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The introduction of an hydrophobic chain on α,α-trehalose via the synthesis of acetals. The detergent properties of these derivatives

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Abstract

Classical transacetalation of trehalose with 2,2-dimethoxyalkanes leads conveniently to a new class of acetals of a great potential due to their detergent properties. The control of the mono- or di-functionalization was possible. © 1997 Elsevier Science Ltd.

Keywords: Carbohydrates; Trehalose; Surfactants; Long-chain cyclic acetals

1. Introduction

As we are involved in a program devoted to synthesis of surfactants, we described in a previous paper [1] the synthesis of long-chain acetals of sucrose. Functionalization of sugars with a lipophilic tail attached by means of an acetal function provided a route for the synthesis of amphiphiles considered as a new class of non-ionic surfactants that are stable in basic medium. The presence of the sugar may confer interesting properties of biodegradability. The control of the *mono-* or *di-*functionalization of sucrose was possible.

Our interest has been turned towards α,α-trehalose [2], as similar detergent properties could be expected for long-chain acetals derived from this biologically important disaccharide. On one hand, long-chain monoacetals should exhibit surfactant properties, and, on the other hand, the structure of their diacetal homologs could be compared to that of the new 'gemini surfactants' [3,4], and, besides, they could be of interest as complexing molecules with a 'wrapping' effect.

The symmetry of this molecule should allow the synthesis of either mono- or di-acetal derivatives depending of the acetalation procedure. Some mono- and di-acetals of trehalose have already been prepared by one of the following methods [5–9]: (i) action of acetone, benzaldehyde or acetaldehyde in the presence of zinc chloride, (ii) transacetalation with 1,1-dimethoxycyclohexane, (iii) reaction with enol ethers in mild acidic conditions.

2. Results and discussion

Reaction of 2,2-dimethoxytridecane with trehalose that had been previously dehydrated (see Experimental part) in *N,N*-dimethylformamide followed by acetylation gave as the major product a compound identified as a mixture of the two diastereoisomers of the monoacetal **1** (30% yield, Scheme 1) by NMR

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[1] Taken in part from the thesis (Ingénieur CNAM) of J. Besson.

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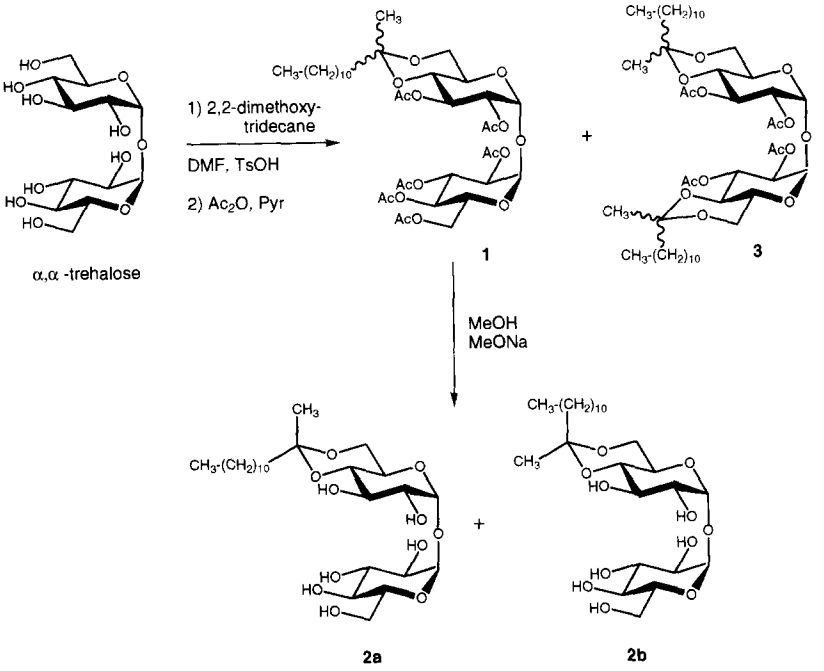


