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Synthesis of sucrose-based surfactants through regioselective sulfonation of acylsucrose and the nucleophilic opening of a sucrose cyclic sulfate

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Abstract

Synthesis of a new class of anionic and amphoteric sucrose-based surfactants is described. Direct sulfonation of 6-*O*-acylsucrose using the pyridine–sulfur trioxide complex led to a mixture of the regioisomeric monosulfates, 6-*O*-acyl-4′–*O*-sulfosucrose and 6-*O*-acyl-1′-*O*-sulfosucrose, while sulfonation of 1′-*O*-acylsucrose afforded a mixture of 1′-*O*-acyl-6′-*O*-sulfosucrose and 1′-*O*-acyl-6-*O*-sulfosucrose. The ratio of regioisomers ranged from 4.7:1.0 to 7.5:1.0, depending on reaction time and the size of the fatty acyl chain. The regiospecific synthesis of 6-*O*-acyl-4-*O*-sulfosucrose derivatives was accomplished by nucleophilic substitution of the sucrose 4,6-cyclic sulfate using various fatty acids. The amphoteric 6-alkylamino-6-deoxy-4-*O*-sulfosucrose surfactants were also synthesized by nucleophilic substitution of the sucrose cyclic sulfate by different fatty amines. All the newly synthesized sucrose-based surfactants displayed excellent surface-active properties.

Keywords: Surfactants; Acylated sucrose; Sulfonation; Cyclic sulfate

1. Introduction

The regioselective synthesis of sucrose monoesters of fatty acids, including lauryl, myristyl, palmityl and stearyl, have already been reported by our group [1,2]. Chemical acylation, using a dibutylstannylene complex [1], affords 6-*O*-acylsucrose with 3-*O*-acylsucrose as the minor product. Enzymatic acylation of sucrose using subtilisin [2] affords 1′-*O*-acylsucrose and 1′,6′-di-*O*-acylsucrose as a minor product. These acylsucrose derivatives display better CMC values than the commercial nonionic surfactants. However, the stearoyl derivatives, having the longest fatty chain and expected to display the best CMC values, were water insoluble. We have focused our attention on the regioselective introduction of a polar sulfate group into these acyl derivatives to improve their water solubility as well as their CMC values.

The direct regioselective synthesis of *O*-acyl, *O*-sulfosucrose derivatives can be achieved by regioselective sulfonation of sucrose, followed by regioselective acylation, or by regioselective

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acylation, followed by regioselective sulfonation. Introduction of *O*-sulfo groups is usually done by directly treating hydroxyl groups with a common sulfonation reagent, including complexes of sulfur trioxide and Lewis base, such as *N,N*-dimethylformamide (DMF), pyridine or trialkylamine [3]. Other sulfonation reagents include sulfuric acid in presence of *N,N'*-dicyclohexylcarbodiimide [4] or acetic anhydride [5], piperidine-*N*-sulfonic acid [6], and chlorosulfonic acid [7,8]. The regioselective sulfonation of partially protected monosaccharides [9,10] and disaccharides [11] proceeds similarly to *O*-acylation. Sulfonation of the primary position is preferred, and the reaction progresses with the formation of isomeric primary monosulfates, followed by sulfonation of secondary hydroxyl groups. Dibutylstannanediyl acetals can also be used for the regioselective sulfonation of partially protected monosaccharides and disaccharides using the sulfur trioxide–triethylamine complex [12–14].

An *O*-sulfo group can also be introduced regiospecifically by performing the nucleophilic opening of a cyclic sulfate, this method being useful for both regiospecific introduction of nucleophile and sulfo groups. These nucleophilic reactions are well known for their high reactivity and the wide variety of available *O*-nucleophiles (phenolate, amine oxides or benzoate [15–18]), *S*-nucleophiles (thiocyanate, thiophenolate [16]), halide nucleophiles (tetraethyl or tetrabutyl ammonium fluoride or chloride [18–20]), *C*-nucleophiles (Grignard reagents [16,21], phenylithium, sodium phenylacetylide [18]), and *N*-nucleophiles (azide [17] and amines [18,22]). No cyclic sulfate synthesis of unprotected carbohydrates, in particular of sucrose, have been reported yet. However, the expected regiospecific opening of a cyclic sulfate makes this approach a very attractive and a potentially powerful way for the regiospecific synthesis of mono-*O*-sulfosucrose derivatives. Moreover, the use of a nucleophile having a fatty chain might lead to a new type of surfactant, in which both hydrophobic and sulfate moities are regiospecifically introduced.

Attempts to synthesize cyclic sulfates of unprotected sugars with sulfuryl chloride and pyridine have been reported [23,24]. However, the reaction has never been clean, and several side products were isolated. For example, reaction of sucrose with sulfuryl chloride at −78 °C afforded the 6,6'-dichloro-6,6'-deoxysucrose and 6'-chloro-6'-deoxysucrose in 43 and 29% yields, respectively. At room temperature, a complex mixture was formed from which 3',4'-anhydro-1',6'-dichloro-1',6'-dideoxy-β-D-*ribo*-hexulofuranoside 2,3-cyclic sulfate was isolated in 17% yield [25], showing that chlorination occured as well as inversion of configuration during cyclic sulfate formation. Thus, the reaction of sulfuryl chloride with carbohydrates containing free hydroxyl groups has become a well established method for the preparation of chlorodeoxysugars [23,26]. The conversion of a vicinal cis diol system to a cyclic sulfate in protected carbohydrates is readily accomplished with sulfuryl chloride. By using SO_2Cl_2, the methyl 4,6-*O*-benzilidene-β-D-mannopyranoside 2,3-cyclic sulfate [27], and 1,6-anhydro-4-*O*-benzyl-β-D-mannopyranoside 2,3-cyclic sulfate [28] were obtained in 60 and 85% yields, respectively.

The reaction of diols with thionyl chloride ($SOCl_2$) in the presence of an amino base give cyclic sulfites directly and in good yield [16], unlike the analogous reaction with sulfuryl chloride (SO_2Cl_2), which usually results in only very low yields of the corresponding cyclic sulfates. The ring strain energy (∼5–6 kcal mol^{-1}) [29] of 1,2 cyclic sulfates is most often cited as the reason of the very poor yields in their direct preparation from a diol and SO_2Cl_2 (or SO_2X_2) [27,30].

Cyclic sulfates are readily prepared through the oxidation of cyclic sulfites. Permanganate oxidation of the sulfite was originally the favored route to cyclic sulfates [31]. In 1981 Denmark [32] (1,3-cyclic sulfites) and in 1983 Lowe and Salamone [33] (1,2-cyclic sulfites) reported that the oxidation step was much cleaner when affected by a stoichiometric amount of ruthenium(IV) tetraoxide (RuO_4). Gao and Sharpless [16] reported the use of a catalytic amount of ruthenium(III) trichloride ($RuCl_3$) with $NaIO_4$ as a preparative method for the synthesis of cyclic sulfates from cyclic sulfites. Various syntheses of cyclic sulfates of mannitol and mannosides, using this method, reportedly gave good yields [28,34–37].

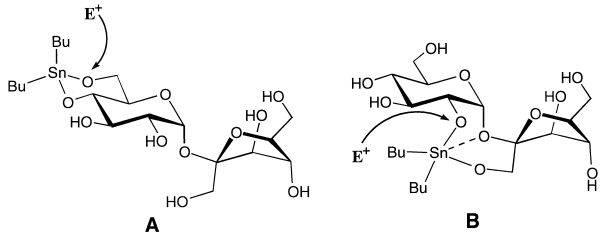
Another approach for the synthesis of cyclic sulfites and sulfates from protected carbohydrates relies on the use of *N,N'*-thionyldiimidazole [33] or *N,N'*-sulfuryldiimidazole [26], respectively. However, this chemistry requires the use of a strong base such as NaH. Phenyl chlorosulfate has also been reported to give the corresponding cyclic sulfate of protected sugars in 60–70% yields [39]. Only 1,2-cyclic sulfites of the unprotected

carbohydrates, glucose, galactose and mannose, have been synthesized using *N,N′*-thionyldiimidazole [39]. These cyclic sulfites were reportedly unstable and were used in situ in the reaction with azide. Klotz and Schmidt [40] recently reported the use of cyclic sulfate to prepare sugar-based surfactants. However, the cyclic sulfates synthesized from 1,2-fatty diols, were used for alkylation of glucose to obtain anomeric alkyl glycosides.

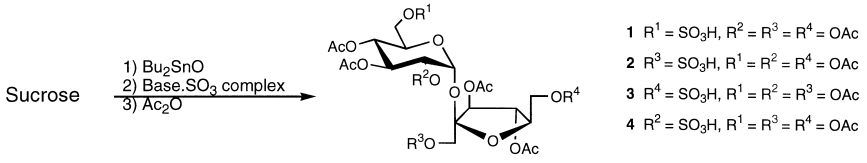
The regioselective introduction of fatty acyl groups into sucrose, either chemically [1] or enzymatically [2], leads to surface-active neutral sucrose esters. The synthesis of new sulfated surfactants in the present work demonstrates the regioselective sulfonation of *O*-acylsucrose derivatives and the nucleophilic opening of an intermediate cyclic sulfate to prepare anionic and amphoteric sucrose-based surfactants.

2. Results and discussion

Regioselective sulfonation of sucrose.—The regioselective sulfonation of sucrose was initially attempted by reacting the dibutylstannylenesucrose complex with various sulfur trioxide complexes including, $Pyr{\cdot}SO_3$, $NMe_3{\cdot}SO_3$ and $DMF{\cdot}SO_3$ complexes. The sucrose–stannylene complex was formed by refluxing sucrose and dibutyltin oxide in methanol for 3 h, followed by evaporation of the methanol. The resulting complex was then dissolved in anhydrous DMF and treated at 25 °C with 1.0 equivalent of sulfonating agent, with reaction time varying from 5 h ($Pyr{\cdot}SO_3$) to 24 h ($NMe_3{\cdot}SO_3$, $DMF{\cdot}SO_3$). The resulting *O*-sulfosucrose derivatives were acetylated to determine their sulfonation pattern by ^1H NMR spectroscopy. When using $Pyr{\cdot}SO_3$, a mixture of the three primary *O*-sulfo derivatives were obtained without any marked regioselectivity, as demonstrated by the ratio 6-*O*-sulfo- (**1**): 1′-*O*-sulfo- (**2**):6′-*O*-sulfo- (**3**) sucrose of 1.9:1.4:1.0 (Scheme 1). A lower temperature (4 °C) did not enhance the regioselectivity giving a ratio of **1:2:3** of 1.5:1.4:1.0. The use of $DMF{\cdot}SO_3$ led to a mixture of 6-*O*-sulfo- and 6′-*O*-sulfosucrose **1** and **3** with a limited regioselectivity of 1.2:1.0. The regioselectivity of this reaction, as well as the regioselective formation of 6-*O*-acyl derivatives during acylation of the sucrose–stannylene complex [1], is different from that observed for the formation of the 2-*O*-esters of some other α-D-hexopyranosides [41]. This sulfonation pattern suggests that sucrose has formed preferred six-membered stannylene acetal intermediate **A**, affording, upon reaction with the sulfur trioxide complex, an electrophilic substitution at the primary C-6 position. Surprisingly, sulfonation of sucrose–stannylene complex using $NMe_3{\cdot}SO_3$, after acetylation, led to a mixture of 1′,3,3′,4,4′,6,6′-hepta-*O*-acetyl-2-*O*-sulfosucrose (**4**, 68%) and 2,3,3′,4,4′,6,6′-hepta-*O*-acetyl-1′-*O*-sulfosucrose (**2**, 11%) (Scheme 1). The 6-*O*-sulfosucrose, which was expected to be the major sulfonation product, was not detected. When the same reaction was performed on uncomplexed sucrose, a mixture of 6-, 1′- and 6′-*O*-sulfosucrose derivatives **1, 2** and **3** was obtained in a ratio of 1.9:1.4:1.2. This different sulfonation pattern implies that the five-membered cyclic dibutylstannylene acetal **B**, involving both the C-2 and C-1′ hydroxyls of the glucopyranoside and fructofuranoside moieties as well as the anomeric oxygen was formed, leading to an electrophilic substitution at the C-2 position in the five-membered stannylene complex **B**.



