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Synthesis of sulfonic acid-containing maltose-type keto-oligosaccharides by an iterative approach

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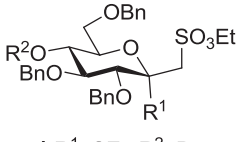
ABSTRACT

Two different series of (2→5)-α-linked homologous keto-oligosaccharides up to tri- and tetrasaccharide were synthesized by an iterative approach, using 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl chloride as a key building block. An iterative cycle consisted of a glycosylation step followed by selective cleavage of the (2-naphthyl)methyl group.

1. Introduction

Sulfated cyclodextrins have exhibited anticancer activity,[1,2] presumably through an anti-angiogenic mechanism. Sulfated maltohexaose also has been identified as a potent inhibitor of in vitro angiogenesis and heparanase activity.[3] Highly sulfated malto-oligosaccharides have the ability to inhibit the biological activity of basic fibroblast growth factor and heparanase in vivo, and act as antitumour and antimetastatic agents in in vivo models of malignancy.[4] Because of the great therapeutical potential of the sulfated malto-oligosaccharides we envisaged the synthesis of their sulfonic acid analogues possessing higher stability against esterases and sulfatases.

Recent work from this laboratory showed that ethyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-2-thio-α-D-*gluco*-hept-2-ulopyranoside **1** (Fig. 1) could be used as glycosyl donor for the synthesis of sulfonic acid analogues of the sialyl Lewis X tetrasaccharide, a natural ligand of transmembrane proteins.[5,6] However, the yields of glycosylation reactions using **1** were moderate since a considerable amount of *exo*-glycal was always formed via elimination of the labile proton next to the electron withdrawing sulfonic acid moiety. The rate of undesirable elimination side-reaction could be decreased by applying the chlorosugar **2** as a glycosyl donor.[7] It has been also shown that both thioglycoside **1** and chloro derivative **2** gave the α-linked ketosyl glycosides exclusively or in high selectivity.[5–8] On the basis of these results, we considered the application of the 1-deoxy-1-ethoxysulfonyl-α-D-gluco-hept-2-ulopyranosyl donor **3** possessing a selectively removable (2-naphthyl)methyl (NAP) protecting group for the preparation of the sulfonic acid analogues of the sulfated malto-oligosaccharides by an iterative approach.



1 R^1=SEt, R^2=Bn
2 R^1=Cl, R^2=Bn
3 R^1=Cl, R^2=NAP

Fig. 1. 1-Deoxy-1-ethoxysulfonyl-D-*gluco*-hept-2-ulopyranosyl donors **1**,[5] **2**[7] and **3**.

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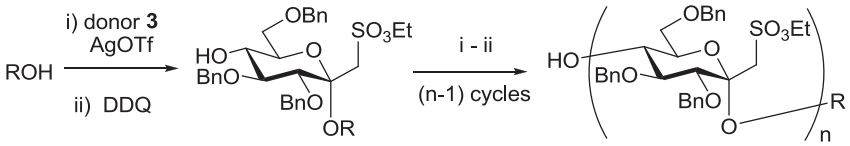
2. Results and discussion

Two series of maltose-type keto-oligosaccharides have been prepared by means of repeating a glycosylation step using **3** as a donor followed by unmasking of the (2-naphthyl)methyl-ether function of the obtained glycoside as outlined in Scheme 1.



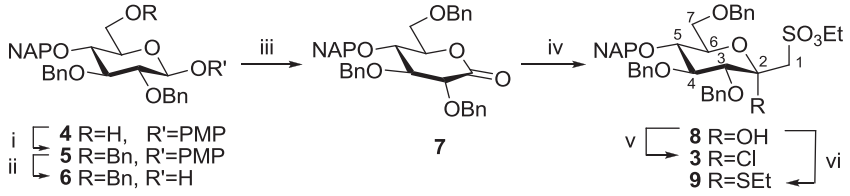
Scheme 1. Iterative synthesis of maltose-type keto-oligosaccharide sulfonic acids.

Synthesis of the key building block **3** started from the known **4**,[9] which was benzylated to afford the fully protected **5** carrying orthogonal protecting groups at the anomeric center and position 4. Selective removal of the 4-methoxyphenyl aglycone with ammonium cerium(IV) nitrate[10] was insufficient, since the (2-naphthyl) methyl group being sensitive towards oxidative cleavage was also affected. Fortunately, acidic hydrolysis produced the hemiacetal **6** in high yield. Compound **6** was oxidised with Dess–Martin periodinane[11] and the obtained gluconolactone **7** was reacted with ethyl methanesulfonate anion generated with *n*-butyllithium. Nucleophilic addition of the sulfonate ester carbanion to the lactone carbonyl gave the 1-deoxy-1-ethoxysulfonyl-hept-2-ulopyranose derivative **8**, exclusively in the α-anomeric form. Reaction of hemiketal **8** with thionyl chloride and pyridine went to completion in 20 min affording the glycosyl chloride **3**, its purification by column chromatography on silica, however, led to partial decomposition. Therefore, the crude reaction product was planned to be utilized for the glycosylation reactions. Another glycosyl donor, the thioglycoside **9** could also be prepared from **8** upon treatment with ethanethiol in the presence of $BF_3 \cdot Et_2O$ (Scheme 2).

Selective removal of the (2-naphthyl)methyl group of the fully protected disaccharide **11** could be achieved by oxidative cleavage using DDQ[15] to give **13** in high yield. Subsequent glycosylation of the disaccharide acceptor **13** with the freshly prepared donor **3** resulted in the maltose-type ketosyl trisaccharide **14** together with the elimination product **12**. Then, another iterative cycle involving NAP-cleavage followed by a glycosylation step furnished the tetrasaccharide **16**. The (2-naphthyl)methyl group of **16** could be split off with high efficacy at a tetrasaccharide level affording **17**, which might be applied as an acceptor for further chain-elongation (Scheme 3).

The other set of sulfonic acid-containing maltose-type keto-oligosaccharides was prepared in form of a methyl glycoside. Reaction of thioglycoside **9** with methanol gave a mixture of the methyl glycosides **18**[16] and **19** in a 4:1 ratio (Scheme 4). The anomeric configuration of the crystalline major product has been verified by X-ray crystallography (an ORTEP view of compound **18** is shown in Fig. 2). Treatment of the α-isomer **18** with DDQ resulted in **20**, which served as an acceptor for the next iterative process.

Glycosylation of **20** with donor **3** gave disaccharide **21** in an acceptable yield. The elimination product **12** potentially formed



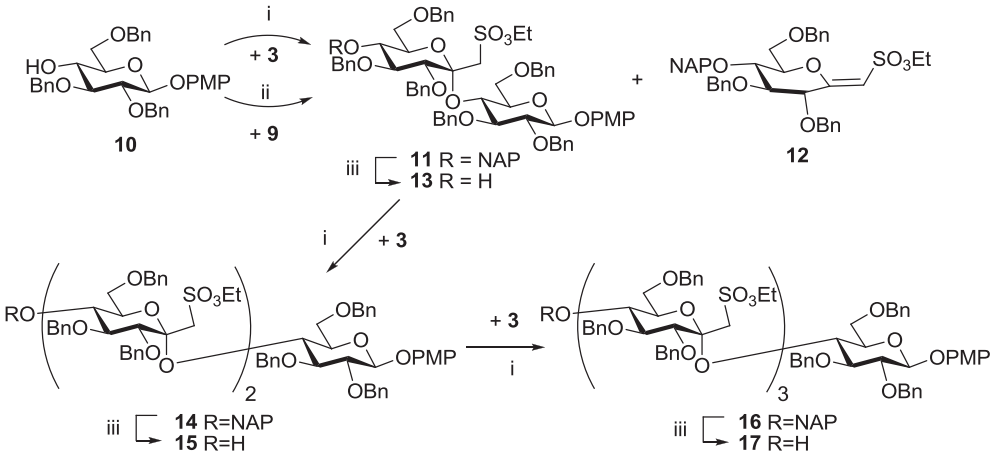
Scheme 2. Synthesis of the glycosyl donors **3** and **9**. Reagents and conditions: (i) NaH, BnBr, DMF, 0 °C, 5 h, 95%; (ii) CH_3CN/HCl_{aq} (10:1), reflux, 3 h, 85%; (iii) Dess–Martin periodinane, CH_2Cl_2, rt, 20 min, 85%; (iv) $(i\text{-}Pr)_2NH$, *n*-BuLi, CH_3SO_3Et, −60 °C, 3 h, 86%; (v) $SOCl_2$, py, CH_2Cl_2, rt, 20 min; (vi) EtSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, −20 °C, 18 h, 94%.

