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Large-scale synthesis of 6-deoxy-6-sulfonatomethyl glycosides and their application for novel synthesis of a heparinoid pentasaccharide trisulfonic acid of anticoagulant activity

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ABSTRACT

Multigram-scale syntheses of three 6-deoxy-6-sulfonatomethyl α-glucosides were accomplished via reactions of the corresponding primary triflate derivatives with the lithiated ethyl methanesulfonate. Chemoselective glycosylation reactions of different 6-*C*-sulfonatomethyl glucoside donors were studied. The sulfonic acid-containing building blocks were utilised in a novel [2+3] block synthesis of a trisulfonic acid isoster of the anticoagulant pentasaccharide idraparinux.

1. Introduction

Heparin is a linear sulfated polysaccharide that plays a crucial role in maintaining the haemostatic state of blood. Binding to antithrombin, a serine protease inhibitor, accelerates its inhibitory activity against thrombin and factor Xa in the blood-coagulation cascade.[1] The anticoagulant properties of heparin have made it an invaluable drug for prevention and treatment of thromboembolic diseases.[2] However, heparin therapy is limited to intravenous administration and may be accompanied by side effects (inflammation, bleeding, liver toxicity and heparin induced thrombocytopenia) due to the polyanionic and heterogeneous nature of the polysaccharide obtained from animal organs.[3] To develop synthetic heparinoid anticoagulants with fewer adverse effects and a better pharmacokinetic profile the antithrombin-binding DEFGH pentasaccharide fragment of heparin and many simplified analogues have been prepared. These research efforts led to the synthetic antithrombotic drug Arixtra (fondaparinux, **1**)[4] as well as to the non-glycosaminoglycan derivative idraparinux (**2**),[5] both possessing selective factor Xa inhibitory activities (Fig. 1).

Our group has been dealing with the synthesis of bioisosteric sulfonic acid analogues of idraparinux to obtain novel selective factor Xa inhibitors.[6–10] Two pentasaccharide sulfonic acids (**3** and **4**) and the reference compound **2** have been prepared until now.[10,11] Evaluation of the inhibitory activities of pentasaccharides **2**–**4** towards the blood-coagulation proteinase factor-Xa revealed that the disulfonate analogue **3** displayed higher activity than idraparinux, however, introduction of the third sulfonic-acid moiety (**4**) resulted in a notable decrease in anti-Xa activity.[10] To gain deeper insight into the structure–activity relationship of the anticoagulant action of the sulfonic acid derivatives we decided to prepare a series of heparinoid pentasaccharides by systematic replacement of the sulfate esters with a sodium sulfonatomethyl moiety, and we also aimed at preparing compounds **3** and **4** in sufficient amounts for detailed STD NMR studies of their interactions with antithrombin. As a beginning of this work, we present here the multigram-scale syntheses of 6-sulfonatomethyl-containing mono- and disaccharides, useful for modular syntheses of the planned pentasaccharide sulfonic acids, and application of the new building blocks in a novel, [2+3] synthesis of the pentasaccharide trisulfonic acid **4**.

2. Results and discussion

Previously we utilised free-radical addition of bisulfite to exo-methylene derivatives for introducing the sulfonatomethyl group onto primary or secondary positions of saccharides (i.e. **5**→**7**,

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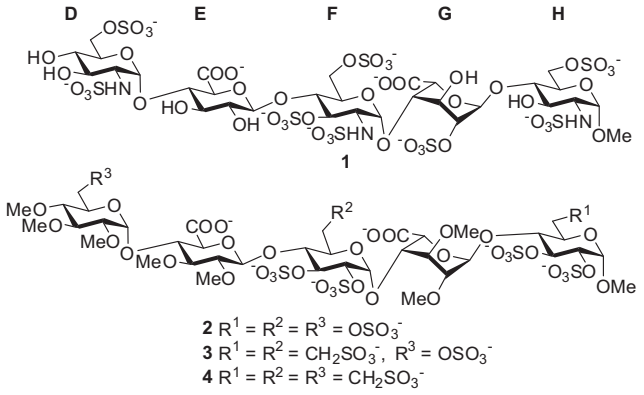
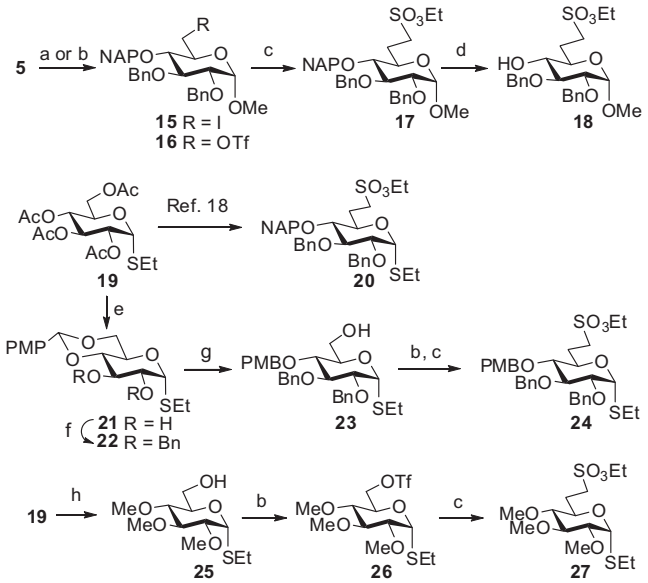


Figure 1. Synthetic pentasaccharides with selective factor Xa inhibitory activity: fondaparinux (**1**), idraparinux (**2**) and its sulfonatomethyl analogues **3** and **4**.

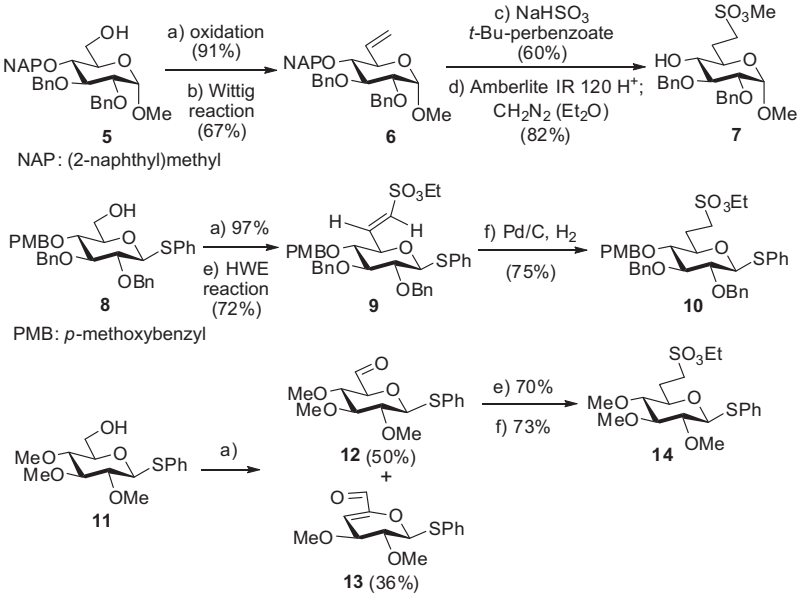
Scheme 1).[6,8,12] As this method, requiring a peroxybenzoate catalysis, is incompatible with the oxidisable thio aglycone, the synthesis of the C6-sulfonatomethyl thioglycosides was accomplished by Horner–Wadsworth–Emmons (HWE) reaction (**8**→**10**, **11**→**14**).[10] However, multistep transformation of compound **5** via addition of the sulfite radical anion to the unsaturated heptoside **6** afforded the glycosyl acceptor building block **7** with only 30% overall yield.[6] Synthesis of the thioglycoside building block **14**[10] from the corresponding 6-hydroxy derivative **11** using HWE olefination[13] proceeded also with unsatisfyingly low 26% overall yield due to the unexpected elimination side reaction[14] that occurred in the oxidation step, either Swern or Dess–Martin oxidation methods were applied (Scheme 1). Thence, we considered both prior approaches to be inefficient for large-scale synthesis of the 6-sulfonatomethyl-containing D and H glycosyl units.

As reaction of a α-lithio sulfonate ester with a primary carbohydrate iodide[15] or triflate[16] appeared in the literature as the most straightforward way to introduce a sulfonatomethyl ester moiety to *O*-glycosides, we decided the exploitation of this facile method for improved synthesis of the glycosyl acceptor building block **7**. The primary iodide **15** prepared from **5**[17] showed low reactivity towards the lithiated ethyl methanesulfonate providing the desired



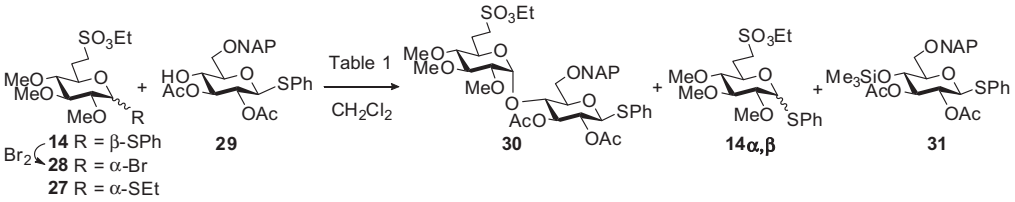
Scheme 2. Synthesis of the sulfonatomethyl-containing glucosyl building blocks by nucleophilic substitution. Reagents and conditions: (a) PPh_3, I_2, imidazole, toluene, 75 °C, 30 min, 90%; (b) Tf_2O, py, CH_2Cl_2, −10 °C, 30 min; (c) *n*-BuLi, THF, CH_3SO_3Et, −78 °C to −20 °C, 2.5 h, 26% from **15**, 88% via **16** over two steps, 33% from **23** over two steps, 88% via **26** over two steps; (d) DDQ, CH_2Cl_2–H_2O (9:1), rt, 30 min 86%; (e) (1) NaOMe, MeOH; (2) 4-methoxybenzaldehyde dimethyl acetal, *p*-toluenesulfonic acid, reflux, 74%; (f) NaH, BnBr, DMF, 0 °C to rt, 90%; (g) $LiAlH_4$–$AlCl_3$ (3:1), CH_2Cl_2–Et_2O, 0 °C, 30 min, 83%; (h) (1) NaOMe, MeOH, (2) TrCl, py, (3) NaH, MeI, DMF, 0 °C to rt, (4) AcOH, 67% over 4 steps.

product **17** with 26% yield (Scheme 2). We attempted to enhance the reactivity of the alkylating agent by adding 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (dimethylpropyleneurea, DMPU) to the reaction mixture that, however, did not lead to higher yield of **17**. Reaction of the α-lithio sulfonate ester with the more reactive triflate derivative **16** proceeded with high efficacy,[18] therefore this transformation was applied in ten-gram-scale to produce the sulfonate ester **17** in excellent 88%. Selective demasking of the 4-OH group by oxidative cleavage of the 2-naphthylmethyl (NAP) ether with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[19]



Scheme 1. Prior syntheses of the 6-deoxy-6-sulfonatomethyl building blocks **7**,[6] **10**[10] and **14**.[10]

Table 1
Syntheses of the DE disaccharide building block **30** by chemoselective glycosylations