The difference of regioselectivity observed when using different sulfur trioxide complexes suggests that both six-membered and five-membered ring stannylene complexes **A** and **B** are formed with sucrose, enhancing the nucleophicity of both the C-6 and C-2 hydroxyls of the glucopyranoside moiety. The fact that the electrophilic substitution occurs preferentially at the C-6 position with



Scheme 1. Sulfonation of sucrose-stannylene complex with trioxide complexes.

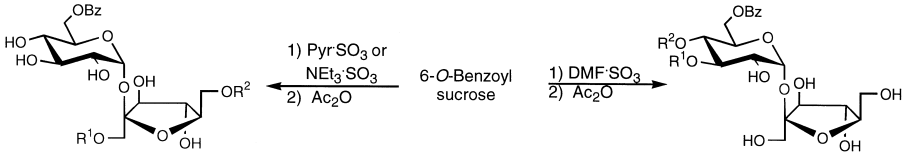
$Pyr{\cdot}SO_3$ and $DMF{\cdot}SO_3$ and at the C-2 position with $NMe_3{\cdot}SO_3$ seems to demonstrate that electrophilic substitutions on the sucrose–stannylene complex are governed by both the base and the nature and structure of the electrophile.

*Regioselective sulfonation of 6-*O*-benzoylsucrose*.—The 6-*O*-benzoylsucrose [42] was first studied as a model compound for *O*-acyl fatty esters of sucrose. Capillary electrophoresis (CE) was used to monitor the sulfonation reactions and to determine the ratio of benzoylsucrose, mono- and di-*O*-sulfo products. Our group has described the use of CE as an analytical tool for monitoring the sulfonation of *O*-benzyl sugars [42]. The sulfonation pattern was determined by ^1H NMR spectroscopy after acetylation of the reaction mixture and purification of the acetylated monosulfate sucrose derivatives. The sulfonation reaction was first performed in anhydrous DMF by adding 1 equiv of $Pyr{\cdot}SO_3$ complex to a solution of 6-*O*-benzoylsucrose. The CE data showed that the sulfonation occurred largely in the first 15 min and that a longer reaction time did not increase the conversion of starting material. To improve this conversion, the sulfonation reaction was next performed by adding 1 equiv of sulfonating agent three times at 15-min intervals ($Pyr{\cdot}SO_3$) or three times at 1.5-h intervals ($NMe_3{\cdot}SO_3$ and $DMF{\cdot}SO_3$). An aliquot of the reaction mixture was removed 15 min after each addition and analyzed by CE, and the ratios of mono- and di-*O*-sulfo derivatives were determined (Table 1). These results show the following: (1) $Pyr{\cdot}SO_3$ afforded faster sulfonation of 6-*O*-benzoylsucrose, the ratio 6-*O*-benzoylsucrose:mono-*O*-sulfo:di-*O*-sulfo derivatives of 1.9:1.0:0.2 being reached in 15 min with $Pyr{\cdot}SO_3$, compared to 1 h with $NMe_3{\cdot}SO_3$ and $DMF{\cdot}SO_3$; (2) $DMF{\cdot}SO_3$ afforded the best conversion of 6-*O*-benzoylsucrose to mono-*O*-sulfo product with little formation of di-*O*-sulfo product, but required longer reaction time; and (3) For both $NMe_3{\cdot}SO_3$ and $Pyr{\cdot}SO_3$, the conversion of 6-*O*-benzoylsucrose should not exceed 50% in order to keep a ratio mono:di-*O*-sulfo derivatives greater than 1.0:1.0.

Sulfonation using $Pyr{\cdot}SO_3$ and $NMe_3{\cdot}SO_3$ occurred as expected at the primary hydroxyls 1′

Table 1
Products ratio for the sulfonation of 6-*O*-benzoylsucrose at room temperature using $Pyr{\cdot}SO_3$, $NMe_3{\cdot}SO_3$ and $DMF{\cdot}SO_3$ complexes

Reaction time	$NMe_3{\cdot}SO_3$			$Pyr{\cdot}SO_3$		
	Benzoylsucrose:monosulfates:disulfates			Benzoylsucrose:monosulfates:disulfates		
1 equiv/15 min	7.5	1.0	0	1.9	1.0	0.2
+1 equiv/15 min	2.7	1.0	0.2	0.8	1.0	0.5
+1 equiv/15 min	1.2	1.0	0.4	0.6	1.0	0.7
					$DMF{\cdot}SO_3$	
1 equiv/15 min	7.5	1.0	0	5.8	1.0	0.10
30 min	nd	nd	nd	3.9	1.0	0.08
1 h	1.9	1.0	0.2	2.1	1.0	0.05
1.5 h	nd	nd	nd	1.1	1.0	0.04
+1 equiv/15 min	0.9	1.0	0.4	1.0	1.0	0.07
30 min	nd	nd	nd	0.6	1.0	0.06
1 h	0.5	1.0	0.8	0.4	1.0	0.06
1.5 h	nd	nd	nd	0.3	1.0	0.05
+1 equiv/15 min	0.3	1.0	0.9	0.2	1.0	0.05
30 min	nd	nd	nd	0.1	1.0	0.06
1 h	0.3	1.0	1.3	0.1	1.0	0.06
1.5 h	nd	nd	nd	0.05	1.0	0.05



5 $R^1 = SO_3H$, $R^2 = H$
6 $R^1 = H$, $R^2 = SO_3H$
7 $R^1 = R^2 = SO_3H$

8 $R^1 = SO_3H$, $R^2 = H$
9 $R^1 = H$, $R^2 = SO_3H$

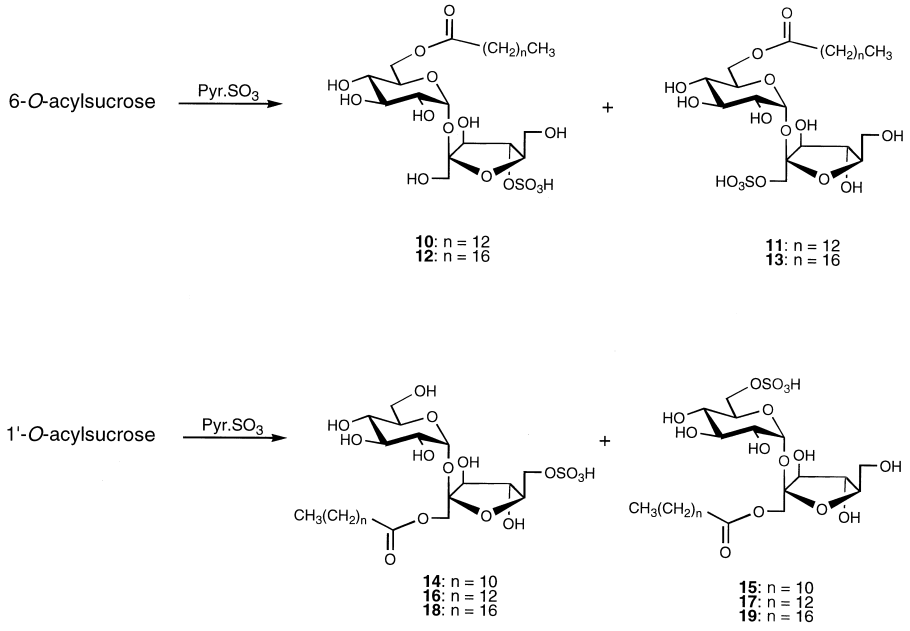
Scheme 2. Sulfation of 6-*O*-benzoylsucrose with sulfur trioxide complexes.

and 6′ but with limited regioselectivity (Scheme 2). A mixture of 2,3,3′,4,4′,6′-hexa-*O*-acetyl-6-*O*-benzoyl-1′-*O*-sulfosucrose **5** and 1′,2,3,3′,4,4′-hexa-*O*-acetyl-6-*O*-benzoyl-6′-*O*-sulfosucrose **6** with a ratio of 1.0:1.2 was obtained in both cases. Regioselectivity was slighty improved from 1.0:1.2 to 1.0:1.6 when the sulfonation with Pyr·SO_3, was performed at reduced temperature (4 °C). In these reactions, the 2,3,3′,4,4′-penta-*O*-acetyl-6-*O*-benzoyl-1′,6′-di-*O*-sulfosucrose **7** was also isolated in lower yield. Surprisingly, sulfonation of the 6-*O*-benzoylsucrose with DMF·SO_3 led to a mixture of 1′,2,3′,4,4′,6′-hexa-*O*-acetyl-6-*O*-benzoyl-3-*O*-sulfosucrose **8** and 1′,2,3,3′,4′,6′-hexa-*O*-acetyl-6-*O*-benzoyl-4-*O*-sulfosucrose **9** in a ratio of 1.2:1.0. Since Pyr·SO_3 gave the fastest sulfonation and the best product ratios, this sulfonation reagent was selected for further studies.

Regioselective sulfonation of 6-O-*acylsucrose and 1′*-O-*acylsucrose*.—Sulfonation of 6-*O*-acylsucrose and 1′-*O*-acylsucrose derivatives was next examined using Pyr·SO_3 complex under various reaction conditions. First, sulfonation of 6-*O*-myristoylsucrose was attempted in pyridine by adding 1 equiv of Pyr·SO_3 complex at three, 15-min intervals. The 6-*O*-myristoyl-4′-*O*-sulfosucrose **10** and 6-*O*-myristoyl-1′-*O*-sulfosucrose **12** were obtained in 25 and 2% yields, respectively (Scheme 3, Table 2). The 4′-*O*-sulfo group in **10** was unambiguously determined by ^{1}H NMR spectroscopy after acetylation of **10**. When the same reaction was performed by adding 1 equiv of Pyr·SO_3 complex two times at 15 min intervals and 1 more equiv for 12 h, the conversion of 6-*O*-myristoylsucrose was higher, and the mono-*O*-sulfo derivatives **10** and **11** were obtained in 70 and 10% yields, respectively (Table 2). If the reaction was run for 48 h after addition of the last equivalent of Pyr·SO_3 complex, the overall yield was improved from 80 to 91%; however, the regioselectivity was reduced from 7.0:1.0 to 1.6:1.0. The same results were observed for 6-*O*-lauroylsucrose and 6-*O*-stearoylsucrose (Table 2). The sulfonation of 1′-*O*-acylsucrose derivatives was performed in the same reaction conditions and led, in every case, to the formation of 1′-*O*-acyl-6′-*O*-sulfosucrose as major products and 1′-*O*-acyl-6-*O*-sulfosucrose as minor products, the yields and regioselectivity ratios being similar to those for the sulfonation of 6-*O*-acylsucrose derivatives (Table 2).

