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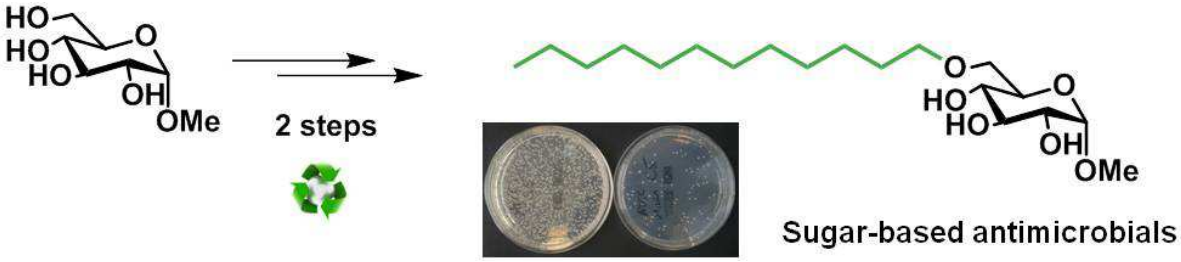

Synthesis, Surfactant Properties and Antimicrobial Activities of Methyl Glycopyranoside Ethers

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Abstract: A series of amphiphilic methyl glucopyranoside ethers incorporating various alkyl chain lengths has been synthesized from commercially available methyl glucopyranosides following an acetalization/hydrogenolysis sequence. The amphiphilic properties of ethers and acetal intermediates were evaluated. Both families exhibit excellent surfactant properties with a maximum efficiency obtained for compounds bearing a linear dodecyl chain (CMC = 0.012 mM, $\gamma_{sat.}$ = 30 mN.m^{-1}). Antimicrobial activity studies revealed an efficient activity (0.03 < MIC < 0.12 mM) against Gram-positive bacteria such as *Listeria monocytogenes*, *Enterococcus faecalis*, *Enterococcus faecium* and *Staphylococcus aureus*. More importantly, these compounds were found to be active against multi-resistant strains such as *vancomycin*-, *methicillin*- and *daptomycin*-resistant strains. Finally, it was found that antimicrobial activities are closely related to physicochemical properties and are also influenced by the nature of the carbohydrate moiety.

Introduction

Antibiotics and other antimicrobials are essential compounds to inhibit or prevent the growth of undesirable microorganisms.[1] In this respect, they are widely used to prevent and cure bacterial infection and they have found many applications in medicine, in food industry,[2] and in other fields such as packaging[3] and textile.[4] However, the consequence of this extensive utilization is the emergence of antimicrobial-resistant infectious agents, which represents a major problem for public health.[5] It is becoming particularly alarming since all known antimicrobial chemotherapies are striving to cure superbug's infections.[6] That is the reason why there is an incentive to seek and develop new effective agents with improved activity against resistant pathogens.[7] Moreover, the attention should also be paid on the cost of such agents in order to guarantee their accessibility to a large part of the World's population. Where is the progress if we have in hands highly sophisticated antimicrobials that no one can afford?

In this context, cheap antimicrobials based on long-chain fatty acids and their corresponding polyol ester derivatives have been developed. One of the most active is monolaurin, a linear C12 glycerol monoester, manufactured under the trademark Lauricidin®. This compound is used as food additive in order to inhibit the growth of various microorganisms.[8] Carbohydrate-derived antimicrobials have also attracted a lot of attention. Indeed, carbohydrates are cheap, natural products, available in bulk quantities from renewable resources. Moreover, they are usually non-toxic and bio-degradable. As a result, they provide an adequate platform for antimicrobials targeting industrial applications. For example, sucrose esters are common carbohydrate fatty acid esters used by the food industry as preservatives.[9] Particularly, sucrose monolaurate was found to be active against *Listeria*

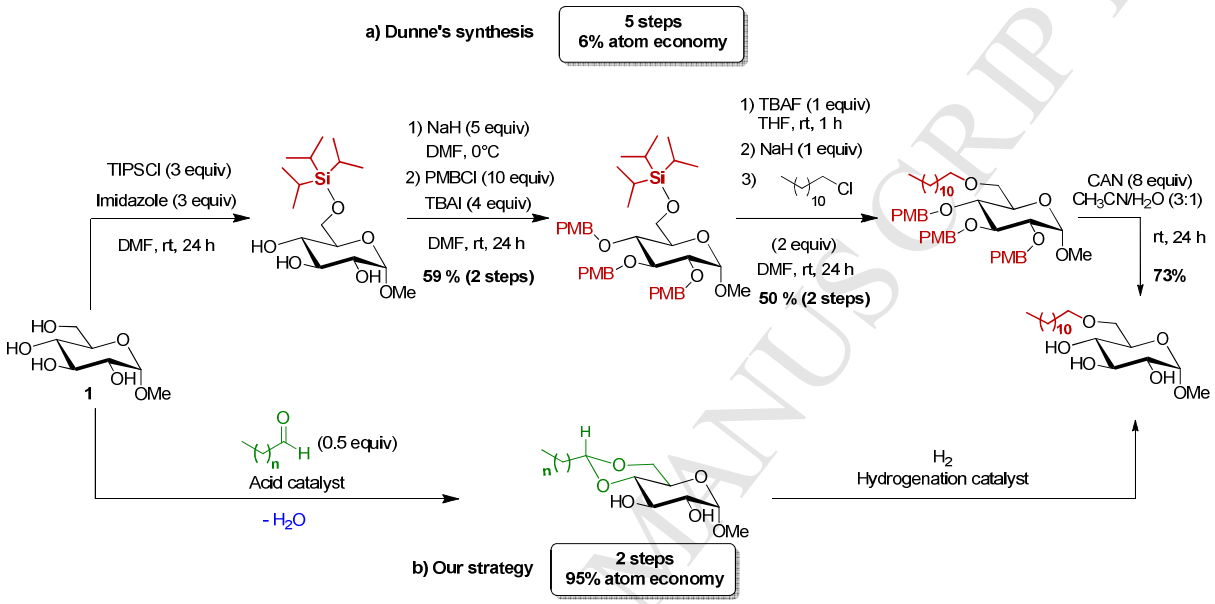
monocytogenes and, to a lesser extent, against *Staphylococcus aureus*.[10] Other carbohydrate fatty acid esters, such as 6'-*O*-lauroylmaltose and 6''-*O*-lauroylmaltotriose were found to inhibit the growth of *Streptococcus sobrinus*, hence they are promising additives in oral-hygiene products.[11] Moreover, these molecules revealed to be active against *Bacillus spp.* and *Lactobacillus plantarum.*[12] Monosaccharide fatty acid esters have also shown interesting antimicrobials properties. For example, methyl 6-*O*-lauroyl-α-D-glucopyranoside displayed activity against *S. aureus* and *Escherichia coli*.[13] Some other analogues were also evaluated and found to be active against *L. innocua* and *L. monocytogenes*.[14] From a mechanistic point of view, carbohydrate fatty acid esters exhibit antimicrobial activity due to their ability to interact with biological membranes.[15] Indeed, their surfactant properties allow the solubilisation of the lipids constituting the cell membrane. This phenomenon impairs the membrane integrity and causes cellular lysis.[16] However, the ester bond of these antimicrobials could be cleaved by cellular esterases, thus releasing the corresponding inactive sugar and free fatty acid.[13b] For example, Ruzin and Novick have shown that monolaurin is rapidly hydrolyzed ($t_{1/2}$ of about 5 min) in the presence of *S. aureus* cells.[17]

