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Synthesis and properties of sulfated alkyl glycosides

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ABSTRACT

Alkyl glycosides were sulfated with sulfur trioxide–pyridine. Dodecyl α- and β-D-glucopyranoside gave the corresponding 6-sulfates in 75 and 51% yields, respectively. Separation from polysulfated compounds was carried out by reversed-phase HPLC. Tetradecyl β-maltopyranoside (**16**) gave a 88:12 mixture of 6′- and 6-sulfates. The sulfated compounds were characterized by ^{1}H-, ^{13}C-, and 2-dimensional NMR spectroscopy. Surfactant and thermotropic liquid-crystalline properties of the sugar derivatives were examined. All of the glycosides show smectic phases (S_A), and the clearing points rise by introduction of sulfate groups. Even glycosides having no unprotected hydroxy groups may show S_A-phases when bearing sulfate groups. The mesomorphic properties cannot be explained by formation of distinct aggregates, but rather must be interpreted by an effective intramolecular contrast.

INTRODUCTION

The glycosaminoglycans[1] — carbohydrates containing sulfate as well as carboxyl and amino groups — as part of mammalian connective tissue and cartilage, form a matrix and hold together the protein components. They are able to form hydrated gels and to resist compressive forces. As a main component of cartilage tissue, 4- and 6-sulfated chondroitin chains are observed, whereas skin consists mainly of dermatan sulfate. The anticoagulant heparin constitutes another highly sulfated glycosaminoglycan. In the myelin plasma-membrane is found galactosylcerebroside 3-sulfate; and its structure is analogous to anionic carbohydrate surfactants. Myelin itself was the first liquid-crystalline system studied[2]. The sulfation of alkyl glycosides has been studied in order to devise regiospecifically sulfated carbohydrates as model anionic surfactants. Sulfated long-chain alkyl glycosides assemble in common a number of interesting biological, chemical, and physical properties as a result of to their amphiphilic character.

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SYNTHESIS

In connection with the synthesis of heparin analogues, polysulfation was performed[3] with an excess of sulfur trioxide–triethylamine complex at 60°. For monosulfation the sulfur trioxide–pyridine complex was used[4], but it led to mixtures that were difficult to separate. This problem may be solved by using suitably protected sugar-derivatives[5]. We have used the sulfur trioxide–pyridine complex for mono- and for poly-sulfation of the unprotected dodecyl and tetradecyl glycosides **1**, **11**, and **16**, followed by separation of the product mixtures by reversed-phase HPLC.

Monosulfation of the dodecyl β- and α-glucosides **1** and **11** with two molar equivalents of sulfur trioxide–pyridine at $-10°$ gave 51 and 75%, respectively, of the 6-sulfates **3** and **13**. Small amounts of other mono- and di-sulfated products could be separated on an RP-2 column. Mono-6-sulfation of tetradecyl β-maltoside (**16**) gave an 88:12 mixture of the two regioisomers **17** and **18**. The tetrasulfated compound **10** was formed in 69% yield by reaction of **1** with 12 mol of the sulfating complex. Sulfation with four molar equivalents of sulfur trioxide–pyridine lead to a complex mixture that could be separated into a di- and tri-sulfated fraction. Isolation of the disulfate isomers **5**, **7**, and **9** was possible by reversed-phase chromatography after acetylation. The α-glucoside **11** with four molar equivalents of the sulfating complex gave selectively the 2,6-disulfated product **13**, probably because of the enhanced nucleophilicity of the 2-hydroxy group.

NMR CHARACTERIZATION

The sulfated derivatives were unequivocally assigned by ^{1}H- and ^{13}C-NMR spectra. The geminal protons of sulfated hydroxy groups show a downfield shift of ~ 0.4 and 1.0 ppm for primary and secondary hydroxy groups, respectively. The β-effect on vicinal protons is 0.12–0.57 ppm. These shifts are thus longer than those caused by acetylation.

The coupling constants are not affected by sulfation, except for the persulfate **10**, where the data indicate a $^{0,3}B$ (D) conformation. The ^{13}C-NMR spectra of the sulfated alkyl glycosides (Table I) could be fully interpreted by C,H-correlated spectra. The results accord with recent NMR data in the literature for monosulfated methyl galactopyranosides[6].

THERMOTROPIC LIQUID-CRYSTALLINE PROPERTIES

As previously demonstrated for the series of of mono-, di- and oligo-saccharides[7], similar trends are observed in going from simple glycosides to ionic glycosides: the propensity for crystallization decreases, the characteristics of the mesophases become less obvious, and often the clearing point becomes identical with the temperature of decomposition.

