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## Preparation of amphiphilic sorbitan monoethers through hydrogenolysis of sorbitan acetals and evaluation as bio-based surfactants†

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Amphiphilic sorbitan acetals have been prepared from sorbitan by acetalisation using linear aliphatic aldehydes or by transacetalisation starting from the corresponding aldehyde diethylacetals. A series of sorbitan acetals has been obtained with 29–81% isolated yields. It has been shown that these sorbitan acetals exist as a mixture of five-membered and six-membered regioisomers. Hydrogenolysis of the mixtures gave the corresponding sorbitan ethers as a mixture of 3 regioisomers with 55–85% isolated yields. A one-pot two-step procedure was also optimized from sorbitan giving similar results. The amphiphilic properties of sorbitan acetals and ethers were evaluated and both families exhibit interesting surfactant properties.

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### Introduction

Surfactants are encountered in many applications such as detergents, cleaning formulations, home and personal care products, pharmaceuticals, paints, textiles, chemicals, and food industries.<sup>1</sup> More particularly, non-ionic surfactants have gained interest and are progressively overtaking ionic ones. They offer many advantages over the ionic surfactants such as being less skin irritant, exhibiting usually higher biodegradability, increased stability, formulating flexibility and wider compatibility. From a physical chemistry point of view, they have a lower CMC (Critical Micellar Concentration) than ionic counterparts, are less sensitive to hard water and their properties are weakly affected by electrolytes. Among the non-ionic class, carbohydrate-based surfactants have attracted a lot of attention due to their low environmental impact profiles. Indeed, they are obtained from renewable resources in bulk quantities and are usually non-toxic and biodegradable.<sup>2,3</sup> Moreover, their relatively low prices make them perfectly adequate for industrial applications and some of them have already been commercially produced for a long time<sup>4</sup> such as

sucrose esters,<sup>5</sup> alkyl polyglucosides (APGs)<sup>6</sup> and sorbitan esters.<sup>7,8</sup>

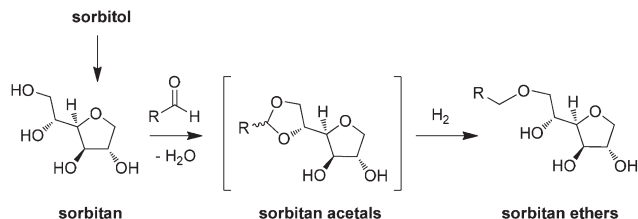
Sorbitan fatty acid esters (SFEs), most commonly known under the trademarks of Span® and Tween® (their polyethoxylated derivatives), are eco-friendly renewable surfactants that possess good surface properties and tunable hydrophilic–lipophilic balances (HLBs).<sup>9</sup> To date, they have found many industrial applications mainly as emulsifiers in food,<sup>10</sup> pharmaceuticals and cosmetics,<sup>11</sup> but they have also been used in paints,<sup>12</sup> explosives and for polymerization processes. However, SFEs could only be used over a limited pH-range due to the vulnerability of the *ester* link towards hydrolysis in acid or basic conditions. In order to circumvent this problem, another category of carbohydrate-based surfactants has been proposed based on the *ether* linkage. Indeed, these compounds usually offer increased stability in both acid and basic media that represents a definite asset to widen the scope of applications of such surfactants. Moreover, a recent study on glycerol-derived ethers has shown that these compounds could have a quite low eco-toxicity.<sup>13</sup> The synthesis of carbohydrate-derived ethers is most often laborious and usually requires protection/deprotection strategies for selectivity reasons.<sup>14</sup> Moreover, polar solvents such as dimethylformamide (DMF) or dimethylacetamide (DMA) are usually needed to improve the solubility of reagents but their utilization is barely acceptable from ecological and economical points of view. Overall, such approaches suffer from low atom-economies and are no longer suitable in the context of green chemistry. Not surprisingly, the preparation of ethers from unprotected sugar derivatives or related polyols is much more difficult due to the great difference of polarity between reactants. However, efficient catalytic

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Scheme 1 Preparation of sorbitan ethers from sorbitan.

approaches have recently emerged such as palladium-catalysed telomerization of butadiene, palladium-catalysed reductive alkylation (reductive etherification), acid-catalysed hydroalkoxylation and etherification, and ring-opening of epoxides. All these methods have been recently reviewed.<sup>15</sup>

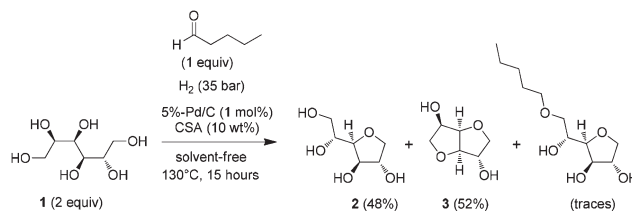
In contrast with the abundant literature concerning sorbitan esters, the access to sorbitan ethers has barely been explored. To the best of our knowledge, only one patent has described the synthesis of sorbitan ethers by reductive alkylation of sorbitol.<sup>16</sup> However, neither yields nor selectivities for the formation of monoethers have been reported in this document.

For several years, our laboratory has been interested in developing green methodologies for the catalytic reductive *N*- or *O*-alkylation of weak nucleophiles using hydrogen as a clean reductant.<sup>17,18</sup> These methods led to the preparation of ether surfactants mainly based on polyols, such as glycerol,<sup>19</sup> and methyl  $\alpha$ -D-glucopyranoside.<sup>20</sup> We report here an economical and environmentally-friendly route to sorbitan ethers from sorbitol through hydrogenolysis of sorbitan acetals (Scheme 1). Moreover, we also describe the physicochemical properties of both ethers and acetal intermediates.

## Results and discussion

We have previously reported the direct reductive alkylation of alcohol, diol and triol such as glycerol using aldehydes, acids or esters as alkylating agents and using hydrogen as a clean reductant for the preparation of the corresponding monoethers. In order to push forward this methodology, we first attempted the direct reductive alkylation of D-sorbitol – a hexol produced from hydrogenolysis of glucose – using our standard conditions. Thus, sorbitol **1** (2 equiv.) was treated with valeraldehyde (1 equiv.) in the presence of 5%-Pd/C (1 mol%), camphorsulfonic acid (CSA, 10 wt%) and hydrogen (35 bar) at 130 °C for 15 hours. Under these conditions, 1,4-D-sorbitan **2** and isosorbide **3** were obtained as a 48 : 52 mixture resulting from two consecutive dehydration of sorbitol. Unfortunately, only traces of sorbitan ethers have been detected by GC-MS (Scheme 2).

As the dehydration of sorbitol was inevitable under these conditions, we decided to prepare sorbitan ethers using sorbitan as starting material. Moreover, we chose to prepare these ethers by an indirect reductive alkylation pathway, involving



Scheme 2 Direct reductive alkylation of sorbitol.

acetal formation and subsequent hydrogenolysis, in order to characterize and study the physicochemical properties of acetal intermediates.

