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Synthesis of disaccharide fragments of the AT-III binding domain of heparin and their sulfonatomethyl analogues

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ABSTRACT

D-Glucuronate and L-iduronate-containing disaccharides related to the antithrombin-binding domain of heparin were prepared. The carboxylic function of the uronic acid unit was formed on a disaccharide level in the case of the glucuronate, while on a monosaccharide level in the case of the iduronate derivatives. Synthesis of their sulfonic acid analogues was carried out analoguosly applying sulfonatomethyl-containing acceptors in the form of either salts or methyl esters. Significant difference could be observed in the methyl ether formation reactions of the sulfonatomethyl-containing uronate disaccharides and the non-sulfonic acid uronates.

1. Introduction

Heparin, a highly sulfated linear polysaccharide belonging to the family of glycosaminoglycans is a well-known blood anticoagulant employed extensively in medical practice.[1] The anticoagulant action of heparin arises from its ability to accelerate the inhibitory activity of antithrombin III (AT-III), a serine protease inhibitor that blocks thrombin and factor Xa in the blood-coagulation cascade.[2] After identification of the exact sequence of heparin that associates with the AT-III (**1**) a concerted drug development programme has been undertaken based on extensive structure–activity studies using synthetic oligosaccharides.[3] These efforts resulted in fondaparinux (**2**), a synthetic pentasaccharide heparin analogue which is used as a new antithrombotic drug under the name Arixtra.[4] Fondaparinux selectively inhibits factor Xa, and it has longer half-life and higher anti-Xa activity than heparin and low molecular-weight heparin. However, its synthesis represents a real challenge, due to the presence of D-glucuronic acid, L-iduronic acid and α-D-glucosamine, most of them N- and O-sulfated on selected positions. Based on the observations of SAR studies that the *N*-sulfate groups could be replaced by *O*-sulfates, and the free hydroxyl groups could be masked with alkyl groups, a family of non-glycosaminoglycan derivatives was created,[5] having simplified structures much easier to synthesize than fondaparinux. In addition, idraparinux[5,6] (**3a**), the most potent representative of these analogues possesses increased anticoagulant activity and longer duration of action (Fig. 1).[4a,5] It turned out, however, that the extremely long elimination half-life of idraparinux (~60 days by clinical trials) may lead to serious bleeding complications, therefore, its development was terminated.[7] Idrabiotaparinux (**3b**), the biotinylated form of **3a** has been developed with the aim to improve the management of bleeding events seen with idraparinux.[8] Idrabiotaparinux displays the same advantageous properties as idraparinux and has the added safety feature of easy and rapid neutralization of its anticoagulant effect by addition of the specific antidote, avidin.[7,8]

Our research group decided the synthesis of the isosteric sulfonic acid analogues of idraparinux (**2**) by systematic replacement of the sulfate esters with sulfonatomethyl moieties to obtain new selective Xa inhibitors and to acquire further information on the structure–activity relationship of the antithrombotic action of heparin pentasaccharide. It is known that the anionic groups are essential for the activation of AT-III, and that the type of charge is also crucial,[3c] however, replacement of the sulfate group with sulfonic acid moiety has not been investigated till now.

Synthesis of sulfonatomethyl analogues of the EF and GH disaccharides (**5**–**7** and **9**–**11**)[9] as well as sulfonatomethyl analogues[10] of the DEF trisaccharide of compound **3a** have been reported recently. Here, we present the synthesis of two uronic acid-containing fragments of idraparinux (**4** and **8**) together with

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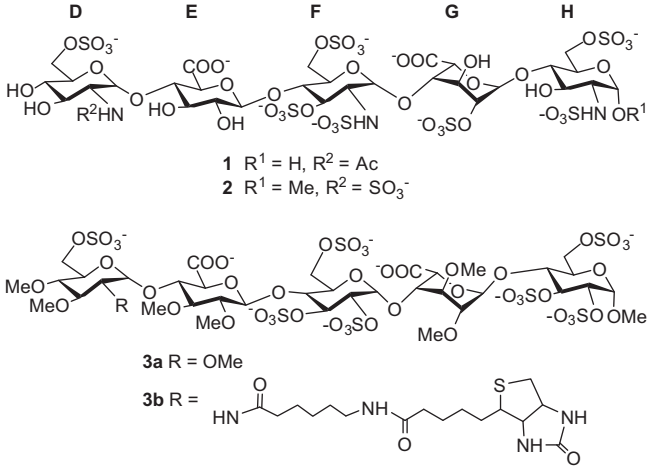


Figure 1. Structures of the antithrombin-binding domain of heparin (**1**), synthetic antithrombotic drug fondaparinux (**2**), the non-glycosaminoglycan analogue idraparinux (**3a**) and its biotinylated derivative idrabiotaparinux (**3b**).

unpublished details of the synthesis of their sulfonic acid mimetics (Fig. 2). Differences in the synthesis of disaccharide uronates with or without sulfonic acid content are also discussed.

2. Results and discussion

For the synthesis of compound **4** the β-(1→4)-linked skeleton was prepared by coupling of donor **12**[11] and acceptor **13**[12] and the disaccharide **14** was isolated in high yield. Zemplén deacetylation of **14** afforded the tetrahydroxy derivative **15**. Selective oxidation of the primary hydroxyl group of compound **15** by TEMPO-based oxidation method[13] using sodium-hypochlorite as co-oxidant gave compound **16**. Treatment of **16** with methyl iodide and sodium hydride to achieve methylation of the three hydroxyl groups of the uronic acid residue resulted in a 3:2 mixture of the desired product **17** and the by-product **18** formed by β-elimination. Catalytic hydrogenation of **17** afforded the triol **19** which was O-sulfated to obtain the target disaccharide **4** (Scheme 1).

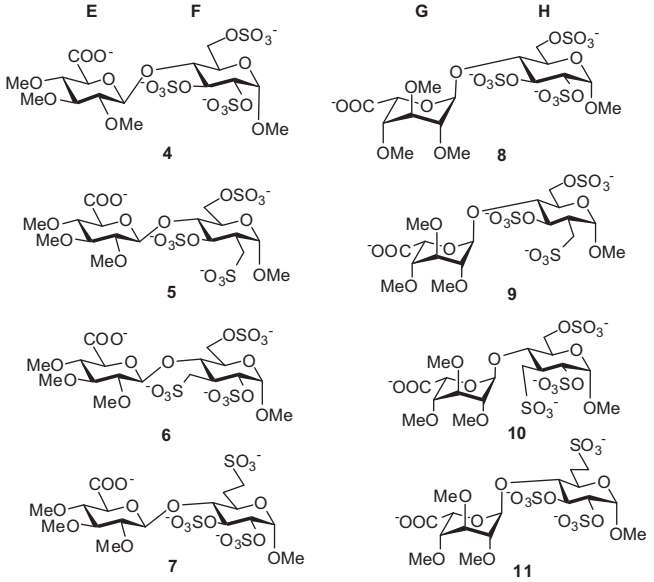
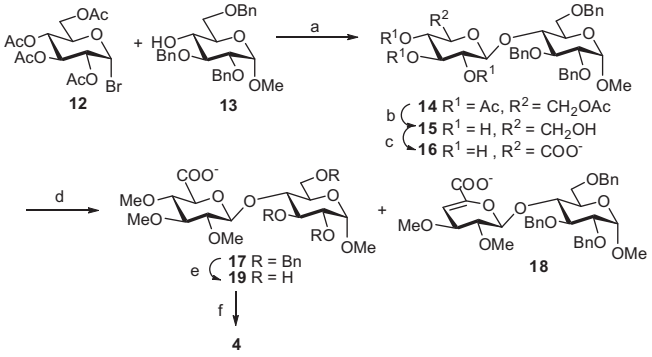


Figure 2. Structures of the EF and the GH fragments of idraparinux (**4** and **8**) and their isosteric sulfonic acid derivatives (**5**–**7** and **9**–**11**).

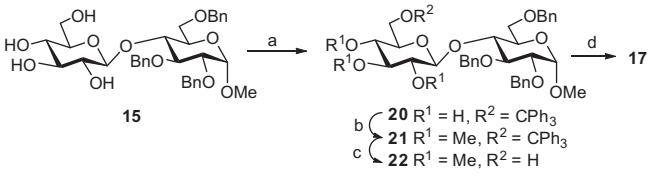


Scheme 1. Synthesis of the EF fragment of idraparinux by selective oxidation. Reagents and conditions: (a) CH_2Cl_2–toluene, 4 Å Ms, AgOTf, −30 °C to rt, 24 h (94%); (b) MeOH, NaOMe, rt, 2 h (97%); (c) satd $NaHCO_3$, KBr, NaOCl, TEMPO, 0 °C to rt, 2 h (78%); (d) DMF, NaH, MeI, 0 °C to rt, 2 h (**17**: 42%, **18**: 40%); (e) ethanol, Pd(C), H_2, 10 atm, rt, 12 h (94%); (f) DMF, SO_3·py, 0 °C to rt, 5 h (70%).