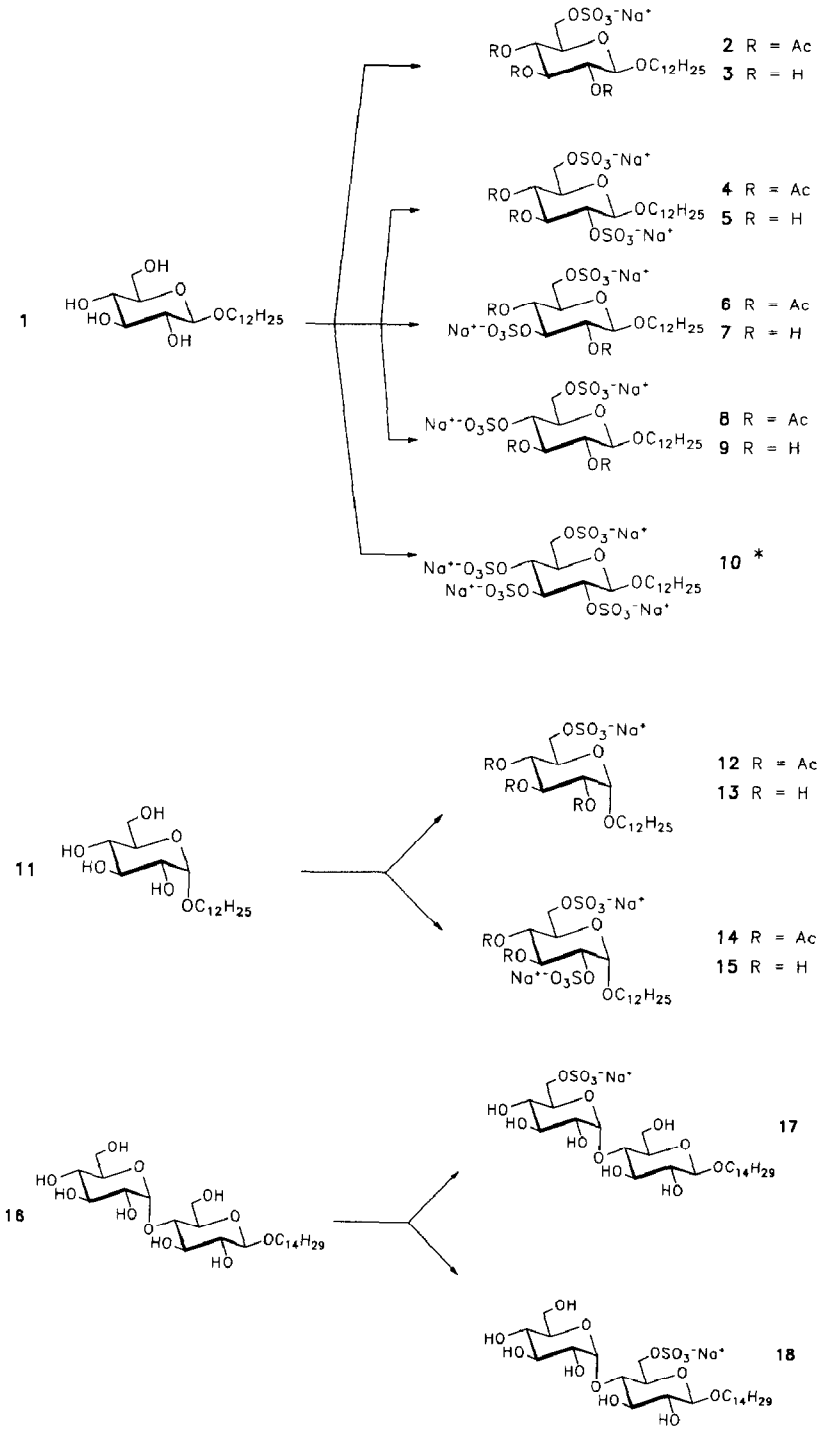

1
2 R = Ac
3 R = H
4 R = Ac
5 R = H
6 R = Ac
7 R = H
8 R = Ac
9 R = H
10 *
11
12 R = Ac
13 R = H
14 R = Ac
15 R = H
16
17
18

TABLE I

^{13}C-NMR data [a] for sulfated dodecyl α- and β-D-glucopyranosides

Compound	Conditions	Chemical shifts (and shifts relative to **1** and **11**)					
	MHz solvent	C-1	C-2	C-3	C-4	C-5	C-6
Dodecyl β-D-gluco-pyranoside (**1**)	75.46 CD_3OD	104.3	75.0	77.8	71.5	78.0	62.7
6-sulfate (**3**)	90.56	104.2	74.9	77.6	71.3	75.8	68.1
	CD_3OD	(−0.1)	(−0.1)	(−9.2)	(−0.2)	(−2.2)	(+5.4)
2,6-disulfate (**5**)	90.56	101.7	80.9	75.6	69.7	74.5	67.2
	D_2O [b]	(−2.6)	(+5.9)	(−2.2)	(−1.8)	(−3.5)	(+4.5)
3,6-disulfate (**7**)	90.56	103.1	72.8	84.8	68.7	74.1	67.4
	D_2O [b]	(−1.2)	(−2.2)	(+7.0)	(−2.8)	(−3.9)	(+4.7)
4,6-disulfate (**9**)	90.56	103.2	73.2	73.8	77.5	75.4	68.0
	D_2O [b]	(−1.1)	(−1.8)	(−4.0)	(+6.0)	(−2.6)	(+5.3)
2,3,4,6-tetra-sulfate (**10**)	90.56	101.1	77.2	76.5	73.5	74.5	68.6
	D_2O [b]	(−3.2)	(+2.2)	(−1.3)	(+2.0)	(−3.5)	(+5.9)
Dodecyl α-D-gluco-pyranoside (**11**)	75.46 CD_3OD	100.0	73.4	75.0	71.6	73.5	62.5
6-sulfate (**13**)	90.56	99.9	73.3	74.7	71.4	71.6	68.1
	CD_3OD	(−0.1)	(−0.1)	(−0.3)	(−0.2)	(−1.9)	(+5.6)
2,6-di-sulfate (**15**)	97.5	78.1	71.5	69.7	70.6	60.9	
	D_2O [b]	(−2.4)	(+4.8)	(−3.2)	(−1.9)	(−2.9)	(+4.4)

