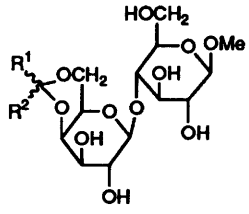
Carbohydrate-derived Surfactants: Synthesis and Phase Behaviour of Methyl 4',6'-Di-*O*-alkyl-β-lactosides

Virginie Langlois and J. Michael Williams*
Chemistry Department, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK

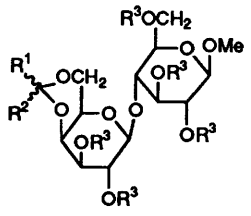
In order to study the physical properties of lactose-derived surfactants, methyl 4',6'-di-*O*-hexyl-β-lactoside and methyl 4',6'-di-*O*-octyl-β-lactoside were prepared. The 4',6'-*O*-isopropylidene ketal was used as a temporary protecting group in the key intermediate. The 3',4'-*O*-benzylidene acetal was identified as a minor by-product in the preparation of methyl 4',6'-*O*-benzylidene-β-lactoside by acid-catalysed transacetalation. The phase behaviour of these derivatives is reported.

During recent years, the surfactant market has experienced frequent changes, which are due to variations in the raw-material base and new requirements from the consumers and legislators. Indeed, there is a need for new ecologically safe surfactants based on renewable resources with high biodegradability. In this context, carbohydrates have recently begun to be considered as interesting starting materials for surfactants in the detergent industry. Only a few of these new 'green' surfactants are commercially available (*e.g.*, alkyl polyglucosides, sucrose esters); consequently it was decided to investigate further the use of carbohydrates in the synthesis of surfactants, and especially the influence of structural changes on physical properties.

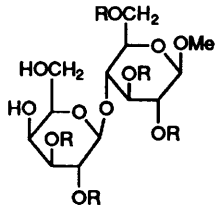
So far, the carbohydrate-derived surfactants found in the current literature are mainly monosubstituted derivatives of monosaccharides, most of these being alkyl glucosides and acylated glucose derivatives; thus, dialkylated derivatives of disaccharides were identified as interesting target molecules. Methyl 4',6'-di-*O*-hexyl-β-lactoside **7** and methyl 4',6'-di-*O*-octyl-β-lactoside **8** were synthesized and their physical properties were investigated.



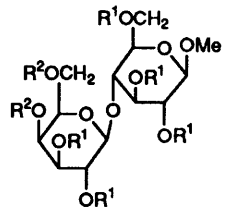
1 R^1 = Ph, R^2 = H
2 R^1 = R^2 = Me



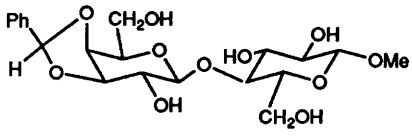
3 R^1 = R^2 = Me, R^3 = CH_2Ph



4 R = CH_2Ph



5 R^1 = CH_2Ph, R^2 = $Me[CH_2]_5$
6 R^1 = CH_2Ph, R^2 = $Me[CH_2]_7$
7 R^1 = H, R^2 = $Me[CH_2]_5$
8 R^1 = H, R^2 = $Me[CH_2]_7$



A

Results and Discussion

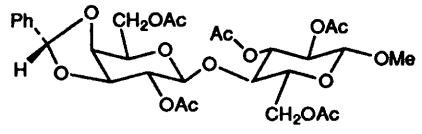
Conversion of methyl β-lactoside [1] into methyl 4',6'-di-*O*-alkyl-β-lactoside was accomplished in five steps by sequential acetalation, benzylation, acid-catalysed deacetalation, alkylation and debenzylation through the intermediates **1**–**6**.

Protection of positions 4' and 6' in methyl β-lactoside could be accomplished *via* methyl 4',6'-*O*-benzylidene-β-lactoside **1**, which was synthesized by the reaction of methyl β-lactoside with benzaldehyde containing zinc chloride.[2] Compound **1** was isolated by column chromatography as a solid in 37–43% yield. In view of the low yields, an acetal-exchange method, in which methyl β-lactoside was condensed at 60 °C with α,α-dimethoxytoluene in dimethylformamide (DMF) containing toluene-*p*-sulfonic acid (PTSA), was next tried.[3] The mixture of products obtained was fractionated by column chromatography; compound **A** was first eluted, followed by compound **1** (42% yield), and starting material. Compound **A** was an isomer of the acetal **1**, the main difference between the 250 MHz spectra of isomers **A** and **1** being the methine C*H*Ph proton, which had a chemical shift of δ_H 6.07 for **A** and δ_H 5.62 for **1**. Thus, compound **A** could be either a positional isomer, a 3',4'-*O*-benzylidene derivative, or a diastereoisomer of compound **1**.