Entry	R (Compound)	Promoter system (equiv)	*T* °C	Reaction time	Yield of **30** (%)	Byproduct
1	β-SPh (**14**)	NIS (1.1)-AgOTf (0.2)	−75 to −15	1.5 h	11	**14α,β** (9%)
2	α-Br (**28**)	AgOTf (1.5)	−30	1.5 h	21	**14α,β** (6%)
3	α-SEt (**27**)	NIS (1.5)-TfOH (0.1)	−75 to −50	3 h	31	Degradation products[a]
4	α-SEt (**27**)	NIS (1.5)-TMSOTf (0.2)	−75 to −55	2 h	44	**31** (8%)
5	α-SEt (**27**)	NIS (1.1)-AgOTf (0.2)	−75 to −55	45 min	66	
6	α-SEt (**27**)	NIS (1.1)-AgOTf (0.2)	−75 to −65	45 min	89[b]	

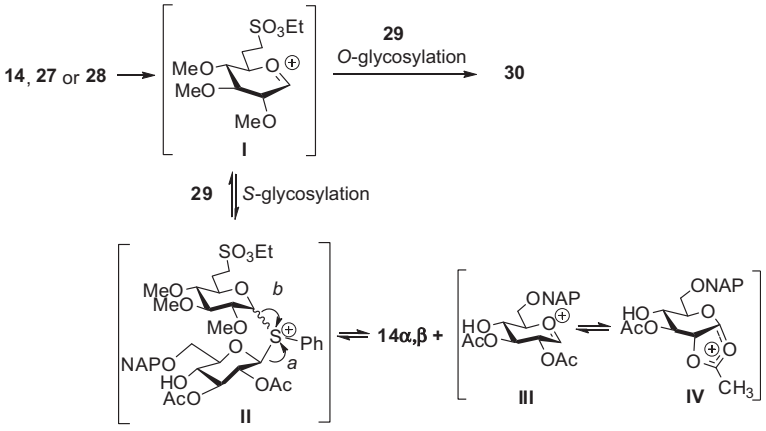
The compounds are represented by bold numbers in Table 1.
[a] Not isolated.
[b] The reaction was carried out in 13 mmol scale to produce 6.0 g of disaccharide **30**.

furnished the glycosyl acceptor building block **18**, the ethyl ester counterpart of the previously prepared **7**, with 86% yield.

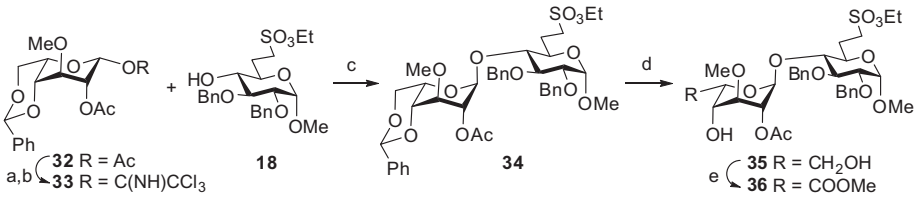
The nucleophilic displacement approach was successfully adapted for the synthesis of thioglucoside **20**, the building block F, as it has been reported very recently.[18] It is important to note that application of α-thioglycoside **19** as the starting material was crucial, because anchimeric assistance of the anomeric group in the displacement of the triflate was observed with β-glycosides.[18,20] In order to cut down the cost of the synthesis of this orthogonally protected glucose unit, the (2-naphthyl)methyl (NAP) masking group at position C-4 was changed to *p*-methoxybenzyl ether, because synthesis of the 4-*O*-PMB-protected derivative **23** via reductive cleavage of the 4,6-*O*-(4-methoxy) benzylidene derivative **22** is significantly cheaper than that of the 4-*O*-NAP congener. Accordingly, the α-thioglucoside **19**, produced stereoselectively in forty-gram-scale by our recently published photoinduced hydrothiolation method,[21] was converted into **23** by routine transformations, involving Zemplén deacetylation followed by acetalation (**21**), benzylation (**22**) and regioselective opening of the 4,6-acetal ring with $LiAlH_4$–$AlCl_3$. Unfortunately, the 4-*O*-PMB protection turned out to be inappropriate for the following two-step nucleophilic procedure. Besides formation of the corresponding triflate, degradation was also observed upon treatment of **23** with triflic anhydride and the subsequent reaction with α-lithio sulfonate ester provided the desired sulfonate ester **24** in a low, 33% yield over two steps.

Large scale synthesis of the terminal 6-sulfonatomethyl-containing building block **27** was also accomplished by the above nucleophilic substitution method. The starting α-thioglucoside **19** was transformed into **25** via Zemplén deacetylation, tritylation, methylation and detritylation. Triflation of the primary free hydroxyl of thioglucoside **25** took place quantitatively, and subsequent nucleophilic displacement of the triflate moiety of **26** with the α-lithiosulfonate ester afforded **27** in 88% yield for two steps (Scheme 2). The latter two-step procedure was carried out in 40 mmol scale to provide almost 13 g of the 6-sulfonatomethyl-containing D building block **27**.

Having the 6C-sulfonatomethyl-glucoside building blocks in large scale in our hands, we started the synthesis of the pentasaccharide trisulfonic acid **4**. Previously, compound **4** was gained via construction of an L-iduronic-acid-containing trisaccharide disulfonic acid as an FGH acceptor, and its elongation with a non-oxidised precursor of the glucuronic acid unit E followed by post-glycosidation oxidation at a tetrasaccharide level, and a subsequent [1+4] coupling. Although the stepwise elongation approach proved to be efficient, this time a [DE+FGH] route to **4** was envisioned for two reasons. First, the block synthesis precludes excessive synthetic steps at the tetrasaccharide level, and second, the sulfonatomethyl-containing DE donor can be utilised in the syntheses of further pentasaccharide mono-, and disulfonic acids. Therefore, we decided to prepare disaccharide **30** as the new non-glucuronide type disaccharide donor. We assumed that either compound **14**, used in prior synthesis of **4**,[10] or the newly prepared **27**, both being armed thioglycosides, could be applied for chemoselective glycosylations[22] of the disarmed thioglycoside **29**[9] (Table 1). When **14** and **29** were reacted in the presence of NIS and AgOTf significant amounts of degradation products were observed and the desired disaccharide **30** was isolated in a disappointingly low 11% yield (Table 1, entry 1). Interestingly, the donor was recovered as an unseparable alpha/beta mixture **14α,β** (α:β ~ 5:1), revealing that the yield of disaccharide formation was decreased by a competitive *S*-glycosylation reaction in which thiophenyl aglycon was transferred from acceptor **29** to donor **14** through the intermediate sulfonium ion **II** (Scheme 3).[23] On the basis of the mechanism of the aglycon transfer depicted in Scheme 3, glycosylation on the sulfur atom of product **30** is also possible.[23g] Therefore, the yield of the process could also be decreased by destroying the product of the O-glycosylation reaction. We attempted to improve the synthesis of disaccharide **30** by condensation of acceptor **29** with donor **28** obtained from thioglucoside **14** by bromination. Although compound **30** was formed with higher yield, aglycon transfer to the detriment of the *O*-glycoside formation was also observed (Table 1, entry 2). The further experiments were carried out with the newly prepared donor **27** (Table 1, entries 3–6). Due to the high reactivity of the ethylthio glycoside **27**, the condensation reactions could be conducted at low temperatures in all runs, which was beneficial for the O-glycosylation reaction. The NIS-TfOH mediated glycosylation gave disaccharide **30** in 31% yield; significant amounts of degradation products were also formed, probably owing to the long reaction time (Table 1, entry 3). Decreasing the reaction time and changing the promoter system from NIS-TfOH to NIS-TMSOTf resulted in a slightly higher yield of **30**, however, the new byproduct **31** appeared in the reaction mixture due to silylation of the acceptor by the TMSOTf catalyst (Table 1, entry 4). The NIS-AgOTf mediated condensation (Table 1, entry 5) turned out to be superior affording disaccharide **30** with 66% yield. Carrying out the reaction in large scale at slightly lower reaction temperature led to more efficient



Scheme 3. Formation of aglycon transfer product **14α,β** during syntheses of disaccharide **30**.



Scheme 4. Synthesis of the GH disaccharide acceptor **36**. Reagents and conditions: (a) $BnNH_2$, THF, rt, 5 h, 70%; (b) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 1 h, 94%; (c) TMSOTf, CH_2Cl_2, 4 Å MS, −40 °C to −15 °C, 1 h, 82%; (d) 70% aq TFA, CH_2Cl_2, 0 °C to rt, 5 h, 87%; (e) (1) TEMPO, BAIB, CH_2Cl_2, H_2O, rt, 3 h, (2) CH_2N_2·Et_2O, THF, 24 h, 70%.

O-glycosylation to produce 6.0 g (89%) of the desired DE building block (Table 1, entry 6).

During previous synthesis of pentasaccharides **3** and **4** the common FGH trisaccharide acceptor bearing a 6-sulfonatomethyl moiety at units F and H has been built up from an L-iduronic acid and two monosaccharide sulfonic acids via a [FG+H] coupling.[10] However, that route had the drawback that conversion of the uronic- and sulfonic-acid-containing FG disaccharide into a donor proceeded with low yield. To avoid this inefficient transformation, now the sequence of the couplings was changed and the GH disaccharide was prepared first.

For the synthesis of the GH unit **36**, the L-idose derivative **32**[9] was converted to donor **33** by selective anomeric deacetylation and subsequent trichloroacetimidoylation of the obtained hemiacetal (Scheme 4). Condensation of **33** and acceptor **18** in the presence of TMSOTf led to the stereoselective formation of the α-linked disaccharide **34**. As application of this building block in future syntheses of pentasaccharide mono-, and disulfonic acids was also planned, it was prepared in 10 mmol scale (6.6 g). Removal of the benzylidene protecting group of the fully protected **34** by acidic hydrolysis afforded diol **35** which was subjected to (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO)-[bis(acetoxy) iodo]benzene (BAIB) mediated selective oxidation[24] followed by treatment with ethereal diazomethane to yield the iduronide acceptor **36** in 61% over the last three steps.