To prevent the hydrolysis of these antimicrobial agents, the *ester* linkage can be advantageously replaced by an *ether* function, insensitive to esterases. For example, the corresponding ether of monolaurin, 1-*O*-dodecylglycerol, has shown greater activity against *E. faecium* than monolaurin itself, probably due to its greater retention in the cell.[18] Similar observations were made with carbohydrate fatty ethers such as methyl 6-*O*-dodecanyl-α-D-glucopyranoside, which exhibits an enhanced activity against *S. aureus*[13] and *Listeria spp.* in comparison to its corresponding ester.[14] Consequently, carbohydrate fatty ethers seem to be promising candidates for new antimicrobial agents with improved activity and half-life in cells. However, the synthesis of carbohydrate-derived ethers usually requires a multi-step route including protection/deprotection strategies for selectivity and solubility reasons. In addition, the ether function is usually introduced using Williamson conditions requiring a strong base and an alkyl halide or pseudo-halide.[19] As a result, the atom economy of such routes is usually quite low and large amount of waste is produced. Finally, such strategies result in a very high production cost which is not suitable for widespread industrial applications. This could probably explain why, to date, no carbohydrate fatty ether antimicrobial is available on the market. In this context, our group has recently developed an efficient methodology to prepare alkyl ethers of carbohydrate derivatives through hydrogenolysis of the corresponding acetals.[20] Herein, we report our efforts to improve and extend the scope of application of this methodology to a range of methyl glycopyranosides. We also describe the amphiphilic properties and antimicrobial activities of a series of methyl glycopyranoside ethers and their acetal intermediates.[21]

Results and Discussion

Synthesis of methyl α-D-glucopyranoside alkyl ethers

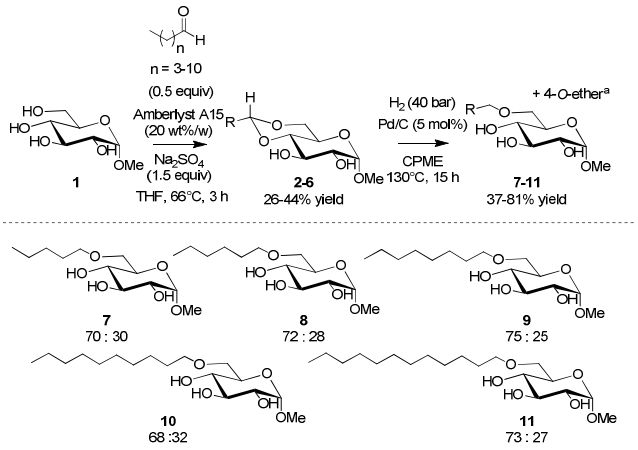
The Dunne's group described the synthesis of methyl 6-*O*-dodecyl-α-D-glucopyranoside from commercially available methyl α-D-glucopyranoside **1** following traditional carbohydrate chemistry (Scheme 1, a).[13a]



Scheme 1: Comparison of synthetic routes to access methyl 6-*O*-dodecyl-α-D-glucopyranoside. TIPS = triisopropylsilyl, DMF = dimethylformamide, PMB = *para*-methoxybenzyl, TBAI = tetrabutylammonium iodide, TBAF = tetrabutylammonium fluoride, CAN = cerium ammonium nitrate.

This five-step sequence involves 13 elemental reactions including TIPS-protection of the primary alcohol, PMB-protection of the secondary alcohols, selective TBAF-deprotection of the primary alcohol followed by the installation of the dodecyl chain using Williamson conditions and final secondary alcohols deprotection with CAN. The desired product was obtained as a single stereoisomer in 21% overall yield and 6 % atom economy.[22] However, this type of synthetic protocol is no longer in line with the green chemistry principles.[23] Consequently, we have developed a two-step acetalisation / hydrogenolysis sequence for the preparation of methyl *O*-alkyl-α-D-glucopyranoside directly from unprotected methyl α-D-glucopyranoside **1** (Scheme 1, b). Following our previously reported procedure,[20] a range of methyl α-D-glucopyranoside 4,6-*O*-acetals **2**-**6** bearing different alkyl chain lengths were synthesized in 26-44% isolated yields (Scheme 2). Subsequent hydrogenolysis of the acetals afforded the corresponding ethers **7**-**11** as a mixture of 6-*O*- and 4-*O*- regioisomers in up to 75 : 25 selectivity and in 37-81% isolated yields (Scheme 2). Methyl 6-*O*-dodecyl-α-D-glucopyranoside **11** was prepared in 10 % overall yield but with an improved 95 %

atom economy.[22] Considering the atom efficiency (1.3% *vs* 11.2%), this strategy is 8.5 times more efficient than Dunne's synthesis.[22] This cheap and environmentally friendly procedure provides a ~~remarkable improvement in carbohydrate chemistry as it allows a~~ convenient and rapid access to alkylated sugars.