Both zinc chloride–benzaldehyde and acetal-exchange methods are acid-catalysed reactions. Since the reaction is reversible under these conditions, the configuration at the benzylidene carbon is thermodynamically controlled, consequently one diastereoisomer is normally present at the true equilibrium. Diastereoisomeric acetals have been shown to form under basic conditions, when the reaction is irreversible and is governed by kinetic control. For instance, benzylidenation of benzyl 2,3-di-*O*-methyl-β-D-galactoside with a *gem* dihalide reagent and a base [4] gave two diastereoisomers of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-galactoside; the NMR (in $CDCl_3$) data given for the benzylic proton were δ_H 6.30 and 5.61, the latter value being due to the thermodynamic isomer. The 3',4'-*O*-benzylidene structure was established for compound **A** by NMR data on the peracetates of isomers **1** and **A**, which were prepared in crystalline form. Assignments of the proton NMR spectra were confirmed by spin decoupling and/or correlation spectroscopy (COSY) measurements and spin simulation. The coupling constants for the galactose moiety of the pentaacetate of compound **A** implied a significant distortion of the pyranose chair conformation. In particular, the smaller value for $J_{2',3'}$ (6.8 Hz) compared with that (10.5 Hz) for the pentaacetate of the 4',6'-acetal **1** and the larger value of $J_{3',4'}$ (6.1 Hz) compared

with that (3.5 Hz) for **1** pentaacetate are consistent with a flattening of the chair to decrease the dihedral angle between 2'-H and 3'-H and between 3'-H and 4'-H. Such a conformation seemed more likely for the 3',4'-*O*-benzylidene derivative **9**.

This structure was supported by the proton and carbon chemical shifts. Thus, 3'-H (δ_H 4.88) in the 4',6'-*O*-benzylidene acetal was more deshielded than 3'-H (δ_H 4.44) in compound **9**, as expected for an O-acetyl group at C-3'. The greater deshielding of 2'-H in the 4',6'-acetal (δ_H 5.26 compared with δ_H 4.98) can also be attributed to the presence of an acetyl group at C-3'. The ^{13}C chemical shifts of the primary carbons, C-6 and C-6', were also of interest. The acetal substituent at C-6' in the 4',6'-acetal (**1**) pentaacetate resulted in the deshielding of one of the two primary carbons (δ_C 61.93 and 68.41) which were detected by a distortionless enhancement by polarization transfer (DEPT) measurement. The primary carbons of the 3',4'-acetal had similar chemical shifts (δ_C 63.16 and 62.08). The acetal (*C*HPh) carbons also differed significantly in chemical shift. This carbon in **1** pentaacetate was close to the signals of the two anomeric carbons (δ_C 101.54, 101.33 and 101.04), while in pentaacetate **9** it was more deshielded (δ_C 103.9, assigned by specific decoupling at δ_H 6.15 corresponding to the benzylic proton) than the anomeric carbons (δ_C 101.47 and 100.54). The signal at δ_C 103.9, as well as the signal at δ_H 6.15 for the benzylic proton, indicated the presence of the *exo* isomer[5] and this was confirmed by nuclear Overhauser effect (NOE) measurements (irradiation of the methine C*H*Ph proton increased the intensity of the signal corresponding to 2'-H by 8%). The presence of a 1,3-dioxolane ring *cis*-fused to a pyranoside ring usually distorts the initial chair conformation of the latter ring,[6] and this agrees with the proposed flattened chair conformation for the galactose part.



