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Semisynthesis of Long-Chain Alkyl Ether Derivatives of Sulfated Oligosaccharides via Dibutylstannylene Acetal Intermediates

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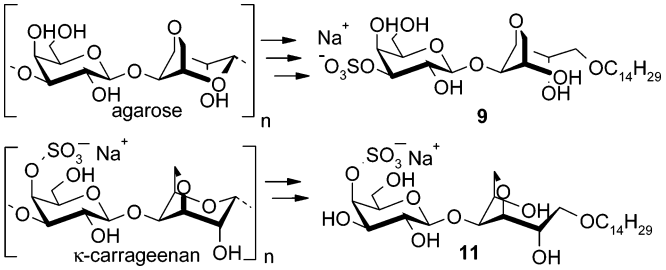

Long-chain alkyl ether derivatives of sulfated oligosaccharides were semisynthesized as follows: two naturally occurring red seaweed galactans (neutral agarose and *κ*-carrageenan) were submitted to partial reductive hydrolysis to give neutral and sulfated oligosaccharide alditols. The neutral disaccharide alditol (**1**) and its trityl ether (**5**) were sulfated and/or alkylated through formation of their dibutylstannylene or (bis)dibutylstannylene acetals. In these reactions, the dibutylstannylene acetals of the terminal 1,2-diols in the alditol units were more reactive than those formed on the *cis*-diols of the galactopyranosidic units. This property allowed the regioselective monoalkylation of a neutral tetrasaccharide alditol (**2**), which contained eleven free hydroxyl groups, the highest selectivity ever observed with dibutylstannylene acetals. An alkylated/sulfated derivative (**11**) was also obtained through the regioselective alkylation of a naturally sulfated disaccharide alditol (**10**, a *κ*-carrageenan derivative).

Introduction

Sulfated polysaccharides are involved in a wide range of biological process such as neuronal development,[1] tumor growth and metastasis,[2,3] inflammation, viral invasion, nerve tissue growth, and plaque formation.[4,5] It is now recognized that the regiochemistry and stereochemistry of the positions of the sulfates are highly significant for their recognition, the "sulfation code."[6−8]

Sulfated polysaccharides have been shown to have antiviral activity against several enveloped virus, such as HSV-1, HSV-2,[9−14] HIV-1, HIV-2, cytomegalovirus,[15−17] influenza A,[18,19] and

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dengue virus.[20−22] The level of antiviral activity increases with increase in both molecular mass and degree of sulfation of these macromolecules.[18,19,23] High-MW heparins, dextran sulfate and some highly sulfated algal polysaccharides are known to be the most active antiviral polysaccharides. On the other hand, low-MW sulfated polysaccharides and oligosaccharides are normally inactive. Exceptions have been reported in relation to HIV-2, which is susceptible to low-MW heparins and sucralfate (sucrose octasulfate).[18,19] The inhibitory effect on virus entry shown by these compounds is based mainly on their ability to interfere with the initial attachment of the virus to the target cell.[11] For example, the initial step of HSV−I entry consists of the binding of the viral glycoprotein C (gC) to the host cell-surface heparan sulfate (HS);[16−20] polysulfates appear to compete with HS, thus preventing its interaction with gC.[24−28]

In addition to the aforementioned polyanionic characteristics, it has been reported that the presence of hydrophobic moieties may be also involved in the antiviral activity of sulfated carbohydrates.[29] This is consistent with the gC N-terminal motif structure: a cluster of basic and hydrophobic amino acids, which has been identified as the major HS-binding domain.[24,29] Furthermore, all the retroviruses and myxoviruses sensitive to polysulfates share a tripeptide (Phe-Leu-Gly) in the external glycoprotein, while other nonsusceptible viruses of the same family lack this sequence.[29] Molecular models of the ionic minimal binding zones of HS and some active sulfated polysaccharides show surfaces with hydrophobic characteristics when their sulfate groups are orientated to the same side of the molecule.[11,30] The sulfated polysaccharide-viral glycoprotein complex is then stabilized through the simultaneous use of both ionic and hydrophobic forces.[11] This fact is consistent with the higher antiviral activity of sulfated fucans compared to carrageenans or dextran sulfate, possibly due to the hydrophobic character of the fucose (C-6 methyl group) when compared with galactose or glucose.[31] More importantly, alkyl glycosides of sulfated oligosaccharides containing hydrophobic groups present high anti-HIV-1 activity, while molecules lacking the hydrophobic moiety are practically inactive.[32] This data suggests that the introduction of the hydrophobic groups may overcome the absence of polymeric characteristics, turning inactive small sulfated carbohydrates into highly active compounds.

There are a few examples of the preparation of sulfated oligosaccharides bearing hydrophobic glycosides as potential antivirals. Katsuraya and co-workers[32,33] prepared dodecyl, fluoroalkyl, and oligoethyleneoxo glycosides of penta and hexa β-(1 → 3)-glucans, followed by nonselective sulfation. The two former hydrophobic types of glycosides were active against the HIV-1 virus, while the latter was inactive. Even though the glycosides having hydrophobic aglycones were active against HIV-1 virus, they were tested as mixtures, being separated as a function of their degree of sulfation.[32]

Obtaining antiviral derivatives that are both specifically sulfated and have a variety of locations for hydrophobic groups is necessary if the relationship between structure and activity is to be understood. In this context, naturally sulfated galactans extracted from some selected red seaweed species present highly repetitive disaccharidic units that can be used as synthons, for example, *Kappaphycus alvarezii* produces κ-carrageenan, which has a (1 → 3)-β-D-Gal*p*-4-SO_3-(1 → 4)-α-D-Gal*p*-3,6-An-repeating unit.[34−41] Partial hydrolysis is an efficient method to obtain specifically sulfated galactose-containing oligosaccharides from galactans that contain 3,6-anhydrogalactopyranosyl residues in reasonable yields[42−49] because the glycosidic bonds of the 3,6-anhydrogalactopyranosyl units are significantly more acid-labile than those of most pyranosides.[50] Partial acidic hydrolyses of these repetitive 3,6-An-α-D-Gal*p*-containing red

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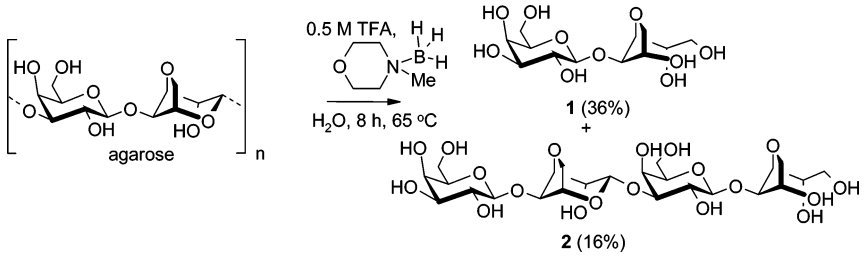
SCHEME 1. Partial Reductive Hydrolysis of Agarose



seaweed galactans, when carried out in the presence of borane-4-methylmorpholine complex (4-MMB− an acid stable reducing agent), yield oligosaccharides having an even number of monosaccharide units with 3,6-AnGalOH residues as terminal units (oligosaccharide alditols). The sulfate groups are substantially retained.[50−55]

The availability of these synthons presented an opportunity to better define the effects of the locations of hydrophobic and sulfate groups in both regiochemical and stereochemical senses on the antiviral activities of sulfated oligosaccharides. Dibutylstannylene acetal intermediates can provide regioselective substitution of diols and polyols using a wide variety of electrophiles,[56] including alkyl groups, and we have recently demonstrated that long alkyl chains can be regioselectively introduced onto galactopyranosides as ethers.[57] In these reactions, one of two or more oxygen atoms of hydroxyl groups reacts preferentially. Dibutylstannylene acetals derived from primary-secondary diols react with electrophiles to give much higher regioselectivity for reaction at the primary oxygen atoms than does direct reaction of the parent diols.[56,58] In reactions of electrophiles with the dibutylstannylene acetal derived from an equatorial-axial pair of oxygen atoms of a *cis*-diol on a pyranose rings, the equatorial oxygen reacts preferentially.[56,59] The most spectacular examples known to date are the regioselective reactions at O-3 of alkyl β-lactosides, which have seven free hydroxyl groups, including two primary hydroxyls.[60−62] We have previously employed trityl protecting groups to allow exposure of only secondary hydroxyls on agarobiitol which allowed selective reaction at the equatorial oxygen atom of the dibutystannylene acetal of its *cis*-diol.[63]

