) 0.1 M NaOH, MeOH; (vi) H_2, 10% Pd/C, H_2, EtOH (97% over two steps); (vii) SO_3·py, DMF (81%).

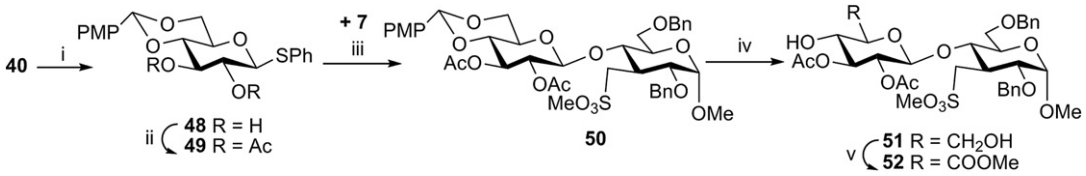


Scheme 9. Formation of the new DE donor by chemoselective glycosylation. Reagents and conditions: (i) 2-naphthaldehyde dimethyl acetal, *p*-toluenesulfonic acid, CH_3CN, reflux (87%); (ii) Ac_2O, pyridine (91%); (iii) Et_3SiH, BF_3·Et_2O, CH_2Cl_2, 0 °C, 30 min (82%); (iv) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −75 °C, 30 min (71%).



Scheme 10. Construction of the 3-sulfonomethyl-containing trisaccharide by DE+F coupling and post-glycosidation oxidation. Reagents and conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −20 °C to 10 °C, 30 min (73%); (ii) DDQ, CH_2Cl_2: H_2O (9:1), 30 min (84%); (iii) BAIB, TEMPO, CH_2Cl_2, H_2O, 1 h; CH_2N_2·Et_2O, THF (68%).

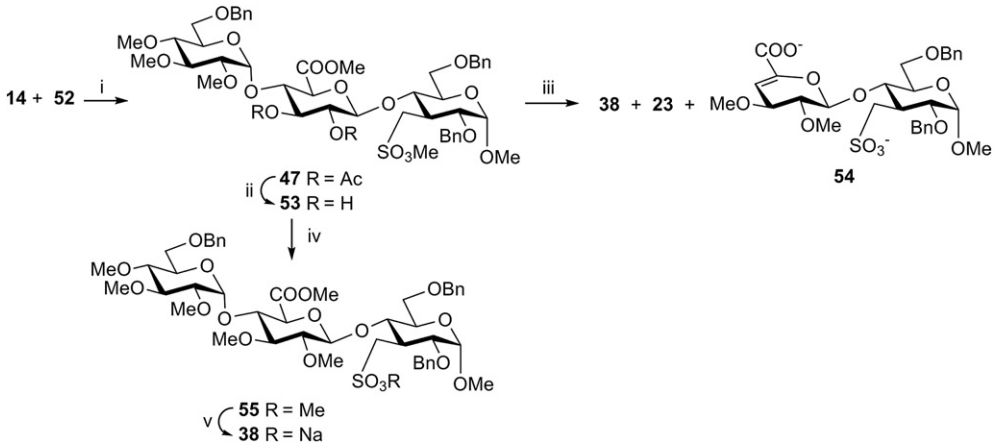
moieties, which unfavourably influenced the glycosylation of **4** and **7**. Deacetalation of the fully protected **50** was carried out under mild conditions due to the high acid sensitivity of the 4-methoxybenzylidene protecting group. TEMPO–BAIB based selective oxidation[25] of **51** gave, after methyl-esterification of the caboxylic acid moiety, the uronate acceptor **52** (Scheme 11).



Scheme 11. Formation of the uronate-containing EF disaccharide **51** by post-glycosidation oxidation. Reagents and conditions: (i) 4-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, CH_3CN, reflux (82%); (ii) Ac_2O, pyridine (94%); (iii) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −20 °C to rt, 1 h (68%); (iv) 80% AcOH, rt, 1 h (81%); (v) BAIB, TEMPO, CH_2Cl_2, H_2O, 1 h, $CH_2N_2{\cdot}Et_2O$, THF (79%).

Glycosylation of the disaccharide acceptor **52** with the thioglycoside donor **14** afforded the desired trisaccharide **47** in high yield. In this case, the overall yield of **47** starting from **40**, **14** and **7** was 29%. It is worth mentioning, that both of the above syntheses of **47** were considerably more effective than the first approach, which provided the corresponding fully protected trisaccharide **36**β in a yield of only 8% starting from the monosaccharides **14**, **15** and **7**. Removal of the *O*-acetyl groups of **47** resulted in the formation of diol **53**. Usual methylation of the liberated hydroxyls with sodium hydride and methyl iodide gave the desired product **38** in a yield of only 49%, and side-products **23** and **54** were also formed, as a result of β-elimination of the base-sensitive uronic acid residue (Scheme 12.). It is interesting to note that in the previous reactions when only one methyl ether had to be introduced into the sulfonic acid-containing trisaccharides **29**, **33** and **37** (Schemes 6–8), the uronic acid residue remained intact under the harsh basic conditions.

ever, this approach was inefficient for the synthesis of the 3-sulfonatomethyl-containing analogue **11** because of the steric hindrance emerged between the carboxylate group of the donor and the sulfonate moiety of the acceptor next to the glycosylation position. For **11**, two improved synthetic routes were carried out, in which the unfavourable steric effect was overcame by application of a non-oxidized precursor of unit E to couple to **7**, and the carboxylic acid function was formed at an oligosaccharide level. Both novel syntheses started from the same monosaccharide building blocks **7**, **14** and **40**. The first approach was based on a [DE+F] coupling using a non-glucuronide DE donor and oxidation of unit E into uronic acid at a trisaccharide level. The other route involved a [D+EF] coupling applying a glucuronide-containing EF acceptor obtained by post-glycosidation oxidation at a disaccharide level. Both routes resulted in a significant improvement in the yield of compound **11**, due to the



Scheme 12. Synthesis of trisaccharide sulfonic acid **11** by D+EF coupling. Reagents and conditions: (i) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −45 °C to −35 °C, 1 h (84%); (ii) MeOH, MeONa (85%); (iii) NaH, MeI, DMF (49% for **38**, 36% for **23** and 39% for **54**); (iv) $CH_2N_2{\cdot}Et_2O$, silica gel, THF (61%); (v) NaI, acetone, rt, 12 h (96%).

To avoid the β-elimination side reaction, methylation of **53** was carried out under slightly acidic conditions applying diazomethane in the presence of silica gel.[26] The silica gel promoted etherification afforded the desired product **55** in a yield of 61%. Deprotection of the sulfonic acid ester by nucleophilic substitution with sodium iodide in acetone gave the sodium salt **38**, which was an intermediate also in the first synthesis route of **11** depicted in Scheme 8.

3. Conclusion

In summary, the DEF trisaccharide fragment of idraparinux and its three methanesulfonic acid analogues in which the sulfate high yielding glycosylations as well as the avoidance of the laborious synthesis of the glucuronic acceptor **18**; the [D+EF] coupling sequence provided the most effective and shortest way to achieve **11**.

As it has been found earlier, the sulfonatomethyl-containing uronate derivatives proved to be significantly more stable under the sodium hydride mediated methylation than the non-sulfonic acid uronate. It turned out, however, that the tendency of base-sensitive uronates to β-elimination is considerably affected by the number of hydroxyls meant to be methylated. The role of sulfonic acid moieties in stabilizing the uronic acid units towards base is worth further investigation.

4. Experimental

4.1. General information

Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by immersing into 5% ethanolic sulfuric acid solution followed by heating. Column chromatography was performed on Silica gel 60 (Merck 0.063–0.200 mm) and Sephadex LH-20 (Sigma–Aldrich, bead size 25–100 μ). Organic solutions were dried over $MgSO_4$, and concentrated in vacuum. The ^1H (200, 360, 400 and 500 MHz) and ^{13}C NMR (50.3, 90.54, 100.28, 125.76 MHz) spectra were recorded with Bruker AC-200, Bruker DRX-360, Bruker DRX-400 and Bruker DRX-500 spectrometers. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^1H) or to the residual solvent signals ($CDCl_3$: 77.00 ppm and CD_3OD: 49.05 for ^{13}C). IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed-ion extraction. The matrix solution was a satd 2,4,6-trihydroxy-acetophenone (THAP) solution in MeCN. Elemental analyses (C, H, S) were performed using an Elementar Vario MicroCube instrument.

4.2. General method A for acetylation (16, 42, 49)

A solution of the appropriate diol (10.0 mmol of **15**, **41** and **48**) in pyridine (10 mL) was cooled to 0 °C, and then Ac_2O (5.00 mL, 52.9 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, and then was poured into ice water. After 30 min stirring the precipitated product was filtered off and washed with water (3×50 mL).

4.3. General method B for glycosylation of uronate acceptor with phenylthio-glucoside (19, 44, 45, 47, 50)

To a mixture of the appropriate 4-OH (0.500 mmol of **7**, **18**, **43** and **52**), and phenylthio-glucoside derivative (0.600 mmol of **14**, **44** and **49**) in dry CH_2Cl_2 (10 mL) 4 Å molecular sieves (0.5 g) were added. The mixture was stirred under argon for 30 min at rt, then cooled (to −45 °C for **18**+**14** and **52**+**14**, to −75 °C for **43**+**14**, to −20 °C for **7**+**44** and to −10 °C for **7**+**49**). After 20 min at this temperature, NIS (135 mg, 0.600 mmol) dissolved in THF (500 μl) and AgOTf (31.0 mg, 0.121 mmol) dissolved in toluene (500 μl) were added. When TLC indicated a complete conversion (30 min to 1 h), Et_3N (50 μl) was added. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and filtered through a pad of Celite. The filtrate was washed successively with 10% aq $Na_2S_2O_3$ (10 mL), H_2O (10 mL), aq $NaHCO_3$ (10 mL) and H_2O again (10 mL), dried and concentrated.

4.4. General method C for glycosylation reaction using imidate derivative as a donor (21, 28, 32, 36α,β)

A mixture of the appropriate 4-OH derivative (0.500 mmol of **5**, **6**, **8** and **7**), imidate **4** (527 mg, 0.750 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (7 mL) was stirred for 15 min at room temperature, then cooled to −20 °C under argon. TMSOTf (0.1 M in CH_2Cl_2, 0.750 mL, 0.075 mmol) was added, and the reaction mixture was allowed to warm up to 0 °C in 2 h. After completion of the reaction it was quenched by addition of Et_3N (0.15 mL). The reaction mixture was then filtered and concentrated.

4.5. General method D for deacetylation (22, 29, 33, 37, 53)

To a solution of the appropriate trisaccharide derivative (0.500 mmol of **21**, **28**, **32**, **36**β and **47**) in MeOH (10 mL), NaOMe (14.0 mg, 0.259 mmol) was added. The reaction mixture was stirred 5–10 h and monitored by TLC. After the complete disappearance of the starting material the mixture was filtered, and concentrated.

4.6. General method E for cleavage of the benzyl groups by catalytic hydrogenation (27, 31, 35, 39)

A mixture of the starting compound (0.500 mmol of **26**, **30a**, **34a** and **38a**) in 96% EtOH/AcOH (19:1, 20 mL), and Pd/C (10%, 120 mg) was stirred in an autoclave under H_2 atmosphere (at 10 bar) for 12 h. The catalyst was filtered off through a pad of Celite and the filtrate was concentrated.

4.7. General method F for introduction of the sulfate ester groups (9, 10, 11, 12)

A solution of the trisaccharide triol or tetraol (0.500 mmol of **27**, **31**, **35** and **39**) in DMF (4 mL) was treated with the SO_3·pyridine complex (5.00 equiv/OH) for 5 h at room temperature, then cold satd $NaHCO_3$ solution was added in excess (pH>7). The resulting mixture was concentrated in vacuo. Then MeOH (10 mL) was added and after stirring for 20 min the insolubles were removed by filtration and the filtrate was concentrated.

