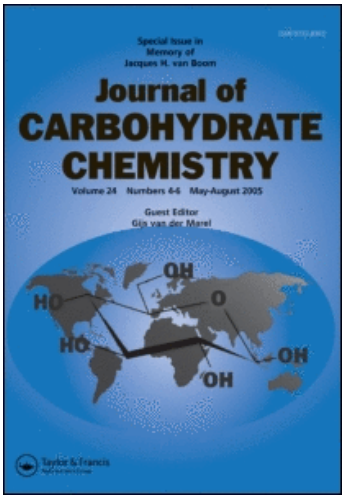

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Replacement of Carbohydrate Sulfates by Sugar C-Sulfonic Acid Derivatives

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Replacement of Carbohydrate Sulfates by Sugar C-Sulfonic Acid Derivatives[#]

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ABSTRACT

3′-Substituted *p*-methoxyphenyl β-lactosides and one of their 3′-epimer were synthesized. The common feature of these compounds is the presence of a strong negative charge at position C-3′ in the form of sulfonic acid moieties. The 3′,4′-diol derivative of *p*-methoxyphenyl lactoside was also glycosylated with the thioglycoside of the sulfoulosonic acid. The two-regioisomeric trisaccharides were isolated but their deprotection failed. The aim of the present study was to find carbohydrate ligand(s), which can inhibit the adhesion between *Helicobacter pylori* and the gastrointestinal epithelial cells.

Key Words: Carbohydrate sulfates; *p*-Methoxyphenyl lactoside; Sulfonic acid; Epithelial cells; Proteins.

[#]This paper is dedicated to Professor Gérard Descotes on the occasion of his 70th birthday.

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INTRODUCTION

The isolation of *Helicobacter pylori*[1] in 1982 opened a new epoch in gastroenterology, and completely changed the diagnosis and therapy of gastritis and peptic ulcer. This bacterium is a human specific gram-negative, urease-positive organism, which is a causative agent in chronic active gastritis, gastric and duodenal ulcers, and presumably gastric malignancies.[2]

It is estimated that 70–90% and 25–50% of the population carry *H. pylori* in developing countries and in the industrialized world, respectively. Independently, of the geographical area, clinical disease occurs in 10–20% of the colonized individuals. The carriage of the bacterium is strongly associated with the development of atrophic gastritis, a precursor lesion to gastric cancer. The latter is the second leading cause of cancer deaths worldwide.[3] Recent investigations suggested that *H. pylori* might be transmitted via the oral route, since the organism has been detected at different sites of the oral cavity.[4]

Presently, therapy is based a combination of antibiotics and a proton pump inhibitor, which results in very low recurrence. Nevertheless, owing to antibiotic resistance,[3] extension of such treatment is not recommended. Efforts focusing on vaccine development are yet unsuccessful,[5] and carbohydrate-based antiadhesion-therapy maybe an alternative. It is well known that many pathogens use highly specific carbohydrate–protein interactions to attack cells and initiate diseases. The first line of defense against the resulting infectious diseases are the oligosaccharide-type ligands in the mucous layer exposed epithelial cells and in saliva, tears and sweat, which act as "mimics" leading to pathogen elimination. These oligosaccharide ligands bind to the carbohydrate-binding proteins of the microorganism, and the pathogens are eliminated by different physiological mechanisms.[6]

Pathogen proteins bind weakly to their oligosaccharide ligands. Such association can be competitively inhibited with low concentrations either of the protein or of the oligosaccharides. The most attractive strategy maybe to use soluble forms of oligosaccharide ligand(s) which are small and non-immunogenic.

Some bacteria carry genes that encode more than one adhesin, each capable of binding a different carbohydrate receptor. In this regard, the carbohydrate-binding specificity of *H. pylori* is unusually high.[7] More than 10 different kinds of carbohydrate-binding specificity have been described, including recognition of sialylated oligosaccharides as well as that of sulfated mono-, oligo-, or polysaccharides. In all cases, multivalency resulted in an increased inhibitor potency.[8–12]

These examples showed that inhibitors of bacterial adhesion maybe successfully used as therapeutic agents for preventing infections caused by *H. pylori*. These findings prompted us to seek not only for sulfated sugars, but also to replace the sulfate esters by C-sulfonic acids. Till now, only one sugar-sulfonic acid, namely 6-sulfoquinovose was found in nature. It is stable in the presence of sulfatases,[13] and belongs to the strongest acids. In our laboratory, a method was developed to synthesize C-sulfonic acid-containing glycosyl donors,[14,15] which were used for the synthesis of sulfoulosonic acid-containing oligosaccharides to mimic sialyl Lewis X derivatives.

It is also worth to mention that the sulfated sugars have very different biological activities, such as antiproliferative,[16] anticoagulant,[17,18] anticancer,[19] and antiviral[20] properties.

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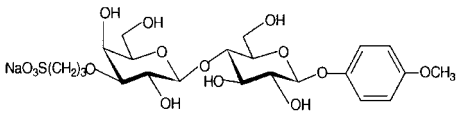
In this paper, we wish to report on the synthesis of some C-sulfonic acid carrying lactose analogs having the following structures:



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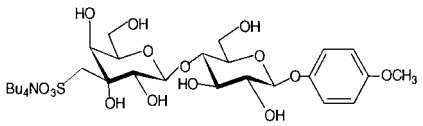

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RESULTS AND DISCUSSION

It is known that treatment of lactosides with 2,2-dimethoxypropane results selectively in the 3′,4′-*O*-isopropylidene derivatives. This selectivity was indeed observed for *p*-methoxyphenyl *β*-lactoside **3**[21] and *p*-methoxyphenyl 3,4-*O*-isopropylidene-*β*-D-galactopyranosyl-(1 → 4)-*β*-D-glucopyranoside (**4**) was obtained in a yield of 67%. All free hydroxyl groups of **4** were benzylated using Brimacombe's conditions[22] to give compound **5** in a quantitative yield. Conventional hydrolysis of the isopropylidene acetal with methanolic HCl resulted in diol **6** (91%). Regioselective alkylation of the vicinal cis-diol was achieved by means of the tin-mediated procedure.[23] The reactive stannylene derivative was prepared using an equimolar amount of Bu_2SnO in methanol, without removal of water.[24] This technique is useful, provided that the stannylene is stable in methanol. Problems may arise with vicinal trans-diequatorial diols. The stannylene derivative was allylated with allyl bromide in DMF to give 3′-*O*-allyl ether **7** (88%). Alternatively, it was treated with 2-bromomethylnaphthalene to furnish the 3′-*O*-(2-naphthyl)methyl ether **8** (3′-ONAP) in 87% yield.