Scheme 2. Preparation of methyl α-D-glucopyranoside ethers by acetalisation / hydrogenolysis sequence. [a] The 6-*O* : 4-*O* regioisomeric ratio was determined by GC chromatography after derivatization. CPME = cyclopentyl methyl ether.

Amphiphilic properties of methyl α-D-glucopyranoside acetals and ethers

The surface tension of aqueous solutions of acetals **2**-**6** and ethers **7**-**11** was evaluated by the rod method, based on the Wilhelmy plate method. The amphiphilic properties of acetals **2**-**6** (abbreviated CxAcMeGlu, with x = number of carbons of the alkyl chain, Ac = acetal, MeGlu = methyl α-D-glucopyranoside) were first investigated (Figure 1). All acetals allow a decrease of the surface tension of water to a plateau of about 30 $mN.m^{-1}$. Different tensiometric curve profiles were observed depending on the alkyl chain length (Figure 1). Neither clear break nor plateau was obtained for C5AcMeGlu **2** and C6AcMeGlu **3**, typical of hydrotropes.[24] Indeed, the alkyl chain of these amphiphiles is too short to promote cooperative association into micelles. Nevertheless, when increasing the concentration they accumulate at the water/air interface and form small aggregates within the aqueous solution thus, lowering the superficial tension. Typical surfactant profiles were yet observed for compounds C8AcMeGlu **4** and C10AcMeGlu **5**. The limit of solubility of **4** and **5** in water revealed to be close to the CMC value implying a very small concentration range for micellar solubilisation. Expectedly, the increase of the alkyl chain length led to a decrease of the MHC / CMC values, from 82 mM for C5AcMeGlu **2** to 0.15 mM for C10AcMeGlu **5** (Table 1, entries 1-4). Finally, acetal **6** (Cx = C12) could not be fully analyzed due to its low solubility in water and the formation of

liquid crystals at low concentrations and at room temperature. However, its CMC has been estimated to be > 0.06 mM (Table 1, entry 5).

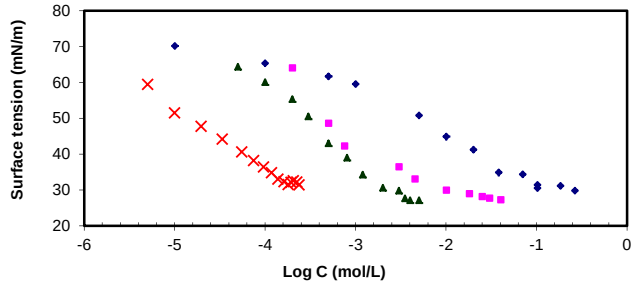


Figure 1. Surface tension *vs* concentration of methyl α-D-glucopyranoside acetals. ◆ C5AcMeGlu **2**, ■ C6AcMeGlu **3**, ▲ C8AcMeGlu **4**, ✕ C10AcMeGlu **5**.

Table 1. Minimal Hydrotropic Concentration (MHC), Critical Micelle Concentration (CMC) and surface tension (γsat) values of methyl a-D-glucopyranoside acetals.

Entry	Methyl α-D-glucopyranoside acetals	MHC or CMC[a] ($mmol.L^{-1}$)	γ_{sat}[a] ($mN.m^{-1}$)
1	C5AcMeGlu **2**	82	31
2	C6AcMeGlu **3**	6.5	31
3	C8AcMeGlu **4**	2.5	28
4	C10AcMeGlu **5**	0.15	32
5	C12AcMeGlu **6**	> 0.06 (solubility limit)	< 33

[a] Determined by tensiometry.

The surface tension of the regioisomeric mixtures of methyl α-D-glucopyranoside ethers **7**-**11** (abbreviated CxEthMeGlu, with x = number of carbons of the alkyl chain, Eth = ether, MeGlu = methyl α-D-glucopyranoside) was next investigated (Figure 2). Similarly, all ethers decrease the surface tension of water to a plateau around 30 $mN.m^{-1}$. Considering that the 6-*O*- : 4-*O*-regioisomeric ratio is similar (around 70 : 30) for all methyl α-D-glucopyranoside ethers, the alkyl chain length is the only parameter influencing the MHC and CMC values. This behavior is commonly observed for other types of surfactants.[25] As for acetals, ethers **7**-**8** bearing a C5 and C6 alkyl chain, exhibit a hydrotropic character with MHC values of 35.0 and 13.4 mM, respectively (Table 2, entries 1-2). With longer alkyl chain, C8EthMeGlu **9** and C10EthMeGlu **10** show characteristic surfactant profiles but with CMC

values poorly defined at low concentrations, *i.e.* 0.43 and 0.28 mM respectively (Table 2, entries 3-4). Gratifyingly, further increase of the alkyl chain length to 12 carbons permits a decrease of the CMC to 0.012 mM (Table 2, entry 5). For a given alkyl chain, the CMC or MHC values of ethers are usually lower than the acetals implying a higher hydrophilicity for the ether family. This trend was previously observed for sorbitan derivatives.[20b]

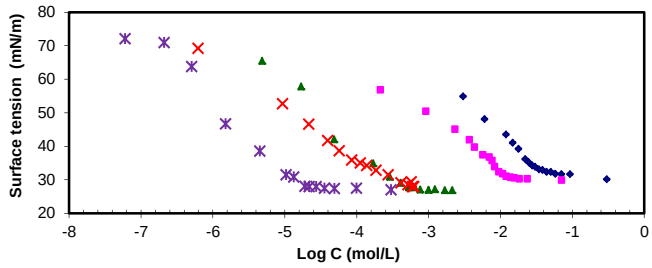


Figure 2. Surface tension *vs* concentration of methyl α-D-glucopyranoside ethers (mixtures of regioisomers). ◆ C5EthMeGlu **7,** ■ C6EthMeGlu **8**, ▲ C8EthMeGlu **9**, ✕ C10EthMeGlu **10,** ✳ C12EthMeGlu **11**.

