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Carbohydrate Research 340 (2005) 2245–2250
Carbohydrate RESEARCH

Regioselective synthesis of long-chain ethers and their sulfates derived from methyl β-D-galactopyranoside and derivatives via dibutylstannylene acetal intermediates

Alan G. Gonçalves,[a,b] Miguel D. Noseda,[b] M. E. R. Duarte[b] and T. Bruce Grindley[a,*]

[a]*Department of Chemistry, Dalhousie University, Halifax, NS, Canada B3H 4J3*
[b]*Biochemistry and Molecular Biology Department, PO Box 19046, Federal University of Paraná, Curitiba, Brazil 81531-990*

Received 11 May 2005; received in revised form 11 July 2005; accepted 11 July 2005
Available online 9 August 2005

Abstract—A number of different conditions were investigated for the alkylation of the dibutylstannylene acetals of methyl β-D-galactopyranoside with long-chain primary alkyl bromides, decyl, dodecyl, and tetradecyl bromide. The best yields of the major products, the 3-*O*-alkyl ethers, were obtained by reaction of the alkyl bromide with the monodibutylstannylene acetal in DMF in the presence of cesium fluoride for extended periods of time at moderate temperatures (65 °C). These products were always accompanied by minor amounts of the 3,6-di-*O*-alkyl derivative. Performing the reaction with excess alkyl halide on the bis(dibutylstannylene) acetal resulted in more of the 3,6-di-*O*-alkyl derivative, particularly for the shorter alkyl bromides, but this product was never predominant. Sulfation of the dibutylstannylene acetal of methyl 3-*O*-tetradecyl-β-D-galactopyranoside resulted in the 6-sulfate in 96% yield.

Keywords: Dibutylstannylene; Alkylation; Antiviral; *cis*-Diol; Sulfation; Methyl β-D-galactopyranoside

1. Introduction

In recent years, glycoconjugates and polysaccharides have been shown to have important antiviral properties against several enveloped virus, such as, HIV-1, HIV-2, and HSV-1.[1,2] The inhibitory effect on virus entry shown by these compounds appears to be based mainly on the ability to interfere with the initial attachment of the virus to the target cell.[3] Furthermore, 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).[4–7] A cluster of basic and hydrophobic amino acids in the gC N-terminal motif has been identified as the major HS-binding domain. Further studies indicated that the presence of hydrophobic moieties in some carbohydrates may be involved in their inhibitory action.[8] This fact is consistent with the higher antiviral activity of fucans compared to carrageenans or dextrans, possibly due to the hydrophobic character of the fucose (C-6 methyl group) when compared with galactose or glucose.[9] In addition, alkyl glycosides of sulfated oligosaccharides with long hydrophobic alkyl chains have much higher anti-HIV-1 activities than their parent sulfated oligosaccharides.[10] These glycosides were prepared by attachment of hydrophobic alkyl groups to the reducing terminus of some oligosaccharides.[10,11]

Thus, it was considered important to evaluate the effect of alkyl group location on antiviral activity. Direct alkylation of hydroxyl groups using alkyl halides with long alkyl chains requires drastic conditions, such as sodium hydride in DMF, and reactions conducted under these conditions are never highly regioselective for polyhydroxy compounds.[12] Dibutylstannylene acetals have been used to provide regioselective substitution of diols and polyols using a wide variety of electrophiles[13–16] but have not been used to introduce long alkyl chains

* Corresponding author. Tel.: +1 902 494 2041; fax: +1 902 494 1310; e-mail: bruce.grindley@dal.ca

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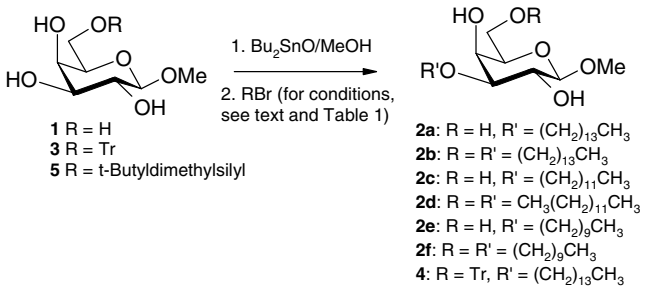
doi:10.1016/j.carres.2005.07.008

regioselectively onto pyranosides as ethers. They have been used to introduce long-chain esters.[17] They have also been used to alkylate glycerol derivatives at primary positions in moderate to good yields[18–20] and to alkylate xylitol at primary positions in moderate yields.[21]

In reactions of dibutylstannylene acetals, one of two oxygen atoms reacts preferentially. In alkylation reactions of an equatorial–axial pair in *cis*-diols on pyranose rings, the equatorial oxygen reacts preferentially. The most spectacular examples are the regioselective reactions at O-3 of alkyl β-D-lactosides, which have seven free hydroxyl groups, including two primary hydroxyls.[22–24] Here, we describe regioselective dibutylstannylene-mediated alkylations of methyl β-D-galactosides using long-chain alkyl bromides as model reactions for the preparation of potential antiviral compounds that contain long-chain ethers attached to galactose-containing oligosaccharides.