### Preparation of 1,4-D-sorbitan

1,4-D-Sorbitan could be directly prepared by mono-dehydration of sorbitol<sup>21</sup> under acidic conditions. The main challenge of this reaction lies in the control of the production of unwanted isosorbide, product of dehydration of sorbitan. The preparation of sorbitan was first investigated under hydrogen pressure. Indeed, Holladay *et al.* have shown that hydrogen could limit the formation of colored by-products resulting from degradation (or polymerization) of sugars.<sup>22</sup> Moreover, these conditions are close to those reported for the direct reductive alkylation. Thus, sorbitol **1** was heated at 140 °C under 50 bars of hydrogen in the presence of CSA (0.1 mol%). Under these conditions, the conversion reached 73% and HPLC analysis<sup>23</sup> revealed a 80 : 20 mixture of 1,4-D-sorbitan **2** and isosorbide **3** (Table 1, entry 1). The replacement of CSA by an ion-exchange resin such as Amberlyst 15 (A15, 0.1 wt%) gave an improved 83% conversion but a lower selectivity (Table 1, entry 2). Increasing the loading to 10 wt% slightly improved the conversion but isosorbide was obtained as the major product (Table 1, entry 3). Without hydrogen pressure, CSA (0.1 mol%) gave a similar conversion (79%) but the sorbitan/isosorbide ratio dropped to 60 : 40 (Table 1, entry 4). Without hydrogen pressure, CSA (0.1 mol%) gave a similar conversion (79%) but the sorbitan/isosorbide ratio dropped to 60 : 40 (Table 1, entry 4).

Table 1 Preparation of sorbitan<sup>a</sup>

Entry	Cat.	Loading (mol%)	H <sub>2</sub> (bar)	Time (h)	Conv. <sup>b</sup> (%)	Ratio <sup>c</sup> 2 : 3 (%)
1	CSA	0.1	50	15	73 (33) <sup>e</sup>	80 : 20
2	A15	0.1 <sup>d</sup>	50	24	83	72 : 28
3	A15	10 <sup>d</sup>	50	24	86	19 : 81
4	CSA	0.1	—	15	79	60 : 40
5	<i>p</i> -TSA	0.1	—	2	71	92 : 8
6	3 M H <sub>2</sub> SO <sub>4</sub>	0.2	—	15	66 (56) <sup>e</sup>	93 : 7

<sup>a</sup> Reaction conditions: 110 mmol of sorbitol, 140 °C. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Determined by HPLC. <sup>d</sup> wt%. <sup>e</sup> Isolated yield in brackets.

Conversely, the use of *para*-toluenesulfonic acid (*p*-TSA, 0.1 mol%) led to sorbitan with a high selectivity of 92% (Table 1, entry 5). Finally, the use of 3 M H<sub>2</sub>SO<sub>4</sub> (0.2 mol%) gave the best results with an excellent selectivity towards 1,4-D-sorbitan (93%) while preserving a decent conversion (Table 1, entry 6).

From a practical point of view, unreacted sorbitol could be easily removed by filtration of the reaction mixture but isosorbide is much more difficult to eliminate during the purification step. Thus, the use of 3 M H<sub>2</sub>SO<sub>4</sub> has been privileged for the dehydration of sorbitol on the large scale (1 kg). Under these conditions, 1,4-D-sorbitan **2** has been prepared with 43% isolated yield and >98% purity after recrystallisation.

### Sorbitan acetals by acetalisation

With sorbitan in hands, we first investigated the formation of sorbitan acetals by direct acetalisation of sorbitan using valeraldehyde as a model substrate. The molar ratio between reagents was first studied under solvent-free conditions and in EtOH. Thus, sorbitan (neat, 2 equiv.) was treated with valeraldehyde in the presence of CSA (10 mol%) at 95 °C for 15 hours. Under these conditions, the conversion reached 79% and sorbitan acetals **4** and **5** were recovered with 40% combined isolated yield (Table 2, entry 1). No attempt to fully characterize the products has been made at this stage of the study. Increasing the sorbitan/aldehyde molar ratio to 3 : 1 did not significantly improve the product yield (Table 2, entry 2). These poor results could be explained by the formation isosorbide. Indeed, due to the biphasic nature of the reaction mixture (one sugar phase, one lipid phase), sorbitan could not react with the aldehyde and condensate on itself. As a consequence, the reaction was then investigated in dilute condition. Sorbitan was treated with a stoichiometric amount of valeraldehyde using EtOH at 80 °C. Under these conditions, a quantitative conversion was obtained and sorbitan acetals **4** and **5**

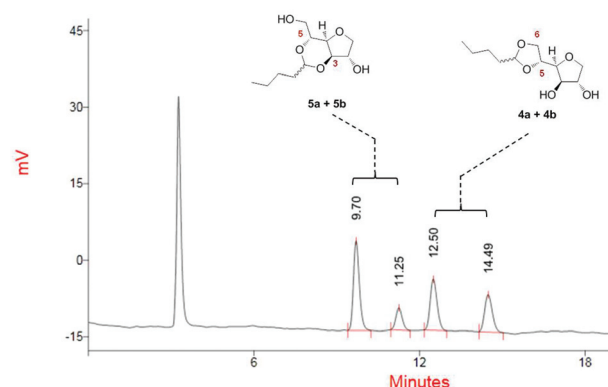


Fig. 1 HPLC chromatogram of the mixture of sorbitan acetals (C18 column, refractive index detection).<sup>23</sup>

were isolated with 58% yield (Table 2, entry 3). Considering the fact that some sorbitan diacetal has been observed as by-product, the reaction was carried out using an excess of sorbitan. Increasing the sorbitan/aldehyde ratio to 2 : 1 and 3 : 1 permitted to improve the isolated yield to 73 and 81%, respectively (Table 2, entries 4 and 5).

HPLC analysis of the isolated mixture of sorbitan acetals revealed the formation of four products (Fig. 1). Further analysis by HPLC-MS, <sup>1</sup>H and <sup>13</sup>C NMR permitted to assign the two first peaks as a pair of diastereoisomers of the six-membered 3,5-O-acetal (Fig. 1, **5a** and **5b**) and the last two peaks as another pair of diastereoisomers of the five-membered 5,6-O-acetal (Fig. 1, **4a** and **4b**).<sup>24</sup>

The nature of the solvent and its influence on the product distribution was next probed. First, the acetalisation of sorbitan (3 equiv.) with valeraldehyde (1 equiv.) in EtOH in the presence of CSA (10 mol%) gave a mixture of four products in the proportions of 26 : 17 : 47 : 10 (Table 3, entry 1). Thereby, the ratio between 5,6-O-acetals **4** and 3,5-O-acetals **5** was calculated to 43 : 57 in favour of the six-membered acetals. Replacing EtOH by <sup>i</sup>PrOH almost gave a complete conversion (97%) but the isolated yield dropped to 66% (Table 3, entry 2). In toluene, the conversion only reached 81% and the yield further dropped to 58% (Table 3, entry 3). The use of aprotic polar solvents, such as THF and 2-MeTHF permitted to increase the yield of acetals to 98 and 94%, respectively (Table 3, entries 4 and 5). Interestingly, solvents with very high polarity like CH<sub>3</sub>CN and DMF<sup>25</sup> gave lower yields (Table 3, entries 6 and 7), probably due to the lipophilic character of the aldehyde.