9

To improve the yield of the acetalation step, the synthesis of methyl 4',6'-*O*-isopropylidene-β-lactoside **2** was next attempted. Kinetic formation of the ketal with 2,2-dimethoxypropane in DMF containing PTSA[7] was thus applied to methyl β-lactoside. After 45 min two spots were detected on TLC, that of lower R_f-value corresponding to the starting material and that of higher R_f-value due to the required product **2**. The reaction was stopped after 2–3 h, when two spots of faster moving products became darker. The different products were separated by column chromatography; compound **2** was thus isolated in 55% yield. The presence of the isopropylidene ketal at positions 4' and 6' was confirmed by ^{13}C NMR spectroscopy; substitution of the primary hydroxy group of the galactose residue shifted the signal of the CH_2O to low field and thus separated the two CH_2O signals (δ_C 63.07 and 61.47) while in methyl β-lactoside these two signals overlapped (δ 61.97). The two faster moving products were identified as methyl 3',4'-*O*-isopropylidene-β-lactoside (thermodynamic product, 15%) and probably methyl 2',3,4',6'-di-*O*-isopropylidene-β-lactoside as this kind of diketal had previously been isolated during the acetonation of benzyl β-lactoside.[8] The proportions diketal/3',4'-isopropylidene/4',6'-isopropylidene/starting material were 1/6/22/4. More starting material was recovered by hydrolysis of the fraction of unseparated isomers, thus increasing the yield of the 4',6'-ketal to 63%.

The following step consisted of blocking the remaining free OH groups in the 4',6'-isopropylidene ketal **2**. Benzyl ethers were chosen as protecting groups because of their stability both to the acidic and basic reaction conditions which were needed in the subsequent steps of the synthesis. Methyl 4',6'-*O*-isopropylidene-β-lactoside **2** was benzylated in dry DMF with oil-free NaH and benzyl bromide during 16 h. The syrupy pentabenzyl derivative **3** was isolated after column chromatography in 81% yield.

Acid hydrolysis of the isopropylidene ketal was performed with 90% aq. trifluoroacetic acid (TFA).[9] Thus, compound **3** was dissolved in 90% TFA at 0 °C and left for 1 h, after which the reaction was complete. The first work-up used involved evaporation of the acid to dryness under reduced pressure at 45 °C followed by partition between water and diethyl ether and washing of the combined organic layers with saturated aq. sodium hydrogen carbonate to remove the remaining acid. However, this work-up gave rise to formation of a trifluoroacetate derivative (characterised by a carbonyl absorption at 1795 cm^{-1}) during the evaporation of the acid under reduced pressure with heating. Therefore the evaporation of TFA was avoided, and partition between water and diethyl ether followed by neutralisation of the acid with saturated aq. sodium hydrogen carbonate was preferred.

Methyl 4',6'-di-*O*-alkyl-2,2',3,3',6-penta-*O*-benzyl-β-lactoside derivatives, **5** and **6**, were readily obtained using the same method as for the benzylation step. Removal of the alkylating reagents by column chromatography was found to be necessary to ensure good yields in the subsequent hydrogenolysis step. Both compounds **5** and **6** were isolated in good yield, 95 and 93% respectively.

Various catalytic hydrogenolysis methods were tried before we found the most suitable one to deprotect the OH groups. The first method, involving hydrogen at atmospheric pressure and Pd/C (10%) as catalyst, was found to be unsatisfactory. Indeed, despite long reaction times (several days) and several additions of catalyst, several spots of incompletely deprotected compounds were still detected by TLC. Therefore, heterogeneous catalytic transfer hydrogenation (HCTH), where hydrogen is produced *in situ* by a hydrogen donor, was thought to be an alternative method to remove the benzyl protecting groups. It had been previously found that HCTH with Pd/C (10%) and ammonium formate[10] as the hydrogen donor or palladium hydroxide/C (20%) and cyclohexene[11] (hydrogen donor) provided an additional means for the removal of benzyl ether groups from carbohydrate derivatives. The use of Pd/C and ammonium formate was not convenient because of the large amounts of catalyst involved (0.36 g/0.2 mmol of substrate) and long reaction times (27 h). However, $Pd(OH)_2/C$ and cyclohexene gave satisfactory results; the benzylated derivatives were dissolved in a mixture of ethanol and cyclohexene (30 times excess) before addition of the catalyst. The reaction mixture was stirred under reflux until UV detection did not show any spots on TLC. A catalyst/substrate ratio of 2:10 (0.2 g of catalyst per 1 mmol of substrate) and reaction times of 6 h were necessary to achieve a complete reaction. This method provided good yields of deprotected derivatives; 95 and 94% for hexyl **7** and octyl **8** derivatives, respectively.