[a] Except dodecyl chain. [b] 1:9 CD_3OD–D_2O.

The sulfated derivatives **3–9**, **12–15**, and **17–18** show extraordinary high clearing points (Table II). As demonstrated in Table II, the introduction of only one sulfate group leads to an increase of clearing points between 60 and 80°. Introduction of a second sulfate group leads to a further rise of the clearing point. The 4,6-disulfated glycoside **9**, having two sulfate groups positioned at the same site of the molecule, shows the highest clearing point of all derivatives examined.

All compounds form S_A-phases (compare Table III), although no obvious textures could be observed. The characteristic fan texture or stepped drops in the case of amphiphilic liquid crystals are obtained by cooling the isotropic phases. Since the isotropic phases of the sulfates rapidly decompose when heated to high temperatures, only those textures (unfortunately not very characteristic) could be observed that formed during heating. These textures strongly resemble lyotropic lamellar phases L_α, which possess a symmetry identical to the S_A-phase.

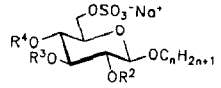
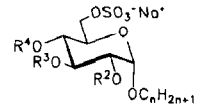
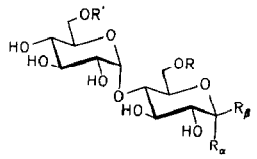
TABLE II

Clearing points (°) of sulfated dodecyl D-glucopyranosides

	Unprotected		6-Sulfate		2,6-Disulfate		4,6-Disulfate	
β	**1**	143°	**3**	220°	**5**	> 210°	**9**	> 240°
α	**11**	149°	**13**	210°	**15**	225°		

TABLE III

Liquid-crystalline properties [a]

Compound	R^2	R^3	R^4	Phase transitions [b]				
								
3	H	H	H	f	109	S	220	d
5	SO_3Na	H	H	f	?	S	> 210	d [c]
7	H	SO_3Na	H	f	200	S	215	d
9	H	H	SO_3Na	f	190	S	240	d
10	SO_3Na	SO_3Na	SO_3Na	Cr	202			d
2	Ac	Ac	Ac	f	?			I
4	SO_3Na	Ac	Ac	f	161			I [d]
6	Ac	SO_3Na	Ac	f	160	S	176	d
8	Ac	Ac	SO_3Na	f	?	S	240	d
								
13	H	H	H	f	≈ 120	S	210	I
15	SO_3Na	H	H	f	205	S	225	I
12	Ac	Ac	Ac	f	< 20			I
14	SO_3Na	Ac	Ac	f	≈ 170			I [d]
								
17	H	SO_3Na		f	155	S	235	I
18	SO_3Na	H		f	172	S	236	I

[a] Abbreviations: Cr is the crystalline phase; f the solid phase; S the smectic phase; I the isotropic phase; and d the decomposition. [b] Temperatures (°). [c] Unknown transition at 210°. [d] S_A-phase formed after annealing at 120° (little decomposition).

Clearing points were reproducible only in freshly dried sulfated derivatives. However, these compounds are highly hygroscopic and absorb water upon being kept in the open air and consequently the clearing points decrease.

For the tetrasulfate **10**, no mesophase could be observed. At room temperature, compound **10** is a solid that shows the highest similarity to regular crystals as compared with the other sulfated derivatives. This optical isotropic-solid form did not change during heating to 202°. At 202°, compound **10** showed a distinct melting point with immediate decomposition, so that a possible mesophase could not be observed.

The acetylated monosulfates **2** and **12** only form lyotropic lamellar phases upon absorption of water. The acetylated 2,6-disulfates **4** and **14** do not show pure

mesophases. However, during annealing at 120° they slowly decompose and a well-pronounced fan texture points to the incipient formation of a S_A-phase. The 3,6- and 4,6-disulfates **6** and **8** show smectic phases. The closer the second sulfate group is positioned to the 6-sulfate, the higher are the measured clearing points.

The results for acetylated sulfates show that free hydroxy groups are not essential for the formation of amphiphilic carbohydrate liquid crystals. Instead of hydrogen-bond formation, the only general and important criteria for formation of amphiphilic liquid crystals is the intramolecular contrast[8,9]. By introduction of a sulfate function into glycosides the intramolecular contrast is intensified. As a consequence, such sterically disfavored molecules as **8** may form mesophases having very high clearing points. The better the separation of moieties of the molecule with different polarity, the higher is the clearing point.