2. Results and discussion

Dibutylstannylene acetals were formed by heating the galactoside with dibutyltin oxide in dry methanol at reflux for 3 h, followed by removing the methanol and any traces of water by azeotropic distillation with toluene for 2 h. A number of conditions were investigated for the alkylation reactions of the dibutylstannylene acetals of methyl β-D-galactopyranoside (**1**) and its derivatives (see Scheme 1), as listed in Table 1. In all cases, the use of 1 equiv of dibutyltin oxide resulted in the preferential formation of the 3-*O*-alkyl derivative with varying amounts of the 3,6-di-*O*-alkyl derivative. The deshielded positions of the C-3 signals in the ^{13}C NMR spectra, assigned via COSY and HSQC experiments, established the structures of these products unambiguously. It is very well known that alkylation reactions performed on dibutylstannylene acetals derived from *cis*-diols on six-membered rings results in alkylation on the equatorial oxygen atom[13,14,25,26] and the current results extend the structures of the alkylating agents used to long-chain alkyl bromides.



Scheme 1. Alkylation of methyl β-D-galactopyranoside and its derivatives.

It was found that the reactions of the long-chain alkyl bromides with dibutylstannylene acetals using the conditions of Danishefsky and Hungate[27] and by Nagashima and Ohno,[28,29] that is, in DMF with added cesium fluoride, gave somewhat better yields than the first conditions developed for alkylation reactions of dibutylstannylene acetals by Veyrières and co-workers,[22] that is, in benzene or toluene with added tetraalkyl ammonium halides (in Table 1, compare entry 2 with entry 4 or 8). Reactions of dibutylstannylene acetals with active alkyl halides, methyl iodide, benzyl iodide, and benzyl bromide occur in DMF with added cesium fluoride at rt;[29] the less active alkyl bromides used here react very slowly at room temperature (see entry 3). Increasing the reaction temperatures resulted in isolation of the desired product (in Table 1, compare entries 3, 4, 6, and 12) but isolated yields decreased as the temperatures were increased beyond about 70 °C. It is presumed that this decrease results from Lewis-acid catalyzed decomposition of starting materials and/or products. Moderate temperatures for longer reaction times (65 °C for 48 h) gave better yields than shorter reaction times at more elevated temperatures (in Table 1, compare entries 4–7 with entries 8–11).

Formation of the bis(dibutylstannylene) acetal by reaction with 2 equiv of dibutyltin oxide followed by reaction with excess alkyl halide at extended reaction times increased the amount of the 3,6-di-*O*-alkyl product but it was not possible to find conditions under which these products were predominant (in Table 1, see entries 5, 9, 11, 13, and 15). The ease of formation of the 3,6-di-*O*-alkyl product increased as the length of the alkyl chain decreased (entries 9, 13, and 15). Expressed as a percentage of the product mixture, the maximum of the dialkyl product obtained for direct reaction of the bisdibutylstannylene acetal with alkyl bromide was 25%, 45%, and 53% for the tetradecyl, dodecyl, and decyl bromides, respectively. It appears that the longest alkyl chain occupies sufficient space as to interfere with the second alkylation. Only when the dibutylstannylene acetal of the purified 3-*O*-tetradecyl derivative **2a** was reacted with the alkyl bromide was the dialkyl derivative **2b** obtained in a reasonable, if modest, yield (entry 18).

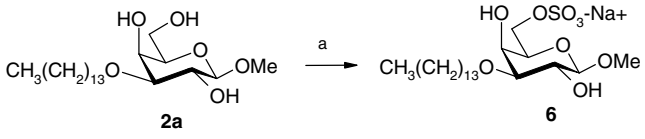
Performing the alkylation reaction on the 6-*O*-trityl derivative **3** resulted in the production of the 3-*O*-alkyl derivative only (Table 1, entry 16). However, the 6-*O*-*tert*-butyldimethylsilyl derivative **5** was not stable to these reaction conditions (entry 17).