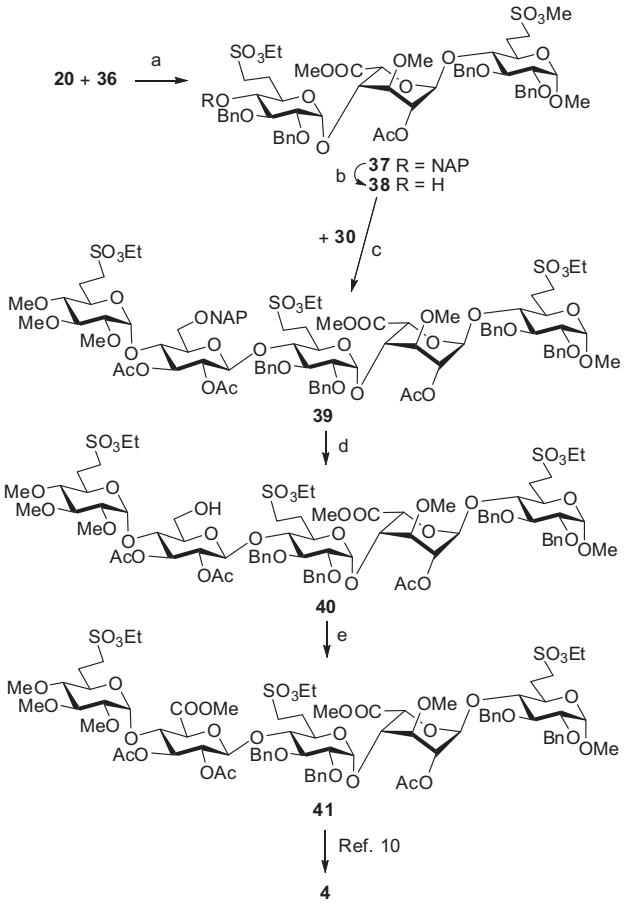
Next, NIS and TfOH promoted glycosylation of **36** with the ethylthio glycoside donor **20**[18] proceeded with full α-selectivity to provide the trisaccharide disulfonic acid **37** with excellent 92% yield (Scheme 5). Liberation of the 4-OH group of the terminal glucose unit of **37** was accomplished by oxidative removal of the NAP-group using DDQ as a reagent,[19] furnishing the trisaccharide acceptor **38** in 79% yield. Condensation of **38** and the disaccharide donor **30** upon NIS-AgOTf activation afforded pentasaccharide **39**, with the required β-linkage between units E and F, in a yield of 65%. The 6-position of the penultimate glucose unit was unmasked by oxidative de-*O*-(2-napthyl)methylation to produce **40** which was transformed to **41** by TEMPO-(BAIB) oxidation[24] followed by treatment with ethereal diazomethane. The fully protected **41** was an intermediate in the previous synthesis route of the pentasaccharide trisulfonic acid **4**. Transformation of **41** into **4**, involving deprotection steps and introduction of the methyl ether and sulfate ester functions were carried out according to the published procedure.[10]

3. Conclusions

The straightforward nucleophilic approach provided easy access to three 6-deoxy-6 sulfonatomethyl α-glucosides from the corresponding 6-OH derivatives in multigram scale. The low yields observed with the 6-deoxy-6-iodo glucoside **15** and the 4-*O*-PMB protected derivative **23** revealed that the nature of both the leaving group at C-6 position and the protecting group at C-4 position is crucial for the efficacy of the nucleophilic procedure.

During synthesis of disaccharide **30** by chemoselective glycosylation, the newly prepared ethyl 6-deoxy-6-*C*-(ethyl sulfonatomethyl)-2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside **27** could be applied efficiently as an armed donor. The failed chemoselective glycosylations with the phenylthio glucoside **14** and glycosyl bromide **28** can be explained by their lower reactivity. Activation of **14** and **28** required a higher activation temperature than that of **27**, at which temperature the chemoselectivity was eroded.

Synthesis of the anticoagulant pentasaccharide trisulfonic acid **4** was accomplished via a new block-synthetic route involving an improved synthesis of the L-iduronic-acid-containing FGH trisaccharide acceptor **38**, its condensation with the disaccharide donor **30** and formation of the D-glucuronide residue at a pentasaccharide level.



Scheme 5. Construction of the pentasaccharide trisulfonic acid **24** by 3+2 coupling and post-glycosidation oxidation of the penultimate glucose unit into glucuronic acid. Reagents and conditions: (a) NIS, TfOH, CH_2Cl_2, THF, 4 Å MS, −60 °C to −50 °C, 3 h, 92%; (b) DDQ, CH_2Cl_2–H_2O (9:1), rt, 30 min, 79%; (c) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −20 °C to rt, 3 h (65%); (d) DDQ, CH_2Cl_2–H_2O (9:1), rt, 45 min (84%); (e) (1) TEMPO, BAIB, CH_2Cl_2, H_2O, rt 5 h, (2) CH_2N_2·Et_2O, THF (62%).

NMR and ITC studies of the interaction of compound **4** with antithrombin, as well as utilisation of the sulfonatomethyl-containing mono- and disaccharide building blocks in the syntheses of further sulfonic acid isosters of idraparinux are in progress.

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). Organic solutions were dried over $MgSO_4$, and concentrated in vacuum. The ^1H NMR (360 and 400 MHz) and ^{13}C NMR (90.54 and 100.28 MHz) spectra were recorded with Bruker DRX-360 and DRX-400 spectrometers at 25 °C. Chemical shifts are referenced to Me_4Si or DSS (0.00 ppm for ^1H) and to the solvent signals ($CDCl_3$: 77.00 ppm for ^{13}C). The ^1H and ^{13}C NMR assignments have been established from 1D NMR spectra and for compounds **30**, **36** and **39** the proton-signal assignments were supported by analysis of two-dimensional ^1H–^1H correlation spectra (COSY), as well as the carbon-signal assignments by two-dimensional ^{13}C–^1H correlation maps (HSQC). 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 saturated 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 introduction of the trifluoromethanesulfonyl group (16, 24, 26)

To a solution of the appropriate alcohol (1 mmol) in dry CH_2Cl_2 (2 mL), dry pyridine (0.25 mL) was added. The stirred mixture was cooled to −10 °C under argon and trifluoromethanesulfonic anhydride (0.24 mL, 1.4 mmol) dissolved in CH_2Cl_2 (0.7 mL) was added. After the complete disappearance of the starting material (30 min), the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed successively with H_2O (15 mL), 1 M HCl (15 mL), H_2O (15 mL), satd aq $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic phase was dried and concentrated at 30 °C. The crude product was used for further reaction without purification.

4.3. General method B for introduction of ethyl sulfonatomethyl group from the appropriate triflate (17, 24, 27)

A solution of methanesulfonic acid ethyl ester (0.2 mL, 2 mmol) in dry THF (5 mL) was cooled to −80 °C under argon and 2.5 M *n*-BuLi (0.8 mL, 2 mmol) in *n*-hexane was added. After stirring at −78 °C for 30 min, a solution of the corresponding triflate (1 mmol) in dry THF (2.5 mL) was added dropwise. The reaction mixture was stirred for 1.5 h while its temperature was raised to −20 °C. The stirred mixture was quenched by the addition of satd aq NH_4Cl solution (10 mL) and diluted with EtOAc (30 mL). The organic phase was washed successively with satd aq NH_4Cl solution (10 mL), H_2O (10 mL), satd aq NaCl solution (10 mL), dried and concentrated.

4.4. General method C for removal of the (2-naphthyl)methyl ether group (18, 38 and 40)

To a vigorously stirred solution of starting material (1 mmol) in CH_2Cl_2/H_2O (9:1, 10 mL) DDQ (1.5 mmol) was added. The reaction mixture was stirred at room temperature for 30 min (18, 38) and 45 min (40), diluted with CH_2Cl_2 (30 mL), washed successively with satd aq $NaHCO_3$ solution (15 mL) and H_2O (15 mL). The organic phase was dried and concentrated. The crude product was purified by column chromatography.

4.5. General method D for TEMPO-BAIB oxidation and subsequent esterification (36, 41)

To a vigorously stirred solution of the appropriate alcohol (1 mmol) in CH_2Cl_2 (25 mL) and H_2O (12.5 mL) were added TEMPO (0.18 mmol) and BAIB (4 mmol), stirred for 3 h (**36**) and 5 h (**41**) at room temperature. The reaction mixture was quenched by the addition of 10% aq $Na_2S_2O_3$ solution (20 mL). The mixture was then extracted twice with CH_2Cl_2 (10 mL), and the combined organic layers were dried, and concentrated. The crude uronic acid was dissolved in THF (3 mL) and treated with ethereal diazomethane at 0 °C. After complete disappearance of the uronic acid, the mixture was concentrated.

4.6. Methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-4-*O*-(2′-naphthyl)methyl-α-D-glucopyranoside (15)

Triphenyl phosphine (765 mg, 2.9 mmol), imidazole (397 mg, 5.8 mmol) and iodine (690 mg, 2.7 mmol) were added to the

solution of **5** (1 g, 1.9 mmol) in dry toluene (16 mL). The stirred mixture was heated and refluxed at 75 °C. After 30 min the reaction was quenched by addition of a solution of $NaHCO_3$ (650 mg, 7.7 mmol) in H_2O (8 mL) and was stirred for 5 min. Satd aq $Na_2S_2O_3$ solution (15 mL) was added to the stirred mixture and it was diluted with EtOAc (50 mL). The organic phase was washed with H_2O (2 × 25 mL), dried and concentrated. Et_2O (15 mL) was added to the residue and the solution was placed in the refrigerator for 1 h. The precipitated Ph_3PO was filtered off and the filtrate was concentrated. The residue was purified by column chromatography to give **15** (1.09 g, 90%) as white crystals. Mp 55–59 °C; R_f 0.46 (8:2 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +12.8 (*c* 0.17, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.84–7.76 (m, 3H, arom), 7.69 (s, 1H, arom), 7.50–7.43 (m, 2H, arom), 7.41–7.25 (m, 11H, arom), 5.08 (d, *J* = 11.2 Hz, 1H, ArC*H*$_2$), 5.02 (d, *J* = 10.9 Hz, 1H, ArC*H*$_2$), 4.87–4.77 (m, 3H, H-1, 2 × ArC*H*$_2$), 4.67 (d, *J* = 12.1 Hz, 1H, ArC*H*$_2$), 4.62 (d, *J* = 3.6 Hz, 1H, H-1), 4.08–4.02 (m, 1H) 3.56 (dd, $J_{2,3}$ = 9.6, $J_{1,2}$ = 3.6 Hz, 1H, H-2), 3.53–3.44 (m, 2H), 3.43–3.35 (m, 1H), 3.42 (s, 3H, OC*H*$_3$), 3.32–3.28 (m, 1H), ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.7, 138.2, 135.6, 133.4, 133.1 (5 × C_q arom), 128.6, 128.6, 128.4, 128.2, 128.1, 127.8, 126.8, 126.3, 126.1, 125.9 (17C, arom), 98.2 (C-1), 81.7, 81.6, 80.3, 69.42 (C-2, C-3, C-4, C-5) 75.9, 75.5, 73.5 (3 × ArCH$_2$), 55.7 (OCH$_3$), 7.9 (C-6) ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (484.32): C, 52.08; H, 5.20; I, 26.20; O, 16.52. Found: C, 51.92; H, 5.31.

4.7. Methyl 2,3-di-*O*-benzyl-4-*O*-(2′-naphthyl)methyl-6-*O*-(trifluoromethanesulfonyl)-α-D-glucopyranoside (16)

Compound **5** (9.5 g, 18.5 mmol) was converted to **16** according to general method **A**. The crude product was used for further reaction without purification. R_f 0.78 (6:4 *n*-hexane/EtOAc).

4.8. Methyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-4-*O*-(2′-naphthyl)methyl-α-D-glucopyranoside (17)[18]

4.8.1. Starting from the appropriate 6-deoxy-6-iodide derivative 15

A solution of methanesulfonic acid ethyl ester (325 μL, 3.1 mmol) and 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU) (375 μL, 3.1 mmol) in dry THF (10 mL) was cooled to −80 °C under argon and 2.5 M *n*-BuLi (1.25 mL, 3.1 mmol) in *n*-hexane was added. After stirring at −78 °C for 30 min, a solution of compound **15** (970 mg, 1.55 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred for 1.5 h while its temperature was raised to −20 °C. The stirred mixture was quenched by the addition of satd aq NH_4Cl solution (15 mL) and diluted with EtOAc (50 mL). The organic phase was washed successively with satd aq NH_4Cl solution (15 mL), H_2O (15 mL), satd aq NaCl solution (15 mL), dried and concentrated. The crude product was purified by column chromatography (7:3 *n*-hexane–EtOAc) to give **17** (253 mg, 26%) as a colourless oil.