For the synthesis of one of the oligosaccharide series, a monosaccharide unit with a free 4-OH group was intended to be used as an acceptor in the first iterative cycle. Thus, compound **10**[12] was glycosylated with freshly prepared chlorosugar **3** in the presence of silver triflate to result in a mixture of the desired disaccharide **11** and the elimination side-product **12**. The anomeric configurations of ketopyranosyl glycosides can be determined either by the measurement of the NOE interactions between H-1 and H-3 or H-4,[13] or on the basis of the NMR C1–$H3_{axial}$ three-bond coupling constant, which is dependent on the dihedral angle in a manner similar to $^3J_{H,H}$.[5–7,13b,14] Applying the latter method the α-interglycosidic linkage of **11** was unambiguously determined by the recorded small coupling constant ($^3J_{C1'H3'} \leq 1$ Hz).

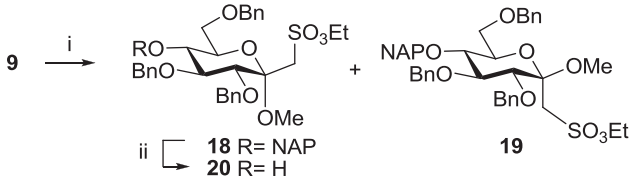
Synthesis of disaccharide **11** was also attempted by utilising the thioglycoside **9**, although it was expected to be a less potent donor than the chlorosugar.[7] Indeed, the thioglycoside **9** upon NIS/TfOH activation proved to be inefficient for glycosylation of the unreactive acceptor **10**;[7] the rapidly formed glycosylium intermediate was mainly stabilized via elimination providing **12** as the main product. Therefore, only compound **3** was used for the further iterative processes.

The prepared ketosyl glycosides up to trisaccharides were deprotected in a two-step procedure. The sulfonic acid esters were transformed into sodiumsulfonato derivatives via nucleophilic substitution using sodium iodide, subsequently, the benzyl protecting groups were removed by catalytic hydrogenation affording the sulfonic acid-containing saccharides **25**–**29** (Scheme 6).

In conclusion, two different series of sulfonic acid-containing (2→5)-α-linked homologous keto-oligosaccharides were synthesized using the ketosyl donor **3** possessing a selectively removable (2-naphthyl)methyl group as the key building block. Although an elimination product was formed from the donor in each glycosylation step, three cycles of the iterative process could be carried out



Scheme 3. Synthesis of the first set of sulfonic acid-containing maltose-type keto-oligosaccharides. Reagents and conditions: (i) AgOTf, CH_2Cl_2/toluene (4:1), 4 Å MS, 0 °C, 5 days, from **10**: **11** (49%) and **12** (25%), from **13**: **14** (37%) and **12** (26%), from **15**: **16** (38%) and **12** (not isolated); (ii) NIS/TfOH, CH_2Cl_2, −40 °C, 75 min, 10% for **11**, 37% for **12**; (iii) DDQ, CH_2Cl_2/H_2O (9:1), rt, 25 min, 87% for **13**, 79% for **15**, 71% for **17**.



Scheme 4. Synthesis of acceptor **2**. Reagents and conditions: (i) MeOH, NIS/TfOH, CH_2Cl_2, 3 Å MS, −50 °C, 20 min, 76% for **18**, 20% for **19**; (ii) DDQ, CH_2Cl_2/H_2O (9:1), rt, 20 min, 89%.

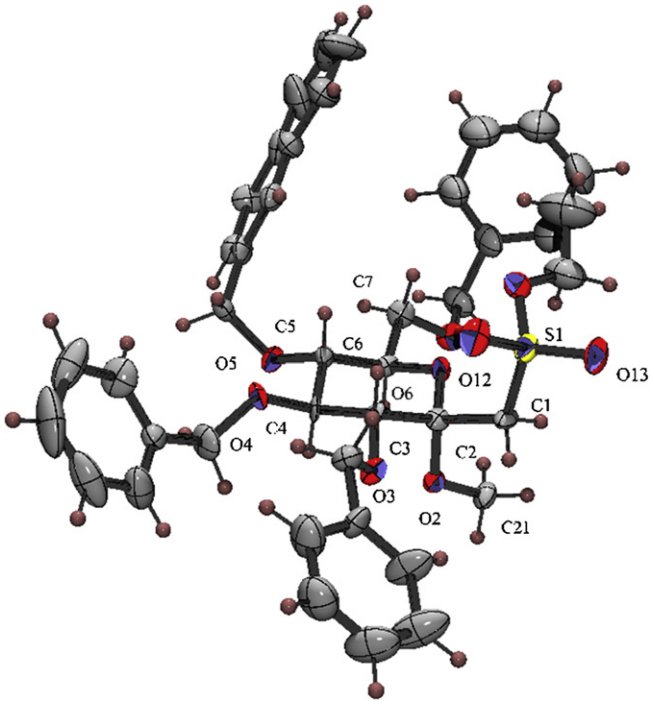
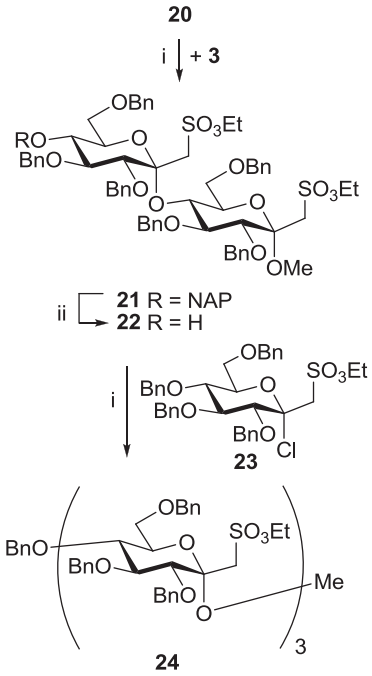


Fig. 2. ORTEP view of compound **18** at 50% probability level.

in acceptable yields. The prepared compounds can be regarded as sulfonic acids analogues of the sulfated malto-oligomers. Biological evaluation of the derivatives as well as the synthesis of higher keto-oligosaccharides are in progress in our laboratory.

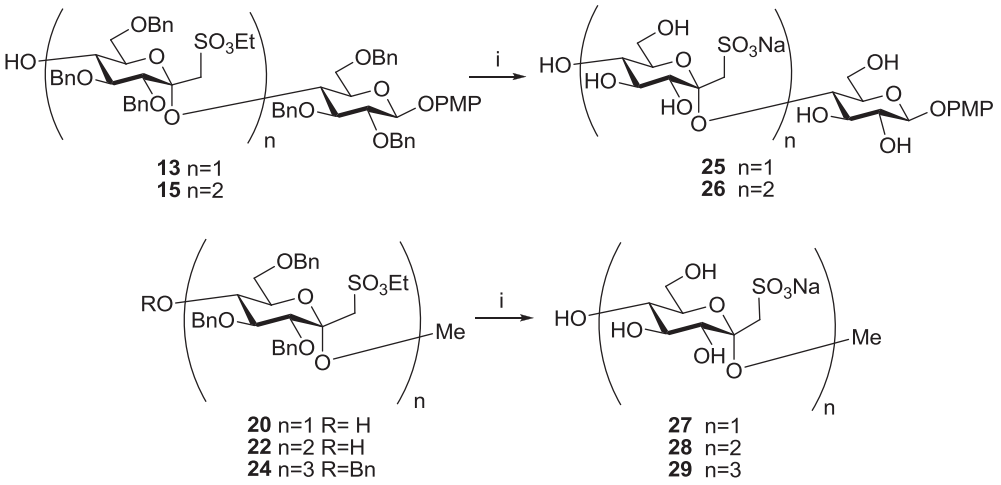


Scheme 5. Synthesis of the second set of sulfonic acid-containing maltose-type keto-oligosaccharides Reagents and conditions: (i) AgOTf, CH_2Cl_2/toluene (4:1), 0 °C, 5 days, 59% for **21**, 34% for **24**; (ii) DDQ, CH_2Cl_2/H_2O (9:1), rt, 25 min, 78%.