Scheme 1.

spectroscopy. The presence of small amounts of the diacetal **3** was also noticed. After deacetylation of **1**, the monoacetals **2a** and **2b** were obtained and partially separated. Their ^{1}H and ^{13}C NMR spectal data (Tables 1 and 2) show similarities with those of long-chain monoacetals of sucrose [1], and the following signals are particularly noteworthy: (i) the signal at 100 ppm is characteristic of the acetalic carbon atom included in a dioxane ring in its chair conformation [10]; (ii) the acetalic methyl groups in the axial and equatorial positions give signals at respectively 17.5 and 26.3 ppm [10]; (iii) at 30.5 and 42.1 ppm are signals corresponding to the first methylene group of the alkyl chain, respectively, in the axial and equatorial positions; (iv) at 1.54 ppm is a unique signal due to the two diastereoisotopic protons of the first methylene group of the side chain in the equatorial position, and at 1.69 and 1.94 ppm are two signals due to these methylene protons of the chain in the axial position; (v) at 1.39 and 1.25 ppm are signals corresponding to the acetalic methyl group respectively in the axial and equatorial positions [10].

Thus, the reaction was regioselective with the monofunctional reactivity under at least partial control, and the two possible stereoisomers on the acetalic carbon atom were obtained. This observation,

Table 1
^{1}H NMR data for compounds **2a** and **2b**

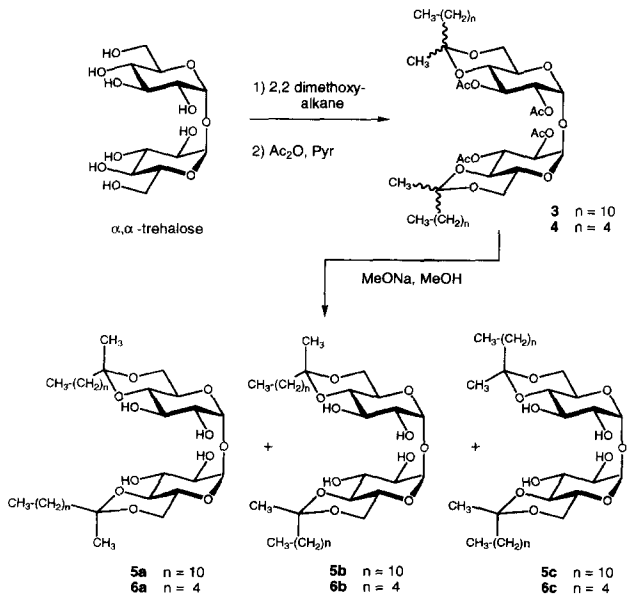
Compound	Solvent	H-1,1′	H-2,2′ H-6,6′	OH	H_3C– (acetal)	$-CH_2-$ (acetal)	$-(CH_2)_n-$	$-(CH_2)_n-CH_3$
2a	Me_2SO-d_6	d 4.92, d 4.88 $J_{1,2}$ 3.0 $J_{1',2'}$ 3,4	m 3.90–3.15	d 4.99 $J_{H,OH}$ 5.3 d 4.95 $J_{H,OH}$ 5.5 d 4.82 $J_{H,OH}$ 6.4 t 4.41 $J_{H,OH}$ 6.0	s 1.39	m 1.54	m 14.0–1.20	t 0.89
	Me_2SO-d_6 + D_2O	d 4.92, d 4.86 $J_{1,2}$ 3.3 $J_{1',2'}$ 3.5	m 3.85–3.10		s 1.35	m 1.52	m 1.35–1.15	t 0.86
2b	Me_2SO-d_6	d 4.93, d 4.88 $J_{1,2}$ 3.0 Hz $J_{1',2'}$ 3,4 Hz $J_{1,2}$ 3.0 Hz	m 3.90–3.15	d 5.06 $J_{H,OH}$ 5.3 d 4.99 $J_{H,OH}$ 5.3 d 4.82 $J_{H,OH}$ 5.0 t 4.42 $J_{H,OH}$ 6.0	s 1.26	m 1.94 m 1.69 J_{gem} 12.0	m 1.40–1.20	t 0.89
	Me_2SO-d_6 + D_2O	d 4.93, d 4.86 $J_{1,2}$ 3.3 $J_{1',2'}$ 3,5	m 3.85–3.10		s 1.25	m 1.90 m 1.67 J_{gem} 12.0	m 1.35–1.15	t 0.86