Physical Properties.—Despite the addition of two CH_2 groups to each alkyl chain, there was, surprisingly, not a big difference between the two melting points of the hexyl **7** and octyl **8** derivatives (181.7–183.7 and 185.5–187 °C, respectively). However, a difference in water solubility was observed for the two compounds. These solubilities were both very low, 3.5×10^{-3} mol dm^{-3} (at room temperature) for **7** and less than 5×10^{-5} mol dm^{-3} (at 70 °C) for **8**. These low solubilities limited the measurement of physical properties such as critical micelle concentration (cmc), surface tension (γ_{cmc}), and area per molecule (A). The thermotropic and lyotropic behaviour of the amphiphilic molecules **7** and **8** could, however, be studied by thermomicroscopy and the 'penetration scan' method. The

methyl 4',6'-di-*O*-alkyl-β-lactoside derivatives melted without forming thermotropic liquid crystals; however, lyo-mesophases were detected during the study of lyotropic behaviour. The Krafft points of compounds **7** and **8** were thus determined: Kp = 71–72 °C and 80 °C, respectively. The lyo-mesophase sequences observed at these temperatures for the hexyl **7** and the octyl **8** derivatives were respectively:

gel L_β/V_2 or L_3, where L_β is a lamellar phase with solid chains V_2 is a reversed-cubic phase and a L_3 is a phase made of extensive micellar aggregates ('sponge phase'); L_1/L_α/Solid where L_1 is a micelle solution and L_α is a lamellar phase.

Conclusions.—The synthesis of methyl 4',6'-di-*O*-alkyl-β-lactosides (both hexyl and octyl derivatives) was achieved in five steps from methyl β-lactoside; the isopropylidene ketal was found to be the more convenient ketal to protect positions 4' and 6' in methyl β-lactoside. In addition, hydrogenolysis involving palladium hydroxide on carbon and cyclohexene was found to be very efficient in deprotecting the five O-benzyl groups in the alkylated derivatives **5** and **6**. The low solubility of the two dialkylated derivatives did not allow the measurement of cmc, γ_{cmc} and *A*; however, their Krafft points could be measured. It is difficult to predict the water solubility of alkylated carbohydrate derivatives, and further studies are needed of the relationship between physical properties and the structure of such derivatives.

Experimental

250 and 400 MHz ^{1}H NMR spectra and 62.9 MHz ^{13}C NMR spectra were recorded on Bruker spectrometers. Spin simulation was performed with the Bruker PANIC program. Unless otherwise stated the deuteriated solvent was $CDCl_3$ containing $SiMe_4$. *J* Values are given in Hz. Mass spectra were determined using a VG 12-250 mass spectrometer for low-resolution electron-impact (EI) and chemical-ionisation (CI) measurements. High-resolution spectra (accurate mass) were measured on a VG Analytical ZAB-E fitted with a 11-250 J system. Column chromatography was carried out with silica gel 60 (230–400 mesh). TLC was achieved on Merck silica gel 60 F_{254} fluorescent plates and detection was effected by either spraying with a 5% solution of sulfuric acid in ethanol followed by heating, or viewing under UV light. M.p.s were determined in a capillary tube and are uncorrected.

Thermotropic and Lyotropic Phase Behaviour.—An Olympus BH2 optical polarising microscope fitted with a Likam TP91 hot-stage and a temperature probe was used to study the thermotropic and lyotropic behaviour of the hexyl **7** and octyl **8** derivatives. Concerning the thermotropic behaviour, the methods consisted in observing the birefringence of crystals under the polarising microscope while the temperature was gradually increased. The lyotropic behaviour was qualitatively studied by 'the penetration scan' method; a small amount of sample was wedged between a microscope slide and a cover-slip, melted, and left to cool to recrystallise; the crystals were then contacted with water to set up a concentration gradient and the temperature was next slowly increased to allow the study of the formation of the lyo-mesophase as a function of both concentration and temperature.

Methyl 4',6'-O-*Benzylidene*-β-*lactoside* **1**: *First Method*.—The zinc chloride-catalysed reaction of methyl lactoside with benzaldehyde gave the acetal **1** in 37% yield after chromatography on silica gel [eluent: $CHCl_3$–MeOH (5:1)]; m.p. 180–200 °C (decomp.) (lit.,[9] 170 °C); δ_C 130.48, 129.09 and 127.47 (ArCH), 104.83, 104.61, 102.11 (C-1, C-1' and PhCH), 70.08 and 61.59 (2 × CH_2), 80.01, 77.08, 76.31, 76.01, 74.66, 73.23, 71.70 and 68.24 (8 × CH) and 57.47 (Me); *m/z* (CI) 462 ($M + MH_4$)$^+$.