In compound **7**, the allyl ether offers a great potential for the generation of various functions. In the present case, we describe the sulfite addition, leading to the 3′-*O*-[3-(sodium sulfonate)propyl]-lactoside derivative **9** (Sch. 1).

The addition of bisulfite to unsaturated compounds is a very common procedure.[25] Kharasch et al.[26] established that this reaction can be interpreted on the basis of a free-radical mechanism, and the addition goes anti-Markovnikov resulting in 1-alkane-sulfonates. More recent studies[27] led to propose a three-step mechanism involving (1) the production of a sulfite radical ion, for example by nitrate-ion oxidation of sulfite ion, (2) a bisulfite ion in the chain-transfer reaction, and (3) termination by sulfite radical-ion oxidation and radical coupling. Analogously to the procedure described for cyclodextrins,[28] compound **7** was treated with $NaHSO_3$ and a catalytic amount of *tert*-butyl perbenzoate in a 70% ethanolic solution.[29] Compound **9** was obtained quantitatively and subsequently hydrogenolyzed to give the target **1** (96%).

Compounds **7** and **8** were benzylated to obtain the fully protected lactoside derivatives (**10** and **11**). The allyl group of compound **10** was removed by use of the Pd/C–TsOH system[30] to give the 3′-OH compound **12** (87%). The same compound was isolated from the fully protected **11** through the removal of the 2-naphthylmethyl (NAP) group by using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). NAP ethers have been described previously,[31–33] and their preparative usefulness was rediscovered[34,35] only very recently. It was demonstrated that NAP ethers can be hydrogenolyzed in the presence of benzyl ethers or esters, and that they are less sensitive to acids than the

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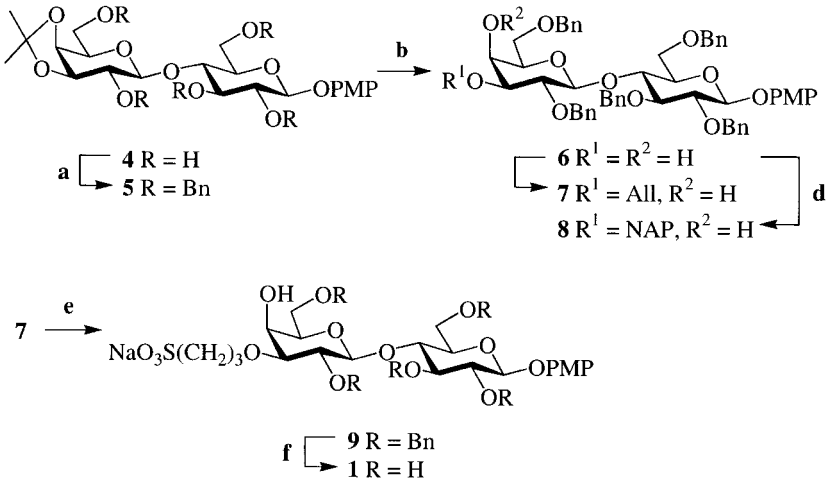

Scheme 1. (a) NaH, BnBr, DMF, quant.; (b) 1M HCl, MeOH, 50°C, 91%; (c) Bu_2SnO, MeOH, reflux, 2 hr; AllBr (2.5 equiv.), DMF, 88%; (d) Bu_2SnO, MeOH, reflux, 2 hr; NAPBr (2.5 equiv.), DMF, 87%; (e) $NaHSO_3$, *tert*-butyl perbenzoate, 70% EtOH, reflux, quant.; (f) Pd–C, H_2, 48 hr, EtOH–EtOAc–DCM (4 : 1 : 1), 96%.

p-methoxybenzyl ethers. The most important observation, however, is that NAP ethers can easily be removed either by DDQ or by ammonium cerium(IV) nitrate (CAN) under conditions when other usual protecting groups such as acetyl, pivaloyl, phthalimido, benzyl, and benzylidene survive.[34,35] These ethers were successfully applied for the synthesis of complex oligosaccharides[35–37] (Sch. 2).

The hydroxyl group of compound **12** was converted into a keto functionality using the Dess–Martin periodinane reagent.[38] The structure of the resulting crystalline **13** was confirmed from its ^{13}C-NMR spectrum ($\delta_{C=0} = 203$ ppm).

The keton **13** was reacted with the ethyl methanesulfonate anion generated with *n*-butyllithium.[14,15] Upon nucleophilic addition of the sulfonate ester carbanion to the carbonyl, *p*-methoxyphenyl 2,4,6-tri-*O*-benzyl-3-*C*-(ethoxysulfonylmethyl)-β-D-gulopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**14**) and its C-3′ epimer (**15**) were obtained in a 4 : 1 ratio. The β-D-gulopyranosyl configuration of the ultimate monosaccharide unit of the main product was determined by NMR on the basis of the $\underline{C}H_2$–H-2′ and $\underline{C}H_2$–H-4′ $^3J_{C,H}$ coupling constants, that depend on the dihedral angle in a manner similar to $^3J_{H,H}$.[15] The small values of both coupling constants ascertained the *equatorial* arrangement of the $-CH_2-SO_3Et$ group. The minor product **15** proved to be the appropriate 3′-epimer by its mass-spectrometric analysis (MALDI-Ms for $C_{64}H_{70}SO_{15}$ (M, 1110.44): m/z 1133.60 $[M + Na]^+$). The ester group of **14** was transformed into the corresponding tetrabutyl ammonium salt, and hydrogenolysis of the latter on Pd/C catalyst resulted in the desired compound **2**.