Here, we utilized partial reductive hydrolysis to produce neutral and sulfated oligosaccharide alditols from two naturally occurring red seaweed galactans: κ-carrageenan and neutral agarose. These oligosaccharides were then activated through formation of dibutylstannylene or (bis)dibutylstannylene acetals for both sulfation and long-chain alkylation reactions. This strategy was defined based on the fact that the neutral disaccharide alditol (**1**) presents two potential sites for the formation of dibutylstannylene acetals: the *cis*-diol on the galactopyranose (at O-3^2 and O-4^2) and 1,2-diol in the 3,6-AnGalOH unit (at O-1^1 and O-2^1). In these reactions, the dibutylstannylene acetals formed on the 1,2-diols in the alditol units were more reactive than the ones formed on the *cis*-diols of the galactopyranosidic units, leading to the preferential formation of *O*-1^1-substituted and *O*-$1,^1O$-3^2-disubstituted derivatives. Selective *O*-3^2 substitutions were achieved by previous blocking of the primary hydroxyl groups with trityl groups as previously.[63] A tetrasaccharide alditol (**2**), which contained eleven free hydroxyl groups, was regioselectively monoalkylated at O-1.[1] A naturally sulfated compound (**12**, κ-carrageenan disaccharide alditol derivative) was also regioselectively alkylated. These short semisynthetic routes allowed the preparation of long-chain alkyl ether derivatives of sulfated oligosaccharides in order to evaluate antiviral activity.

Results and Discussion

Alkylation of the Agarose-Derivative Oligosaccharide Alditols. For the preparation of neutral oligosaccharide alditols, type 1 agarose (3-linked β-D-Gal*p* and 4-linked 3,6-An-α-L-Gal*p*) was submitted to partial reductive hydrolysis.[50−55] The hydrolyzate was worked up by sequential steps involving precipitation with organic solvents, as previously described,[63] to give an oligosaccharide mixture as a precipitate. The precipitate was chromatographed on a silica gel column, rendering two fractions, the disaccharide and tetrasaccharide alditols, agarobiitol (**1**, 36%) and agarotetraitol (**2**, 16%), respectively (Scheme 1). Agarobiitol has been isolated previously from hydrolyzates of some red seaweed galactans during their structural characterization.[50,52,54] Because most of the studied polysaccharides were highly or partially sulfated, this neutral disaccharide was the product obtained from nonsulfated blocks within the polysaccharide structures[50,52] or as a result of desulfation during hydrolysis.[54] Chromatographic steps of anion exchange followed by gel filtration chromatography are usually performed for the separation of the mixtures of neutral and acidic oligosaccharide alditols. For these reasons, the yields are always very low and the amount of material produced is normally sufficient only for the structural characterization of the oligosaccharide produced. To obtain enough agarobiitol for the present semisynthesis, we utilized a preparative process that was developed recently.[63] By employing a completely neutral red seaweed galactan as the starting material and by utilizing precipitation with organic solvents and flash chromatography for purification, we achieved much higher yields than the

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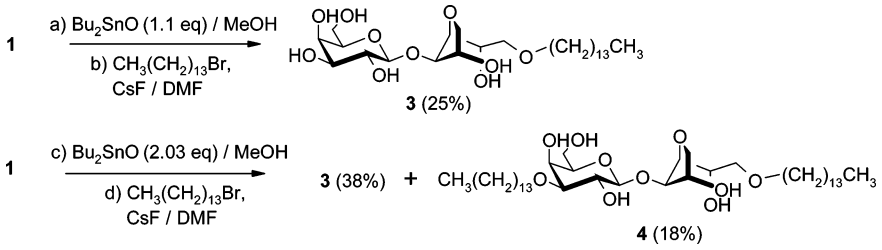
SCHEME 2. Alkylation Reactions of Compound 1



traditional preparative process. Agarotetraitol (**2**) was obtained from this process also because the hydrolysis was incomplete.[55] The agarotetraitol isolated contained 11% (from integration of anomeric proton signals) of an impurity with a slightly more deshielded anomeric proton than that of **2**, probably due to agarohexaitol. Some 3,6-anhydrogalactosidic bonds were left unbroken, yielding tetrasaccharides, and to a lesser extent, higher oligosaccharides having even numbers of monosaccharide units.

To define the strategy for long-chain alkylation and sulfation reactions, we observed that the oligosaccharide alditols obtained were structurally unique since they had 3,6-AnGalOH units in place of reducing ends in their structures. Because of the presence of the 3,6-anhydro ring and the O-4 glycosidic substitution, the terminal alditol unit presented only OH-5 and a primary-secondary diol (OH-1 and OH-2) as free hydroxyl groups. This latter structural feature matches the regioselectivity of dibutylstannylene-mediated reactions, which gives high regioselectivity at primary oxygen atoms of terminal 1,2-diols.[56,58] This property could be useful because these oligosaccharide alditols also present at least one more primary hydroxyl group (OH-6) in the Gal*p* unit. However, there is another preferred site for the formation of dibutylstannylene acetals in these oligosaccharide alditol structures: the OH-3/OH-4 *cis*-diol of the terminal galactopyranosidic units. In the dibutylstannylene acetal derived from an equatorial−axial pair of oxygen atoms of a *cis*-diol on a pyranose ring, the equatorial oxygen reacts preferentially; therefore, O-3 in a galactopyranosidic ring is the most reactive oxygen atom.[56,64] Thus, agarobiitol and agarotetraitol present two reactive positions under these conditions: O-1 of the 3,6-AnGalOH unit and O-3 of the terminal β-D-Gal*p* unit.

For long-chain alkylation, compound **1** was first reacted with 1.1 equiv of dibutyltin oxide under reflux in dry methanol for 3 h, and then the methanol and any traces of water were removed by azeotropic distillation with toluene for 2 h. The dibutylstannylene acetal was alkylated under the conditions of Danishefsky and Hungate[65] and of Nagashima and Ohno[66,67] in DMF with added cesium fluoride. It has been found previously that alkylation with long-chain alkyl bromides gives the best yields (although still moderate) when alkylations are conducted for extended times at moderate temperatures (~65 °C).[57] The use of higher temperatures resulted in byproducts resulting from degradation.[57] As outlined in Scheme 2, reaction under these conditions gave one product, a monoalkylated derivative (**3**, 25%). TLC indicated that starting material remained but no byproducts were evident. Because of limited solubility in single deuterated solvents, NMR experiments for **3** were performed in a mixture of $CDCl_3$:CD_3OD (2:1). The location of the *O*-alkyl substituent was demonstrated unambiguously by means of an HMBC experiment, which showed correlations between the protons attached to the O-linked carbon of the alkyl chain with the C-1 of the alditol unit. Formation of the (bis)dibutylstannylene acetal by reaction of **1** with 2 equiv of dibutyltin oxide followed by alkylation with excess 1-bromotetradecane gave compound **3** (38%) and a dialkylated product (**4**, 18%). With the introduction of an additional long-chain alkyl group, compound **4** was hydrophobic enough to be soluble in $CDCl_3$ for NMR experiments. The deshielded positions of the C-3 signal of the Gal*p* unit in the ^{13}C NMR spectrum, as well as the C-1 signal from the alditol unit, indicated that compound **4** was the 1,$1$3^2-di-O-alkylated derivative.