In order to avoid the elimination side reaction caused by methylation of the base-sensitive uronate derivative, compound **17** was prepared from **15** by permuting the oxidation and methylation steps. The primary hydroxyl of **15** was protected temporarily in form of trityl ether, then the secondary hydroxyls of **20** were methylated to afford **21**. Removal of the trityl group gave **22** whose TEMPO-based oxidation resulted in the fully protected glucuronide **17** in good yield (Scheme 2). Synthesis of **4** starting from **12** and **13** through the 6-*O*-trityl intermediate **20** required eight steps and resulted in the target glucuronide disaccharide with 27% overall yield.

To obtain the sulfonic acid analogues of disaccharide **4**, first the sulfonatomethyl-containing glucoside acceptors have to be prepared.[9] The key step of their synthesis was the addition of hydrogen sulfite to the exomethylene moiety of the appropriate glucoside resulting exclusively in the primary alkane sulfonate in a radical chain reaction using *tert*-butyl peroxybenzoate as radical initiator.[14,15]

Previously, the 2-deoxy-2-sulfonatomethyl and the 3-deoxy-3-sulfonatomethyl acceptors (**24** and **27**) have been prepared by the following sequence of reactions: the exomethylene derivatives **23**[16] and **26**,[17] were reacted with $NaHSO_3$, respectively, followed by regioselective hydrogenolysis of the 4,6-*O*-benzylidene acetal. However, the 4-OH derivatives **24** and **27** could be isolated only with moderate yields due to partial hydrolysis of the benzylidene acetal under the slightly acidic conditions of the first addition step.[9] We attempted to increase the yield of the two-step procedure by reversing the acetal reduction and the addition. In the case of the 3-exomethylene derivative **26** regioselective opening of the 4,6-*O*-acetal ring using a triethylsilane–BF_3·Et_2O reagent combination[18] (**28**), and subsequent sulfonation afforded the desired **27** with increased yield compared to the previous pathway (65% vs 47% over two steps). However, treatment of **23** with Et_3SiH/BF_3·Et_2O resulted in the unexpected 2-methyl glycal **25** as the main



Scheme 2. Improved synthesis of the methylated uronate **17**. Reagents and conditions: (a) py, TrCl, 0 °C to rt, 24 h (83%); (b) DMF, NaH, MeI, 0 °C to rt, 2 h (86%); (c) 80% AcOH, 50 °C, 2 h (98%); (d) satd $NaHCO_3$, KBr, NaOCl, TEMPO, 0 °C to rt, 2 h (64%).

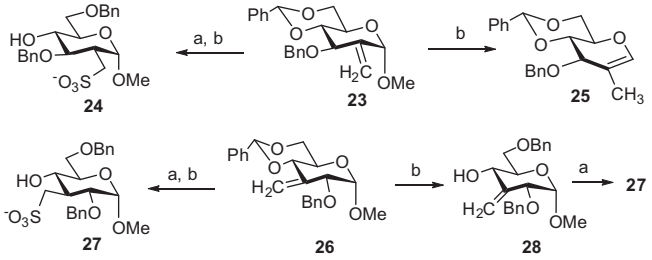
product. The reaction can be explained by the formation of a stabilized allylic cation (allyl oxocarbenium ion) whose reaction with the hydride donor reagent gave the 2-deoxy-2-methyl glycal derivative (Scheme 3).

Cleavage of the glycosidic bond upon reductive opening of benzylidene-type acetals is extremely rare, however, not unprecedented.[19,20]

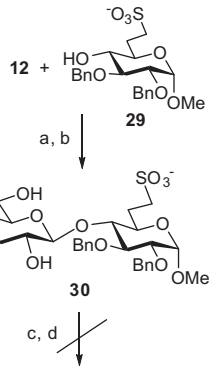
The 2-(sodium sulfonatomethyl)- and 3-(sodium sulfonatomethyl)-containing analogues of disaccharide **4** have been synthesized through the appropriate 6′-*O*-trityl intermediates, starting from the acetobromo glucose **12** and acceptors **24** and **27**, respectively, as we published recently.[9] It is worth to mention that the sulfonic acid salts proved to be excellent acceptors, and similar overall yields could be achieved for the sulfonic acid-containing disaccharides **5** and **6** as for compound **4**.

However, preparation of the 6-(sodium sulfonatomethyl)-containing derivatives **7** via tritylation was failed. Glycosylation of the sulfonic acid heptoside **29**[9] in a salt form with the acetobromo glucose donor **12** upon silver triflate activation and the following deacetylation took place smoothly affording the desired disaccharide **30** in a 48% yield.[9] However, subsequent tritylation of **30** failed, despite a high excess of the reagent, addition of dimethylamino pyridine and prolongation of the reaction time (Scheme 4). Silylation using *tert*-butyldiphenylsilyl chloride was also unsuccessful.

Geometry optimization on the structures sampling from high temperature molecular dynamics simulations trajectory for **30** gave explanation for the failure of substitution of the 6′-hydroxyl group. In the lowest energy conformations the hydroxyl group is inaccessible by the bulky reagents being in a pocket formed by



Scheme 3. Previously described (a followed by b) and recent (b followed by a) reaction routes for the 2-deoxy-2-sulfonatomethyl and the 3-deoxy-3-sulfonatomethyl acceptors. Reagents and conditions: (a) 70% EtOH, *t*Bu–peroxybenzoate, $NaHSO_3$, reflux, 4 h (55% from **23**, 53% from **26**, 74% from **28**); (b) CH_2Cl_2, Et_3SiH, $BF_3{\cdot}Et_2O$, 0 °C to rt, 4 h (**24**: 87%, **27**: 88%, **25**: 41%, **28**: 78%).



Scheme 4. Attempted synthesis of the 6-deoxy-6-sulfonatomethyl analogue of the EF fragment of idraparinux via tritylation. Reagents and conditions: (a) CH_2Cl_2–toluene, 4 Å Ms, AgOTf, −30 °C to rt, 24 h (64%); (b) MeOH, NaOMe, rt, 2 h (75%); (c) TrCl (3 equiv), py, DMAP; (d) TBDPSCl, imidazole, DMF.

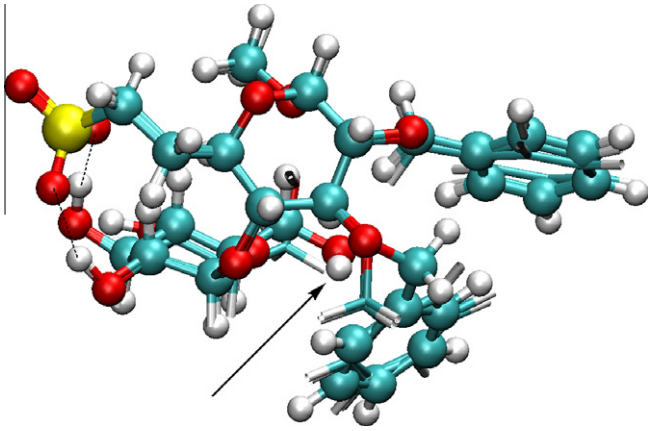
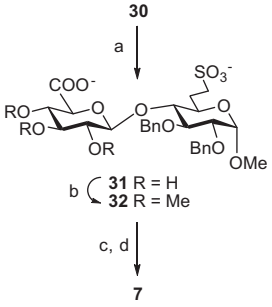


Figure 3. Superposition of the six lowest energy conformations of **30** from the high temperature molecular dynamics (ball-and-stick representation: lowest energy conformer; stick representation: conformers 2–6).



Scheme 5. Synthesis of the 6-deoxy-6-sulfonatomethyl analogue of the EF fragment of idraparinux by selective oxidation. Reagents and conditions: (a) satd $NaHCO_3$, KBr, NaOCl, TEMPO, 0 °C to rt, 2 h (91%); (b) DMF, NaH, MeI, 0 °C to rt, 2 h (79%); (c) ethanol, Pd(C), H_2, 10 atm, rt, 12 h (96%); (d) DMF, $SO_3{\cdot}$py, 0 °C to rt, 5 h (65%).

the two benzyl groups and the sugar ring (Fig. 3). These conformations are probably stabilized by hydrogen bonds between the sulfonate moiety and the 2′- or 3′-hydroxyls. (For the most stable geometry the corresponding distances between the sulfonate oxygens and the 2′- or 3′-hydroxyl hydrogens are 1.84 Å for 2′-OH and 1.91 Å for 3′-OH from DFT calculations while 1.77 Å for 2′-OH and 1.64 Å for 3′-OH were predicted by the AMBER-GAFF force field.) The above assumptions were confirmed by NMR experiments: the hydrogen of the 6′-OH could be exchanged for deuterium immediately, while deuteration of 2′-OH and 3′-OH was slow.