Second Method.—A solution of methyl β-lactoside (0.38 g, 1.07 mmol) in dry DMF (10 cm^3) was treated with α,α-dimethoxytoluene (0.78 cm^3, 5.2 mmol) in the presence of PTSA monohydrate (30 mg) at 50 °C under reduced pressure.[3] The reaction mixture was poured into diethyl ether (20 cm^3) and filtration of the cooled (−5 °C) mixture gave the 4',6'-O-benzylidene derivative (0.16 g, 34%). The filtrate was extracted with water (3 × 20 cm^3) and the combined aqueous layers were neutralised with saturated aq. sodium hydrogen carbonate and freeze dried. Extraction of the residue with methanol, followed by chromatography on silica gel [eluent: Et_2O–MeOH (5:1)], gave methyl 3',4'-*O*-benzylidene-β-lactoside (product **A**, 45 mg, 9.5%) as a syrup followed by 4',6'-O-benzylidene derivative **1** (39 mg, 7%) and starting material.

Methyl 2,2',3,3',6-*penta*-O-*acetyl*-4',6'-O-*benzylidene*-β-*lactoside*.—The 4',6'-O-benzylidene lactoside **1** (50 mg) was acetylated with an excess of acetic anhydride in pyridine, the product being isolated in 70% yield upon pouring of the reaction mixture into ice–water; m.p. 225–227 °C; δ_C 170.92, 170.39, 170.19, 169.76 and 168.88 (5 × *C*OMe), 137.39 (ArC), 129.21, 128.23 and 126.48 (ArCH), 101.53, 101.33 and 101.04 (3 × acetal CH), 75.97, 73.08, 72.79, 72.36, 72.07, 71.42, 68.94 and 66.41 (8 × CH), 68.41 and 61.93 (2 × OCH_2), 57.05 (OMe) and 20.87, 20.83, 20.75, 20.66 and 20.64 (5 × *Me*CO); δ_H 7.36–7.48 (5 H, m, ArH), 5.47 (1 H, s, PhC*H*), 5.26 (1 H, dd, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.3, 2'-H), 5.22 (1 H, t, *J* 9.5, 3-H), 4.91 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 9.5, 2-H), 4.88 (1 H, dd, $J_{2',3'}$ 10.5, $J_{3',4'}$ 3.5, 3'-H), 4.53 (1 H, dd, $J_{5,6a}$ 1.8, $J_{6a,6b}$ −11.9, 6-H^a), 4.47 (1 H, d, *J* 7.9, 1'-H), 4.39 (1 H, d, *J* 7.9, 1-H), 4.33 (1 H, d, $J_{3',4'}$ 3.5, 4'-H), 4.30 (1 H, dd, $J_{5',6'a}$ ~ 1, $J_{6'a,6'b}$ − 12.5, 6'-H^a), 4.13 (1 H, dd, $J_{5,6b}$ 4.9, $J_{6a,6b}$ −11.9, 6-H^b) 4.04 (1 H, dd, $J_{5',6'b}$ 1, 6'-H^b), 3.79 (1 H, t, *J* 9.5, 4-H), 3.61 (1 H, oct, 5-H), 3.48 (3 H, s, OMe), 3.46 (1 H, br s, 5'-H) 2.12 (3 H, s, OAc) and 2.04 (12 H, s, 4 × OAc).

Methyl 2,2',3,6,6'-*Penta*-O-*acetyl*-3',4'-O-*benzylidene*-β-*lactoside* **9**.—The 3',4'-O-benzylidene lactoside **A** was peracetylated as for compound **1** above, and the *product* **9** was isolated as a crystalline solid, m.p. 75–77 °C [Found: *m/z*, 672.250. $C_{30}H_{42}NO_{16}$ ($M + NH_4$) requires *m/z*, 672.250]; δ_H 7.35–7.43 (5 H, m, ArH), 6.15 (1 H, s, PhC*H*), 5.22 (1 H, t, *J* 9.3, 3-H), 4.98 (1 H, t, *J* 6.8, 2'-H), 4.91 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 9.3, 2-H), 4.50 (1 H, dd, $J_{5,6a}$ 2.1, $J_{6a,6b}$ −12.1, 6-H^a), 4.44 (1 H, t, *J* ~ 6.4, 3'-H), 4.43 (1 H, d, *J* 6.8, 1'-H), 4.39 (1 H, d, *J* 7.9, 1-H), 4.38–4.28 (2 H, m, 6'-H_2), 4.19 (2 H, six peaks = 2 dd, $J_{5,6b}$ 4.8, $J_{6a,6b}$ −12.1, 6-H^b; and $J_{3',4'}$ 6.1, $J_{4',5'}$ 1.8, 4'-H), 3.92 (1 H, m, 5'-H), 3.77 (1 H, t, *J* 9.5, 4-H) 3.63 (1 H, oct, 5-H), 3.48 (3 H, s, OMe), 2.12 (3 H, s, OAc), 2.10 (6 H, s, 2 × OAc) and 2.06 and 2.05 (each 3 H, s, 2 × OAc).