These observations (and others to follow) are consistent with the dibutylstannylene acetal formed from the 1,2-diol being considerably more reactive than the dibutylstannylene acetal formed from the *cis*-diol. Under the extended reaction times at 65 °C in DMF, the dibutylstannylene units migrate freely among all available diol sites.[56,68] The products of alkylation, the dibutylbromostannylethers[69] are ineffective as alkylation catalysts. The conditions and reaction times for these two reactions were very similar, except that two equiv of dibutyltin oxide were used in the second reaction. The conditions selected were based on preliminary experiments published previously.[57] Considering that the amount of tetradecyl bromide (~6 equiv) was about the same for both dibutylstannylene and (bis)-dibutylstannylene acetal alkylations, the higher yield of the 1-O^1 alkyl product obtained in the reaction using 2 equiv of the dibutyltin oxide suggests that the rate of reaction at the 1-O^1 site is slowed by distribution of dibutylstannyl groups among the four possible sites for dibutylstannylene acetal formation in agarobiitol.

Regioselective monoalkylation of compound **1** at O-3 was achieved as depicted in Scheme 3. The primary hydroxyl groups of **1** were protected with trityl groups by reaction with 2.2 equiv of trityl chloride to give the 1,$1$6^2-di-*O*-trityl product (**5**, 40%).[63] Compound **5** was then alkylated through formation of its dibutylstannylene acetal with 1.3 equiv of Bu_2SnO, using the same conditions as for the previous alkylations. In this reaction, the alkylation occurred regioselectively at *O*-3 of the Gal*p* unit to give the 3^2-*O*-tetradecyl-1,$1$6^2-di-*O*-trityl product (**6**, 23%). The yield for this reaction was unexpectedly lower than those ones obtained for the previously described O-3 long-chain alkylation of methyl β-D-galactopyranosides,[57] which ranged from 61 to 68%. The trityl groups were removed by treating

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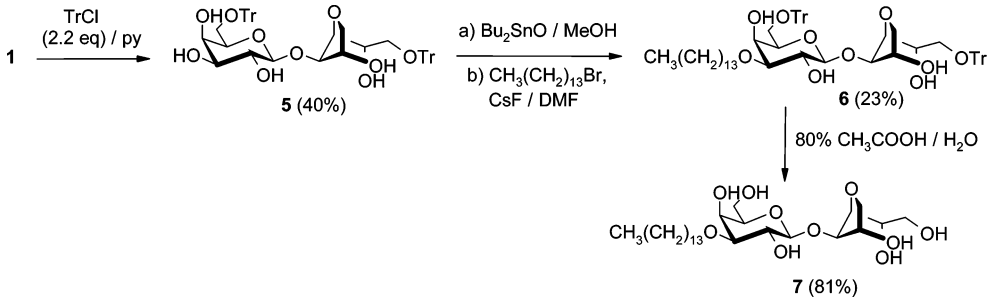
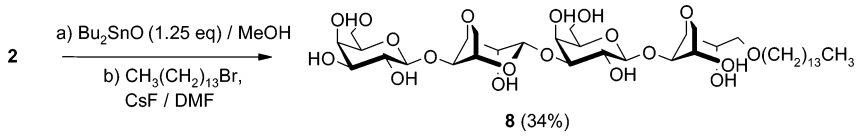
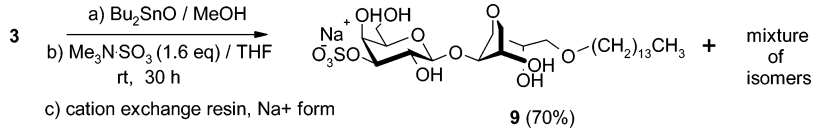
SCHEME 3. Semisynthesis of Compound 7



SCHEME 4. Alkylation of Compound 2



SCHEME 5. Sulfation of Compound 3



compound **6** with 80% aqueous acetic acid for 2 h at 40 °C to give the O-3[2] alkylated compound (**7**, 81%).

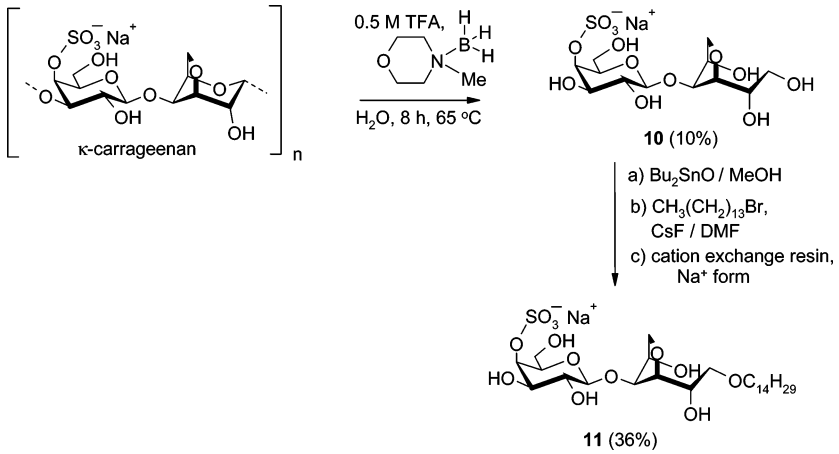
The *O*-1[1]-monoalkylated derivative of the tetrasaccharide **2** (**8**, 34%) was obtained by reaction with 1.3 equiv of Bu_2SnO and then with excess tetradecyl bromide (Scheme 4). On the basis of the results for alkylation of the dibutylstannylene acetals of compound **1**, it was expected that the O-1[1] position would be preferred for **2**. However, a regioselective reaction in which one hydroxyl is selected from eleven free hydroxyls, of which three are primary, is remarkable. As far as we are aware, this is the greatest selectivity ever observed in reactions of dibutylstannylene acetals.

Sulfation of the Neutral Glycosides. For the sulfation reactions, the dibutylstannylene acetals were formed with ~1 equiv of Bu_2SnO, following the same procedure utilized in the intermediate formation for the alkylation reactions. Sulfation of the dibutylstannylene acetals was performed with the sulfur trioxide-trimethylamine complex (1.2−1.9 equiv) in THF under an argon atmosphere. The sulfated products were converted into the sodium salt by cation replacement using a cationic exchange resin column.[57,63]

Sulfation of the dibutylstannylene acetal of compound **3** gave a monosulfated glycoside (**9**, 70%) as the main product (Scheme 5). For the NMR experiments, a mixture of $CDCl_3/CD_3OD/D_2O$ (2:2:1) provided better solubility for the sulfated alkyl derivative than any single solvent. NMR analysis indicated that sulfation occurred at O-3, as expected, to give the 3[2]-sulfate-1[1]-*O*-tetradecyl product. The key observations were that the chemical shift of H-3[2] changed from 3.65 ppm in the ^{1}H NMR spectrum of **3**[63] to 4.26 ppm in that of **9** and that the chemical shift of C-3[2] changed from 72.5 ppm in the ^{13}C NMR spectrum of **3**[63] to 81.5 ppm in that of **9**. This reaction also produced a mixture of three products that could not be resolved. Negative-ion mode ESI MS analysis of the mixture gave a clean spectrum presenting two peaks with *m*/*z* 340 and 703, corresponding to the ions expected for a disulfated/monoalkylated compound, $[M - 2Na]^{2-}$ and $[M - Na]^-$. The mass spectral data with the NMR analysis indicated that the components of the mixture were isomers, all containing the alkyl group at O-1,[1] one sulfonato group at O-3,[2] and the other in different positions of the agarobiitol structure. The relative percentages of the three components in the mixture were estimated from the peak heights of their anomeric signals being 104.0:103.0:102.9 ppm 19:37:44%. The most abundant isomer was the O-3,[2] O-6[2] disulfated isomer because in the ^{13}C NMR spectrum of the mixture, the tallest C-6[2] signal appeared at 67.2 ppm (assigned from the DEPT experiment) while the other two appeared at 62.1 and 61.9 ppm, similar to the chemical shifts of the analogous carbon atom of **3**. The other two isomers were probably the O-5,[1] O-3[2] (37%), and O-2,[1] O-3[2] (19%) disulfated isomers, because the ^{1}H NMR spectrum of the mixture contained two signals that were more deshielded than those of the anomeric protons. One, a narrow signal at 4.91 ppm that appeared to be a pentet with a splitting of 2.4 Hz, was probably the signal of H-5[1], but this pattern probably was a doublet of triplets with *J* values of 4.8 Hz for the doublet coupling and 2.4 Hz for the triplet coupling, consistent with the presence of 3 H vicinal to H-5[1] with restricted motion due to their presence in a tetrahydrofuran ring. The second was a broadened doublet of doublets ($^3J_{H,H}$ 9.4 and 4.8 Hz), probably that of H-2[1] which is also vicinal to 3H; however, the acyclic nature of the C-1[1] C-2[1] bond allows one H-1[1] to be close to anti to H-2 (see Supporting Information). The appearances of the proton signals on the other secondary carbon atoms that could bear sulfates would have been different: H-2[2] would be a triplet (*J* values ~9 Hz) that would be more shielded; H-4[2] in galactose derivatives is always a doublet of doublets with *J* values of about 3.4 and 1 Hz. The chemical shift of H-2[1] in the compound sulfated at O-2[1] is similar to that reported for agarobiitol derivatives monosulfated at that position.[55]