3. Experimental

3.1. General

Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. All reactions were performed under anhydrous conditions (using argon) and monitored by TLC on Kieselgel 60 F_{254} (Merck) visualized under UV light and charred with 5% sulfuric acid in ethanol. Column chromatography was performed on Silica Gel 60 (Merck 0.062–0.200 nm). Chemicals were purchased from Aldrich and Fluka and used without further purification. Molecular sieves were activated by heating to 360 °C overnight and were cooled over P_2O_5 in vacuo. The organic solutions were dried over $MgSO_4$, and



Scheme 6. (i) Deprotection procedures. Reagents and conditions: NaI, acetone, 3 h, reflux, then Pd/C, H_2, AcOH, EtOH/H_2O, 62% for **25**, 68% for **26**, 64% for **27**, 61% for **28**, 59% for **29**.

concentrated in vacuum. The ^{1}H (200, 360 and 500 MHz) and ^{13}C NMR (50, 90 and 125 MHz) spectra were recorded with Bruker WP-200SY, Bruker AM-360 and Bruker DRX-500 spectrometers. Chemical shifts are referenced to Me_4Si (0.00 ppm for ^{1}H) or to the residual solvent signals (77.00 ppm for ^{13}C). The ^{13}C/^{1}H long-range coupling constants were measured from ^{1}H-coupled ^{13}C NMR spectra. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. X-ray data collection was performed using a Bruker-Nonius MACH3 diffractometer equipped with a point detector using graphite-monochromated Mo Kα radiation, λ=0.71073 Å. The structure was solved using direct methods by the SIR-92 program[17] and refined by full-matrix least-squares method on F^2, with all non-hydrogen atoms refined with anisotropic thermal parameters. A few benzyl carbon atoms were regulated using several restraints. Refinement was performed using the SHELXL-97 package.[18] Publication material was prepared with the WINGX suite.[19] Hydrogen atoms were located geometrically. MALDI-TOF MS spectra were recorded on a Bruker Biflex III spectrometer in the positive, linear mode using satd 2,4,6-trihydroxyacetophenone in water as matrix. Elemental analyses (C, H, S) were performed using an Elementar Vario MicroCube instrument.

3.2. General method A for removal of (2-naphthyl)methyl-ether

To a stirred solution of the starting material (0.5 mmol) in a mixture of CH_2Cl_2 and water (9:1, 10 mL/mg), DDQ (0.75 mmol, 1.5 equiv) was added and it was vigorously stirred at room temperature. When TLC showed complete conversion (20–25 min) the mixture was diluted with CH_2Cl_2, washed twice with satd aq $NaHCO_3$ and water, dried, filtered and concentrated.

3.3. General method B for glycosylation using donor 3

To a solution of the acceptor (0.6 mmol) in toluene (1.5 mL) and CH_2Cl_2 (4.5 mL), 4 Å powdered molecular sieves and AgOTf (0.6 mmol) were added and it was stirred overnight. The reaction mixture was cooled to 0 °C, then donor **3** (0.3 mmol) in dry CH_2Cl_2 (1.5 mL) was added, and the temperature was kept at 0 °C until TLC showed complete conversion of the donor (~5 days). The insoluble materials were removed by filtration; the filtrate was diluted with CH_2Cl_2, washed with 10% aq $Na_2S_2O_3$ and water, dried, filtered and concentrated. The crude product was purified by column chromatography. The remaining acceptor was recovered in each case.

3.4. General method C for deprotection

To a solution of the starting material (0.05 mmol) in acetone, NaI (1.2 equiv/sulfonate ester functional group) was added and stirred for 2 days. The mixture was then concentrated and the crude product was purified by column chromatography in CH_2Cl_2/MeOH 8:2. The obtained sodium salt was dissolved in EtOH/H_2O/EtOAc (9:1:0.5, 5 mL), 10% Pd/C (60–100 mg) was added and it was stirred in an autoclave under a H_2 atmosphere at 20 bar until TLC indicated a complete conversion. The catalyst was filtered off through a pad of Celite, and the filtrate was concentrated. The product was purified by column chromatography in CH_2Cl_2/MeOH/H_2O=5:4:1.

3.5. *p*-Methoxyphenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2-naphthyl) methyl-β-D-glucopyranoside (5)

Compound **4** (4.87 g, 8.03 mmol) was dissolved in dry *N*,*N*-dimethylformamide (80 mL) and 60% NaH (0.48 g, 12.05 mmol, 1.5 equiv) was added to the cooled mixture (0 °C). After 30 min benzyl bromide (15 mL, 9.64 mmol 1.2 equiv) was added and it was stirred for 5 h. Then MeOH was added, and the reaction mixture was concentrated. The residue was diluted with CH_2Cl_2, washed twice with water, dried, filtered and concentrated. The crude product was crystallized from EtOH to yield **5** (5.30 g, 95%) as white needles. Mp 98–100 °C; $[\alpha]_D$ −15.4 (*c* 0.81, $CHCl_3$); R_f 0.65 (*n*-hexane/EtOAc 7:3); ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.84–7.21 (m, 22H, arom.), 7.04, 6.81 (2d, 4H, PMP arom.), 5.06 (d, 1H, *J*=10.9 Hz, CH_2Ar), 4.99 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.97 (d, 1H, *J*=10.9 Hz, CH_2Ar), 4.92–4.88 (m, 1H, skeleton), 4.84 (d, 1H, *J*=11.0 Hz, CH_2Ar), 4.83 (d, 1H, *J*=11.0 Hz, CH_2Ar), 4.72 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.60 (d, 1H, *J*=12.0 Hz, CH_2Ar), 4.51 (d, 1H, *J*=12.1 Hz, CH_2Ar), 3.84–3.78 (m, 1H, skeleton), 3.77 (s, 3H, OCH_3), 3.76–3.67 (m, 4H, skeleton), 3.65–3.55 (m, 1H, skeleton); ^{13}C NMR (90 MHz, $CDCl_3$): δ 155.2, 151.5 (2C-quat., PMP), 138.5, 138.2, 138.1 (3C-quat., Ph), 135.4, 133.2, 132.9 (3C-quat., NAP), 128.5–125.6 (arom.), 118.4 (2×), 114.5 (2×) (4C-arom., PMP), 102.8 (C-1), 84.7, 82.1, 77.7, (C-2, C-3, C-4), 75.0 (C-5), 75.7, 75.1, 75.0, 73.4 (4CH_2Ar), 68.8 (C-6), 55.6 (OCH_3). Anal. Calcd for $C_{45}H_{44}O_7$ (696.83 g/mol): C, 77.56; H, 6.36. Found: C, 77.44; H, 6.48.

3.6. 2,3,6-Tri-*O*-benzyl-4-*O*-(2-naphthyl)methyl-α,β-D-glucopyranose (6)

To a solution of compound **5** (2.36 g, 3.39 mmol) in acetonitrile (40 mL) a mixture of cc. HCl/water (1:1, 4 mL) was added and it

was heated at reflux temperature for 3 h. After cooling it was concentrated, the residue was dissolved in CH_2Cl_2, washed twice with water, 1 M aq NaOH (10 mL) and water, dried, filtered and concentrated. The crystalline crude product was recrystallized from EtOH to yield **6** (1.70 g, 85%) as a mixture of the α and β anomers (α/β ~3:2). Mp 96–98 °C (EtOH); $[\alpha]_D$ −2.1 (*c* 0.24; $CHCl_3$), R_f 0.42, 0.48 (*n*-hexane/EtOAc 6:4); IR ν_{max} (KBr) 3398, 3087, 3060, 3029, 2917, 2861, 1603, 1508, 1496, 1453, 1401, 1362, 1326, 1271, 1258, 1208, 1147, 1086, 1045, 1027, 1001, 945, 905, 854, 817, 780, 735, 696, 620, 608, 550, 475, 418 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.92–7.37 (m, 33H, arom.), 5.35 (d, 1H, *J*=3.0 Hz, H-1α), 5.11–4.52 (m, 12.5H), 4.22–4.16 (m, 1H), 4.13 (t, 1H, *J*=9.0 Hz, skeleton-α), 4.01 (br s, 0.5H, OH-β) 3.84–3.62 (m, 6.5H, skeleton), 3.53 (t, 0.5H, *J*=7.5 Hz, skeleton-β), 3.44 (br s, 1H, OH-α); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.7–137.8 (6C-quat., Ph), 135.7–132.9 (3C-quat., NAP), 128.4–125.8 (arom.), 97.5 (C-1β), 91.3 (C-1α), 84.6, 83.1 (C-2β, C-3β or C-4β), 81.8, 80.0, 77.7, 70.3 (skeleton), 75.6–73.2 (CH_2Ar), 68.9 (C-6β), 68.6 (C-6α). Anal. Calcd for $C_{38}H_{38}O_6$ (590.70 g/mol): C, 77.26; H, 6.48. Found: C, 77.39; H, 6.35.

