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# Eco-conception of highly salt-tolerant alkyl ether carboxylate hydrotropes with a glyceryl spacer

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**Abstract:** New alkyl ether carboxylates including a glyceryl spacer instead of ethylene glycol units have been synthesized using environmentally friendly methodology. A cascade synthesis of acetalisation and hydrogenolysis was developed to obtain products containing an alkyl chain linked to glycerol unit bearing a carboxylate polar head. These products were methylated using trimethyl phosphate to observe the influence of an alcohol free or methoxylated on physicochemical properties. Finally, saponification gave the carboxylate anionic group of the new hydrotropes. The study of the amphiphilicity, the tolerance to sodium and calcium ions and the solubilizing power of these bio-based ionic/nonionic hydrotropes has shown that they exhibit significantly improved application properties compared to similar petro-based hydrotropes.

## Introduction

Surfactants are defined by specific physicochemical criteria, namely a substance which, at low concentration (typically  $\ll 10^{-2}$  mol/L), significantly lowers the surface tension of water to a minimum value where they form micelles. On the other hand, hydrotropes are usually defined by their main application property, namely a substance which, at high concentration (typically  $\gg 0.1$  mol/L), facilitates the solubilization of hydrophobic solutes in water without forming micelles.<sup>[1,2]</sup> Because of this broad and relatively "vague" definition formulators, who are the main users of hydrotropes, include under this term a wide variety of nonionic (urea, isopropanol, glycol ether) or ionic (sodium xylenesulfonate, sodium benzoate) compounds. More recently, Eastoe et al. provided a more precise and restrictive definition namely "hydrotropes are small amphiphilic molecules with hydrophilic character, having the ability to increase solubility of organic compounds in water".<sup>[3]</sup> According to this definition, sodium n-alkyl sulphates  $n\text{-C}_n\text{H}_{2n+1}\text{SO}_4\text{Na}$  will be considered either as surfactants when the hydrophobic chain is long enough ( $n \geq 8$ ) to form micelles or as hydrotropes when the alkyl chains are shorter. Most common hydrotropes are petro-based chemicals and some of the widespread ethylene glycol ethers are classified as reprotoxic. They have been replaced by harmless propylene glycol ethers but these hydrotropes are less amphiphilic and

therefore less effective than ethylene glycol ethers. Under the double pressure of the public and new regulations, more demanding in terms of biodegradability and safety for living beings and the environment, academic and industrial communities have mobilized to find bio-based alternatives to glycol ethers. This led to the emergence, of a wide variety of non-ionic hydrotropes made up of short hydrocarbon chains (C3 - C7) covalently bound to various bio-based hydrophilic synthon such as glycerol,<sup>[4-6]</sup> isosorbide,<sup>[7,8]</sup> pentose or glucose.<sup>[9,10]</sup> In addition, for a small number of them, the synthetic routes respect the requirement of the sustainable chemistry.<sup>[11,12]</sup>

Many end-use formulations containing anionic amphiphiles are faced with the effect of electrolytes for different reasons. Firstly, electrolytes can be voluntarily introduced into formulas to improve their application properties.<sup>[13,14]</sup> Likewise, in drilling fluids, generally seawater-based, large amount of barite is introduced to increase the density and the viscosity of the liquid mixture.<sup>[15]</sup> Second, formulations such as laundry detergents are inevitably confronted with the divalent  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  cations present in many tap waters. However, it is well established that the detergency performance of typical anionic surfactants decreases due to the precipitation of their calcium salts.<sup>[16]</sup> Therefore, laundry formulas contain up to 25 wt.% of anti-limescale builders such as zeolites, EDTA or citric acid. Nonionic surfactants such as polyethoxylated alcohols, also present in detergent formulations, tolerate mono- and divalent electrolytes much better, but their detergency properties are insufficient to be used alone.