It has previously been shown that regioselective sulfation can be performed via dibutylstannylene derivatives,[30–33] although examples of the preferential sulfation of primary hydroxyls are less common.[34] Tributyltin ethers have been shown to give selective substitution at primary hydroxyls.[33] The 3-*O*-tetradecyl derivative **2a** was sulfated at O-6 in very high yield

Table 1. Di- and monoalkylation of methyl β-galactosides via dibutylstannylene acetals

Entry	Substrate	Eq. of Bu_2SnO	$Br(CH_2)_nCH_3$ (equiv)	Added nucleophile (equiv)[a]	Temp (°C)	Time (h)	Product (% yield)
1	**1**	1.01	$n = 13$ (1.41)	TBAB (1.03)	Reflux	5	—
2	**1**	1.2	$n = 13$ (3.45)	TBAB (2.00)	80	15	**2a** (37), **2b** (9)
3	**1**	1.00	$n = 13$ (1.00)	CsF (1.00)	rt	16	—
4	**1**	1.20	$n = 13$ (1.20)	CsF (2.50)	80	16	**2a** (53), **2b** (8)
5	**1**	2.02	$n = 13$ (4.33)	CsF (4.07)	80	16	**2a** (45), **2b** (16)
6	**1**	1.10	$n = 13$ (2.40)	CsF (2.07)	140	16	**2a** (25), **2b** (5)
7	**1**	1.02	$n = 13$ (4.00)	CsF (2.33)	120	17	**2a** (25), **2b** (7)
8	**1**	1.13	$n = 13$ (1.81)	CsF (2.66)	65	48	**2a** (61), **2b** (3)
9	**1**	2.04	$n = 13$ (5.35)	CsF (2.79)	65	96	**2a** (55), **2b** (10)
10	**1**	1.00	$n = 13$ (26.27)	CsF (3.19)	70	72	**2a** (42), **2b** (10)
11	**1**	2.00	$n = 13$ (26.27)	CsF (3.19)	70	72	**2a** (48), **2b** (16)
12	**1**	1.05	$n = 11$ (1.82)	CsF (2.61)	65	48	**2c** (67), **2d** (7)
13	**1**	2.01	$n = 11$ (5.20)	CsF (5.03)	65	96	**2c** (40), **2d** (33)
14	**1**	1.05	$n = 9$ (2.16)	CsF (2.53)	65	48	**2e** (68), **2f** (6)
15	**1**	2.00	$n = 9$ (5.28)	CsF (2.93)	65	96	**2e** (36), **2f** (40)
16	**3**	1.04	$n = 13$ (3.38)	CsF (3.32)	80	15	**4** (61)
17	**5**	1.07	$n = 13$ (3.23)	CsF (3.41)	80	16	**2a** (30)
18	**2a**	1.10	$n = 13$ (3.52)	CsF (3.21)	65	96	**2b** (32)
19	**1**	2.00	$n = 9$ (27.53)	CsF (3.19)	70	72	[b]

[a] Reactions using tetra-*n*-butylammonium bromide (TBAB) as the added nucleophile were performed in toluene. Those using CsF as the added nucleophile were performed in *N*,*N*-dimethylformamide.
[b] Complex mixture containing at least five different products.



Scheme 2. Sulfation of methyl 3-*O*-tetradecyl-β-D-galactopyranoside. Reagents and conditions: (a) (i) Bu_2SnO/toluene, reflux 15 h; (ii) $SO_3{\cdot}NMe_3$/THF, rt 48 h; (iii) cation-exchange resin (Na^+), 96%.

through reaction of the dibutylstannylene acetal with the sulfur trioxide–trimethylamine complex in THF (Scheme 2). The process of cation replacement using a cation exchange resin followed by silica gel chromatography removed tin-containing impurities efficiently, overcoming a difficulty noted recently.[35]

3. Conclusions

The monodibutylstanylene acetal of methyl β-D-galactopyranoside reacts with long-chain primary alkyl bromides in DMF containing cesium fluoride to give the 3-*O*-alkyl ethers in yields ranging from 61% to 68% if the reaction is conducted at moderate temperatures (65 °C) for 48 h. Small amounts (3–7%) of the 3,6-di-*O*-alkyl derivatives are obtained along with the major products. The bisdibutylstanylene acetal yields more of the di-*O*-alkylated products but conditions could not be found where these were predominant. Sulfation of the dibutylstannylene acetal of methyl 3-*O*-tetradecyl-β-D-galactopyranoside yielded the 6-sulfate in excellent yield. The methods described in this publication for both regioselective alkylation and sulfation are now being applied to the synthesis of long-chain alkyl ethers and the sulfates of galactose-containing oligosaccharides. The antiviral activities of these compounds will be reported shortly.