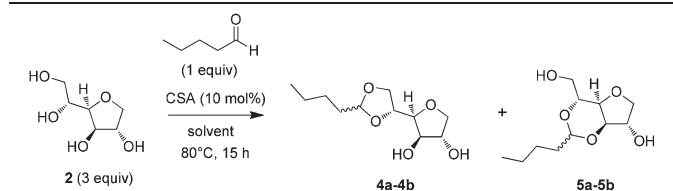
More importantly, it seems that the ratio between regioisomers **4** and **5** is not significantly altered with the nature of the solvent and the six-membered 3,5-O-acetals **5** were recovered as the major regioisomers. However, DMF was found to be an exception, giving predominantly the five-membered 5,6-O-acetals **4** as the major regioisomers.

It is important to note that the lack of selectivity is not detrimental from an industrial point of view since mixtures of surfactants are frequently used in formulations.

Table 2 Influence of the molar ratio for the acetalisation of sorbitan with valeraldehyde<sup>a</sup>

Entry	Molar ratio 2 : ald	Solvent	Temp. (°C)	Conv. <sup>b</sup> (%)	Isolated yield <sup>c</sup> (%)
1	2 : 1	—	95	79	40
2	3 : 1	—	95	79	43
3	1 : 1	EtOH	80	>98	58
4	2 : 1	EtOH	80	>98	73
5	3 : 1	EtOH	80	>98	81

<sup>a</sup> Reaction conditions: 1 mmol of valeraldehyde, CSA (10 mol%), 1.4 mL of solvent if any, 15 hours. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Purification by silica gel chromatography, combined yield of sorbitan acetals **4** and **5**. The yields were calculated based on the limiting reagent (the aldehyde).

Table 3 Solvent screening<sup>a</sup>

Entry	Solvent	Conv. <sup>b</sup> (%)	Isolated yield <sup>c</sup> (%)	Ratio 4 : 5 <sup>d</sup> (4a : 4b : 5a : 5b) (%)
1	EtOH	>98	81	43 : 57 (26 : 17 : 47 : 10)
2	<sup>1</sup> PrOH	97	66	37 : 63 (21 : 16 : 54 : 09)
3	toluene	81	58	36 : 64 (18 : 18 : 56 : 08)
4	THF	>98	98	44 : 56 (26 : 18 : 45 : 11)
5	2-MeTHF	>98	94	34 : 66 (18 : 16 : 56 : 10)
6	CH <sub>3</sub> CN	>98	75	31 : 69 (20 : 11 : 60 : 09)
7	DMF	>98	80	79 : 21 (41 : 38 : 07 : 14)

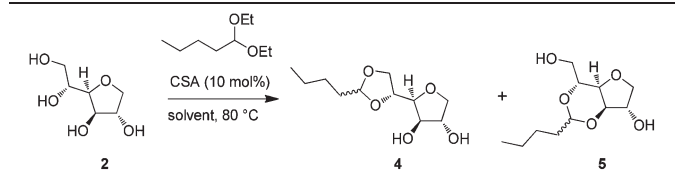
<sup>a</sup> Reaction conditions: 3 mmol of sorbitan, 1 mmol valeraldehyde (1 equiv.), CSA (10 mol%), 1.4 mL of solvent, 80 °C, 15 hours.

<sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Purification by silica gel chromatography, combined yield of sorbitan acetals 4 and 5. The yields were calculated based on the limiting reagent (the aldehyde). <sup>d</sup> Determined by HPLC.

### Sorbitan acetals by transacetalisation

We have previously identified EtOH and 2-MeTHF as green solvents for the direct acetalisation of sorbitan with valeraldehyde in acidic conditions. However, to date, the high cost of 2-MeTHF could not permit to consider potential industrial applications and EtOH will be much preferred for economic reasons. From a mechanistic point of view, the reaction in EtOH in the presence of CSA could proceed by direct acetalisation of sorbitan with valeraldehyde and/or through the *in situ* formation of a diethylacetal and its subsequent transacetalisation with sorbitan. From this observation, we envisioned that sorbitan acetals could be prepared by transacetalisation of a diethylacetal and EtOH released in this process could be recycled by distillation (Fig. 2).

The preparation of sorbitan acetals by transacetalisation was first tested in EtOH. Treatment of 1,1-diethoxypentane (DEP) with 2 equivalents of sorbitan in the presence of CSA (10 mol%) gave 94% conversion but only 22% isolated yield (Table 4, entry 1). The product was isolated as a 50 : 50 mixture of 5,6-*O*- and 3,5-*O*-regioisomers. When using a stoichiometric amount of sorbitan, the conversion dropped but the yield was

Table 4 Sorbitan acetals by transacetalisation<sup>a</sup>

Entry	Molar ratio 2 : DEP	Solvent	Time (h)	Conv. <sup>c</sup> (%)	Isolated yield <sup>d</sup> (%)	Ratio 4 : 5 <sup>e</sup> (%)
1	2 : 1	EtOH	33	94	22	50 : 50
2	1 : 1	EtOH	15	77	27	53 : 47
3 <sup>b</sup>	1 : 2	EtOH	15	63	49	49 : 51
4 <sup>b</sup>	1 : 2	—	15	85	34	63 : 37
5	1 : 1	—	15	81	66	48 : 52

<sup>a</sup> Reaction conditions: 3 mmol of DEP, CSA (10 mol%), 1.4 mL of solvent, 80 °C. <sup>b</sup> 3 mmol of sorbitan. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Purification by silica gel chromatography, combined yield of sorbitan acetals 4 and 5. The yields were calculated based on the limiting reagent: DEP for entries 1–2 and sorbitan for entries 3–5. <sup>e</sup> Determined by HPLC. DEP = 1,1-diethoxypentane.

slightly improved to 27% (Table 4, entry 2). With 2 equivalents of diethoxypentane (DEP), the yield was improved to 49% and the ratio of regioisomers was hardly altered under these conditions (Table 4, entry 3). The transacetalisation process was next investigated under solvent-free conditions. With a 1 : 2 ratio of sorbitan 2 and DEP, a poor yield of 34% was obtained (Table 4, entry 4). Surprisingly, the ratio 4 : 5 was switched in favour of the six-membered 3,5-*O*-acetals 5. Finally, the yield was improved to 66% when using a stoichiometric ratio between 2 and DEP (Table 4, entry 5).