We also attempted the preparation of a trisaccharide-type sulfonic acid derivative of lactoside **17**. Glycosylation of compound **6** with ethyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-2-thio-α-D-*gluco*-hept-2-ulopyranoside (**16**)[14] using NIS-TfOH activation afforded a separable 4 : 1 mixture of the trisaccharides **17** and presumably **18**. During the reaction, a considerable amount of *exo*-glycal **19**[14] was formed. Determination of the

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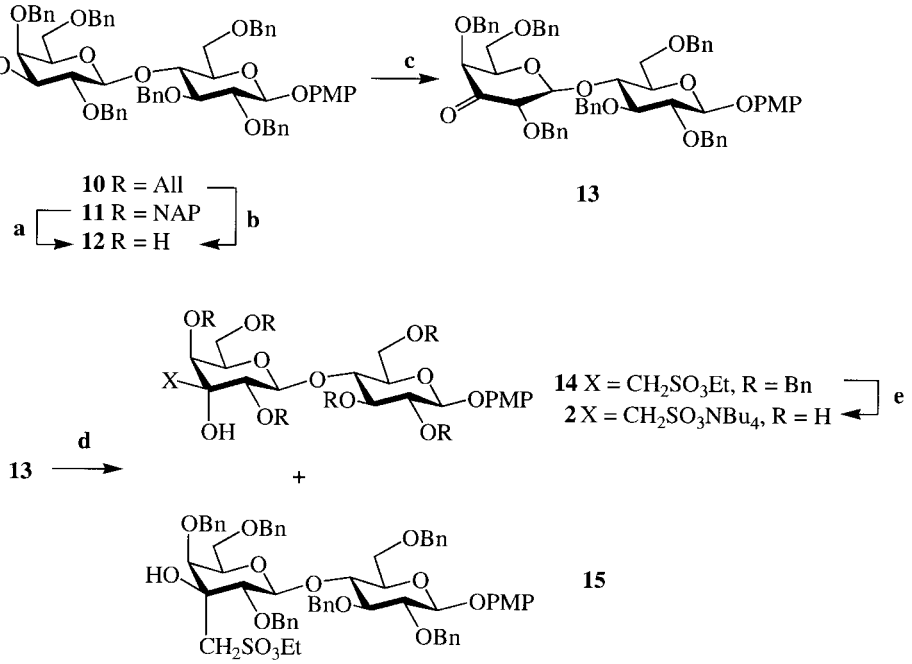


Scheme 2. (a) DDQ (1.2 equiv.), DCM : MeOH (4 : 1), 1 drop of water, 2 hr, 89%; (b) 10% Pd–C, TsOH (0.1 g/1 mmol), EtOH : EtOAc (5 : 1), 80°C, 2 hr, 87%; (c) Dess–Martin periodinane (1.2 equiv.), abs. DCM, 30 min, quant.; (d) *n*-BuLi, CH_3SO_3Et, −70°C, 71% for **14**, 18% for **15**; (e) Bu_4NBr, CH_3CN, 50°C; Pd–C, H_2, EtOH, 93%.

anomeric configuration of the newly formed interglycosidic bond of **17** could be achieved by the measurement of the $^3J_{C1-H3}$ coupling constant and its small value (<1.8 Hz) verified the exclusive formation of the α-anomer (Sch. 3).

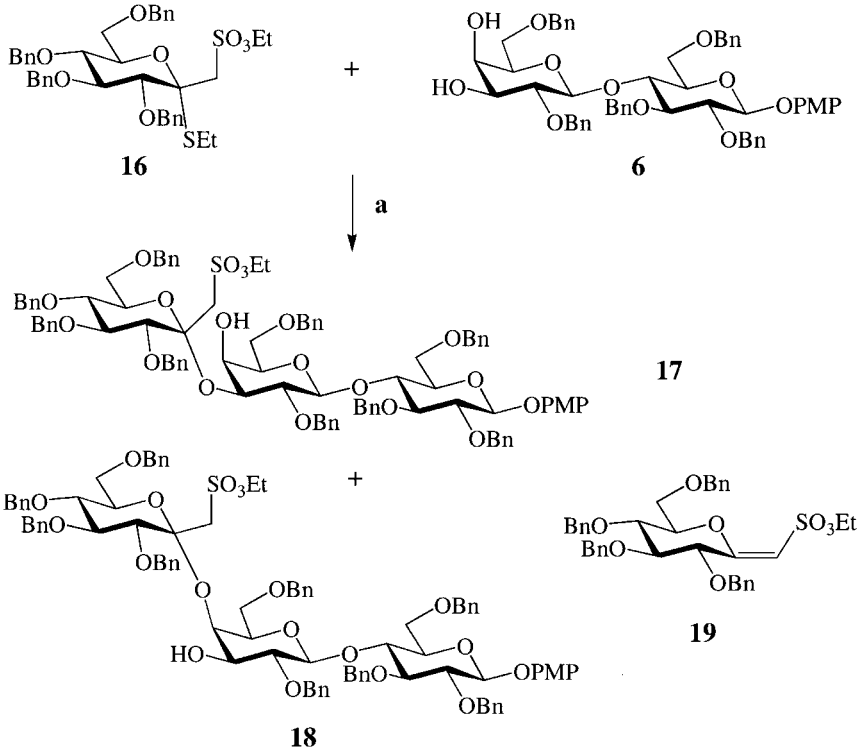
Removal of the protecting groups from **17** was attempted via nucleophilic attack of bromide ion and subsequent catalytic hydrogenation.[15] However, decomposition of the trisaccharide was occurred during deprotection. The failure of the deprotection step is under investigation in our laboratory.