3.7. 2,3,6-Tri-*O*-benzyl-4-*O*-(2-naphthyl)methyl-D-glucono-1,5-lactone (7)

To a stirred solution of compound **6** (2.20 g, 3.72 mmol) in dry CH_2Cl_2 (20 mL) Dess–Martin periodinane (3.16 g, 7.44 mmol, 2.0 equiv) was added at room temperature and stirred for 30 min. After 30 min it was diluted with diethyl ether, 1.3 M aq NaOH (25 mL) was added and stirred for 20 min. The organic layer was separated, washed with 1.3 M aq NaOH (20 mL) and water, dried, filtered and concentrated. The product was purified by column chromatography (CH_2Cl_2/acetone 98:2) to yield **7** (1.73 g, 85%) as white needles. Mp 45–47 °C (EtOH); $[\alpha]_D$ −0.6 (*c* 0.17, $CHCl_3$); R_f 0.36 (CH_2Cl_2/acetone 98:2); ^1H NMR (360 MHz, $CDCl_3$): δ 7.81–7.21 (m, 22H, arom.), 4.99 (d, 1H, *J*=11.4 Hz, CH_2Ar), 4.84 (d, 1H, *J*=11.4 Hz, CH_2Ar), 4.72 (d, 1H, *J*=11.3 Hz, CH_2Ar), 4.66 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.64 (d, 1H, *J*=11.3 Hz, CH_2Ar), 4.58 (d, 1H, *J*=11.3 Hz, CH_2Ar), 4.51 (d, 1H, *J*=12.0 Hz, CH_2Ar), 4.49–4.45 (m, 1H, H-5), 4.40 (d, 1H, *J*=12.0 Hz, CH_2Ar), 4.13 (d, 1H, *J*=6.6 Hz, H-2), 4.01 (t, 1H, *J*=6.8 Hz, H-4), 3.94 (t, 1H, *J*=6.7 Hz, H-3), 3.71 (dd, 1H, $J_{5,6}$=2.4 Hz, J_{gem}=11.0 Hz, H-6a), 3.65 (dd, 1H, $J_{5,6}$=3.2 Hz, J_{gem}=11.0 Hz, H-6b); ^{13}C NMR (90 MHz, $CDCl_3$): δ 169.2 (C-1), 137.5 (2×), 136.9, 134.9, 133.1, 132.9 (6C-quat., arom.), 128.4–125.8 (arom.), 80.9, 78.1, 77.3, 75.9 (C-2, C-3, C-4, C-5), 73.9, 73.6 (2×), 73.4 (4CH_2Ar), 68.2 (C-6). Anal. Calcd for $C_{38}H_{36}O_6$ (588.69 g/mol): C, 77.53; H, 6.16. Found: C, 77.44; H, 6.25.

3.8. 3,4,7-Tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranose (8)

To a solution of $(i\text{-Pr})_2NH$ (42 μL, 0.3 mmol, 1.5 equiv) in dry THF (5 mL), 2.5 M *n*-BuLi (120 μL, 0.3 mmol, 1.5 equiv) was added at −15 °C and stirred for 15 min. The reaction mixture was cooled to −60 °C, CH_3SO_3Et (320 μL, 0.3 mmol, 1.5 equiv) was added and stirred for further 15 min. Then it was cooled to −78 °C and the solution of compound **7** (1.18 g, 0.20 mmol) in dry THF (1 mL) was added. After 3 h stirring at −60 °C the mixture was allowed to warm up to room temperature, and concentrated. The residue was diluted with 5 mL of water and extracted with dichloromethane (3×20 mL). The collected organic solution was dried, filtered and concentrated. The product was purified by column chromatography (*n*-hexane/EtOAc 6:4) to yield **8** (1.43 g, 86%) as white crystals. Mp 97–98 °C (ethanol); $[\alpha]_D$ −65.8 (*c* 0.5, $CHCl_3$); R_f 0.46 (*n*-hexane/EtOAc 6:4); IR ν_{max} (KBr) 3474, 3060, 3031, 2981, 2916, 2864, 2368, 2309, 1496, 1454, 1350, 1335, 1308, 1271, 1154, 1084, 1027, 1002, 928, 862, 823, 734, 698, 618, 547, 477, 419 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.78–7.09 (m, 22H, arom.), 4.92–4.52 (m, 6H, CH_2Ar), 4.43 (d, 1H, *J*=12.0 Hz, CH_2Ar), 4.34 (d, 1H, *J*=12.0 Hz, CH_2Ar), 4.10 (q, 2H, *J*=7.1 Hz, $SO_3CH_2CH_3$), 4.06–3.91 (m, 2H, skeleton), 3.74–3.51 (m, 3H, skeleton), 3.31 (d, 1H, $J_{3,4}$=9.0 Hz, H-3), 3.30 (d, 1H, *J*=15.0 Hz, H-1a), 2.89 (d, 1H, *J*=15.0 Hz, H-1b), 1.18 (t, 3H, *J*=6.7 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 137.8, 137.3 (3C-quat. Ph), 135.4, 133.2, 132.9 (3C-quat., NAP), 128.7–125.7 (arom.), 95.8 (C-2), 82.9, 80.9, 77.9 (C-3–C-5), 75.6, 75.1, 75.0, 73.4 (4CH_2Ar), 71.9 (C-6), 68.3 (C-7), 67.9 ($SO_3CH_2CH_3$), 55.2 (C-1, $^3J_{C1,H3}\leq$2.0 Hz), 14.9 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{41}H_{44}O_9S$ (712.85 g/mol): C, 69.08; H, 6.22; S, 4.50. Found: C, 69.01; H, 6.28 S, 4.52.

3.9. 3,4,7-Tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1,2-dideoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl chloride (3)

To a stirred solution of compound **8** (213 mg, 0.30 mmol) in dry CH_2Cl_2 (2 mL), pyridine (26 μL, 0.33 mmol, 1.1 equiv) and $SOCl_2$ (24 μL, 0.33 mmol, 1.1 equiv) were added. After 20 min the reaction mixture was diluted with CH_2Cl_2, washed with 2 M aq HCl, water, satd $NaHCO_3$ and water, the organic layer was dried, filtered and concentrated. The crude product was used without further purification. R_f 0.80 (CH_2Cl_2/acetone 98:2); ^1H NMR (360 MHz, $CDCl_3$): δ 7.45–7.78 (m, 22H, arom.), 5.06 (d, 1H, *J*=11.5 Hz, CH_2Ar), 4.98 (d, 1H, *J*=11.0 Hz, CH_2Ar), 4.96–4.88 (m, 3H, CH_2Ar, skeleton), 4.78 (d, 1H, *J*=11.0 Hz, CH_2Ar), 4.59, 4.44 (2d, each 1H, *J*=11.9 Hz, CH_2Ar), 4.36 (d, 1H, $J_{3,4}$=9.1 Hz, H-3), 4.28–4.19 (m, 2H, skeleton), 4.13 (q, 2H, *J*=8.0 Hz, $SO_3CH_2CH_3$), 4.00 (d, 1H, *J*=15.1 Hz, H-1a), 3.97–3.84 (m, 3H, skeleton), 3.72 (d, 1H, *J*=11.1 Hz), 1.22 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (90 MHz, $CDCl_3$): δ 138.1, 137.8, 137.7 (3C-quat. Ph), 135.2, 133.1, 132.9 (3C-quat., NAP), 128.5–125.7 (arom.), 104.3 (C-2), 83.6, 79.7, 76.6 76.4, (C-3–C-6), 75.6, 75.3, 75.1, 73.3 (4CH_2Ar), 68.1 (C-7), 67.8 ($SO_3CH_2CH_3$), 57.8 (C-1, $^3J_{C1,H3}\leq$1 Hz), 15.0 ($SO_3CH_2CH_3$).