Since selective protection of the sterically hindered 6′-hydroxyl group failed, the tetrahydroxy derivative **30** was converted directly into the uronic acid **31** by TEMPO-based selective oxidation. Methylation of **31** with methyl iodide and sodium hydride was considered to be a risky step that might lead to β-elimination of the uronic acid residue as it happened to **16**. Surprisingly, methylation in the presence of the strong base proceeded smoothly and no elimination was observed (Scheme 5). The obtained **32** could be converted into the targeted 6-deoxy-6-sulfonatomethyl-containing disaccharide **7** by catalytic hydrogenation and subsequent sulfation of the liberated two hydroxyls. Applying the selective oxidation method a 22% overall yield could be obtained for **7** in a six-step procedure.[9]

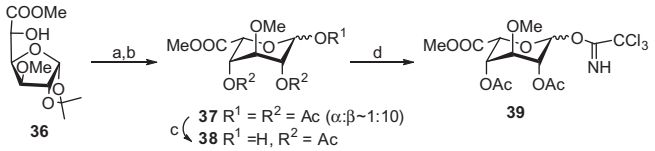
For the incorporation of uronic acid residues into oligosaccharides two distinct strategies exist: glycosylation followed by oxidation (post-glycosidation oxidation) and oxidation of the monosaccharide building blocks followed by glycosylation

(pre-glycosidation oxidation).[21] Although the glucuronide-containing disaccharides were prepared successfully by post-glycosidation oxidation, the other strategy that is glycosylation with an iduronic donor was selected to synthesize our targeted GH analogue disaccharides **8**–**11**. Since neither idose nor iduronic acid is readily available from natural and commercial sources and preparation of both type of donors requires a lengthy synthetic procedure,[22] the pre-glycosidation oxidation seemed to be more efficient.

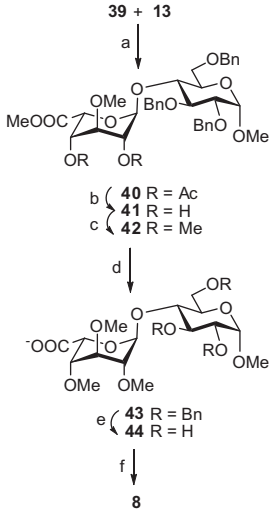
L-Iduronic acid trichloroacetimidate **39** was prepared on the basis of the well-established procedure elaborated for the appropriate 3-*O*-benzyl-L-iduronate donor.[22h,23] The iduronic acid **36** was prepared from the corresponding D-glucofuranuronic acid derivative[24] by means of a two-step epimerization at C-5.[23] Deisopropylidenation of **36** with trifluoroacetic acid afforded the desired hemiacetal as a mixture of pyranoses and furanoses. Acetylation of the crude reaction mixture, followed by column chromatography gave **37** with 36% yield over the two steps. Selective deacetylation of the anomeric position (**38**) and imidate formation then resulted in the iduronic acid donor **39** (Scheme 6).

Coupling of the acceptor **13** with the imidate donor **39** upon trimethylsilyl triflate activation afforded the disaccharide **40** and its Zemplén deacetylation resulted in diol **41**. Attempted methylation with methyl iodide and sodium hydride failed leading to complete β-elimination of the iduronic acid residue, therefore, the strong base was exchanged into freshly prepared silver(I)oxide. Under such conditions, the methylated **42** was obtained in high yield and no elimination occurred. The uronic ester was treated with aqueous sodium hydroxide to give the sodium uronate **43**. Removal of the benzyl protecting groups by catalytic hydrogenation resulted in the triol **44** which upon sulfation with the SO_3·pyridine complex furnished the GH fragment of idraparinux (**8**, Scheme 7). Overall yield for **8** was 37% starting from **39** and **13**.

Coupling of the sulfonatomethyl glucosides in salt form (**24**, **27** and **29**) with the iduronic acid donor failed, therefore, the sulfonic acids in the form of the methyl esters were resorted as the acceptors. The methyl ester **45** was prepared from the salt **24** by liberation of the sulfonic acid followed by esterification with ethereal diazomethane.[9] Glycosylation of the 2-deoxy-2-sulfonatomethyl glucoside acceptor **45** with the donor **39** afforded the desired α-linked disaccharide whose deacetylation gave **46** in a high yield. Usual methylation was attempted applying sodium hydride and methyl iodide, since similar methylation of the sulfonic acid-containing glucuronate **31** took place smoothly. However, with **46** an inseparable mixture of the desired product **47** and the by-product **48** (as a result of β-elimination of the base-sensitive iduronic acid residue) was formed in a ratio of ~3:1. To overcome this difficulty, methylation of **46** was carried out under slightly acidic conditions with diazomethane[25] applying silica gel[25b] or BF_3·Et_2O[25c] to catalyse the reaction. The silica gel promoted methylation proved to be more efficient affording the desired product **49**[49] in high yield. Compound **49**, carrying two ester functions, was converted into the disodium salt in two steps; the sulfonic ester was treated with sodium iodide in acetone to give sodium sulfonate in a nucleophilic substitution reaction, then the crude product was reacted with aqueous sodium hydroxide in methanol to hydrolyse the carboxylic ester giving sodium uronate. Catalytic hydrogenation and subsequent sulfation afforded the 2-deoxy-2-sulfonatomethyl-containing disaccharide **9** with 55% overall yield over eight steps (Scheme 8).[9]



Scheme 6. Synthesis of the L-iduronate donor. Reagents and conditions: (a) 90% F_3CCOOH, rt, 15 min; (b) py, Ac_2O, 0 °C to rt, 24 h (36% for two steps); (c) THF, $BnNH_2$, rt, 3 h (79%); (d) CH_2Cl_2, DBU, trichloroacetonitrile, 0 °C, 30 min (72%).



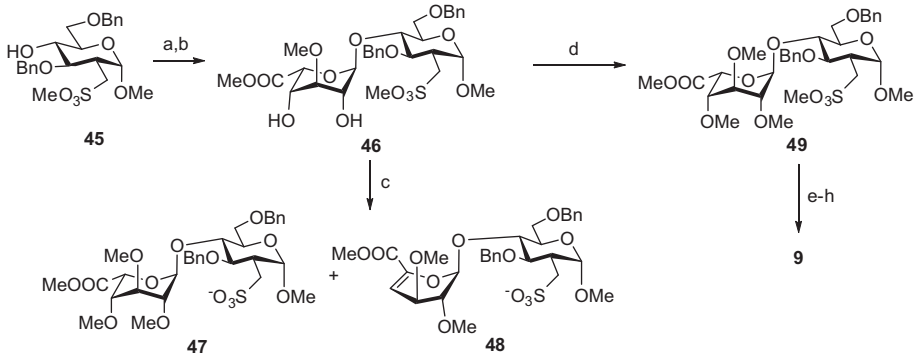
Scheme 7. Synthesis of the GH fragment of idraparinux. Reagents and conditions: (a) CH_2Cl_2, 4 Å Ms, TMSOTf, −20 °C, 30 min (94%); (b) MeOH, NaOMe, rt, 1 h (95%); (c) DMF, Ag_2O, MeI, rt, 96 h (76%); (d) 0.1 M NaOH, rt, 24 h (68%); (e) ethanol, Pd(C), H_2, rt, 12 h (85%); (f) DMF, SO_3·py, 0 °C to rt, 5 h (94%).

In conclusion, the EF and GH disaccharide fragments of idraparinux were prepared following two different strategies. The glucuronic acid containing EF disaccharide was synthesized by post-glycosidation oxidation using an acetobromo glucose donor to build up the disaccharide skeleton and TEMPO-based oxidation to form the carboxylic function at a disaccharide level. Preparation of the iduronic acid-containing GH disaccharide was carried out by pre-glycosidation oxidation using an iduronic acid donor to achieve the disaccharide uronate.

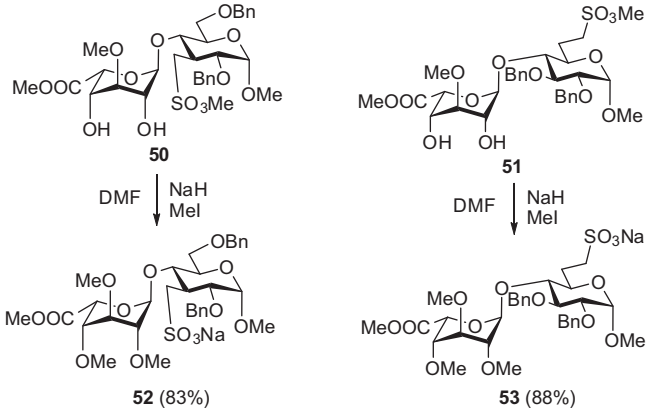
Synthesis of the sulfonic acid analogues could be carried out analoguosly applying sulfonatomethyl-containing acceptors in the form of salts and methyl esters. The sulfonatomethyl glucosides in the form of salts were efficient acceptors when reacting with the acetobromo glucose donor. The glycosylation reactions failed when the sulfonic acid salt acceptors were reacted with the iduronic acid donor with inherently low reactivity. In that case the sulfonic acid acceptors in the form of esters were applied to effectuate the glycosylations in high yields.