4.8.2. Starting from the appropriate 6-*O*-triflate derivative 16

Compound **16** (9.7 mg, 15 mmol) was converted to **17** according to general method **B**. The crude product was purified by column chromatography (7:3 *n*-hexane–EtOAc) to give **17** (10.27 g, 88%) as a colourless oil. The analytical data of compound **17** are consistent with those are given in the literature.[18]

4.9. Methyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (18)

Compound **17** (390 mg, 0.63 mmol) was converted to **18** according to general method **C**. The crude product was purified by column chromatography (6:4 *n*-hexane–EtOAc) to give **18** (259 mg, 86%) as a colourless oil. R_f 0.34 (6:4 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +15.21 (*c* 0.72, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37–7.23 (m, 10H, arom), 4.98 (d, *J* = 11.4 Hz, 1H, PhC*H*$_2$), 4.74–4.69 (m, 2H, PhC*H*$_2$), 4.62 (d, *J* = 12.1 Hz, 1H, PhC*H*$_2$), 4.54 (d, *J* = 3.4 Hz, 1H, H-1), 4.23 (q, *J* = 7.1 Hz, 2H, $SO_3CH_2CH_3$), 3.72 (t, *J* = 9.2 Hz, 1H, H-4), 3.57 (m, 1H, H-5), 3.45 (dd, *J* = 9.6, *J* = 3.4 Hz, 1H, H-2), 3.32 (s, 3H, OC*H*$_3$), 3.29–3.15 (m, 2H, H-3, H-7a), 3.09 (m, 1H, H-7b), 2.72 (s, 1H, O*H*), 2.40–2.28 (m, 1H, H-6a), 1.95–1.84 (m, 1H, H-6b), 1.34 (t, *J* = 7.1 Hz, 3H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.6, 137.9 (2 × C_q arom), 128.4, 128.4, 127.9, 127.8, 127.7 (10C, arom), 97.9 (C-1), 81.0, 79.6, 73.4, 68.5 (C-2, C-3, C-4, C-5), 75.2, 72.9 (2 × PhCH$_2$), 66.1 ($SO_3CH_2CH_3$), 55.2 (OCH$_3$), 46.5 (C-7), 25.9 (C-6), 15.0 ($SO_3CH_2CH_3$) ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (480.57): C, 59.98; H, 6.71; O, 26.63; S, 6.67. Found: C, 60.06; H, 6.81; S, 6.55.

4.10. Ethyl 4,6-*O*-(4-methoxybenzylidene)-1-thio-α-D-glucopyranoside (21)

To the solution of compound **19** (22 g, 56.2 mmol) in MeOH (100 mL) was added NaOMe (250 mg, 4.6 mmol) and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched by addition of Amberlite IR-120 (H^+) resin. The crude product (11.9 g) was dissolved in DMF (30 mL) and 4-methoxybenzaldehyde dimethyl acetal (10.4 mL, 58.9 mmol) and *p*-toluenesulfonic acid (149 mg, 0.87 mmol) were added. After 4 h stirring at 50 °C on 100 mbar pressure, the mixture was concentrated. The residue was dissolved in CH_2Cl_2 (150 mL), washed successively with satd aq $NaHCO_3$ solution (30 mL), H_2O (2 × 30 mL), dried and concentrated. The residue was purified by crystallisation from CH_2Cl_2 (40 mL) and *n*-hexane (80 mL) to give 21 (14.24 g, 74% for 2 steps) as white crystals.

Mp 120–124 °C; R_f 0.45 (6:4 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +134.5 (*c* 0.07, $CHCl_3$); IR ν_{max} (KBr) 3418, 2969, 2927, 1681, 1601, 1517, 1457, 1426, 1373, 1302, 1254, 1170, 1108, 1076, 1036, 979, 1036, 979, 830, 787, 634, 607 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H, arom), 6.89 (d, *J* = 8.5 Hz, 2H, arom), 5.49 (s, 1H, ArC*H*), 5.39 (d, *J* = 5.3 Hz, 1H, H-1), 4.30–4.14 (m, 2H), 4.02–3.69 (m, 4H), 3.80 (s, 3H, OC*H*$_3$), 3.48 (t, *J* = 9.2 Hz, 1H), 2.72–2.66 (m, 2H, SC*H*$_2$CH$_3$), 1.33 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$,) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 129.9 (2 × C_q arom), 127.8, 113.9, (2C, arom), 101.3 (PMPCH), 84.3 (C-1), 81.3, 78.8, 78.7, 62.8 (C-2, C-3, C-4, C-5), 75.2, 72.9, (2 × *C*H$_2$Ph), 68.9 (C-6), 55.5 (OCH$_3$), 26.1 (SCH$_2$CH$_3$), 15.2 (SCH$_2$CH$_3$) ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (342.41): C, 56.12; H, 6.48; O, 28.04; S, 9.36. Found: C, 56.17; H, 6.39; S, 9.42.

4.11. Ethyl 2,3-di-*O*-benzyl-4,6-*O*-(4-methoxybenzylidene)-1-thio-α-D-glucopyranoside (22)

The solution of **21** (14 g, 40.9 mmol) in dry DMF was cooled to 0 °C under argon and 60% NaH (4.9 g, 0.12 mol) was added in portions to the reaction. After 30 min benzyl bromide (11.7 mL, 98 mmol) was added to the mixture and stirred for 12 h. The reaction was quenched with addition of MeOH and concentrated in vacuo. The residue was dissolved with CH_2Cl_2 (300 mL), washed successively with satd aq $NaHCO_3$ (100 mL) and H_2O (2 × 100 mL). The organic phase was dried and concentrated. The residue was purified by crystallisation from EtOAc (25 mL) and *n*-hexane (50 mL) to give **22** (19.24 g, 90%) as white crystals. Mp 86–91 °C; R_f 0.46 (8:2 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +81.2 (*c* 0.12, $CHCl_3$); IR ν_{max} (KBr) 3442, 3065, 3033, 2898, 2864, 1614, 1517, 1496, 1455, 1423, 1367, 1303, 1252, 1214, 1171, 1091, 1031, 959, 931, 822 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44–7.21 (m, 12H, arom), 6.89 (d, *J* = 8.7 Hz, 2H, arom), 5.50 (s, 1H, PMPC*H*), 5.37 (d,

J = 5.5 Hz, 1H, H-1), 4.88–4.67 (m, 4H, PhCH_2), 4.31–4.17 (m, 2H), 3.91 (t, J = 9.1 Hz, 1H), 3.84–3.80 (m, 1H), 3.78 (s, 3H, OCH_3), 3.71 (t, J = 9.7 Hz, 1H), 3.59 (t, J = 9.1 Hz, 1H), 2.61–2.47 (m, 2H, SCH_2-CH$_3$), 1.27 (t, J = 7.4 Hz, 3H, SCH$_2$CH_3) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 138.8, 137.9, 130.0 (4 × C_q arom), 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.6, 127.4, 113.6, (14C, arom), 101.3 (PMPCH), 84.1 (C-1), 81.9, 79.0, 78.9, 62.9 (C-2, C-3, C-4, C-5), 75.3, 72.8, (2 × CH_2Ph), 68.9 (C-6), 55.3 (OCH_3), 23.8 (SCH$_2$CH$_3$), 14.9 (SCH$_2$CH_3) ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (522.65): C, 68.94; H, 6.56; O, 18.37; S, 6.14. Found: C, 68.29; H, 6.52; S, 5.80.

4.12. Ethyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-1-thio-α-D-glucopyranoside (23)

To a stirred solution of **22** (17 g, 32.5 mmol) in a mixture of dry CH_2Cl_2 (300 mL) and dry Et_2O (130 mL) $LiAlH_4$ (5.55 g, 0.15 mol) and a solution of $AlCl_3$ (6.5 g, 48.8 mmol) in dry Et_2O (100 mL) were successively added under argon at 0 °C. When the TLC (7:3 *n*-hexane/EtOAc) indicated complete disappearance of the starting material (30 min), the reaction mixture was cooled in an ice-bath, the excess reagent decomposed by careful addition of EtOAc (200 mL) and H_2O (50 mL), and the mixture stirred for an additional 10 min. The obtained heterogeneous mixture containing a finely precipitated solid was filtered through a pad of Celite, and the filter cake was washed with EtOAc (2 × 30 mL). The combined filtrates were transferred into a separating funnel and diluted with EtOAc (50 mL), the layers were separated and the organic phase was washed with H_2O (3 × 50 mL), dried and concentrated. The residue was purified by column chromatography (65:35 *n*-hexane/EtOAc) to give **23** (14.18 g, 83%), as white crystals. Mp 47–49 °C; R_f 0.33 (7:3 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +112.1 (*c* 0.39, $CHCl_3$); NMR (360 MHz, $CDCl_3$) δ 7.40–7.24 (m, 10H, arom), 7.20 (d, J = 8.6 Hz, 2H, arom), 6.84 (d, J = 8.6 Hz, 2H, arom), 5.34 (d, J = 5.4 Hz, 1H, H-1), 4.95 (d, J = 10.9 Hz, 1H, ArCH_2), 4.79 (dd, J = 10.8, 2.7 Hz, 2H, ArCH_2), 4.72 (d, J = 11.8 Hz, 1H, ArCH_2), 4.64 (d, J = 11.7 Hz, 1H, ArCH_2), 4.57 (d, J = 10.7 Hz, 1H, ArCH_2), 4.07–4.03 (m, 1H), 3.87 (t, J = 9.2 Hz, 1H), 3.80–3.66 (m, 3H), 3.76 (s, 3H, OCH_3), 3.51 (t, J = 9.4 Hz, 1H), 2.60–2.42 (m, 2H, SCH_2CH$_3$), 1.76–1.68 (m, 1H, O*H*), 1.26 (t, J = 7.4 Hz, 3H, SCH$_2$CH_3) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.4, 138.9, 137.9, 130.4 (4 × C_q arom), 129.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 114.0 (14C, arom), 83.1 (C-1), 82.5, 79.8, 77.0, 71.2 (C-2, C-3, C-4, C-5), 75.7, 74.7, 72.4 (3 × ArCH$_2$), 62.0 (C-6), 55.3 (OCH$_3$), 23.8 (SCH$_2$CH$_3$), 14.8 (SCH$_2$CH$_3$) ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (524.67): C, 68.68; H, 6.92; O, 18.30; S, 6.11. Found: C, 68.82; H, 6.77; S, 6.21.