Table 2. Minimal Hydrotropic Concentration (MHC), Critical Micellar Concentration (CMC) and surface tension (γ_{sat}) values of methyl α-D-glucopyranoside ethers (mixtures of regioisomers).

Entry	Methyl α-D-glucopyranoside ethers	Ratio[a] (%)	MHC or CMC[b] ($mmol.L^{-1}$)	γ_{sat}[b] ($mN.m^{-1}$)
1	C5EthMeGlu **7**	70 : 30	35.0	33
2	C6EthMeGlu **8**	72 : 28	13.4	31
3	C8EthMeGlu **9**	75 : 25	0.434	27
4	C10EthMeGlu **10**	68 : 32	0.277	30
5	C12EthMeGlu **11**	73 : 27	0.012	28

[a] 6-*O* : 4-*O* regioisomeric ratio. [b] Determined by tensiometry.

To probe the influence of regioisomers on amphiphilic properties, physicochemical analyses were also performed on pure 4-*O*- and 6-*O*-C12EthMeGlu **11a** and **11b** regioisomers (Figure 3). Pure regioisomers were separated from the mixture by column chromatography on silica gel. Similar profiles were obtained for both regioisomers, however, 4-*O*-isomer **11a** (brown triangles) showed a short plateau with a solubilisation limit close to its CMC, while a better surfactant profile was obtained for 6-*O*-isomer **11b** (green squares). In addition, the CMC and $\gamma_{sat.}$values of the two pure 4-*O*- and 6-*O*-isomers are relatively close, with 0.046 and 0.030 mM, and 31 and 29 $mN.m^{-1}$ respectively (Table 3, entries 1-2). Consequently, these results prove that the position of the alkyl chain on the

sugar scaffold does not induce major changes on neither the surface tension nor the CMC values. Interestingly, when using a 73 : 27 mixture of 6-*O*- and 4-*O*-isomers **11** (purple crosses), the CMC decreases to 0.012 mM (Table 3, entry 3). This non-ideal behavior is very common when mixing two surfactants. It is attributed to an attractive interaction between two surfactants located at the surface monolayer and within mixed aggregates. This leads to a stabilization of the mixed superficial layer and the co-micelles.[26] We applied the equations of the regular solution theory to this specific isomeric ratio, which gave an interaction parameter $\beta = -4.7$ and a mole fraction of isomer 6-*O* in the mixed micelle $X_1 = 0.61$ (see references 26a and 26b for calculation details). Even if CMC measurements on other isomeric ratios are required to get a more accurate value of interaction parameter, this strong negative β value clearly indicates preferential attractive interactions between the two regioisomers.

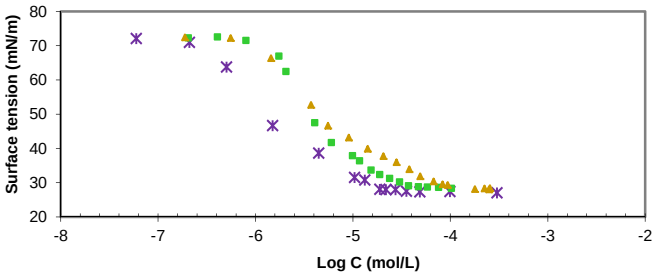


Figure 3. Surface tension *vs* concentration of methyl dodecyl-α-D-glucopyranoside: ▲ 4-*O*-isomer **11a**, ■ 6-*O*-isomer **11b**, and ✱ a 73 : 27 mixture of 6-*O*- and 4-*O*-isomers **11**.

Table 3. Critical Micelle Concentration (CMC) and surface tension (γ_{sat}) values of regioisomers 6-*O* and 4-*O* of C12EthMeGlu **11**.

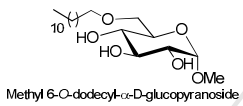
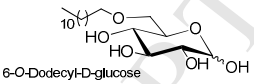
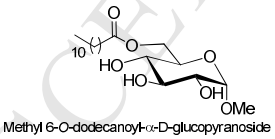
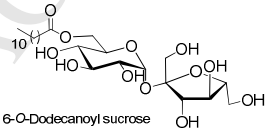
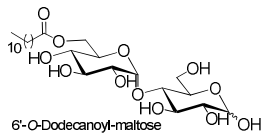
Entry	Methyl α-D-glucopyranoside ethers	Ratio[a]	CMC[b] (mmol.L^{-1})	γ_{sat}[b] (mN.m^{-1})
1	4-*O*-C12EthMeGlu **11a**	0 : 100	0.046	31
2	6-*O*-C12EthMeGlu **11b**	100 : 0	0.030	29
3	(6+4)-*O*-C12EthMeGlu **11**	73 : 27	0.012	30

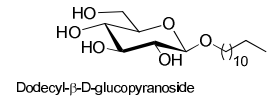
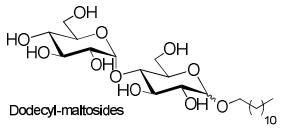
[a] 6-*O* : 4-*O* regioisomeric ratio. [b] Determined by tensiometry.

In order to evaluate the efficiency of these surfactants, a comparison of methyl 6-*O*-dodecyl-α-D-glucopyranoside **11b** with known sugar-based non ionic surfactants was next carried out (Table 4).