Table 2
^{13}C NMR data for compounds **2a** and **2b**

Compound	Solvent	C-1,1′	C-2,2′ C-5,5′		C-6,6′	H_3C– (acetal)	*C* (acetal)	$-CH_2-$ (acetal)	$-(CH_2)_n-$	$-(CH_2)_n-CH_3$
2a	Me_2SO-d_6	94.24	73.94	72.95	61.97	17.46	100.02	42.11	31.62–22.39	14.08
		93.82	72.73	72.48	61.02					
			71.62	70.27						
			70.04	63.61						
2b	Me_2SO-d_6	94.21	73.56	72.70	61.53	26.31	100.47	30.47	31.34–22.15	13.99
		93.79	72.63	72.19	60.71					
			71.45	70.00						
			69.75	63.05						

together with the ^1H NMR spectral data, shows the presence of a severe *syn*-axial interaction between a methyl group or the first methylene group of the side chain and the axial hydrogen atoms of the 1,3-dioxane ring that limits rotation around the C-7–C-8 bond [1].

When the acetalation was carried out with an excess of reagent (2,2-dimethoxytridecane or 2,2-dimethoxyhexane), a diacetal (**3** or **4**) was obtained in 60% yield after acetylation (Scheme 2). In this case, only diacetalation occurred. Deacetylation of **3** (respectively **4**) afforded a mixture of the three diastereoisomers **5a**, **5b** and **5c** (respectively, **6a**, **6b**, and **6c**), which have been identified by NMR spectroscopy. In this connection, the same remarks as made for compounds **2a** and **2b** may be noted; the symmetry of compounds **5a** and **5b** (respectively, **6a** and **6b**) is noteworthy.



Scheme 2.

In addition, we found that pyridine was also a convenient solvent for the transacetalation of oligosaccharides. Pyridine has been previously used as solvent for acetalation of sucrose with enol ethers (C. Fayet, and J. Gelas, unpublished results). The reaction of trehalose with 2,2-dimethoxytridecane or 2,2-dimethoxyhexane was carried out in refluxing pyridine in the presence of a catalytic amount of *p*-toluenesulfonic acid. After classical acetylation in the same flask, the monoacetal **1** and the diacetals **3** and **4** were obtained. Yields were dependent on the reaction conditions, as shown in Table 3, and the mono- or di-functionalization could be controlled. The same regioselectivity was observed since only the 4,6- and the 4′,6′-*O*-acetals were obtained. The presence of the two possible stereoisomers on the acetalic carbon atom was also observed. But the control of the monofunctionalization was easier when using pyridine as solvent (ratio mono-:di-acetal 4:1) rather than *N*,*N*-dimethylformamide (ratio mono-:di-acetal 2:1). It may be also noted that dehydration of the starting molecule, acetalation and acetylation were achieved in a one-pot procedure.