Methyl 4',6'-O-*Isopropylidene*-β-*lactoside* **2**.—Methyl β-lactoside (4 g, 11.2 mmol) was dissolved in stirred, dry DMF (30 cm^3) containing PTSA (0.2 g) and 2,2-dimethoxypropane (8.2 cm^3, 66.8 mmol) was added dropwise. After 1 h a further portion (50 mg) of acid catalyst was added, and the reaction was quenched 2 h later by the addition of triethylamine (0.21 cm^3). DMF was removed under reduced pressure and the resulting residue was chromatographed on silica gel with ethyl acetate–methanol (20:1) to give the 4',6'-O-*isopropylidene derivative* **2** as a crystalline solid (2.43 g, 55%), m.p. 194–196 °C (from EtOH); δ_H(250 MHz; [$^2H_5$]pyridine) 5.09 (1 H, d, *J* 7.9, 1- or 1'-H), 4.64 (1 H, d, *J* 7.7, 1'- or 1-H), 4.6–3.5 (20 H, m, 5 × OH, OMe, 12 × CH) and 1.46 and 1.43 (6 H, 2 s, 2 × Me); δ_C 105.29 and 104.81 (C-1 and -1'), 98.89 (acetal C), 79.68, 76.56, 76.37,

74.67, 73.41, 71.21, 69.68 and 67.39 (8 × CH), 63.08 and 61.47 (2 × CH_2), 56.80 (OMe) and 29.66 and 18.71 (2 × Me) (Found: C, 48.7; H, 7.3. $C_{16}H_{28}O_{11}$ requires C, 48.5; H, 7.1%).

Methyl 2,2′,3,3′,6-*Penta*-O-*benzyl*-4′,6′-O-*isopropylidene*-β-*lactoside* **3**.—A solution of methyl 4′,6′-*O*-isopropylidene-β-lactoside **2** (2.13 g, 5.4 mmol) in dry DMF (200 cm^3) was added slowly to stirred, oil-free NaH (3.2 g, 5 mol. equiv.) under nitrogen. The suspension was stirred for 30 min and benzyl bromide (12.8 cm^3) was added. After 16 h, methanol was added to destroy any unchanged NaH, and the product was isolated by partition between water (400 cm^3) and diethyl ether (3 × 200 cm^3). The combined ether extracts were washed with water, evaporated to dryness, and the residue was co-distilled with water to remove some benzyl bromide. The dried residual syrup was chromatographed on silica gel, benzyl bromide (3.85 g) being eluted first followed by the *penta*-O-*benzyl* derivative **3** as a syrup (3.7 g, 81%); δ_H(250 MHz) 7.5–7.2 (25 H, m, ArH), 5.14 (1 H, d, AB system, *J* 10.6, PhCH*H*), 4.86 (2 H, d, *J* 11.1, PhCH_2), 4.78–3.26 (24 H, m, OMe + lactoside protons + remaining PhCH_2) and 1.48 and 1.41 (6 H, 2 s, 2 × Me) [Found: *m*/*z*, 869.3890. $C_{51}H_{58}NaO_{11}$(M + Na) requires *m*/*z*, 869.3877].

Methyl 2,2′,3,3′,6-*Penta*-O-*benzyl*-β-*lactoside* **4**.—The preceding compound (3.55 g, 4.2 mmol) was dissolved in 90% TFA (16 cm^3) at 0 °C. After 1.8 h the solution was poured into water (100 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The combined extracts were washed successively with saturated aq. $NaHCO_3$ and water. Drying over $MgSO_4$ and evaporation to dryness gave the *penta*-O-*benzyllactoside* **4** as a crystalline solid (4.06 g, 90%), m.p. 122–132 °C; 138–139 °C after recrystallisation from aq. ethanol; δ_H(250 MHz) 7.5–7.2 (25 H, m, ArH), 4.97 (1 H, d, *J* 10.7, PhC*H*H), 4.89 (1 H, d, *J* 11.1, PhCH*H*), 4.80–4.68 (6 H, m), 4.57 and 4.37 (2 H, 2, d, *J* 12.1, PhCH_2), 4.36 (1 H, d, *J* 7.8, 1- or 1′-H), 4.3 (1 H, d, *J* 7.7, 1′- or 1-H), 3.94–3.1 (15 H, m) and 2.12 (2 H, br, 2 × OH) (Found: C, 71.45; H, 6.85. $C_{48}H_{54}O_{11}$ requires C, 71.4; H, 6.7%).