Only compounds bearing a C12 alkyl chain were selected in order to establish a structure / properties relationship. First of all, methyl 6-*O*-dodecyl-α-D-glucopyranoside (CMC = 0.030 mM) was found by far more efficient than its glucose analog (CMC = 0.5 mM), showing the importance of the substitution at the anomeric position (Table 4, entries 1-2). Moreover, the replacement of the *ester* function in methyl 6-*O*-dodecanoyl-α-D-glucopyranoside (CMC = 0.052 mM) by an *ether* link does not have a significant impact on the CMC (Table 4, entry 3). However, the introduction of a second carbohydrate unit in 6-*O*-dodecanoyl-sucrose and in 6'-*O*-dodecanoyl-maltose leads to an important increase of the CMC to 0.25 and 0.24 mM, respectively (Table 4, entries 4-5). Higher CMC values were also obtained with the corresponding commercially available dodecyl α-D-glucopyranoside and dodecyl maltoside (Table 4, entries 6-7). This means that, in the case of methyl 6-*O*-dodecyl-α-D-glucopyranoside **11**, about 12 to 17 times less product is required to obtain the same performances than these commercial surfactants. Finally, this study highlights the potential of ether **11** as new bio-sourced non-ionic surfactant with improved robustness in comparison to esters, broadening the scope of applications of such amphiphilic compounds.

Table 4. Comparison of CMC values (mM) of known sugar-based non-ionic surfactants.

Entry	Carbohydrate surfactants	CMC (mmol.L^{-1})	Ref.
1	 Methyl 6-*O*-dodecyl-α-D-glucopyranoside	0.012 (mixture of isomers) 0.03 (6-*O*-isomer)	This work
2	 6-*O*-Dodecyl-D-glucose	0.5	[27]
3	 Methyl 6-*O*-dodecanoyl-α-D-glucopyranoside	0.052	[28]
4	 6-*O*-Dodecanoyl sucrose	0.25	[29]
5	 6'-*O*-Dodecanoyl-maltose	0.24	[29]

6	 Dodecyl-β-D-glucopyranoside	0.19	[30]
7	 Dodecyl-maltosides	0.15 (α-isomer) 0.20 (β-isomer)	[31]

Antimicrobial activities of methyl α-D-glucopyranoside acetals and ethers

The antimicrobial activities of methyl α-D-glucopyranoside acetals and ethers were first evaluated against Gram-negative bacteria such as *E. coli* (ATCC® 8739™) and *Pseudomonas aeruginosa* (ATCC® 27853™) and their efficacy was determined using the Minimum Inhibitory Concentration values (MIC).[32] Unfortunately, no antimicrobial activity was detected against these bacteria at a concentration up to 4.0 mM for neither acetal nor ether derivatives under the conditions used.[33] Similar results were obtained against this type of microorganism in Dunne's studies on carbohydrate fatty esters, with MIC values reaching 10-20 mM.[13a] The bacterial species tested represent two of the most frequently Gram-negative pathogens isolated in humans, our results suggest that these compounds cannot be used to target Gram-negative bacterial infections. In fact, one of the structural feature of Gram-negative bacteria is the presence of a external membrane surrounding each bacterial cell wall. Thus, one possible explanation would be ~~we hypothesized~~ that the derivatives are enable to go through the outer lipopolysaccharide membrane, preventing them to penetrate into the cells.

Consequently, the antimicrobial activities of methyl α-D-glucopyranoside acetals and ethers were next evaluated against Gram-positive bacteria, namely, *L. monocytogenes* (CIP 103575), *S. aureus* (ATCC® 29213™) and *E. faecalis* (ATCC® 29212™). The results are gathered in Table 5.

Table 5. Antimicrobial activities of methyl α-D-glucopyranoside acetals **2-6** and ethers **7-11** against Gram positive bacteria. MICs (Minimum Inhibitory Concentration) in mmol.L^{-1}. MBCs (Minimum Bactericidal Concentration) in mmol.L^{-1} are given in brackets.

Entry	Compounds	Bacteria strains		
		L. mono-cytogenes (CIP 103575)	*S. aureus* (ATCC® 29213™)	*E. faecalis* (ATCC® 29212™)
1	C5AcMeGlu **2**	> 4	> 4	> 4

2	C5EthMeGlu **7**	> 4	> 4	> 4
3	C6AcMeGlu **3**	> 4	> 4	> 4
4	C6EthMeGlu **8**	> 4	> 4	> 4
5	C8AcMeGlu **4**	2	> 4	> 4
6	C8EthMeGlu **9**	2	2	> 4
7	C10AcMeGlu **5**	nd[a]	nd[a]	nd[a]
8	C10EthMeGlu **10**	0.5 (0.5)	2 (2)	0.5 (0.5)
9	C12AcMeGlu **6**	nd[a]	nd[a]	nd[a]
10	C12EthMeGlu **11**	0.03 (0.03)	0.12 (0.12)	0.03 (0.03)
11[b]	C12EthMeGlu **11b**	0.04	0.04	nd
12[b]	C12EstMeGlu	0.08	0.32	nd

[a] Nd: not determined due to the insolubility of the compounds when mixed with the inoculum. [b] MIC values from reference 13.

No significant antimicrobial activity (MIC = 2 or > 4 mM) was detected for acetals and ethers bearing a short C5, C6 or a medium C8 alkyl chain (Table 5, entries 1-6). Furthermore, the MICs of acetals **5** and **6** could not be determined due to their poor solubility in water (Table 5, entries 7 and 9). However, increasing the alkyl chain length of methyl α-D-glucopyranoside ethers from C8 to C12 led to an important decrease of the MIC values (Table 5, entries 6, 8 and 10). The best antimicrobial activities were obtained for C12EthMeGlu **11** (73 : 27 mixture of regioisomers) with a MIC of 0.03 mM for both *L. monocytogenes* and *E. faecalis* and of 0.12 mM for the more virulent *S. aureus strain* (Table 5, entry 10). These results are comparable with those obtained with regioisomerically pure methyl 6-*O*-dodecyl-α-D-glucopyranoside **11b** (Table 5, entry 11). This reveals that the alkyl chain position has a minor impact on the biological activity. Thus, it highlights the interesting properties of these mixtures obtained through step-economical acetalisation/hydrogenolysis sequence. Finally, *ether* derivative C12EthMeGlu **11** was found more active than its corresponding *ester* C12EstMeGlu which is in accordance with the literature[13,18] (Table 5, entry 12).