Concerning compound **2**, the critical micelle concentration (CMC) and the surface tension in water were determined (Fig. 1). The data clearly show the interesting detergent properties of this acetal, with a CMC (41 mg/L) similar to the CMC of its sucrose analogue and comparable to those of commercially available alkylpolyglucosides [1]. On the contrary,

Table 3
Transacetalation of trehalose in pyridine

Reagent (mol equiv)	Time (h)	Residual trehalose	Monoacetal (**8**)	Diacetal (**9**)
2	2	40%	35–40%	10%
4	4	traces	5–10%	35–40%
6	4	–	traces	40%

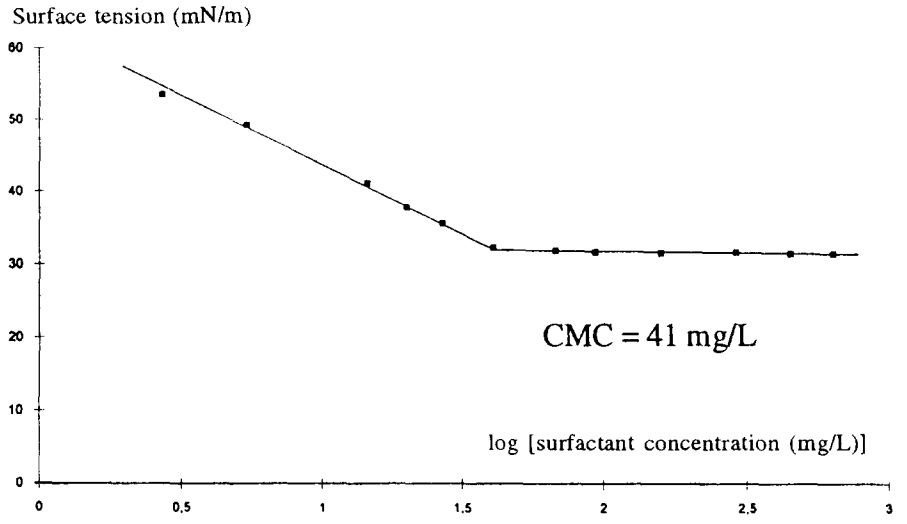


Fig. 1.

the presence of two lipophilic tails on the sugar leads to compounds **5** and **6**, which are insoluble in water, even when the alkyl chain is shorter.

In conclusion, the acetalation of trehalose was achieved with 2,2-dimethoxyalkanes, which led to mono- and di-acetals. As a substitute for *N,N*-dimethylformamide solvent, pyridine could conveniently be used for these reactions. Control of the mono- or di-functionalization was achieved. The monoacetal **2** of trehalose showed interesting detergent properties.

3. Experimental

General methods.—Anhydrous α,α-trehalose was obtained by repeated distillation of anhydrous MeOH under reduced pressure (5 times removal of 10 mL of anhydrous MeOH added to 2 g of α,α-trehalose). Melting points were determined on a Büchi apparatus. Evaporations were performed under reduced pressure. Optical rotations were measured at 20 °C on a Perkin–Elmer 141 polarimeter in 1 dm tubes. TLC was carried on precoated plates (E. Merck 5724), with detection by charring with H_2SO_4, and column chromatography was carried out with Silica Gel 60 (E. Merck 70–230 mesh). ^1H NMR spectra (60 or 400 MHz) were recorded on a Varian T-60 spectrometer or on a Bruker AC 400 instument. Chemical shift data are given in ppm measure downfield from internal Me_4Si, and spin–spin coupling data are in Hz. ^{13}C NMR spectra were recorded on a JEOL FX 60 or on a Bruker AC 400 spectrometer. Surface tension was measured with a Prolabo TD 2000 tensiometer. Elemental analyses were carried out by the Service Central d'Analyses du CNRS in Lyon, France (the percentage of oxygen has been measured by pyrolysis).

2,3,2',3',4',6'-Hexa-O-acetyl 4,6-O-(1-methyl dodecylidene)-α,α-trehalose (**1**) *and 4,6-O-(1-methyl dodecylidene)-α,α-trehalose* (**2**).—To a solution of α,α-trehalose (6.48 g) in anhydrous *N,N*-dimethylformamide were added 5 g (1 mol equiv) of 2,2-dimethoxytridecane and a catalytic amount of *p*-toluenesulfonic acid. After 30 min the reaction mixture was neutralized with Na_2CO_3, centrifuged and filtered. The solvent was evaporated under reduced pressure. The crude syrupy mixture was acetylated (30 mL of 1:1 acetic anhydride–pyridine) at 0 °C and overnight at room temperature. After the usual treatment and solvent evaporation, the crude mixture was submitted to column chromatography (1:1 AcOEt–hexane). The diacetal **3** was first eluted: 2.5 g (15%); then the monoacetal **1** (mixture of **1a** and **1b**) was obtained: 4.6 g (30%).