From these results, it appears that the transacetalisation method is particularly attractive under solvent-free conditions, however, the direct acetalisation using aldehyde as alkylating agent in EtOH gave better yields. These conditions have been preferred to further study the scope of the reaction.

### Scope of sorbitan acetals

Optimized conditions were used for the synthesis of aliphatic sorbitan acetals. The direct acetalisation of sorbitan (3 equiv.) with a range of linear alkyl aldehydes (1 equiv.) was performed in the presence of CSA (10 mol%) in EtOH at 80 °C for 15 hours (Table 5).

The reaction of short alkyl chain aldehydes such as pentanal, hexanal and octanal gave complete conversion while longer alkyl chain aldehydes – decanal and dodecanal – afforded incomplete ones (Table 5, entries 1–5). Similarly, the isolated yields of the corresponding sorbitan acetals dropped from 81% with pentanal to 29% with dodecanal (Table 5, entries 1–5). These observations could be explained by the difference of polarity between reagents and this effect is more pronounced with long alkyl chain. Finally, a range of sorbitan acetals have been produced by direct acetalisation of sorbitan in EtOH as benign solvent. These compounds could be evaluated as non-ionic surfactants with various hydrophilic-

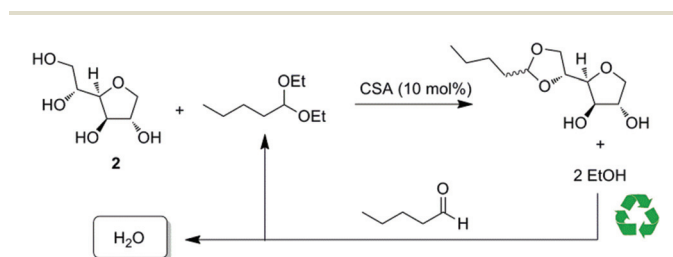
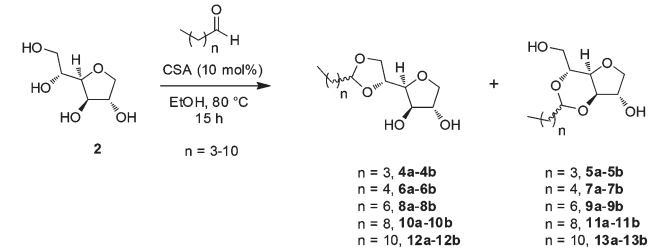


Fig. 2 Envisioned process for transacetalisation with sorbitan.



Table 5 Scope of sorbitan acetals by acetalisation<sup>a</sup>


Entry	Aldehyde	Conv. <sup>b</sup> (%)	Isolated yield <sup>c</sup> (%)	Acetals	Product ratio <sup>d</sup> (%)
1	Pentanal	>98	81	4-5	43 : 57 (26 : 17 : 47 : 10)
2	Hexanal	>98	58	6-7	57 : 43 (32 : 25 : 31 : 12)
3	Octanal	>98	37	8-9	61 : 39 (32 : 29 : 28 : 11)
4	Decanal	77	32	10-11	64 : 36 (35 : 29 : 25 : 11)
5	Dodecanal	81	29	12-13	48 : 52 (25 : 23 : 40 : 12)

<sup>a</sup> Reaction conditions: 3 mmol of sorbitan, 1 mmol of aldehyde, CSA (10 mol%), EtOH (1.4 mL), 80 °C, 15 h. <sup>b</sup> Determined by <sup>1</sup>H NMR.

<sup>c</sup> Purification by silica gel chromatography, combined yield of sorbitan acetals. The yields were calculated based on the limiting reagent (the aldehydes). <sup>d</sup> Determined by HPLC.

lipophilic balances and could be further reduced to the corresponding ethers.

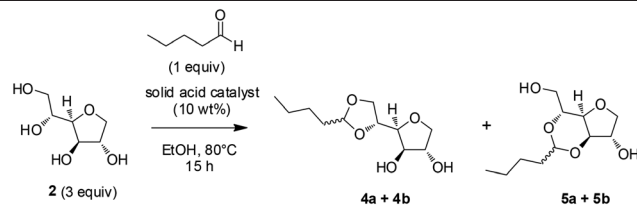
### Heterogeneous catalysts screening

From both economical and environmental points of view, the use of CSA could represent a limitation for this method. Consequently, the possible replacement of CSA by a solid acid catalyst was also investigated. The acetalisation of sorbitan **2** was carried out under the optimized conditions using valeraldehyde, 10 wt% of a solid acid catalyst in EtOH at 80 °C (Table 6). Using a perfluorinated sulfonic acid resin such as Nafion® NR50, the conversion was complete and the corresponding sorbitan acetals **4** and **5** were obtained with 69% isolated yield (Table 6, entry 1). Similar results were obtained using Amberlyst A15 dry (Table 6, entry 2). However, when using Amberlyst A36 dry, the yield of the desired sorbitan monoacetals **4** and **5** decreased to 29% (Table 6, entry 3). The use of an acidic zeolite such as H-ZSM-5 (Si/Al ratio = 23), previously calcined at 650 °C for 3 h, afforded a complete conversion and the desired products were isolated with 73% yield (Table 6, entry 4). Finally, the reaction was also feasible using a mesoporous silica such as MCM-41 but a lower yield was obtained (Table 6, entry 5).

These results indicate that CSA could be advantageously replaced by a heterogeneous solid acid catalyst. Interestingly, the ratio between five-membered 5,6-*O*-acetals **4** and six-membered 3,5-*O*-acetals **5** is not significantly altered by the nature of the acid catalyst.

### Hydrogenolysis of sorbitan acetals to sorbitan ethers

We have previously reported the palladium-catalysed reductive cleavage of α-D-methyl glucoside acetals to the corresponding ethers using hydrogen as a clean reducing agent.<sup>20a</sup> With sorbitan acetals in hands, we envisioned that applying the pre-

Table 6 Solid acid catalyst screening<sup>a</sup>


Entry	Catalyst	Conv. <sup>b</sup> (%)	Isolated yield <sup>c</sup> (%)	Ratio 4 : 5 <sup>d</sup> (%)
1	Nafion® NR50	>98	69	56 : 44
2	Amberlyst A15 dry	>99	70	49 : 51
3	Amberlyst A36 dry	>99	29	45 : 55
4	Zeolite H-ZSM-5	>97	73	48 : 52
5	MCM-41	>99	59	46 : 54

<sup>a</sup> Reaction conditions: 3 mmol of sorbitan, 1 mmol of valeraldehyde, solid acid catalyst (10 wt%), 1.4 mL of EtOH, 80 °C, 15 h. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Purification by silica gel chromatography, combined yield of sorbitan acetals **4** and **5**. The yields were calculated based on the limiting reagent (the aldehyde). <sup>d</sup> Determined by HPLC.

viously optimized conditions will furnish the desired sorbitan ethers.<sup>26</sup> Thus, a mixture of five-membered and six-membered pentyldiene sorbitan acetals **4** and **5** in cyclopentyl methyl ether (CPME)<sup>27</sup> was treated under hydrogen pressure (30 bar) in the presence of 5%-Pd/C (5 mol%) at 120 °C for 15 h (Table 7).