4.13. Ethyl 2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-4-*O*-(4-methoxybenzyl)-1-thio-α-D-glucopyranoside (24)

Compound **23** (14 g, 1.55 mmol) was converted to the corresponding triflate according to general method **A**. The crude triflate (17.3 g) was converted to **24** according to general method **B**. The crude product was purified by column chromatography to give **24** (5.6 g, 33%) as a colourless oil. R_f 0.59 (7:3 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +95.17 (*c* 0.13, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.20 (m, 12H, arom), 6.85 (d, J = 8.6 Hz, 2H, arom), 5.28 (d, J = 5.0 Hz, 1H, H-1), 4.95 (d, 1H, ArCH_2), 4.83–4.61 (m, 4H, ArCH_2), 4.54 (d, J = 10.7 Hz, 1H, ArCH_2), 4.27–4.17 (m, 2H, SO$_3$CH_2CH$_3$), 4.06–4.00 (m, 1H), 3.83–3.73 (m, 2H), 3.75 (s, 3H, OCH_3), 3.19–2.95 (m, 3H), 2.53–2.42 (m, 2H, SCH_2CH$_3$), 2.34–2.25 (m, 1H, H-6a), 1.93–1.80 (m, 1H, H-6b), 1.34, 1.26 (2 × t, 6H, SCH$_2$CH_3, SO$_3$-CH$_2$CH_3) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.4, 138.6, 137.7, 129.9 (4 × C_q arom), 129.8, 128.4, 128.4, 128.0, 127.9, 127.9, 127.6, 113.9 (14C, arom), 82.9 (C-1), 82.2, 80.3, 79.6, 68.7 (C-2, C-3, C-4, C-5), 75.6, 74.7, 72.3 (3 × ArCH$_2$), 66.0 (SO$_3$CH$_2$CH$_3$), 55.2 (OCH$_3$), 46.9 (C-7), 25.8 (C-6), 23.8 (SCH$_2$CH$_3$), 15.1 (SO$_3$CH$_2$CH$_3$), 14.7 (SCH$_2$CH$_3$), ppm; Anal. Calcd for $C_{99}H_{118}O_{27}$ (630.81): C, 62.83; H, 6.71; O, 20.29; S, 10.17. Found: C, 62.89; H, 6.62; S, 10.24.

4.14. Ethyl 2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside (25)

To a solution of **19** (40 g, 0.1 mol) in MeOH (200 mL) a catalytic amount of NaOMe was added. After 2 h stirring, the mixture was neutralised with Amberlite IR-120 (H^+) to give the corresponding tetrahydroxy derivative (22.8 g). To a solution of the crude product (22.8 g) in pyridine (100 mL) TrCl (57 g, 0.2 mol) was added. The mixture was stirred for 48 h at room temperature. After completion of the reaction, the mixture was concentrated in vacuo to give the 6-*O*-trityl derivative (47.5 g) To the solution of the residue in DMF (2 × 400 mL) at 0 °C were successively added 60% NaH (40.77 g, 1.02 mol) and MeI (151 mL, 0.82 mol). After 1 h stirring at this temperature, MeOH (2 × 45 mL) was added. The reaction mixture was stirred for 15 min, and the solvents were evaporated. A solution of the crude 2,3,4-tri-*O*-methyl-6-*O*-triphenylmethyl derivative (56.2 g) in AcOH (80%, 400 mL) was stirred for 1 h at 30 °C. The mixture was then concentrated in vacuo and the residue was purified by column chromatography to give **25** (18.15 g, 67% for 4 steps). Mp 38–41 °C; $[\alpha]_D^{25}$ +270.21 (*c* 0.523, $CHCl_3$); R_f 0.23 (98:2 CH_2Cl_2/CH_3OH); Anal. Calcd for $C_{88}H_{110}O_{27}$ (266.35): C, 49.60; H, 8.33; O, 30.03; S, 12.04. Found: C, 49.84; H, 8.11; S, 11.87.

4.15. Ethyl 2,3,4-tri-*O*-methyl-6-*O*-(trifluoromethanesulfonyl)-1-thio-α-D-glucopyranoside (26)

Compound **25** (10.5 g, 39.5 mmol) was converted to **26** according to general method **A**. The crude product (13.59 g) was used for further reaction without purification. R_f 0.64 (6:4 *n*-hexane/EtOAc).

4.16. Ethyl 6-deoxy-6-*C*-(ethyl sulfonatomethyl)-2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside (27)

Compound **26** (13.59 g, 39.5 mmol) was converted to **27** according to general method **B**. The crude product was purified by column chromatography to give **27** (12.87 g, 88% for two steps) as a light brown oil; R_f 0.50 (6:4 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +139.49 (*c* 3.27, $CHCl_3$); IR ν_{max} (KBr): 3635, 2936, 2835, 1445, 1352, 1174, 1089, 1006, 974, 920, 814, 643, 574, 529, 472 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.40 (d, J = 5.4 Hz 1H, H-1), 4.31 (q, J = 7.1 Hz, 2H, SO$_3$CH_2CH$_3$), 3.97–3.91 (m, 1H, J = 5.5 Hz, 9.6 Hz, H-5), 3.59, 3.56, 3.48 (3 × s, 9H, 3 × OC*H3*), 3.45–3.41 (m, 1H, H-2), 3.34–3.24 (m, 2H, H-4, H-7a), 3.13–3.05 (m, 1H, H-7b), 2.83 (t, 1H, J = 9.5 Hz, 8.8 Hz, H-3), 2.56–2.50 (m, 2H; SCH_2CH$_3$), 2.42–2.32 (m, 1H; H-6a), 2.02–1.91 (m, 1H, H-6b), 1.42 (t, J = 7.1 Hz, 3H; SO$_3$CH$_2$CH_3), 1.29 (t, J = 7.4 Hz, 3H; SCH$_2$CH_3),[13]C NMR (90 MHz, $CDCl_3$): δ 83.5 (C-1), 83.2, 82.4, 81.3, 68.5 (C-2, C-3, C-4, C-5), 66.0 (SO$_3$CH$_2$CH$_3$), 60.6, 60.5, 57.9 (3 × OCH$_3$), 46.9 (C-7), 25.8 (C-6), 23.8 (SCH$_2$CH$_3$), 14.9 (SO$_3$CH$_2$CH$_3$), 14.5 (SCH$_2$CH$_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 395.12. Found: 395.08. Anal. Calcd for $C_{88}H_{110}O_{27}$ (372.50): C, 45.14; H, 7.58; O, 30.07; S, 17.22. Found: C, 44.97; H, 7.75; S, 17.43.

4.17. Phenyl [6-deoxy-6-*C*-(ethyl sulfonatomethyl)-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 (30), phenyl 6-deoxy-6-*C*-(ethyl sulfonatomethyl)-2,3,4-tri-*O*-methyl-1-thio-α-D-glucopyranoside (14α,β) and phenyl 2,3-di-*O*-acetyl-6-*O*-(2′-naphthyl)methyl-4-*O*-trimethylsilyl-1-thio-α-D-glucopyranoside (31)

Method I (entry 1): To a solution of donor **14**[10] (200 mg, 0.47 mmol), and acceptor **29**[9] (252 mg, 0.31 mmol) in dry CH_2Cl_2

(10 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −75 °C under argon. After 30 min at this temperature, NIS (116 mg, 0.52 mmol) dissolved in THF (155 μL) and AgOTf (29 mg, 0.11 mmol) dissolved in toluene (155 μL) were added. The temperature was increased to −15 °C in 1.5 h. The reaction mixture was quenched with Et_3N (50 μL), diluted with CH_2Cl_2 (200 mL) and filtered through a pad of Celite. The filtrate was concentrated. The crude product was purified by column chromatography (1:1 *n*-hexane/EtOAc) to give **30** (45 mg, 11%) and **14α,β** (17 mg, 9%) each as a colourless syrup.

Method II (entry 2): A solution of 14 (200 mg, 0.47 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0 °C under argon. To the solution Br_2 (24 μL) was added and stirred for 30 min. The reaction mixture was concentrated at 30 °C and co-evaporated with toluene (2 × 5 mL). The obtained glycosyl bromide and acceptor **29** (252 mg, 0.31 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and 4 Å molecular sieves (0.50 g) were added. The solution was stirred for 15 min at room temperature then further 15 min at –30 °C. AgOTf (185 mg, 0.70 mmol) dissolved in toluene (900 μL) was added and the mixture was allowed to warm up to room temperature in 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and filtered through a pad of Celite. The filtrate was washed successively with aq $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic phase was dried and concentrated. The crude product was purified by column chromatography (1:1 *n*-hexane/EtOAc) to give 30 (55 mg, 14%) and **14α,β** (12 mg, 6%).

Method III (entry 3): To a solution of acceptor **29** (250 mg, 0.50 mmol) and donor **27** (263 mg, 0.71 mmol) in dry CH_2Cl_2 (10 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −75 °C under argon. After 30 min at this temperature, a mixture of NIS (174 mg, 0.78 mmol) and TfOH (29 μL, 0.03 mmol) dissolved in THF (500 μL) was added. After 3 h stirring at −50 °C, Et_3N (50 μL) was added. The reaction mixture was diluted with CH_2Cl_2 (250 mL), washed successively with H_2O (50 mL), aq $NaHCO_3$ (50 mL), H_2O (60 mL), dried and concentrated. The crude product was purified by column chromatography (55:45 *n*-hexane/EtOAc) to give 30 (165 mg, 31%,) as a colourless syrup.

Method IV (entry 4): To a solution of acceptor **29** (500 mg, 1.01 mmol) and donor **27** (525 mg, 1.40 mmol) in dry CH_2Cl_2 (20 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −75 °C under argon. After 20 min at this temperature, a mixture of TMSOTf (36 μL, 0.20 mmol) and NIS (349 mg, 1.55 mmol) in THF (500 μL) was added and the reaction mixture was allowed to warm up to −55 °C in 2 h. The mixture was diluted with CH_2Cl_2 (50 mL) washed successively with aq $Na_2S_2O_3$ (15 mL), H_2O (15 mL), aq $NaHCO_3$ (15 mL) and H_2O (15 mL), dried and concentrated. The crude product was purified by column chromatography (55:45 *n*-hexane/EtOAc) to give **30** (350 mg, 44%) and **31** (45 mg, 8%) as a colourless syrup.

Method V (entry 5): To a solution of donor **27** (113 mg, 0.30 mmol), and acceptor **29** (100 mg, 0.20 mmol) in dry CH_2Cl_2 (10 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −75 °C under argon. After 30 min at this temperature, NIS (75 mg, 0.33 mmol) dissolved in THF (100 μL) and AgOTf (19 mg, 0.07 mmol) dissolved in toluene (100 μL) were added. The temperature was increased to −55 °C in 45 min. The reaction mixture was quenched with Et_3N (50 μL), diluted with CH_2Cl_2 (100 mL) and filtered through a pad of Celite. The filtrate was concentrated. The crude product was purified by column chromatography (55:45 *n*-hexane/EtOAc) to give 30 (106 mg, 66%).

Method VI (entry 6): To a solution of donor **27** (5 g, 13.42 mmol), and acceptor **29** (4.16 g, 8.39 mmol) in dry CH_2Cl_2 (190 mL), 4 Å molecular sieves (2.0 g) were added. The stirred mixture was cooled to −75 °C under argon. After 30 min at this temperature, NIS (3.32 g, 14.76 mmol) dissolved in THF (4.5 mL) and AgOTf (828 mg, 3.22 mmol) dissolved in toluene (4.5 mL) were added. The temperature was increased to −65 °C in 45 min. The reaction mixture was quenched with Et_3N (500 μL), diluted with CH_2Cl_2 (300 mL) and filtered through a pad of Celite. The filtrate was concentrated. The crude product was purified by column chromatography (55:45 *n*-hexane/EtOAc) to give **30** (6.02 g, 89%) as a colourless syrup.