4.8. General method G for introduction of the methyl groups using MeI and NaH (23, 24, 30, 34, 38)

To a solution of the starting trisaccharide (0.500 mmol of **22**, **29**, **33**, **37** and **53**) in DMF (5 mL) at 0 °C were successively added NaH (2.00 equiv/OH) and MeI (1.50 equiv/OH). After 2 h stirring at this temperature, MeOH (1 mL) was added. The reaction mixture was stirred for 15 min, then the solvents were evaporated.

4.9. General method H for TEMPO–BAIB oxidation and subsequent esterification (47, 52)

To a vigorously stirred solution of the appropriate alcohol (0.100 mmol, **46** and **51**) in CH_2Cl_2 (1 mL) and H_2O (0.5 mL) were added TEMPO (3.00 mg, 0.019 mmol) and BAIB (2.50 equiv for **51**, and 4.00 equiv for **46**). The reaction mixture was quenched by the addition of 10% aq $Na_2S_2O_3$ solution (4 mL). The mixture was then extracted twice with CH_2Cl_2 (10 mL), and the combined organic layers were dried, and concentrated. The crude glucuronic acid was dissolved in THF (3 mL) and treated with diazomethane in ether at 0 °C. After complete disappearance of the glucuronic acid, the mixture was concentrated.

4.10. Phenyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-1-thio-β-D-glucopyranoside (14)[12]

To a solution of **13**[13] (5.00 g, 15.9 mmol) in DMF (80 mL) at 0 °C NaH (60%, 954 mg, 23.9 mmol) was added in portion. After 30 min stirring at this temperature, BnBr (2.27 mL, 19.1 mmol) was added, and the reaction mixture was allowed to warm up to rt. After completion of the reaction (4 h), MeOH (10 mL) was added. The reaction mixture was stirred for 15 min, then the solvents were evaporated. The residue was diluted with CH_2Cl_2 (300 mL), washed with H_2O (3×100 mL), dried and concentrated. The crude product was purified by silica gel chromatography (7:3 *n*-hexane/EtOAc) to give **14**[12] (6.17 g, 96%) as a white powder; R_f 0.33 (6:4 *n*-hexane/EtOAc).

4.11. 1,2-Di-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-methyl-D-glucopyranose (16)

Compound **15**[14] (2.40 g, 8.50 mmol) was converted to **16** by method *A* to give 2.90 g (93%) of **16** (α/β ~15:1) as a white powder;

mp: 106–108 °C; $[\alpha]_D^{25}$ +76.5 (*c* 0.20, $CHCl_3$); $R_{f\alpha,\beta}$ 0.42 (7:3 *n*-hexane/EtOAc); IR ν_{max} (KBr): 3465, 2868, 1748, 1638, 1451, 1373, 1240, 1219, 1176, 1146, 1096, 1073, 1027, 978, 941, 759, 701, 545 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.50–7.37 (m, 5H, arom), 6.27 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1α), 5.58 (s, 1H, C*H*Ph), 5.72 (d, 1H, $J_{1,2}$ 8.1 Hz, H-1β), 4.99 (dd, 1H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.99–3.92 (m, 1H), 3.80–3.66 (m, 4H), 3.60 (s, 3H, OCH_3), 2.16, 2.08 (2s, 6H, 2×CH_3) ppm; ^{13}C NMR of the α isomer ($CDCl_3$, 90 MHz): δ=169.8, 169.0 (2×*C*O), 136.9 (C_q arom), 129.0, 128.2, 128.2, 125.9, 125.9 (5C, arom), 101.3 (*C*HPh), 89.8 (C-1), 81.4, 77.3, 71.0 (C-2, C-3, C-4), 68.5 (C-6), 64.8 (C-5), 60.8 (OCH_3), 20.8, 20.6 (2×CH_3) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 398.12. Found: 398.39. Anal. Calcd for $C_{18}H_{22}O_8S$ (366.36): C, 59.01; H, 6.05. Found: C, 59.09; H, 6.01.

4.12. 1,2-Di-*O*-acetyl-3-*O*-methyl-D-glucopyranose (17)[12]

A solution of **16** (19.0 g, 51.9 mmol) in AcOH (80%, 100 mL) was stirred for 3 h at 70 °C. The mixture was then concentrated in vacuo. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2/CH_3OH) to give **17** (12.7 g, 88%) as a colourless syrup; R_f 0.34 (95:5 CH_2Cl_2/CH_3OH).

4.13. Methyl-1,2-di-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyluronate (18)[12]

To a solution of **17** (11.3 g, 40.6 mmol) in CH_2Cl_2 (62 mL) containing TEMPO (157 mg, 1.00 mmol) was added a solution of satd aq $NaHCO_3$ (41 mL) containing KBr (2.23 g, 18.7 mmol) and Bu_4NBr (935 mg, 2.90 mmol). The mixture was cooled to 0 °C, and then $Ca(ClO)_2$ (17.6 g, 123 mmol) was added slowly in portions under vigorous stirring. After 20 min of vigorous stirring at 0 °C the reaction was quenched by the addition of a satd solution of NaCl (41.5 mL) and $NaHSO_3$ (15.9 g). After further stirring for 5 min, AcOH was added to adjust the final pH value of the mixture to pH 3. The resulting mixture was diluted with EtOAc (100 mL). The organic phase was separated and the remaining aqueous phase was extracted with EtOAc. The combined organic phase was dried and concentrated under reduced pressure. The crude glucuronic acid was dissolved in THF (62 mL) and treated with diazomethane in ether at 0 °C. After complete disappearance of the glucuronic acid, the mixture was concentrated. The crude product was purified by silica gel chromatography (8:2 CH_2Cl_2/EtOAc) to give **18**[12] (7.11 g, 59%) as a colourless syrup; R_f 0.37 (7:3 *n*-hexane/EtOAc).

4.14. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-1,2-di-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyluronate (19α) and methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-β-D-glucopyranosyl)-(1→4)-1,2-di-*O*-acetyl-3-*O*-methyl-α-D-glucopyranosyluronate (19β)

Compound **18** (200 mg, 0.653 mmol) was glycosylated with **14** (317 mg, 0.784 mmol) according to general method *B*. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2/acetone) to give a mixture of **19**α and **19**β (325 mg, 82%). This mixture was separated by silica gel chromatography (7:3 *n*-hexane/EtOAc) to give **19**α[12] (282 mg, 72%; R_f 0.41 in 6:4 *n*-hexane/acetone) and **19**β (16.0 mg, 4%) as a colourless oil.

Compound ***19****β*: $[\alpha]_D^{25}$ +48.7 (*c* 0.12, $CHCl_3$); R_f 0.33 (6:4 *n*-hexane/acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ=7.34–7.27 (m, 5H, arom), 6.29 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.97 (dd, 1H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.4 Hz, H-2), 4.62, 4.56 (2d, 2H, *J* 12.0, 12.0 Hz, CH_2Ph), 4.30 (d, 1H, $J_{4,5}$ 9.3 Hz, H-5), 4.29 (d, 1H, $J_{1',2'}$ 7.7 Hz, H-1′), 4.07 (dd, 1H, *J* 8.6, 9.2 Hz), 3.80 (s, 3H), 3.74–3.66 (m, 3H), 3.61 (s, 3H), 3.51–3.49 (m, 9H), 3.29–3.20 (m, 2H), 3.11 (dd, 1H, *J* 8.8, 8.6 Hz), 2.90 (dd, 1H, *J* 7.9, 8.9 Hz), 2.16, 2.06 (2s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=169.7, 168.7, 168.5 (3×*C*O), 138.3 (C_q arom), 128.3, 128.3, 127.6, 127.6, 127.5 (5C, arom), 103.5 (C-1′), 89.3 (C-1), 86.7, 83.9, 79.2, 78.4, 78.2, 74.8, 72.7, 70.2 (8C, skeleton carbons), 73.4 (*C*H_2Ph), 68.8 (C-6′), 60.7, 60.6, 2×60.3 (4×OCH_3), 52.7 (COOCH_3), 20.8, 20.7 (2×CH_3) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 623.23. Found: 623.36. Anal. Calcd for $C_{28}H_{40}O_{14}$ (600.61): C, 55.99; H, 6.71. Found: C, 55.85; H, 6.65.

4.15. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2-*O*-acetyl-3-*O*-methyl-D-glucopyranosyluronate (20)

To a solution of **19** (1.20 g, 2.00 mmol) in THF (12 mL), benzylamine (875 μL, 8.00 mmol) was added. The reaction mixture was stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with 1 M aq HCl (20 mL), H_2O (20 mL), aq $NaHCO_3$ (20 mL), H_2O (20 mL), dried and concentrated. Column chromatography (7:3 *n*-hexane/acetone) gave **20** (1.03 g, 92%) as a colourless oil; $[\alpha]_D^{25}$ +129.9 (*c* 0.13, $CHCl_3$); R_f 0.38 (6:4 *n*-hexane/acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ=7.34–7.27 (m, 5H, arom), 5.45 (d, 1H, $J_{1',2'}$ 3.6 Hz, H-1′), 5.41 (d, 1H, $J_{1,2}$ 2.8 Hz, H-1), 5.02 (s, 1H, O*H*), 4.76 (dd, 1H, $J_{1,2}$ 2.8 Hz, $J_{2,3}$ 9.1 Hz, H-2), 4.67, 4.48 (2d, 2H, *J* 12.1, 12.1 Hz, CH_2Ph), 4.60 (d, 1H, $J_{4,5}$ 9.0 Hz, H-5), 4.16–4.04 (m, 2H, H-3, H-4), 3.69–3.26 (m, 20H, H-3′, H-4′, H-5′, H-6a′, H-6b′, 5×OCH_3), 3.18 (dd, 1H, $J_{1',2'}$ 3.6 Hz, $J_{2',3'}$ 9.8 Hz, H-2′), 2.13 (s, 3H, *C*H_3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=170.3, 169.9 (2×*C*O), 138.0 (C_q arom), 128.2, 128.2, 127.7, 127.7, 127.5 (5C, arom), 96.9 (C-1′), 90.3 (C-1), 82.8, 81.8, 79.6, 79.0, 74.7, 70.6, 69.9 (8C, skeleton carbons), 73.4 (*C*H_2Ph), 67.6 (C-6′), 60.5, 60.3, 59,6, 59.6 (4×OCH_3), 52.3 (COOCH_3), 21.0 (*C*H_3) ppm. Anal. Calcd for $C_{26}H_{38}O_{13}$ (558.57): C, 55.91; H, 6.86. Found: C, 55.84; H, 6.88.

4.16. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2-*O*-acetyl-3-*O*-methyl-1-*O*-trichloroacetimidoyl-D-glucopyranosyluronate (4)

A solution of **20** (900 mg, 1.61 mmol) in dry CH_2Cl_2 (7 mL) was cooled to 0 °C, trichloroacetonitrile (1.93 mL, 19.3 mmol) and DBU (66.0 μL, 0.442 mmol) were added. After stirring for 30 min, the mixture was concentrated under reduced pressure, and purified by column chromatography (95:5 CH_2Cl_2/acetone) to give **4** (962 mg, 85%) as a syrup; R_f 0.57 (95:5 CH_2Cl_2/acetone).