These results show that the presence of a long acyl chain induced a good regioselectivity during the sulfonation of acylsucrose. As expected, the sulfonation of 1′-*O*-acylsucrose derivatives occured at the primary C-6′ and C-6 hydroxyls. However, sulfonation of 6-*O*-acylsucrose derivatives occured primaraly at the secondary C-4′ hydroxyl and at the primary C-1′ hydroxyl.

Synthesis of sucrose cyclic sulfate.—The synthesis of the cyclic sulfite of unprotected sucrose was first attempted using thionyl chloride ($SOCl_2$) under a variety of conditions. When sucrose was



Scheme 3. Sulfonation of 6-*O*-acyl and 1′-*O*-acylsucrose with Pyr.SO_3 complex.

Table 2
Yields and CMC of sucrose-based surfactants

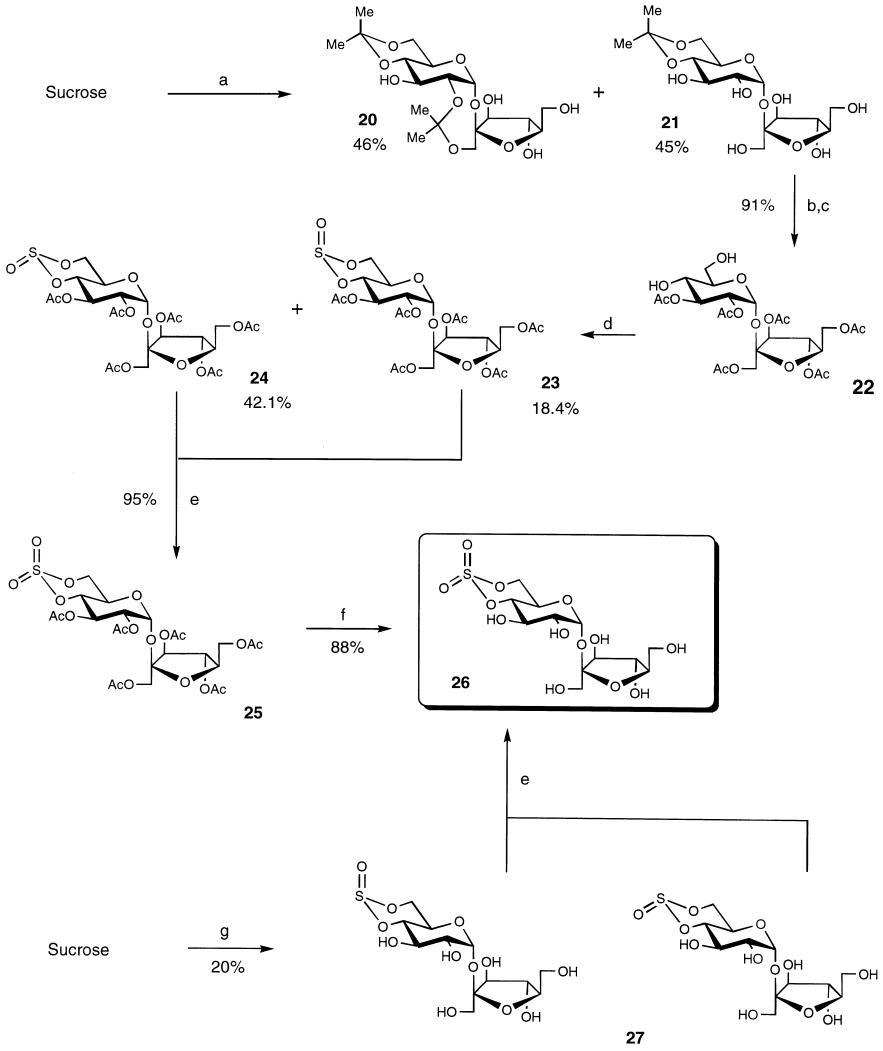
Entry	Surfactants	Yield			CMC	
		Direct sulfation		Cyclic sulfate opening	mol/L	mg/L
		12 h	48 h			
1	1′-*O*-lauroyl-6′-sulfosucrose **14**	75	56		6.5×10^{-5}	39.3
2	1′-*O*-lauroyl-6-sulfosucrose **15**	10	39		7.1×10^{-5}	42.9
3	1′-*O*-myristoyl-6′-sulfosucrose **16**	70	54		4.8×10^{-5}	30.3
4	1′-*O*-myristoyl-6-sulfosucrose **17**	15	35		5.2×10^{-5}	32.9
5	1′-*O*-stearoyl-6′-sulfosucrose **18**	67	60		4.7×10^{-6}	3.2
6	1′-*O*-stearoyl-6-sulfosucrose **19**	10	32		5.6×10^{-6}	3.9
7	6-*O*-myristoyl-4′-sulfosucrose **10**	70	56		5.3×10^{-5}	33.5
8	6-*O*-myristoyl-1′-sulfosucrose **11**	10	35		5.9×10^{-5}	37.3
9	6-*O*-stearoyl-4′-sulfosucrose **12**	74	64		3.3×10^{-6}	2.3
10	6-*O*-stearoyl-1′-sulfosucrose **13**	10	31		3.8×10^{-6}	2.6
11	6-*O*-palmitoyl-4-sulfosucrose **28**			75	4.8×10^{-5}	31.7
12	6-*O*-stearoyl-4-sulfosucrose **29**			72	1.1×10^{-5}	7.6
13	6-*O*-eicosanoyl-4-sulfosucrose **30**			60	n.s.	n.s.
14	6-*O*-hexadecylamino-4-sulfosucrose **31**			76	1.45×10^{-5}	9.4
15	6-*O*-octadecylamino-4-sulfosucrose **32**			60	n.s.	n.s.
16	1′-*O*-lauroylsucrose				1.5×10^{-4}	70.6
17	1′-*O*-myristoylsucrose				9.1×10^{-5}	50.2
18	1′-*O*-stearoylsucrose				n.s.	n.s.
19	6-*O*-lauroylsucrose				4.0×10^{-4}	209.6
20	6-*O*-myristoylsucrose				1.3×10^{-4}	71.8
21	6-*O*-stearoylsucrose				n.s.	n.s.
22	$C_{11}H_{25}SO_3Na$ [55]				1.2×10^{-3}	326.5
23	$C_{14}H_{23}SO_3Na$ [56]				2.5×10^{-3}	735.2
24	$C_{12}H_{25}OSO_3Na$ [57]				8.6×10^{-3}	2477.3
25	$C_{14}H_{23}OSO_3Na$ [58]				2.1×10^{-3}	651.0

n.s.—value not determined because of water insolubility of sample.

reacted in DMF with $SOCl_2$ (1.05 equiv) and pyridine (2.1 equiv) at room temperature, the formation of a major compound having a polarity similar to sucrose was observed by TLC. The ^{1}H NMR spectrum of this derivative, purified by flash chromatography (113 mg from 100 mg sucrose), showed a downfield shift for H-3′ ($\Delta\delta$ ~0.2 ppm) and upfield shifts for H-1′a,b ($\Delta\delta$ ~0.2 ppm), H-4′ ($\Delta\delta$ ~0.7 ppm), and one H-6′ ($\Delta\delta$ ~0.2 ppm). Protons attached to carbons involved in a cyclic sulfite are known to be shifted downfield. Thus the isolated compound was not a cyclic sulfite, and no further characterization of this product was performed. When the same reaction was performed in 1:1 DMF–CH_2Cl_2, an orange gel-like suspension was formed, and no product could be isolated. Next, reaction conditions were chosen which were as close as possible to those described in the literature, i.e., using protected sucrose and ethyl acetate solvent. The 1′,2,3,3′,4′,6′-hexa-*O*-acetylsucrose **22** was first synthesized using standard methods (Scheme 4).

Isopropylidenation of sucrose using 2,2′-dimethoxypropane (DMP) led to a mixture of 1′,2:4,6-di-*O*-isopropylidenesucrose **20** and 4,6-mono-*O*-isopropylidenesucrose **21** in 46 and 45% yields, respectively. Peracetylation of **22**, followed by deacetalation using acetic acid, afforded the 4,6-free diol **22** in 91% yield. The corresponding cyclic sulfites **22** and **23** were obtained by reacting **22** with $SOCl_2$ and pyridine in ethyl acetate at room temperature for 1.5 h. An excess of thionyl chloride (1.05 equiv, followed after 45 min by 0.5 equiv) was required for the complete conversion of **22**. The two new compounds observed by TLC were isolated, purified by silica gel chromatography and characterized. Fast-atom-bombardment mass spectrometry (FABMS) analysis of both compounds **23** and **24** showed a molecular ion peak $[M+Na]^+$ of 663, consistent with the molecular formula of the cyclic sulfite, suggesting that they were diastereomers. The structures of the cyclic sulfites **23** and **24** were confirmed by ^{1}H NMR spectroscopy. From NMR spectroscopy it was also possible to determine the configuration of the sulfoxide group. The significant deshielding [43–47] of protons that are syn-axial to an axial sulfoxide group can be used to assign the configuration at

the S→O center. For **23**, the chemical shifts of H-4 and one of the H-6 are significantly deshielded, compared to the free diol **22** ($\Delta\delta = 1.12$ ppm for H-4 and $\Delta\delta = 0.76$ ppm for H-6). From these observations it appeared that the sulfoxide group in **23** adopts an axial configuration. For **24**, the chemical shifts of H-5 and one of the H-6 are largely deshielded ($\Delta\delta = 0.74$ ppm for both), but H-4 is considerably less deshielded than in **23** ($\Delta\delta = 0.45$ ppm). These observations are in accordance with the



Reagents and conditions: (a) DMP (12 equiv), *p*-TsOH (cat), DMF, RT, 2 h; (b) Ac_2O, pyr., RT, 12 h; (c) 60% AcOH, 80 °C, 10 min; (d) $SOCl_2$ (1.5 x 1.05 equiv), pyr (1.5 x 2.05 equiv), EtOAc, RT, 1.5 h; (e) $RuCl_3$ (cat), $NaIO_4$ (2 equiv), 1:1.5 CH_3CN-H_2O, RT, 1 h; (f) NEt_3 (1.1 equiv), CH_3OH, RT, 12 h; (g) $SOCl_2$ (1.5 x 1.05 equiv), pyr (1.5 x 2.05 equiv), 1:1 DMF-EtOAc, RT, 1.5 h.

Scheme 4. Synthesis of sucrose 4,6-cyclic sulfate.