Methyl 2,2′,3,3′,6-*Penta*-O-*benzyl*-4′,6′-*di*-O-*hexyl*-β-*lactoside* **5**.—A solution of the lactoside diol **4** (1.6 g, 1.99 mmol) in DMF was added under nitrogen to oil-free NaH (0.476 g, 19.8 mmol) and the suspension was stirred for 30 min. Hexyl bromide (1.13 cm^3, 8.05 mmol) was added over a period of 20 min and after 16 h the excess of NaH was destroyed by addition of methanol (5 cm^3). The reaction mixture was poured into ice–water (100 cm^3), and extraction with diethyl ether (3 × 100 cm^3), followed by washing of the extract with water (3 × 100 cm^3), drying over $MgSO_4$, and evaporation under reduced pressure, gave a syrup. Chromatography on silica gel with toluene–ethyl acetate (10:1) gave first unchanged hexyl bromide and then the *di*-O-*hexyl derivative* **5** as a syrup (1.83 g, 95%); δ_H(250 MHz) 7.44–7.21 (25 H, m, ArH), 5.04 (1 H, d, *J* 10.7, PhC*H*H), 4.87 (1 H, d, *J* 11, PhCH*H*), 4.83–4.62 (6 H, m, PhCH_2), 4.52 and 4.39 (2 H, 2 d, AB system, *J* 12.2, PhCH_2), 4.41 (1 H, d, *J* 7.6, 1- or 1′-H), 4.29 (1 H, d, *J* 7.7, 1′- or 1-H), 3.91–3.20 (19 H, m), 1.58–1.45 (4 H, m, 2 × $CH_2CH_2[CH_2]_3$-Me), 1.36–1.25 (12 H, m, 2 × $[CH_2]_3$) and 0.88 (6 H, 2 t, 2 × Me) [Found: *m*/*z*, 997.5490. $C_{60}H_{78}NaO_{11}$(M + Na) requires *m*/*z*, 997.5442].

Methyl 2,2′,3,3′,6-*Penta*-O-*benzyl*-4′,6′-*di*-O-*octyl*-β-*lactoside* **6**.—The preceding procedure was used to alkylate the lactoside diol **4** (1.443 g, 1.79 mmol) by using NaH (0.43 g) and octyl bromide (1.24 cm^3, 7.18 mmol). The pure 4′,6′-*di*-O-*octyl derivative* **6** was isolated after column chromatography as a soft solid (1.71 g, 93%); δ_H(250 MHz) 7.44–7.19 (25 H, m, ArH), 5.03 (1 H, d, *J* 10.6, PhC*H*H), 4.87 (1 H, d, *J* 11, PhCH*H*), 4.83–4.71 (6 H, m, PhCH_2), 4.52 and 4.38 (2 H, 2 d, AB system, *J* 12.1, PhCH_2), 4.41 (1 H, d, *J* 7.6, 1- or 1′-H), 4.29 (1 H, d, *J* 7.7, 1′- or 1-H), 3.96–3.22 (19 H, m), 1.54–1.41 (4 H, m, 2 × $CH_2CH_2[CH_2]_5$Me), 1.28 (20 H, m, 2 × $[CH_2]_5$) and 0.87 (6 H, m, 2 × Me) (Found: M^+, 1030.6098. $C_{64}H_{86}O_{11}$ requires M, 1030.6171).

Methyl Di-O-*alkyl*-β-*lactosides*.—*General procedure*. The protected lactoside was dissolved in a mixture of ethanol and cyclohexene (2.5:1) and palladium hydroxide (20% on charcoal; 0.2 g per mmol of starting material) was added. The mixture was stirred under reflux for 6 h, filtered, and evaporated to dryness to give the product.