Compound **30**: R_f 0.30 (55:45 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +28.29 (*c* 0.48, $CHCl_3$); IR ν_{max} (KBr): 3444, 3052, 2933, 1754, 1441, 1359, 1238, 1169, 1096, 1072, 1034, 997, 916, 820, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ7.87–7.75, 7.52–7.45, 7.27–7.21 (3 × m, 12H, arom), 5.29 (t, *J* = 9.1 Hz, 1H, H-3), 5.00 (d, 1H, *J* = 3.1 Hz, H-1′), 4.94 (t, *J* = 9.6 Hz, 1H, H-2), 4.80–4.69 (m, 3H, H-1, ArC*H*$_2$), 4.08 (q, *J* = 7.1 Hz, 2H, $SO_3CH_2CH_3$), 3.93 (t, *J* = 9.3 Hz, 1H, H-4), 3.88–3.78 (m, 2H, H-6a, H-6b), 3.61–3.48 (m, 2H, H-5, H-5′), 3.52, 3.49, 3.40 (3 × s, 9H; 3 × OC*H*$_3$), 3.43–3.31 (m, 1H, H-3′), 3.23–3.12 (m, 1H, H-7a′), 3.05–2.93 (m, 2H; H-7b′, H-2′), 2.71 (t, *J* = 9.2 Hz, 1H, H-4′), 2.28–2.19 (m, 1H, H-6a′), 2.07, 2.02 (2 × s, 6H, COC*H*$_3$), 1.93–1.79 (m, 1H, H-6b′), 1.27–1.23 (m, 3H, $SO_3CH_2CH_3$) ^{13}C NMR (90 MHz, $CDCl_3$): δ169.4, 169.1 (2 × *C*O), 135.1, 132.9, 132.7, 131.6 (4 × C_q arom), 132.9, 129.0, 128.3, 128.2, 128.0, 127.8, 126.7, 126.2, 126.0, 125.9, (12C, arom), 96.7 (C-1′), 84.9 (C-1), 83.0 (C-4), 82.2 (C-3′), 81.5 (C-2′), 78.8 (C-5), 75.3 (C-3), 73.9 (C-4), 73.3 (Ar*C*H$_2$), 70.2 (C-2), 69.0 (C-5′), 67.7 (C-6), 65.7 ($SO_3CH_2CH_3$), 60.2, 58.7 (3 × *C*H$_3$), 46.3 (C-7′), 25.7 (C-6′), 20.6, 20.4 (2 × *C*H$_3$CO), 14.7 ($SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 829.25. Found: 828.95. Anal. Calcd for $C_{88}H_{110}O_{27}$ (806.94): C, 58.05; H, 6.25; O, 27.76; S, 7.95. Found: C, 57.87; H, 6.02; S, 8.10.

Compound **14α,β**: (α:β ~ 5:1) R_f 0.36 (6:4 *n*-hexane/EtOAc); IR ν_{max} (KBr): 3630, 3516, 2979, 2934, 2834, 1752, 1444, 1353, 1239, 1173, 1090, 1002, 915, 816, 642, 575, 528, 472 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.46–7.49 (m, 2H, arom), 7.36–7.22 (m, 4H, arom), 5.78 (d, *J* = 5.3 Hz, 1H, H-1α), 4.47 (d, *J* = 9.8 Hz, 0.20H, H-1β), 4.25–4.10 (m, 2.40H, $SO_3CH_2CH_3$), 3.92 (dt, *J* = 9.8, 2.4 Hz, 1H), 3.64 (s, 3H, OC*H*$_3$), 3.62 (s, 0.60H), 3.59–3.49 (m, 8.40H), 3.44 (t, *J* = 9.0 Hz, 1.20H), 3.23–3.13 (m, 1H, 0.60), 3.07–2.98 (m, 0.40H), 2.90–2.80 (m, 2.20H), 2.68–2.58 (m, 1H), 2.43–2.27 (m, 1.20H), 1.97–1.78 (m, 1.20H), 1.65 (s, 0.5H), 1.40–1.32 (m, 3.60H, $SO_3CH_2CH_3$); ^{13}C NMR (90 MHz, MeOD) δ 133.4 (1 × C_q arom), 131.4, 129.1, 127.2 (5C, arom), 84.7 (C-1α), 83.7, 83.4, 81.7, 69.4 (C-2, C-3, C-4, C-5), 66.1 ($SO_3CH_2CH_3$), 61.0, 60.9, 58.3 (3 × OCH$_3$), 46.6 (C-7), 25.7 (C-6), 15.0 ($SO_3CH_2CH_3$); Anal. Calcd for $C_{88}H_{110}O_{27}$ (420.54): C, 51.41; H, 6.71; O, 26.63; S, 15.25. Found: C, 51.27; H, 6.65; S, 15.27.

Compound **31**: R_f 0.77 (6:4 *n*-hexane/EtOAc); IR ν_{max} (KBr): 3056, 2925, 1754, 1583, 1509, 1478, 1440, 1371, 1237, 1050, 906, 876, 843, 748, 691, 608, 475 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02–7.93, 7.69–7.59, 7.42–7.33 (3 × m, 12H, arom), 5.26 (t, *J* = 9.2 Hz, 1H), 5.05 (t, *J* = 9.6 Hz, 1H), 4.95–4.84 (m, 3H), 4.03–3.84 (m, 3H), 3.71–3.64 (m, 1H), 2.22, 2.19 (2 × s, 6H, 2 × COC*H*$_3$), 0.21 (s, 9H, 3 × *C*H$_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.2, 169.8 (2 × *C*O), 135.8, 133.4, 133.1, 132.4 (4 × C_q arom), 132.9, 129.0, 128.2, 128.1, 128.0, 127.8, 126.3, 126.2, 125.9, 125.8 (12C, arom), 85.7 (C-1), 80.5, 70.8, 69.3 (C-2, C-3, C-4, C-5), 73.7 (Ar*C*H$_2$), 68.8 (C-6), 21.2, 20.9 (2 × COCH$_3$), 0.4 (3 × *C*H$_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 591.05. Found: 591.18. Anal. Calcd for $C_{88}H_{110}O_{27}$ (568.75): C, 63.35; H, 6.38; O, 19.69; S, 5.64; Si, 4.94. Found: C, 63.42; H, 6.46; S, 5.58.

4.18. 2-*O*-Acetyl-4,6-*O*-(benzylidene)-3-*O*-methyl-α,β-L-idopyranosyl-trichloroacetimidate (33α,β)

To the solution of compound **32** (7.5 g, 20.47 mmol) in THF (200 mL), benzylamine (8 mL, 71.7 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. The mixture was poured on 1 M aq HCl (300 mL). The aqueous phase was extracted

with EtOAc (3 × 150 mL). The combined organic phase was dried and concentrated. The crude product was purified by column chromatography (9:1 CH_2Cl_2/acetone) to give an α/β-mixture of the appropriate hemiacetal (4.65 g, 70%) as a colourless syrup. The solution of the crude product (4.59 g, 14.15 mmol) in dry CH_2Cl_2 (85 mL) was cooled to 0 °C and trichloroacetonitrile (28.1 mL, 0.28 mol) and DBU (550 μL, 0.85 mmol) were added. The reaction mixture was stirred for 1 h then concentrated in vacuo at 30 °C. The residue was purified by column chromatography (80:18:2 CH_2Cl_2/EtOAc/Et_3N) to give **33**α,β (6.25 g, 94%) as a colourless syrup; R_f 0.73 (8:2 CH_2Cl_2/EtOAc);

4.19. Methyl [2-*O*-acetyl-4,6-*O*-(benzylidene)-3-*O*-methyl-α-L-idopyranosyl]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (34)

To the solution of acceptor **18** (4.85 g, 10.1 mmol) and donor **33** (6.25 g, 13.3 mmol) in dry CH_2Cl_2 (200 mL), 4 Å molecular sieves (4.5 g) were added. The stirred mixture was cooled to −40 °C under argon. After 20 min at this temperature, TMSOTf (2.39 mL, 0.133 mmol) was added and the mixture was allowed to warm up to −15 °C in 1 h. The mixture was diluted with CH_2Cl_2 (250 mL) washed successively with aq $NaHCO_3$ (120 mL) and H_2O (120 mL), dried and concentrated. The crude product was purified by column chromatography (6:4 *n*-hexane/EtOAc) to give 34 (6.58 g, 82%) as white crystals. Mp 119–124 °C; R_f 0.30 (6:4 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ −4.03 (*c* 0.59, $CHCl_3$); IR ν_{max} (KBr): 3444, 2983, 2935, 2907, 2837, 1747, 1637, 1628, 1508, 1497, 1454, 1397, 1370, 1356, 1237, 1168, 1139, 1101, 1046, 1005 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47–7.24 (m, 15H, arom), 5.33 (s, 1H, PhC*H*), 5.08 (d, *J* = 2.2 Hz, 1H, H-1′), 5.04 (d, *J* = 10.8 Hz, 1H, PhCH_2), 4.93 (dd, *J* = 4.5, 2.5 Hz, 1H, H-2′), 4.78–4.62 (m, 3H, PhCH_2), 4.51 (d, *J* = 3.6 Hz, 1H, H-1), 4.28 (q, *J* = 7.1 Hz, *J* = 7.1 Hz, 2H, $SO_3CH_2CH_3$), 3.92–3.72 (m, 5H), 3.54–3.43 (m, 3H), 3.49, 3.34 (2 × s, 6H, 2 × OCH_3), 3.33–3.21 (m, 2H), 3.15–3.05 (m, 1H, H-7b), 2.43–2.31 (m, 1H, H-6a), 2.05 (s, 3H, COCH_3), 1.97–1.85 (m, 1H, H-6b), 1.39 (t, *J* = 7.1 Hz, 3H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.11 (*C*O), 138.9, 138.1, 138.0 (4 × C_q arom), 129.0, 128.5, 128.3, 128.2, 128.1, 127.7, 127.6, 126.3 (15C, arom), 100.5 (PhCH), 98.1, 97.9 (C-1, C-1′), 80.4, 79.6, 77.6, 77.1, 73.5, 68.4, 67.3 60.5, (C-2, C-2′, C-3, C-3′, C-4, C-4′, C-5, C-5′), 75.5, 73.4 (2 × PhCH_2), 69.2 (C-6′), 66.1 ($SO_3CH_2CH_3$), 58.3, 55.5 (2 × OCH_3), 46.8 (C-7), 26.1 (C-6), 20.9 (COCH_3), 15.2 ($SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 809.28. Found: 809.30. Anal. Calcd for $C_{88}H_{110}O_{27}$ (786.88) C: 61.05; H, 6.40; O, 28.47; S, 4.07. Found: C: 61.23; H, 6.44; S, 3.87.