4. Experimental

4.1. General methods

Melting points were determined using a Fisher–Johns melting point apparatus and were uncorrected. Optical rotations were determined with a Rudolph Instruments Digipol 781 automatic polarimeter. Thin-layer chromatography (TLC) was performed on silica gel coated aluminum sheets 60 F_{254} (Silicycle) using solvent mixtures measured on a v/v basis. After chromatography, galactosides were visualized by spraying the plate with a solution of 0.5% orcinol in ethanol/concd H_2SO_4 (20/1) and heating on a hot plate until coloration was observed. Purification of compounds was carried out with flash column chromatography using TLC grade silica gel 60 (Silicycle). ^1H and ^{13}C NMR spectra were recorded in 5 mm NMR tubes on a Bruker Avance-500 NMR spectrometer operating at 500.13 and 125.77 MHz, respectively, in $CDCl_3$ unless otherwise specified. Chemical shifts are given in parts per million and referenced to internal Me_4Si (0.00 ppm), or the central line of $CDCl_3$ (77.16 ppm) for ^1H and ^{13}C NMR spectra, respectively. All assignments were performed with the aid of COSY, HSQC, and/or HMBC experiments. Assignments and magnitudes of coupling constants were obtained for

^{1}H NMR spectra by first-order analyses. The appearance of signals is indicated using the abbreviations br, s, d, t, q, p, and m for broad, singlet, doublet, triplet, quartet, pentet, and multiplet, respectively. Low resolution electrospray mass spectra (LR ESI MS) were recorded on a Finnegan LCQ. High resolution electrospray mass spectra (HR ESI MS) were recorded on a Micromass/Waters LCT mass spectrometer with samples dissolved in CH_3OH using trilysine KKK or rifampicin as references. Microanalyses were performed by the Canadian Microanalytical Service, Delta, BC. All solvents used in the experiments were dried and purified by standard methods and distilled before use.

4.2. Starting materials

Methyl β-D-galactopyranoside (**1**) was prepared by methanolysis of acetobromogalactose in the presence of iodine[36] followed by standard deacetylation, as colorless crystals from ethanol, mp 175–178 °C, lit.[37] mp 179–180 °C; $[\alpha]_D^{23}$ −15.5 (*c* 1.0, CH_3OH), lit.[37] $[\alpha]_D^{23}$ −17; methyl 6-*O*-trityl-β-D-galactopyranoside (**3**) was obtained from **1** as previously;[38,39] methyl 6-*O*-*tert*-butyldimethylsilyl-β-D-galactopyranoside (**5**) was also obtained as previously described as a colorless syrup.[40]

4.3. General method for alkylation reactions

Galactosides (0.5–1 mmol) and dibutyltin oxide (equivalents listed in Table 1) were heated for 3 h at reflux in CH_3OH and then at reflux in toluene for 2 h with the azeotropic removal of H_2O. Compound **5** was heated at reflux in toluene with dibutyltin oxide with the azeotropic removal of H_2O for 15 h. After toluene evaporation, the dibutylstannylene acetal of the methyl galactopyranosides were used for the following step without purification. Dry solvent (toluene or DMF, 5–8 mL), nucleophile, and alkyl halide (Table 1) were then added at room temperature. The resulting mixtures were stirred vigorously under the conditions given in Table 1. After the given reaction time, the solvent was removed under vacuum and the residue was stirred with EtOAc and then filtered. The filtrate was concentrated and purified by flash chromatography using solvent gradients from hexanes/EtOAc (8:1) to EtOAc as eluents. The following compounds were obtained in the yields shown in Table 1.