Methyl 4′-6′-*di*-O-*hexyl*-β-*lactoside* **7**: 95%, m.p. 182–184 °C, 183–184 °C (after recrystallisation from ethyl acetate); δ_H(250 MHz) 4.75 (1 H, br s, OH), 4.38 (1 H, d, *J* 6.8, 1- or 1′-H), 4.26 (1 H, d, *J* 7.6, 1′- or 1-H), 3.92–3.37 (23 H, m, 12 × H + 4 × OH from lactoside, 2 × OCH_2R, OMe), 1.59–1.43 (4 H, m, 2 × $CH_2CH_2[CH_2]_3$Me), 1.29 (12 H, m, 2 × $[CH_2]_3$) and 0.88 (6 H, t, *J* 6.5, 2 × Me); δ_C 103.65 and 103.57 (C-1 and -1′), 79.78, 76.71, 75.03, 74.56, 74.07, 73.36 and 71.33 (8 × CH), 74.22, 71.77, 68.75 and 61.82 (4 × OCH_2), 57.24 (OMe), 31.74, 31.71, 30.08, 29.52, 25.79, 25.66, 22.68 and 22.65 (8 × CH_2) and 14.02 (2 × Me) (Found: C, 56.9; H, 9.4. $C_{25}H_{48}O_{11}$ requires C, 57.2; H, 9.2%).

Methyl 4′6′-*di*-O-*octyl*-β-*lactoside* **8**: 94%, m.p. 185.5–187 °C, 187–188 °C (after recrystallisation from ethyl acetate); δ_H 4.38 (1 H, d, *J* 6.6, 1- or 1′-H), 4.25 (1 H, d, *J* 7.6, 1′- or 1-H), 4.1–3.4 (24 H, m, 12 × CH + 5 × OH of lactoside, 2 × OCH_2, OMe), 1.5–1.4 (4 H, m, 2 × $CH_2CH_2[CH_2]_5$Me), 1.27 (20 H, m, 2 × $[CH_2]_5$) and 0.88 (6 H, t, *J* 6.4, 2 × Me); δ_C 103.65 and 103.53 (C-1 + -1′), 79.81, 76.64, 75.00, 74.52, 74.08, 73.99, 73.37 and 71.31 (8 × CH), 74.23, 71.76, 68.68 and 61.89 (4 × OCH_2), 57.22 (OMe), 31.88, 31.86, 30.13, 29.54, 29.49, 29.36, 29.32, 26.12, 26.00 and 22.67 (12 × CH_2) and 14.13 (2 × Me) (Found: C, 60.0; H, 9.8. $C_{29}H_{56}O_{11}$ requires C, 60.0; H, 9.7%).

Acknowledgements

We gratefully acknowledge financial support from Unilever Research (Portsunlight UK) and the assistance of Drs. R. Crawford, I. P. Stott and L. G. Thompson (Unilever). We also thank Mr. M. Nettle for NMR spectra and the SERC centres for mass spectra (Dr. J. A. Ballantine) and NMR spectra (Dr. O. W. Haworth).

References

1 F. Smith and J. W. Van Cleve, *J. Am. Chem. Soc.*, 1952, **74**, 1912.
2 R. S. Bhatt, L. Hough and A. C. Richardson, *Carbohydr. Res.*, 1975, **43**, 57.
3 M. E. Evans, *Carbohydr. Res.*, 1972, **21**, 473; D. H. Horton and W. Weckerle, *Carbohydr. Res.*, 1975, **44**, 227.
4 N. Baggett, J. M. Duxbury, A. B. Foster and J. M. Webber, *Carbohydr. Res.*, 1965, **1**, 22.
5 A. Neszmelyi, A. Liptak and P. Nanasi, *Carbohydr. Res.*, 1977, **58**, C7.
6 J. Harangi, A. Liptak, Z. Szurmai and P. Nanasi, *Carbohydr. Res.*, 1985, **136**, 241.
7 H. Baer and S. Abbas, *Carbohydr. Res.*, 1979, **77**, 117.
8 M. Alonso-Lopez, J. Barbat, E. Fanton, A. Fernandez-Mayoralas, J. Gelas, D. Horton, M. Martin-Lomas and S. Penades, *Tetrahedron*, 1987, **43**, 1169.
9 D. D. Cox, E. K. Metzner and E. J. Reist, *Carbohydr. Res.*, 1978, **63**, 139.
10 T. Bieg and W. Szeja, *Synthesis*, 1985, 76.
11 S. Hanessian, T. J. Liak and B. Vanasse, *Synthesis*, 1981, 396.

Paper 4/01494D
Received 14*th March* 1994
Accepted 19*th April* 1994