The bactericidal activities of ethers **10** and **11** were then assessed for each bacteria strain by the measurement of the Minimum Bactericidal Concentration (MBC).[34] Indeed, the MBC corresponds to the lowest concentration of antimicrobial agent required to induce the death of a microorganism,

corresponding to a decrease of the initial bacterial inoculum by at least 99.9%. The MBC values obtained for C10EthMeGlu **10** and C12EthMeGlu **11** were ~~identical to their corresponding MICs~~ close enough to MIC values in order to place them in the same serial dilution interval (Table 5, entries 8 and 10, results in brackets). This observation suggests ~~clearly indicates~~ that these compounds are not only efficient to stop the bacterial growth but also induce the death of the microorganisms.

The antimicrobial activities of methyl α-D-glucopyranoside ethers were further compared to their amphiphilic properties (Table 6).

Table 6. Comparison of the Critical Micelle Concentration (CMC) and Minimum Inhibitory Concentration (MIC) of methyl α-D-glucopyranoside ethers **7**-**11**.

Entry	Methyl α-D-glucopyranoside ethers	CMC ($mmol.L^{-1}$)	MIC ($mmol.L^{-1}$)
1	C5EthMeGlu **7**	35	> 4
2	C6EthMeGlu **8**	13.4	> 4
3	C8EthMeGlu **9**	0.434	2 – 4
4	C10EthMeGlu **10**	0.277	0.5 – 2
5	C12EthMeGlu **11**	0.012	0.03 – 0.12

An increase of the alkyl chain length (from C5 to C12) on methyl α-D-glucopyranoside ethers induce both, a decrease of the CMC from 35 to 0.012 mM and of the MIC from >4 to about 0.03-0.12 mM. Noticeably, the antimicrobial activities correlate quite well with the amphiphilic properties of compounds **7**-**11** with MICs about 2 to 10 times the CMC values (Table 6, entries 1-5). These amphiphilic compounds might interact with the cell bi-layer membrane, exerting a variety of effects,[35] thus leading to the cell lysis. Having identified that 12 carbons was the optimal alkyl chain length to reach efficient antimicrobial activity, the effects of the monosaccharide core and the anomeric carbon configuration were next probed. For this purpose, methyl α-D-mannopyranoside, α-D-galactopyranoside, β-L-rhamnopyranoside and β-D-glucopyranoside were subjected to acetalisation with dodecanal to give the corresponding acetals **12**-**15** with unoptimized 11-49% isolated yields.[36] The hydrogenolysis of these acetals gave three new alkylated sugars **16**-**18** with unoptimized 27-34% isolated yields[36] (Figure 4). Unfortunately, all attempts to reduce acetal **15** to the desired ether failed under our conditions. This could be explained by the difference of adsorption energies of α-

and β-isomers on palladium during the hydrogenolysis step.[37] As a result, only β-C12AcMeGlu **15** was considered for further tests.

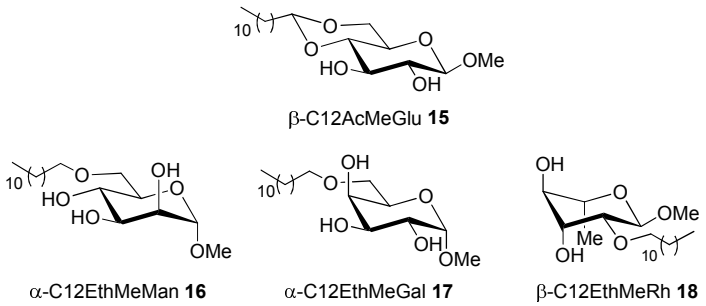


Figure 4. Range of acetal and ether derivatives obtained from acetalisation / hydrogenolysis sequence.

With these molecules in hands, antimicrobial activity studies were next carried out on a wide range of Gram-positive bacteria. The efficacy of the derivatives was first studied against *L. monocytogenes* strains such as the reference (CIP 103575) and three clinical isolated strains (LM1: 015189074801, LM2: 015170199001, LM3: 015181840701) using amoxicillin as control (Table 7). The glucose derivative **11** gave the best activities against all these strains with MICs of 0.02 mM while mannose-based compound **16** was slightly less active (Table 7, entries 1-2). However, galactose derivative **17** was by far less efficient with a MIC of 0.18 mM on all strains (Table 7, entry 3). Interestingly, rhamnose derivative **18** was also active but to a lesser extent (Table 7, entry 4). Finally, acetal **15** was also quite active against these *L. monocytogenes* strains, proving that this class of compounds could also been interesting as antimicrobials, provided their solubility (Table 7, entry 5).

Table 7. Antimicrobial activities of compounds **11, 15-18** against *L. monocytogenes* strains. MICs (Minimum Inhibitory Concentration) in $mmol.L^{-1}$.

Entry	Compounds	*L. monocytogenes* strains			
		CIP 103575	LM1	LM2	LM3
1	C12EthMeGlu **11**	0.02	0.02	0.02	0.02
2	C12EthMeMan **16**	0.09	0.02	0.04	0.04
3	C12EthMeGal **17**	0.18	0.18	0.18	0.18
4	C12EthMeRh **18**	0.09	0.09	0.09	0.09

5	β-C12AcMeGlu **15**	0.04	0.04	0.04	0.18
6	amoxicillin	0.002	0.002	0.004	0.002

The activity of compounds **11**, **15-18** was next studied against *E. faecalis* (ATCC® 29212™ and 015206179901) and *E. faecium* strains (CIP 103510, Van A 0151850763, 015205731401 and 015205261801) using amoxicillin as control (Table 8). A good level of activity was observed for sugar derivatives **11**, **16** and **18** against the six *Enterococcus* strains studied (MIC ≤ 0.09 mM), particularly for glucose derivative **11** with a MIC of 0.02 mM for most strains (Table 8, entries 1, 2 and 4). More importantly, this compound was also active against a vancomycin-resistant strain at 0.02 mM (Van A). Once again, galactose derivative **17** was the least active indicating that the nature of the carbohydrate could affect the antimicrobial efficacy. However, great differences could be observed between strains as the MIC varies from 0.02 to > 0.71 mM (Table 8, entry 3). Similar phenomenon is observed with acetal **15** with MICs ranging from 0.02 to 0.18 mM (Table 8, entry 5)

Table 8. Antimicrobial activities of compounds **11, 15-18** against *E. faecalis* and *E. faecium* strains. MICs (Minimum Inhibitory Concentration) in mmol.L^{-1}.