Table 3
Cyclic sulfite synthesis from 1′,2,3,3′,4′,6′-hexa-*O*-acetylsucrose (**22**)

Entry	Equiv $SOCl_2$	Base	Equiv base	T	**23**	**24**	Ratio **23:24**	Overall yield
1	1.05 + 0.5	Pyr	2.10 + 1.05	RT	18.4%	42.1%	1.0:2.3	60.5%
2	1.05 + 0.5	Pyr	2.10 + 1.05	0 °C	17.4%	22.9%	1.0:1.3	40.3%
3	1.05 + 0.5	NEt_3	2.10 + 1.05	RT	36.1%	18.3%	2.0:1.0	54.4%
4	1.05 + 0.5	NEt_3	2.10 + 1.05	0 °C	30.8%	13.7%	2.2:1.0	44.5%
5	1.05 + 0.5	Pyr	5.25 + 2.5	RT	25.3%	9.0%	2.8:1.0	34.3%
6	1.50	Im	6.0	0 °C	27.9%	11.9%	2.3:1.0	39.8%

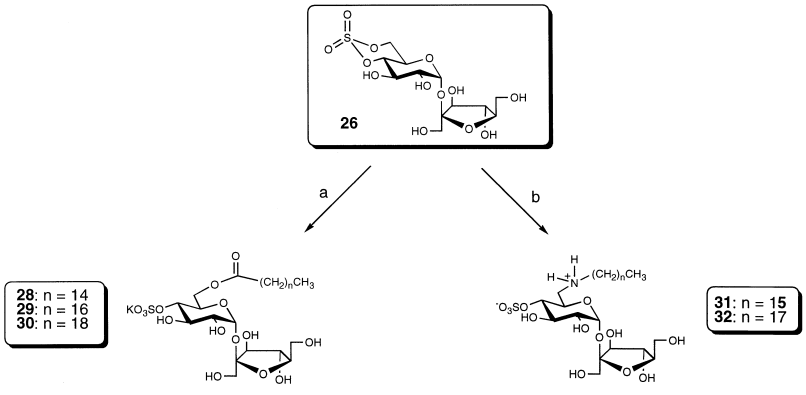
equatorial configuration of the sulfoxide in **24**. This reaction was repeated with different bases and at different temperatures, and the resulting overall yields ranged from 34 to 61% (Table 3). For a given base, the yields in cyclic sulfites **23** and **24** were 10–20% higher when the reaction was performed at room temperature than at 0 °C (Table 3). These results also show that the formation of the axial sulfite **23** was favored by a lower reaction temperature and by the presence of triethylamine. It should be noted that at the end of each reaction the pH of the reaction mixture was acidic (pH 2–3), which could explain the relatively modest yields obtained. When the same reaction was performed with an excess of pyridine to neutralize this acidity, the axial cyclic sulfite **23** became the predominant product, but the resulting overall yield did not increase. This could result from a partial hydrolysis of the cyclic sulfite, which is known to occur at pH >7 [48]. *N,N′*-thionyldiimidazole was also used in an effort to avoid the formation of acid during the reaction, but no improvement in yield was obtained (Table 3).

Cyclic sulfites **23** and **24** were oxidized using a catalytic amount of $RuCl_3$ with a stochiometric amount of sodium periodate ($NaIO_4$) in a mixture of acetonitrile and water (1.0:1.5). The cyclic sulfate **25** was readily obtained in excellent yield (95%). Deacetylation of 25 under standard conditions (triethylamine and methanol) led to the corresponding cyclic sulfate **26** in 88% yield. The cyclic sulfate was stable under deacetylation conditions, while the cyclic sulfite was not.

Next, the same reaction was performed on unprotected sucrose in a mixture of 1:1 DMF–ethyl acetate using $SOCl_2$ (1.5×1.05 equiv) and pyridine (1.5×2.10 equiv). After 2 h, the 4,6-cyclic sulfite **27** was isolated in a 20% yield. Some glucose derivatives were also obtained, indicating that hydrolysis of the glycosidic bound occured under the reaction conditions. Unfortunately, catalytic oxidation of the cyclic sulfite only afforded trace amounts of the cyclic sulfate by TLC. The presence of free hydroxyls might have been responsible for the loss of catalyst activity of the ruthenium tetroxide [49–51].

Cyclic sulfate opening with an O-*nucleophile*.— Once the sucrose cyclic sulfate had been synthesized, we focused our attention on the nucleophilic opening of the cyclic sulfate using *O*-nucleophiles (palmitic, stearic and eicosanoic acids) and *N*-nucleophiles (hexadecylamine and octadecylamine), as shown in Scheme 5. When cyclic sulfate **26** was reacted at room temperature in DMF with a slight excess (1.2 equiv) of palmitic acid and potassium bicarbonate, no reaction occured. However, when heated at 80 °C for 3 h, the 6-*O*-palmityl-4-*O*-sulfosucrose **28** was regiospecifically obtained in 75% yield. The 4-position of O-sulfonation was confirmed by acid catalyzed hydrolysis of **28**. The ^1H NMR spectrum of the resulting compound showed that the chemical shift of H-4 was largely deshielded ($\Delta\delta = -0.95$ ppm) while the H-5, H-6a and H-6b chemical shifts were moderately shielded ($\Delta\delta = +0.1$a, -0.30 and $+0.10$ ppm, respectively). The same reaction, performed with stearic acid and eicosanoic acid under identical conditions, led to the 6-*O*-stearoyl-4-*O*-sulfosucrose **29** and 6-*O*-eicosanoyl-4-*O*-sulfosucrose **30** in 72 and 70% yields, respectively (Scheme 5).

Cyclic sulfate opening with an N-*nucleophile*.— Reaction of the sucrose cyclic sulfate **28** with a



Reagents and conditions: (a) $CH_3(CH_2)_nCO_2H$ (1.2 equiv), K_2CO_3 (1.2 equiv), DMF, 80 °C, 2 h; (b) $CH_3(CH_2)_nNH_2$, DMF, 80 °C, 20 h

Scheme 5. Nucleophilic opening of sucrose-4,6-cyclic sulfate by O- and N-nucleophiles.

slight excess of hexadecylamine or octadecylamine in DMF, at 80 °C for 17 h led to the corresponding amphoteric 6-deoxy-6-hexadecylamino-4-*O*-sulfosucrose **33** and 6-deoxy-6-octadecylamino-4-*O*-sulfosucrose **34** in 76 and 60% yields, respectively.

Surface activity of O-*acyl*-O-*sulfosucrose derivatives*.—All the new synthesized *O*-acyl-*O*-sulfosucrose derivatives displayed surface-active properties (Table 2). In aqueous solution, at a specific concentration known as the critical micellar concentration (CMC), these molecules aggregate in micelles. This CMC value is of practical importance since it is the minimal concentration of surfactant required to solubilize hydrophobic molecules in water. Our laboratory recently demonstrated that a colorimetric method for CMC determination was useful for the accurate analysis of sucrose-based surfactants [2]. This dye solubilization method was used to determine the CMC of the sulfated sucrose surfactants.

The CMC values measured for the 6- and 1′-*O*-acylsucrose derivatives were more than an order of magnitude lower than that of commercially prepared ionic and nonionic surfactants (Table 2). As expected, the CMC values decrease with longer acyl chain. The introduction of an *O*-sulfo group into these *O*-acylsucrose derivatives led to improved surface activity, resulting in CMC values of 1–2 orders of magnitude lower than the corresponding *O*-acylsucrose derivatives, the *O*-stearoyl-*O*-sulfosucrose derivatives **12, 13, 29** displayed exceptionally low CMC values, while the *O*-eicosanoyl-*O*-sulfosucrose **31** was insufficiently soluble in water to determine its CMC value. The 6-*O*-hexadecylamino-4-*O*-sulfosucrose derivative **31** also has a very low CMC value, making this amphoteric sufactant a very attractive target for further study. At a given acyl chain size, the 1′-*O*-acyl monoesters and their *O*-sulfo derivatives show slightly lower CMC values than the corresponding 6-*O*-acyl derivatives. In both the 1′-*O*-acyl and 6-*O*-acyl series, the different sulfonation position, 6′/6 or 4′/1′, respectively, does not affect the CMC value. However, the 6-*O*-stearoyl-4-*O*-sulfosucrose **29** displays a CMC value 3-times higher than the 6-*O*-stearoyl-4′-*O*-sulfosucrose **12** and 6-*O*-stearoyl-1′-*O*-sulfosucrose **13**. These difference in surface activity could be the result of the relative position of both acyl chain and sulfate group. In aqueous solution, these anionic surfactants lead to micelles in which the hydrophobic acyl chains constitue the interior of the micelle, while the hydroxyl and sulfo groups are localized on the external surface of the micelle. These structures are easier to form if the acyl chain and sulfo group are far apart from each other. The proximity of the 6-*O*-acyl chain and the 4-*O*-sulfo group in **29** could then explain this increase of CMC value.

3. Conclusions

New *O*-acyl-*O*-sulfosucrose-based surfactants have been synthesized using two different approaches. The first one, involving the direct sulfonation of fatty *O*-acylsucrose, occurs regioselectively at the 4′- and 1′- positions for the 6-*O*-acylsucrose derivatives and at the 6′- and 6-positions for the 1′-*O*-acylsucrose derivatives. The best yields, 77–85%, and regioselectivities, 4.7:1.0 to 7.5:1.0, were obtained by adding 1 equiv of the $Pyr{\cdot}SO_3$ three times at 15 min intervals with a 12 h reaction time. A second approach was also described that involved the regiospecific nucleophilic opening of an intermediate sucrose 4,6-cyclic sulfate. Ring opening with fatty acids led to anionic sucrose-based surfactants in 70–75% yields, having the fatty acyl chain and the sulfate group in the 6- and 4-positions, respectively, while amphoteric 6-deoxy-6-alkylamino-4-*O*-sulfosucrose surfactants were obtained in 60–76% yields using fatty amines.

All these new anionic and amphoteric sucrose-based-surfactants display exceptional surface-active properties with CMC values from two to three orders of magnitude lower than those of commercial anionic surfactants. These new sucrose-based surfactants are prepared using inexpensive renewable starting materials, display very good surface-active properties, should be biodegradable, and thus, may represent surfactants of potential commercial value.

4. Experimental

General procedures.—^{1}H NMR spectra were recorded at 25 °C in deuteried solvent on a Varian Unity 500 MHz spectrometer. Chemical shifts were recorded in ppm (δ) and coupling constants in Hz, relative to tetramethylsilane as internal standard. The ^{1}H NMR spectra were fully assigned by the use of single-frequency decoupling. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. CE was performed on a Dionex CE

system (Sunnyvale, CA) equipped with a variable wavelength detector. All analyses used a fused silica capillary tube (75 μm i.d., 375 μm o.d., and 75 cm long) from Dionex. Operating buffer was 10 mM sodium borate, 50 mM sodium dodecylsulfate adjusted to pH 8.8 with N HCl. Thin-layer chromatography (TLC) was performed using E. Merck plates of Silica Gel 60 with fluorescent indicator. Visualization was effected by spraying plates with Von's reagent (1.0 g of ceric ammonium sulfate and 24.1 g of ammonium molybdate in 31 mL of sulfuric acid and 470 mL of water), followed by heating at 140 °C. Flash chromatography was conducted with silica gel (230–430 mesh, E. Merck). Dichloromethane (CH_2Cl_2), *N,N*-dimethylformamide (DMF), ethyl acetate (EtOAc) and pyridine (Pyr) were anhydrous solvents available from Aldrich. The colorimetric CMC determination [52] used uniformly precoated plastic balls that were purchased from Pro Chem, Inc. (Rockford, IL). The absorption of the dye was measured at 612 nm on Shimadzu UV-60 spectrophotometer. All the acylsulfosucrose derivatives were hygroscopic, preventing their elemental analysis by ordinary combustion methods. The purity and identity of these surfactants were assessed based on the absence of extraneous signals in their ^{1}H NMR spectra and on the expected molecular ion by high-resolution mass spectrometry.