Deacetylation of **1** according to the Zemplén procedure was carried out as follows: 4.2 g of **1** (1.5 mmol) were dissolved in 50 mL of anhydrous MeOH, and 15 mL of a freshly prepared 1 M solution of sodium methanolate were added. After 2 h, the reaction was complete, and the solution was then neutralized with Amberlite IR-120 (H^+) resin and filtered, and the solvent was evaporated. The mixture of **2a** and **2b** was then obtained and only partially separated by column chromatography (eluant: 12:3:2 AcOEt–EtOH–H_2O).

Data for **1**: $[\alpha]_D$ +125° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.48 (m, 1 H, H-3), 5.40 (m, 1 H, H-3'), 5.32 (m, 1 H, H-1'), 5.20 (m, 1 H, H-1), 5.00 (m, 3

H, H-2,2',4'), 4.24 (m, 1 H, H-6'), 4.07 (m, 2 H, H-5',6'), 3.74 (m, 3 H, H-4,5,6), 2.12–2.00 (m, 18 H, OAc), 1.97, 1.62 and 1.57 (m, 2 H, CH_2), 1.40–1.20 (m, 21 H, 9 $-CH_2-$, CH_3), 0.87 (t, 3 H, $-CH_3$); ^{13}C NMR ($CDCl_3$): δ 170.60–169.64 (OAc), 101.79 and 101.14 (C acetal), 93.30 and 93.09 (C-1'), 91.89 and 91.76 (C-1), 71.76–63.90 (C-2,3,4,5,2',3',4',5'), 61.82 and 61.70 (C-6,6'), 41.88–29.36 ($-CH_2-$), 26.22 (CH_3), 23.98–22.70 ($-CH_2-$), 20.82–20.53 (OAc), 17.43 (CH_3), 14.13 ($-CH_3$). Anal. Calcd for $C_{27}H_{58}O_{17}$: C, 57.35; H, 7.55; O, 35.10. Found: C, 57.40; H, 7.78; O, 34.69.

Data for **2a** and **2b**: $[\alpha]_D$ +119° (*c* 1, EtOH); mp 200–201 °C. For ^1H NMR and ^{13}C NMR data, see Tables 1 and 2.

2,2',3,3'-Tetra-O-*acetyl-4,6:4',6'-di*-O-*(1-methyl dodecylidene)-α,α-trehalose* (**3**) *and 2,2',3,3'-tetra*-O-*acetyl-4,6:4',6'-di*-O-*(1-methyl dodecylidene)-α,α-trehalose* (**4**).—To a solution of α,α-trehalose (3.42 g) in anhydrous *N*,*N*-dimethylformamide, were added 2 mol equiv of 2,2-dimethoxytridecane (or 2,2-dimethoxyhexane) and a catalytic amount of *p*-toluenesulfonic acid. The reaction was followed by TLC (1:1 AcOEt–acetone). After 1 h, 2 additional mol equiv of reagent were added and stirring was continued. The same operation was repeated after 1 h. After 4 h, the solution was neutralized and filtered, and the solvent was evaporated. The crude mixture was acetylated (1:1 acetic anhydride–pyridine) and then purified by column chromatography (1:2 AcOEt–hexane). The diacetal **3** (or **4**) was obtained in 60% yield. Quantitative deacetylation of **3** (respectively **4**) according to Zemplén (see previous example) was carried out, and the mixture was partially separated to give pure **5a**, **5b**, and **5c** (respectively **6a**, **6b**, and **6c**).