In conclusion, oligosaccharide derivatives having C-sulfonic acid substituent at position 3 of the nonreducing end of a lactoside, or a *p*-methoxyphenyl β-D-gulopyranosyl-(1 → 4)-β-D-glucopyranoside analog were synthesized. The potential of the synthetic targets to inhibit adhesion between *H. pylori* and the epithelial cells of the gastric antrum are underway in two independent laboratories.

EXPERIMENTAL

General Methods

Optical rotations were measured at rt with a Perkin–Elmer 241 automatic polarimeter. Melting points were determined on a Kofler hot-stage apparatus and are uncor-



Scheme 3. (a) NIS-TfOH, DCM, 4Å MS, −40°C, 47% for **17**, 11% for **18**, 32% for **19**.

rected. TLC was performed on Kieselgel 60 F_{254} (Merck) with detection by charring with 50% aq. sulfuric acid. Column chromatography was performed on Silica Gel 60 (E. Merck 0.062–0.200 nm). The organic solutions were dried over $MgSO_4$ and concentrated in vacuum. The ^1H (200, 360, and 500 MHz) and ^{13}C NMR (50.3, 90.54, 125.76 MHz) spectra were recorded with Bruker WP-200SY, Bruker AM-360 and Bruker DRX-500 spectrometers for solutions in $CDCl_3$. Internal references: TMS (0.00 ppm for ^1H), $CDCl_3$ (77.00 ppm for ^{13}C). COSY and HSQC spectra were used to assign carbon signals of compound **14**.

4-Methoxyphenyl 3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (4). To a solution of 4-methoxyphenyl β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (15 g, 33.4 mmol) in DMF (80 mL) 2,2-dimethoxypropane (10 mL) and *p*-toluenesulfonic acid (200 mg) were added and the mixture was stirred for 4 hr at 80°C, then neutralized with Serdolit Blue (HO^-) ion exchange resin. The resin was filtered off and the filtrate was concentrated. The residue was crystallized from ethanol to give **4** (11 g, 66%) as white needles, mp: 222–224°C; $[\alpha]_D + 7.1$ (*c* 0.41, DMSO); ^1H-NMR (200 MHz, DMSO-d_6) δ (ppm): 7.07, 6.84 (2m, each 2H, Ph), 5.50 (m, 2H), 4.92 (broad t, 1H), 4.84 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.72 (m, 2H), 4.34 (d, 1H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.19–3.22 (m, OCH_3, and 13H), 1.44, 1.29 (2s, each 3H, $C(CH_3)_2$); ^{13}C-NMR (50 MHz, DMSO-d_6) δ (ppm): 154.4, 151.4, 117.7, 114.5 (Ph),

108.8 ($C(CH_3)_2$), 102.7, 101.1 (*C*-1, *C*-1′) 80.2, 79.3, 74.9 (2C), 73.4, 73.1 (2C), 72.5 (8 skeleton *C*), 60.5, 60.1 (*C*-6, *C*-6′), 55.4 (OCH_3), 28.2, 26.4 ($C(CH_3)_2$). Anal. calcd for $C_{22}H_{32}O_{12}$: C, 54.08; H, 6.61. Found: C, 54.06; H, 6.63.

4-Methoxyphenyl 2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (5). To a solution of **4** (8.0 g, 16.3 mmol) in dry DMF 80% NaH (3 g, 0.10 mol) was added in small portions at 0°C. The reaction mixture was stirred for 30 min and benzyl bromide (12 mL, 0.10 mol) was added. After 2 hr, t.l.c. showed complete conversion (DCM : acetone, 98 : 2), then MeOH was added in order to decompose the excess of hydride. The solvent was evaporated, the residue was dissolved in DCM (1200 mL), washed with distilled water (3 × 400 mL), dried, filtered, and evaporated. The sirupy crude product (15 g) was used for the next step without purification.

4-Methoxyphenyl 2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (6). A stirred mixture of **5** (15 g, ∼16 mmol) in methanol (500 mL) and 1 M HCl was heated for 50°C. After 2 hr, t.l.c. showed complete conversion, the solution was evaporated and the solid residue was crystallized from methanol to give **6** (13 g, 89% for two steps), mp: 120–124°C; $[\alpha]_D + 1.9$ (*c* 0.58, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.42–6.77 (m, 29H, Ph), 5.01 (dd, 2H), 4.90–4.76 (m, *H*-1 and 3H), 4.67, 4.56 (2d, each 1H, $J_{gem} = 12$ Hz, CH_2Ph), 4.49–4.33 (m, 3H, and H-1′), 4.10–3.35 (m, 12H, and OCH_3), 2.33 (broad s, 2H, OH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 154.4–114.4 (Ph), 102.4, 102.3 (*C*-1, *C*-1′), 82.8, 81.5, 80.1, 76.4, 75.2, 73.5, 73.0, 68.8 (skeleton *C*), 75.2, 75.1, 75.0, 73.5, 73.2 (5 CH_2Ph), 68.7, 68.3 (*C*-6, *C*-6′), 55.7 (OCH_3). MALDI-MS for $C_{54}H_{58}O_{12}$ (M, 898.38): m/z 922.28 $[M + Na]^+$.