Comparing the efficacy of the synthesis of disaccharides with or without sulfonic acid content similar overall yields could be reached for the non-sulfonic acid disaccharides (**4** and **8**) and their sulfonatomethyl-containing analogues (**5**–**7** and **9**–**11**).

Interestingly, the sulfonatomethyl-containing uronate disaccharides proved to be significantly more stable under the basic conditions of methylation than the non-sulfonic acid uronates. There was only one precedent for β-elimination of the base-sensitive uronates of the sulfonic acid analogues (namely, the reaction of **46** with sodium hydride and methyl iodide). In that case,



Scheme 8. Synthesis of the 2-deoxy-2-sulfonatomethyl analogue of the GH fragment of idraparinux. Reagents and conditions: (a) **39**, CH_2Cl_2, 4 Å Ms, TMSOTf, −20 to 0 °C, 15 min (80%); (b) MeOH, NaOMe, rt, 2 h (97%); (c) DMF, NaH, MeI (d) CH_2Cl_2, CH_2N_2, silicagel, 0 °C (88%); (e) acetone, NaI, rt, 2 h; (f) 0.1 M NaOH, rt, 24 h (96% over two steps); (g) ethanol, Pd(C), H_2, 10 atm, rt, 12 h (97%); (h) DMF, SO_3·py, 0 °C to rt, 5 h (87%).



Scheme 9. Synthesis of the 3-deoxy-3-sulfonatomethyl and 6-deoxy-6-sulfonatomethyl analogues of compound **8**.

methylation was carried out under acidic conditions applying ethereal diazomethane in the presence of silica gel.

Synthesis of the pentasaccharide analogues of idraparinux by applying the presented methods, as well as biological investigations of the prepared sulfonic acid derivatives is in progress.

3. Experimental

3.1. 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 soln 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 ^{1}H (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 ^{1}H) or to the residual solvent signals ($CDCl_3$: 77.00 ppm for ^{13}C).

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.

The molecular dynamics simulations (100 ns, 1200 K constant temperature, 1fs time step) and the preliminary geometry optimizations using the suitably developed GAFF empirical force field on the equidistantly saved 100,000 trajectory snapshot geometries were carried out by means of the AMBER molecular dynamics simulation package.[26,20] The B3LYP/6-31G(d) density functional calculation on the lowest energy conformer was carried out using the GAUSSIAN 03 package.[27] Ball-and-stick and stick representations of the conformers were generated by the VMD software.[28]

3.2. Methyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (14)

To a mixture of compound **13** (1.00 g, 2.16 mmol) and acetobromoglucose (**12**, (1.78 g, 4.32 mmol)) in dry CH_2Cl_2 (20 mL) powdered 4 Å molecular sieves (1.5 g) was added. The stirred mixture was cooled to 0 °C under argon. After 1 h at this temperature, AgOTf (1.2 g, 4.68 mmol) dissolved in toluene (4 mL) was added. After another hour the reaction was allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered through a pad of Celite. After filtration Et_3N (1 mL) was added, and the solvents were evaporated in vacuo. The crude product was purified by silica gel chromatography (1:1 *n*-hexane–EtOAc) to give **14** (1.61 g, 94%) as a colourless syrup. $[\alpha]_D$ −6.2 (*c* 0.11, $CHCl_3$); R_f 0.42 (1:1 *n*-hexane–EtOAc); ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.38–7.27 (m, 15H, arom.), 5.01–4.39 (m, 10H), 4.15 (m, 1H), 3.91–3.35 (m, 9H), 3.37 (s, 3H, OCH_3), 2.00, 1.98, 1.95 (3 × s, 12H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 170.4, 170.0, 169.2, 168.8 (4C, 4 × CO), 139.2, 138.1, 137.5 (3C, 3 × C_q arom.), 128.5–127.0 (arom.), 99.8, 98.2 (C-1, C-1′), 79.7, 78.7, 77.1, 73.0, 71.7, 71.3, 69.5, 67.9 (skeleton carbons), 74.9, 73.5, 73.3 (3 × PhCH_2), 67.4 (C-6′), 61.5 (C-6), 55.2 (OCH_3), 20.5, 20.4, 20.3 (4 × CH_3); MALDI-TOF (positive ion): *m*/*z* 817.17 $[M+Na]^+$ (calcd 817.30). Anal. Calcd for $C_{42}H_{50}O_{15}$ (794.84): C, 63.47; H, 6.34. Found: C, 63.33; H, 6.29.

3.3. Methyl (β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15)

To a solution of **14** (1.45 g, 1.82 mmol) in MeOH (25 mL) a catalytic amount of NaOMe (11 mg, 0.2 mmol) was added. After 2 h stirring, the mixture was neutralized with Amberlite IR-120 H^+ ion-exchange resin, filtered and concentrated to give **15** (1.11 g, 97%) as a colourless syrup. $[\alpha]_D$ +5.4 (*c* 0.19, MeOH); R_f 0.42 (9:1 CH_2Cl_2–MeOH); ^{1}H NMR (CD_3OD, 360 MHz): δ (ppm) 7.44–7.26 (m, 15H, arom.), 4.96 (d, 1H, *J* 10.3 Hz, PhCH_2), 4.76 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.70–4.51 (m, 5H, PhCH_2), 4.41 (d, 1H, $J_{1',2'}$ 7.3 Hz, H-1′), 4.00–3.95 (m, 2H), 3.86–3.69 (m, 4H), 3.55–3.46 (m, 2H), 3.37 (s, 3H, OCH_3), 3.30–3.17 (m, 4H); ^{13}C NMR (CD_3OD, 90 MHz): δ (ppm) 139.5 (3 × C_q arom.), 129.9–128.7 (arom.),

103.5 (C-1′), 99.0 (C-1), 81.6, 80.6, 78.8, 77.9, 76.5, 75.7, 72.1, 71.6 (skeleton carbons), 77.3, 74.2, 74.1 (3 × PhCH$_2$), 69.2 (C-6), 63.3 (C-6′), 55.6 (OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 649.22 [M+Na]$^+$ (calcd 649.26). Anal. Calcd for $C_{34}H_{42}O_{11}$ (626.69): C, 65.16; H, 6.76. Found: C, 64.87; H, 6.70.

3.4. Methyl (sodium β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (16)

A stirred mixture of compound **15** (200 mg, 0.319 mmol) satd $NaHCO_3$ solution (2.6 mL), KBr (20 mg, 0.16 mmol) and TEMPO (5 mg, 0.031 mmol) was cooled to 0 °C, and then 5% NaOCl solution (2.6 mL, ~1.75 mmol) was added slowly in portions. After 2 h the reaction mixture was extracted with CH_2Cl_2 (10 mL), and the aqueous phase was concentrated. Then MeOH (10 mL) was added and after stirring for 20 min, the insolubles were removed by filtration. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography in 85:15 CH_2Cl_2–MeOH, to give the uronic acid salt **16** as a white powder (158 mg, 78%). $[\alpha]_D$ +39.4 (*c* 0.13, MeOH); R_f 0.33 (85:15 CH_2Cl_2–MeOH); ^{1}H NMR (CD_3OD, 360 MHz): δ (ppm) 7.46–7.21 (m, 15H, arom.), 4.51–3.60 (m, 18H), 3.25 (s, 3H, OC*H*$_3$); ^{13}C NMR (CD_3OD, 90 MHz): δ (ppm) 140.4, 139.6 139.5 (3 × C$_q$ arom.), 129.4–128.4 (arom.), 104.2 (C-1′), 99.0 (C-1), 81.4, 81.1, 78.1, 77.6, 76.4, 75.4, 73.5, 71.4 (skeleton carbons), 76.1, 74.4, 74.0 (3 × PhCH$_2$), 69.9 (C-6), 55.5 (OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 685.39 [M+Na]$^+$ (calcd 685.22). Anal. Calcd for $C_{34}H_{39}NaO_{12}$ (662.66): C, 61.63; H, 5.93. Found: C, 61.54; H, 6.01.