Regioselective sulfonation of the stannylene-sucrose complex.—A mixture of sucrose (500 mg, 1.46 mmol), di-*n*-butyltin oxide (375 mg, 1.50 mmol) and CH_3OH (10 mL) was refluxed for 3 h. The clear solution was evaporated in vacuo to dryness. The resulting white crystals were coevaporated three times with 10 mL of anhydrous toluene. Anhydrous DMF (5 mL) and sulfur trioxide complex (mg, 1.50 mmol) were added under inert gas. The reaction mixture was stirred at room temperature for 5 h with Pyr·SO_3 complex or 24 h with NMe_3·SO_3 and DMF·SO_3 complexes. The reaction mixture was extracted twice with petroleum ether to remove the organotins and evaporated in vacuo. The residue was dissolved in water and eluted on a resin Dowex-1×2 200-mesh ion-exchange (Cl^-) resin. The unreacted sucrose was eluted first with water, and the sulfonated products were then eluted with aqueous sodium chloride. This fraction was concentrated by evaporation in vacuo and desalted by elution through a Bio-Gel P-2 column. The resulting sulfonated mixture was acetylated under standard conditions (acetic anhydride and pyr), and the acetyl sulfosucrose derivatives were purified by chromatography on silica gel (9:1 $CHCl_3$–CH_3OH). The acetylated 2-, 6-, 1′- and 6′-*O*-sulfosucroses **1–4** were not separable. The ratios of the different reaction mixtures were determined by ^{1}H NMR spectroscopy.

Direct O-*sulfonation of acylsucrose esters*.—Acylsucrose [1,2] (150 mg) was dissolved in 5 mL of pyr at room temperature, under nitrogen. At three, 15-min intervals Pyr·SO_3 complex (1 equiv) was added. The reaction mixture was stirred for 12 h (or 48 h) at room temperature, under nitrogen. Solvent was evaporated in vacuo, and the last traces of pyr were removed by co-evaporation three times with a 10-mL portion of toluene. The remaining residue was subjected to flash chromatography (4:1 $CHCl_3$–CH_3OH).

Synthesis of 6-O-*acyl-4*-O-*sulfosucrose derivatives*.—To a solution of sucrose cyclic sulfate (50 mg, 0.12 mmol) in anhydrous DMF (5 mL) under nitrogen was added K_2CO_3 (1.2 equiv) and the fatty acid (1.2 equiv). The reaction mixture was heated at 80 °C for 3 h. After cooling at room temperature, the reaction mixture was evaporated in vacuo. Purification by chromatography on silica gel (3:1, $CHCl_3$–CH_3OH) afforded the corresponding 6-*O*-acyl-4-*O*-sulfosucrose derivative.

Synthesis of 6-O-*alkylamino-6*-O-*deoxy-4*-O-*sulfosucrose derivatives*.—To a solution of cyclic sulfate sucrose (50 mg, 0.12 mmol) in anhydrous DMF (5 mL) and under nitrogen the fatty amine (1.2 equiv) was added. The reaction mixture was heated at 80 °C for 17 h. After cooling at room temperature, the reaction mixture was evaporated in vacuo. Purification by chromatography on silica gel (3:1 $CHCl_3$–CH_3OH) afforded the corresponding 6-*O*-alkylamino-6-*O*-deoxy-4-*O*-sulfosucrose derivatives.

1′,2,3,3′,4,4′,6′-Hepta-O-*acetyl-6*-O-*sulfosucrose* (**1**).—Sulfonation of the sucrose–stannylene complex (sucrose 500 mg) using Pyr·SO_3 (24 mg) or DMF·SO_3 (23 mg) complexes afforded, after acetylation and purification by chromatography on silica gel, **1** in 47 and 43% yields, respectively. Compound **1** could not be separated from the regioisomeric monosulfates **2** and **3**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.20 (m, 21 H, 7 C(O)CH_3), 4.24–4.36 (m, 7 H, H-1′a, H-1′b, H-5, H-5′, H-6b, H-6′a and H-6′b), 4.42–4.46 (m, 1 H, H-6a), 4.94 (1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.9 Hz, H-2), 5.07 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.6 Hz, H-4), 5.42 (t, 1 H, $J_{3',4'}$

and $J_{4',5'}$ 6.6 Hz, H-4′), 5.43 (t, 1 H, H-3), 5.45 (d, 1 H, H-3′), 5.62 (d,1 H, H-1).

2,3,3′,4,4′,6,6′-Hepta-O-*acetyl-1′*-O-*sulfosucrose* (**2**).—Sulfonation of the sucrose–stannylene complex (sucrose 500 mg) using Pyr·SO_3 (24 mg) or DMF·SO_3 (23 mg) afforded, after acetylation and purification by chromatography on silica gel, **2** in 24 and 11% yields, respectively. Compound **2** could not be separated from the regioisomeric monosulfates, **1** and **3**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.18 (m, 21 H, 7 C(O)CH_3), 4.02 (d, 1 H, $J_{1'a,b}$ 12.1 Hz, H-1′b), 4.31–4.35 (d, 1 H, H-1′a), 4.14–4.26 (m, 6 H, H-1′a, H-5′, H-6a, H-6b, H-6′a and H-6′b), 4.27–4.31 (m, 1 H, H-5), 4.82 (dd, 1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.9 Hz, H-2), 5.06 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.9 Hz, H-4), 5.42 (m, 2 H, H-3 and H-4′), 5.51 (d, 1 H, $J_{3',4'}$ 6.2 Hz, H-3′), 5.62 (d, 1 H, H-1).

1′,2,3,3′,4,4′,6-Hepta-O-*acetyl-6′*-O-*sulfosucrose* (**3**).—Sulfonation of the sucrose–stannylene complex (sucrose 500 mg) using Pyr·SO_3 (24 mg) or DMF·SO_3 (23 mg) complexes afforded, after acetylation and purification by chromatography on silica gel, **3** in 34 and 36% yields, respectively. Compound **3** could not be separated from the regioisomeric monosulfates **1** and **2**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.20 (m, 21 H, 7 C(O)CH_3), 4.05 (dd, 1 H, $J_{5',6'a}$ 4.5 Hz, $J_{6'a,b}$ 11.8 Hz, H-6′b), 4.12 (m, 1 H, H-6′a), 4.24–4.36 (m, 5 H, H-1′a, H-1′b, H-5, H-5′ and H-6b), 4.38 (m, 1 H, H-6a), 4.82 (1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.92 Hz, H-2), 5.06 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.7 Hz, H-4), 5.42 (t, 1 H, H-3), 5.46 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 6.6 Hz, H-4′), 5.52 (d, 1 H, H-3′), 5.74 (d, 1 H, H-1).

1′,3,3′,4,4′,6,6′-Hepta-O-*acetyl-2*-O-*sulfosucrose* (**4**).—Sulfonation of the sucrose–stannylene complex (sucrose 500 mg) using the NMe_3·SO_3 complex (21 mg) afforded, after acetylation and purification by chromatography on silica gel, **4** in a 68% yield. Compound **4** could not be separated from the regioisomeric monosulfate **2**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.03–2.19 (m, 21 H, 7 C(O)CH_3), 4.14–4.18 (m, 3 H, H-1′a, H-1′b and H-6′b), 4.20 (m, 1 H, H-5′), 4.22 (d, 1 H, $J_{6a,b}$ 12.1 Hz, H-6b), 4.30 (m, 1 H, H-5), 4.34 (dd, 1 H, $J_{5',6'a}$ 3.8 Hz, $J_{6'a,b}$ 12.1 Hz, H-6′a), 4.43 (d, 1 H, H-6a), 4.48 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.85 Hz, H-2), 5.05 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.6 Hz, H-4), 5.35 (t, 1 H, H-3), 5.45 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.7 Hz, H-4′), 5.53 (d, 1 H, H-3′), 5.83 (d, 1 H, H-1).

2,3,3′,4,4′,6′-Hexa-O-*acetyl-6*-O-*benzoyl-1′*-O-*sulfosucrose* (**5**) *and 1′,2,3,3′,4,4′-hexa*-O-*acetyl-6*-O-*benzoyl-6′*-O-*sulfosucrose* (**6**).—To 6-*O*-benzoylsucrose (45 mg, 0.1 mmol) dissolved in anhydrous DMF (1.0 mL) and maintained under nitrogen was added Pyr·SO_3 (16 mg) three times at 15-min intervals, and the reaction mixture was stirred at room temperature. A 5-μL sample of the reaction mixture was removed 15-min after the addition of each equivalent of sulfonating agent, quenched with 15-μL of water, and analyzed by CE. At the end of the reaction, the reaction mixture was quenched with water and evaporated in vacuo. The residue was acetylated under standard conditions and purified by chromatography on silica gel (9:1 $CHCl_3$–CH_3OH) to afford **5** (22%) and **6** (18%). The regioisomeric sulfosucrose **5** and **6** could not be separated. Data for **5**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.09 (m, 18 H, 6 C(O)CH_3), 4.06 (dd, 1 H, $J_{1'a,b}$ 12.1 Hz, H-1′b), 4.16–4.28 (m, 3 H, H-5′, H-6′a and H-6′b), 4.24 (d, 1 H, H-1′a), 4.36–4.44 (m, 2 H, H-5 and H-6b), 4.53 (d, 1 H, $J_{6a,b}$ 12.1 Hz, H-6a), 4.82 (dd, 1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.7 Hz, H-2), 5.28 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.4 Hz, H-4), 5.30 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.8 Hz, H-4′), 5.47 (t, 1 H, H-3), 5.61 (d, 1 H, H-3′), 5.73 (d, 1 H, H-1). Data for **6**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.00–2.09 (m, 18 H, 6 C(O)CH_3), 4.23–4.29 (m, 5 H, H-1′a, H-1′b, H-5′, H-6′a and H-6′b), 4.36–4.43 (m, 2 H, H-5 and H-6b), 4.66 (d, 1 H, $J_{6a,b}$ 12.2 Hz, H-6a), 4.88 (dd, 1 H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.7 Hz, H-2), 5.20 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.3 Hz, H-4), 5.36 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 6.9 Hz, H-4′), 5.45 (t, 1 H, H-3), 5.61 (d, 1 H, H-3′), 5.65 (d, 1 H, H-1).