4-Methoxyphenyl 3-*O*-allyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (7). To a suspension of **6** (9 g, 10 mmol) in MeOH (150 mL) was added dibutyltin oxide (3.1 g, 12.5 mmol). The mixture was stirred for 2 hr at reflux temperature, MeOH was evaporated, and the residue was dried under high vacuum for 1 hr. To a suspension of the crude mixture in DMF (30 mL) was added allyl bromide (2.6 mL, 30 mmol). After being stirred for 48 hr at rt, the mixture was concentrated in vacuum and purified by column chromatography (DCM : acetone, 97 : 3) to give **7** (8.2 g, 88%) as white needles mp: 102–104°C (from ethyl acetate–*n*-hexane; $[\alpha]_D$ 0 (*c* 0.34, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.50–6.80 (m, 29H, Ph), 5.99 (m, 1H, CH_2=C*H*) 5.42–5.21 (m, 2H), 5.07 (2d, 2H, $J_{gem} = 12$ Hz, CH_2Ph), 4.96–4.79 (m, 5H), 4.60–4.40 (m, 5H), 4.31–4.00 (m, 4H), 3.89–3.32 (m, OCH_3, and 10H), 2.36 (broad s, 1H, O*H*); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 154.4–114.4 (Ph), 134.4 (CH_2=*C*H), 117.0 (CH_2=CH), 103.0, 102.8 (*C*-1, *C*-1′) 82.9, 81.8, 81.1, 79.5, 76.8, 75.5, 73.0, 66.4 (skeleton *C*), 75.6, 75.3, 75.1, 73.6, 73.2 (5 CH_2Ph), 71.2 (CH_2=CH–CH_2O), 68.7, 68.3 (*C*-6, *C*-6′), 55.7 (OCH_3). Anal. calcd for $C_{57}H_{62}O_{12}$: C, 72.90; H, 6.66. Found: C, 73.04; H, 6.56.

4-Methoxyphenyl 2,6-di-*O*-benzyl-3-*O*-(2-naphthyl)methyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (8). To a suspension of **6** (4.5 g, 5 mmol) in MeOH (80 mL) was added dibutyltin oxide (1.5 g, 6 mmol). The mixture was stirred for 2 hr at reflux temperature, MeOH was evaporated, and the residue was dried under high vacuum for 1 hr. To a suspension of the crude mixture in DMF (20 mL) was added 2-bromomethyl-naphthalene (2.87 g, 13 mmol). After being stirred for 48 hr at rt, the mixture was concentrated in vacuum and purified by column chromatography (DCM : acetone, 98 : 2) to give **8** (4.4 g, 85%) as white needles mp: 131–133°C

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(from ethyl acetate–*n*-hexane); $[\alpha]_D + 8.9$ (*c* 0.10, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.90–6.78 (m, 36H, Ph), 5.09–4.77 (m, 8H and H-1), 4.58–4.35 (m, 4H and H-1′), 4.14–3.96 (m, 2H), 3.88–3.34 (m, 10H), 3.79 (s, 3H, OCH_3), 2.00 (s, 1H, OH). ^{13}C-NMR (200 MHz, $CDCl_3$) δ (ppm): 102.8 (*C*-1′), 102.7 (*C*-1), 83.0 (2C), 81.6, 81.0, 79.6, 75.5, 72.8, 66.3 (8 skeleton C), 75.4, 75.4, 75.1, 73.6, 73.1, 72.0 (CH_2-Np and CH_2-Ph), 68.5 (*C*-6), 68.3 (*C*-6′), 55.7 (OCH_3). Anal. calcd for $C_{65}H_{66}O_{12}$: C, 75.11; H, 6.41. Found: C, 74.96; H, 6.43.

4-Methoxyphenyl 2,6-di-*O*-benzyl-3-*O*-[3-(sodium sulfonate)propyl]-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (9). To a solution of **7** (750 mg, 0.8 mmol) in 70% aq EtOH (75 mL) were added $NaHSO_3$ (500 mg, 4.8 mmol) and *tert*-butyl perbenzoate (45 μL, 0.24 mmol). The mixture was stirred for 4 hr at reflux temperature, then concentrated in vacuum. The solid residue was dissolved in 1 mL of DCM and purified by column chromatography (DCM : methanol, 8 : 2) to give **9** (758 mg, 91%); $[\alpha]_D + 10.8$ (*c* 0.17, $CHCl_3$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 155.2–114.4 (Ph), 102.8, 102.6 (*C*-1, *C*-1′) 82.6, 81.9, 81.4, 79.2, 76.9, 75.2, 73.1, 66.6 (8 skeleton *C*), 75.0 (2C), 75.0, 73.4, 73.2, 73.0 (5 CH_2Ph and $-CH_2O$), 68.7, 68.3 (*C*-6, *C*-6′), 55.7 (OCH_3), 49.1 (CH_2SO_3), 24.5 ($-CH_2-CH_2-CH_2O$). MALDI-MS for $C_{57}H_{63}SO_{15}Na$ (M, 1042.38): m/z 1065.54 $[M + Na]^+$.

4-Methoxyphenyl 3-*O*-[3-(sodium sulfonate)propyl]-β-D-galactopyranosyl-(1 → 4)-β-D-glucopyranoside (1). Compound **9** (500 mg, 0.47 mmol) was dissolved in a EtOH/EtOAc/DCM mixture (4 : 1 : 1, 60 mL) and hydrogenated in the presence of 10% Pd–C (100 mg). After 48 hr the mixture was filtered through a pad of celite, washed with water, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (DCM : methanol : water, 7 : 3 : 0.5) to give **1** (267 mg, 96%) as an amorphous solid $[\alpha]_D - 6.5$ (*c* 0.19, H_2O); ^{1}H-NMR (200 MHz, D_2O) δ (ppm): 7.11 and 6.97 (2d, each 2H, Ph), 5.04 (d, 1H, $J_{1,2} = 7.5$ Hz, *H*-1), 4.49 (d, 1H, $J_{1',2'} = 7.5$ Hz, *H*-1′), 4.17 (d, 1H, $J = 2$Hz), 4.04–3.41 (m, OCH_3 and 13H), 3.02 (m, 2H, CH_2), 2.04 (m, 2H, CH_2); ^{13}C-NMR (50 MHz, D_2O) δ (ppm): 155.2–114.4 (Ph), 103.3, 101.6 (*C*-1, *C*-1′) 80.7, 78.3, 75.6, 75.1, 74.2, 72.9, 70.1, 65.2 (8 skeleton *C*), 67.6 ($-CH_2O$), 61.3, 61.1 (*C*-6, *C*-6′), 56.9 (OCH_3), 48.9 (CH_2SO_3), 24.9 ($-CH_2-CH_2O$). MALDI-MS for $C_{22}H_{33}SO_{15}Na$ (M, 592.14): m/z 615.21 $[M + Na]^+$.