4.17. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2-*O*-acetyl-3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (21)

Compound **5** (200 mg, 0.431 mmol) was glycosylated with **4** (455 mg, 0.647 mmol) according to general method *C*. The crude product was purified twice by silica gel chromatography, using first CH_2Cl_2/acetone (95:5), and then *n*-hexane/acetone (7:3) as eluents to give **21** (320 mg, 74%) as a colourless oil; $[\alpha]_D^{25}$ +64.8 (*c* 0.24, $CHCl_3$); R_f 0.29 (95:5 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3444, 3019, 1750, 1652, 1456, 1374, 1219, 1100, 1038, 772, 698, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.42–7.21 (20H, arom), 5.34 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.96 (d, 1H, *J* 11.1 Hz, PhCH_2), 4.87 (dd, 1H, $J_{1',2'}$ 8.1 Hz, $J_{2',3'}$ 9.3 Hz, H-2′), 4.75–4.63 (m, 4H, H-1, PhCH_2), 4.56–4.42 (m, 5H, PhCH_2, H-1′), 4.04 (t, 1H, *J* 9.2, 9.2 Hz), 3.87–3.23 (m, 31H), 3.16 (dd, 1H, *J* 3.6, 9.4 Hz), 2.00 (s, 3H, *C*H_3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=168.9, 168.0 (2×*C*O), 139.3, 138.2, 138.0, 137.7 (4×C_q arom), 128.6–126.9 (20C, arom), 100.4 (C-1′), 98.2 (C-1), 96.8 (C-1″), 83.3, 83.0, 81.4, 79.8, 78.9, 78.7, 77.3, 74.8, 74.5, 69.7, 67.7, 67.5 (skeleton carbons), 75.2, 73.6, 73.4, 73.4 (4×PhCH_2), 67.7, 67.5 (C-6, C-6″), 60.6, 60.3, 59.0, 58.8, 55.3, 52.3 (6×OCH_3), 20.9 (*C*H_3) ppm. Anal. Calcd for $C_{54}H_{68}O_{18}$ (1005.11): C, 64.53; H, 6.82. Found: C, 64.40; H, 6.80.

4.18. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (22)

Compound **21** (500 mg, 0.497 mmol) was converted into **22** according to general method *D*. Column chromatography (92:8 CH_2Cl_2/acetone) gave **22** (413 mg, 86%) as a colourless oil; $[\alpha]_D^{25}$ +70.2 (*c* 0.16, $CHCl_3$); R_f 0.41 (9:1 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3465, 2927, 2836, 2361, 2348, 2309, 1753, 1637, 1497, 1454, 1365, 1287, 1261, 1214, 1167, 1146, 1102, 1037, 908, 740, 698, 602, 570, 467 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.35–7.26 (20H, arom), 5.44 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.95, 4.79 (2d, 2×1H, *J* 11.1, 11.1 Hz, PhCH_2), 4.73–4.63 (m, 3H), 4.57–4.45 (m, 5H), 4.00–3.92 (m, 4H), 3.75–3.20 (m, 30H), 3.15 (dd, 1H, *J* 3.6, 9.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=168.4 (*C*O), 139.0, 138.0, 137.9, 137.3 (4×C_q arom), 128.4–126.9 (20C, arom), 103.1 (C-1′), 98.1 (C-1), 96.4 (C-1″), 84.9, 83.0, 81.4, 80.3, 79.2, 78.7, 77.4, 74.6, 74.3, 74.2, 70.5, 69.3 (skeleton carbons), 75.0, 73.5, 73.3, 73.3 (4×PhCH_2), 68.3, 67.7 (C-6, C-6″), 60.5, 60.2, 59.8, 58.9, 55.1, 52.1 (6×OCH_3) ppm. Anal. Calcd for $C_{52}H_{66}O_{17}$ (963.07): C, 64.85; H, 6.91. Found: C, 64.68; H, 6.86.

4.19. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (23) and methyl (sodium 4-deoxy-2,3-di-*O*-methyl-α-L-*threo*-hex-4-enopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (24)

To a solution of compound **22** (200 mg, 0.208 mmol) in DMF (2 mL) at 0 °C were successively added 60% NaH (25.0 mg, 0.625 mmol) and MeI (65.0 μL, 1.04 mmol). After 2 h stirring at this temperature, MeOH (0.5 mL) was added. The reaction mixture was stirred for 15 min, and the solvents were evaporated. The reaction gave a mixture of **23** and **24**, which were separated by silica gel chromatography (9:1 CH_2Cl_2/acetone and 9:1 CH_2Cl_2/MeOH).

Compound **23**: 24.4 mg, 36%, colourless oil; R_f 0.60 (9:1 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3489, 3067, 2934, 2835, 1722, 1603, 1452, 1376, 1315, 1276, 1198, 1161, 1098, 1046, 995, 900, 746, 714, 512 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.36–7.26 (5H, arom), 4.84 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.65, 4.54 (2d, 2×1H, *J* 12.1, 12.1 Hz, PhCH_2), 3.72–3.59 (m, 6H), 3.53–3.47 (m, 7H), 3.41 (s, 3H), 3.27–3.21 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=137.9 (C_q arom), 128.2, 128.2, 127.6, 127.6, 127.5 (5C, arom), 97.4 (C-1), 83.5, 81.6, 79.3, 69.9 (skeleton carbons), 73.3 (PhCH_2), 68.5 (C-6), 60.7, 60.3, 58.8, 55.0 (4×OCH_3) ppm. Anal. Calcd for $C_{17}H_{26}O_6$ (326.38): C, 62.56; H, 8.03. Found: C, 62.33; H, 7.95.

*Compound **24***: 103 mg, 76%, colourless oil; R_f 0.44 (9:1 CH_2Cl_2/MeOH); $[\alpha]_D^{25}$ +42.7 (*c* 0.1, $CHCl_3$); (lit.[10b] $[\alpha]_D$ +42.8).

4.20. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (25)

To a solution of **22** (200 mg, 0.208 mmol) in DMF (4.5 mL) at rt were successively added freshly prepared Ag_2O (193 mg, 0.832 mmol) and MeI (37.0 μL, 2.08 mmol). After 48 h stirring at this temperature, the mixture was diluted with CH_2Cl_2, filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by silica gel chromatography (75:25 *n*-hexane/acetone) to give **25** as a colourless syrup (160 mg, 79%); $[\alpha]_D^{25}$ +68.3 (*c* 0.12, $CHCl_3$); R_f 0.38 (7:3 *n*-hexane/acetone); IR ν_{max} (KBr): 3446, 2359, 1219, 1040, 772, 686, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.40–7.21 (20H, arom), 5.44 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 5.01 (d, 1H, *J* 10.9 Hz, PhCH_2), 4.75–4.47 (m, 8H, H-1, PhCH_2), 4.32 (d, 1H, $J_{1',2'}$ 7.9 Hz, H-1′), 3.95–3.81 (m, 4H), 3.69–3.27 (m, 30H), 3.19–3.14 (m, 2H), 2.98 (dd, 1H, *J* 8.1, 8.9 Hz) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=168.7 (*C*O), 139.4, 138.4, 138.2, 138.0 (4×C_q arom), 128.6–127.1 (20C, arom), 103.0 (C-1′), 98.4 (C-1), 96.8 (C-1″), 85.6, 83.8, 83.2, 81.6, 80.3, 79.0, 78.9, 77.8, 75.1, 74.4, 70.7, 70.0 (skeleton carbons), 75.5, 73.6, 73.5, 73.4 (4×PhCH_2), 67.9, 67.8 (C-6, C-6″), 60.7, 60.6, 60.4, 60.2, 59.2, 55.4, 52.3 (7×OCH_3) ppm. Anal. Calcd for $C_{53}H_{68}O_{17}$ (977.10): C, 65.15; H, 7.01. Found: C, 65.04; H, 6.94.

4.21. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (26)

Compound **25** (140 mg, 0.143 mmol) was dissolved in MeOH (12 mL) and treated with 0.1 M aq NaOH solution (12 mL). After 24 h stirring at rt the TLC showed complete conversion of the carboxylic ester into sodium salt. The mixture was neutralized with acetic acid, concentrated in vacuo and the residue was purified by silica gel chromatography (97:3 CH_2Cl_2/CH_3OH) to give **26** as a white powder (133 mg, 94%); 116–140 °C decomposed; $[\alpha]_D^{25}$ +91.1 (*c* 0.57, CH_3OH); R_f 0.44 (95:5 CH_2Cl_2/CH_3OH); IR ν_{max} (KBr): 2931, 2309, 1748, 1454, 1363, 1219, 1166, 1100, 1071, 1043, 1028, 772, 698 cm^{-1}; ^1H NMR (CD_3OD, 360 MHz): δ=7.41–7.21 (20H, arom), 5.40 (d, 1H, $J_{1'',2''}$ 3.7 Hz, H-1″), 5.02 (d, 1H, *J* 10.8 Hz, PhCH_2), 4.67–4.46 (m, 8H, H-1, PhCH_2), 4.40 (d, 1H, $J_{1',2'}$ 7.9 Hz, H-1′), 3.97–3.09 (m, 33H), 2.95 (dd, 1H, *J* 8.0, 9.0 Hz) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=171.9 (*C*O), 140.2, 139.7, 139.7, 139.4 (4×C_q arom), 129.9–128.5 (20C, arom), 104.1 (C-1′), 99.2 (C-1), 98.1 (C-1″), 86.9, 85.5, 84.4, 83.1, 81.4, 80.6, 80.4, 78.6, 76.8, 76.3, 72.0, 71.6 (skeleton carbons), 76.8, 74.6, 74.4, 74.4 (4×PhCH_2), 69.4, 69.0 (C-6, C-6″), 61.1, 61.0, 61.0, 60.8, 59.8, 55.7 (6×OCH_3) ppm. Anal. Calcd for $C_{52}H_{65}NaO_{17}$ (985.05): C, 63.40; H, 6.65. Found: C, 63.31; H, 6.60.

4.22. Methyl (2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-α-D-glucopyranoside (27)

Compound **26** (70.0 mg, 71.1 μmol) was converted to **27** according to general method *E*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **27** as a white powder (40.5 mg, 91%); 120–158 °C decomposed; $[\alpha]_D^{25}$ +116.9 (*c* 0.14, CH_3OH); R_f 0.30 (6:4 CH_2Cl_2/CH_3OH); IR ν_{max} (KBr): 3442, 2943, 2845, 2081, 1638, 1146, 1072, 1023, 1000, 760 cm^{-1}; ^1H NMR (D_2O, 360 MHz): δ=5.48 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.79 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.59 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 3.96–3.85 (m, 3H), 3.81–3.73 (m, 5H), 3.64–3.47 (m, 20H), 3.41 (s, 3H), 3.34–3.23 (m, 3H) ppm; ^{13}C NMR (D_2O, 90 MHz): δ=176.6 (*C*O), 102.0 (C-1′), 98.9 (C-1), 96.0 (C-1″), 85.2, 83.0, 81.8, 80.4, 78.9, 78.2, 74.5, 73.7, 71.4, 70.9, 70.9, 70.4 (skeleton carbons), 59.8, 59.4 (C-6, C-6″), 60.3, 60.2, 59.8, 59.6, 58.9, 55.0 (6×OCH_3) ppm. Anal. Calcd for $C_{24}H_{41}NaO_{17}$ (624.56): C, 46.15; H, 6.62. Found: C, 46.23; H, 6.66.