2,3,3′,4,4′-Penta-O-*acetyl-6*-O-*benzoyl-1′,6′-di*-O-*sulfosucrose* (**7**).—Compound **7** (28%) was isolated from the previous reaction mixture, together with some other minor disulfate regioisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99–2.19 (5 s, 15 H, 5 C(O)CH_3), 4.02 (dd, 1 H, $J_{1'a,b}$ 11.0 Hz, H-1′b), 4.17 (d, 1 H, H-1′a), 4.22 (m, 1 H, H-6′b), 4.14–4.37 (m, 2 H, H-5′ and H-6′a), 4.47–4.50 (m, 2 H, H-5 and H-6b), 4.57 (m, 1 H, $J_{6a,b}$ 12.1 Hz, H-6a), 4.92 (dd, 1 H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.3 Hz, H-2), 5.21 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 5.34 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 5.6 Hz, H-4′), 5.47 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 5.59 (d, 1 H, H-3′), 5.68 (d, 1 H, H-1).

1′,2,3′,4,4′,6′-Hexa-O-*acetyl-6*-O-*benzoyl-3*-O-*sulfosucrose* (**8**) *and 1′,2,3,3′,4′,6′-hexa*-O-*acetyl-6*-O-*benzoyl-4*-O-*sulfosucrose* (**9**).—To 6-*O*-benzoylsucrose (45 mg, 0.1 mmol) dissolved in anhydrous DMF (1.0 mL) and maintained under nitrogen, was added DMF·SO_3 (15 mg) three times at 1.5 h intervals, and the reaction mixture was stirred at room temperature. A 5-μL sample of the reaction

mixture was removed 15 min, 30 min, 1 h and 1.5 h after addition of each equiv of sulfonating agents, quenched with 15 μL of water, and analyzed by CE. At the end of the reaction, the reaction mixture was quenched with water and evaporated in vacuo. The residue was acetylated under standard conditions and purified by chromatography on silica gel (9:1 $CHCl_3$–CH_3OH) to afford **8** (38%) and **9** (32%). The regioisomers **8** and **9** were not separable. Data for **8** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99–2.16 (m, 18 H, 6 C(O)CH_3), 4.02 (m, 1 H, H-5′), 4.25 (m, 1 H, H-5), 4.31 (m, 1 H, H-6′b), 4.37 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, $J_{6a,b}$ 12.0 Hz, H-6b), 4.41–4.45 (d, 2 H, H-1′a and H-1′b), 4.55 (m, 1 H, H-6a), 4.59 (m, 1 H, H-6′a), 4.81 (t, 1 H, $J_{2,3}$ and $J_{3,4}$ 9.3 Hz, H-3), 5.15 (d, 1 H, $J_{3',4'}$ 7.6 Hz, H-3′), 5.26 (t, 1 H, $J_{4,5}$ 10.1 Hz, H-4), 5.30 (dd, 1 H, $J_{1,2}$ 3.9 Hz, H-2), 5.76 (t, 1 H, $J_{4',5'}$ 8.0 Hz, H-4′), 6.24 (d, 1 H, H-1). Data for **9**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99–2.16 (m, 18 H, 6 COCH_3), 4.02 (m, 1 H, H-5′), 4.25 (m, 1 H, H-5), 4.31–4.36 (m, 2 H, H-6b and H-6′b), 4.41–4.45 (d, 2 H, H-1′a and H-1′b), 4.54 (m, 1 H, H-6a), 4.55 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.6 Hz, H-4), 4.58–4.61 (m, 1 H, H-6′a), 5.10 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 10.4 Hz, H-2), 5.18 (d, 1 H, $J_{3',4'}$ 7.8 Hz, H-3′), 5.21 (t, 1 H, $J_{4',5'}$ 9.2 Hz, H-4′), 5.51 (t, 1 H, H-3), 6.30 (d, 1 H, H-1).

6-O-*Myristoyl-4′*-O-*sulfosucrose* (**10**).—Sulfonation of 6-*O*-myristoylsucrose (150 mg, 0.27 mmol) with Pyr·SO_3 (3×43 mg) afforded **10** in a 70% yield; mp 165–170 °C (dec); $[\alpha]_D^{22}$ +40.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{26}H_{48}O_{15}S$ [M−H]$^-$ 631.1481; Found: 631.1484; ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 0.90 (t, 3 H, CH_3), 1.39–1.50 (m, 20 H, 10 CH_2), 1.61 (quint., 2 H, C(O)CH_2CH_2), 2.35 (t, 2 H, C(O)CH_2), 3.02 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.18 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.32 (s, 1 H, H-1′b), 3.35 (s, 1 H, H-1′a), 3.48 (t, 1 H, H-3), 3.57 (d, 1 H, $J_{6'a,b}$ 10.7 Hz, H-6′b), 3.69 (d, 1 H, H-6′a), 3.76 (d, 1 H, $J_{3',4'}$ 7.6 Hz, H-3′), 3.87 (t, 1 H, $J_{4',5'}$ 7.5 Hz, H-4′), 3.93–3.99 (m, 2 H, H-5 and H-5′), 4.01 (dd, 1 H, $J_{5,6b}$ 5.4 Hz, $J_{6a,b}$ 10.2 Hz, H-6b), 4.20 (d, 1 H, H-6a), 5.14 (d,1 H, H-1).

6-O-*Myristoyl-1′*-O-*sulfosucrose* (**11**).—Sulfonation of 6-*O*-myristoylsucrose (150 mg, 0.27 mmol) with Pyr·SO_3 (3×43 mg) afforded **11** in 10% yield; mp 160–165 °C (dec); $[\alpha]_D^{22}$ 45.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{26}H_{48}O_{15}S$ [M−H]$^-$ 631.1481; Found 631.1479; ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 0.96 (t, 3 H, CH_3), 1.24–1.36 (m, 20 H, 10 CH_2), 1.50 (quint., 2 H, C(O)CH_2CH_2), 2.34 (t, 2 H, C(O)CH_2), 3.04 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.17 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.47 (t, 1 H, H-3), 3.71–3.74 (m, 3 H, H-1′a, H-1′b and H-5′), 3.77 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.6 Hz, H-4′), 3.84–3.90 (m, 2 H, H-6′a and H-6′b), 3.92 (d, 1 H, H-3′), 3.95–4.00 (m, 1 H, H-5), 4.04 (dd, 1 H, $J_{5,6b}$ 6.0 Hz, $J_{6a,b}$ 11.5 Hz, H-6b), 4.17 (d, 1 H, H-6a), 5.12 (d,1 H, H-1).

6-O-*Stearoyl-4′*-O-*sulfosucrose* (**12**).—Sulfonation of 6-*O*-stearoylsucrose (150 mg, 0.25 mmol) with Pyr·SO_3 (3×39 mg) afforded **12** in a 75% yield; mp 183–185 °C (dec); $[\alpha]_D^{22}$ +35.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{30}H_{56}O_{15}S$ [M−H]$^-$ 687.2107; Found: 687.2105; ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 0.90 (t, 3 H, CH_3), 1.39–1.50 (m, 28 H, 14 CH_2), 1.60 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.02 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.6 Hz, H-4), 3.18 (dd, 1 H, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.34 (s, 1 H, H-1′b), 3.37 (s, 1 H, H-1′a), 3.48 (t, 1 H, H-3), 3.56 (dd, 1 H, H-6′b), 3.69 (d, 1 H, H-6′a), 3.75 (d, 1 H, $J_{3',4'}$ 7.6 Hz, H-3′), 3.87 (t, 1 H, $J_{4',5'}$ 7.6 Hz, H-4′), 3.87–3.98 (m, 2 H, H-5 and H-5′), 4.00 (d, 1 H, H-6b), 4.18 (dd, 1 H, $J_{6a,b}$ 11.1 Hz, H-6a), 5.13 (d,1 H, H-1).

6-O-*Stearoyl-1′*-O-*sulfosucrose* (**13**).—Sulfonation of 6-*O*-stearylsucrose (150 mg, 0.25 mmol) with Pyr·SO_3 (3×39 mg) afforded **13** in a 10% yield; mp 203–206 °C (dec); $[\alpha]_D^{22}$ +30.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{30}H_{56}O_{154}S$ [M−H]$^-$ 687.3262; Found: 687.3262; ^{1}H NMR (500 MHz, D_2O): δ 0.90 (t, 3 H, CH_3), 1.39–1.50 (m, 28 H, 14 CH_2), 1.60 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.31 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.7 Hz, H-4), 3.47 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.68 Hz, H-2), 3.69 (t, 1 H, H-3), 3.99–4.02 (m, 3 H, H-1′a, H-1′b and H-5′), 4.06–4.09 (m, 3 H, H-4′, H-6′a and H-6′b), 4.14–4.21 (m, 3 H, H-3′, H-5 and H-6b), 4.32 (d, 1 H, $J_{6a,b}$ 11.8 Hz, H-6a), 5.32 (d,1 H, H-1).

1′-O-*Lauroyl-6′*-O-*sulfosucrose* (**14**).—Sulfonation of 6-*O*-lauroylsucrose (150 mg, 0.29 mmol) with Pyr·SO_3 (3×46 mg) afforded **14** in a 75% yield; mp 210–215 °C (dec); $[\alpha]_D^{22}$ +30.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{24}H_{44}O_{15}S$ [M−H]$^-$ 603.2323; Found: 603.2332; ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 0.84 (t, 3 H, CH_3), 1.23–1.34 (m, 16 H, 8 CH_2), 1.51 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.18 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.7 Hz, H-4), 3.27 (dd, 1 H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.48 (t, 1 H, H-3), 3.52–3.62 (m, 2 H, H-6a and H-6b), 3.78 (m, 1 H, H-5), 3.82–3.98 (m, 3 H, H-3′, H-5′and H-6′b), 3.94–3.98

(m, 2 H, H-4′, and H-6′a), 4.03 (d, 1 H, $J_{1'a,b}$ 12.1 Hz, H-1′b), 4.10 (d, 1 H, H-1′a), 5.17 (d,1 H, H-1).

1′-O-*Lauroyl-6*-O-*sulfosucrose* (**15**).—Sulfonation of 6-*O*-lauroylsucrose (150 mg, 0.29 mmol) with Pyr·SO_3 (3×46 mg) afforded **15** in a 10% yield; mp 195–200 °C (dec); $[\alpha]_D^{22}$ +35.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{24}H_{44}O_{15}S$ $[M-H]^-$ 603.2323; Found: 603.206; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.86 (t, 3 H, CH_3), 1.23–1.34 (m, 16 H, 8 CH_2), 1.51 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.11 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.18 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.44 (t, 1 H, H-3), 3.58 (m, 1 H, H-5′), 3.74 (m, 1 H, H-5), 3.80–3.85 (m, 5 H, H-3′, H-4′, H-6′a, H-6b and H-6′b), 3.96 (m, 1 H, H-6a), 4.03 (d, 1 H, $J_{1'a,b}$ 12.0 Hz, H-1′b), 4.12 (d, 1 H, H-1′a), 5.12 (d,1 H, H-1).