4-Methoxyphenyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (10). To a solution of **7** (2.8 g, 3.0 mmol) in dry DMF 80% NaH (140 mg, 4.5 mmol) was added at 0°C and stirred for 30 min. Then benzyl bromide (0.45 mL, 3.6 mmol) was added to the mixture. After 1 hr, t.l.c. showed complete conversion (hexane : EtOAc, 7 : 3), then MeOH was added in order to decompose the excess of hydride. The residue was dissolved in DCM (600 mL), washed with distilled water (3 × 70 mL), dried and evaporated. The crude product was crystallized from EtOAc–*n*-hexane to give **10** (2.8 g, 91%) as white crystals: mp 80–82°C; $[\alpha]_D - 12.9$ (*c* 0.28, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.40–6.75 (m, 34H, Ph), 5.99 (m, 1H, CH_2=C*H*) 5.33 (dd, 1H, $J = 17.5$ Hz, 1.5 Hz, CH_2=CH), 5.17 (dd, 1H, $J = 10.5$ Hz, 1.5 Hz, CH_2=CH), 5.10–4.69 (m, 8H), 4.60–4.10 (m, 8H), 4.01–3.30 (m, OCH_3 and 12H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 154.4–114.4 (Ph), 134.6 (CH_2=*C*H), 116.3 (CH_2=CH), 102.9, 102.8 (*C*-1, *C*-1′), 82.9, 82.3, 81.5, 79.8, 76.8, 75.5, 73.5, 73.1, (8 skeleton *C*), 75.6, 75.4, 75.2, 74.6, 73.4, 72.9 (6 CH_2Ph), 71.5 (CH_2=CH–CH_2O), 68.4, 68.2 (*C*-6, *C*-6′), 55.9 (OCH_3). Anal. calcd for $C_{64}H_{68}O_{12}$: C, 74.67; H, 6.66. Found: C, 74.60, H, 6.63.

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4-Methoxyphenyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-naphthyl)methyl-β-D-galactopyranoside-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (11). To a solution of **8** (2.8 g, 2.7 mmol) in dry DMF, 80% NaH (120 mg, 4 mmol) was added at 0°C. The mixture was stirred for 30 min, then benzyl bromide (0.4 mL, 3.3 mmol) was added. After 1 hr, t.l.c. showed complete conversion, the mixture was worked up as described for the synthesis of **10**. The solid crude product was crystallized from EtOAc–hexane to afford **11** (2.7 g, 89%) as white crystals: mp. 115–118°C; $[\alpha]_D + 2.3$ (*c* 0.43, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.82–6.84 (m, 41H, Ph), 5.16–4.28 (m, 19H), 4.86 (d, 1H, $J_{1,2} = 6.5$ Hz, *H*-1), 4.08–3.40 (m, 9H, and OC*H*$_3$). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 102.8, 102.7 (*C*-1, *C*-1′), 83.0, 82.4, 81.6, 79.9, 76.9, 75.4, 73.6, 73.0, (8 skeleton C), 75.4, 75.3, 75.1, 74.7, 73.4, 73.1, 72.6 (*C*H$_2$-Np, 5 *C*H$_2$-Ph), 68.39 (*C*-6), 68.04 (*C*-6′), 55.76 (O*C*H$_3$). Anal. calcd for $C_{72}H_{72}O_{12}$: C, 76.56; H, 6.43. Found: C 76.80; H, 6.49.

4-Methoxyphenyl 2,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (12). (a) A solution of **10** (1.0 g, 1 mmol) in EtOAc (14 mL) and 96% EtOH (70 mL) was treated with *p*-toluenesulfonic acid (95 mg, 0.5 mmol) in the presence of 10% Pd-C (200 mg) at 80°C for 2 hr, then filtered through a layer of Celite, treated with Et_3N, and concentrated. The crude product was crystallized from EtOH to afford **12** (850 mg, 87%).

(b) A solution of **11** (1.2 g, 1 mmol) in a DCM : MeOH mixture (4 : 1, 5 mL) was treated with DDQ (290 mg, 1.2 mmol) at rt for 1 hr, then concentrated and purified by column chromatography (DCM : acetone, 98 : 2) to afford **12** (880 mg, 89%) as white crystals. Compound **12** has mp. 102–104°C (from EtOH), $[\alpha]_D - 7.6$ (*c* 0.36, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.46–6.58 (m, 34H, Ph), 5.16–4.28 (m, 14H), 4.11–3.42 (m, 12H and OC*H*$_3$), 2.08 (s, 1H, O*H*). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 102.8 (2C, *C*-1′ and *C*-1), 82.9, 81.6, 80.7, 76.8, 75.9, 75.2, 74.2, 73.3 (8 skeleton C), 75.4, 75.1 (2C), 75.0, 73.4, 73.1 (6 *C*H$_2$-Ph), 68.38 (*C*-6), 68.02 (*C*-6′), 55.80 (O*C*H$_3$). Anal. calcd for $C_{61}H_{64}O_{12}$ (988.43): C, 74.06; H, 6.53. Found: C, 73.87; H, 6.48.