Evidently, the class of ionic glycosides connect amphiphilic carbohydrate surfactants with thermotropic soaps. Although ionic glycosides cannot form more hydrogen bonds than their neutral analogues, they show markedly higher clearing points. Even the acetylated compounds that have no free hydroxy groups show clearing points above 200°. As a consequence it is obvious that only the intramolecular contrast within the derivatives can serve as an explanation for this liquid-crystalline behavior.

SURFACTANT PROPERTIES

The surface tension was measured according to the method of du Nouy[10] (Table IV). Introduction of an additional sulfate group increases the critical micellar

TABLE IV

Surfactant properties

Compound	Critical micelle concentration (mmol/L)	Surface tension (mN/m)	Concentration (mmol/L)
H_2O		72.0	
1	0.080 [a]	36.0	0.080
3	> 11.1	34.5	11.1
5	> 1.8	60.0	1.8
7	> 3.6	40.5	3.6
8 (acetate)	> 1.6	62.0	1.6
9	> 1.8	50.0	1.8
10	> 13.2	38.5	13.2
11	0.072	28.0	0.072
13	> 11.1	34.5	11.1
14	> 1.6	62.0	1.6
15	> 18.1	42.0	18.1
16	0.015 [b]	34.5	0.015
17	> 1.6	48.5	1.6

[a] Reported[11] value 0.19. [b] Reported[12] value 0.02.

concentration approximately 100-fold as a result of the electrostatic repulsions of the sulfate groups. For the disulfate **15**, no micelle formation could be observed up to a concentration of 18.1 mmol/L.

EXPERIMENTAL

General methods. — Reactions were monitored by TLC on Silica Gel 60 or reversed-phase RP-2 or RP-18 (GF_{254}, Merck) with detection by charring with 20% ethanolic H_2SO_4 and subsequent heating. For membrane filtration, glass-fiber filters (GF 2, Machery-Nagel) in a Sartorius membrane filter, and Minisart SRP 15 were used. For HPLC separation, Knaur equipment and the following columns were used: Nucleosil 100 (5 μm; 250 × 32, 16, or 8 mm; flow 40, 16, or 6 mL/min; 250, 50, or 5 mg samples) and reversed-phase RP-2 Nucleosil C_2 (7 μm; 250 × 20, or 10 mm; flow 24, or 6 mL/min; 250, or 50 mg sample). Specific rotations were determined at 20° with a Perkin–Elmer polarimeter. Microanalyses were performed by the Microanalytical Laboratory of the Organisch-Chemisches Institut, Universität Münster. NMR spectra were measured with Bruker WM 300 (^{1}H 300 MHz, ^{13}C 75.46 MHz) and AM 360 (^{1}H 360 MHz, ^{13}C 90.56 MHz) spectrometers. ^{1}H 2D-COSY and C,H-correlated spectra employed Bruker software 85 and 87 and an Aspect 3000 computer. Phase-transition temperatures were determined with an Olympus polarization microscope BH equipped with a Mettler FB 82 heating-stage. The liquid-crystalline phases were identified by characteristic textures as well as by contact preparations with reference compounds (non modified alkyl glycosides).

Solvent systems for separation of the sulfated alkyl glycosides. — *For TLC. A* (RP-2), 3:2 MeOH–H_2O; *B* (silica gel), 8:5:1:3 EtOAc–pyridine–AcOH–H_2O; *C* (silica gel), 10:4:1 butanol–AcOH–H_2O.

For chromatographic purification. Column *1* (MeOH–H_2O), reversed-phase RP-2 silica gel (40–63 μm), 110 × 40 mm column, normal pressure, maximum flow; column *2* (MeOH–H_2O), Nucleosil 100 RP-2 (7 μm), 250 × 40 mm column, 24 mL/min flow, 150–300 mg/mL.

6-Sulfated dodecyl glucosides (Method I). — Dodecyl glucoside (348 mg, 1 mmol) in dry pyridine (1.5 mL) was treated with a suspension of SO_3–pyridine complex (318 mg, 2 mmol) in dry pyridine (2 mL) at −10°. The mixture was allowed to warm to room temperature and stirring was continued for 24 h. The mixture was adjusted to pH 8–9 with M NaOH, diluted with H_2O and MeOH, and concentrated. The mixture of products was pre-separated on column *1* (9:11 MeOH–H_2O) into 4 fractions: 1, Na_2SO_4 and NaOH; 2, di- and 6-mono-sulfated products; 3, monosulfated product; 4, monosulfated products; (solvent systems *A* or *B*). Fractions 2, 3 and 4 were concentrated, filtered from traces of RP-2 silica gel by membrane filtration, and evaporated. The 6-monosulfated product was then isolated by repeated HPLC separation on column *2* (21:29 MeOH–H_2O). The

purified product was dissolved in H_2O and freeze-dried. The resultant fraction of disulfated products could be separated according to method *II*.