Satisfyingly, the conversions were complete and the corresponding ethers **14a-c** were recovered with 69% isolated yield after purification by column chromatography (Table 7, entry 1). As expected from the hydrogenolysis of the mixture of sor-

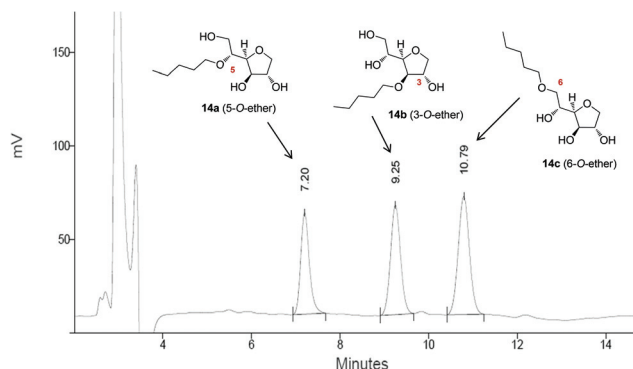
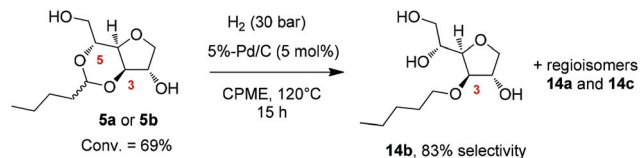
**Table 7** Hydrogenolysis of sorbitan acetals to sorbitan ethers<sup>a</sup>

Entry	Sorbitan acetals	Conv. <sup>b</sup> acetals (%)	Products	Isolated yield <sup>c</sup> (%) (a, b, c)
1	4–5	>98	14a–c	69 (26 : 33 : 41)
2	6–7	>98	15a–c	65 (33 : 16 : 51)
3	8–9	>98	16a–c	85 (33 : 22 : 45)
4	10–11	98	17a–c	59 (32 : 16 : 52)
5	12–13	97	18a–c	55 (27 : 33 : 40)

<sup>a</sup> Reaction conditions: 300 mL stainless steel autoclave with mechanical stirrer, mixture of sorbitan acetals (20 mmol), 5%-Pd/C (5 mol%), H<sub>2</sub> (30 bar), CPME (200 mL), 120 °C, 15 h. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Purification by silica gel chromatography, combined yield of sorbitan ethers.

bitan acetals, HPLC analysis revealed the formation of 3 regioisomers in the proportions 26 : 33 : 41 (Fig. 3). Further analysis by 1D and 2D NMR permitted to assign the first peak as the 5-O-pentylether **14a**, the second peak as the 3-O-pentylether **14b** and the third peak as the 6-O-pentylether **14c** by order of elution. Hydrogenolysis of hexylidene **6** and **7** and octylidene **8** and **9** sorbitan acetals afforded the corresponding sorbitan ethers **15a–c** and **16a–c** with moderate isolated yields (65–85%), respectively (Table 7, entries 2 and 3).

Increasing the alkyl chain length of sorbitan acetals to decylidene and dodecylidene gave lower reactivity and the corresponding sorbitan ethers **17a–c** and **18a–c** were obtained with 59 and 55% isolated yields, respectively (Table 7, entries 4–5). It should be noted that the proportions of sorbitan ethers could vary depending on the alkyl chain length but the 6-O-regioisomer has always been formed as the major compound.

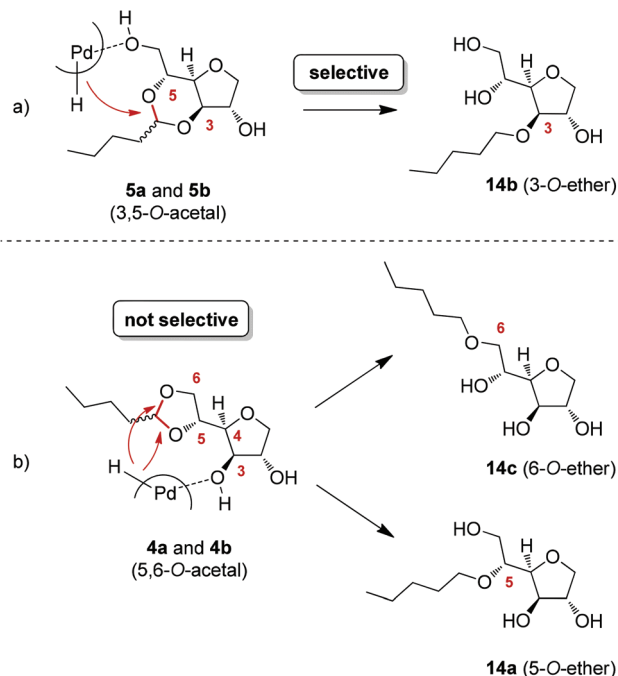
**Fig. 3** HPLC chromatogram of the mixture of sorbitan ethers **14a–c** (C18 column, refractive index detection).<sup>28</sup>**Scheme 3** Hydrogenolysis of a pure sorbitan acetal.

The mixtures of sorbitan alkyl ethers have been next evaluated as renewable surfactants.

### Mechanistic considerations

In order to get insights on the mechanism of the reductive cleavage of sorbitan acetals to ethers, a pure sample of a 3,5-O-pentylidene sorbitan **5a** or **5b** was isolated and submitted to hydrogenolysis [30 mL stainless steel autoclave with magnetic stirrer, hydrogen pressure (30 bar), 5%-Pd/C (5 mol%), CPME, 120 °C, 15 h]. Under these conditions, the conversion reached 69% and 3-O-pentyl-sorbitan **14b** was obtained as the major product with 83% selectivity (Scheme 3). The presence of small amounts of compound **14c** could be attributed to the formation of sorbitan acetals **4a** and/or **4b** by Pd/C-catalysed scrambling of the acetal function and subsequent hydrogenolysis.

From this result, we propose a mechanism to account for the distribution of products observed. Starting from the 3,5-O-pentylidene sorbitans **5a** and **5b**, the acetal function could be activated by Pd with the assistance of the 6-hydroxyl group of the sorbitan moiety (Fig. 4a, top). In this configuration,

**Fig. 4** Mechanism proposal for the hydrogenolysis of sorbitan acetals.

hydrogen could be preferentially delivered to the C–O(5) bond that breaks to furnish 3-*O*-pentylsorbitan **14b** as the major regioisomer. By analogy, 5,6-*O*-pentylidene sorbitans **4a** and **4b** could coordinate to Pd with the assistance of the free hydroxyl group at the O(3)-position (Fig. 4b, bottom). However, in that case, both C–O(5) and C–O(6) bonds could be cleaved due to the free rotation around C(4)–C(5)-bond to give a mixture of 5-*O*-pentylsorbitan **14a** and 6-*O*-pentylsorbitan **14c** with almost no selectivity. Assuming that the formation of the 3-*O*-ethers is almost regioselective, the ratio between 5-*O*-ethers and 6-*O*-ethers has been evaluated to around 40 : 60 based on the **a** : **c** ratio for all sorbitan ethers **14–18** (Table 7, entries 1–5). Finally, these models could explain why all the regioisomers have been obtained with similar proportions.