4.4. Methyl 3-*O*-tetradecyl-β-D-galactopyranoside (2a)

White powder from hexanes: mp 82–83 °C; $[\alpha]_D^{23}$ +5.6 (*c* 0.5, $CHCl_3$); R_f 0.37 (EtOAc); ^{1}H NMR: δ_H, 0.88 (t, 3H, CH_2CH_3), 1.23–1.36 (br, 22H, $11\times CH_2$), 1.63 (p, 2H, OCH_2CH_2), 2.21 (dd, 1H, OH-6), 2.41 (br s, 1H, OH-2), 2.55 (br s, 1H, OH-4), 3.31 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.54 (br m, 1H, H-5), 3.58 (br, 4H, OCH_3, $OCHH'CH_2$), 3.66 (m, 1H, $OCH'HCH_2$), 3.69 (m, 1H, H-2), 3.87 (ddd, 1H, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 11.6 Hz, $J_{6,OH\text{-}6}$ 8.2 Hz, H-6), 4.00 (ddd, 1H, $J_{5,6'}$ 6.3 Hz, $J_{6',OH\text{-}6}$ 3.7 Hz, H-6′), 4.06 (br s, 1H, H-4), 4.21 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR: δ_C, 14.1 (1C, CH_2CH_3), 22.7 (1C, CH_2CH_3), 26.1 (1C, $OCH_2CH_2CH_2$), 29.4–29.7 (8C, $8\times CH_2$), 29.9 (1C, OCH_2CH_2), 31.9 (1C, $CH_2CH_2CH_3$), 57.1 (1C, OCH_3), 62.5 (1C, C-6), 66.6 (1C, C-4), 70.3 (1C, OCH_2), 70.6 (1C, C-2), 74.3 (1C, C-5), 81.1 (1C, C-3), 104.0 (1C, C-1); HR ESI MS *m*/*z* calcd for $C_{21}H_{42}O_6Na^+$: 413.2879. Found: 413.2886; calcd for $2(C_{21}H_{42}O_6)Na^+$: 803.5860. Found: 803.5864.

4.5. Methyl 3,6-di-*O*-tetradecyl-β-D-galactopyranoside (2b)

White powder from 95% ethanol: mp 41–43 °C; $[\alpha]_D^{23}$ +4.2 (*c* 0.5, $CHCl_3$); R_f 0.60 (hexanes/EtOAc, 3:2); ^{1}H NMR: δ_H, 0.88 (t, 6H, $2\times CH_2CH_3$), 1.33–1.22 (br, 44H, $2\times(CH_2)_{11}CH_3$), 1.58 (m, 2H, C-6 OCH_2CH_2), 1.63 (m, 2H, C-3 OCH_2CH_2), 2.44 (br s, 1H, OH-2), 2.49 (br s, 1H, OH-4), 3.28 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.51 (m, 2H, C-6 O–CH_2CH_2), 3.55 (m, 1H, C-3 $OCHH'CH_2$), 3.56 (s, 3H, OCH_3), 3.57 (br m, 1H, H-5), 3.67 (m, 1H, C-3 $OCHH'CH_2$), 3.68 (m, 1H, H-6), 3.70 (m, 1H, H-2), 3.78 (m, 1H, H-6′), 4.05 (br s, 1H, H-4), 4.19 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR: δ_C, 14.1 (2C, $2\times CH_2CH_3$), 22.7 (2C, $2\times CH_2CH_3$), 26.1 (2C, $2\times OCH_2CH_2CH_2$), 29.4–29.7 (16C, $16\times CH_2$), 29.6 (1C, C-6 OCH_2CH_2), 29.9 (1C, C-3 OCH_2CH_2), 31.9 (2C, $2\times CH_2CH_2CH_3$), 56.9 (1C, OCH_3), 66.6 (1C, C-4), 69.6 (1C, C-6), 70.1 (1C, C-3 OCH_2), 70.7 (1C, C-2), 72.0 (1C, C-6 OCH_2), 73.5 (1C, C-5), 81.3 (1C, C-3), 103.9 (1C, C-1); HR ESI MS *m*/*z* calcd for $C_{35}H_{70}O_6Na^+$: 609.5070. Found: 609.5061; calcd for $2(C_{35}H_{70}O_6)Na^+$: 1196.0243. Found: 1196.0275.