3.10. Ethyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-2-thio-α-D-*gluco*-hept-2-ulopyranoside (9)

Compound **8** (8.37 g, 11.74 mmol) was dissolved in CH_2Cl_2 (80 mL) then EtSH (1.3 mL, 17.61 mmol, 1.5 equiv) and $BF_3{\cdot}Et_2O$ (3.6 mL, 29.35 mmol, 2.5 equiv) were added at 0 °C and stirred for 18 h. The product was purified by column chromatography (*n*-hexane/EtOAc 3:2) to yield **12** (8.36 g, 94%) as white needles. Mp 84–85 °C (ethanol); $[\alpha]_D$ +61.1 (*c* 0.31, $CHCl_3$); R_f 0.77 (*n*-hexane/EtOAc 3:2); IR ν_{max} (KBr) 3060, 3029, 2979, 2931, 2886, 2865, 2348, 2309, 1496, 1454, 1395, 1350, 1281, 1308, 1207, 1177, 1158, 1124, 1082, 1043, 1027, 1005, 943, 860, 822, 757, 735, 698, 556, 478, 457 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 7.82–7.20 (m, 22H, arom.), 5.04 (d, 1H, *J*=11.9 Hz, CH_2Ar), 4.99 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.92 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.87 (d, 1H, *J*=11.9 Hz, CH_2Ar), 4.86 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.77 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.61 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.59 (d, 1H, *J*=9.2 Hz, skeleton), 4.50 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.28–4.13 (m, 3H, skeleton), 4.13–4.06 (m, 1H, skeleton), 3.84 (d, 1H, *J*=15.1 Hz, H-1a), 3.82–3.72 (m, 3H, skeleton), 3.69 (d, 1H, *J*=15.1 Hz, H-1b), 2.47 (m, 2H, *J*=7.2 Hz, SCH_2CH$_3$), 1.23 (t, 3H, *J*=7.5 Hz, SCH$_2$CH_3), 1.22 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (90 MHz, $CDCl_3$): δ 138.3, 138.2, 138.1 (3C-quat. Ph), 135.3, 133.1, 132.8 (3C-quat., NAP), 128.5–125.7 (arom.), 89.0 (C-2), 83.9, 79.5, 77.9 (C-3–C-5), 75.4, 75.2, 75.1 (3CH_2Ar), 74.0 (C-6), 73.2 (CH_2Ar), 68.8 (C-7), 67.2 ($SO_3CH_2CH_3$), 55.9 (C-1, $^3J_{C1,H3}\leq$2.7 Hz), 19.8 (SCH_2CH$_3$), 15.0 ($SO_3CH_2CH_3$), 13.7 (SCH$_2$CH_3). Anal. Calcd for $C_{43}H_{48}O_8S_2$ (756.97 g/mol): C, 68.23; H, 6.39; S, 8.47. Found: C, 68.34; H, 6.32; S, 8.44.

3.11. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl) methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (11) and 2,6-anhydro-3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl) methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-1-enitol (12)

Acceptor **10**[12] (6.26 g, 11.25 mmol) was coupled with donor **3** (4.11 g, 5.63 mmol, 0.5 equiv) according to the general method **B**. The obtained mixture of the α and β anomers was separated by silica gel chromatography (CH_2Cl_2/acetone 98:2) to yield **11** (2.48 g, 49%): and **12** 976 mg (25%). Compound **11**: $[\alpha]_D$ +9.0 (*c* 0.19, $CDCl_3$); R_f 0.85 (CH_2Cl_2/acetone 98:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85–6.75 (m, 41H, arom.), 5.09–4.35 (m, 15H), 4.28–4.11 (m, 4H), 4.02–3.93 (m, 3H), 3.90 (q, 2H, $SO_3CH_2CH_3$), 3.80–3.58 (m, 7H), 3.76 (s, 3H, OCH_3), 1.10 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.2, 151.3 (2C-quat., PMP), 138.5, 138.3 (2×), 138.3, 138.1, 138.0 (6C-quat. Ph), 135.5, 133.2, 132.9 (3C-quat., NAP), 128.5–125.8 (arom.), 118.2 (2×), 114.5 (2×) (4C-arom., PMP), 102.1 (C-1), 100.2 (C-2′), 82.6, 82.6, 80.6, 80.1, 78.3, 76.7 (C-2–C-4, C-3′–C-5′), 75.3, 75.2, 75.1, 74.6, 74.2, 73.4, 73.3 (7CH_2Ar), 73.4, 73.3 (C-5, C-6′), 70.2 ($SO_3CH_2CH_3$), 68.9, 67.0 (C-6, C-7′), 55.6 (OCH_3), 51.9 (C-1′, $J_{C1',H3'} \leq 1$ Hz), 14.9 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{75}H_{78}O_{15}S$ (1251.48 g/mol): C, 71.98; H, 6.28; S, 2.56. Found: C, 71.89; H, 6.33; S, 2.59.

Compound **12**: R_f 0.58 (CH_2Cl_2/acetone 98:2); IR ν_{max} (KBr) 3032, 2925, 2868, 2368, 2349, 2309, 1670, 1635, 1456, 1354, 1219, 1071, 1074, 1027, 1006, 916, 843, 820, 772, 698, 671, 598, 569, 526, 475, 418 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84–7.15 (m, 22H, arom.), 5.67 (s, 1H, H-1), 4.84 (d, 1H, *J*=11.4 Hz, CH_2Ar), 4.74 (s, 1H, CH_2Ar), 4.69 (s, 1H, CH_2Ar), 4.67–4–52 (s, 4H, CH_2Ar), 4.51 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.36–4.28 (m, 1H), 4.16 (q, 2H, *J*=7.1 Hz, $SO_3CH_2CH_3$), 4.00–3.75 (m, 5H), 1.21 (t, 3H, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.9 (C-2), 137.9, 137.3, 136.5, 134.9, 133.1, 133.0 (6C-quat., arom.), 128.6–125.8 (arom.), 104.1 (C-1), 82.2, 78.4, 76.8, 76.4 (C-3, C-4, C-5, C-6), 73.7, 73.4, 73.2, 72.3 (4CH_2Ar), 67.8 (C-7), 66.7 ($SO_3CH_2CH_3$), 14.8 ($SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{41}H_{42}NaO_8S^+$ $[M+Na]^+$: 717.25; found: 717.61.

Title compounds **11** (10%) and **12** (37%) were also obtained from the reaction of **10** and **9**, upon NIS/TfOH activation.

3.12. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (13)

Compound **11** (1.29 g, 1.03 mmol) was treated with DDQ according to general method **A** and the product was purified by column chromatography (*n*-hexane/EtOAc 6:4), to yield **13** (0.90 g, 87%) as a syrup; $[\alpha]_D$ +5.7 (*c* 0.11, $CHCl_3$); R_f 0.49 (*n*-hexane/EtOAc 6:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.02 (m, 30H, Ph), 6.97, 6.80 (2m, each 2H, PMP arom.), 5.12–5.04 (m, 1H, skeleton), 4.97 (d, 1H, *J*=11.6 Hz, CH_2Ph), 4.89 (d, 1H, *J*=11.1 Hz, CH_2Ph), 4.86 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.82–4.47 (m, 7H, CH_2Ph), 4.45 (s, 2H, CH_2Ph), 4.24–4.07 (m, 3H, skeleton), 4.02–3.53 (m, 11H, skeleton), 3.85 (2q, 2H, *J*=7.1 Hz, $SO_3CH_2CH_3$), 3.75 (s, 3H, OCH_3), 2.54 (s, 1H, OH), 1.10 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 151.2 (2C-quat., PMP), 138.4 (2×), 138.2, 138.0, 138.0, 137.9, (7C-quat., Ph), 128.7–127.1 (Ph), 118.2 (2×), 114.5 (2×) (4C-arom, PMP), 102.1 (C-1), 100.2 (C-2′), 82.5, 82.0, 80.6, 79.8, 76.6, 73.1, 72.6, 72.0 (C-2–C-5, C-3′–C-6′); 75.1 (2×), 74.5, 74.2, 73.5, 73.3 (6CH_2Ph), 70.4, 70.0 (C-6, C-7′), 66.8 ($SO_3CH_2CH_3$), 55.5 (OCH_3), 51.8 (C-1′), 14.8 ($SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{64}H_{70}NaO_{15}S^+$ $[M+Na]^+$: 1133.43; found: 1133.08.

3.13. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl) methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (14)

Acceptor **13** (987 mg, 0.89 mmol, 1.0 equiv) was glycosylated with donor **3** (605 mg, 0.88 mmol, 1.0 equiv) according to general method **B** to give **14** (590 mg, 37%) as a syrup; $[\alpha]_D$ +28.2 (*c* 0.22, $CHCl_3$); R_f 0.51 (CH_2Cl_2/acetone 98:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80–6.70 (m, 56H, arom.), 5.06 (d, 1H, *J*=7.1 Hz, H-1), 5.00–3.58 (m, 46H), 3.67 (s, 3H, OCH_3), 1.11, 1.03 (2t, 6H, $2SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.1, 151.2 (2C-quat., PMP), 138.6, 138.4, 138.3, 138.2, 138.2, 138.1, 138.1 (2×), 138.0 (9C-quat., Ph), 135.3, 133.1, 132.9 (3C-quat., NAP), 128.4–125.8 (arom.), 118.3 (2×), 114.4 (2×) (4C-arom, PMP), 102.0 (C-1), 100.2 (C-2′), 99.3 (C-2″), 82.6, 82.4, 81.7, 80.3, 80.1, 78.6, 78.3, 76.0, 73.6, 73.1, 73.1, 72.4 (C-2–C-5, C-3′–C-6′, C-3″–C-6″), 75.3 (2×), 75.2, 74.9, 74.5, 74.0, 73.9, 73.5, 73.3, 73.2, (10 CH_2Ar), 69.6, 69.5, 68.8 (C-6, C-7″, C-7″), 66.9, 66.5 ($2SO_3CH_2CH_3$), 55.4 (OCH_3), 52.3, 51.4 (C-1′, C-1″), 14.8, 14.7 ($2SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{105}H_{112}NaO_{23}S_2^+$ $[M+Na]^+$: 1827.67; found: 1828.51.