Data for **3**: $[\alpha]_D$ +104° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.43 (m, 2 H, H-3,3'), 5.25 (m, 2 H, H-1,1'), 4.94 (m, 2 H, H-2,2'), 3.75 (m, 6 H, H-4,4',5,5',6,6'), 2.15, 2.13 and 2.05 (3 s, 12 H, OAc), 1.97 and 1.62 (m, CH_2-CH_3), 1.57 (m, CH_2-CH_3), 1.42–1.20 (m, 42 H, 2-$(CH_2)_9-$, $-CH_3$), 0.88 (t, 6 H, 2-CH_3); ^{13}C NMR ($CDCl_3$): δ 170.37 and 169.55 (OAc), 101.74 and 101.10 (C acetal), 92.92, 92.71 and 92.52 (C-1,1'), 71.83–63.73 (C-2,3,4,5,2',3',4',5'), 61.88 and 61.74 (C-6,6'), 41.91–26.96 ($-CH_2-$), 26.24 (CH_3), 24.00–22.73 ($-CH_2-$), 20.85 and 20.61 (OAc), 17.45 ($-CH_3$), 14.15 ($-CH_3$). Anal. Calcd for $C_{46}H_{78}O_{15}$: C, 63.42; H, 9.03; O, 27.55. Found: C, 63.26; H, 9.11; O, 27.14.

Table 4
^1H NMR data for compounds **5a,b,c** and **6a,b,c**

Compound	Solvent	H-1,1'	H-2,2' H-6,6'	OH	H_3C (acetal)	$-CH_2$ (acetal)	$-(CH_2)_n-$	$-(CH_2)_n-CH_3$
5a	Me_2SO-d_6	d 4.87	m 4.00–3.30	d 5.14 d 4.97	s 1.38	m 1.55	m 1.45–1.20	t 0.88
5b	Me_2SO-d_6	d 4.85	m 4.00–3.30	d 5.19 d 5.17 d 5.06 d 5.0	s 1.40 s 1.28	m 1.95 m 1.68 m 1.55	m 1.45–1.20	t 0.88
5c	Me_2SO-d_6	d 4.86	m 4.00–3.30	d 5.18 d 5.06	s 1.27	m 1.94 m 1.68	m 1.45–1.20	t 0.88
6a	Me_2SO-d_6	d 4.88 $J_{1,2}$ 3.8 $J_{1',2'}$ 3.8	m 4.00–3.30	d 5.15 $J_{H,OH}$ 6.0 d 4.99 $J_{H,OH}$ 5.2	s 1.40	m 1.55	m 1.45–1.20	t 0.88
6b	Me_2SO-d_6	d 4.88 $J_{1,2}$ 3.5 $J_{1',2'}$ 3.5	m 4.00–3.30	d 5.19 $J_{H,OH}$ 6.4 d 5.17 $J_{H,OH}$ 6.9 d 5.06 $J_{H,OH}$ 5.2 d 5.00 $J_{H,OH}$ 5.2	s 1.39 s 1.26	m 1.96 m 1.68 J_{gem} 12.0 m 1.55	m 1.45–1.20	t 0.91 t 0.88
	Me_2SO-d_6 + D_2O	d 4.88	m 3.80–3.30		s 1.36 s 1.23	m 1.89 m 1.68 J_{gem} 12.0 m 1.51	m 1.38–1.15	t 0.87 t 0.84
6c	Me_2SO-d_6	d 4.87 $J_{1,2}$ 3.5 $J_{1',2'}$ 3.5	m 4.00–3.30	d 5.20 $J_{H,OH}$ 5.8 d 5.07 $J_{H,OH}$ 5.2	s 1.28	m 1.96 m 1.68 J_{gem} 12.0	m 1.45–1.20	t 0.91