4.6. Methyl 3-*O*-dodecyl-β-D-galactopyranoside (2c)

White powder from hexanes, mp 83–85 °C; $[\alpha]_D^{23}$ +7.6 (*c* 0.5, $CHCl_3$); R_f 0.34 (EtOAc); ^{1}H NMR: δ_H, 0.88 (t, 3H, CH_2CH_3), 1.34–1.24 (br, 18H, $(CH_2)_9CH_3$), 1.63 (p, 2H, OCH_2CH_2), 2.33 (dd, 1H, OH-6), 2.49 (br s, 1H, OH-2), 2.61 (br s, 1H, OH-4), 3.30 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.53 (br, 1H, H-5), 3.58 (br m, 4H, OCH_3, $OCHH'CH_2$), 3.66 (m, 1H, $OCH'HCH_2$), 3.69 (m, 1H, H-2), 3.86 (ddd, 1H, $J_{5,6}$ 4.7 Hz, $J_{6,6'}$ 11.6 Hz, $J_{6,OH\text{-}6}$ 8.4 Hz, H-6), 3.99 (ddd, 1H, $J_{5,6'}$ 6.4 Hz, $J_{6',OH\text{-}6}$ 4.0 Hz, H-6′), 4.06 (br, 1H, H-4), 4.21 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR: δ_C 14.1 (1C, CH_2CH_3), 22.7 (1C, CH_2CH_3), 26.1 (1C, $OCH_2CH_2CH_2$), 29.4–29.7 (6C, $6\times CH_2$), 29.9 (1C, OCH_2CH_2), 31.9 (1C, $CH_2CH_2CH_3$), 57.1 (1C, OCH_3), 62.5 (1C, C-6), 66.6 (1C, C-4), 70.3 (1C, OCH_2), 70.7 (1C, C-2), 74.3 (1C, C-5), 81.1 (1C, C-3), 104.0 (1C, C-1); LR ESI MS *m*/*z*

calcd for $C_{19}H_{38}O_6Na^+$: 385.26. Found: *m*/*z* 385.3; calcd for $2(C_{19}H_{38}O_6)Na^+$: 747.5. Found: *m*/*z* 747.1.

Anal. Calcd for $C_{19}H_{38}O_6$: C, 62.95; H, 10.67. Found: C, 62.90; H, 10.74.

4.7. Methyl 3,6-di-*O*-dodecyl-β-D-galactopyranoside (2d)

Colorless syrup; $[\alpha]_D^{23}$ +1.7 (*c* 0.8, $CHCl_3$), R_f 0.57 (hexanes/EtOAc 3:2); ^1H NMR: δ_H, 0.88 (t, 6H, $2\times CH_2CH_3$), 1.33–1.23 (br, 36H, $2\times(CH_2)_9CH_3$), 1.58 (m, 2H, C-6 OCH_2CH_2), 1.63 (m, 2H, C-3 OCH_2CH_2), 2.35 (br s, 1H, OH-2), 2.46 (br s, 1H, OH-4), 3.28 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.51 (m, 2H, C-6 O–CH_2), 3.55 (m, 1H, C-3 $OCHH'CH_2$), 3.56 (s, 3H, OCH_3), 3.57 (br m, 1H, H-5), 3.67 (m, 1H, C-3 $OCHH'CH_2$), 3.68 (m, 1H, H-6), 3.70 (m, 1H, H-2), 3.78 (m, 1H, H-6), 4.05 (br, 1H, H-4), 4.19 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR: δ_C, 14.1 (2C, $2\times CH_2CH_3$), 22.7 (2C, $2\times CH_2CH_3$), 26.1 (2C, $2\times OCH_2CH_2CH_2$), 29.4–29.7 (12C, $12\times CH_2$), 29.6 (1C, C-6 OCH_2CH_2), 29.9 (1C, C-3 OCH_2CH_2), 31.9 (2C, $2\times CH_2CH_2CH_3$), 56.9 (1C, OCH_3), 66.1 (1C, C-4), 69.6 (1C, C-6), 70.2 (1C, C-3 OCH_2), 70.7 (1C, C-2), 72.0 (1C, C-6 OCH_2), 73.5 (1C, C-5), 81.3 (1C, C-3), 103.9 (1C, C-1); HR ESI MS *m*/*z* calcd for $C_{31}H_{62}O_6Na^+$: 553.4444. Found: 553.4435; calcd for $2(C_{31}H_{62}O_6)Na^+$: 1083.8991. Found: 1083.8992.