3.14. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (15)

Prepared from **14** (444 mg, 0.25 mmol) according to general method **A** and purified by column chromatography (CH_2Cl_2/acetone 99:1) to yield **15** (287 mg, 79%) as a syrup; $[\alpha]_D$ +25.2 (*c* 0.21, $CHCl_3$); R_f 0.38 (CH_2Cl_2/acetone 99:1). ^{1}H NMR (500 MHz, $CDCl_3$): 7.36–7.02 (m, 45H, Ph), 7.00, 6.78 (2m, 4H, PMP arom.), 5.08 (d, 1H, *J*=7.1 Hz, H-1), 5.99–4.35 (m, 18H, CH_2Ph), 4.34–3.52 (m, 26H), 3.74 (s, 3H, OCH_3), 2.58 (s, 1H, OH), 1.12, 1.10 (2t, 6H, *J*=7.1 Hz, $2SO_3CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 155.2, 151.2 (2C-quat., PMP), 138.7, 138.5 (2×), 138.3, 138.1 (3×), 138.0, 137.9 (9C-quat., Ph), 128.6–126.9 (Ph), 118.5 (2×), 114.6 (2×) (4C-arom, PMP), 102.2 (C-1), 100.3 (C-2′), 99.4 (C-2″), 82.6, 82.1, 81.8, 80.6, 79.8, 76.2, 74.8, 73.9, 73.3, 73.1, 72.6, 72.2 (C-2–C-5, C-3′–C-6′, C-3″–C-6″), 75.3, 75.3, 75.2, 74.6, 74.3, 73.8, 73.7, 73.4, 73.0 (9CH_2Ph), 70.5, 69.6 (2×) (C-6, C-7′, C-7″), 66.9, 66.7 ($2SO_3CH_2CH_3$), 55.6 (OCH_3), 51.5 (2×) (C-1′, C-1″), 15.0, 14.9 ($2SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{94}H_{104}NaO_{23}S_2^+$ $[M+Na]^+$: 1687.63; found: 1688.73.

3.15. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl) methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-ulopyranosyl-(2→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (16)

Acceptor **15** (320 mg, 0.19 mmol, 1.0 equiv) was glycosylated with donor **3** (605 mg, 0.88 mmol, 1.0 equiv) according to general method **B** to give tetrasaccharide **16** (610 mg, 38%) as a syrup; $[\alpha]_D$ +36.8 (*c* 0.2, $CHCl_3$); R_f 0.54 (CH_2Cl_2/acetone 98:2). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76–6.71 (m, 71H, arom.), 5.04 (d, 1H, *J*=7.1 Hz, H-1), 4.94–3.50 (m, 62H), 3.65 (s, 3H, OCH_3), 1.07, 1.01, 0.99 (3t, 9H, $3SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.2, 151.3 (2C-quat., PMP), 138.7 (2×), 138.4 (2×), 138.4, 138.3, 138.2, 138.2, 138.0 (2×), 138.0, 137.9 (12C-quat., Ph), 135.5, 133.2, 133.0 (3C-quat., NAP), 128.5–125.8 (arom.), 118.3 (2×), 114.5 (2×) (4C-arom., PMP), 102.2 (C-1), 100.3, 99.5, 99.3 (C-2′, C-2″, C-2‴), 82.9, 82.3, 81.7, 81.5, 81.2, 81.0, 80.6, 79.9, 78.1, 76.2, 74.4, 73.5, 73.3, 72.6, 71.8, 71.6 (C-2–C-5, C-3′–C-6′, C-3″–C-6″, C-3‴–C-6‴), 75.3 (2×), 75.2, 75.0,

74.7, 74.5, 74.4, 74.1, 73.6, 73.5, 73.4 (2×), 73.2 3 (13CH_2Ar), 69.6, 69.3, 69.2, 68.7 (C-6, C-7′, C-7″, C-7‴), 67.1, 66.6, 66.5 (3$SO_3CH_2CH_3$), 55.5 (OCH_3), 52.0 (3×) (C-1′, C-1″, C-1‴), 15.0, 14.9 (2×) (3$SO_3CH_2CH_3$). Anal. Calcd for $C_{135}H_{146}O_{31}S_3$ (2360.78 g/mol): C, 68.68; H, 6.23; S, 4.07. Found: C, 68.51; H, 6.26; S, 4.13.

3.16. *p*-Methoxyphenyl 3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (17)

Prepared from **16** (163 mg, 0.69 mmol) according to general method **A** and purified by column chromatography (CH_2Cl_2/acetone 99:1) to yield **17** (109 mg, 71%) as a syrup; $[\alpha]_D$ −8.95 (*c* 0.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 7.37–6.73 (m, 64H, arom.), 5.05 (d, 1H, *J*=7.3 Hz, H-1), 4.96–3.46 (m, 60H), 3.68 (s, 3H, OCH_3), 2.67 (br s, 1H, OH), 1.10, 1.03, 1.02 (3t, each 3H, *J*=7.1 Hz, 3$SO_3CH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 155.5–114.6 (arom.), 102.2 (C-1), 100.2 (C-2′), 99.6 (C-2″, C-2‴), 83.1, 82.1, 81.9 (2×), 81.1, 79.8, 75.9, 74.8, 73.9, 73.3, 73.1, 72.6, 72.2 (C-2–C-5, C-3′–C-6′, C-3″–C-6″), 75.3, 75.3, 75.2, 74.6, 74.3, 73.8, 73.7, 73.4, 73.0 (9CH_2Ph), 70.5, 69.6 (2×) (C-6, C-7′, C-7″), 66.9, 66.7 (2$SO_3CH_2CH_3$), 55.6 (OCH_3), 51.5 (2×) (C-1′, C-1″), 15.0, 14.9 (2$SO_3CH_2CH_3$); MALDI-MS: *m*/*z* calcd for $C_{124}H_{138}NaO_{31}S_3^+$ $[M+Na]^+$: 2242.84; found: 2243.13.

3.17. Methyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranoside (18) and methyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-β-D-*gluco*-hept-2-ulopyranoside (19)

To a solution of thioglycoside donor **9** (2.27 g, 3.00 mmol) in CH_2Cl_2 (45 mL) were added successively 3 Å molecular sieves (3 g) and dry MeOH (1.83 mL, 45 mmol, 15 equiv), and the mixture was stirred at rt for 3 h. The mixture was then cooled to −20 °C and a solution of NIS (0.81 g, 3.60 mmol, 1.2 equiv) and TfOH (107 μL, 1.21 mmol, 0.4 equiv) in dry THF was added. The mixture was kept at −20 °C until the TLC showed complete conversion of the donor (20–30 min). The reaction was quenched by addition of Et_3N (0.5 mL), insoluble materials were removed by filtration, the filtrate was diluted with CH_2Cl_2, extracted three times with water, dried and concentrated. The residue was then purified by column chromatography (*n*-hexane/EtOAc 7:3) to yield **18** (1.65 g, 76%) as white needles. Mp 72–74 °C (ethanol); $[\alpha]_D$ +22.4 (*c* 0.11, $CHCl_3$); R_f 0.48; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86–7.22 (m, 22H, arom.), 5.08–4.92 (m, 4H, CH_2Ar), 4.85 (d, 1H, *J*=11.3 Hz, CH_2Ar), 4.76 (d, 1H, *J*=11.0 Hz, CH_2Ar), 4.62 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.50 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.314.04 (m, 4H), 3.87–3.67 (m, 4H), 3.57 (s, 2H), 3.27 (s, 3H, OCH_3), 1.23 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.4, 138.1, 138.0 (3C-quat., Ph), 135.4, 133.1, 132.9 (3C-quat., NAP), 128.4–125.7 (arom.), 99.0 (C-2), 83.1, 79.7, 78.0 (C-3–C-5), 75.5, 75.4, 75.1, 73.3 (4CH_2Ar), 72.9 (C-6), 68.5 (C-7), 67.4 ($SO_3CH_2CH_3$), 50.4 (C-1, $J_{C1,H3}\leq$1 Hz), 47.8 (OCH_3), 15.0 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{42}H_{46}O_9S_2$ (726.87 g/mol): C, 69.40; H, 6.38; S, 4.41. Found: C; 69.24; H, 6.49; S, 4.47.