Table 5
^{13}C NMR data for compounds **5a,b,c** and **6a,b,c**

Compound	Solvent	C-1,1′	C-2,2′ C-5,5′		C-6,6′	H_3C– (acetal)	*C* (acetal)	$-CH_2-$ (acetal)	$-(CH_2)_n-$	$-(CH_2)_n-CH_3$
5a	Me_2SO-d_6	94.75	73.71	72.13	61.71	17.42	99.83	41.86	31.94–22.13	13.96
			69.68	63.52						
5b	Me_2SO-d_6	94.84	73.73	73.50	61.73	26.31	100.49	41.89	31.35–22.16	14.00
			72.13	72.05	61.55	17.45	99.86	30.46		
			69.69	69.60						
			63.56	63.10						
5c	Me_2SO-d_6	94.92	73.48	72.05	61.51	26.29	100.47	30.46	31.35–22.15	13.99
			69.61	63.16						
6a	Me_2SO-d_6	94.74	73.76	72.16	61.76	17.48	99.87	41.84	31.66–22.19	14.04
			69.71	63.55						
6b	Me_2SO-d_6	94.90	73.71	73.47	61.70	26.28	100.47	41.78	31.64–22.08	14.00
			72.11	72.00	61.49	17.47	99.82	30.37		13.91
			69.62	69.57						
			63.52	63.13						
6c	Me_2SO-d_6	94.92	73.47	71.99	61.49	26.29	100.47	30.37	31.28–22.07	13.99
			69.55	63.16						

Data for **4**: ^1H NMR ($CDCl_3$): d 5.44 (m, 2 H, H-3,3′); 5.25 (m, 2 H, H-1,1′); 4.94 (m, 2 H, H-2,2′); 3.75 (m, 6 H, H-4,4′,5,5′,6,6′); 2.14, 2.13 and 2.06 (s, 12 H, 4 CH_3CO_2); 1.98, 1.62 (m, 2 H, CH_2); 1.58 (t, 2 H, CH_2); 1.42–1.20 (m, 18 H, 6 CH_2, 2 CH_3); 0.90 (t, 3 H, CH_3); 0.87 (t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): δ 170.39 and 169.54 (OAc); 101.75, 101.13 (C acetal); 92.94, 92.74, 92.55 (C-1,1′); 71.85–63.74 (C-2–C-5, C-2′–C-5′); 61.81, 61.76 (C-6,6′); 41.84–30.70 ($-CH_2-$); 26.25 (CH_3); 23.66–22.63 ($-CH_2-$); 20.87, 20.64 (OAc); 17.50 (CH_3); 14.08, 14.00 (CH_3). Anal. Calcd for $C_{34}H_{54}O_{15}$: C, 58.11; H, 7.74; O, 34.15. Found: C, 58.25; H, 7.79; O, 33.40.

Data for **5a**, **5b**, and **5c**: mp 123–125 °C. For ^1H NMR and ^{13}C NMR data, see Tables 4 and 5. Anal Calcd for $C_{38}H_{70}O_{11}$: C, 64.93; H, 10.04; O, 25.04. Found: C, 64.68; H, 10.25; O, 25.09.

Data for **6a**, **6b**, and **6c**: mp 156–157 °C. For ^1H NMR and ^{13}C NMR data, see Tables 4 and 5. Anal. Calcd for $C_{26}H_{46}O_{11}$: C, 58.41; H, 8.67; O, 32.92. Found: C, 57.56; H, 8.70; O, 33.24. For ^1H NMR and ^{13}C NMR data, see Tables 3 and 4.

*General method for the preparation of acetals **1**, **3**, and **4** in pyridine.*—A solution of α,α-trehalose (2 g, 2.6 mmol) in 100 mL of anhydrous pyridine was refluxed in a Dean–Stark trap until 50 mL of distillate was obtained. The reagent was added, and the solution was refluxed for several hours. The mixture was then cooled to room temperature. Acetic anhydride (25 mL) was added at 0 °C, and the mixture was stirred overnight at room temperature. After usual treatment and solvent evaporation, the crude mixture was submitted to column chromatography.

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