4.8. Methyl 3-*O*-decyl-β-D-galactopyranoside (2e)

White powder from hexanes, mp 84–86 °C; $[\alpha]_D^{23}$ +8.6 (*c* 0.5, $CHCl_3$); R_f 0.31 (EtOAc); ^1H NMR: δ_H, 0.88 (t, 3H, CH_2CH_3), 1.34–1.24 (br, 14H, $(CH_2)_7CH_3$), 1.63 (p, 2H, OCH_2CH_2), 2.30 (dd, 1H, OH-6), 2.47 (br s, 1H, OH-2), 2.60 (br s, 1H, OH-4), 3.30 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.53 (br m, 1H, H-5), 3.58 (br m, 4H, OCH_3, $OCHH'CH_2$), 3.66 (m, 1H, $OCHH'CH_2$), 3.68 (m, 1H, H-2), 3.86 (m, 1H, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 11.6 Hz, $J_{6,OH\text{-}6}$ 8.0 Hz, H-6), 3.99 (m, 1H, $J_{5,6'}$ 6.4 Hz, $J_{6',OH\text{-}6}$ 4.6 Hz, H-6′), 4.06 (br s, 1H, H-4), 4.21 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR δ 14.1 (1C, CH_2CH_3), 22.7 (1C, CH_2CH_3), 26.1 (1C, $OCH_2CH_2CH_2$), 29.3–29.6 (4C, $4\times CH_2$), 29.9 (1C, OCH_2CH_2), 31.9 (1C, $CH_2CH_2CH_3$), 57.1 (1C, OCH_3), 62.5 (1C, C-6), 66.6 (1C, C-4), 70.3 (1C, OCH_2), 70.7 (1C, C-2), 74.3 (1C, C-5), 81.1 (1C, C-3), 104.0 (1C, C-1); LR ESI MS *m*/*z* calcd for $C_{17}H_{34}O_6Na^+$: 357.23. Found: 357.2; calcd for $2(C_{17}H_{34}O_6)Na^+$: 691.46. Found: 691.1.

Anal. Calcd for $C_{17}H_{34}O_6$: C, 61.05; H, 10.25. Found: C, 60.92; H, 10.03.

4.9. Methyl 3,6-di-*O*-decyl-β-D-galactopyranoside (2f)

Colorless syrup; $[\alpha]_D^{23}$ +1.5 (*c* 0.7, $CHCl_3$), R_f 0.54 (hexanes/EtOAc, 3:2); ^1H NMR: δ_H, 0.88 (t, 6H, $2\times CH_2CH_3$), 1.34–1.23 (br, 28H, $2\times(CH_2)_7CH_3$), 1.58 (m, 2H, C-6 OCH_2CH_2), 1.63 (m, 2H, C-3 OCH_2CH_2), 2.36 (br s, 1H, OH-2), 2.46 (br s, 1H, OH-4), 3.28 (dd, 1H, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 3.4 Hz, H-3), 3.55 (m, 1H, C-3 $OCHH'CH_2$), 3.56 (s, 3H, OCH_3), 3.57 (m, 3H, H-5, C-6 OCH_2), 3.67 (m, 1H, C-3 $OCHH'CH_2$), 3.68 (m, 1H, H-6), 3.69 (m, 1H, H-2), 3.77 (m, 1H, H-6), 4.05 (br, 1H, H-4), 4.19 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR: δ_C, 14.1 (2C, $2\times CH_2CH_3$), 22.7 (2C, $2\times CH_2CH_3$), 26.1 (2C, $2\times OCH_2CH_2CH_2$), 29.3–29.6 (8C, $8\times CH_2$), 29.6 (1C, C-6 OCH_2CH_2), 29.9 (1C, C-3 OCH_2CH_2), 31.9 (2C, $2\times CH_2CH_2CH_3$), 56.9 (1C, OCH_3), 66.1 (1C, C-4), 69.6 (1C, C-6), 70.2 (1C, C-3 OCH_2), 70.7 (1C, C-2), 72.1 (1C, C-6 OCH_2), 73.6 (1C, C-5), 81.3 (1C, C-3), 103.9 (1C, C-1); HR ESI MS *m*/*z* calcd for $C_{27}H_{54}O_6Na^+$: 497.3818. Found: 497.3828; calcd for $2(C_{17}H_{34}O_6)Na^+$: 971.7738. Found: *m*/*z* 971.7742.