3.5. Methyl (sodium 2,3,4-tri-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (17) 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 (18)

To a solution of compound **16** (117 mg, 0.183 mmol)) in DMF (2 mL) at 0 °C were successively added 60% NaH (44 mg, 1.1 mmol) and MeI (154 μL, 2.47 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 **17** and **18** which were separated by silica gel chromatography (1:1 *n*-hexane–acetone). Compound **17** (53 mg, 42%): $[\alpha]_D$ +7.0 (*c* 0.13, $CHCl_3$); R_f 0.59 (1:1 *n*-hexane–acetone); ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.40–7.20 (m, 15H, arom.), 4.97–4.41 (m, 7H), 2.28 (m, 1H, $J_{1',2'}$ 7.4 Hz, H-1′), 3.85–3.65 (m, 5H), 3.53, 3.41, 3.31 (4 × s, 12H, 4 × OC*H*$_3$), 3.56–3.33 (m, 2H), 3.01–2.80 (m, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 138.3, 138.0, 137.7 (3 × C$_q$ arom), 128.3–127.3 (arom.), 102.0 (C-1′), 98.1 (C-1), 85.2, 83.2, 80.7, 79.8, 79.1, 76.4, 69.9 (skeleton carbons), 75.4, 73.4, 73.2 (3 × PhCH$_2$), 67.8 (C-6), 60.4, 60.3, 60.0, 55.1 (4 × OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 727.19 [M+Na]$^+$ (calcd 727.27). Anal. Calcd for $C_{37}H_{45}NaO_{12}$ (704.74): C, 63.06; H, 6.44. Found: C, 62.91; H, 6.33. Compound **17** was prepared also from **22** according to the method described for the synthesis of **16** in a yield of 64%.

Compound **18** (50 mg, 40%): $[\alpha]_D$ +42.8 (*c* 0.60, $CHCl_3$); R_f 0.42 (1:1 *n*-hexane–acetone); ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.32–7.29 (15H, arom.), 6.07 (d, 1H $J_{3',4'}$ 2.9 Hz, H-4′), 4.9–4.85 (m, 3H), 4.81–4.42 (m, 5H), 3.94–3.81 (m, 4H), 3.78–3.51 (m, 3H), 3.45, 3.42, 3.37 (3 × s, 9H, 3 × OC*H*$_3$), 3.21 (t, 1H, *J* 6.6 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 161.9 (*C*O), 140.6 (C-5′), 138.1, 138.0, 137.6 (3 × C$_q$ arom.), 128.4–127.9 (arom.), 109.2 (C-4′), 101.3 (C-1′), 98.2 (C-1), 79.6, 79.5, 79.0, 76.9, 76.6, 69.7 (skeleton carbons), 75.8, 73.5, 73.4 (3 × PhCH$_2$), 67.8 (C-6), 59.9, 56.9, 55.3 (3 × OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 695.33 [M+Na]$^+$ (calcd 695.24). Anal. Calcd for $C_{36}H_{41}NaO_{11}$ (672.69): C, 64.28; H, 6.14. Found: C, 64.08; H, 6.09.

3.6. Methyl (sodium 2,3,4-tri-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-α-D-glucopyranoside (19)

A mixture of compound **17** (196 mg, 0.287 mmol) and Pd/C (10%, 80 mg) in 96% EtOH–AcOH (19:1, 15 mL) 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 under reduced pressure to give **19** (111 mg, 94%) as a white powder. $[\alpha]_D$ +58.6 (*c* 0.11, MeOH); R_f 0.24 (1:1 CH_2Cl_2–MeOH); ^{1}H NMR (CD_3OD, 360 MHz): δ (ppm) 4.73 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.50 (d, 1H, $J_{1',2'}$ 7.1 Hz, H-1′), 3.93–3.68 (m, 5H), 3.61, 3.55, 3.52, 3.43 (4 × s, 12H, 4 × OC*H*$_3$), 3.63–3.35 (m, 2H), 3.25–3.07 (m, 3H); ^{13}C NMR (CD_3OD, 90 MHz): δ (ppm) 176.6 (*C*O), 104.2 (C-1′), 100.9 (C-1), 87.2, 84.3, 82.7, 80.6, 76.7, 73.3, 73.1, 72.3 (skeleton carbons), 61.2, 61.1, 60.8, 55.7 (4 × OCH$_3$), 61.0 (C-6); MALDI-TOF (positive ion): *m*/*z* 457.17 [M+Na]$^+$ (calcd 457.13). Anal. Calcd for $C_{16}H_{27}NaO_{12}$ (434.37): C, 44.24; H, 6.27. Found: C, 44.30; H, 6.29.

3.7. Methyl (sodium 2,3,4-tri-*O*-methyl-β-D-glucopyranosyluronate)-(1→4)-2,3,6-tri-*O*-sodium-sulfonato-α-D-glucopyranoside (4)

A solution of compound **19** (101 mg, 0.245 mmol) in DMF (3 mL) was treated with the SO_3·pyridine complex (585 mg, 3.675 mmol) 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 (5 mL) was added and after stirring for 20 min the insolubles were removed by filtration. The filtrate was concentrated under reduced pressure. The crude product was purified by Sephadex LH 20 column chromatography in MeOH to give **4** (124 mg, 70%) as a white powder. $[\alpha]_D$ +37.9 (*c* 0.11, MeOH); R_f 0.34 (4:6 CH_2Cl_2–MeOH); ^{1}H NMR (D_2O, 500 MHz): δ (ppm) 5.17 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.67–4.63 (m, 2H, H-1′, H-3), 4.39–4.37 (m, 3H, H-2, H-6a,b), 4.09 (m, 1H, H-5), 4.03 (m, 1H, H-4), 3.70 (d, 1H, $J_{4',5'}$ 10.0 Hz, H-5′), 3.63, 3.61, 3.49, 3.48 (4 × s, 12H, 4 × OC*H*$_3$), 3.45 (t, 1H, *J* 9.2 Hz, H-4′), 3.88 (m, 1H, H-3′), 3.23 (t, 1H, *J* 8.8 Hz H-2′); ^{13}C NMR (D_2O, 125 MHz): δ (ppm) 175.7 (*C*O), 100.8 (C-1′), 97.2 (C-1), 84.2 (C-3′), 82.2 (C-2′), 81.6 (C-4), 76.4 (C-5′), 76.2 (C-3), 75.0 (C-2), 73.5 (C-4), 69.1 (C-5), 66.1 (C-6), 61.1, 60.6, 56.0 (4 × OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 763.14 [M+Na]$^+$ (calcd 762.95). Anal. Calcd for $C_{16}H_{24}Na_4O_{21}S_3$ (740.50): C, 25.95; H, 3.27; S, 12.99. Found: C, 25.84; H, 3.26; S, 12.84.

3.8. Methyl (6-*O*-triphenylmethyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (20)

To a solution of compound **15** (1.11 g, 1.77 mmol) in pyridine (18 mL) triphenylmethyl chloride (988 mg, 3.54 mmol) was added. The mixture was stirred for 24 h at room temperature. After completion of the reaction, the mixture was concentrated in vacuo.

The crude product was purified by silica gel chromatography (75:25 CH_2Cl_2–acetone + 1% Et_3N) to give **20** (1.27 g, 83%) as a colourless syrup. $[\alpha]_D$ −8.4 (*c* 0.27, $CHCl_3$); R_f 0.54 (75:25 CH_2Cl_2–acetone); ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm) 8.54–7.25 (m, 30H, arom.), 4.88–4.44 (m, 8H), 4.05–3.57 (m, 4H), 3.55–3.39 (m, 7H), 3.32 (s, 3H, OC*H*$_3$), 3.29–3.21 (m, 4H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 149.5–123.6 (arom.), 102.8 (C-1′), 98.1 (C-1), 86.9 (Ph$_3$*C*), 80.5, 79.4, 76.4, 76.1, 74.3, 73.9, 71.8, 69.4 (skeleton carbons), 74.7, 73.5, 73.3 (3 × PhCH$_2$), 68.4, 63.8 (2 × C-6), 55.0 (OCH$_3$); MALDI-TOF (positive ion): *m*/*z* 891.35 calcd for [M+Na]$^+$ (calcd 891.37). Anal. Calcd for $C_{53}H_{56}O_{11}$ (869.01): C, 73.25; H, 6.50. Found: C, 73.15; H, 6.38.