4.23. Methyl [6-*O*-(sodium sulfonato)-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl]-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-(sodium sulfonato)-α-D-glucopyranoside (9)

Compound **27** (40.0 mg, 64.0 μmol) was converted to **9** according to general method *F*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **9** as a white powder (40.0 mg, 61%); 126–150 °C decomposed; $[\alpha]_D^{25}$ +64.1 (*c* 0.26, CH_3OH); R_f 0.34 (1:1 CH_2Cl_2-CH_3OH); IR ν_{max} (KBr): 3503, 1219, 772, 685, 674 cm^{-1}; ^1H NMR (D_2O, 360 MHz): δ=5.46 (d, 1H, $J_{1'',2''}$ 3.7 Hz, H-1″), 5.15 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.66 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.63 (t, 1H, *J* 9.4, 9.4 Hz), 4.38–4.34 (m, 3H), 4.28 (d, 1H, *J* 9.8 Hz), 4.14–4.07 (m, 2H), 3.99 (dd, 1H, *J* 9.3, 9.6 Hz), 3.92–3.87 (m, 2H), 3.73 (d, 1H, *J* 9.8 Hz), 3.63–3.51 (m, 17H), 3.47 (s,

3H), 3.36–3.25 (m, 4H) ppm; ^{13}C NMR (D_2O, 90 MHz): δ=175.9 (*C*O), 102.0 (C-1′), 98.2 (C-1), 97.0 (C-1″), 86.6, 83.9, 82.8, 81.4, 79.0, 77.8, 77.1, 76.1, 75.3, 73.9, 70.1, 69.7 (skeleton carbons), 66.9, 66.9 (C-6, C-6″), 61.2, 61.2, 60.9, 60.4, 59.9, 56.3 (6×O*C*H$_3$) ppm. Anal. Calcd for $C_{24}H_{37}Na_5O_{29}S_4$ (1032.74): C, 27.91; H, 3.61; S, 12.42. Found: C, 27.72; H, 3.53; S, 12.28.

4.24. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(methyl 2-acetyl-3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (28)

Compound **6** (300 mg, 0.640 mmol) was reacted with **20** (720 mg, 1.02 mmol) according to general method *C*. The crude product was purified by silica gel chromatography to give **28**[12] as a colourless oil (433 mg, 67%); R_f 0.41 (3:2 hexane/acetone); MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1029.38. Found: 1029.66.

4.25. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(methyl 3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (29)

Trisaccharide **28** (220 mg, 0.218 mmol) was deacetylated according to general method *D*. The crude product was purified by silica gel chromatography to give **29** as a colourless oil (176 mg, 80%); $[\alpha]_D^{25}$ +100.9 (*c* 0.11, $CHCl_3$); R_f 0.20 (65:35 hexane/acetone); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.39–7.26 (m, 15H, arom), 5.38 (d, 1H, $J_{1'',2''}$ 2.6 Hz, H-1″), 5.04–5.02 (m, 2H, PhC*H*$_2$), 4.74–4.34 (m, 6H, 2×PhC*H*$_2$, H-1, H-1′), 4.02–3.92 (m, 3H), 3.75–3.72 (m, 3H), 3.67, 3.61, 3.60, 3.52, 3.51, 3.44, 3.32 (7×s, 21H, 7×OC*H*$_3$), 3.64–3.43 (m, 6H), 3.31–3.28 (m, 2H), 3.22–3.03 (m, 4H), 2.38–2.31 (m, 1H, H-2) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ=168.3 (*C*O, arom), 138.1, 137.9, 137.5 (3×C_q arom), 128.7–127.4 (15C, arom), 102.5, 97.7, 96.6 (3×C-1), 84.9, 83.0, 81.3, 78.7, 78.2, 77.2, 74.8, 74.4, 74.1, 70.7, 69.8 (skeleton carbons), 74.6, 73.4, 73.3 (3×PhCH_2), 67.9, 67.7 (C-6, C-6″), 60.5, 60.2, 60.0, 58.9, 55.4, 55.0, 52.1 (7×O*C*H$_3$), 46.2 (C-7), 41.6 (C-2) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 987.38. Found: 987.67. Anal. Calcd for $C_{47}H_{64}O_{19}S$ (965.06): C, 58.49; H, 6.68; S, 3.32. Found: C, 58.38; H, 6.52; S, 3.25.

4.26. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(methyl 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (30)

Compound **29** (70.0 mg, 0.073 mmol) was converted to **30** according to general method *G*. The residue was purified by Sephadex LH-20 column chromatography eluting with MeOH to give **30** (65.0 mg, 90%) as a colourless oil; $[\alpha]_D^{25}$ +78.7 (*c* 0.19, $CHCl_3$); R_f 0.55 (8:2 CH_2Cl_2/MeOH); IR ν_{max} (KBr): 3443, 2064, 1651, 1633, 1219, 1042, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$+CD_3OD, 360 MHz): δ=7.40–7.22 (m, 15H, arom), 5.33 (d, 1H, $J_{1'',2''}$ 3.5 Hz, H-1″), 5.21 (d, 1H, $J_{1,2}$ 2.9 Hz, H-1), 4.98 (d, 1H, $J_{1',2'}$ 11.2 Hz, H-1′), 4.73–4.36 (m, 6H, 3×PhCH_2), 4.03–3.92 (m, 2H), 3.82–3.64 (m, 5H), 3.59, 3.58, 3.52, 3.46, 3.45, 3.37 (6×s, 21H, 7×OCH_3), 3.41–3.30 (m, 3H), 3.23–3.09 (m, 4H), 2.97–2.85 (m, 3H), 2.38–2.30 (m, 1H, H-2) ppm; ^{13}C NMR ($CDCl_3$+CD_3OD, 90 MHz): δ=170.1 (*C*O), 139.8, 139.4 (3×C_q arom), 129.7–128.4 (15C, arom), 104.1, 100.2, 97.9 (C-1, C-1′, C-1″), 86.5, 85.2, 84.3, 82.8, 80.3, 79.5, 78.8, 77.0, 75.7, 72.1, 71.9 (skeleton carbons), 75.3, 74.5, 74.4 (3×PhCH_2), 69.3, 69.2 (C-6, C-6″), 61.1, 60.9, 59.5, 55.7, 53.0 (7×O*C*H$_3$), 44.1 (C-2), 30.7 (*C*H_2SO$_3$Na) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1009.35. Found: 1009.61. Anal. Calcd for $C_{47}H_{63}NaO_{19}S$ (987.05): C, 57.19; H, 6.43; S, 3.25. Found: C, 57.36; H, 6.52; S, 3.21.

4.27. Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2-deoxy-2-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (31)

Compound **30** (70.0 mg, 0.071 mmol) was dissolved in MeOH (3 mL) and treated with 0.1 M aq NaOH solution (2 mL). After 24 h stirring at rt the TLC showed complete conversion of the carboxylic ester into sodium salt. The mixture was neutralized with acetic acid, concentrated in vacuo and the residue was purified by Sephadex LH-20 column chromatography eluting with MeOH to give the disodium salt **30a** as a white powder (65.0 mg, 92%). The disodium salt intermediate (85.0 mg, 0.085 mmol) was converted to the title compound according to general method *E*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **31** as a white powder (60.3 mg, 98%).

Compound ***30a***: 112–152 °C decomposed; $[\alpha]_D^{25}$ +80.9 (*c* 0.21, $CHCl_3$); R_f 0.27 (8:2 CH_2Cl_2/MeOH); IR ν_{max} (KBr): 3417, 2925, 2853, 2398, 1722, 1602, 1455, 1377, 1218, 1142, 1099, 1045, 916, 771, 700, 668, 563, 529 cm^{-1}; ^{1}H NMR ($CDCl_3$+CD_3OD, 360 MHz): δ=7.40–7.23 (m, 15H, arom), 5.45 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 5.19 (d, 1H, $J_{1,2}$ 2.9 Hz, H-1), 5.02 (d, 1H, $J_{1',2'}$ 11.3 Hz, H-1′), 4.70–4.43 (m, 6H, 3×PhCH_2), 3.99–3.88 (m, 3H), 3.72–3.64 (m, 7H), 3.61, 3.59, 3.55, 3.53, 3.45, 3.36 (6×s, 18H, 6×OCH_3), 3.46–3.25 (m, 5H), 3.21–3.02 (m, 3H), 2.85–2.81 (m, 1H), 2.35–2.25 (m, 1H, H-2) ppm; ^{13}C NMR ($CDCl_3$+CD_3OD, 90 MHz): δ=139.3, 139.2, 139.0 (3×C_q arom), 130.2–128.5 (15C, arom), 103.9, 99.9, 97.4 (C-1, C-1′, C-1″), 86.9, 85.3, 84.0, 82.9, 80.1, 79.4, 78.8, 77.5, 76.3, 71.7, 71.3 (skeleton carbons), 75.6, 74.4, 74.3 (3×PhCH_2), 68.9 (C-6, C-6″), 61.0, 60.9, 60.6, 59.7, 55.6 (6×O*C*H$_3$), 43.6 (C-2), 30.5 (*C*H_2SO$_3$Na) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1017.31. Found: 1017.49. Anal. Calcd for $C_{46}H_{60}Na_2O_{19}S$ (995.00): C, 55.53; H, 6.08; S, 3.22. Found: C, 55.38; H, 5.79; S, 2.99.

Compound ***31***: 103–140 °C decomposed; $[\alpha]_D^{25}$ +66.5 (*c* 0.15, MeOH); R_f 0.42 (1:1 CH_2Cl_2/MeOH); ^{1}H NMR (D_2O, 360 MHz): δ=5.46 (d, 1H $J_{1'',2''}$ 2.9 Hz, H-1″), 5.11 (s, 1H, Hz, H-1), 4.56 (d, 1H, $J_{1',2'}$ 7.5 Hz, H-1′), 3.95–3.91 (m, 1H), 3.86–3.68 (m, 8H), 3.64, 3.62, 3.61. 3.56, 3.54, 3.39 (6×s, 18H, 6××OCH_3), 3.32–3.22 (m, 4H), 3.08–3.01 (m, 1H), 2.25–2.18 (m, 1H, H-2) ppm; ^{13}C NMR (D_2O, 90 MHz): δ=103.1 (C-1′), 99.4 (C-1), 96.9 (C-1″), 86.5, 84.2, 82.7, 81.6, 81.1, 79.3, 77.1, 75.0, 71.5, 70.2 (skeleton carbons), 61.3, 61.1, 60.8, 60.4, 59.9, 56.1 (6×OCH_3), 61.0, 60.6 (C-6, C-6″), 49.3 (*C*H_2SO$_3$Na), 43.6 (C-2) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+2Na]^+$ 769.15. Found: 769.58. Anal. Calcd for $C_{25}H_{42}Na_2O_{19}S$ (724.63): C, 41.44; H, 5.84; S, 4.42. Found: C, 41.25; H, 5.55; S, 4.29.

4.28. Methyl [6-*O*-(sodium sulfonato)-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl]-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2-deoxy-3,6-di-*O*-(sodium sulfonato)-2-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (10)[12]

Compound **31** (25.0 mg, 34.5 μmol) was converted to **10** according to general method *F*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **10**[12] as a white powder (29.0 mg, 81%); R_f 0.32 (1:1 CH_2Cl_2/CH_3OH).

4.29. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(methyl 2-acetyl-3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (32)[12]

Compound **8** (180 mg, 0.386 mmol) was reacted with **20** (540 mg, 0.772 mmol) according to general method *C*. The crude product was purified by silica gel chromatography to give **32** as a colourless oil (235 mg, 61%); R_f 0.21 (1:1 hexane/EtOAc); MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1029.38. Found: 1029.58.

4.30. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(methyl 3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (33)

Trisaccharide **32** (295 mg, 0.258 mmol) was deacetylated as described for the synthesis of **29**. The crude product was purified by silica gel chromatography to give **33** as a colourless oil (247 mg, 88%); $[\alpha]_D^{25}$ +62.4 (*c* 0.13, $CHCl_3$); R_f 0.39 (9:1 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3477, 2928, 1750, 1496, 1453, 1359, 1218, 1161, 1101, 1037, 909, 771, 698, 574 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ=7.32–7.26 (m, 15H, arom), 5.40 (d, 1H, $J_{1'',2''}$ 2.6 Hz, H-1″), 4.89 (s, 2H, PhC*H*$_2$), 4.67–4.48 (m, 6H, 2×PhC*H*$_2$, H-1′, H-1″), 3.98–3.87 (m, 3H), 3.86 (s, 3H, OC*H*$_3$), 3.75–3.72 (m, 1H), 3.60, 3.56, 3.50, 3.43, 3.33 (5×s, 18H, 6×OC*H*$_3$), 3.61–3.30 (m, 10H), 3.17–3.13 (m, 3H), 2.58–2.48, 2.03–1.93 (2×m, 2H, H-6a,b) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=168.3 (*C*O), 138.6, 137.9, 137.6 (3×C_q arom), 128.2–127.0 (15C, arom), 102.9, 97.5, 96.4 (3×C-1), 84.9, 82.9, 81.2, 80.1, 79.6, 79.3, 78.6, 74.7, 74.1, 73.4, 70.5, 67.6 (skeleton carbons), 74.9, 73.2, 73.1 (3×PhC*H*$_2$), 67.5 (C-6″), 60.5, 60.2, 59.9, 59.0, 55.3, 55.2, 52.2 (7×OC*H*$_3$), 45.6 (C-7), 25.2 (C-6) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 987.37. Found: 987.52. Anal. Calcd for $C_{47}H_{64}O_{19}S$ (965.06): C, 58.49; H, 6.68; S, 3.32. Found: C, 58.39; H, 6.59; S, 3.29.