4.10. Methyl 3-*O*-tetradecyl-6-*O*-triphenylmethyl-β-D-galactopyranoside (4)

Colorless syrup; $[\alpha]_D^{23}$ −8.6 (*c* 1.3, $CHCl_3$); R_f 0.62 (hexanes/EtOAc, 3:2); ^1H NMR: δ_H, 0.88 (t, 3H, CH_2CH_3), 1.36–1.23 (br, 22H, $(CH_2)_{11}CH_3$), 1.62 (p, 2H, OCH_2CH_2), 2.41 (br s, 1H, OH-2), 2.31 (br s, 1H, OH-4), 3.25 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 3.3 Hz, H-3), 3.40 (m, 1H, H-6), 3.48 (m, 1H, H-6′), 3.51 (br m, 1H, H-5), 3.54 (m, 1H, $OCHH'CH_2$), 3.57 (s, 3H, OCH_3), 3.65 (m, 1H, $OCHH'CH_2$), 3.68 (m, 1H, H-2), 4.03 (br, 1H, H-4), 4.17 (d, 1H, $J_{1,2}=7.8$ Hz, H-1), 7.22–7.47 (complex m, 15H, Ar–H); ^{13}C NMR δ 14.1 (1C, CH_2CH_3), 22.7 (1C, CH_2CH_3), 26.0 (1C, $OCH_2CH_2CH_2$), 29.3–29.7 (8C, $8\times CH_2$), 29.9 (1C, OCH_2CH_2), 31.9 (1C, $CH_2CH_2CH_3$), 56.7 (1C, OCH_3), 63.1 (1C, C-6), 66.2 (1C, C-4), 70.2 (1C, OCH_2), 70.8 (1C, C-2), 73.8 (1C, C-5), 81.3 (1C, C-3), 86.9 (1C, $OCPh_3$) 103.8 (1C, C-1), 127.1 (3ArCH), 127.9 (6ArCH), 128.7 (6ArCH), 143.9 (3ArqC); HR ESI MS *m*/*z* calcd for $C_{40}H_{56}O_6Na^+$: 655.3975. Found: 655.3966; calcd for $2(C_{17}H_{34}O_6)Na^+$: 1287.8052. Found: 1287.8049.

4.11. Methyl 3-*O*-tetradecyl-6-*O*-sulfonato-β-D-galactopyranoside, sodium salt (6)

Compound **2a** (0.5224 g, 1.338 mmol) and dibutyltin oxide (0.340 g, 1.02 equiv) were heated at reflux in toluene for 15 h, and then concentrated. The residue was taken up in dry THF (15 mL) and $SO_3{\cdot}Me_3$ (0.465 g, 2.50 equiv) was added. After being stirred for 48 h at rt under argon, the reaction mixture was concentrated. The residue was diluted with CH_3OH (5 mL), then loaded onto a cation exchange resin column (Dowex 50X2-100, Na+, 1.5×7 cm). The column was eluted with CH_3OH. The eluent was concentrated to a residue that was purified by flash chromatography on silica gel using $EtOAc/CH_3OH/H_2O$, 24:2:1 as eluent to give

solid **6** (0.6391 g, 96%), crystallized from hexanes/EtOAc (4:1) as colorless cubes, mp 171–173 °C; $[\alpha]_D^{23}$ +12.0 (*c* 0.9, CH_3OH), R_f 0.24 ($EtOAc/CH_3OH/H_2O$, 24:2:1); ^1H NMR (DMSO-d_6): δ_H, 0.85 (t, 3H, CH_2CH_3), 1.34–1.18 (br, 22H, $(CH_2)_{11}CH_3$), 1.49 (p, 2H, OCH_2CH_2), 3.05 (dd, 1H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 3.2 Hz, H-3), 3.33 (br, 1H, H-2), 3.36 (m, 1H, $OCHH'CH_2$), 3.37 (s, 3H, OCH_3), 3.52 (m, 1H, H-5), 3.55 (m, 1H, $OCHH'CH_2$), 3.80 (m, 2H, H-4, H-6), 3.86 (m, 1H, H-6′), 4.00 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1); ^{13}C NMR (DMSO-d_6): δ_c, 13.9 (1C, CH_2CH_3), 22.1 (1C, CH_2CH_3), 25.6 (1C, $OCH_2CH_2CH_2$), 28.7–29.1 (8C, $8 \times CH_2$), 29.6 (1C, OCH_2CH_2), 31.3 (1C, $CH_2CH_2CH_3$), 55.9 (1C, OCH_3), 64.8 (1C, C-4), 65.0 (1C, C-6), 68.7 (1C, OCH_2), 69.2 (1C, C-2), 72.8 (1C, C-5), 81.3 (1C, C-3), 104.4 (1C, C-1); HR ESI MS *m*/*z* calcd for $C_{21}H_{41}O_9S^-$: 469.2471. Found: 469.2464; calcd for $2(C_{21}H_{41}O_9S)Na^-$: 961.4840. Found: *m*/*z* 961.4835.

Acknowledgments

T.B.G. thanks NSERC for support. M.D.N. is a research member of the National Research Council of Brazil (CNPq). A.G. is grateful for a scholarship from CNPq Brazil to spend a year at Dalhousie. NMR spectra were recorded at the Atlantic Region Magnetic Resonance Centre. We thank Dr. Yun Ling of the Department of Chemistry, UBC for the high resolution ESI mass spectra.

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