Entry	Compounds	*E. faecalis* strains		*E. faecium* strains			
		ATCC 29212	015206179901	CIP	Van A	015205731401	015205261801
1	C12EthMeGlu **11**	0.02	0.04	0.02	0.02	0.02	0.02
2	C12EthMeMan **16**	0.04	0.09	0.09	0.04	0.04	0.04
3	C12EthMeGal **17**	0.18	0.18	> 0.71	0.35	0.09	0.02
4	C12EthMeRh **18**	0.05	0.05	0.05	0.05	0.02	0.05
5	β-C12AcMeGlu **15**	0.18	0.09	0.09	0.09	0.04	0.02
6	amoxicillin	0.002	0.002	0.06	0.5	0.25	0.25

The activity of compounds **11**, **15-18** was next studied against a wide range of *S. aureus* strains using oxacillin as control. Two reference strains were considered as well as six methicillin-resistant and three daptomycin-resistant strains (Table 9). Indeed, the development of resistance during therapy is becoming a major health issue highlighted in numerous reports.[38] Similar activities were observed for glucose **11**, mannose **16** and rhamnose **18** derivatives with MIC values from 0.04 to 0.09 mM for

reference strains (Table 9, entries 1, 2 and 4). However, slighly lower activities (0.18-0.37 mM) were observed with acetal **15** (Table 9, entry 5). In accordance with our previous results on *Listeria* and *Enterococcus* strains, galactose derivative **17** gave no significant activity with MIC > 0.71 mM for all strains studied (Table 9, entry 4). Gratifyingly, good antimicrobial activities (0.04-0.09 mM) were obtained with glucose derivative **11** against methicillin- and daptomycin-resistant strains (Table 9, entry 1). Interestingly, a similar level of activity was displayed against sensitive and resistant strains for all compounds.

These results clearly indicate that carbohydrate fatty ethers are promising candidates for the treatment of resistant bacteria. They could find various applications in the food industry, in the medical field and could also be incorporated in various formulations.

Table 9. Antimicrobial activities of compounds **11**, **15-18** against *S. aureus* strains (references), methicillin- and daptomycin-resistant *S. aureus* strains. MICs in mmol.L^{-1}.

Entry	Compounds	*S. aureus* references		Methicillin resistant *S. aureus*						Daptomycin resistant *S. aureus*		
		ATCC 25923	ATCC 29213	LAC USA 300	MU3	HT 2004-0012	LY 199-0053	HT 2002-0417	HT 2006-1004	ST 2015-0188	ST 2014-1288	ST 2015-0989
1	C12EthMeGlu **11**	0.04	0.09	0.09	0.09	0.09	0.04	0.04	0.09	0.09	0.09	0.09
2	C12EthMeMan **16**	0.09	0.09	0.09	0.18	0.09	0.09	0.09	0.18	0.18	0.09	0.18
3	C12EthMeGal **17**	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71	> 0.71
4	C12EthMeRh **18**	0.09	0.05	0.09	0.18	0.05	0.09	0.09	0.09	0.18	0.09	0.18
5	β-C12AcMeGlu **15**	0.18	0.18	0.18	0.18	0.18	0.18	0.37	0.18	0.18	0.18	0.18
6	oxacillin	0.05	0.001	0.16	0.64	0.08	0.16	0.16	0.32	0.16	0.16	0.32

Mechanistic considerations

We hypothesize that the antimicrobial activity arises from the ability of carbohydrate alkyl ethers to form micelles and thus to solubilize the lipids constituting the cell membrane. However, important MIC differences were observed between C12EthMeGlu **11** and C12EthMeGal **17**, indicating that the carbohydrate moiety can also play a crucial role on antimicrobial activity. Consequently, a recognition phenomenon might also be operating between the carbohydrate core and the cell walls of bacteria. Alternatively, modification of the OH group configuration (from equatorial in glucose to

axial in galactose) could induce a drastic change of the CMC also impacting the activity. In order to verify this hypothesis, the CMC value of C12EthMeGal **17** was measured and compared to C12EthMeGlu **11** (Figure 5).

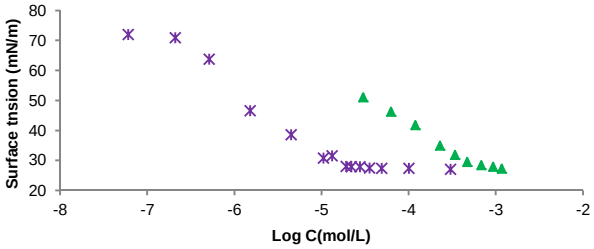


Figure 5. Surface tension of methyl α-D-glucopyranoside ether *vs* methyl α-D-galactopyranoside ether ✱ C12EthMeGlu **11**, ▲ C12EthMeGal **17**.

Table 10. Antimicrobial activities *vs* CMC of compounds **11** and **17.**

Entry	Compounds	MIC[a] (mmol.L^{-1})	CMC[b] (mmol.L^{-1})
1	C12EthMeGlu **11**	0.02-0.09	0.012
2	C12EthMeGal **17**	0.02-0.71	0.47

[a] MIC (Minimum Inhibitory Concentration) range including results against against *Staphylococcus, Enterrococcus* and *Listeria* strains. [b] Determined by tensiometry.

The CMC of galactose derivative **17** is 40 times higher than glucose **11** (Table 10). Galactoside **17** is therefore more hydrophilic than **11** which is in accordance with previous work on HPLC separation of methyl glycosides.[39] This phenomenon is directly linked to the inversion of the 4-OH group configuration (from equatorial for **11** to axial in **17**). Based on Simon's DFT calculations[40] and Hüneberger's conformational analyses,[41] we postulate that the lower hydrophilicity of **11** is due to the high occurrence of hydrogen-bond networks (Figure 6, left). In the contrary, these interactions are not favored in the case of galactoside **17** due to the axial 4-OH group, therefore increasing the sugar polarity (Figure 6, right).