4.31. Methyl 6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (34)

Compound **33** (28.0 mg, 0.029 mmol) was converted to **34** according to general method *G*. The residue was purified by silica gel chromatography (85:15 CH_2Cl_2/MeOH) to give **34** (25.4 mg, 89%) as a colourless syrup; $[\alpha]_D^{25}$ +70.3 (*c* 0.07, MeOH); R_f 0.41 (85:15 CH_2Cl_2-MeOH); IR ν_{max} (KBr): 3467, 2924, 2853, 1746, 1487, 1453, 1376, 1165, 1075, 1042, 947, 771, 698, 620, 528 cm^{-1}; ^1H NMR (CD_3OD, 360 MHz): δ=7.34–7.23 (m, 15H, arom), 5.38 (d, 1H, $J_{1'',2''}$ 3.5 Hz, H-1″), 4.98 (d, 1H, $J_{1',2'}$ 11.2 Hz, H-1′), 4.65–4.49 (m, 7H, 3×PhC*H*$_2$, H-1), 3.90–3.62 (m, 6H), 3.60, 3.58, 3.55, 3.48, 3.46, 3.44, 3.35 (7×s, 21H, 7×OC*H*$_3$), 3.41–3.17 (m, 7H), 3.10–2.99 (m, 3H), 2.68–2.56, 1.95–1.85 (2×m, 2H, H-6a,b) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=170.4 (*C*O), 140.5, 139.5, 139.4 (3×C_q arom), 129.4–128.2 (15C, arom), 104.7 (C-1′), 98.7, 97.8 (C-1, C-1″), 86.7, 85.4, 84.2, 83.4, 82.7, 81.2, 81.0, 80.3, 76.7, 75.5, 72.0, 70.3 (skeleton carbons), 76.3, 74.4, 74.1 (3×PhC*H*$_2$), 69.3 (C-6″), 61.2, 61.0, 60.9, 60.8, 59.4, 55.6, 53.0 (7×OC*H*$_3$), 27.8 (C-6) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1009.35. Found: 1009.55. Anal. Calcd for $C_{47}H_{63}NaO_{19}S$ (987.05): C, 57.19; H, 6.43; S, 3.25. Found: C, 57.23; H, 6.49; S, 3.28.

4.32. Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranosyl-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-6-deoxy-6-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (35)

Compound **34** (85.0 mg, 0.086 mmol) was dissolved in MeOH (2 mL) and treated with 0.1 M aq NaOH solution (1 mL). After 24 h stirring at rt the TLC showed complete conversion of the carboxylic ester into sodium salt. The mixture was neutralized with acetic acid, concentrated in vacuo and the residue was purified by Sephadex LH-20 column chromatography eluting with MeOH to give the disodium salt **34a** as a white powder (79.0 mg, 92%). The disodium salt (75 mg, 0.075 mmol) was converted to **35** by method *E*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **35** as a white powder (53.5 mg, 98%).

Compound ***34a***: 108–150 °C decomposed; $[\alpha]_D^{25}$ +77.0 (*c* 0.11, MeOH); R_f 0.37 (8:2 CH_2Cl_2/MeOH); IR ν_{max} (KBr): 3443, 2064, 1633, 1455, 1218, 1158, 1042, 771, 697 cm^{-1}; ^1H NMR (CD_3OD, 360 MHz): δ=7.42–7.18 (m, 15H, arom), 5.45 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 5.03 (d, 1H, $J_{1',2'}$ 11.3 Hz, H-1′), 4.68–4.49 (m, 7H, 3×PhC*H*$_2$, H-1), 3.93–3.69 (m, 7H), 3.58, 3.56, 3.54, 3.49, 3.42, 3.33 (6×s, 18H, 6×OC*H*$_3$), 3.38–3.25 (m, 5H), 3.10–3.04 (m, 3H), 2.85–2.81 (m, 1H), 2.62–2.52, 1.96–1.86 (2×m, 2H, H-6a,b) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=140.5, 139.5 (3×C_q arom), 129.5–128.2 (15C, arom), 103.9 (C-1′), 98.7, 97.7 (C-1, C-1″), 87.2, 85.7, 84.2, 83.1, 82.6, 81.1, 80.8, 80.3, 78.1, 76.6, 71.6, 70.3 (skeleton carbons), 76.2, 74.5, 74.0 (3×PhCH_2), 69.2 (C-6″), 60.9, 60.7, 60.6, 59.6, 55.6 (6×OCH_3), 28.0 (C-6) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+Na]^+$ 1017.31. Found: 1017.55. Anal. Calcd for $C_{46}H_{60}Na_2O_{19}S$ (995.00): C, 55.53; H, 6.08; S, 3.22. Found: C, 55.50; H, 6.02; S, 3.15.

Compound ***35***: 112–138 °C decomposed; $[\alpha]_D^{25}$ +64.1 (*c* 0.14, H_2O); R_f 0.29 (1:1 CH_2Cl_2/MeOH); IR ν_{max} (KBr): 3448, 2928, 1438, 1363, 1219, 1161, 1043, 772, 685, 673 cm^{-1}; ^1H NMR (D_2O, 360 MHz): δ=5.47 (d, 1H $J_{1'',2''}$ 3.5 Hz, H-1″), 4.77 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.62 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 3.86–3.72 (m, 8H), 3.65, 3.64, 3.63. 3.56, 3.54, 3.41 (6×s, 18H, 6×OCH_3), 3.52–3.44 (m, 2H), 3.31–3.03 (m, 6H), 2.48–2.38, 1.94–1.84 (2×m, 2H, H-6a,b) ppm; ^{13}C NMR (D_2O, 90 MHz): δ=103.3 (C-1′), 99.7 (C-1), 96.8 (C-1″), 86.5, 84.4, 84.1, 82.6, 81.5, 79.2, 77.0, 74.9, 72.5, 71.9, 71.5, 69.3 (skeleton carbons), 61.4, 61.1, 60.8, 60.4, 59.9, 56.1 (6×OCH_3), 60.5 (C-6″), 48.2 (C-7), 26.7 (C-6) ppm; MALDI-TOF (positive ion): *m*/*z* calcd for $[M+2Na]^+$ 769.15. Found: 769.69. Anal. Calcd for $C_{25}H_{42}Na_2O_{19}S$ (724.63): C, 41.44; H, 5.84; S, 4.42. Found: C, 41.39; H, 5.77; S, 4.34.

4.33. Methyl [6-*O*-(sodium sulfonato)-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl]-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-6-deoxy-2,3-di-*O*-(sodium sulfonato)-6-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (12)[12]

Compound **35** (54.0 mg, 74.5 μmol) was converted to **12** by method *F*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **12**[12] as a white powder (58.0 mg, 76%); R_f 0.21 (7:6:1 CH_2Cl_2/CH_3OH/H_2O).

4.34. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2-*O*-acetyl-3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (36α,β)

Compound **7** (217 mg, 0.465 mmol) was glycosylated with **4** (490 mg, 0.697 mmol) according to general method *C*. The crude product was twice purified by silica gel chromatography. Using first *n*-hexane/acetone (7:3), and then CH_2Cl_2/acetone (95:5) as eluents to give a mixture of **36**α and **36**β (374 mg, α/β ~1:1, 80%) as a colourless oil (in the second purification step the mixture of α and β could be partly separated).

Compound ***36***α (colourless oil): R_f 0.45 (92:8 CH_2Cl_2/acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ=7.38–7.26 (15H, arom), 5.39 (d, 1H, $J_{1'',2''}$ 3.7 Hz, H-1″), 5.13 (d, 1H, $J_{1',2'}$ 3.3 Hz, H-1′), 4.99 (dd, 1H, $J_{1',2'}$ 3.3 Hz, $J_{2',3'}$ 9.9 Hz, H-2′), 4.66–4.63 (m, 4H, H-1, PhC*H*$_2$), 4.50–4.47 (m, 3H, PhC*H*$_2$), 4.34 (d, 1H, *J* 9.4 Hz), 4.16 (dd, 1H, *J* 9.6, 10.6 Hz), 4.06 (dd, 1H, *J* 8.6, 9.2 Hz), 3.88–3.28 (m, 33H), 3.17 (dd, 1H, *J* 3.6, 9.5 Hz), 2.70–2.62 (m, 1H, H-3), 2.17 (s, 3H, C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=170.1, 169.1 (2×*C*O), 138.1, 138.1, 137.9 (3×C_q arom), 128.4–127.5 (15C, arom), 98.5 (C-1′), 97.2 (C-1), 95.7 (C-1″), 83.2, 81.5, 79.8, 78.9, 76.6, 75.3, 74.8, 72.0, 71.6, 70.9, 70.5 (skeleton carbons), 73.5, 73.2, 72.3 (3×PhCH_2), 67.7, 67.5 (C-6, C-6″), 60.7, 60.4, 60.0, 59.2, 55.1, 54.4, 52.5 (7×OCH_3), 45.6 (*C*H_2SO$_3$), 39.2 (C-3), 21.0 (*C*H_3) ppm. Anal. Calcd for $C_{49}H_{66}O_{20}S$ (1007.10): C, 58.44; H, 6.61; S, 3.18. Found: C, 58.60; H, 6.55; S, 3.26.

Pure **36**β was isolated after chemoselective deacetylation of **36**α. The obtained mixture of **36**α and **36**β (374 mg, α/β ~1:1) was dissolved in MeOH (5 mL) and treated with NaOMe (10 mg). When the

TLC showed the complete disappearance of **36**α the mixture was filtered, and concentrated. The crude product was purified by silica gel chromatography (92:8 CH_2Cl_2/acetone) to give **36**β[12] as a colourless oil (140 mg, 30% over two steps: glycosylation+chemoselective deacetylation of **36**α); R_f 0.39 (92:8 CH_2Cl_2/acetone).