4-Methoxyphenyl 2,4,6-tri-*O*-benzyl-β-D-*xylo*-hex-3-ulopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (13). A solution of **12** (1.0 g, 1 mmol) in DCM (10 mL) was treated with Dess–Martin's periodinane (1.2 mmol) at rt and stirred for 30 min. Then, 20 mL of diethyl ether and 20 mL of 1.3 M NaOH were added, and the mixture was stirred for further 10 min. The mixture was diluted with DCM (30 mL), washed with water, dried and concentrated in vacuum. The residue was crystallized from EtOAc–*n*-hexane to give **13** (930 mg, 95%), mp. 122–124°C, $[\alpha]_D - 37.4$ (*c* 0.33, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.34–6.86 (m, 34H, Ph), 5.08–4.23 (m, 14H), 4.09–3.38 (m, 11H and OC*H*$_3$). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 203.1 (CO), 103.6 (*C*-1′), 102.6 (*C*-1), 83.4, 83.2, 82.2, 81.3, 78.1, 75.54, 73.8 (7 skeleton C), 75.4, 75.1, 73.6, 73.3, 73.1, 72.5 (*C*H$_2$Ph), 68.8 (*C*-6), 68.4 (*C*-6′), 55.9 (O*C*H$_3$). Anal. calcd for $C_{61}H_{64}O_{12}$: C, 74.06; H, 6.53. Found: C, 73.87; H, 6.48.

4-Methoxyphenyl 2,4,6-tri-*O*-benzyl-3-*C*-ethoxysulfonylmethyl- β-D-gulopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (14). To a solution of 2.5 M *n*-BuLi (2 equiv., 0.72 mmol, 300 μL solution in hexane) in dry THF under argon atmosphere at −60°C ethyl methanesulfonate was added (1.5 equiv., 0.54 mmol, 60 μL). The mixture was kept at −60°C for 15 min, then it was cooled to −78°C and the ulose compound **13** (1 equiv., 0.36 mmol, 360 mg,) was added. The mixture was kept at −78°C for 30 min. Then, it was allowed to warm to rt, stirred for further 30 min, and concentrated.

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Then, the residue was diluted with 50 mL of DCM and extracted with water (3 × 10 mL). The organic layer was dried ($MgSO_4$) and evaporated. The products were separated by column chromatography (DCM : acetone, 98 : 2) to give **14** (280 mg, 71%) and **15** (70 mg, 18%)

Compound **14**: $[\alpha]_D$ − 5.6 (*c* 0.55, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 7.04–6.56 (m, 34H, aromatic), 4.96 (d, 1H, $J_{1',2'} = 7.7$ Hz, H-1′), 4.90 (d, 1H, $J_{1,2} = 7.2$ Hz, H-1), 4.27 (m, 1H, H-5′), 4.15 (m, 1H, H-5), 4.14 (m, 2H, $CH_3CH_2SO_3Et$), 3.89 (dd, 1H, $J_{5,6a} = 5.2$ Hz, $J_{gem} = 10.6$ Hz, H-6a,), 3.83 (dd, 1H, $J_{5,6b} = 2$ Hz, $J_{gem} = 10.6$ Hz, H-6b,), 3.83 (s, 3H, OCH_3), 3.76 (dd, 1H, H-2, $J_{2,3} = 8.7$ Hz), 3.73 (dd, 1H, H-3, $J_{3,4} = 8.7$ Hz), 3.62 (dd, 1H, H-6′a), 3.58 (dd, 1H, H-6′b), 3.57 (m, 1H, H-4′), 3.32 (dd, 1H, H-2′). ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 102.6 (C-1), 100.2 (C-1′), 82.5 (C-3), 81.2 (C-2), 77.5 (C-2′), 76.3 (C-4), 76.2 (C-5), 76.0 (C-4′), 71.4 (C-5′), 70.9 (C-3′), 75.3 (4C), 74.9, 73.3 (6 CH_2Ph), 68.2 (C-6), 67.7 (C-6′), 55.6 (OCH_3), 51.8 (CH_2SO_3Et, $^3J_{CH_2,H\text{-}4'} \cong {}^3J_{CH_2,H\text{-}2'} < 2.8$ Hz), 15.0 ($SO_3CH_2CH_3$). MALDI-MS for $C_{64}H_{70}SO_{15}$ (M, 1110.44): m/z 1133.60 $[M + Na]^+$.

Compound **15**: $[\alpha]_D$ − 36.2 (*c* 0.21, $CHCl_3$); MALDI-MS for $C_{64}H_{70}SO_{15}$ (M, 1110.44): m/z 1133.60 $[M + Na]^+$.

4-Methoxyphenyl 3-*C*-(tetrabutylammonium sulfonato)methyl-β-D-gulopyranosyl-(1 → 4)-β-D-glucopyranoside (2). Compound **14** was treated with Bu_4NBr in acetonitrile at reflux temperature for 1 hr, when t.l.c showed complete conversion. The solution was evaporated, the residue was dissolved in ethanol, and hydrogenated in the presence of 10% Pd–C (100 mg). After 48 hr the mixture was filtered through celite, washed with water, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (acetone : water, 9 : 1) to give **2** (267 mg, 96%) $[\alpha]_D$ − 6.5 (*c* 0.19, H_2O); ^{1}H-NMR (200 MHz, D_2O) δ (ppm): 7.1 (m, 2H, Ph), 6.9 (m, 2H, Ph), 5.04 (d, 1H, $J_{1,2} = 7.9$ Hz, H-1), 4.63 (d, 1H, $J_{1',2'} = 8.5$ Hz, H-1′), 4.43 (s, 1H), 4.02–3.54 (m, 10H and OCH_3), 3.40 (s, 2H), 3.19, 1.64, 1.38 (3m, each 8H, 12 CH_2), 0.95 (t, 12H, 4 CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 155.3, 151.5 (Ph), 118.8 (2C), 115.6 (2C) (Ph), 101.6 (2C, C-1, C-1′), 78.7, 75.5, 75.0 (2C), 74.9, 73.4, 73.2, 68.9 (8 skeleton C), 62.3, 60.5 (C-6, C-6′), 58.7 (SO_3CH_2–), 56.4 (OCH_3), 51.6 (CH_2SO_3–), 23.7, 19.8 (CH_2CH_2 butyl), 13.5 (CH_3 butyl). MALDI-MS for $C_{22}H_{33}SO_{15}Na$ (M, 592.54): m/z 618 $[M + Na]^+$.