Disulfated dodecyl glucosides (Method II).—Dodecyl glycoside (348 mg, 1 mmol) in dry pyridine (3.5 mL) was stirred with a suspension of SO_3–pyridine complex (636 mg, 4 mmol) in dry pyridine (4 mL) for 24 h at room temperature. The mixture was adjusted to pH 8–9 with M NaOH, diluted with H_2O and MeOH and concentrated. Pre-separation into 4 fractions was performed on column *1* (2:3 MeOH–H_2O): 1, Na_2SO_4 and NaOH; 2, tri- and di-sulfated products; 3, disulfated products; 4, di- and mono-sulfated products. Fractions 2, 3, and 4 were combined, evaporated, filtered from traces of RP-2 silica gel by membrane filtration and again evaporated in vacuo. Repeated HPLC separation on column *2* (7:13 MeOH–H_2O) gave a mixture of disulfated products.

For further purification the mixture (553 mg, 1 mmol) of disulfated glucosides was acetylated in dry pyridine (10 mL) with Ac_2O (756 μL, 8 mmol) for 24 h at room temperature. Following evaporation with *p*-xylene (10 mL) from the product pre-separation on column *1* (1:1 MeOH–H_2O) gave two fractions. After evaporation and membrane filtration, purification was completed by two-fold chromatography on column *2* (7:13 MeOH–H_2O).

The individual acetates (637 mg, 1 mmol) were deacetylated in dry MeOH (5 mL) at room temperature with a catalytic amount of solid NaOMe (TLC, system *A*). Water (1 mL) was then added and the pH adjusted to ~ 8 with Amberlite IR-120 (H^+) resin. The deacetylated sulfate was separated from NaOH chromatography on column *2* (2:3 MeOH–H_2O), dissolved in H_2O, and freeze-dried.

Sodium dodecyl β-D-glucopyranoside 6-sulfate (**3**).—This compound was obtained from dodecyl β-D-glucopyranoside (**1** 2.50 g, 7.17 mmol) and SO_3–pyridine (2.28 g, 14.3 mmol) according to method *I* to yield 2.41 g (75%) of **3**; T_c 220.0° (dec.), $[\alpha]_{365}$ −52.8° (*c* 1, MeOH) together with disulfated glucosides (0.48 g, 12%); ^{1}H-NMR of **3** (300 MHz, CD_3OD): δ 4.31 (dd, H-6a), 4.28 (d, H-1), 4.13 9dd, H-6b), 3.86 (dt, H-1a-alkyl), 3.53 (dt, H-1b-alkyl), 3.49 (ddd, H-5), 3.38 (m_c, 2 H, H-3, H-4), 3.19 (dd ≈ t, H-2), 1.62 (q, 2 H, H-2-alkyl), 1.31 (br. s, 18 H, H-alkyl), 0.91 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.6, $J_{2,3}$ 9.4, $J_{4,5}$ 9.6, $J_{5,6a}$ 2.0, $J_{5,6b}$ 5.6, and $J_{6a,6b}$ 11.1 Hz; ^{13}C-NMR, see Table 1.

Anal. Calcd for $C_{18}H_{35}NaO_9S$

Sodium dodecyl 2,3,4-tri-O-acetyl-β-D-glucopyranoside 6-sulfate (**2**).—This compound was synthesised from **3** according to method *II*. ^{1}H-NMR (300 MHz, CD_3OD): δ 5.28 (dd ≈ t, H-3), 5.03 (dd ≈ t, H-4), 4.92 (dd, H-2), 4.67 (d, H-1), 4.13 (dd, H-6a), 4.08 (dd, H-6b), 3.94 (ddd, H-5), 3.91 (dt, H-1a-alkyl), 3.55 (dt, H-1b-alkyl), 2.07, 2.05, 2.00 (each s, 3 H, 3 OAc), 1.60 (q, 2 H, H-2-alkyl), 1.35 (br. s, 18 H, H-alkyl), 0.96 (t, 3H, CH_3-alkyl); $J_{1,2}$ 7.7, $J_{2,3}$ 9.7, $J_{3,4}$ 9.3, $J_{4,5}$ 10.3, $J_{5,6a}$ 3.6, $J_{5,6b}$ 5.1, and $J_{6a,6b}$ 10.3 Hz.

Disulfated dodecyl β-D-glucopyranosides.—These compounds were obtained from dodecyl β-D-glucopyranoside (**1**, 650 mg, 1.87 mmol) and SO_3–pyridine (1.19 g, 7.46 mmol) according to method *II* to yield a mixture of di (645 mg, 62%) and

tri-sulfated (230 mg, 12%) glucosides. The procedure according to method *II* gave the products described next.

Sodium dodecyl 3,4-di-O-acetyl-β-D-glucopyranoside 2,6-disulfate (**4**).—$[\alpha]_D$ +3.2° (*c* 1, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 5.29 (dd ≈ t, H-3), 5.01 (dd ≈ t, H-4), 4.62 (d, H-1), 4.34 (dd, H-2), 4.12 (dd, H-6a), 4.07 (dd, H-6b), 3.91 (ddd, H-5), 3.89 (dt, H-1a-alkyl), 3.63 (dt, H-1b-alkyl), 2.06 (s, 6 H, 2 OAc), 1.67 (q, 2 H, H-2-alkyl), 1.35 (br s, 18 H, H-alkyl), 0.94 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.5, $J_{2,3}$ 9.0, $J_{3,4}$ 9.4, $J_{4,5}$ 10.0, $J_{5,6a}$ 3.4, $J_{5,6b}$ 5.4, and $J_{6a,6b}$ 11.1 Hz.