4.35. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 3-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (37)

Compound **36**β (59.0 mg, 58.6 μmol) was converted to **37** according to general method *D*. Column chromatography (8:2 CH_2Cl_2/acetone) gave **37** (40.0 mg, 71%) as a colourless oil; $[\alpha]_D^{25}$ +79.8 (*c* 0.17, $CHCl_3$); R_f 0.31 (9:1 CH_2Cl_2/acetone); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.40–7.26 (15H, arom), 5.40 (d, 1H, $J_{1'',2''}$ 3.7 Hz, H-1″), 4.67–4.57 (m, 5H, H-1, PhCH_2), 4.51, 4.48 (2d, 2×1H, *J* 12.1, 12.1 Hz, PhCH_2), 4.28 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.17 (dd, 1H, *J* 9.4, 10.5 Hz, H-4), 3.95 (dd, 1H, *J* 9.0, 8.8 Hz, H-4′), 3.86–3.82 (m, 2H), 3.77–3.57 (m, 19H), 3.52 (s, 3H), 3.44–3.28 (m, 10H), 3.22 (t, 1H, *J* 8.7, 8.7 Hz), 3.17 (dd, 1H, $J_{1'',2''}$ 3.7 Hz, $J_{2'',3''}$ 9.5 Hz, H-2″), 2.80 (s, 1H, OH), 2.55–2.47 (m, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=168.6 (*C*O), 138.1, 138.0, 137.7 (3×C_q arom), 128.5–127.6 (15C, arom), 103.1 (C-1′), 96.7 (C-1), 96.1 (C-1″), 85.1, 83.1, 81.5, 78.8, 75.6, 75.6, 74.6, 74.4, 73.6, 70.8, 70.1 (skeleton carbons), 73.5, 73.4, 72.2 (3×PhCH_2), 68.7, 67.8 (C-6, C-6″), 60.7, 60.3, 59.8, 59.1, 55.2, 54.9, 52.5 (7×O*C*H_3), 45.6 (*C*H_2SO_3), 39.1 (C-3) ppm. Anal. Calcd for $C_{47}H_{64}O_{19}S$ (965.06): C, 58.49; H, 6.68; S, 3.32. Found: C, 58.28; H, 6.55; S, 3.37.

4.36. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (38)

Compound **37** (38.0 mg, 39.4 μmol) was converted to **38** according to general method *G*. The residue was purified by silica gel chromatography (9:1 CH_2Cl_2/CH_3OH) to give **38** (32.0 mg, 82%) as a colourless syrup; $[\alpha]_D^{25}$ +67.6 (*c* 0.09, CH_3OH); R_f 0.52 (9:1 CH_2Cl_2/CH_3OH); IR ν_{max} (KBr): 3445, 2932, 2309, 1716, 1611, 1454, 1409, 1372, 1281, 1219, 1190, 1093, 1046, 917, 871, 772, 699, 526 cm^{-1}; ^{1}H NMR (CD_3OD, 360 MHz): δ=7.45–7.26 (15H, arom), 5.37 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.75 (d, 1H, *J* 11.2 Hz, PhCH_2), 4.64–4.57 (m, 4H, H-1, PhCH_2), 4.51, 4.49 (2d, 2×1H, *J* 11.9, 12.0 Hz, PhCH_2), 4.39–4.33 (m, 2H, H-1′, H-4), 4.06 (dd, 1H, *J* 3.4, 11.3 Hz), 3.85–3.63 (m, 9H), 3.58–3.45 (m, 16H), 3.36–3.17 (m, 9H), 3.09 (dd, 1H, *J* 3.7, 9.7 Hz), 2.96 (dd, 1H, *J* 9.5, 8.1 Hz), 2.33–2.25 (m, 1H, H-3) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=170.9 (*C*O), 140.2, 139.7, 139.6 (3×C_q arom), 129.7–128.8 (15C, arom), 103.9 (C-1′), 97.9 (C-1, C-1″), 87.2, 85.2, 84.4, 82.9, 80.4, 77.1, 76.5, 76.4, 75.4, 72.1, 72.1 (skeleton carbons), 74.5, 74.3, 73.4 (3×PhCH_2), 70.2, 69.4 (C-6, C-6″), 61.1, 61.1, 60.9, 60.9, 59.6, 55.4, 53.3 (7×O*C*H_3), 47.6 (*C*H_2SO_3), 40.5 (C-3) ppm. Anal. Calcd for $C_{47}H_{63}NaO_{19}S$ (987.05): C, 57.19; H, 6.43; S, 3.25. Found: C, 57.00; H, 6.54; S, 3.13.

4.37. Methyl (2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-3-deoxy-3-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (39)

Compound **38** (40.0 mg, 40.5 μmol) was dissolved in MeOH (4 mL) and treated with 0.1 M aq NaOH solution (2 mL). After 12 h stirring at rt the TLC showed complete conversion of the carboxylic ester into sodium salt. The mixture was neutralized with acetic acid, concentrated in vacuo and the residue was purified by Sephadex LH-20 column chromatography eluting with MeOH to give the disodium salt **38a** as a white powder (40.3 mg). Compound **38a** (40.3 mg, 40.5 μmol) was converted to **39** by method *E*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **39** as a white powder (28.5 mg, 97% over two steps).

*Compound **38a***: 112–160 °C decomposed; $[\alpha]_D^{25}$ +43.3 (*c* 0.10, CH_3OH); R_f 0.38 (85:15 CH_2Cl_2/CH_3OH); IR ν_{max} (KBr): 3447, 2927, 1618, 1414, 1220, 1098, 1045, 772 cm^{-1}; ^{1}H NMR (CD_3OD, 360 MHz): δ=7.45–7.25 (15H, arom), 5.41 (d, 1H, $J_{1'',2''}$ 3.7 Hz, H-1″), 4.71 (d, 1H, *J* 11.5 Hz, PhCH_2), 4.65–4.59 (m, 4H, H-1, PhCH_2), 4.54, 4.47 (2d, 2×1H, *J* 12.1, 12.0 Hz, PhCH_2), 4.33 (d, 1H, $J_{1',2'}$ 7.9 Hz, H-1′), 4.14 (t, 1H, $J_{3,4}$ 10.1 Hz, $J_{4,5}$ 10.1 Hz, H-4), 3.89–3.65 (m, 9H), 3.58–3.42 (m, 16H), 3.35–3.21 (m, 7H), 3.10 (dd, 1H, *J* 3.7, 9.8 Hz), 3.02 (t, 1H, *J* 8.3, 8.3 Hz), 2.34–2.27 (m, 1H, H-3) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=178.3 (*C*O), 140.0, 139.7, 139.6 (3×C_q arom), 129.6–128.7 (15C, arom), 104.4 (C-1′), 97.7 (C-1, C-1″), 87.4, 85.5, 84.3, 83.3, 80.4, 78.8, 77.4, 77.3, 76.6, 72.3, 71.5 (skeleton carbons), 74.5, 74.5, 73.2 (3×PhCH_2), 69.8, 69.4 (C-6, C-6″), 60.9, 60.8, 60.7, 60.6, 59.8, 55.4 (6×O*C*H_3), 48.8 (*C*H_2SO_3), 40.5 (C-3) ppm. Anal. Calcd for $C_{46}H_{60}Na_2O_{19}S$ (995.00): C, 55.53; H, 6.08; S, 3.22. Found: C, 55.44; H, 5.98; S, 3.13.

*Compound **39***: 105–145 °C decomposed; $[\alpha]_D^{25}$ +77.7 (*c* 0.12, H_2O); R_f 0.32 (6:4 CH_2Cl_2/CH_3OH); IR ν_{max} (KBr): 3446, 2931, 2309, 1620, 1418, 1220, 1167, 1046, 772 cm^{-1}; ^{1}H NMR (D_2O, 360 MHz): δ=5.47 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.76 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.53 (d, 1H, $J_{1',2'}$ 7.8 Hz, H-1′), 3.97 (d, 1H, *J* 10.4 Hz), 3.89–3.45 (m, 33H), 3.36–3.25 (m, 3H), 3.18 (dd, 1H, *J* 6.4, 14.9 Hz), 2.44–2.37 (m, 1H, H-3) ppm; ^{13}C NMR (D_2O, 90 MHz): δ=175.4 (*C*O), 101.9 (C-1′), 98.5 (C-1), 96.3 (C-1″), 86.2, 83.7, 82.2, 81.1, 78.8, 77.1, 74.8, 74.7, 72.0, 70.9, 70.9 (skeleton carbons), 60.6, 60.1 (C-6, C-6″), 60.9, 60.6, 60.1, 59.9, 59.4, 55.3 (6×O*C*H_3), 50.1 (*C*H_2SO_3), 39.5 (C-3) ppm. Anal. Calcd for $C_{25}H_{42}Na_2O_{19}S$ (724.63): C, 41.44; H, 5.84; S, 4.42. Found: C, 41.27; H, 5.87; S, 4.23.

4.38. Methyl [6-*O*-(sodium sulfonato)-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl]-(1→4)-(sodium 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-3-deoxy-2,6-di-*O*-(sodium sulfonato)-3-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (11)[12]

Compound **39** (25.0 mg, 34.5 μmol) was converted to **11** according to general method *F*. The residue was purified by Sephadex LH-20 column chromatography eluting with H_2O to give **11** as a white powder (29.0 mg, 81%); R_f 0.32 (1:1 CH_2Cl_2/CH_3OH).

4.39. Phenyl 4,6-*O*-(2′-naphthyl)methylene-1-thio-β-D-glucopyranoside (41)

To a solution of **40** (5.00 g, 18.4 mmol) in acetonitrile (150 mL), 2-(dimethoxymethyl)naphthalene (5.57 g, 27.5 mmol) and *p*-toluenesulfonic acid (180 mg, 0.946 mmol) were added. The reaction mixture was stirred at 60 °C for 30 min. After completion of the reaction, solid $NaHCO_3$ (84.0 mg, 1.00 mmol) was added and the stirred reaction mixture was allowed to cool to rt. Then the solvent was evaporated. The solid residue was suspended in a mixture of *n*-hexane and H_2O (200 mL, 1:1) in an Erlenmeyer flask and the mixture was stirred vigorously for 5 min. The precipitated product was filtered off and washed successively with water (2×50 mL) and *n*-hexane (2×50 mL). The product was recrystallized from EtOH to give 6.56 g (87%) of **41** as a white powder; mp 168–170 °C; $[\alpha]_D^{25}$ −27.1 (*c* 0.18, $CHCl_3$); R_f 0.38 (9:1 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3566, 3466, 3224, 2878, 1632, 1481, 1439, 1386, 1352, 1272, 1243, 1177, 1116, 1089, 1011, 960, 903, 825, 795, 735, 688, 600, 576, 479 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.95–7.81 (m, 4H, arom), 7.59–7.46 (m, 5H, arom), 7.35–7.34 (m, 3H, arom), 5.67 (s, 1H, PhC*H*), 4.63 (d, 1H, $J_{1,2}$ 9.7 Hz, H-1), 4.41 (dd, 1H, $J_{5,6a}$ 4.4 Hz, $J_{6a,6b}$ 10.7 Hz, H-6a), 3.88–3.79 (m, 2H, H-3, H-6b), 3.59–3.45 (m, 3H,

H-2, H-4, H-5), 3.08, 2.85 (2s, 2H, 2×O*H*) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=134.1, 133.7, 132.8, 131.3 (4×C_q arom), 133.0–123.6 (12C, arom), 102.0 (Ph*C*H), 88.6 (C-1), 80.2, 74.5, 72.6, 70.5 (skeleton carbons), 68.6 (C-6) ppm. Anal. Calcd for $C_{23}H_{22}O_5S$ (410.48): C, 67.30; H, 5.40; S, 7.81. Found: C, 67.57; H, 5.44; S, 7.89.

4.40. Phenyl 2,3-di-*O*-acetyl-4,6-*O*-(2′-naphthyl)methylene-1-thio-β-D-glucopyranoside (42)

Compound **41** (3.00 g, 7.31 mmol) was converted to **42** according to general method *A* to give 3.29 g (91%) of **42** as a white powder. The product was recrystallized from EtOAc; mp 199–202 °C; $[\alpha]_D^{25}$ −57.2 (*c* 0.20, $CHCl_3$); R_f 0.35 (8:2 *n*-hexane/EtOAc); IR ν_{max} (KBr): 3437, 3060, 2943, 2871, 1747, 1480, 1440, 1373, 1236, 1098, 1076, 1035, 902, 826, 748, 690, 613, 484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.89–7.33 (m, 12H, arom), 5.63 (s, 1H, PhC*H*), 5.37 (dd, 1H, $J_{2,3}$ 9.0 Hz, $J_{3,4}$ 8.7 Hz, H-3), 5.03 (dd, 1H, $J_{1,2}$ 9.8 Hz, $J_{2,3}$ 9.0 Hz, H-2), 4.82 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.45–4.39 (m, 1H, H-6a), 3.83 (dd, 1H, *J* 9.1, 9.8 Hz, H-6b), 3.71 (dd, 1H, $J_{3,4}$ 8.7 Hz, $J_{4,5}$ 9.1 Hz, H-4), 3.64–3.58 (m, 1H, H-5), 2.10, 2.03 (2s, 6H, 2×C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=170.0, 169.4 (2×*C*O), 134.0, 133.6, 132.7, 131.7 (4×C_q arom), 132.9–123.6 (12C, arom), 101.6 (Ph*C*H), 86.5 (C-1), 78.1, 72.8, 70.7, 70.6 (skeleton carbons), 68.6 (C-6), 20.7, 20.7 (2×*C*H$_3$) ppm. Anal. Calcd for $C_{27}H_{26}O_7S$ (494.56): C, 65.57; H, 5.30; S, 6.48. Found: C, 65.26; H, 5.48; S, 6.51.