4.20. Methyl [2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (35)

The solution of **34** (2.75 g, 3.5 mmol) in CH_2Cl_2 (75 mL) was cooled to 0 °C, 70% aq trifluoroacetic acid (8.5 mL) was added and the mixture was allowed to warm up to room temperature in 5 h. The reaction was quenched with addition of solid $NaHCO_3$ (9.3 g, 0.11 mol), the mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (2 × 100 mL). The organic phase was dried and concentrated. The crude product was purified by column chromatography by using first CH_2Cl_2-acetone (93:7) and then CH_2Cl_2-MeOH (95:5) as the eluents to give 35 (2.13 g, 87%) as a colourless oil. $[\alpha]_D^{25}$ +5.12 (*c* 3.25, $CHCl_3$); R_f 0.39 (85:15 CH_2Cl_2/acetone); IR ν_{max} (KBr): 3466, 3061, 3031, 2937, 2906, 2837, 1743, 1497, 1455, 1370, 1356, 1221, 1166, 1103, 1044, 1000, cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39–7.27 (m, 10H, arom), 5.04 (d, *J* = 10.4 Hz, 1H, PhCH_2), 4.92 (s, 1H,H-2′), 4.88 (d, 1H, *J* = 10.4 Hz, H-1′), 4.79 (d, *J* = 12.0 Hz, 1H, PhCH_2), 4.70–4.64 (m, 2H, PhCH_2), 4.50 (d, *J* = 3.6 Hz, 1H, H-1), 4.33–4.23 (m, 3H), 3.86 (t, *J* = 9.4 Hz, 1H), 3.81–3.75 (m, 1H), 3.57–3.46 (m, 3H), 3.51, 3.34 (2 × s, 6H, OCH_3), 3.42–3.27 (m, 3H), 3.20–3.08 (m, 2H), 2.42–2.31 (m, 1H, H-6a), 2.08 (s, 3H, COCH_3), 2.04 (s, 1H, O*H*), 1.99–1.87 (m, 1H, H-6b), 1.40 (t, *J* = 7.1 Hz, 3H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.4 (*C*O), 138.2, 137.9 (2 × C_q arom), 128.6, 128.5, 128.2, 128.2, 128.0 (10C, arom), 100.1, 97.8 (C-1, C-1′), 80.4, 79.7, 77.6, 76.5, 68.3, 67.6, 67.1, 67.1 (C-2, C-2′, C-3, C-3′, C-4, C-4′, C-5, C-5′), 76.0, 73.5 (PhCH_2), 66.2 ($SO_3CH_2CH_3$), 62.7 (C-6′), 58.3, 55.5 (2 × OCH_3), 46.5 (C-7), 25.8 (C-6), 21.0 (COCH_3), 15.2 ($SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 721.25. Found: 721.26. Anal. Calcd for $C_{88}H_{110}O_{27}$ (698.77): C, 56.72; H, 6.64; O, 32.05; S, 4.59. Found: C, 56.82; H, 6.57; S, 4.66.

4.21. Methyl [methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (36)

Compound **35** (865 mg, 1.24 mmol) was converted to **36** according to general method **D**. The crude product was purified by column chromatography to give **36** (627 mg, 70%) as a colourless oil. R_f 0.44 (6:4 *n*-hexane/acetone); $[\alpha]_D^{25}$ +5.91 (*c* 1.00, $CHCl_3$); IR ν_{max} (KBr): 3480, 2985, 2938, 2838, 1745, 1637, 1630, 1497, 1455, 1371, 1357, 1221, 1166, 1104, 1045, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 10H, arom), 5.13 (s, 1H, H-1′), 4.96–4.93 (m, 2H, PhCH_2, H-5′), 4.88 (s, 1H, H-2′), 4.85–4.80, 4.73–4.67, 4.58–4.52 (3 × m, 3H, PhCH_2), 4.47 (s, 1H, H-1), 4.32–4.27 (m, 2H, $SO_3CH_2CH_3$), 3.94 (s, 1H, H-4′), 3.85–3.74 (m, 2H, H-3, H-5), 3.56–3.45 (m, 3H, H-2, H-3′, H-4), 3.51, 3.49, 3.33 (3 × s, 9H, 3 × OCH_3,), 3.37–3.27 (m, 1H, H-7a), 3.16–3.74 (m, 1H, H-7b), 2.71 (s, 1H, O*H*), 2.42–2.36 (m, 1H, H-6a), 2.07 (s, 3H, COCH_3), 1.97–1.89 (m, 1H, H-6b), 1.40 (t, *J* = 7.0 Hz, 3H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.5, 168.9 (2 × *C*O), 138.6, 137.7 (2 × C_q arom), 128.3, 128.0, 127.8, 127.3, 127.0 (10C, arom), 97.6 (C-1), 97.5 (C-1′), 80.2, 77.9, 76.5, (C-2, C-3′, C-4), 79.1 (C-3), 74.9, 73.2 (2PhCH_2), 68.1 (C-5′), 67.8 (C-5), 66.9 (C-4′), 66.6 (C-2′), 65.9 ($SO_3CH_2CH_3$), 58.1, 55.4, 51.9 (3 × OCH_3), 46.4 (C-7), 25.8 (C-6), 20.7 (COCH_3), 15.0 ($SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for $[M+Na]^+$ 749.29. Found: 749.21. Anal. Calcd for $C_{88}H_{110}O_{27}$ (726.26): C, 56.19; H, 6.38; O, 33.02; S, 4.41. Found: C, 56.04; H, 6.23; S, 4.56.

4.22. Methyl [2,3-di-*O*-benzyl-4-*O*-(2′-naphthyl)methyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (37)

To a solution of acceptor **36** (700 mg, 0.96 mmol) and donor **20**[18] (940 mg, 1.45 mmol) in dry CH_2Cl_2 (30 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −60 °**C** under argon. After 30 min at this temperature, a mixture of NIS (488 mg, 2.17 mmol) and TfOH (38 μL, 0.43 mmol) dissolved in THF (1.2 mL) was added. After 3 h stirring at −50 °**C**, Et_3N (50 μL) was added. The reaction mixture was diluted with CH_2Cl_2 (150 mL), washed successively with 10% aq $Na_2S_2O_3$ solution (20 mL). H_2O (50 mL), aq $NaHCO_3$ (50 mL), H_2O (50 mL), dried and concentrated. The crude product was purified by column chromatography (1:1 *n*-hexane/acetone) to give **37** (1.17 g, 92%,) as a colourless syrup. R_f 0.42 (1:1 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +15.51 (*c* 0.20, $CHCl_3$); IR ν_{max} (KBr): 3439, 3061, 3031, 2983, 2934, 1739, 1604, 1497, 1455, 1356, 1238, 1166, 1105, 1070, 1048, 1029, 1001, 1070 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.01–7.82 (m, 4H, arom), 7.66–7.38 (m, 23H, arom), 5.41 (d, *J* = 1.0 Hz, 1H, H-1′), 5.25–5.14 (m, 1H), 5.10 (d, *J* = 10.9 Hz, 2H, ArCH_2), 5.05–4.90 (m, 7H), 4.90–4.79 (m, 2H), 4.73 (d, *J* = 12.0 Hz, 1H, ArCH_2), 4.64 (d,

J = 3.5 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H, $SO_3CH_2CH_3$), 4.28 (q, J = 7.0 Hz, 2H, $SO_3CH_2CH_3$), 4.19–3.83 (m, 7H), 3.73–3.44 (m, 12H), 3.44–3.24 (m, 4H, 2 × H-7a,b), 2.62–2.52 (m, 1H), 2.47 (m, 1H), 2.22 (s, 3H, $COCH_3$), 2.17–2.00 (m, 2H), 1.55 (t, J = 7.1 Hz, 3H, $SO_3CH_2CH_3$), 1.41 (t, J = 7.0 Hz, 3H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.1, 169.4 (2 × *C*O), 138.9, 138.4, 138.0, 138.0, 135.5, 133.2, 133.0 (7 × C_q arom), 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.3, 126.4, 126.2, 126.0, 125.7 (27C, arom), 98.7, 97.9, 97.8 (3 × C-1), 81.4, 81.1, 80.3, 79.4, 78.3, 76.6, 74.5, 69.6, 68.7, 68.1, 67.7 (12C, skeleton carbons), 75.4, 75.1, 75.0, 73.6, 73.4 (5 × Ar*C*H$_2$), 66.2, 66.1 (2 × SO_3-*C*H$_2$CH$_3$), 58.4, 55.5, 51.9 (3 × OCH_3), 46.6, 46.4 (2 × C-7), 26.0, 25.9 (2 × C-6), 21.0 ($COCH_3$), 15.1, 15.0 (2 × $SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for [M+Na]$^+$ 1337.46. Found: 1337.25 Anal. Calcd for $C_{88}H_{110}O_{27}$ (1315.50): C, 62.09; H, 6.28; O, 26.76; S, 4.87. Found: C, 61.97; H, 6.15; S, 4.96.

4.23. Methyl [2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (38)

Compound **37** (1.14 g, 0.87 mmol) was converted to **38** according to the general method **C**. The crude product was purified by column chromatography to give **38** (805 mg, 79%) as a colourless oil. R_f 0.37 (1:1 *n*-hexane/EtOAc); $[\alpha]_D^{25}$ +23.57 (*c* 0.08, $CHCl_3$); IR ν_{max} (KBr): 3525, 3031, 2935, 1740, 1606, 1497, 1455, 1369, 1355, 1234, 1166, 1107, 1053, 1029, 997, 919, cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38–7.23 (m, 20H, arom), 5.23 (d, J = 2.7 Hz, 1H, H-1′), 4.93–4.83 (m, 4H), 4.79 (dd, J = 7.9, 3.0 Hz, 2H), 4.74–4.68 (m, 4H), 4.64 (d, J = 11.8 Hz, 1H, PhC*H*$_2$), 4.56 (d, J = 12.0 Hz, 1H, PhC*H*$_2$), 4.47 (d, J = 3.5 Hz, 1H), 4.27 (m, 4H, $SO_3CH_2CH_3$), 3.91–3.87 (m, 1H), 3.82 (t, J = 9.2 Hz, 1H), 3.77–3.61 (m, 4H), 3.57–3.45 (m, 5H), 3.43–3.28 (m, 9H), 3.26–3.05 (m, 4H, 2 × H-7a,b), 2.51 (d, J = 3.1 Hz, 1H, O*H*), 2.45–2.34 (m, 1H, H-6a), 2.34–2.21 (m, 1H, H-6a), 2.02 (s, 3H, $COCH_3$), 1.99–1.87 (m, 2H, 2 × H-6b), 1.44–1.33 (m, 6H, $SO_3CH_2CH_3$) ppm; ^{13}C NMR (91 MHz, $CDCl_3$) δ 170.06, 169.42 (2 × *C*O), 138.90, 138.49, 138.00, 137.89 (4 × C_q arom), 128.61, 128.56, 128.45, 128.14, 128.01, 127.95, 127.87, 127.82, 127.57, 127.27 (20C, arom), 98.75, 97.92, 97.83 (3 × C-1), 80.72, 80.15, 79.89, 79.37, 78.49, 76.91, 74.56, 73.39, 69.95, 69.32, 68.42, 68.12 (12C; skeleton carbons), 75.08, 73.46, 73.34 (PhCH$_2$), 66.32, 66.19 (2 × $SO_3CH_2CH_3$), 58.43, 55.52, 51.87 (3 × OCH_3), 46.66, 46.26 (2 × C-7), 25.83 (2 × C-6), 20.97 ($COCH_3$), 15.11 (2 × $SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for [M+Na]$^+$ 1197.40. Found: 1197.34. Anal. Calcd for $C_{88}H_{110}O_{27}$ (1175.31): C, 58.25; H, 6.35; O, 29.95; S, 5.46. Found: C, 58.34; H, 6.21; S, 5.48.