In the reaction of the 1,[1]3[2]-di-*O*-alkylated agarobiitol (**4**) with dibutyltin oxide, a five-membered ring dibutylstannylene acetal cannot be formed.[56] In this case, it is expected that the 4,[2]6[2]-*O*-dibutylstannylene acetal would be preferred. Guilbert et al.[70]

SCHEME 6. Semisynthesis of Compound 11



demonstrated that in sulfation reactions of β-lactosides, using conditions similar to those utilized in the present work, the main product (3^2-*O*-sulfonato) is normally accompanied by minor amounts of the 3,6-di-*O*-sulfonato derivative. Furthermore, the previously described 4,6-*O*-dibutylstannylene-mediated sulfation of the methyl 3-*O*-tetradecyl-β-D-galactopyranoside gave the 6-*O*-sulfonato derivative in very high yield (96%).[57] These results led us to expect that OH-6^2 would be the most reactive position in compound **4** under these conditions. However, the sulfation reaction of the dibutylstannylene intermediate of **4** gave a mixture of products that could not be resolved by chromatography. NMR and negative-ion mode ESI MS analyses (*m*/*z* 798 [M − Na]$^-$) indicated that two isomeric monosulfated/dialkylated derivatives (15%) were formed in a 3:2 ratio from peak heights of the anomeric carbon signals in the ^{13}C NMR spectrum. Attempts to perform the reaction with different amounts of sulfation reagent and different temperatures also yielded mixtures. The ^{13}C NMR spectrum indicated that the major product had the expected structure because the signal of C-6^2 had been deshielded to 64.4 ppm, compared to the value of 60.0 ppm for the other isomer, consistent with substitution by sulfate on O-6.[2] The minor product appears to be the O-5^1 sulfate because a deshielded pentet (4.62 ppm) was present in the ^{1}H NMR spectrum with splittings similar to that observed for the components sulfated at O-5^1 obtained in the mixture discussed above. Apparently reactions of the seven-membered ring dibutylstannylene acetal ring involving O-2^1 and O-5^1 compete with those of the anticipated six-membered ring intermediate. These results and the fact that the second sulfation of compound **3** did not occur predominantly at O-6 are unexpected. Even though the agarobiitol derivatives (**3** and **4**) contain β-D-galactopyranosyl units, they do not give the same regioselective dibutyltin-mediated sulfation at O-6 previously observed for β-D-galactopyranoside and β-D-lactoside derivatives.

Alkylation of the κ-Carrageenan-Derivative Disaccharide Alditol. κ-Carrageenan [→3)-β-D-Gal*p*-4-sulfate-(1 → 4)-3,6-An-α-D-Gal*p*-(1 →] from *Kappaphycus alvarezii* was subjected to partial reductive hydrolysis, and the hydrolyzate was directly chromatographed on a anion exchange DEAE-Sephadex (Cl$^-$) column. The main NaCl-gradient oligosaccharidic fraction was desalted and freeze-dried to give carrabiitol 4^2-sulfate (**10**, 10%).[55]

Utilization of a sulfate-containing carbohydrate as a starting material in synthetic steps is always a challenge. The presence of a highly acidic group results in low solubility in most common organic solvents and, for this reason, its introduction is normally performed in the final steps of the synthesis. Desulfation processes as well as sulfate-mediated degradation may also be problems. However, one of our main objectives was the utilization of the specificity of the sulfation of algal polysaccharides to obtain rapid and facile preparation of antiviral derivatives. In accordance with this aim, the same procedures utilized for the neutral oligosaccharide alditols were employed to perform long-chain alkylation of the naturally sulfated compound (**10**). The O-4^2 sulfation provided natural protection for *O*-3^2 alkylation by preventing formation of the 3,^{2}4^2-*O*-dibutylstannylene acetal. Since compound **10** presented just one available position for alkylation, a larger excess of both dibutyltin oxide (1.85 equiv) and tetradecyl bromide (9.7 equiv) were used to achieve more efficient monosubstitution at O-1^1. This reaction gave the 4^2-sulfate-1^1-*O*-tetradecyl product (**11**) in a yield of 36% (Scheme 6), contaminated by small amounts of unidentified byproducts. Despite the fact that this yield is modest, the abundance of κ-carrageenan sources and the simplicity of the ether preparation process make this semisynthesis route attractive and practicable, and it can be utilized for other algal sulfated polysaccharides.

Compounds **3**, **4**, **7**, **8**, **9**, **11**, the isomeric mixtures obtained in the sulfation reactions of compounds **3** and **4**, and some compounds prepared during previous work of our research group[55,63] have been tested against some strains of herpes simplex virus (HSV). Their antiviral activities as well as a detailed structure−activity relationship determination will be reported shortly.

Conclusion

We have demonstrated that abundant naturally occurring red seaweed galactans can serve as convenient sources of synthons for the semisynthesis of a variety of sulfated long-chain alkyl ether derivatives of oligosaccharides. For this purpose, the isolated polysaccharides were submitted to partial reductive hydrolysis to produce neutral and sulfated oligosaccharide alditols (compounds **1**, **2**, and **10**). Regioselective introduction of long-chain alkyl and sulfate groups were performed via dibutylstannylene-mediated reactions. The neutral oligosaccharide alditols **1** and **2** presented both a 1,2-diol and a *cis*-diol in their structures. The dibutylstannylene acetal of the 1,2-diol was

(70) Guilbert, B.; Davis, N. J.; Pearce, M.; Aplin, R. T.; Flitsch, S. L. *Tetrahedron: Asymmetry* **1994**, *5*, 2163−2178.

considerably more reactive than the one derived from the *cis*-diol on the galactopyranosyl ring. Tetrasaccharide alditol **2**, which contained eleven free hydroxyl groups, was regioselectively monoalkylated, the highest regioselectivity ever observed for dibutylstannylene acetals. We also prepared a sulfated long-chain alkyl ether (**11**) from a naturally sulfated carbohydrate through a very short semisynthetic route.

Experimental Section

For general experimental methods, see the Supporting information.