4.41. Phenyl 2,3-di-*O*-acetyl-6-*O*-(2′-naphthyl)methyl-1-thio-β-D-glucopyranoside (43)

To a solution of **42** (1.57 g, 3.17 mmol) in dry CH_2Cl_2 (23 mL) at 0 °C, Et_3SiH (6.07 mL, 38.0 mmol) and $BF_3{\cdot}Et_2O$ (782 μL, 6.34 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (150 mL), washed with satd $NaHCO_3$ (2×50 mL) and H_2O (50 mL), then dried and concentrated. The crude product was purified by silica gel chromatography (96:4 CH_2Cl_2/acetone) to give **43** as a colourless syrup (1.29 g, 82%); $[\alpha]_D^{25}$ −29.3 (*c* 1.26, $CHCl_3$); R_f 0.22 (7:3 *n*-hexane/acetone); IR ν_{max} (KBr): 3453, 3057, 2868, 1751, 1631, 1479, 1440, 1372, 1240, 1050, 907, 820, 750, 691, 608, 475 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.82–7.75 (m, 4H, arom), 7.50–7.41 (m, 5H, arom), 7.25–7.23 (m, 3H, arom), 5.08 (t, 1H, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 4.94 (dd, 1H, *J* 9.8, 9.4 Hz, H-2), 4.75–4.67 (m, 3H, H-1, C*H*$_2$NAP), 3.81 (d, 2H, *J* 4.5 Hz, H-6a,b), 3.73 (ddd, 1H, $J_{4,OH}$ 4.1 Hz, *J* 9.5, 9.3 Hz, H-4), 3.59–3.54 (m, 1H, H-5), 3.12 (d, 1H, $J_{4,OH}$ 4.2 Hz, O*H*), 2.07, 2.05 (2s, 6H, 2×C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=171.2, 169.5 (2×*C*O), 135.0, 133.1, 132.9, 132.2 (4×C_q arom), 132.4–125.5 (12C, arom), 85.6 (C-1), 78.5, 76.6, 70.0, 69.9 (skeleton carbons), 73.7 (*C*H$_2$Ph), 69.8 (C-6), 20.7, 20.7 (2×*C*H$_3$) ppm. Anal. Calcd for $C_{27}H_{28}O_7S$ (496.57): C, 65.31; H, 5.68; S, 6.46. Found: C, 65.17; H, 5.60; S, 6.31.

4.42. Phenyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-2,3-di-*O*-acetyl-6-*O*-(2′-naphthyl) methyl-1-thio-β-D-glucopyranoside (44)

Compound **43** (600 mg, 1.21 mmol) was glycosylated with **14** (587 mg, 1.45 mmol) according to general method *B*. The crude product was purified twice by silica gel chromatography using first *n*-hexane/EtOAc (7:3), and then CH_2Cl_2/acetone (95:5) as eluents to give **44** (678 mg, 71%) as a colourless oil; $[\alpha]_D^{25}$ +30.9 (*c* 0.37, $CHCl_3$); R_f 0.39 (95:5 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3444, 1634, 1219, 772, 685, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.85–7.75 (m, 4H, arom), 7.52–7.42 (m, 5H, arom), 7.30–7.21 (m, 8H, arom), 5.32 (t, 1H, $J_{2,3}$ 9.2 Hz, $J_{3,4}$ 9.2 Hz, H-3), 5.11 (d, 1H, $J_{1',2'}$ 3.5 Hz, H-1′), 4.92 (dd, 1H, *J* 9.7, 9.5 Hz, H-2), 4.72–4.65 (m, 3H, H-1, C*H*$_2$NAP), 4.44, 4.27 (2d, 2×1H, *J* 12.1, 12.1 Hz, C*H*$_2$Ph), 3.98–3.90 (m, 2H), 3.83 (d, 1H, *J* 10.5 Hz), 3.63–3.57 (m, 5H), 3.49–3.35 (m, 9H), 3.17 (dd, 1H, *J* 9.6, 9.4 Hz), 3.07 (dd, 1H, *J* 3.5, 9.8 Hz), 2.07, 2.01 (2s, 6H, 2×C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=169.7, 169.5 (2×*C*O), 137.9, 135.7, 133.1, 132.8, 131.8 (5×C_q arom), 132.8–125.6 (17C, arom), 97.8 (C-1′), 85.1 (C-1), 83.0, 81.6, 79.1, 79.0, 75.7, 74.2, 71.1, 70.4 (skeleton carbons), 73.3, 73.1 (2×*C*H$_2$Ph), 68.6, 68.2 (C-6, C-6′), 60.6, 60.3, 59.2 (3×O*C*H$_3$), 20.9, 20.7 (2×*C*H$_3$) ppm. Anal. Calcd for $C_{43}H_{50}O_{12}S$ (790.91): C, 65.30; H, 6.37; S, 4.05. Found: C, 65.27; H, 6.54; S, 3.88.

4.43. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-[2,3-di-*O*-acetyl-6-*O*-(2′-naphthyl) methyl-β-D-glucopyranosyl]-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (45)

Compound **7** (200 mg, 0.423 mmol) was glycosylated with **44** (402 mg, 0.508 mmol) according to general method *B*. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2/acetone) to give **45** (354 mg, 73%) as a colourless syrup; $[\alpha]_D^{25}$ +62.1 (*c* 0.38, $CHCl_3$); R_f 0.50 (6:4 *n*-hexane/acetone); IR ν_{max} (KBr): 3445, 2933, 2359, 2342, 1756, 1455, 1361, 1240, 1218, 1162, 1101, 1042, 996, 900, 856, 819, 784, 741, 699, 590, 477 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.83–7.79 (m, 4H, arom), 7.47–7.21 (18H, arom), 5.13–5.09 (m, 2H, H-1″, H-3′), 4.84 (dd, 1H, $J_{1',2'}$ 8.1 Hz, $J_{2',3'}$ 9.5 Hz, H-2′), 4.76–4.64 (m, 4H, H-1, C*H*$_2$NAP, PhC*H*$_2$), 4.54 (s, 2H, PhC*H*$_2$), 4.45, 4.44 (2d, 2×1H, *J* 12.2, 12.2 Hz, PhC*H*$_2$), 4.36 (d, 1H, $J_{1',2'}$ 8.1 Hz, H-1′), 4.28 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 4.10 (dd, 1H, *J* 10.0, 10.3 Hz), 4.03–3.88 (m, 3H), 3.78–3.57 (m, 13H), 3.48–3.29 (m, 13H), 3.18 (t, 1H, *J* 9.5, 9.5 Hz), 3.06 (dd, 1H, *J* 3.3, 9.7 Hz), 2.55–2.47 (m, 1H, H-3), 2.00, 1.93 (2s, 6H, 2×C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=169.7, 169.1 (2×*C*O), 137.8, 137.8, 137.4, 135.8, 133.1, 132.7 (6×C_q arom), 128.5–125.6 (22C, arom), 100.0 (C-1′), 97.5 (C-1), 95.9 (C-1″), 82.9, 81.7, 79.0, 75.8, 74.6, 74.6, 74.6, 73.8, 71.9, 71.0, 70.4 (skeleton carbons), 73.4, 73.0, 73.0, 71.7 (4×*C*H$_2$Ph), 68.3, 68.1, 67.3 (C-6, C-6′, C-6″), 60.5, 60.1, 58.8, 55.3, 54.9 (5×O*C*H$_3$), 46.1 (*C*H$_2$SO$_3$), 38.4 (C-3), 20.8, 20.5 (2×*C*H$_3$) ppm. Anal. Calcd for $C_{60}H_{74}O_{20}S$ (1147.28): C, 62.81; H, 6.50; S, 2.79. Found: C, 62.69; H, 6.33; S, 2.66.

4.44. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(2,3-di-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (46)

To a vigorously stirred solution of **45** (150 mg, 0.131 mmol) in CH_2Cl_2 (1.8 mL) and H_2O (0.2 mL) was added DDQ (45.0 mg, 0.197 mmol). After 30 min the mixture was diluted with CH_2Cl_2 (50 mL) and extracted with satd aq $NaHCO_3$ (2×10 mL), H_2O (10 mL), dried, and concentrated. Column chromatography (91:9 CH_2Cl_2/acetone) gave **46** (111 mg, 84%) as a colourless oil; $[\alpha]_D^{25}$ +45.8 (*c* 0.04, $CHCl_3$); R_f 0.48 (9:1 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3454, 2938, 1755, 1633, 1455, 1371, 1242, 1160, 1102, 1038, 993, 899, 742, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.42–7.28 (m, 15H, arom), 5.14–5.09 (m, 2H, H-1″, H-3′), 4.79 (dd, 1H, *J* 8.4, 7.3 Hz, H-2′), 4.73 (d, 1H, *J* 11.9 Hz, PhC*H*$_2$), 4.69 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.65 (d, 1H, *J* 12.1 Hz, PhC*H*$_2$), 4.59 (s, 2H, PhC*H*$_2$), 4.50, 4.46 (2d, 2×1H, *J* 12.3, 11.7 Hz, PhC*H*$_2$), 4.43 (d, 1H, $J_{1',2'}$ 7.6 Hz, H-1′), 4.35 (t, 1H, *J* 10.4, 10.4 Hz), 3.98–3.52 (m, 18H), 3.45–3.37 (m, 7H), 3.28–3.10 (m, 7H), 2.46–2.39 (m, 1H, H-3), 2.00, 1.91 (2s, 6H, 2×C*H*$_3$) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=169.7, 169.3 (2×*C*O), 138.0, 137.9, 137.4 (3×C_q arom), 128.6–127.5 (15C, arom), 99.5 (C-1′), 97.8 (C-1), 96.1 (C-1″), 83.2, 81.4, 79.2, 75.8, 75.2, 75.1, 73.6, 72.5, 71.5, 71.2, 70.7 (skeleton carbons), 73.5, 73.4, 71.8 (3×*C*H$_2$Ph), 68.4, 67.4 (C-6, C-6″), 60.3 (C-6′), 60.6, 60.3, 59.3, 55.3, 55.0 (5×O*C*H$_3$), 45.2 (*C*H$_2$SO$_3$), 39.3 (C-3), 20.9, 20.6 (2×*C*H$_3$) ppm. Anal. Calcd for $C_{49}H_{66}O_{20}S$ (1007.10): C, 58.44; H, 6.61; S, 3.18. Found: C, 58.27; H, 6.58; S, 3.12.

4.45. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2,3-di-*O*-acetyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (47)[12]

Method 1: compound **46** (105 mg, 0.104 mmol) was converted to **47** according to general method *H*. Column chromatography (95:5 CH_2Cl_2/acetone) gave **47** (73.0 mg, 68%) as a colourless oil.