1′-O-*Myristoyl-6′*-O-*sulfosucrose* (**16**).—Sulfonation of 6-*O*-myristoylsucrose (150 mg, 0.27 mmol) with Pyr·SO_3 (3×43 mg) afforded **16** in a 70% yield; mp 187–191 °C (dec); $[\alpha]_D^{22}$ +45.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{26}H_{48}O_{15}S$ $[M-H]^-$ 631.2636; Found: 631.2637; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.84 (t, 3 H, CH_3), 1.23–1.34 (m, 20 H, 10 CH_2), 1.51 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.11 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.17 (dd, 1 H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.45 (t, 1 H, H-3), 3.51–3.61 (m, 2 H, H-6a and H-6b), 3.66 (m, 1 H, H-5), 3.73–3.82 (m, 3 H, H-3′, H-5′and H-6′b), 3.87–3.93 (m, 3 H, H-1′b, H-4, and H-6′a), 4.11 (dd, 1 H, $J_{1'a,b}$ 12.0 Hz, H-1′a), 5.12 (d, 1 H, H-1).

1′-O-*Myristoyl-6*-O-*sulfosucrose* (**17**).—Sulfonation of 6-*O*-myristoylsucrose (150 mg, 0.27 mmol) with Pyr·SO_3 (3×43 mg) afforded **17** in a 10% yield; mp 195–200 °C (dec); $[\alpha]_D^{22}$ 40.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{26}H_{48}O_{15}S$ $[M-H]^-$ 631.1481; Found: 631.1485; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.86 (t, 3 H, CH_3), 1.28–1.40 (m, 20 H, 10 CH_2), 1.50 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.11 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.18 (dd, 1 H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.44 (t, 1 H, H-3), 3.58 (m, 1 H, H-5′), 3.74 (m, 1 H, H-5), 3.80–3.85 (m, 2 H, H-6′a and H-6′b), 3.91–4.03 (m, 5 H, H-1′b, H-3′, H-4′, H-6a, H-6b), 4.09 (d, 1 H, $J_{1'a,b}$ 12.0 Hz, H-1′a), 5.13 (d,1 H, H-1).

1′-O-*Stearoyl-6′*-O-*sulfosucrose* (**18**).—Sulfonation of 6-*O*-stearoylsucrose (150 mg, 0.25 mmol) with Pyr·SO_3 (3×39 mg) afforded **18** in a 67% yield; mp 175–180 °C (dec); $[\alpha]_D^{22}$ +35.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{30}H_{56}O_{18}S$ $[M-H]^-$ 687.2107; Found: 687.2094; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.92 (t, 3 H, CH_3), 1.22–1.36 (m, 28 H, 14 CH_2), 1.60 (quint., 2 H, C(O)CH_2CH_2), 2.36 (t, 2 H, C(O)CH_2), 3.17 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz, H-4), 3.23 (dd, 1 H, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.51 (t, 1 H, H-3), 3.53–3.61 (m, 2 H, H-6a and H-6b), 3.68 (m, 1 H, H-5), 3.76 (m, 1 H, H-5′), 3.82–3.88 (m, 2 H, H-3′ and H-6′b), 3.92-3.97 (m, 2 H, H-4′, and H-6′a), 4.03 (dd, 1 H, $J_{1'a,b}$ 12.0 Hz, H-1′b), 4.17 (dd, 1 H, H-1′a), 5.19 (d,1 H, H-1).

1′-O-*Stearoyl-6*-O-*sulfosucrose* (**19**).—Sulfonation of 6-*O*-stearoylsucrose (150 mg, 0.25 mmol) with Pyr·SO_3 (3×39 mg) afforded **19** in a 10% yield; mp 170–175 °C (dec); $[\alpha]_D^{22}$ +40.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{30}H_{56}O_{18}S$ $[M-H]^-$ 687.2107; Found: 687.2102; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.92 (t, 3 H, CH_3), 1.22–1.36 (m, 28 H, 14 CH_2), 1.60 (quint., 2 H, C(O)CH_2CH_2), 2.36 (t, 2 H, C(O)CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.17 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.6 Hz, H-4), 3.19 (dd, 1 H, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.46 (t, 1 H, H-3), 3.57 (m, 1 H, H-5′), 3.74 (m, 1 H, H-5), 3.79–3.88 (m, 5 H, H-3′, H-4′, H-6b, H-6′a and H-6′b), 3.97 (m, 1 H, H-6a), 4.03 (dd, 1 H, $J_{1'a,b}$ 12.1 Hz, H-1′b), 4.11 (d, 1 H, H-1′a), 5.13 (d,1 H, H-1).

Preparation of 1′2:4,6-di-O-*isopropylidenesucrose* (**20**) *and 4,6-mono*-O-*isopropylidenesucrose* (**21**) *[53]*.—To a solution of sucrose (1.0 g, 2.9 mmol) in anhydrous DMF (10 mL) under argon were added 2,2′-dimethoxypropane (4.3 mL, 35.1 mmol) and a catalytic amount of *p*-toluenesulfonic acid. After 2 h at room temperature, the reaction mixture was neutralized by addition of NEt_3, and the mixture was concentrated in vacuo. Purification by chromatography on silica gel (9:1 $CHCl_3$–CH_3OH) afforded **20** (566 mg, 46%) and **21** (504 mg, 45%) as white amorphous solids. Compound **21** was used without further characterization.

Preparation of 1′,2,3,3′,4′,6′-hexa-O-*acetylsucrose* (**22**) *[54]*.—To a solution of **21** (595 mg, 1.56 mmol) in anhydrous pyr (5 mL) acetic anhydride (1.4 mL, 14.0 mmol) was added under nitrogen. After 12 h at room temperature, the reaction mixture was quenched with CH_3OH and concentrated in vacuo. The resulting residue was dissolved in 60% acetic acid and heated at 80 °C for 15 min. After concentration in vacuo and purification by chromatography on silica gel (1:2 hexane–ethyl acetate), **22** was obtained in 91% yield (848 mg). ^1H NMR (500 MHz, $CDCl_3$): δ 2.10–2.19 (m, 18 H, 6 OAc), 3.65 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.5 Hz,

H-4), 3.81 (dd, 1 H, $J_{5,6b}$ 5.0 Hz, $J_{6a,b}$ 12 Hz, H-6b), 3.92 (d, 1 H, H-6a), 4.01 (m, 1 H, H-5), 4.16–4.18 (dd, 2 H, H-1′a and H-1′b), 4.22 (m, 1 H, H-6′b), 4.23 (m, 1 H, H-5′), 4.88 (m, 1 H, H-6′a), 4.77 (dd, 1 H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 9.8 Hz, H-2), 5.33 (t, 1 H, H-3), 5.39 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 6.0 Hz, H-4′), 5.45 (d, 1 H, H-3′), 5.64 (d,1 H, H-1). The intermediate hexa-*O*-acetylsucrose was used without further purification.

1′,2,3,3′,4′,6′-Hexa-O-*acetylsucrose 4,6-cyclic sulfite* (**23**) *and* (**24**).—To a solution of **22** (141 mg, 0.24 mmol) in anhydrous EtOAc (2 mL) maintained under nitrogen were added $SOCl_2$ (19 μL, 0.25 mmol) and anhyd pyr (20 μL, 0,50 mmol). After 1 h at room temperature, $SOCl_2$ (10 μL, 0.13 mmol) and anhydrous pyr (10 μL, 0,25 mmol) were added. After an additional 30 min, the reaction mixture was quenched by addition of water and extracted with EtOAc. The organic extract was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (1:2 hexane–EtOAc) afforded **23** (28 mg, 18%) and **24** (64 mg, 42%) as white amorphous solids. **23** $[\alpha]_D^{22}$ +69.1° (*c* 0.1, $CHCl_3$); FABMS (positive-ion) *m/z* 641, 663 $[M+H^+]^+$, $[M+Na^+]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.07–2.20 (6s, 18 H, 6 OAc), 4.13 (overlapped dd, 1 H, H-6b), 4.13–4.20 (dd, 2 H, H-1′a and H-1′b), 4.21 (m, 1 H, H-5′), 4.24 (dd, overlapped with H-5, 1 H, H-6′b), 4.32 (dd, 1 H, $J_{5',6'a}$ 3.8 Hz, $J_{6'a,b}$ 12 Hz, H-6′a), 4.20 (m, 1 H, H-5), 4.68 (t, 1 H, $J_{6a,b}$ 10.7 Hz, H-6a), 4.77 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 10.0 Hz, H-4), 4.85 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.0 Hz, H-2), 5.38 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 6.0 Hz, H-4′), 5.45 (d, 1 H, H-3′), 5.50 (t, 1 H, H-3), 5.75 (d, 1 H, H-1). Anal. Calcd for $C_{24}H_{32}O_{18}S$ (640.6) C 45.00, H 5.04; Found: C 45.12, H 5.08. Data for **24**: $[\alpha]_D^{22}$ +47.0° (*c* 0.1, $CHCl_3$); FABMS (positive-ion) *m/z* 641, 663 $[M+H^+]^+$ $[M+Na^+]^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08–2.22 (6 s, 18 H, 6 OAc), 4.10 (t, 1 H, $J_{3,4}$ and $J_{4,5}$ 9.9 Hz, H-4), 4.12 (m, 1 H, H-6b), 4.13–4.19 (dd, 2 H, H-1′a and H-1′b), 4.19 (m, 1 H, H-5′), 4.24 (m, 1 H, H-6′b), 4.29 (dd, 1 H, $J_{5',6'a}$ 4.5 Hz, $J_{6'a,b}$ 12 Hz, H-6′a), 4.66 (dd, 1 H, $J_{5,6a}$ 6.2 Hz, $J_{6a,b}$ 11.1 Hz, H-6a), 4.75 (m, 1 H, H-5), 4.82 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.1 Hz, H-2), 5.36 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 5.9 Hz, H-4′), 5.45 (d, 1 H, H-3′), 5.54 (t, 1 H, H-3), 5.71 (d,1 H, H-1). Anal. Calcd for $C_{24}H_{32}O_{18}S$ (640.6) C 45.00, H 5.04; Found: C 45.03, H 5.18.

1′,2,3,3′,4′,6′-Hexa-O-*acetylsucrose 4,6-cyclic sulfate* (**25**).—To a solution of **23** or **24** (307 mg, 0.48 mmol) in a mixture of 3:2 H_2O–CH_3CN (5 mL) was added $RuCl_3$ (catalytic amount) and $NaIO_4$ (205 mg, 0.96 mmol). After 1 h at room temperature, the reaction mixture was extracted with $CHCl_3$. The organic extract was washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (1:2 hexane–EtOAc) afforded **25** (299 mg, 95%). $[\alpha]_D^{22}$ +56.0° (*c* 0.1, $CHCl_3$); FABMS (positive-ion) *m/z* 679 $[M+Na^+]^+$; HRFABMS (positive-ion): Calcd for $C_{24}H_{32}O_{19}S$ $[M+Li]^+$ 663.1419; Found: 663.1426. ^{1}H NMR (500 Hz, $CDCl_3$): δ 2.04–2.19 (6 s, 18 H, 6 OAc), 4.12 (dd, 1 H, $J_{6'a,b}$ 11.7 Hz, H-6′b), 4.19–4.24 (m, 3 H, H-1′a, H-1′b and H-5′), 4.33 (dd, 1 H, $J_{5',6'a}$ 3.2 Hz, H-6′a), 4.58–4.69 (m, 4 H, H-4, H-5, H-6a and H-6b), 4.80 (dd, 1 H, $J_{1,2}$ 3.75 Hz, $J_{2,3}$ 10.0 Hz, H-2), 5.35 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 5.8 Hz, H-4′), 5.44 (d, 1 H, H-3), 5.58 (t, 1 H, $J_{3,4}$ 9.7 Hz, H-3), 5.47 (d, 1 H, H-1).