Compound **19** was isolated as a colourless syrup (0.47 g, 22%); $[\alpha]_D$ +42.4 (*c* 0.14, $CHCl_3$); R_f 0.43; ^{1}H NMR (200 MHz, $CDCl_3$): δ ^{1}H NMR (200 MHz): δ 7.84–7.15 (m, 22H, arom.), 4.97 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.87 (d, 1H, *J*=11.5 Hz, CH_2Ar), 4.80 (d, 1H, *J*=11.5 Hz, CH_2Ar), 4.77 (d, 1H, *J*=11.4 Hz, CH_2Ar), 4.74 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.64 (d, 1H, *J*=10.8 Hz, CH_2Ar), 4.62 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.48 (d, 1H, *J*=12.1 Hz, CH_2Ar), 4.26 (q, 2H, *J*=7.1 Hz, $SO_3CH_2CH_3$), 4.13–3.55 (m, 8H, skeleton), 3.44 (s, 3H, OCH_3), 1.34 (t, 3H, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 138.0, 137.5 (3C-quat., Ph), 135.5, 133.1, 132.8 (3C-quat., NAP), 128.4–125.6 (arom.), 100.1 (C-2), 82.9, 78.4, 76.8 (C-3–C-5), 74.7, 74.0 (2CH_2Ar), 73.7 (C-6), 73.3 (2×) (2CH_2Ar), 68.5 (C-7), 66.7 ($SO_3CH_2CH_3$), 48.7 (C-1, $J_{C1,H3}$=2.6 Hz), 47.8 (OCH_3), 14.9 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{42}H_{46}O_9S_2$ (726.87 g/mol): C, 69.40; H, 6.38; S, 4.41. Found: C, 69.28; H, 6.45; S, 4.48.

3.18. Methyl 3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranoside (20)

Prepared from **18** (364 mg, 0.50 mmol) according to general method **A** and purified by column chromatography (CH_2Cl_2/acetone 98:2) to yield **20** (261 mg, 89%) as a syrup; $[\alpha]_D$ +17.2 (*c* 0.14, $CHCl_3$); R_f 0.20; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44–7.14 (m, 15H, Ph), 5.00 (d, 1H, *J*=11.3 Hz, CH_2Ph), 4.90 (d, 1H, *J*=11.6 Hz, CH_2Ph), 4.86–4.74 (m, 2H, CH_2Ph), 4.61 (d, 1H, *J*=12.1 Hz, CH_2Ph), 4.53 (d, 1H, *J*=11.9 Hz, CH_2Ph), 4.29–4.05 (m, 3H, skeleton, and $SO_3CH_2CH_3$), 3.92 (t, 1H, *J*=8.6 Hz, skeleton), 3.81–3.46 (m, 6H, skeleton), 3.25 (s, 3H, OCH_3), 2.72 (s, 1H, OH), 1.24 (t, 3H, *J*=7.1 Hz, $SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.3, 137.8 (2×) (3C-quat., Ph), 128.4–127.2 (Ph), 98.8 (C-2), 82.5, 79.2, 72.4, 71.2 (C-3–C-6), 75.2, 75.0, 73.3 (3CH_2Ph), 69.5 (C-7), 67.1 ($SO_3CH_2CH_3$), 50.1 (C-1), 47.7 (OCH_3), 14.8 ($SO_3CH_2CH_3$). Anal. Calcd for $C_{31}H_{38}O_9S$ (586.69 g/mol): C, 63.46; H, 6.53; S, 5.47. Found: C, 63.69; H, 6.48; S, 5.43.

3.19. .19Methyl 3,4,7-tri-*O*-benzyl-5-*O*-(2-naphthyl)methyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranoside (21)

Acceptor **20** (690 mg, 1.18 mmol) was glycosylated with donor **3** (860 mg, 1.18 mmol, 1.0 equiv) according to general method **B**. The crude product was purified by column chromatography (CH_2Cl_2/acetone 98:2) to give **21** (890 mg, 59%) as a syrup; $[\alpha]_D$ +18.4 (*c* 0.13, $CDCl_3$); R_f 0.73; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86–7.03 (m, 37H, arom.), 5.19 (d, 1H, *J*=11.6 Hz, CH_2Ar), 5.00 (d, 1H, *J*=10.9 Hz, CH_2Ar), 4.91 (s, 2H, CH_2Ar), 4.90 (d, 1H, *J*=11.1 Hz, CH_2Ar), 4.80–4.50 (m, 9H, CH_2Ar), 4.50–3.95 (m, 12H), 3.94–3.78 (m, 2H), 3.77–3.54 (m, 6H), 3.25 (s, 3H, OCH_3), 1.19, 1.09 (2t, 6H, 2$SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.2, 138.9, 138.6, 138.6, 138.4 (2×) (6C-quat., Ph), 135.5, 133.6, 133.3 (3C-quat., NAP), 128.8–126.3 (arom.), 100.4 (C-2), 98.8 (C-2′), 82.9, 82.6, 80.8, 79.5, 79.0, 74.0, 73.6, 73.5 (C-3–C-6, C-3′–C-6′), 76.0, 75.8, 75.7, 75.6 (2×), 73.8, 73.7 (7CH_2Ar), 69.6, 69.5 (C-7, C-7′), 67.2, 67.1 (2$SO_3CH_2CH_3$), 51.1, 50.6 (C-1, C-1′), 48.7 (OCH_3), 15.4, 15.2 (2$SO_3CH_2CH_3$); MALDI-MS *m*/*z* calcd for $C_{72}H_{80}NaO_{17}S_2^+$ $[M+Na]^+$: 1303.47; found: 1302.98.

3.20. Methyl 3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranoside (22)

Prepared from **21** (750 mg, 0.59 mmol) according to general method **A** and purified by column chromatography (CH_2Cl_2/acetone 99:1) to yield **22** (519 mg, 78%) as white needles. Mp 111–112 °C (ethanol); $[\alpha]_D$ +23.2 (*c* 0.13, $CHCl_3$); R_f 0.20 (*n*–hexane–EtOAc 6:4); ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.36–7.09 (m, 30H, arom.), 5.20 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.88–4.48 (m, 11H, CH_2Ph), 4.40–4.35 (m, 2H), 4.21–3.52 (m, 18H), 3.25 (s, 3H, OCH_3), 2.46 (s, 1H, OH), 1.20, 1.10 (2t, 6H, 2CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ 138.8, 138.5, 138.3, 138.0, 138.0, 137.9 (6C-quat. arom.), 128.6–127.0 (arom.), 100.1, 98.5 (C-2, C-2′), 82.3, 81.8, 80.2, 79.2, 73.6, 73.4, 72.7, 71.8 (C-3–C-6, C-3′–C-6′), 75.7, 75.4, 75.3, 75.1, 73.7, 73.5 (6CH_2Ph), 70.6, 69.3 (C-7, C-7′), 67.0, 66.7 (2$SO_3CH_2CH_3$), 50.7, 50.2 (C-1, C-1′), 48.3 (OCH_3), 15.1, 14.9 (2$SO_3CH_2CH_3$); MALDI-MS *m*/*z* calcd for $C_{61}H_{72}NaO_{17}S_2^+$ $[M+Na]^+$: 1163.41; found: 1163.15.