Method 2: compound **52** (250 mg, 0.337 mmol) was glycosylated with **14** (163 mg, 0.404 mmol) according to general method *B*. The crude product was purified twice by silica gel chromatography using first *n*-hexane/acetone (7:3), and then CH_2Cl_2/EtOAc (75:25) as eluents to give **47** (293 mg, 84%) as a colourless oil; R_f 0.30 (95:5 CH_2Cl_2/acetone).

4.46. Phenyl 4,6-*O*-(4-methoxybenzylidene)-1-thio-β-D-glucopyranoside (48)

To a solution of **40** (6.00 g, 22.0 mmol) in acetonitrile (180 mL), 4-methoxybenzaldehyde dimethyl acetal (6.02 g, 33.1 mmol) and *p*-toluenesulfonic acid (215 mg, 1.13 mmol) were added. The reaction mixture was stirred at 80 °C for 2 h. After completion of the reaction, solid $NaHCO_3$ (97.0 mg, 1.15 mmol) was added and the stirred reaction mixture was allowed to cool to rt, then the solvent was evaporated. The solid residue was suspended in a mixture of *n*-hexane and H_2O (240 mL, 1:1) in an Erlenmeyer flask and the mixture was stirred vigorously for 5 min. The precipitated product was filtered off and washed successively with water (2×60 mL) and *n*-hexane (2×60 mL). The product was recrystallized from EtOH to give 7.05 g (82%) of **48** as a white powder; mp: 173–176 °C (EtOH); $[\alpha]_D^{25}$ −38.8 (*c* 0.19, $CHCl_3$). Spectral data of **48** were the same as those described in the literature.[24]

4.47. Phenyl 2,3-di-*O*-acetyl-4,6-*O*-(4-methoxybenzylidene)-1-thio-β-D-glucopyranoside (49)[12]

Compound **48** (0.700 g, 1.79 mmol) was converted to **49** by method *A* to give 0.800 g (94%) of **49**[12] as a white powder. The product was recrystallized from EtOAc; mp 225–228 °C; R_f 0.60 (95:5 CH_2Cl_2/EtOAc).

4.48. Methyl (2,3-di-*O*-acetyl-4,6-*O*-(4-methoxybenzylidene)-β-D-glucopyranosyl)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (50)[12]

Compound **7** (200 mg, 0.423 mmol) was glycosylated with **49** (241 mg, 0.508 mmol) according to general method *B*. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2/acetone) to give **50** (239 mg, 68%) as a colourless syrup; R_f 0.54 (95:5 CH_2Cl_2/acetone).

4.49. Methyl (2,3-di-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (51)

A solution of **50** (83.0 mg, 0.100 mmol) in AcOH (80%, 3 mL) was stirred for 1 h at rt. The mixture was then concentrated, and the crude product was purified by silica gel chromatography (8:2 CH_2Cl_2/acetone) to give **51** (58.0 mg, 81%) as a colourless syrup; $[\alpha]_D^{25}$ +35.9 (*c* 0.03, $CHCl_3$); R_f 0.41 (8:2 CH_2Cl_2/acetone); ^{1}H NMR ($CDCl_3$, 360 MHz): δ=7.44–7.27 (10H, arom), 4.84–4.76 (m, 3H, H-2′, H-3′, PhCH_2), 4.70 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 4.59 (s, 2H, CH_2Ph), 4.42 (d, 1H, *J* 12.1 Hz, PhCH_2), 4.37 (d, 1H, $J_{1',2'}$ 7.4 Hz, H-1′), 4.35 (t, 1H, *J* 10.4, 10.4 Hz), 3.97 (d, 1H, *J* 12.1 Hz), 3.85–3.51 (m, 12H), 3.36 (s, 1H, OH), 3.29 (s, 3H, OCH_3), 3.20–3.14 (m, 1H), 2.45–2.38 (m, 1H, H-3), 2.06, 1.93 (2s, 6H, 2×CH_3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=171.2, 169.2, (2×*C*O), 137.9, 137.4, (2×C_q arom), 128.7–127.7 (10C, arom), 99.6 (C-1′), 96.1 (C-1), 76.5, 76.0, 75.1, 71.8, 71.4, 70.6, 68.1 (skeleton carbons), 73.6, 71.8 (2×PhCH_2), 67.2, (C-6), 60.4 (C-6′), 55.3, 55.0 (2×OCH_3), 45.1 (CH_2SO$_3$), 39.3 (C-3), 20.8, 20.6 (2×CH_3) ppm. Anal. Calcd for $C_{33}H_{44}O_{15}S$ (712.76): C, 55.61; H, 6.22; S, 4.50. Found: C, 55.60; H, 6.10; S, 4.73.

4.50. Methyl (methyl 2,3-di-*O*-acetyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (52)[12]

Compound **51** (50.0 mg, 0.070 mmol) was converted to **52** by method *H*. Column chromatography (88:12 CH_2Cl_2/acetone) gave **52** (41.0 mg, 79%) as a colourless oil; R_f 0.59 (88:12 CH_2Cl_2/acetone).

4.51. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (53)

Compound **47** (290 mg, 0.280 mmol) was converted to **53** by method *D*. Column chromatography (97:3 CH_2Cl_2/CH_3OH) gave **53** (226 mg, 85%) as a colourless oil; $[\alpha]_D^{25}$ +64.0 (*c* 0.09, $CHCl_3$); R_f 0.54 (95:5 CH_2Cl_2/CH_3OH); ^{1}NMR ($CDCl_3$, 360 MHz): δ=7.35–7.26 (15H, arom), 4.99 (d, 1H, $J_{1'',2''}$ 3.4 Hz, H-1″), 4.87 (s, 1H, OH), 4.66–4.47 (m, 7H, H-1, 3×PhCH_2), 4.27 (d, 1H, $J_{1',2'}$ 6.8 Hz, H-1′), 4.17 (dd, 1H, *J* 9.8, 10.3 Hz, H-4), 3.96 (dd, 1H, *J* 3.2, 11.2 Hz), 3.74–3.55 (m, 22H), 3.46–3.37 (m, 6H), 3.33–3.27 (m, 5H), 3.19 (dd, 1H, $J_{1'',2''}$ 3.4 Hz, $J_{2'',3''}$ 9.6 Hz, H-2″), 2.55–2.49 (m, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ=167.6 (*C*O), 137.7, 137.7, 137.7 (3×C_q arom), 128.2–127.4 (15C, arom), 102.9 (C-1′), 100.4 (C-1), 98.8 (C-1″), 83.6, 82.5, 82.2, 78.7, 75.6, 75.5, 74.9, 74.4, 72.3, 70.9, 70.0 (skeleton carbons), 73.2, 72.9, 71.9 (3×PhCH_2), 68.0, 67.5 (C-6, C-6″), 60.5, 60.2, 59.9, 54.8, 54.6, 52.2 (6×OCH_3), 45.6 (CH_2SO$_3$), 38.7 (C-3) ppm. Anal. Calcd for $C_{46}H_{62}O_{19}S$ (951.04): C, 58.09; H, 6.57; S, 3.37. Found: C, 57.84; H, 6.56; S, 3.31.

4.52. Methyl (sodium 4-deoxy-2,3-di-*O*-methyl-α-L-*threo*-hex-4-enopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (54)

Compound **53** (160 mg, 0.168 mmol) was treated with sodium hydride and methyl iodide according to general method *G* to give a mixture of **23**, **38** and **54** by method *G*. The products were separated by silica gel chromatography (9:1 CH_2Cl_2/acetone **23**, 9:1 CH_2Cl_2/CH_3OH **38**, 7:3 CH_2Cl_2/CH_3OH **54**) to give **23** (20.0 mg, 36%), **38** (81.0 mg, 49%) and **54** (45.0 mg, 39%, colourless syrup); $[\alpha]_D^{25}$ +16.5 (*c* 0.65, $CHCl_3$); R_f 0.27 (7:3 CH_2Cl_2/CH_3OH); ^{1}H NMR (CD_3OD, 360 MHz): δ=7.44–7.24 (m, 10H, arom), 6.07 (d, 1H, $J_{3',4'}$ 3.7 Hz, C*H*=), 5.39 (s, 1H), 4.74 (d, 1H, *J* 11.0 Hz), 4.65–4.61 (m, 5H), 4.22 (dd, 1H, *J* 3.5, 11.6 Hz), 3.83 (dd, 1H, *J* 4.9, 11.2 Hz), 3.71–3.57 (m, 3H), 3.40–3.30 (m, 12H), 2.28–2.22 (m, 1H, H-3) ppm; ^{13}C NMR (CD_3OD, 90 MHz): δ=169.5 (*C*O), 146.1 (C-5′), 140.3, 139.6 (2×C_q arom), 129.6–128.8 (10C, arom), 106.1 (C-4′), 100.7 (C-1′), 97.8 (C-1), 78.4, 77.4, 76.5, 74.4, 72.1 (skeleton carbons), 74.4, 73.3 (2×PhCH_2), 70.6 (C-6), 58.5, 56.9, 55.3 (3×OCH_3), 47.3 (CH_2SO$_3$), 41.2 (C-3) ppm. Anal. Calcd for $C_{30}H_{36}Na_2O_{13}S$ (682.64): C, 52.78; H, 5.32; S, 4.70. Found: C, 52.70; H, 5.29; S, 4.66.

4.53. Methyl (6-*O*-benzyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosyl)-(1→4)-(methyl 2,3-di-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,6-di-*O*-benzyl-3-deoxy-3-*C*-(methyl sulfonatomethyl)-α-D-glucopyranoside (55)

To a stirred solution of **53** (300 mg, 0.315 mmol) in CH_2Cl_2 (1 mL), silica gel (2.50 g) and diazomethane in Et_2O (~5 equiv)

were added at 0 °C. After 2 h another portion of silica gel was added and the mixture was stirred overnight and allowed to warm up to rt. The silica gel was removed by filtration, the filtrate was concentrated. The above-described procedure was repeated three times. The residue was purified by silica gel chromatography (93:7 CH_2Cl_2/acetone) to give syrupy **55** (188 mg, 61%); $[\alpha]_D^{25}$ +36.9 (*c* 0.13, $CHCl_3$); R_f 0.41 (92:8 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3443, 2933, 2838, 1752, 1633, 1496, 1454, 1361, 1289, 1221, 1166, 1102, 1028, 995, 904, 844, 785, 742, 699, 565, 463 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ=7.36–7.28 (15H, arom), 5.42 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1″), 4.66–4.60 (m, 5H, H-1, 2×PhCH_2), 4.52, 4.49 (2d, 2×1H, *J* 12.1, 12.1 Hz, PhCH_2), 4.21 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.13 (dd, 1H, *J* 10.1, 10.3 Hz), 3.90–3.83 (m, 2H), 3.76–3.14 (m, 37H), 2.99 (t, 1H, *J* 8.5, 8.5 Hz), 2.54–2.46 (m, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz) δ=168.7 (CO), 138.2, 138.1, 138.0 (3×C_q arom), 128.5–127.6 (15C, arom), 103.1 (C-1′), 96.8 (C-1), 96.2 (C-1″), 85.6, 83.5, 83.1, 81.6, 78.9, 75.7, 74.9, 74.5, 74.2, 70.7, 70.7 (skeleton carbons), 73.5, 73.4, 72.1 (3×PhCH_2), 67.8, 67.8 (C-6, C-6″), 60.7, 60.6, 60.3, 60.3, 59.2, 55.3, 55.1, 52.5 (8×OCH_3), 45.9 (*C*HSO_3), 39.0 (C-3) ppm. Anal. Calcd for $C_{48}H_{66}O_{19}S$ (979.09): C, 58.88; H, 6.79; S, 3.27. Found: C, 58.99; H, 6.85; S, 3.11.

Acknowledgements

The work was supported by the TÁMOP 4.2.1/B-09/1/KONV-2010-0007 project. The project is co-financed by the European Union and the European Social Fund. Financial support of the Hungarian Research Fund (K 62802) is also acknowledged.

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