4-Methoxyphenyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2 → 3)-2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (17), 4-methoxyphenyl 3,4,5,7-tetra-*O*-benzyl-1-deoxy-1-ethoxysulfonyl-α-D-*gluco*-hept-2-ulopyranosyl-(2 → 4)-2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (18), and 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-ethoxysulfonyl-D-*gluco*-hept-1-enitol (19). A mixture of **6** (450 mg, 0.5 mmol), **16** (530 mg, 1.5 equiv.) and molecular sieves (4 Å) in dry DCM was stirred for 3 hr under Ar. It was then cooled to −50°C and a solution of 1.5 equiv. of NIS and 0.35 equiv. of TfOH in abs THF was added. The mixture was kept at −40°C untill t.l.c. (hexane : EtOAc, 65 : 35) showed the disappearance of **16** (∼30 min). The mixture was allowed to warm up to rt, neutralized with Et_3N, filtered, diluted with DCM, washed with water, dried, and concentrated. Column chromatography (hexane : EtOAc, 65 : 35) of the residue afforded **19** (32%, R_f: 0.66), **17** (47%, R_f: 0.57), and **18** (11%, R_f: 0.31).

Compound **17** has $[\alpha]_D$ + 35.11 (*c* 0.410, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.58–6.83 (m, 49H, Ph), 5.15–4.38 (m, 22H), 4.30–4.13 (m, 5H), 4.02–3.56

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(m, 11H and OCH_3), 2.82 (broad s, 1H, OH), 1.25 (3H, t, $J = 7$ Hz, $SO_3CH_2CH_3$), ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 155.2–114.4 (Ph), 102.7 (C-1′), 102.2 (C-1), 99.5 (C-2″), 83.2, 82.7, 81.4 (2C), 79.9, 78.5, 77.6, 76.8, 76.5, 74.5, 73.0, 72.5 (12 skeleton C) 75.6, 75.3, 75.1, 74.8, 74.7 (2C), 73.5 (2C), 73.3 (9 CH_2Ph), 68.3, (2C), 68.1 (C-6, C-6′, C-7″), 67.8 ($SO_3CH_2CH_3$), 55.5 (OCH_3), 53.0 (C-1″, $J_{C\text{-}1'',H\text{-}3''} < 1.8$ Hz), 15.2 ($SO_3CH_2CH_3$). MALDI-MS for $C_{91}H_{98}SO_{20}$ (M, 1542.64): m/z 1566.26 $[M + Na]^+$.

Compound **18** has $[\alpha]_D + 14.30$ (c 0.36, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.46–6.77 (m, 49H, Ph), 5.18, 5.00 (2d, each 1H, $J_{gem} = 11$ Hz, CH_2PH), 4.98–4.70 (m, 8H), 4.56–4.33 (m, 8H), 4.25–3.92 (m, 10H), 3.82–3.41 (m, 15H and OCH_3), 1.25 (3H, t, $J = 7$ Hz, $SO_3CH_2CH_3$), ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 155.2–114.4 (Ph), 103.5 (C-1′), 102.7 (C-1), 99.3 (C-2″), 83.0, 82.5, 81.5, 81.8, 80.0, 78.3, 77.9, 75.6, 74.0, 72.9, 72.8, 72.2 (12 skeleton C) 75.5 (2C), 75.2, 75.1 (2C), 74.9, 73.5, 72.9 (9 CH_2Ph), 68.9, 68.1, 67.7, 67.3 (C-6, C-6′, C-7″, $SO_3CH_2CH_3$), 55.6 (OCH_3), 52.4 (C-1″, $J_{C\text{-}1'',H\text{-}3''} < 3$ Hz), 15.0 ($SO_3CH_2CH_3$). MALDI-MS for $C_{91}H_{98}SO_{20}$ (M, 1542.64): m/z 1566.24 $[M + Na]^+$.

Compound **19** has $[\alpha]_D + 67.2$ (c 0.56, $CHCl_3$); lit.[15] $[\alpha]_D + 64.1$ (c 0.23, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.49–7.26 (m, 20H, Ph), 5.77 (s, 1H, H-1), 4.82–4.61 (8d, 8H, 4 CH_2Ph), 4.41 (m, 1H, H-6), 4.24 (q, 2H, $J_{gem} = 14$ Hz, $SO_3CH_2CH_3$), 3.96–3.91 (m, 4H, H-3, H-4, H-5, H-7a), 3.88 (dd, 1H, $J_{6,7a} = 3$ Hz, $J_{gem} = 11.5$ Hz, H-7b), 1.30 (t, 3H, $J = 7$ Hz, $SO_3CH_2CH_3$), ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 161.7 (C-2), 137.8–127.4 (Ph), 103.8 (C-1), 81.9 (C-4), 78.6 (C-6), 76.6, 76.5 (C-3, C-5), 73.4, 73.2, 72.9, 72.1 (4 CH_2Ph), 67.6 (C-7), 66.6 ($SO_3CH_2CH_3$), 14.6 ($SO_3CH_2CH_3$). MALDI-MS for $C_{37}H_{40}SO_8$ (M, 644.24): m/z 667.31 $[M + Na]^+$.

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