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

Compound **20** (1.20 g, 1.38 mmol) was methylated according to the method described for the synthesis of **17**. The crude product was purified by silica gel chromatography (65:35 *n*-hexane–EtOAc + 1% Et_3N) to give **21** (1.08 g, 86%) as a colourless syrup. $[\alpha]_D$ +9.1 (*c* 0.16, $CHCl_3$); R_f 0.42 (65:35 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.50–7.09 (m, 30H, arom.), 5.03–4.47 (m, 8H), 4.34 (m, 1H), 4.01–3.92 (m, 2H), 3.78–3.70 (m, 4H), 3.59, 3.45, 3.39, 3.23 (4 × s, 12H, 4 × OCH_3), 3.55–3.26 (m, 3H), 2.99–2.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 143.8–126.7 (arom.), 102.2 (C-1′), 98.3 (C-1), 86.1 (Ph_3C), 86.9, 84.4, 79.8, 79.5, 79.2, 75.6, 74.4, 70.0 (skeleton carbons), 74.6, 73.4, 73.2 (3 × PhCH_2), 68.6, 61.4 (2 × C-6), 60.6, 60.4, 60.2, 55.2 (4 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 933.41 $[M+Na]^+$ (calcd 933.42). Anal. Calcd for $C_{56}H_{62}O_{11}$ (911.08): C, 73.82; H, 6.86. Found: C, 73.69; H, 6.78.

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

A solution of compound **21** (1.00 g, 1.01 mmol) in AcOH (80%, 18 mL) was stirred for 2 h at 50 °C. The mixture was then concentrated in vacuo. The crude product was purified by silica gel chromatography (9:1 CH_2Cl_2–acetone) to give **22** (716 mg, 98%) as a colourless syrup. $[\alpha]_D$ +21.3 (*c* 0.15, $CHCl_3$); R_f 0.42 (9:1 CH_2Cl_2–acetone); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.37–7.24 (m, 15H arom.), 4.97–4.45 (m, 7H), 4.23 (d, 1H, $J_{1'2'}$ 7.5 Hz, H-1′), 3.91–3.67 (m, 6H), 3.59, 3.50, 3.46, 3.38 (4 × s, 12H, 4 × OCH_3), 3.58–3.26 (m, 3H), 2.98–2.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 139.2–126.9 (arom.), 102.4 (C-1′), 98.2 (C-1), 86.3, 84.1, 79.9, 79.6, 78.8, 77.1, 74.6, 70.0 (skeleton carbons), 75.0, 73.4, 73.2 (3 × PhCH_2), 67.8 (C-6), 61.7 (C-6′), 60.5, 60.4, 60.1, 55.2 (4 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 691.28 $[M+Na]^+$ (calcd 691.31). Anal. Calcd for $C_{37}H_{48}O_{11}$ (668.77): C, 66.45; H, 7.23. Found: C, 66.36; H, 7.18.

3.11. 1,5-Anhydro-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-D-*arabino*-hex-1-enitol (25)

To a solution of compound **23** (366 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C Et_3SiH (1.91 mL, 12.0 mmol) and $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol) were added. The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (200 mL), washed with satd $NaHCO_3$ (2 × 100 mL), dried and concentrated. The crude product was purified by silica gel chromatography (4:1 *n*-hexane–EtOAc) to give 140 mg (41%) of **25** as white needles. Mp: 110–112 °C; $[\alpha]_D$ −1.0 (*c* 0.19, $CHCl_3$); R_f 0.71 (97:3 CH_2Cl_2–EtOAc); ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.54–7.20 (m, 10H, arom.), 6.17 (s, 1H, H-1), 5.62 (s, 1H, C*H*Ph), 4.94–4.69 (dd, 2H, *J* 11.8 Hz, PhCH_2), 4.36 (m, 1H, H6a), 4.24 (d, 1H, $J_{3,4}$ 7.3 Hz, H-3), 4.06 (dd, 1H, $J_{4,5}$ 9.4 Hz, H-4), 3.86–3.80 (m, 2H, H-5, H-6b), 1.63 (s, 3H, 2-CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ (ppm) 139.9 (C-1), 138.7, 137.4 (C_{quat}, arom), 128.9–125.9 (arom.), 110.3 (C-2), 101.1 (*C*HPh), 81.1 (C-4), 75.9 (C-3), 68.6 (C-5), 73.3 (PhCH_2), 68.5 (C-6), 13.8 (2-CH_3); MALDI-TOF (positive ion): *m*/*z* 361.42 $[M+Na]^+$ (calcd 361.14). Anal. Calcd for $C_{21}H_{22}O_4$ (338.41): C, 74.54; H, 6.55. Found: C, 74.35; H, 6.46.

3.12. Methyl 2,6-di-*O*-benzyl-3-deoxy-3-*C*-methylene-α-D-ribo-hexopyranoside (28)

Compound **26** (1.0 g, 2.714 mmol) was converted to **28** by the method described for the synthesis of **25**. The crude product was purified by silica gel chromatography (7:3 *n*-hexane–EtOAc) to give 784 mg (78%) of **28** as a colourless syrup. $[\alpha]_D$ +39.6 (*c* 0.27, $CHCl_3$); R_f 0.30 (7:3 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 7.36–7.24 (m, 10H, arom.), 5.38, 5.32 (2 × s, 2H, CH_2=), 4.77 (d, 1H, PhCH_2), 4.71 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.62–4.52 (m, 3H, PhCH_2), 4.07 (d, 1H, $J_{4,5}$ 8.9 Hz, H-4), 3.94 (d, 1H, H-2), 3.74, 3.67 (2 × dd, 2H, H-6a,b), 3.58 (m, 1H, H-5), 3.38 (s, 3H, OCH_3), 2.65 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 143.0 (C-3), 137.8–127.6 (arom.), 105.3 (CH_2=), 98.5 (C-1), 76.3 (C-2), 72.3 (C-4), 73.5, 71.9 (2 × PhCH_2), 70.1 (C-6), 69.4 (C-5), 55.1 (OCH_3); Anal. Calcd for $C_{22}H_{26}O_5$ (370.44): C, 71.33; H, 7.07. Found: C, 71.25; H, 7.05.

3.13. Methyl 2,6-di-*O*-benzyl-3-deoxy-3-*C*-(triethylammonium sulfonatomethyl)-α-D-glucopyranoside (27)

To a solution of compound **28** (500 mg, 1.35 mmol) in aqueous EtOH (70%, 80 mL) $NaHSO_3$ (1.4 g, 13.5 mmol) and *tert*-butyl peroxybenzoate (128 μL, 0.675 mmol) were added and the mixture was heated under reflux for 4 h. After cooling, triethylamine was added, the mixture was diluted with EtOH, the insolubles were removed by filtration and the filtrate was concentrated in vacuo. The crude product was purified by silica gel chromatography (90:9:1 CH_2Cl_2–MeOH–Et_3N) to give 553 mg (74%) of **27**[9] as a colourless syrup. $[\alpha]_D$ +50.1 (*c* 0.22, $CHCl_3$), lit.[9] +50.3. The ^1H and ^{13}C NMR data were in agreement with those published.[9]

3.14. Methyl (β-D-glucopyranosyl)-(1→4)-2,3-di-*O*-benzyl-6-deoxy-6-*C*-(triethylammonium sulfonatomethyl)-α-D-glucopyranoside (33)[9]

Monitoring the proton deuterium exchange the initial proton spectrum was recorded in DMSO, then D_2O was added. ^1H NMR (DMSO, 400 MHz): δ (ppm) 7.39–7.29 (m, 10H, arom.), 5.08 (d, 1H, *J* 4.5 Hz, 2′-O*H*; 0.4H intensity 16 scans after adding D_2O), 4.94–4.89 (m, 3H, 3′-O*H*, 4′-O*H*, PhCH_2; 1.6H intensity 16 scans after adding D_2O), 4.77 (d, 1H, $J_{1,2}$ 3.1 Hz, H-1), 4.71 (d, 1H, PhCH_2), 4.61 (s, 2H, PhCH_2), 4.48 (d, 1H, $J_{1',2'}$ 7.5 Hz, H-1′), 4.41–4.38 (m, 1H, 6′-O*H*, the signal disappeared 16 scans after adding D_2O), 3.72 (t, 1H, H-4), 3.61–3.46 (m, 3H), 3.43–3.35 (m, 4H), 3.29 (s, 3H, OCH_3), 3.18–3.15 (m, 1H, H-2), 3.08–3.03 (m, 6H, Et_3N–CH_2), 3.01–21.98 (m, 1H, H-2′), 2.68–2.52 (m, 3H), 2.32 (m, 1H, H-6a), 1.77 (m, 1H, H-6b), 1.19 (m, 9H, Et_3N–CH_3); ^{13}C NMR (D_2O, 90 MHz): δ (ppm) 138.9, 138.6 (C_q arom.), 129.5–128.9 (arom.), 103.2 (C-1′), 98.2 (C-1), 80.8, 80.3, 80.0, 77.5, 76.9, 75.3, 71.2, 69.9 (skeleton carbons), 76.6, 74.0 (2 × PhCH_2), 62.3 (C-6′), 55.8 (OCH_3), 48.3 (C-7), 47.6 (NCH_2), 27.3 (C-6), 9.2 (NCH_3).