3.21. Methyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-3,4,7-tri-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranoside (24)

Acceptor **22** (423 mg, 371 mg, 1.0 equiv) was glycosylated with donor **23**[7] (860 mg, 1.18 mmol, 1.0 equiv) according to general method **B**. The product was isolated and purified by column chromatography (CH_2Cl_2/acetone 98:2) to obtain **24** (184 mg, 28%) as a syrup; R_f 0.73 (CH_2Cl_2/acetone 98:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–6.91 (m, 50H, arom.), 5.15 (d, 1H, J=11.4 Hz), 4.97–4.46 (m, 19H), 4.36–4.09 (m, 13H), 4.00–3.89 (m, 4H), 3.83–3.79 (m, 13H), 3.15 (s, 3H, OCH_3), 1.20, 1.14, 1.04 (3t, 9H, $3SO_3CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.8, 138.7, 138.5 (2×), 138.4, 138.2, 138.1 (2×), 138.0 (2×) (10C-quat., arom.), 128.4–127.1 (arom.), 100.2 (C-2), 99.5 (C-2′), 98.6 (C-2″), 82.8, 82.3, 81.5, 80.2, 79.7 (2×), 79.2, 78.6, 74.0, 73.9, 73.4 (2×) (C-3–C-6, C-3′–C-6′, C-3″–C6″), 75.6, 75.4 (5×), 75.3, 75.2, 73.8, 73.7 ($10CH_2Ph$), 69.7, 69.4, 68.8 (C-7, C-7′, C-7″), 67.0, 67.0, 66.6 ($3SO_3CH_2CH_3$), 50.4 (3×) (C-1, C-1′, C-1″), 48.2 (OCH_3), 15.1, 14.9, 14.8 ($3SO_3CH_2CH_3$); MALDI-MS m/z calcd for $C_{98}H_{112}NaO_{25}S_3^+$ $[M+Na]^+$: 1807.65; found: 1808.28.

3.22. *p*-Methoxyphenyl 4-*O*-(1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl)-β-D-glucopyranoside (25)

Compound **13** (110 mg, 91 μmol) was converted into compound **25** (colourless syrup, 31 mg, 62%) according to general method **C**; $[\alpha]_D$ +12.6 (c 0.1, H_2O); IR ν_{max} (KBr) 3408, 2938, 1733, 1635, 1559, 1508, 1418, 1301, 1218, 1106, 1044, 936, 902, 834, 800, 753, 640, 594, 527 cm^{-1}; ^{1}H NMR (200 MHz, D_2O): δ 7.13–6.98 (m, 4H, arom.), 5.00 (d, 1H, J=7.7 Hz), 4.21 (m, 1H), 3.97–3.30 (m, 14H, skeleton), 3.82 (s, 3H, OCH_3); ^{13}C NMR (90 MHz, D_2O): δ 154.7, 150.8 (2C-quat., PMP), 118.1 (2×), 115.0 (2×) (4C-arom., PMP), 101.0 (C-1), 99.9 (C-2′), 75.4 (2×), 73.5, 73.3, 72.5, 72.3, 71.4, 69.4 (C-2–C-5, C-3′–C-6′), 61.0, 60.1 (C-6, C-7′), 55.7 (OCH_3), 52.8 (C-1′). Anal. Calcd for $C_{20}H_{29}NaO_{15}S$ (564.49 g/mol): C, 42.55; H, 5.18; S, 5.68. Found: C, 42.69; H, 5.07; S, 5.72.

3.23. *p*-Methoxyphenyl 1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl-(2→4)-β-D-glucopyranoside (26)

Compound **15** (98 mg, 56 μmol) was converted into compound **26** (colourless syrup, 32 mg, 70%) according to general method **C**; $[\alpha]_D$ +39.9 (c 0.1, H_2O); ^{1}H NMR (360 MHz, D_2O): δ 7.13, 7.00 (2d, 4H, arom.), 4.99 (d, 1H, J=7.7 Hz), 4.29 (d, 1H, J=9.7 Hz), 4.21 (d, 1H, J=9.5 Hz), 4.03 (t, 1H, J=8.9 Hz, J=9.3 Hz), 3.94–3.69 (m, 12H), 3.83 (s, 3H, OCH_3), 3.65–3.57 (m, 6H), 3.43 (t, 1H, J=9.6 Hz, J=9.4 Hz); ^{13}C NMR (90 MHz, D_2O): δ 155.8, 152.1 (2C-quat., PMP), 119.3 (2×), 116.0 (2×) (4C-arom., PMP), 102.3 (C-1), 101.0, 100.9 (C-2′, C-2″), 76.6, 76.4, 74.6 (2×), 74.3, 74.0, 73.7, 73.5, 73.1, 72.5 (2×), 70.5 (C-2–C-5, C-3′–C-6′, C-3″–C-6″), 62.1, 61.6, 61.1 (C-6, C-7′, C-7″), 56.8 (OCH_3), 54.0, 53.9 (C-1′, C-1″). Anal. Calcd for $C_{27}H_{40}Na_2O_{23}S_2$ (842.70 g/mol): C, 38.48; H, 4.78; S, 7.61. Found: C, 38.35; H, 4.71; S, 7.57.

3.24. Methyl-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranoside (27)

Compound **20** (108 mg, 0.19 mmol) was converted into compound **27** (colourless syrup, 33 mg, 54%) according to general method **C**; IR ν_{max} (KBr) 3419, 2946, 2843, 1635, 1471, 1417, 1308, 1198, 1094, 1045, 992, 937, 903, 816, 794, 719, 671, 640, 609, 529, 503 cm^{-1}; ^{1}H NMR (360 MHz, D_2O): δ 3.92 (d, 1H, J=9.5 Hz), 3.72 (dd, 1H, J=12.1, 1.5 Hz), 3.66–3.57 (m, 2H), 3.36–3.27 (m, 3H), 3.23–3.19 (m, 4H, 1H and OCH_3); ^{13}C NMR (90 MHz, D_2O): δ 100.6 (C-2), 75.2 (2×), 74.3, 71.1 (C-3–C-6), 62.2 (C-7), 53.8 (C-1), 48.5 (OCH_3). Anal. Calcd for: $C_8H_{15}NaO_9S$ (310.25 g/mol), C: 30.97, H: 4.87, S: 10.34, Found C: 30.91, H: 4.92, S: 10.39.

3.25. Methyl-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranoside (28)

Compound **22** (124 mg, 0.11 mmol) was converted into compound **28** according to general method **C**. The product was purified by Sephadex gel G-25 in H_2O to give **28** as a syrup (40 mg, 64%); $[\alpha]_D$ +82.0 (c 0.06, H_2O); IR ν_{max} (KBr) 3419, 2938, 1636, 1418, 1194, 1144, 1108, 1041, 903, 833, 797, 759, 670, 640, 608, 546 cm^{-1}; ^{1}H NMR (360 MHz, D_2O): δ 4.19 (d, 1H, J=9.7 Hz), 4.14 (d, 1H, J=9.2 Hz), 3.97–3.72 (m, 8H), 3.64–3.55 (m, 3H), 3.49–3.40 (m, 3H), 3.29 (s, 3H, OCH_3); ^{13}C NMR (90 MHz, D_2O): δ 101.3, 100.3, (C-2, C-2′), 75.0, 74.9 (2×), 74.2, 74.1, 73.1, 72.9, 70.9 (C-3–C-6, C-3′–C-6′), 62.5, 62.1 (C-7, C-7′), 54.4, 52.9 (C-1, C-1′), 49.1 (OCH_3). Anal. Calcd for $C_{15}H_{26}Na_2O_{17}S_2$ (588.47 g/mol): C, 30.62; H, 4.45; S, 10.90. Found: C, 30.55; H, 4.51; S, 10.86.

3.26. Methyl-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranosyl-(2→5)-1-deoxy-1-sodiumsulfonato-α-D-*gluco*-hept-2-ulopyranoside (29)

Compound **24** (135 mg, 76 μmol) was converted into compound **29** according to general method **C**. The product was purified by Sephadex gel G-25 in H_2O to give **29** as a syrup (36 mg, 52%); $[\alpha]_D$ +76.4 (c 0.1, H_2O); ^{1}H NMR (360 MHz, D_2O): δ 4.26 (d, 1H, J=9.7 Hz), 4.20 (d, 1H, J=9.5 Hz), 4.14 (d, 1H, J=9.2 Hz), 4.04–3.70 (m, 13H), 3.65–3.55 (m, 5H), 3.50–3.40 (m, 3H), 3.29 (s, 3H, OCH_3); ^{13}C NMR (90 MHz, D_2O): δ 100.9, 100.7, 99.9 (C-2, C-2′, C-2″), 74.5 (2×), 74.4 (2×), 73.9, 73.7 (2×), 73.1, 72.6, 72.5 (2×), 70.5, (C-3–C-6, C-3′–C-6′, C-3″–C-6″), 62.1, 61.6 (2×), (C-7, C-7′, C-7″), 53.9 (2×), 52.5 (C-1, C-1′, C-1″), 48.6 (OCH_3). Anal. Calcd for $C_{22}H_{37}Na_3O_{25}S_3$ (866.68 g/mol): C, 30.49; H, 4.30; S, 11.10. Found C, 30.54; H, 4.25; S, 11.02.

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