***β*-D-Galactopyranosyl-(1→4)-3,6-anhydro-L-galactitol (1) and *β*-D-Galactopyranosyl-(1→4)-3,6-anhydro-α-L-galactopyranosyl-(1→3)-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-L-galactitol (2).** Commercial agarose type 1 was submitted to partial reductive hydrolysis:[50] 1.000 g of the polysaccharide was dissolved in water (75 mL), the solution was heated to 60 °C, and borane 4-methylmorpholine complex (6.75 g) was added followed by 25 mL of 2 M CF_3COOH aqueous solution (final concentration of 0.5 M CF_3-COOH). The mixture was kept at 65 °C for 8 h and the acid was then evaporated with the aid of added water (4 × 150 mL). The hydrolyzate was dissolved in water (50 mL), treated with ethanol (3 vol), and then filtered. The filtrate was concentrated, and the residue was resuspended in methanol (50 mL) followed by addition of ethyl acetate (10 vol). The precipitate was collected by centrifugation, and the pellet was chromatographed by flash chromatography on silica gel using ethyl acetate/methanol/water (8:2:1) as eluent to give **1** (0.3617 g, 36%) and **2** (0.1630 g, 16%).

Compound 1. Colorless syrup $[\alpha]^{22}_D = -8.3$ (*c* 0.4, H_2O); $R_f = 0.29$ (ethyl acetate/methanol/H_2O, 8:2:1). ^1H NMR and ^{13}C NMR (D_2O) data were consistent with those reported previously.[63]

Compound 2. Colorless syrup $[\alpha]^{22}_D = -10.6$ (*c* 0.9, H_2O); $R_f = 0.17$ (ethyl acetate/methanol/H_2O, 8:2:1). ^1H NMR (CD_3OD, 500.13 MHz): δ 5.15 (d, 1H, $J_{1,2} = 2.0$ Hz, H-1^3), 4.66 (b, 1H, H-4^3), 4.46 (b, 2H, H-5,^{3} H-1^2), 4.44 (b, 1H, H-3^3), 4.39 (b, 1H, H-1^4), 4.28 (b, 2H, H-4,^{1} H-5^1), 4.12 (b, 1H, H-6′^{3}), 4.04 (b, 1H, H-6^3), 4.00 (q, 1H, H-2^3), 3.93 (m, 2H, H-3$_1$, H-6′^{1}), 3.87 (m, 2H, H-4,^{4} H-2^1), 3.82 (b, 1H, H-6^1), 3.80−3.70 (m, 4H, H-6′,^{2} H-6,^{2} H-6′,^{4} H-6^4), 3.67−3.61 (m, 4H, H-1′,^{1} H-1,^{1} H-2,^{2} H-3^2), 3.58 (b, 2H, H-5,^{2} H-5^4), 3.50 (d, 2H, H-2,^{4} H-3^4). ^{13}C NMR (CD_3OD, 125.77 MHz): δ 104.4 (C-1^2), 104.3 (C-1^4), 99.5 (C-1^3), 87.4 (C-4^1), 85.4 (C-3^1), 83.4 (C-3^2), 81.7 (C-3^3), 78.4 (C-4^3), 76.9 (C-5$_1$, C-5^3), 76.8 (C-5^2), 76.5 (C-5^4), 75.0 (C-3^4), 74.7 (C-6^1), 72.6 (C-2^1), 72.4 (C-2^4), 71.7 (C-2^2), 71.5 (C-2^3), 70.5 (C-4,^{2} C-4^4), 70.3 (C-6^3), 64.6 (C-1^1), 62.7 (C-6,^{2} C6^4). HR ESI MS: *m*/*z* calcd for $C_{24}H_{40}O_{19}Na$ (M + Na), 655.2056; found, 655.2009.

***β*-D-Galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-tetradecyl-L-galactitol (3)** Compound **1** (0.1448 g, 0.4437 mmol) and dibutyltin oxide (0.1213 g, 0.4873 mmol, 1.10 equiv) were reacted in dry methanol (5 mL) at reflux for 3 h. The reaction mixture was concentrated then taken up in toluene (20 mL). The mixture was refluxed for 2 h with azeotropic removal of water and methanol, then concentrated. The residue was taken up in dry DMF (4 mL), and then 6.5 equiv of tetradecyl bromide (0.80 mL, 3.1 mmol) and CsF (0.2151 g, 1.416 mmol, 3.19 equiv) were added. The reaction mixture was kept at 65 °C for 72 h, and then the concentrated residue was loaded onto a silica gel column using solvent gradient from ethyl acetate to ethyl acetate/methanol/H_2O (12:2:1) as eluent to give compound **3** as a colorless solid: yield 0.0575 g, 25%; mp 57−59 °C; $[\alpha]^{22}_D = -19.0$ (*c* 0.5, $CHCl_3$); $R_f = 0.2$ (ethyl acetate/methanol/H_2O, 12:2:1). ^1H NMR δ ($CDCl_3$: CD_3OD, 2:1, 500.13 MHz) 4.37 (d, 1H, $J_{1,2} = 7.5$ Hz, H-1^2), 4.25 (m, 2H, H-4,^{1} H-5^1), 3.97 (m, 2H, H-2,^{1} H-3^1), 3.92 (dd, 1H, H-6′^{1}), 3.81 (m, 3H, H-4,^{2} H-6,^{1} H-6′^{2}), 3.69 (dd, 1H, H-6^2), 3.54−3.43 (complex m, 7H, H-1′,^{1} H-1,^{1} H-2,^{2} H-3,^{2} H-5,^{2} OC*H*′HCH$_2$, OCH′*H*CH$_2$),), 1.55 (p, 2H, OCH$_2$C*H*$_2$), 1.26−1.24 (br, 22H, 11 × CH$_2$), 0.86 (t, 3H, CH$_3$); ^{13}C NMR δ ($CDCl_3$:CD_3OD, 2:1, 125.77 MHz) 104.0 (C-1^2), 86.8 (C-4^1), 84.3 (C-3^1), 76.4 (C-5^2), 76.0 (C-5^1), 74.4 (C-3^2), 74.2 (C-6^1), 72.6 (C-1^1), 72.4 (O*C*H$_2$), 71.9 (C-2^2), 69.9 (C-2^1), 69.8 (C-4^2), 62.4 (C-6^2), 32.6 (*C*H$_2$CH$_2$CH$_3$), 30.4−29.4 (9 × *C*H$_2$), 26.7 (OCH$_2$CH$_2$*C*H$_2$), 23.3 (*C*H$_2$CH$_3$), 14.4 (CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{26}H_{50}O_{10}Na$ (M + Na), 545.3296; found, 545.3301; *m*/*z* calcd for $C_{52}H_{100}O_{20}Na$ (2M + Na), 1067.6700; found, 1067.6702.

***β*-D-Galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-tetradecyl-L-galactitol (3) and 3-*O*-Tetradecyl-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-tetradecyl-L-galactitol (4).** Compound **1** (0.317 g, 0.971 mmol) was reacted with dibutyltin oxide (0.490 g, 1.97 mmol, 2.03 equiv) in dry methanol (8 mL) at reflux for 3 h, followed by removal of methanol and any traces of water by azeotropic distillation with toluene for 2 h. The reaction mixture was concentrated, and then 1-bromotetradecane (1.4 mL, 5.4 mmol, 5.6 equiv), cesium fluoride (0.442 g, 2.912 mmol, 3.00 equiv), and dry DMF (6 mL) were added. The reaction mixture was kept at 65 °C for 72 h and then concentrated to a residue that was fractionated on a silica gel column using solvent gradient from ethyl acetate to ethyl acetate/methanol/H_2O (12:2:1) as eluent. Chromatography gave two different fractions that corresponded to compounds **3** (0.192 g, 38%) and **4** (0.126 g, 18%).