3.15. Methyl 1,2,4-tri-*O*-acetyl-3-*O*-methyl-α,β-L-idopyranosyluronate (37)

A solution of **36** (5.0 g, 19.065 mmol) in aqueous 90% trifluoroacetic acid (40 mL) was kept at room temperature for 15 min, evaporated to dryness, and the residue was coevaporated with H_2O (2 × 10 mL). The obtained crude product was acetylated using pyridine (28 mL) and acetic anhydride (14 mL). After 24 h at room temperature, the mixture was concentrated under reduced pressure, and traces of pyridine and acetic anhydride were coevaporated three times with toluene. Column chromatography (1:1 *n*-hexane–EtOAc) gave **59** (2.39 g, 36% for 2 steps, α:β ~1:10) as a colourless oil.

α: R_f 0.38 (1:1 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 360 MHz): δ (ppm) 6.22 (s, 1H, H-1), 5.18 (s, 1H), 4.89 (s, 1H), 4.87 (s, 1H), 3.80 (s, 3H, COOCH_3), 3.63 (s, 1H, H-3), 3.54 (s, 3H, OCH_3), 2.12, 2.09, 2.08 (3s, 9H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 90 MHz): δ (ppm) 169.6, 169.2, 168.4, 168.1 (4 × *C*O), 91.0 (C-1), 73.4, 67.5, 67.0, 65.3 (skeleton carbons), 58.4 (OCH_3), 52.5 (COOCH_3), 20.8, 20.7,

20.6 (3 × CH_3). Anal. Calcd for $C_{14}H_{20}O_{10}$ (348.30): C, 48.28; H, 5.79. Found: C, 48.19; H, 5.74.

β: R_f 0.30 (1:1 *n*-hexane–EtOAc); $[\alpha]_D$ +22.3 (*c* 0.10, $CHCl_3$); mp 123–124 °C. The ^1H and ^{13}C NMR data have been published.[9] Anal. Calcd for $C_{14}H_{20}O_{10}$ (348.30): C, 48.28; H, 5.79. Found: C, 48.37; H, 5.77.

3.16. Methyl 2,4-di-*O*-acetyl-3-*O*-methyl-α,β-L-idopyranosyluronate (38)

To a solution of **37** (2.0 g, 5.742 mmol) in THF (50 mL) benzyl amine (2.51 mL, 22.97 mmol) was added. The reaction mixture was stirred for 4 h and monitored by TLC. The reaction was poured into 1 M aq HCl (50 mL), and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried, and evaporated to dryness. Column chromatography (85:15 CH_2Cl_2–acetone) gave **38** (1.39 g, 79%) as a colourless oil. $[\alpha]_D$ +4.7 (*c* 0.10, $CHCl_3$); R_f 0.43 (85:15 CH_2Cl_2–acetone); ^1H NMR ($CDCl_3$, 500 MHz): *δ* (ppm) 5.33 (s, 0.6H), 5.31 (s, 0.4H), 5.19 (s, 0.6H), 5.12 (s, 0.4H), 5.10 (s, 0.6H), 4.99 (s, 0.6H), 4.88 (s, 0.4H), 4.82 (s, 0.6H), 4.62 (s, 0.8H), 3.78, 3.77, 3.60, 3.55 (4 × s, 6H, 4 × OCH_3), 3.45, 3.44 (2 × s, 1H), 2.08, 2.06, 2.04 (3 × s, 6H, 4 × CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (ppm) 92.6, 91.7 (C-1α, C-1β), 74.8, 74.2, 72.2, 67.4, 66.6, 66.5, 65.3 (skeleton carbons), 58.9, 58.6 (2 × OCH_3), 52.4, 52.3 (2 × COOCH_3), 20.6, 20.5, 20.4, 20.3 (4 × CH_3); Anal. Calcd for $C_{12}H_{18}O_9$ (306.27): C, 47.06; H, 5.92. Found: C, 46.93; H, 5.98.

3.17. Methyl (methyl 2,4-di-*O*-acetyl-3-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (40)

A mixture of compound **13** (400 mg, 0.861 mmol), imidate **39** (582 mg, 1.292 mmol) and 4 Å molecular sieves in dry CH_2Cl_2 (8 mL) was stirred for 15 min at room temperature, then cooled to −20 °C under argon. TMSOTf (0.1 M in CH_2Cl_2, 1.29 mL, 0.13 mmol) was added, and the reaction mixture was allowed to warm up to 0 °C in 30 min. After completion of the reaction it was quenched by addition of Et_3N (0.2 mL). The reaction mixture was then filtered and concentrated. The crude product was purified by silica gel chromatography (7:3 *n*-hexane–acetone) to give **40** as a colourless oil (609 mg, 94%). $[\alpha]_D$ −25.1 (*c* 0.15, $CHCl_3$); R_f 0.48 (1:1 *n*-hexane–EtOAc); ^1H NMR ($CDCl_3$, 360 MHz): *δ* (ppm) 7.35–7.26 (m, 15H, arom.), 5.11–4.98 (m, 4H), 4.79–4.49 (m, 7H), 3.99–3.71 (m, 6H), 3.63–3.58 (m, 1H), 3.52, 3.36, 3.33 (3 × s, 9H, 3 × OCH_3), 2.00, 1.99 (2 × s, 6H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 90 MHz): *δ* (ppm) 169.8, 169.5, 168.5 (3 × *C*O), 138.6, 137.9, 137.8 (3 × C_q arom.), 128.2–126.9 (arom.), 97.8, 96.8 (2 × C-1), 80.0, 79.5, 74.2, 73.9, 69.9, 67.1, 66.7, 65.8 (skeleton carbons), 74.8, 73.2, 73.0 (3 × Ph*C*H_2), 68.0 (C-6), 58.2, 55.0, 51.8 (3 × OCH_3), 20,7, 20.6 (2 × CH_3); MALDI-TOF (positive ion): *m*/*z* 775.39 $[M+Na]^+$ (Calcd 775.29). Anal. Calcd for $C_{40}H_{48}O_{14}$ (752.80): C, 63.82; H, 6.43. Found: C, 63.68; H, 6.46.

3.18. Methyl (methyl 3-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (41)

Compound **40** (88 mg, 0.117 mmol) was deacetylated as described for the synthesis of **15**. The crude product was purified by silica gel chromatography (85:15 CH_2Cl_2–acetone) to give **41** as a colourless oil (74 mg, 95%). $[\alpha]_D$ −17.3 (*c* 0.15, $CHCl_3$); R_f 0.50 (85:15 CH_2Cl_2–acetone); ^1H NMR ($CDCl_3$, 360 MHz): *δ* (ppm) 7.33–7.25 (m, 15H, arom.), 5.03 (s, 1H), 4.93–4.51 (m, 8H), 3.92–3.71 (m, 5H), 3.68–3.54 (m, 5H), 3.47–3.44 (m, 1H), 3.40, 3.33 (2 × s, 9H, 3 × OCH_3), ^{13}C NMR ($CDCl_3$, 90 MHz): *δ* (ppm) 170.5 (*C*O), 138.7, 137.8. 137.5 (3 × C_q arom.), 128.2–126.8 (arom.), 100.1, 97.7 (2 × C-1), 79.9, 79.6, 77.5, 74.6, 69.8, 68.3, 67.5, 66.8 (skeleton carbons), 74.7, 73.3, 73.2 (3 × PhCH_2), 68.5 (C-6), 57.8, 54.9, 51.7 (3 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 691.35 $[M+Na]^+$ (calcd 691.27). Anal. Calcd for $C_{36}H_{44}O_{12}$ (668.73): C, 64.66; H, 6.63. Found: C, 64.59; H, 6.61.

3.19. Methyl (methyl 2,3,4-tri-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (42)

To a solution of **41** (134 mg, 0.200 mmol) in DMF (4.5 mL) at rt were successively added freshly prepared Ag_2O (370 mg, 1.6 mmol, 4 equiv/OH) and MeI (37 μL, 0.6 mmol, 1.5 equiv/OH). After 96 h of stirring at this temperature, the mixture was diluted with CH_2Cl_2, filtered off through a pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (95:5 CH_2Cl_2–acetone) to give **42** as a colourless syrup (105 mg, 76%). $[\alpha]_D$ −19.6 (*c* 0.10, $CHCl_3$); R_f 0.49 (95:5 CH_2Cl_2–acetone); ^1H NMR ($CDCl_3$, 360 MHz): *δ* (ppm) 7.39–7.27 (m, 15H, arom.), 5.17 (d, 1H, *J* 5.3 Hz), 4.87 (dd, 2H, PhCH_2), 4.75–4.55 (m, 6H), 3.91–3.56 (m, 7H), 3.53, 3.48, 3.42, 3.41, 3.36 (5 × s, 15H, 5 × OCH_3), 3.35–3.30 (m, 1H), 3.04–2.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz): *δ* (ppm) 169.5 (*C*O), 139.0, 138.1, 137.9 (3 × C_q arom.), 128.2–127.0 (arom.), 99.6, 98.0 (2 × C-1), 81.3, 79.9, 79.6, 79.5, 78.8, 75.8, 70.7, 70.1 (skeleton carbons), 75.1, 73.4, 73.3 (3 × PhCH_2), 68.2 (C-6), 59.7, 59.5, 58.8, 55.1, 51.5 (5 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 719.35 $[M+Na]^+$ (calcd 719.30). Anal. Calcd for $C_{38}H_{48}O_{12}$ (696.78): C, 65.50; H, 6.94. Found: C, 65.64; H, 6.97.