Sucrose 4,6-cyclic sulfate (**26**).—To a solution of **25** (286 mg, 0.44 mmol) in anhydrous methanol (5 mL) maintained under argon was added NEt_3 (0.73 mL, 5.23 mmol). After 15 h at room temperature, the reaction mixture was neutralized with Amberlite IR 120 (H^+) resin, filtered and concentrated in vacuo. Purification by chromatography on silica gel (4:1 $CHCl_3$–CH_3OH) afforded **26** (155 mg, 88%). $[\alpha]_D^{22}$ +26.0° (*c* 0.1, CH_3OH); FABMS (positive-ion) *m/z* 411 $[M+Li^+]^+$; HRFABMS (positive-ion): Calcd for $C_{12}H_{20}O_{13}S$ $[M+Li]^+$ 411.0785; Found: 411.0792. ^{1}H NMR (500 MHz, CD_3OD): δ 3.55 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.1 Hz, H-2), 3.60 (s, 1 H, H-1′b), 3.63 (s, 1 H, H-1′a), 3.66 (dd, 1 H, $J_{5',6'a}$ 4.5 Hz, $J_{6'a,b}$ 12.0 Hz, H-6′b), 3.74–3.79 (m, 2 H, H-6′a and H-5′), 4.00 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 4.02 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 8.4 Hz, H-4′), 5.47 (d, 1 H, H-3′), 4.41 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4), 4.54–4.60 (m, 3 H, H-5, H-6a and H-6b), 5.47 (d, 1 H, H-1).

Sucrose 4,6-cyclic sulfite (**27**).—Sucrose (100 mg, 0.29 mmol) was dissolved at 80 °C in anhyd DMF (1 mL). The solution was cooled at room temperature, and EtOAc (1 mL) was added under argon. To the resulting suspension was added $SOCl_2$ (22 μL, 0.31 mmol) and anhyd pyr (50 μL, 0.61 mmol). After 1 h, $SOCl_2$ (22 μL, 0.31 mmol) was added. After 1 additional h, the reaction mixture was neutralized by addition of NEt_3, and concentrated in vacuo. Purification by chromatography on silica gel (4:1 $CHCl_3$–CH_3OH) afforded **27** (23 mg, 20%). $[\alpha]_D^{22}$ +20.0° (*c* 0.1, CH_3OH);

Calcd for $C_{12}H_{20}O_{12}S$ $[M+Li]^+$ 395.0791; Found: 395.0796. ^1H NMR (500 MHz, CD_3OD): δ 3.56 (dd, 1 H, $J_{1,2}$ +4.0 Hz, $J_{2,3}$ 9.5 Hz, H-2), 3.63–3.68 (m, 3 H, H-1′a, H-1′b and H-6′b), 3.74–3.80 (m, 2 H, H-5′ and H-6′a), 3.92 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 4.03 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 8.5 Hz, H-4′), 4.04 (m, 1 H, H-6b), 4.12 (d, 1 H, H-3′), 4.33 (m, 1 H, H-5), 4.48 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.55 (t, 1 H, $J_{6a,b}$ 11.1 Hz, H-6a), 5.43 (d,1 H, H-1).

6-O-*Palmitoyl-4*-O-*sulfosucrose* (**28**).—Reaction of sucrose cyclic sulfate **26** (33 mg, 0.08 mmol) with palmitic acid (23 mg, 0.09 mmol) led to **28** as an amorphous white solid in 75% yield. $[\alpha]_D^{22}$ +40.1° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{28}H_{52}O_{15}S$ $[M-H]^-$ 659.2949; Found: 659.2946; ^1H NMR (500 MHz, Me_2SO-d_6): δ 0.86 (t, 3 H, CH_3), 1.25–1.30 (m, 22 H, 11 CH_2), 1.51–1.53 (quint., 2 H, C(O)CH_2CH_2), 2.30 (t, 2 H, C(O)CH_2), 3.32 (dd, 1 H, $J_{1,2}$ 3.75 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.40 (s, 2 H, H-1′a,b), 3.53 (m, 1 H, H-6′b), 3.61 (m, 2 H, H-5′ and H-6′a), 3.56 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.8 Hz, H-4′), 3.77 (t, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 3.84 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 3.87 (d, 1 H, H-3′), 3.98 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, $J_{6a,b}$ 11.9 Hz, H-6b), 4.07 (m, 1 H, H-5), 4.24 (d, 1 H, H-6a), 5.19 (d,1 H, H-1).

6-O-*Stearoyl-4*-O-*sulfosucrose* (**29**).—Reaction of sucrose cyclic sulfate **26** (109 mg, 0.27 mmol) with stearic acid (53 mg, 0.32 mmol) led to **29** as an amorphous white solid in 72% yield. $[\alpha]_D^{22}$ +35.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{30}H_{56}O_{15}S$ $[M-H]^-$ 687.3262; Found: 687.3276; ^1H NMR (500 MHz, CD_3OD): δ 0.95 (t, 3 H, CH_3), 1.22–1.38 (m, 28 H, 14 CH_2), 1.63 (m, 2 H, C(O)CH_2CH_2), 2.38 (t, 2 H, C(O)CH_2), 3.59 (dd, 1 H, $J_{1,2}$ 3.82 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.62 (d, 1 H, $J_{1'a,b}$ 12.2 Hz, H-1′b), 3.68 (d, 1 H, H-1′a), 3.76–3.82 (m, 3 H, H-5′, H-6′a and H-6′b), 4.02 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.6 Hz, H-4′), 4.04 (t, 1 H, $J_{3,4}$ 8.2 Hz, H-3), 4.07 (d, 1 H, H-3′), 4.19–4.21 (m, 1 H, H-5), 4.22 (t, 1 H, $J_{4,5}$ 8.2 Hz, H-4), 4.27 (dd, 1 H, $J_{5,6b}$ 4.7 Hz, $J_{6a,b}$ 12.1 Hz, H-6b), 4.41 (d, 1 H, H-6a), 5.42 (d,1 H, H-1).

6-O-*Eicosanoyl-4*-O-*sulfosucrose* (**30**).—Reaction of sucrose cyclic sulfate **26** (27 mg, 0.07 mmol) with eicosanoic acid (25 mg, 0.08 mmol) led to **31** as an amorphous white solid in 60% yield. $[\alpha]_D^{22}$ +28° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{32}H_{60}O_{15}S$ $[M-H]^-$ 715.3575; Found: 715.3562; ^1H NMR (500 MHz, CD_3OD): δ 0.90 (t, 3 H, CH_3), 1.25–1.35 (m, 32 H, 16 CH_2), 1.61 (quint., 2 H, C(O)CH_2CH_2), 2.37 (t, 2 H, C(O)CH_2), 3.54 (dd, 1 H, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.59 (d, 1 H, $J_{1'a,b}$ 12.3 Hz, H-1′b), 3.64 (d, 1 H, H-1′a), 3.72–3.79 (m, 3 H, H-5′, H-6′a and H-6′b), 3.98 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 8.1 Hz, H-4′), 4.01 (t, 1 H, $J_{3,4}$ 9.7 Hz, H-3), 4.07 (d, 1 H, H-3′), 4.19–4.24 (m, 3 H, H-4, H-5 and H-6b), 4.40 (d, 1 H, $J_{6a,b}$ 11.4 Hz, H-6a), 5.39 (d,1 H, H-1).

6-O-*Deoxy-6*-O-*hexadecylamine-4*-O-*sulfosucrose* (**31**).—Reaction of sucrose cyclic sulfate **26** (39 mg, 0.10 mmol) with hexadecylamine (28 mg, 0.11 mmol) led to **31** as an amorphous white solid in 76% yield. $[\alpha]_D^{22}$ −18.0° (*c* 0.1, CH_3OH); HRFABMS (negative-ion): Calcd for $C_{28}H_{55}NO_{13}S$ $[M-H]^-$ 644.3316; Found: 644.3323; ^1H NMR (500 MHz, CD_3OD): δ 0.91 (t, 3 H, CH_3), 1.25–1.43 (m, 26 H, 13 CH_2), 1.68 (quint., 2 H, NCH_2CH_2), 2.98 (t, 2 H, NCH_2), 3.17 (dd, 1 H, $J_{5,6b}$ 8.1 Hz, $J_{6a,b}$ 13.1 Hz, H-6b), 3.44 (dd, 1 H, $J_{5,6a}$ 2.75 Hz, H-6a), 3.58 (dd, 1 H, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.68 (dd, 1 H, $J_{5',6'b}$ 6.87 Hz, $J_{6'a,b}$ 11.8 Hz, H-6′b), 3.74–3.80 (m, 3 H, H-1′a, H-1′b and H-5′), 3.83 (dd, 1 H, $J_{5,6'a}$ 2.6 Hz, H-6′a), 3.91 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.98 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.3 Hz, H-4′), 4.07 (t, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 4.14 (d, 1 H, H-3′), 4.32 (m, 1 H, H-5), 5.46 (d,1 H, H-1).

6-O-*Deoxy-6*-O-*octadecylamine-4*-O-*sulfosucrose* (**32**).—Reaction of sucrose cyclic sulfate **26** (58 mg, 0.14 mmol) with octadecylamine (47 mg, 0.17 mmol) led to **32** as an amorphous white solid in 60% yield. $[\alpha]_D^{22}$ +48.0° (*c* 0.1, 1:1 CH_3OH–$CHCl_3$); HRFABMS (negative-ion): Calcd for $C_{30}H_{59}NO_{13}S$ $[M-H]^-$ 672.3629; Found: 672.3619; ^1H NMR (500 MHz, CD_3OD): δ 0.90 (t, 3 H, CH_3), 1.26–1.42 (m, 30 H, 15 CH_2), 1.68 (quint., 2 H, NCH_2CH_2), 3.00 (t, 2 H, NCH_2), 3.18 (dd, 1 H, $J_{5,6b}$ 8.3 Hz, $J_{6a,b}$ 13.3 Hz, H-6b), 3.45 (dd, 1 H, $J_{5,6a}$ 2.6 Hz, H-6a), 3.56 (dd, 1 H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.70 Hz, H-2), 3.68 (dd, 1 H, $J_{5',6'b}$ 7.2 Hz, $J_{6'a,b}$ 11.5 Hz, H-6′b), 3.74–3.79 (m, 3 H, H-1′a, H-1′b and H-5′), 3.83 (dd, 1 H, $J_{5,6'a}$ 2.7 Hz, H-6′a), 3.89 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.97 (t, 1 H, $J_{3',4'}$ and $J_{4',5'}$ 7.5 Hz, H-4′), 4.06 (t, 1 H, $J_{4,5}$ 8.9 Hz, H-4), 4.14 (d, 1 H, H-3′), 4.32 (m, 1 H, H-5), 5.46 (d,1 H, H-1).

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