Compound 4. Colorless solid; mp 32−34 °C; $[\alpha]^{22}_D = -3.0$ (*c* 0.8, $CHCl_3$); $R_f = 0.4$ (ethyl acetate). ^1H NMR δ ($CDCl_3$, 500.13 MHz): 4.46 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1^2), 4.31 (b, 1H, H-4^1), 4.29 (b, 1H, H-5^1), 4.06 (b, 2H, H-2,^{1} H-3^1), 3.96 (b, 1H, H-4^2), 3.93 (m, 1-H, H-6′^{2}), 3.91 (m, 1H, H-6′^{1}), 3.86 (b, 1H, H-6^1), 3.72 (m, 1H, H-6^2), 3.67 (b, 1H, H-2^2), 3.64 (m, 1H, C-3^2 OC*H*′HCH$_2$), 3.56 (m, 1H, C-3^2 OCH′*H*CH$_2$, H-5$_2$), 3.54 (m, 1H, H-1′^{1}), 3.46 (m, 3H, H-1,^{1} C-1^1 OC*H*′HCH$_2$, OCH′*H*CH$_2$),), 3.29 (dd, 1H, $J_{2,3} = 9.3$ Hz, $J_{3,4} = 3.1$ Hz, H-3^2), 1.62 (m, 2H, C-3^2 OC*H*′HCH$_2$, OCH′*H*CH$_2$),), 1.57 (m, 2H, C-1^1 OCH$_2$C*H*$_2$), 1.40−1.20 (br, 44H, 2 × (C*H*$_2$)$_{11}$CH$_3$), 0.88 (t, 6H, 2 × CH$_3$). ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 102.9 (C-1^2), 86.5 (C-4^1), 83.5 (C-3^1), 81.3 (C-3^2), 75.7 (C-5^1), 75.4 (C-5^2), 74.0 (C-6^1), 72.0 (C-1^1 O*C*H$_2$), 71.9 (C-1^1), 70.6 (C-3^2 O*C*H$_2$), 70.3 (C-2^2), 69.3 (C-2^1), 66.8 (C-4^2), 62.2 (C-6^2), 32.0 (2 × *C*H$_2$CH$_2$CH$_3$), 30.1−29.5 (18 × *C*H2), 26.1−26.2 (2 × OCH$_2$CH$_2$*C*H$_2$), 22.8 (2 × *C*H$_2$CH$_3$), 14.2 (2 × CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{40}H_{78}O_{10}Na$ (M + Na), 741.5487; found, 741.5492.

3-*O*-Tetradecyl-6-*O*-trityl-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-trityl-L-galactitol (6). Compound **5**[63] (0.201 g, 0.248 mmol) was alkylated as described for **3** and **4** using 1.3 equiv of Bu_2SnO (0.0800 g, 0.322 mmol) and then 4.37 equiv of tetradecyl bromide (0.3 mL, 1.081 mmol) with added CsF (0.100 g, 0.659 mmol, 2.66 equiv) in dry DMF (4 mL). The resulting mixture was concentrated under vacuum, and the residue was purified by flash column chromatography using hexanes/ethyl acetate (3:1) as eluent to give compound **6** as a colorless syrup (0.0612 g, 23%), $[\alpha]^{22}_D = -8.7$ (*c* 1.8, MeOH); $R_f = 0.17$ (hexanes/ethyl acetate, 3:1); ^1H NMR: δ (acetone-d_6, 500.13 MHz) 7.53−7.20 (complex m, 30 H, Ar−H, Ar−H′), 4.46 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1^2), 4.40 (b, 1H, H-4^1), 4.18 (b, 1H, H-5^1), 4.15 (b, 1H, H-3^1), 4.07 (b, 1H, H-4^2), 4.05 (b, 1H, H-2^1), 3.86 (m, 1H, H6′^{1}), 3.72 (m, 1H, H-6^1), 3.70 (m, 1H, OC*H*′HCH$_2$), 3.67 (m, 1H, H-5^2), 3.61 (b, 1H, H-2^2), 3.59 (m, 1H, OCH′*H*CH$_2$), 3.46 (b, 1H, H-6′^{2}), 3.35 (m, 1H, H-6^2), 3.10 (dd, 1H, $J_{2,3} = 9.3$ Hz, $J_{3,4} = 3.2$ Hz, H-3^2), 1.58 (p, 2H, OCH$_2$C*H*$_2$), 1.40−1.20 (br, 22H, 11 × CH$_2$), 0.88 (t, 3H, CH$_3$). ^{13}C NMR δ ($CDCl_3$:CD_3OD, 2:1, 125.77 MHz) 145.3 (3ArqC, 3ArqC′), 129.7 (6ArCH, 6ArCH′), 128.7 (6ArCH, 6ArCH′), 127.9 (3ArCH, 3ArCH′), 103.8 (C-1^2), 87.5 (O*C*Ph$_3$^{1}, O*C*Ph$_3$^{2}), 86.7 (C-4^1), 85.2 (C-3^1), 82.9 (C-3^2), 75.7 (C-5^1), 75.2 (C-6^1), 75.0 (C-5^2), 71.3 (C-2^1), 71.2 (C-2^2), 70.7 (O*C*H$_2$), 67.3 (C-4^2), 66.0 (C-1^1), 64.2 (C-6^2), 32.7 (*C*H$_2$CH$_2$CH$_3$), 30.5−29.6 (9 × *C*H$_2$), 26.9 (OCH$_2$-CH$_2$*C*H$_2$), 23.4 (*C*H$_2$CH$_3$), 14.4 (CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{64}H_{78}O_{10}Na$ (M + Na), 1029.5487; found, 1029.5496.

3-*O*-Tetradecyl-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-L-galactitol (7). Compound **6** (0.0193 g, 0.0191 mmol) was dissolved in 80% aqueous acetic acid (3 mL), and the solution was kept at 40 °C for 2 h, then concentrated. The residue was loaded onto a

silica gel column using ethyl acetate/methanol/H_2O (16:2:1) as eluent to give the title compound (**7**, 0.0081 g, 81%) as a colorless solid: mp 80−82 °C; $[\alpha]^{22}_D = -14.1$ (*c* 0.2, MeOH); $R_f = 0.47$ (ethyl acetate/methanol/H_2O, 16:2:1). ^{1}H NMR: δ ($CDCl_3/CD_3OD$, 2:1, 500.13 MHz) 4.39 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1^2), 4.25 (b, 2H, H-4,^{1}H-5^1), 3.98 (b, 2H, H-3,^{1} H-4^2), 3.92 (dd, 1H, H-6′^{1}), 3.87 (b, 1H, H-2^1), 3.79 (b, 2H, H-6′,^{2} H-6^1), 3.71 (dd, 1H, H-6^2), 3.66 (d, 1H, OC*H*′HCH$_2$), 3.63 (d, 2H, H-1′,^{1} H-1^1), 3.58 (b, 1H, H-2^2), 3.52 (d, 1H, OCH′*H*CH$_2$), 3.48 (q, 1H, H-5^2), 3.22 (dd, 1H, $J_{2,3} = 9.6$ Hz, $J_{3,4} = 3.4$ Hz, H-3^2), 1.61 (p, 2H, OCH$_2$C*H*$_2$), 1.30−1.20 (br, 22H, 11 × CH$_2$), 0.86 (t, 3H, CH$_3$). ^{13}C NMR δ ($CDCl_3$:CD_3OD, 2:1, 125.77 MHz) 104.1 (C-1^2), 86.9 (C-4^1), 84.5 (C-3^1), 82.4 (C-3^2), 76.2 (C-5^1), 76.3 (C-5^2), 74.2 (C-6^1), 71.9 (C-2^1), 71.0 (C-2,^{2} O*C*H$_2$), 66.8 (C-4^2), 64.2 (C-1^1), 62.6 (C-6^2), 32.7 (*C*H$_2$CH$_2$CH$_3$), 30.6−29.6 (9 × *C*H$_2$), 26.8 (OCH$_2$CH$_2$*C*H$_2$), 23.4 (*C*H$_2$CH$_3$), 14.5 (CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{26}H_{50}O_{10}Na$ (M + Na), 545.3296; found, 545.3301; calcd for $C_{52}H_{100}O_{20}Na$ (2M + Na), 1067.6700; found, 1067.6708.