3.20. Methyl (sodium 2,3,4-tri-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-(2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (43)

Compound **42** (184 mg, 0.260 mmol) was dissolved in MeOH (20 mL) and treated with 0.1 M aq NaOH solution (20 mL). After 24 h stirring at rt the TLC showed complete conversion of carboxylic ester into sodium salt. The mixture was neutralized with acetic acid, concentrated in vacuo and the residue was purified by silica gel chromatography (95:5 CH_2Cl_2–MeOH) to give **43** as a colourless syrup (126 mg, 68%), $[\alpha]_D$ +23.1 (*c* 0.19, MeOH); R_f 0.25 (9:1 CH_2Cl_2–MeOH); ^1H NMR (CD_3OD, 360 MHz): *δ* (ppm) 7.34–7.25 (m, 15H, arom.), 5.17 (d, 1H, *J* 4.0 Hz), 4.88 (s, 1H), 4.73–4.50 (m, 7H), 3.81–3.70 (m, 5H), 3.58–3.53 (m, 2H), 3.47–3.44 (m, 1H), 3.48, 3.39, 3.36, 3.32 (4 × s, 12H, 4 × OCH_3), 3.15–3.11 (m, 1H); ^{13}C NMR (CD_3OD, 90 MHz): *δ* (ppm) 174.0 (*C*O), 140.1, 139.5, 139.4 (3 × C_q arom.), 129.3–128.3 (arom.), 100.7, 98.8 (2 × C-1), 81.3, 80.9, 81.0, 80.9, 79.7, 79.1, 77.1, 71.7 (skeleton carbons), 76.2, 74.4, 73.9 (3 × PhCH_2), 69.8 (C-6), 59.7, 59.3, 59.0, 55.5 (4 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 705.42 (uronic acid) $[M+Na]^+$ (calcd 705.29). Anal. Calcd for $C_{37}H_{45}NaO_{12}$ (704.74): C, 63.06; H, 6.44. Found: C, 63.07; H, 6.40.

3.21. Methyl (sodium 2,3,4-tri-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-α-D-glucopyranoside (44)

Compound **43** (110 mg, 0.156 mmol) was debenzylated according to the method described for the synthesis of **19**. The crude product was purified by silica gel chromatography (1:1 CH_2Cl_2–MeOH) to give **44** as a white powder (58 mg, 85%). $[\alpha]_D$ +54.0 (*c* 0.10, MeOH); R_f 0.21 (1:1 CH_2Cl_2–MeOH); ^1H NMR (D_2O, 360 MHz): *δ* (ppm) 5.06 (s, 1H), 4.80 (s, 1H), 4.65 (s, 1H), 3.88–3.85 (m, 1H), 3.81–3.56 (m, 8H), 3.52, 3.49, 3.42, 3.40 (4 × s, 12H, 4 × OCH_3); ^{13}C NMR (D_2O, 90 MHz): *δ* (ppm) 175.9 (*C*O), 99.3, 99.0 (2 × C-1), 77.4, 77.2, 76.9, 75.9, 71.7, 71.4, 70.5, 69.6 (skeleton carbons), 60.1 (C-6), 58.3, 57.9, 54.9 (4 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 457.32 (sodium salt) $[M+Na]^+$ (calcd 457.13). Anal. Calcd for $C_{16}H_{27}NaO_{12}$ (434.37): C, 44.24; H, 6.27. Found: C, 44.31; H, 6.30.

3.22. Methyl (sodium 2,3,4-tri-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-2,3,6-tri-*O*-(sodium sulfonato)-α-D-glucopyranoside (8)

Compound **44** (50 mg, 0.115 mmol) was *O*-sulfated according to the method described for the synthesis of **4**. The crude product was purified by Sephadex LH-20 column chromatography eluted with H_2O to give **8** as a white powder (80 mg, 94%). $[\alpha]_D$ +36.8 (*c* 0.15, MeOH); R_f 0.10 (8:5:1 CH_2Cl_2–MeOH-H_2O); ^1H NMR (D_2O, 500 MHz): δ (ppm) 5.19 (d,1H, $J_{1,2}$ 3.5 Hz, H-1), 5.06 (d, 1H, $J_{1',2'}$ 3.3 Hz, H-1′), 4.82 (d, 1H, $J_{4',5'}$ 2.7 Hz, H-5′), 4.67 (t, 1H, *J* 9.4 Hz, H-3), 4.43 (m, 1H, H-6a), 4.41 (m, 1H, H-2), 4.32 (m, 1H, H-6b), 4.12 (m, 1H, H-5), 4.03 (t, 1H, *J* 9.7 Hz, H-4), 3.82 (m, 1H, H-4′), 3.67 (m, 1H, H-3′), 3.58, 3.57, 3.51, 3.48 (4 × s, 12H, 4 × OCH_3), 3.50 (m, 1H, H-2); ^{13}C NMR (D_2O, 125 MHz) δ (ppm) 99.6 (C-1′), 97–2 (C-1), 79.0 (C-4′), 78.1 (C-3′), 78.0 (C-2′), 76.1 (C-3), 75.3 (C-2), 73.3 (C-4), 70.9 (C-5′), 68.8 (C-5), 66.3 (C-6), 58.8, 58.4, 58.0, 55.3 (4 × OCH_3); MALDI-TOF (positive ion): *m*/*z* 763.03 (tetrasodium salt) $[M+Na]^+$ (calcd 762.95). Anal. Calcd for $C_{16}H_{24}Na_4O_{21}S_3$ (740.50): C, 25.95; H, 3.27; S, 12.99. Found: C, 25.76; H, 3.22; S, 12.89.

3.23. Methyl (methyl 2,3,4-tri-*O*-methyl-α-L-idopyranosyluronate)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (47); and methyl (methyl 4-deoxy-2,3-di-*O*-methyl-α-L-*threo*-hex-4-enopyranosyluronate)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-*C*-(sodium sulfonatomethyl)-α-D-glucopyranoside (48)

Compound **46** (190 mg, 0.28 mmol) was methylated according to the method described for the synthesis of **17** to give a mixture of **47** and **48** (140 mg) which could not be separated by silica gel chromatography. R_f of the mixture: 0.71 (7:3 CH_2Cl_2–MeOH), 0.22 (*n*-hexane–EtOAc).

Compound **47**: ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 169.9 (*C*O), 138.3–127. (arom.), 99.8, 98.7 (C-1, C-1′), 82.2, 80.3, 79.2, 77.4, 76.5, 71.2, 70.6 (skeleton carbons), 73.2 (2 × $PhCH_2$) 68.3 (C-6), 60.0, 59.7, 58.8, 55.2, 51.8 (5 × OCH_3), 48.1 ($CH_2SO_3^-$), 42.4 (C-2); MALDI-TOF (positive ion): *m*/*z* 729.31 $[M+Na]^+$ (calcd 729.25).

For NMR measurments 35 mg of the mixture of **47** and **48** in DMF (1 mL) was treated with NaH (5 mg) to give **48** as a colourless oil; ^1H NMR ($CDCl_3$, 500 MHz); δ (ppm) 7.32–7.15 (m, 10H, arom.), 5.95 (d, 1H, $J_{3',4'}$ 3.0 Hz, H-4′), 5.17 (s, 1H), 4.90–4.41 (m, 5H), 4.07 (t, 1H, *J* 9.5 Hz), 3.81–3.57 (m, 4H), 3.48, 3.44, 3.41, 3.20 (4 × s, 12H, 4 × OCH_3), 3.23–3.20 (m, 1H), 3.06–2.90 (m, 3H), 2.53 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 162.5 (*C*O), 141.8 (C-5′), 138.1, 137.9 (2 × C_q arom.), 128.1–127.6 (arom.), 109.0 (C-4′), 101.4, 99.0 (C-1, C-1′), 79.3, 78.6, 76.6, 70.4 (skeleton carbons), 73.2 (2 × $PhCH_2$), 68.1 (C-6), 59.9, 57.0, 55.3, 52.5 (4 × OCH_3), 47.7 ($CH_2SO_3^-$), 42.3 (C-2); MALDI-TOF (positive ion): *m*/*z* 697.31 $[M+Na]^+$ (calcd 697.21).

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