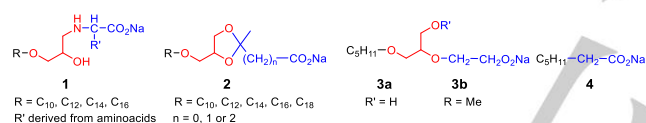
An elegant solution to limit, or even avoid, the addition of sequestering agents is to resort to anionic/nonionic "hybrid" surfactants which include a nonionic spacer between the hydrophobic tail and the anionic hydrophilic head. Currently, hybrid surfactants available on the market are ethoxylated or propoxylated sodium sulfate or carboxylate derivatives. Thus, sodium lauryl ethersulfate ( $\text{C}_{12}\text{EO}_j\text{SO}_4\text{Na}$ ) with a low level of ethoxylation ( $j \leq 3$ ) is ubiquitous in shampoos as a foaming agent, while surfactants with longer chains ( $\text{C}_{16-18}\text{PO}_j\text{SO}_4\text{Na}$ ) and poly(propoxylated) spacers ( $j = 2$  to 7) are widely used for EOR (enhanced oil recovery) applications.<sup>[17]</sup> As regards to the hybrid surfactants bearing a carboxylate group, they also include a polyethoxylated spacer between the hydrophobic tail and the sodium (or potassium) methylenecarboxylate unit. Despite the

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presence of the anionic carboxylate head, they support electrolytes very well and are used in personal care products due to their softness to the skin.<sup>[18]</sup>

Thus, one of the main challenges to be met to obtain more sustainable surfactants and hydrotropes is to replace the petro-based—ethylene oxide units with bio-Based, abundant and inexpensive hydrophilic groups such as glycerol, sorbitol or glucose. This route has been widely exploited to prepare bio-based nonionic surfactants, the most emblematic of which are alkylpolyglycosides (APGs), polyglycerol esters of fatty acids and N-alkanoyl-N-methylglucamides.<sup>[19]</sup> In the same vein, some alkyl ethers of glycerol<sup>[20,21]</sup> or isosorbide<sup>[7,8]</sup> with short alkyl chain (C3 to C6) have been developed as alternatives to glycol ethers hydrotropes. Similarly, amyl xyloside and heptylglucoside have recently been put on the market as bio-based and biodegradable hydrotropes.<sup>[9,10]</sup>

Surprisingly, little work has been published in the literature on hybrid amphiphiles comprising a bio-based spacer linked to an anionic group such as the sodium (or potassium) sulfate, sulfonate, phosphate or carboxylate. This later function is by far the most attractive anionic group for eco-designing surfactants especially those intended for general public formulations. Indeed, soap-like surfactants are well accepted by consumers who are familiar with soap, the carboxylic group is chemically stable even at high temperature and pH and it is already present in the chemical structure of many bio-based building blocks. Three families of hybrid surfactants **1**, **2** and **3** including a glyceryl spacer and a terminal carboxylic function have already been described (scheme 1).<sup>[22-25]</sup>



**Scheme 1.** Hybrid amphiphiles with a glyceryl spacer and a terminal carboxylic function

Surfactants **1**, prepared from epichlorohydrin, fatty alcohol and various amino acids, have improved surface properties compared to ordinary soaps but their tolerance to electrolytes has not been examined. For compounds **2**, the acetal function ensures good biodegradability but their stability to hydrolysis is weak compared to ether bond.<sup>[23,26]</sup> Pentyl glyceryl ether carboxylates **3a** and **3b** are two amphiphiles recently described in a publication focusing on the design of extremely salt-tolerant hydrotropes.<sup>[25]</sup> Compound **3a** is prepared from epichlorohydrin, pentanol, sodium methoxide and sodium chloroacetate while **3b** follows the same synthetic route but requires a further protection/deprotection step of the terminal OH group with a benzyl group. Their solubility with respect to highly concentrated aqueous solutions of NaCl and CaCl<sub>2</sub> were compared to that of sodium heptanoate **4** which is the soap the most similar to **3** except that the glyceryl spacer is absent. At room temperature, all compounds **3** and **4** remain soluble in concentrated brine (20 wt.% NaCl) but differentiate clearly in the presence of CaCl<sub>2</sub>. Thus, soap **4** precipitates at a low concentration of calcium ion (< 0.05 wt.% CaCl<sub>2</sub>), while **3a** requires 10 times more calcium ion to precipitate ( $\approx 0.4 \text{ wt.}\% = 3.6 \times 10^{-2} \text{ mol/L}$ ). The most surprising result is that the hydrotrope **3b** although less hydrophilic than **3a** due to the methyl group on the glyceryl unit, remains in solution even in the presence of 20 wt.% CaCl<sub>2</sub>. This unexpected result was rationalized by molecular