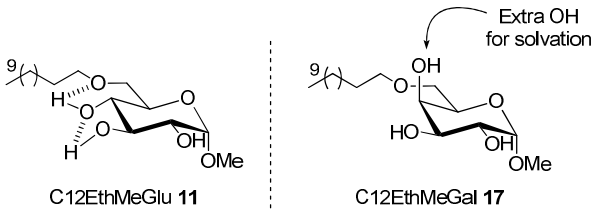


Figure 6. Model proposed to explain the polarity difference between C12EthMeGlu **11** and C12EthMeGal **17** (only one conformer showed).

As shown above, minor structural modifications could have significant impacts on the antimicrobial activity. Consequently, we also envisioned to investigate the role of the methyl group in compound **11** by preparing the corresponding demethylated compound. Unfortunately, all attempts to remove the methyl group from compound **11** following standard conditions (TMS-OTf / Ac_2O in CH_2Cl_2)[42] failed and gave a complex mixture of products. However, based on our previous analysis and the CMC values (Table 4, entries 1-2), we can assume that the antimicrobial activity of 6-*O*-dodecyl-D-glucose should be considerably lower than the corresponding methyl dodecylglucopyranosides. Further works will be necessary to confirm this hypothesis.

Finally, this study demonstrates that the CMC is the crucial parameter influencing the MIC, however the sugar recognition can still not be ruled out. Further structural/activity studies of sugar-based surfactants and computational analyses are currently on going.

Conclusions

In conclusion, a series of amphiphilic methyl glycopyranoside alkyl ethers were prepared from the corresponding unprotected methyl glycopyranosides following a two-step acetalization/hydrogenolysis sequence. This route provides a straightforward access to carbohydrate alkyl ethers with high-atom economy and low waste production in comparison to traditional routes involving protection/deprotection steps. The amphiphilic properties of these ethers (but also the acetal intermediates) were measured and a C12 alkyl chain has the optimum length to decrease the surface tension of water (CMC = 0.012 mM, γsat. = 30 mN.m^{-1}). The antimicrobial activities were also evaluated on Gram-negative and Gram-positive bacteria. No activity was found against Gram-negative bacteria (MIC > 4 mM). On the contrary, interesting antimicrobial activities (MIC ≥ 0.02 mM) were obtained on Gram-positive bacteria such as *L. monocytogenes*, *E. faecalis, E. faecium* and *S. aureus* for methyl glycopyranosides bearing a C12 alkyl chain. More importantly, some of these

compounds are also active against antibiotic-resistant bacteria which represent a major public health problem. These compounds have a great potential to be used as additives in pharmaceutical and/or cosmetic formulations and can find applications in food industry, in hospital and in other non-medical fields.

Experimental Section

General procedure A: acetalisation of methyl pyranosides

In a dry two-necked round bottom flask, the corresponding methyl glycopyranoside (2.0 equiv) and sodium sulfate (1.5 equiv) were added in dry THF under argon. Dodecanal (1.0 equiv) was added portionwise over a 1-min period, followed by Amberlyst 15 (20wt%/aldehyde). The mixture was stirred at 66°C for the time stated. After cooling down to room temperature, the reaction mixture was filtered, washed with CH_2Cl_2 (2×25 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (Cyclohexane : EtOAc) to give the corresponding methyl pyranoside acetals **6, 12-15**. See supporting information for characterization details.

General procedure B: reductive cleavage of methyl pyranoside acetals

In a 100-mL stainless steel autoclave, the corresponding methyl dodecylidene pyranoside (1.0 equiv) was dissolved in dry CPME (cyclopentyl methyl ether) and 5%-Pd/C (5 mol% in Pd) was added. The reactor was tightly closed, purged three times with hydrogen and pressurized at 40 Bar. The solution was then heated at 130°C for 16 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was 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 (Cyclohexane : EtOAc) to give the corresponding methyl pyranoside ethers **11, 16-18**. See supporting information for characterization details.

Physico-chemical studies

The surface tensions were measured at (25.0 ± 0.1)°C with a K100MK2 Krüss tensiometer using a platinum rod as the probe, allowing to carry out experiments in small vessels. A total of 2.5 mL of water was first introduced in the vat. The solution was gradually concentrated with a stock surfactant solution (a manual dilution keeping volume constant was performed) and for each concentration the surface tension was measured until a stable value was obtained (standard deviation of the 5 final values of 0.2 $mN.m^{-1}$).

Antimicrobial assays

The minimal inhibitory concentration experiments were realized on Gram-positive strain in accordance with the Clinical-Laboratory-Standards-Institute (6th ed. Approved standard M100-S17. CLSI, Wayne, PA, 2007) recommendations.

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[32] Minimum Inhibitory Concentration (MIC) values are defined as the lowest concentration of compound that shows no cell growth for all the replicates compared to the negative control after 18h.

[33] See supporting information for experimental details and the MIC values obtained against gram-negative strains.

[34] The Minimum Bactericidal Concentration (MBC) was determined by diluting the well below the MIC. The enumeration was then carried out after plating for 18 h. The MBC corresponds to the lowest concentration of antimicrobial agent required to decrease the initial bacterial inoculum by at least 99.9%.

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Highlights

- Amphiphilic carbohydrate ethers were prepared through step-economical acetalization/hydrogenolysis sequence
- Best surfactant properties for sugar derivatives bearing a linear dodecyl chain (CMC = 0.012 mM, $\gamma_{sat.}$ = 30 mN.m^{-1})
- The compounds exhibit antimicrobial activity against Gram-positive bacteria (0.03 < MIC < 0.12 mM)
- Antimicrobial activities against multi-resistant strains such as *vancomycin*-, *methicillin*- and *daptomycin*-resistant strains