Sodium dodecyl β-D-glucopyranoside 2,6-disulfate (**5**).—Yield: 185 mg (18%), T_c > 224.0° (dec.), $[\alpha]_D$ +25.5° (*c* 2.7, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 4.47 (d, H-1), 4.37 (dd, H-6a), 4.19 (dd, H-6b), 4.09 (dd, H-2), 3.88 (dt, H-1a-alkyl), 3.70 (dd ≈ t, H-3), 3.59 (dt, H-1b-alkyl), 3.56 (ddd, H-5), 3.47 (dd, H-4), 1.66 (q, 2 H, H-2-alkyl), 1.35 (br s, 18 H, H-alkyl), 0.94 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.6, $J_{2,3}$ 9.0, $J_{3,4}$ 8.6, $J_{4,5}$ 10.0, $J_{5,6a}$ 1.8, $J_{5,6b}$ 5.5, and $J_{6a,6b}$ 11.1 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{34}Na_2O_{12}S_2$ (552.6): C, 39.13; H, 6.20. Found: C, 38.91; H, 6.03.

Sodium dodecyl 2,4-di-O-acetyl-β-D-glucopyranoside 3,6-disulfate (**6**).—$[\alpha]_D$ −8.1° (*c* 1, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 5.03 (dd ≈ t, H-4), 4.90 (dd, H-2), 4.63 (d, H-1), 4.61 (dd ≈ t, H-3), 4.14 (dd, H-6a), 4.08 (dd, H-6b), 3.91 (dt, H-1a-alkyl), 3.89 (ddd, H-5), 3.55 (dt, H-1b-alkyl), 2.13, 2.10 (each s, 3 H, 2 OAc), 1.59 (q, 2 H, H-2-alkyl), 1.35 (br s, 18 H, H-alkyl), 0.96 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 8.0, $J_{2,3}$ 9.6, $J_{3,4}$ 9.2, $J_{4,5}$ 10.2, $J_{5,6a}$ 2.8, $J_{5,6b}$ 5.2, and $J_{6a,6b}$ 11.2 Hz.

Sodium dodecyl β-D-glucopyranoside 3,6-disulfate (**7**).—Yield: 290 mg (28%), T_c 215.0°, $[\alpha]_D$ −11.4° (*c* 1, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 4.40 (dd, H-6a), 4.39 (d, H-1), 4.29 (dd ≈ t, H-3), 4.15 (dd, H-6b), 3.92 (dt, H-1a-alkyl), 3.61 (ddd, H-5), 3.59 (dd, H-4), 3.58 (dt, H-1b-alkyl), 3.40 (dd, H-2), 1.66 (q, 2 H, H-2-alkyl), 1.35 (br s, 18 H, H-alkyl), 0.95 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.8, $J_{2,3}$ 9.3, $J_{3,4}$ 8.5, $J_{4,5}$ 10.0, $J_{5,6a}$ 1.8, $J_{5,6b}$ 5.8, and $J_{6a,6b}$ 10.8 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{34}Na_2O_{12}S_2$ (552.6): C, 39.13; H, 6.20. Found: C, 38.87; H, 6.08.

Sodium dodecyl 2,3-di-O-acetyl-β-D-glucopyranoside 4,6-disulfate (**8**).—$[\alpha]_D$ −10.2° (*c* 1, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 5.29 (dd ≈ t, H-3), 4.89 (dd, H-2), 4.65 (dd, H-6a), 4.61 (d, H-1), 4.28 (dd ≈ t, H-4), 4.09 (dd, H-6b), 3.94 (dt, H-1a-alkyl), 3.86 (ddd, H-5), 3.54 (dt, H-1b-alkyl), 2.05, 2.04 (each s, 3 H, 2 OAc), 1.59 (q, 2 H, H-2-alkyl), 1.34 (br s, 18 H, H-alkyl), 0.95 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 8.0, $J_{2,3}$ 9.7, $J_{3,4}$ 9.1, $J_{4,5}$ 10.0, $J_{5,6a}$ 2.0, $J_{5,6b}$ 8.3, and $J_{6a,6b}$ 11.4 Hz.

Sodium dodecyl β-D-glucopyranoside 4,6-disulfate (**9**).—Yield: 170 mg (16%); T_c > 240° (dec.), $[\alpha]_D$ −2.5° (*c* 1, H_2O); ^{1}H-NMR (300 MHz, 1:1 D_2O–CD_3OD): δ 4.52 (dd, H-6a), 4.43 (d, H-1), 4.09 (dd, H-4), 4.05 (dd, H-6b), 3.94 (dt, H-1a-alkyl), 3.81 (ddd, H-5), 3.74 (dd ≈ t, H-3), 3.65 (dt, H-1b-alkyl), 3.37 (dd, H-2), 1.66 (q, 2 H, H-2-alkyl), 1.31 (br s, 18 H, H-alkyl), 0.91 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 8.0, $J_{2,3}$ 9.0, $J_{3,4}$ 9.4, $J_{4,5}$ 10.0, $J_{5,6a}$ 1.9, $J_{5,6b}$ 8.1, and $J_{6a,6b}$ 11.3 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{34}Na_2O_{12}S_2$ (552.6): C, 39.13; H, 6.20. Found: C, 38.95; H, 6.11.