4.24. Methyl [2,3,4-tri-*O*-methyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[2,3-di-*O*-acetyl-6-*O*-(2′-naphthyl)methyl-β-D-glucopyranosyl]-(1→4)-[2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (39)

To a solution of trisaccharide acceptor **38** (790 mg, 0.67 mmol) and disaccharide donor **30** (825 mg, 1.01 mmol) in dry CH_2Cl_2 (26 mL), 4 Å molecular sieves (0.50 g) were added. The stirred mixture was cooled to −60 °C under argon. After 30 min at this temperature, NIS (340 mg, 1.51 mmol) dissolved in THF (300 μL) and AgOTf (86 mg, 0.32 mmol) dissolved in toluene (300 μL) were added. After 3 h stirring at −20 °C, Et_3N (50 μL) was added. The reaction mixture was diluted with CH_2Cl_2 (150 mL), washed successively with H_2O (50 mL), aq $NaHCO_3$ (50 mL), H_2O (60 mL), dried and concentrated. The crude product was purified by column chromatography (93:7 CH_2Cl_2/acetone) to give **39** (813 mg, 65%,) as a colourless syrup. R_f 0.31 (93:7 CH_2Cl_2/acetone); $[\alpha]_D^{25}$ +29.85 (*c* 0.08, $CHCl_3$); NMR (400 MHz, $CDCl_3$) δ 7.86–7.75 (m, 3H, arom), 7.65 (s, 1H, arom), 7.46 (m, 2H, arom), 7.36–7.13 (m, 21H, arom), 5.22–5.14 (m, 2H, H-3-E, H-1-G), 5.01–4.76 (m, 8H, H-1-D, H-2-E, H-5-G, H-2-G, Ar*C*H$_2$), 4.76–4.62 (m, 4H, H-1-F, H-1-E, Ar*C*H$_2$), 4.57–4.51 (m, 4H, Ar*C*H$_2$), 4.48 (d, J = 3.5 Hz, 1H, H-1-H), 4.31–4.25 (m, 4H, $SO_3CH_2CH_3$), 4.09 (q, J = 7.1 Hz, 2H, $SO_3CH_2CH_3$), 3.91–3.70 (m, 6H, H-4-E, H-4-G, H-3-F, H-3-H, H-5-H, H-5-F), 3.65 (t, J = 3.7 Hz, 1H, H-3-G), 3.55–3.42 (m, 4H, H-5-D, H-2-H, H-6a,b-E), 3.53, 3.50, 3.49, 3.38, 3.33, 3.32 (6 × s, 18H, O*CH*$_3$), 3.42–3.18 (m, 7H, H-4-F, H-2-F, H-4-H, H-3-D, H-5-E, 2 × H-7a), 3.15–3.03 (m, 3H, H-7a, 2 × H-7b), 2.92–2.82 (m, 2H, H-2-D, H-7b), 2.66 (t, J = 9.2 Hz, 1 H, H-4-D), 2.42–2.82 (m, 1H, H-6a), 2.30–2.22 (m, 1H, H-6a), 2.16–2.12 (m, 1H, H-6a), 2.08, 2.01, 2.00 (3 × s, 9H, 3 × COC*H*$_3$) 1.98–1.88 (m, 1H, H-6b), 1.84–1.73 (m, 2H, 2 × H-6b), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.8, 169.4 (4 × *C*O), 139.1, 138.9, 137.9, 137.8, 135.4, 133.3, 133.0 (7 × C_q arom), 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.4, 127.2, 127.1, 126.4, 126.4, 126.2, 125.9, 125.6 (27C, arom), 101.2 (C-1-E), 98.1 (C-1-F), 97.8 (C-1-H), 97.7 (C-1-G), 96.9 (C-1-D), 83.29 82.42, 82.05, 82.01, 80.28, 79.76, 79.47, 79.32, 78.36, 76.28, 75.20, 74.60, 74.5 74.00 72.64, 69.33, 69.06, 68.73 68.07, 67.46 (20C, skeleton carbons), 75.0, 74.4, 73.8, 73.5, 73.4 (5 × Ar*C*H$_2$), 66.2, 65.9 (3 × $SO_3CH_2CH_3$), 60.6, 59.0, 58.3, 55.5, 51.9 (6 × O*C*H$_3$), 46.7, 46.7, 46.5 (3 × C-7), 26.1, 26.0, 25.8 (3 × C-6), 21.0, 20.9, 20.7 (3 × COC*H*$_3$), 15.1, 15.1 (3 × $SO_3CH_2CH_3$) ppm; MALDI-TOF (positive ion): *m/z* calcd for [M+Na]$^+$ 1893.65. Found: 1893.64. Anal. Calcd for $C_{88}H_{110}O_{27}$ (1872.07): C, 57.74; H, 6.35; O, 30.77; S, 5.14. Found: C, 57.67; H, 6.41; S, 5.20.

4.25. Methyl [2,3,4-tri-*O*-methyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[2,3-di-*O*-acetyl-β-D-glucopyranosyl]-(1→4)-[2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (40)

Compound **39** (775 mg, 0.41 mmol) was converted to **40** according to general method **C**. The crude product was purified by column chromatography to give compound **40** (600 mg, 84%) as a colourless oil. R_f 0.20 (6:4 *n*-hexane/acetone); $[\alpha]_D^{25}$ +32.32 (*c* 0.16, $CHCl_3$); IR ν_{max} (KBr): 3443, 2935, 1755, 1633, 1497, 1454, 1356, 1240, 1220, 1166, 1099, 1042, 919, 820, 740, 700, 593 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41–7.19 (m, 20H, arom), 5.31–5.15 (m, 3H), 5.01 (d, J = 3.3 Hz, 1H), 4.96–4.51 (m, 12H), 4.48 (d, J = 3.4 Hz, 1H), 4.32–4.26 (m, 6H, 3 × $SO_3CH_2CH_3$), 3.88–3.62 (m, 7H), 3.55, 3.52, 3.49, 3.41, 3.33, 3.32 (6 × s, 18H, 6 × O*CH*$_3$), 3.59–3.27 (m, 15H), 3.24–3.18 (m, 3H), 3.17–3.09 (m, 3H), 3.01 (dd, J = 9.7, 3.4 Hz, 1H), 2.73 (t, J = 9.2 Hz, 1H), 2.45–2.21 (m, 3H), 2.07, 2.03, 2.02 (3 × s, 9H, 3 × COC*H*$_3$), 2.15–1.83 (m, 4H), 1.44–1.38 (m, 9H, 3 × $SO_3CH_2CH_3$), ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.1, 169.8, 169.5 (4x *C*O), 138.9, 138.8, 137.9, 137.8 (4 × C_q arom), 128.5, 128.5, 128.4, 128.1, 128.0, 127.6, 127.4, 127.2, 126.1 (20C, arom), 100.8, 98.3, 97.8, 97.6, 96.7 (5 × C-1), 83.7, 82.7, 81.9, 81.6, 80.3, 79.3, 79.0, 78.3, 76.3, 75.2, 74.8, 74.1, 72.5, 72.2, 69.5, 69.2, 68.7, 68.0, 67.5 (20C, skeleton carbons), 75.0, 74.5, 73.8, 73.4 (PhCH$_2$), 66.1, 66.1 (3 × SO_3CH_2-*C*H$_3$), 60.7, 60.6, 59.3, 58.2, 55.5, 51.9 (6 × O*C*H$_3$), 46.7, 46.6, 46.5 (3 × C-7), 26.3, 25.9, 25.4 (3 × C-6), 20.9, 20.9, 20.5 (3 × SO_3CH_2-*C*H$_3$), 15.1 (3 × COC*H*$_3$) ppm; Anal. Calcd for $C_{88}H_{110}O_{27}$ (1731.89): C, 54.79; H, 6.40; O, 33.26; S, 5.55. Found: C, 54.84; H, 6.52; S, 5.43.

4.26. Methyl [2,3,4-tri-*O*-methyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2,3-di-*O*-acetyl-β-D-glucopyranosyl) uronate]-(1→4)-[2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranosyl]-(1→4)-[methyl (2-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyl) uronate]-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(ethyl sulfonatomethyl)-α-D-glucopyranoside (41)

Compound **40** (600 mg, 0.35 mmol) was converted to **41** according to general method **D**. The crude product was purified by column chromatography to give compound **41** (380 mg, 62%) as a colourless oil. R_f 0.62 (9:1 CH_2Cl_2/acetone); $[\alpha]_D^{25}$ +39.44 (*c* 0.04, $CHCl_3$); NMR (360 MHz, $CDCl_3$) δ 7.36–7.14 (m, 20H, arom), 5.30–5.16 (m, 2H), 4.97–4.47 (m, 14H), 4.47 (d, J = 3.4 Hz, 1H), 4.33–4.24 (m, 6H), 3.86–3.60 (m, 7H), 3.58–3.06 (m, 12H), 3.55, 3.5, 3.48, 3.41, 3.33, 3.31 (6 × s, 21H, 7 × OCH_3), 2.98 (dd, J = 9.7, 3.2 Hz, 1H), 2.70 (t, J = 9.2 Hz, 1H), 2.45–2.31 (m, 1H), 2.31–2.13 (m, 2H), 2.08, 2.02 (2 × s, 9H, 3 × $COCH3$), 2.10–1.74 (m, 3H), 1.43–1.38 (m, 9H, 3 × $SO_3CH_2CH_3$) ppm; ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.3, 169.7, 169.6, 169.5, 167.8 (5 × *C*O), 139.0, 138.9, 138.0, 137.7 (4 × C_q arom), 128.5, 128.3, 128.2, 128.0, 127.5, 127.3, 127.2, 126.8 (20C, arom), 101.4, 98.3, 97.9, 97.7, 97.2 (5 × C-1), 83.2, 82.6, 81.7, 80.3, 80.0, 79.4, 79.2, 78.3, 76.3, 75.3, 74.6, 74.4, 73.7, 72.0, 69.4, 68.9, 68.6, 68.1, 67.3 (20C, skeleton carbons), 75.1, 74.5, 73.8, 73.4 (4 × Ph*C*H_2), 66.2 (3 × $SO_3CH_2CH_3$), 60.7, 60.7, 59.3, 58.3, 55.6, 52.7, 51.9 (7 × OCH_3), 46.7, 46.5 (3 × C-7), 26.0, 25.8 (3 × C-6), 21.0, 20.8, 20.6 (3 × $SO_3CH_2CH_3$), 15.2 (3 × $COCH_3$) ppm; Anal. Calcd for $C_{88}H_{110}O_{27}$ (1759.90): C, 54.60; H, 6.30; O, 33.64; S, 5.47. Found: C, 54.66; H, 6.32; S, 5.57.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres. 2014.02.012.

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