### Acetalisation/hydrogenolysis sequence

Having synthesized sorbitan ethers from the corresponding acetals, we envisioned that sorbitan ethers could be directly obtained from sorbitan following an acetalisation/hydrogenolysis sequence without purification of acetal intermediates. Unfortunately, these two steps present some incompatibilities. Indeed, the acetalisation step was carried out in EtOH and requires the presence of an acid catalyst. However, we have previously showed that both EtOH and an acid co-catalyst are deleterious for the hydrogenolysis step, leading to the hydrolysis of acetals.<sup>20a</sup> In order to avoid such inconvenience, the acetalisation of sorbitan was performed in the same solvent than the hydrogenolysis step (CPME) and an acid resin was used for easiness of separation. Moreover, Na<sub>2</sub>SO<sub>4</sub> was used as a dehydrating agent and incorporated at the beginning of the sequence. Thus, sorbitan was treated with valeraldehyde in the presence of Amberlyst 15 (20 wt%), in CPME at 80 °C (Table 8). After 15 hours, <sup>1</sup>H NMR revealed a conversion of 75% in aldehyde (Table 8, entry 1). The solid acid catalyst was removed by filtration and the crude product was submitted to hydrogenolysis under 30 bar of hydrogen using 5%-Pd/C (5 mol%) at 120 °C for 15 hours. The conversion of acetals **4a–b** and **5a–b** was complete and the desired pentyl sorbitans **14a–c** were isolated with 56% overall yield after purification by column chromatography (Table 8, entry 1). By comparison, the reductive cleavage of purified sorbitan acetals **4a–b** and **5a–b** gave full conversion and a 53% isolated yield (Table 8, entry 2). The same strategy has been applied to a longer alkyl chain such as decanal and the resulting decyl sorbitans **17a–c** were obtained with 22% isolated yield without purification of the acetal intermediates (Table 8, entry 3).

Once again, a similar result (21% yield) was obtained when using purified acetals **10a–b** and **11a–b** (Table 8, entry 4). Finally, these experiments have shown that the hydrogenolysis could be directly performed on the crude reaction mixture as similar results were obtained with or without purification of the acetals. These conditions could be advantageous for the large scale production of sorbitan ethers.

**Table 8** Hydrogenolysis of crude sorbitan acetals<sup>a</sup>

Entry	<i>n</i>	Conv. <sup>b</sup> ald. (%)	Purif. acetals	Conv. <sup>b</sup> acetals (%)	Sorbitan ethers	Isolated yield <sup>c</sup> (%)
1	3	75	No	>98	<b>14a–c</b>	56
2	3	—	Yes	>98	<b>14a–c</b>	53
3	8	24	No	>98	<b>17a–c</b>	22
4	8	—	Yes	97	<b>17a–c</b>	21

<sup>a</sup> Reaction conditions: sorbitan (60 mmol, 2 equiv.), aldehyde (30 mmol, 1 equiv.), A15 (20 wt%), Na<sub>2</sub>SO<sub>4</sub> (1.5 equiv.), CPME, 80 °C, 15 h then, 5%-Pd/C (5 mol%), H<sub>2</sub> (30 bar), CPME, 120 °C, 15 h in a 500 mL stainless steel autoclave with mechanical stirrer. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Purification by silica gel chromatography, combined yield of all ether regioisomers. Overall yields are given from sorbitan and are calculated based on the limiting reagent (the aldehyde).

### Acetalisation/transacetalisation cascade

The preparation of sorbitan ethers from sorbitan by an acetalisation/hydrogenolysis sequence is mainly limited by the acetalisation step. This is particularly true for the synthesis of sorbitan ethers bearing a long alkyl chain due to the great difference of polarity between starting materials (sorbitan and fatty aldehyde). In order to improve the yield of these long chain sorbitan acetals, an acetalisation/transacetalisation cascade was designed using short chain aldehyde as “solubility relay” (Fig. 5).<sup>29</sup> In this strategy, short chain sorbitan acetals could be formed in the sorbitan polar phase and migrate in the non-polar phase to undergo *trans*-acetalisation with a long chain aldehyde to give the desired long chain sorbitan acetals.

The viability of this concept was first investigated in homogeneous conditions. Thus, sorbitan was treated with valeraldehyde (0.5 equiv.) in CPME at 80 °C for 3 h to give the corresponding sorbitan acetals **4a–b** and **5a–b**. Transacetalisation with dodecanal (0.5 equiv.) gave a 46 : 54 mixture of pentylidene- **4a–b** and **5a–b** and dodecylidene-acetals **12a–b** and **13a–b** (Table 9, entry 1). The yield of dodecylidene sorbitan has been calculated to 58% based on the overall mass recovered and the HPLC ratio. By comparison, the direct acetalisation of sorbitan with dodecanal in CPME gave only 24% isolated yield of the desired product (Table 9, entry 2). The phenomenon is even more pronounced under solvent-free conditions. The previous yield of 36% obtained by direct acetalisa-

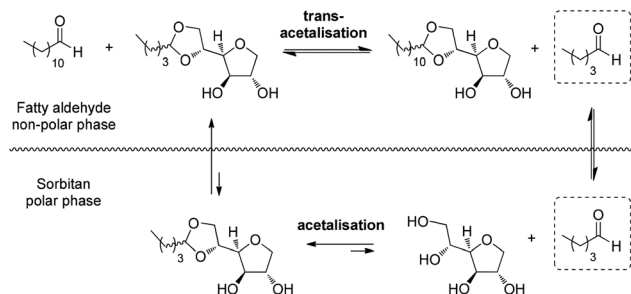


Fig. 5 Principle of the acetalisation/transacetalisation cascade using short chain aldehyde as "solubility relay".

Table 9 Acetalisation/transacetalisation cascade<sup>a</sup>

Entry	Solvent	Conv. C5 ald. <sup>b</sup> (%)	Conv. C12 ald. <sup>b</sup> (%)	Ratio C5 : C12 <sup>c</sup>	Yield 12a-b + 13a-b (%)
1	CPME	76	76	46 : 54	58 <sup>d</sup>
2	CPME	—	79	—	24
3	—	96	94	38 : 62	82 <sup>d</sup>
4	—	—	60	—	36

<sup>a</sup> Reaction conditions: sorbitan (1 equiv.), valeraldehyde (30 mmol, 0.5 equiv.), A15 (20 wt%), dry CPME (30 mL), Na<sub>2</sub>SO<sub>4</sub> (0.75 equiv.), 80 °C, 3 h; then, dodecanal (30 mmol, 0.5 equiv.), 80 °C, 3 h. <sup>b</sup> Conversions were determined by <sup>1</sup>H NMR. <sup>c</sup> Ratio of sorbitan acetals were determined by HPLC. <sup>d</sup> Calculated based on the overall mass recovered and the C5/C12 HPLC ratio and based on the limiting reagent (dodecanal).

tion increased to 82% using this cascade procedure (Table 9, entries 3–4).