Sodium dodecyl β-D-glucopyranoside 2,3,4,6-tetrasulfate (**10**).—Dodecyl α-D-glucopyranoside (**1**, 0.65 g, 1.87 mmol), in dry pyridine (20 mL) was treated with SO_3–pyridine (3.56 g, 22.4 mmol) for 24 h at room temperature. Work-up was according to method *I* with the following modifications. Pre-separation on column *1* (1:4 MeOH–H_2O) gave 3 fractions: 1, Na_2SO_4 and NaOH; 2, tetrasulfate; 3, trisulfate. HPLC separation of fractions 2 and 3 on column *2* (1:4 MeOH–H_2O) yielded **10** (0.97 g, 69%), T_c 202.0°, $[\alpha]_D$ −21.7° (*c* 1, H_2O) and trisulfated glucosides (0.3 g, 25%); ^{1}H-NMR (300 MHz, D_2O): δ 4.74 (d, H-1), 4.63 (dd ≈ t, H-3), 4.42 (dd ≈ t, H-4), 4.30 (ddd ≈ t, H-2), 4.26 (dd, H-6a), 4.09 (dd, H-6b), 4.04 (m_c, H-5), 3.74 (dt, H-1a-alkyl), 3.52 (dt, H-1b-alkyl), 1.47 (q, 2 H, H-2-alkyl), 1.13 (br s, 18 H, H-alkyl), 0.69 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 4.8, $J_{2,3}$ 4.2, $J_{3,4}$ 5.4, $J_{4,5}$ 5.0, $J_{5,6a}$ 2.4, $J_{5,6b}$ 8.0, and $J_{6a,6b}$ 9.0 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{32}Na_4O_{18}S_4$ (756.7): C, 28.57; H, 4.26. Found: C, 28.01; H, 4.41.

Sodium dodecyl α-D-glucopyranoside 6-sulfate (**13**).—Dodecyl α-D-glucopyranoside (2.50 g, 7.17 mmol, **11**) was treated with SO_3–pyridine (2.28 g, 14.3 mmol) according to method *I* to yield **13** (1.65 g, 51%), T_c 210°, $[\alpha]_D$ +66.2° (*c* 1, MeOH), and disulfated glucosides (0.9 g, 23%); ^{1}H-NMR of **13** (300 MHz, CD_3OD): δ 4.75 (d, H-1), 4.22 (dd, H-6a), 4.16 (dd, H-6b), 3.73 (ddd, H-5), 3.71 (dt, H-1a-alkyl), 3.65 (dd ≈ t, H-3), 3.42 (dt, H-1b-alkyl), 3.40 (dd, H-2), 3.36 (dd ≈ t, H-4), 1.62 (q, 2 H, H-2-alkyl), 1.29 (br s, 18 H, H-alkyl), 0.89 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 3.8, $J_{2,3}$ 9.6, $J_{3,4}$ 9.0, $J_{4,5}$ 10.1, $J_{5,6a}$ 2.2, $J_{5,6b}$ 4.9, and $J_{6a,6b}$ 10.9 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{35}NaO_9S$ (450.5): C, 47.99; H, 7.83. Found: C, 47.40; H, 7.57.

Sodium dodecyl 2,3,4-tri-O-acetyl-α-D-glucopyranoside 6-sulfate (**12**).—This compound was obtained from **13** according to method *II*; ^{1}H-NMR (300 MHz, CD_3OD): δ 5.46 (dd ≈ t, H-3), 5.08 (d, H-1), 5.04 (dd ≈ t, H-4), 4.86 (dd, H-2), 4.12 (ddd, H-5), 4.09 (m_c, 2 H, H-6a, H-6b), 3.83 (dt, H-1a-alkyl), 3.46 (dt, H-1b-alkyl), 2.07, 2.05, 2.02 (each s, 3 H, 3 OAc), 1.68 (q, 2 H, H-2-alkyl), 1.41 (br s, 18 H, H-alkyl), 0.97 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 3.8, $J_{2,3}$ 10.4, $J_{3,4}$ 9.4, $J_{4,5}$ 9.5, $J_{5,6a}$ 3.2, and $J_{5,6b}$ 5.2 Hz.

Sodium dodecyl 3,4-di-O-acetyl-α-D-glucopyranoside 2,6-disulfate (**14**).—This compound was obtained from dodecyl α-D-glucopyranoside according to method *II*: $[\alpha]_D$ +80.1° (*c* 1, MeOH; ^{1}H-NMR (300 MHz, CD_3OD): δ 5.40 (dd ≈ t, H-3), 5.21 (d, H-1), 5.08 (dd ≈ t, H-4), 4.38 (dd, H-2), 4.08 (m_c, 3 H, H-5,6a,6b), 3.79 (dt, H-1a-alkyl), 3.55 (dt, H-1b-alkyl), 2.08, 2.07 (each s, 3 H, 2 OAc), 1.70 (q, 2 H, H-2-alkyl), 1.37 (br s, 18 H, H-alkyl), 0.96 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 3.7, $J_{2,3}$ 10.1, $J_{3,4}$ 9.4, and $J_{4,5}$ 10.1 Hz.