***β*-D-Galactopyranosyl-(1→4)-3,6-anhydro-α-L-galactopyranosyl-(1→3)-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-tetradecyl-L-galactitol (8).** Compound **2** (0.163 g, 0.258 mmol) was alkylated as described for **3** and **4** using 1.25 equiv of Bu_2SnO (0.0800 g, 0.322 mmol) then 5.59 equiv of tetradecyl bromide (0.4 mL, 1.44 mmol) with added CsF (0.150 g, 0.773 mmol, 3.84 equiv) in dry DMF (3 mL). Normal workup was followed by flash chromatography on a silica gel column with ethyl acetate/methanol/H_2O (8:2:1) as eluent. An additional chromatography step with ethyl acetate/methanol/H_2O (17:2:1) was necessary for the elimination of minor impurities, giving compound **8** as a colorless syrup (0.0716 g, 34%) $[\alpha]^{22}_D = -13.7$ (*c* 0.3, MeOH); $R_f = 0.46$ (ethyl acetate/methanol/H_2O, 8:2:1). ^{1}H NMR δ (CD_3OD, 500.13 MHz): 5.16 (d, 1H, $J_{1,2} = 2.0$ Hz, H-1^3), 4.66 (d, 1H, H-4^3), 4.47 (d, 1H, H-1^2), 4.46 (s, 1H, H-5^3), 4.42 (d, 1H, H-1^4), 4.39 (b, 1H, H-3^3), 4.28 (b, 2H, H-4,^{1} H-5^1), 4.12 (d, 1H, H-6′^{3}), 4.03 (m, 1H, H-2^1), 4.01 (m, 1H, H-6^3), 4.00 (m, 1H, H-2^3), 3.91 (m, 3H, H-3,^{1} H-6′,^{1} H-4^2), 3.85 (b, 1H, H-4^4), 3.80 (b, 1H, H-6^1), 3.77 (complex m, 4H, H-6′,^{2} H-6,^{2} H-6′,^{4} H-6^4), 3.65 (m, 2H, H-2,^{2}H-3^2), 3.58 (b, 1H, H-5^2), 3.57 (m, 1H, H-5^4), 3.50 (m, 2H, H-2,^{4} H-3^4), 3.48 (complex m, 4H, H-1′,^{1} H-1,^{1} OC*H*′HCH$_2$, OCH′*H*CH$_2$), 1.58 (p, 2H, OCH$_2$C*H*$_2$), 1.40−1.20 (br, 22H, 11 × CH$_2$), 0.90 (t, 3H, CH$_3$). ^{13}C NMR: δ (CD_3OD, 125.77 MHz) 104.4 (C-1^2), 104.3 (C-1^4), 99.5 (C-1^3), 87.3 (C-4^1), 85.4 (C-3^1), 83.3 (C-3^2), 81.7 (C-3^3), 78.4 (C-4^3), 76.9 (C-5^3), 76.8 (C-5,^{1} C-5^2), 76.5 (C-5^4), 75.0 (C-3^2), 74.7 (C-6^1), 73.3 (C-1^1), 72.7 (O*C*H$_2$), 72.4 (C-2^4), 71.7 (C-2^2), 71.5 (C-2^3), 70.6 (C-6^3), 70.5 (C-4^2), 70.3 (C-2^1), 70.2 (C-4^4), 62.7−62.6 (C-6,^{2} C-6^4), 33.2 (*C*H$_2$CH$_2$CH$_3$), 31.1−29.6 (9 × *C*H$_2$), 27.4 (OCH$_2$CH$_2$*C*H$_2$), 23.8 (*C*H$_2$CH$_3$), 14.6 (CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{38}H_{67}O_{19}$ (M − H), 827.4282; found, 827.4265.

Sodium 3-*O*-Sulfonato-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-1-*O*-tetradecyl-L-galactitol (9). The dibutylstannylene acetal of compound **3** (0.0800 g, 0.153 mmol) was formed with 1.10 equiv of Bu_2SnO (0.0419 g, 0.168 mmol) as for **3** and **4**. The dibutylstannylene acetal was then reacted with 1.64 equiv of $Me_3N.SO_3$ complex (0.0350 g, 0.251 mmol) in dry THF (5 mL) for 15 h at room temperature under an argon atmosphere. The solvent was removed under vacuum, and the residue was resuspended in methanol (2 mL) and loaded onto a cation exchange resin column (Dowex 50 × 2−100, Na^+, 1.5 × 7 cm in methanol). The eluent was concentrated to a residue that was purified by flash chromatography on silica gel using ethyl acetate/methanol/H_2O (12:2:1) as eluent to give two fractions.

The first fraction was compound **9**, a colorless solid (0.0669 g, 70%), mp 123−125 °C; $[\alpha]^{23}_D = -10.2$ (*c* 0.2, MeOH); $R_f = 0.15$ (ethyl acetate/methanol/H_2O, 12:2:1); ^{1}H NMR: δ ($CDCl_3/CD_3OD/D_2O$, 2:1:1, 500.13 MHz) 4.55 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1^2), 4.32 (b, 1H, H-5^1), 4.31 (b, 1H, H-4^1), 4.26 (b, 1H, H-3^2), 4.24 (b, 1H, H-4^2), 4.01 (m, 1H, H-2^1), 3.94 (dd, 1H, H-6′^{1}), 3.92 (b, 1H, H-3^1), 3.80 (b, 1H, H-6^1), 3.79 (b, 1H, H-6′^{2}), 3.73 (b, 1H, H-6^2), 3.70 (b, 1H, H-2^2), 3.63 (q, 1H, H-5^2), 3.52 (b, 2H, H-1′,^{1} H-1^1), 3.48 (m, 2H, OC*H*′HCH$_2$, OCH′*H*CH$_2$), 1.57 (p, 2H, OCH$_2$C*H*$_2$), 1.34−1.20 (br, 22H, 11 × CH$_2$), 0.87 (t, 3H, CH$_3$). ^{13}C NMR δ ($CDCl_3/CD_3OD/D_2O$, 2:1:1, 125.77 MHz) 103.6 (C-1^2), 86.7 (C-4^1), 84.4 (C-3^1), 81.5 (C-3^2), 76.2 (C-5^1), 76.0 (C-5^2), 74.1 (C-6^1), 72.9 (C-1^1), 72.7 (O*C*H$_2$), 70.1 (C-2^2), 69.8 (C-2^1), 68.0 (C-4^2), 62.2 (C-6^2), 32.8 (*C*H$_2$CH$_2$CH$_3$), 30.5−29.8 (9 × *C*H$_2$), 26.8 (OCH$_2$CH$_2$*C*H$_2$), 23.4 (*C*H$_2$CH$_3$), 14.4 (CH$_3$). IR (KBr): 1240 cm^{-1} (S=O stretch), 828 cm^{-1} (C−O−S bend). HR ESI MS: *m*/*z* calcd for $C_{26}H_{49}O_{13}S$, (M − H), 601.2899; found, 601.2886.