### Amphiphilic properties

The surface tension of aqueous solutions of the mixtures of sorbitan acetals (abbreviated C<sub>x</sub>AcSorb, with *x* = number of carbons of the alkyl chain, Ac = acetal, Sorb = sorbitan) were first measured by the Wilhelmy plate method using a platinum rod as probe (Fig. 6). All sorbitan acetals induce a strong decrease of the surface tension of water to a plateau value of about 30 mN m<sup>-1</sup>.

However, quite different profiles are observed depending on the alkyl chain length. C8 to C12 sorbitan acetals exhibit typical surfactant profiles with poorly defined CMC appearing at low concentrations whereas C5 and C6 sorbitan acetals display a smoother decrease and a plateau value at quite high concentrations (Table 10). These later profiles are typical of short chain amphiphiles exhibiting behaviour of hydrotropes which have no CMC since they cannot form true micelles.

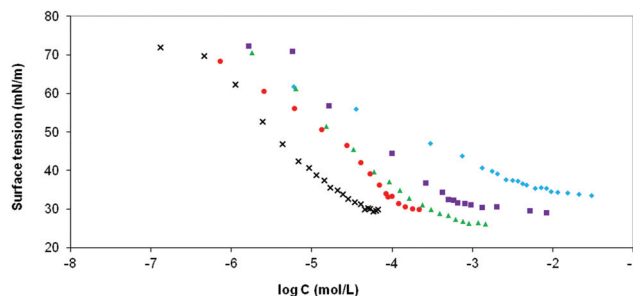


Fig. 6 Surface tension vs. concentration of sorbitan acetals. xC12AcSorb, ●C10AcSorb, ▲C8AcSorb, ■C6AcSorb, ◆C5AcSorb.

Table 10 Critical micellar concentrations (CMC) and minimum aggregation concentrations (MAC) of sorbitan acetals

Entry	Sorbitan acetals	Ratio <sup>a</sup> (%)	CMC/MAC <sup>b</sup> (mmol L <sup>-1</sup> )	γ <sup>b</sup> (mN m <sup>-1</sup> )
1	C5AcSorb	43 : 57	6.3	35
2	C6AcSorb	57 : 43	0.51	32
3	C8AcSorb	61 : 39	0.29	28
4	C10AcSorb	64 : 36	0.12	30
5	C12AcSorb	50 : 50	0.034	30

<sup>a</sup> Ratio of five-membered and six-membered regioisomers were determined by HPLC. <sup>b</sup> Determined by tensiometry.

Instead, they give small aggregates above an ill-defined Minimum Aggregation Concentrations (MAC).

Sorbitan acetals bearing a short C5 or C6 alkyl chain are less efficient than their longer chain counterparts (Table 10, entries 1–2). Nevertheless, these compounds could present valuable properties since they facilitate the solubilisation of high concentrations of hydrophobic compounds in water without forming viscous liquid crystals unlike true surfactants.<sup>30</sup> C8AcSorb was found to be the best compound to reduce the surface tension of water with a saturated value of 28 mN m<sup>-1</sup> but its MAC (0.29 mmol L<sup>-1</sup>) is too high to be interesting for surfactant applications (Table 10, entry 3). Further increasing the alkyl chain length to C10 and C12 permitted to decrease the MAC to 0.12 and 0.034 mmol L<sup>-1</sup>, respectively (Table 10, entries 4 and 5). Moreover, both compounds exhibit a saturated value of 30 mN m<sup>-1</sup> that makes them good candidates as bio-based surfactants.

Similarly, the amphiphilic properties of sorbitan ethers (abbreviated C<sub>x</sub>EthSorb, with *x* = number of carbons of the alkyl chain, Eth = ether, Sorb = sorbitan) were next investigated. Again, all sorbitan ethers allow the reduction of the surface tension of water and a plateau value is reached for each compound above a characteristic concentration (Fig. 7).

The reduction of surface tension with concentration is even smoother than what was observed in the case of acetals, which could be due to the presence of mixtures of isomers. However, it allows defining CMC or MAC values for each chain length and again, a distinction can be made between compounds



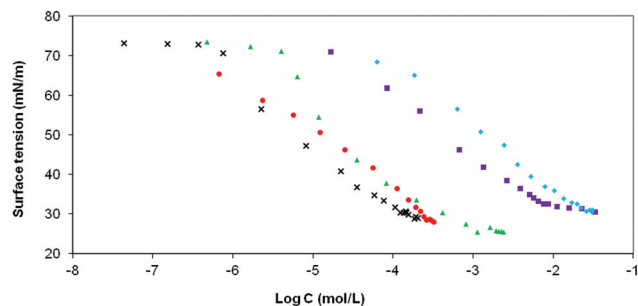


Fig. 7 Surface tension vs. concentration of sorbitan ethers.  $\times$  C12EthSorb,  $\bullet$  C10EthSorb,  $\blacktriangle$  C8EthSorb,  $\blacksquare$  C6EthSorb,  $\blacklozenge$  C5EthSorb.

Table 11 Critical micellar concentrations (CMC) and minimum aggregation concentrations (MAC) of sorbitan ethers

Entry	Sorbitan ethers	Ratio <b>a</b> : <b>b</b> : <b>c</b> <sup>a</sup> (%)	CMC/MAC <sup>b</sup> (mmol L <sup>-1</sup> )	$\gamma^b$ (mN m <sup>-1</sup> )
1	C5EthSorb	26 : 33 : 41	7.6	32
2	C6EthSorb	33 : 16 : 51	20.9	30
3	C8EthSorb	33 : 22 : 45	0.59	26
4	C10EthSorb	32 : 16 : 52	0.35	28
5	C12EthSorb	27 : 33 : 40	0.091	30

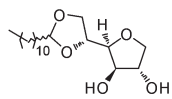
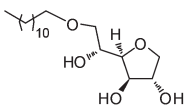
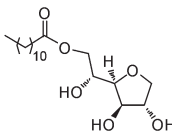
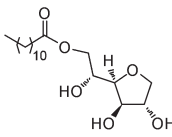
<sup>a</sup> Determined by HPLC. <sup>b</sup> Determined by tensiometry.

self-associating at quite high concentrations (C5, C6, C8) and those being closer in behaviour to true surfactants (C10 and C12). The CMC/MAC values determined from the curves are summarized in Table 11.