Sodium dodecyl α-D-glucopyranoside 2,6-disulfate (**15**).—This compound was obtained from dodecyl α-D-glucopyranoside (2.0 g, 5.74 mmol, **11**) and SO_3–pyri-

dine (3.65 g, 22.96 mmol) according to method *II*; yield: 2.3 g, 73%, T_c 240° (dec.), $[\alpha]_D$ +58.3° (*c* 1, CH_3OH). The yield of trisulfated products was 650 mg (17%). ^{1}H-NMR (300 MHz, CD_3OD): δ 5.13 (d, H-1), 4.22 (dd, H-6a), 4.19 (dd, H-6b), 4.17 (dd, H-2), 3.86 (dd ≈ t, H-3), 3.82 (ddd, H-5), 3.75 (dt, H-1a-alkyl), 3.50 (dt, H-1b-alkyl), 3.49 (dd, H-4), 1.66 (q, 2 H, H-2-alkyl), 1.35 (br. s, 18 H, H-alkyl), 0.96 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 3.7, $J_{2,3}$ 9.9, $J_{3,4}$ 9.0, $J_{4,5}$ 9.9, $J_{5,6a}$ 2.4, $J_{5,6b}$ 5.0, and $J_{6a,6b}$ 9.9 Hz; ^{13}C-NMR, see Table I.

Anal. Calcd for $C_{18}H_{34}Na_2O_{12}S_2$ (552.6): C, 39.13; H, 6.20. Found: C, 38.87; H, 6.06.

Sodium tetradecyl 4-O-(α-D-glucopyranosyl)-β-D-glucopyranoside 6'-sulfate (**17**) *and sodium tetradecyl 4-O-(α-D-glucopyranosyl)-β-D-glucopyranoside 6-sulfate* (**18**). —Tetradecyl 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranoside (**16**: 230 mg, 0.43 mmol) in dry pyridine (2 mL) was treated with a suspension of SO_3–pyridine (272 mg, 1.71 mmol) in dry pyridine (8 mL) at −10° according to method *I* with the following exceptions. Pre-separation on column *1* (11:9 MeOH–H_2O) gave 3 fractions: 1, Na_2SO_4 and NaOH; 2, disulfated products; 3, monosulfated products. HPLC separation of fraction 3 on column *2* (1:1 MeOH–H_2O) gave **17** (156 mg, 57%) and **18** (21 mg, 8%).

Compound **17** had $[\alpha]_D$ +33.2° (*c* 1, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 5.17 (d, H-1'), 4.33 (dd, H-6a'), 4.31 (d, H-1), 4.17 (dd, H-6b'), 4.02–3.24 (m, 14 H, ring protons, H-1a-alkyl, H-1b-alkyl), 1.68 (q, 2 H, H-2-alkyl), 1.36 (br. s, 22 H, H-alkyl), 0.95 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.8, $J_{1',2'}$ 3.8, $J_{5',6a'}$ 1.8, $J_{5',6b'}$ 5.8, and $J_{6a',6b'}$ 11.1 Hz; ^{13}C-NMR (90.56 MHz, CD_3OD): δ 104.2 (C-1), 103.0 (C-1'), 81.7 (C-4), 77.7 (C-3), 76.6 (C-5), 74.9 (C-3'), 74.0 (C-2, C-2'), 72.8 (C-5'), 71.2 (C-4'), 71.0 (OCH_2), 68.3 (C-6'), 62.2 (C-6), 33.0 (C-12-alkyl), 30.8, 30.7, 30.6 (C-alkyl), 30.4 (C-2-alkyl), 27.1 (C-3-alkyl), 23.7 (C-13-alkyl), and 14.4 (C-14-alkyl).

Anal. Calcd for $C_{26}H_{49}NaO_{14}S$ (640.7): C, 48.74; H, 7.71. Found: C, 48.40; H, 7.57.

Compound **18** had $[\alpha]_D$ +37.3° (*c* 0.2, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ 5.23 (d, H-1'), 4.43 (dd, H-6a), 4.31 (d, H-1), 4.21 (dd, H-6b), 3.97–3.22 (m, 12 H, ring protons, H-1a-alkyl, H-1b-alkyl), 1.66 (q, 2 H, H-2-alkyl), 1.35 (br. s, 22 H, H-alkyl), 0.95 (t, 3 H, CH_3-alkyl); $J_{1,2}$ 7.9, $J_{5,6a}$ 1.6, $J_{5,6b}$ 5.5, $J_{6a,6b}$ 11.0, and $J_{1',2'}$ 3.7 Hz.

Anal. Calcd for $C_{26}H_{49}NaO_{14}S$ (640.7): C, 48.74; H, 7.71. Found: C, 48.32; H, 7.45.

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