The second fraction [$R_f = 0.10$ (ethyl acetate/methanol/H_2O, 12:2:1)] was a mixture containing three disulfated components (see text) (0.0040 g, 4%), termed l (large), m (medium), and s (small) from ^{13}C NMR peak heights. Partial ^{1}H NMR: δ ($CDCl_3/CD_3OD/D_2O$, 2:1:1, 500.13 MHz) 4.91 (symmetrical pentet, splitting between lines 2.4 Hz, H-5^1 in m), 4.75 (br dd, $J = 9.4$, 4.8 Hz), 4.68 (d, $J_{1,2} = 7.9$ Hz, H-1^2 in m), 4.59 (d, $J_{1,2} = 7.8$ Hz, H-1^2 in l). ^{13}C NMR: δ ($CDCl_3/CD_3OD/D_2O$, 2:1:1, 125.77 MHz) 104.0 (C-1^2 s), 103.0 (C-1^2 m), 102.9 (C-1^2 l), 87.2 (C-4^1 s), 86.1 (C-4^1 l), 84.5 (C-3^1 l), 84.3, 84.1, 83.3 (all m), 82.2, 81.1 (both s), 80.9 (l), 76.8 (s), 75.9 (l), 75.8 (s), 75.7 (m), 74.2 (l either OCH$_2$ or C-1^1), 73.3 (m), 72.7, 72.5, 72.4 (remaining OCH$_2$ and C-1^1), 69.8 (s), 69.6 (l), 69.3 (m), 69.3 (m), 67.9 (m), 67.5 (m), 67.2 (C-6^2 l), 62.1 (C-6^2 s), 61.9 (C-6^2 m), 55.4 (Me_3NH), 32.6 (*C*H$_2$CH$_2$CH$_3$), 30.3−30.0 (remaining CH$_2$), 26.6, 26.5 (OCH$_2$CH$_2$*C*H$_2$), 23.3 (*C*H$_2$CH$_3$), 14.5 (CH$_3$).

Sulfation of Compound 4. Compound **4** (0.0618 g, 0.0859 mmol) was reacted with Bu_2SnO (0.0235 g, 0.0944 mmol, 1.10 equiv) following the procedure described for the preparation of compounds **3** and **4**. The product was then stirred with the $Me_3N{\cdot}SO_3$ complex (0.0144 g, 0.1035 mmol, 1.20 equiv) in dry THF (4 mL) for 24 h at room temperature under an Ar atmosphere. The solvent was removed under vacuum, and the residue was resuspended in methanol (2 mL) and loaded onto a cation exchange resin column (Dowex 50 × 2−100, Na^+, 1.5 × 7 cm in methanol). The eluent was concentrated to a residue that was purified by flash chromatography on silica gel using ethyl acetate/methanol/H_2O (24:2:1) as eluent to give a mixture of two isomers that could not be separated (0.0103 g, 15%); $R_f = 0.18$ (ethyl acetate/methanol/H_2O, 24:2:1). From the peak heights of the two anomeric carbons, the ratio of the two isomers was 2 to 3 (s to l). Partial ^{1}H NMR: δ (DMSO-d_6, 500.13 MHz) 4.62 (symmetrical pentet, splitting between lines 2.4 Hz, H-5^1 in s), 4.32 (d, $J_{1,2} = 7.8$ Hz, H-1^2 in s), 4.29 (d, $J_{1,2} = 7.7$ Hz, H-1^2 in l). ^{13}C NMR: δ (DMSO-d_6, 125.77 MHz) 102.7 (C-1^2 s), 102.5 (C-1^2 l), 85.1 (C-4^1 s), 83.5 (C-4^1 l), 83.4 (s), 81.7 (s), 81.3 (l), 80.2 (s), 75.0 (s), 74.6 (l), 73.1 (C-1^1 or OCH$_2$, s), 72.8 (l), 72.0 (C-1^1 or OCH$_2$, s), 71.7 (C-1^1 or OCH$_2$, l), 71.0 (C-1^1 or OCH$_2$, s), 71.5 (C-1^1 or OCH$_2$, s and l), 69.4 (s), 69.1 (l), 68.9 (l), 68.8 (l), 68.7 (C-1^1 or OCH$_2$, l), 64.44 (l), 64.40 (C-6,^{2} l), 60.0 (C-6,^{2} s), 31.3 (*C*H$_2$CH$_2$CH$_3$), 29.5−29.7 (remaining CH$_2$), 25.7, 25.6 (OCH$_2$CH$_2$*C*H$_2$), 22.1 (*C*H$_2$CH$_3$), 14.0 (CH$_3$).

Sodium 4-*O*-Sulfonato-*β*-D-galactopyranosyl-(1→4)-3,6-anhydro-D-galactitol (10). Partial reductive hydrolysis of *κ*-carrageenan (0.40 g), obtained as previously described,[55] was conducted as described for the preparation of **1** and **2**. The hydrolyzate was worked up as previously;[55] acid was evaporated with the aid of added water; the residue was resuspended in water (≅ 4 mL) and applied to a DEAE-Sephadex A-25 (Cl-) column (2.5 cm × 12 cm × 33 mL/h). Elutions were carried out with water and then with NaCl continuous gradient (0−0.15 M). Anion exchange chromatography gave two fractions. The main fraction was desalted by water elution on a BioGel P-2 column (1.5 cm × 100 cm × 20 mL/h) to give the title product (**10**) as a colorless syrup (0.0095 g, 10%): $[\alpha]^{23}_D = +9.8$ (*c* 1.0, H_2O); $R_f = 0.34$ (ethyl acetate/methanol/H_2O, 6:3:1). ^{1}H NMR and ^{13}C NMR (D_2O) data were consistent with those reported previously.[55]

Sodium 4-*O*-Sulfonato-*β*-D-galactopyranosyl-(1 → 4)-3,6-anhydro-1-*O*-tetradecyl-D-galactitol (11). Compound **10** (0.127 g, 0.296 mmol), dried under vacuum at ∼60 °C in the presence of phosphorus pentoxide for 12 h, was reacted with 1.85 equiv of Bu_2-

SnO (0.137 g, 0.547 mmol) then with 9.8 equiv of tetradecyl bromide (0.80 mL, 2.9 mmol) and 3.83 equiv of CsF (0.173 g, 0.133 mmol) in dry DMF (3 mL) as described for the preparation of **3** and **4**. The resulting mixture was concentrated; the residue was resuspended in methanol (2 mL) and loaded onto a cation exchange resin column (Dowex 50 × 2−100, Na^+, 1.5 cm × 7 cm in methanol). The eluent was concentrated to a residue that was purified by dry flash column chromatography using ethyl acetate/methanol/H_2O (12:2:1) to give compound **11** as a colorless syrup (0.0660 g, 36%), $[\alpha]^{22}_D = +2.4$ (*c* 0.5, MeOH); $R_f = 0.15$ (ethyl acetate/methanol/H_2O, 12:2:1); ^{1}H NMR δ: (DMSO d_6, 500.13 MHz) 4.38 (d, 1H, H-4^2), 4.18 (d, 1H, $J_{1,2} = 7.8$ Hz, H-1^2), 4.16 (b, 1H, H-5^1), 3.98 (t, 1H, H-4^1), 3.76 (q, 1H, H-6′^{1}), 3.72 (t, 1H, H-3^1), 3.69 (b, 1H, H-2^1), 3.60 (q, 1H, H-6^1), 3.56 (m, 1H, H-5^2), 3.51 (m, 2H, H-6′,^{2} H-6^2), 3.42 (b, 1H, H-3^2), 3.39 (b, 1H, H-1′^{1}), 3.61 (b, 2H, OC*H*′HCH$_2$, OCH′*H*CH$_2$), 3.33 (b, 1H, H-1^1), 3.20 (m, 1H, H-2^2), 1.47 (p, 2H, OCH$_2$C*H*$_2$), 1.30−1.10 (br, 22H, 11 × CH$_2$), 0.85 (t, 3H, CH$_3$). ^{13}C NMR: δ (DMSO d_6, 125.77 MHz) 103.1 (C-1^2), 86.6 (C-4^1), 83.2 (C-3^1), 75.3 (C-5^1), 74.0 (C-4,^{2} C-5^2), 72.8 (C-6^1), 72.5 (C-3^2), 71.9 (C-1^1), 71.5 (C-2^2), 70.6 (O*C*H$_2$), 69.1 (C-2^1), 60.4 (C-6^2), 31.3 (*C*H$_2$CH$_2$CH$_3$), 29.2−25.7 (11 × *C*H$_2$), 22.1 (*C*H$_2$CH$_3$), 14.0 (CH$_3$). HR ESI MS: *m*/*z* calcd for $C_{26}H_{49}O_{13}S$ (M − H), 601.2899; found, 601.2916.

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Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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