As expected, the CMC/MAC of sorbitan ethers decreases gradually with the increase of the alkyl chain length, from 7.6 mmol L<sup>-1</sup> for C5EthSorb to 0.091 mmol L<sup>-1</sup> for C12EthSorb (Table 11, entries 1–5). Interestingly, the reduction of the surface tension of water is slightly better for sorbitan ethers compared to the corresponding acetals (Table 11, entries 1–5). It should also be pointed out that for a given chain length, CMCs/MACs are higher for sorbitan ethers than for their acetal counterparts, which shows the hydrophilic contribution of the hydroxyl group released during the cleavage of sorbitan acetals to ethers. The mixture of C6EthSorb exhibits an unexpected high MAC value (Table 11, entry 2), which could be due to a different ratio between regioisomers. Indeed, one can expect that regioisomeric effects have a great impact on the amphiphilic properties of these compounds, as already observed in the case of isosorbide ethers.<sup>31</sup> Comparing the MAC values of C5AcSorb (6.3 mmol L<sup>-1</sup>) and C5EthSorb (7.6 mmol L<sup>-1</sup>) to that of the 5-*O*-monopentyl ether of isosorbide (C5EthIso, 230 mmol L<sup>-1</sup>)<sup>32</sup> and the 1-*O*-monopentyl ether of glycerol (C5EthGly, 250 mmol L<sup>-1</sup>)<sup>33</sup> shows that the short-chain sorbitan acetals and ethers could be used as particularly efficient hydrotropes.

In order to rank the effectiveness of these new surfactants, the two longest compounds, namely dodecylidenesorbitan

Table 12 Comparison of Critical micelle concentration (CMC)

Entry	Surfactant	HLB <sup>a</sup>	CMC <sup>b</sup> (mmol L <sup>-1</sup> )	$\gamma^b$ (mN m <sup>-1</sup> )
1	 dodecylidenesorbitan (mixture of regioisomers)	—	0.034	30
2	 dodecylsorbitan (mixture of regioisomers)	9.80	0.091	30
3	 6- <i>O</i> -lauroylsorbitan (pure)	8.60	0.056	30
4	 6- <i>O</i> -lauroylsorbitan (Span 20®)	—	0.041	31

<sup>a</sup> Calculated with the Griffin method. <sup>b</sup> Determined by tensiometry.

(C12AcSorb) and dodecylsorbitan (C12EthSorb), were compared to commercially available surfactants and other benchmarks (Table 12). Only compounds bearing a C12 alkyl chain have been selected for better comparison. With CMCs of 0.034 and 0.091 mmol L<sup>-1</sup> respectively, C12 sorbitan acetal and ether exhibit similar performance than the synthesized<sup>34</sup> C12 sorbitan ester (Table 12, entries 1–3). Moreover, their performances are also close to those of commercially available Span 20® which is an industrial product with a mixture of various alkyl chain lengths (Table 12, entry 4). These results validate our approach that *ester* surfactants could be replaced with similar molecules bearing an *ether* function without significant loss of activity. Their improved stability towards hydrolysis could potentially widen the scope of applications of these sorbitan-based surfactants.

## Conclusions

In conclusion, we have developed cheap and environmentally friendly<sup>35</sup> access to sorbitan ethers through hydrogenolysis of the corresponding acetals. These acetals were prepared by direct acetalisation or transacetalisation of sorbitan using aldehydes or their corresponding diethylacetals and were isolated

with moderate to good yields (29–81%). It has been shown that these sorbitan acetals exist as a mixture of five-membered and six-membered regioisomers. The hydrogenolysis of the mixtures gave the corresponding sorbitan ethers as a mixture of 3 regioisomers with 55–85% isolated yields. In order to avoid the isolation of sorbitan acetals, an acetalisation/hydrogenolysis sequence has been optimized giving the corresponding ethers with similar isolated yields. Moreover, an acetalisation/transacetalisation cascade has been developed to increase the yield of the limiting step (acetalisation) using a mixture of short and long chain aldehydes. Finally, the physico-chemical properties have been determined for all sorbitan derivatives. Both C12 sorbitan acetals and ethers exhibit surfactant properties with similar performance than commercially available Span 20®. These new surfactants could find applications in processes or products requiring to work under (strong) acid or basic conditions.

## Experimental

### General information

Sorbitol **1** (>98% purity) was purchased from Sigma-Aldrich. Valeraldehyde, hexanal, octanal, decanal and dodecanal were supplied by Sigma-Aldrich or Alfa-Aesar. Amberlyst 15 dry and Amberlyst 36 were bought from Rohm and Haas. Pd/C (5 or 10%, Pd on activated carbon, reduced and dry, Escat 1431) was purchased from Strem Chemicals. All other reagents and solvents were used as received without further purification. See ESI† for further details.

### General procedure for the preparation of sorbitan acetals.

In a round bottom flask equipped with a condenser fitted with a CaCl<sub>2</sub> guard, under an argon atmosphere, 1,4-D-sorbitan **2** (5.00 g, 30.5 mmol, 3 equiv.) was dissolved in dry EtOH. The aldehyde (10.2 mmol, 1 equiv.) was added dropwise, followed by camphorsulfonic acid (10 wt%/aldehyde). Then, the mixture was magnetically stirred at 80 °C for 15 hours. The mixture was cooled down to room temperature and the solvent was evaporated under reduced pressure. The residue was triturated in EtOAc and the excess of sorbitan was filtered off and washed with cold EtOAc. This operation was repeated in order to remove any traces of sorbitan. The residue was concentrated and purified by flash chromatography to give the desired sorbitan acetals as a mixture of 5,6-*O*-alkylidene- and 3,5-*O*-alkylidene-1,4-D-sorbitan regioisomers. Each regioisomer was obtained as a mixture of diastereoisomers. The ratio of compounds has been determined by HPLC.

### General procedure for the preparation of sorbitan ethers.

The mixture of 1,4-D-sorbitan acetals (20 mmol) was diluted in dry CPME (200 mL) and 5%-Pd/C (1.00 g, 5 mol% in Pd) was added in a 300 mL stainless steel autoclave. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (30 bar). The system was heated at 120 °C and mechanically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in absolute EtOH

(100 mL) and filtered (Millipore Durapore filter 0.01 µm). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography to give sorbitan ethers as mixtures of 3 regioisomers. The ratio of compounds has been determined by HPLC.

### General procedure for the surface tension measurements.

The surface tensions were measured at room temperature (23 ± 1)°C with a K100MK2 Krüss tensiometer using a platinum rod as a probe. Measurements were made on 2.5 mL samples. The surface tension of pure water was first measured and the concentration was then gradually increased while keeping a constant sample volume. When the surface tension was stable (standard deviation of the 5 final measurements lower than 0.1 mN m<sup>-1</sup>), a precise volume of the solution was removed and the same volume of a concentrated stock solution was added under stirring. For a given compound, the measurement was stopped once the surface tension no longer decreased while increasing the concentration.

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