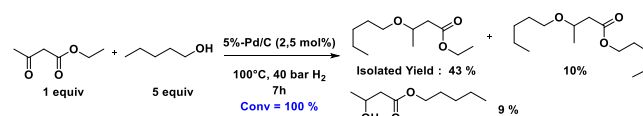
dynamics which reveals that the methyl bound to the pendant glyceryl OH group impedes the bridging interaction with calcium ions. This work demonstrates that the potentially bio-based methylglyceryl spacer can advantageously replace the ethylene oxide units within the conventional alkyl ether carboxylates. Indeed, the authors showed that a single methylglyceryl reduces the CMC value as much as four ethylene oxide units, while retaining excellent salt tolerance to calcium ion.

The excellent tolerance of hydrotrope **3b** towards calcium ions makes it very attractive as an additive to modulate the effective packing parameter of SOW systems. The objective of the present work is to prepare by sustainable methodologies and from bio-based starting materials new hydrotropes related to **3b** and to evaluate their main application properties. The structural modifications of the glyceryl spacer and the moiety bearing the CO<sub>2</sub>Na function of **3b** will be carried out in order to improve our understanding of the molecular criteria influencing the tolerance of hydrotropes to high concentrations of Ca<sup>2+</sup> cations. Finally, we will show, on the example of the solubilization of isopropyl myristate, how the salinity can be a key formulation parameter for adjusting the effective hydrophilic hydrophobic ratio of these new anionic hydrotropes so as to increase their water-solubilizing power.

## Results and Discussion

### Reductive alkylation of keto-esters

Keto-esters such as methyl pyruvate, acetoacetate or levulinic acid were identified as interesting bio-based building blocks to introduce a carboxylic acid. Such platforms have been recently used by Tulchinsky et al. for the etherification of levulinic acid and aliphatic alcohols under reductive atmosphere in the presence of Pd/C at 200°C.<sup>[27]</sup> In these conditions, the etherification is not selective, and esterification takes place. Yields between 54% and 77% were obtained depending on the alcohol. Lemaire et al. have developed the reductive alkylation of glycerol and a carbonyl (aldehyde, acid, ester or ketone) under hydrogen pressure, using recyclable heterogeneous catalysts, with good yields. As a starting point of this study, the conditions developed in our group were tested with ethyl acetoacetate and pentanol (Scheme 2).<sup>[28]</sup>



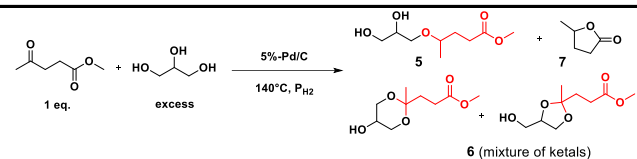
**Scheme 2.** Etherification of pentanol through the reductive alkylation of ethyl acetoacetate

The reaction was carried out at 100°C under 40 bar of hydrogen for 7h. Complete conversion was reached and the etherified product was characterized (43% yield). By-products were also identified as 10% of transesterification and 9% of the reduction of the ketone. Aliphatic alcohol was substituted by glycerol and ethyl acetoacetate by methyl levulinate, both being bio-based. Acid co-catalyst was not used to avoid competitive transesterification and formation of polymers. Different conditions were tried and summarized in table 1. After 7h at 140°C under 10 bar of hydrogen, using an excess of 40 equivalents of glycerol to avoid the di-alkylation, 93% conversion of methyl levulinate was reached (Table 1, entry 1). Acetals **6** were mainly identified (41%),

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and only 17% of the ether **5** were isolated. The hydrogen pressure and the reaction time were increased to improve the reduction of acetals to ethers.

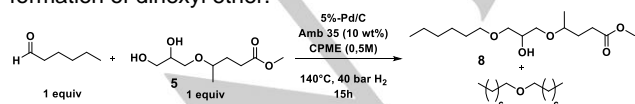
**Table 1.** Reductive alkylation of levulinic methyl ester with glycerol.



Entry	t(h)	P <sub>H2</sub> (bar)	Gly. (equiv)	Conv (%) <sup>[a]</sup>	<b>5</b> <sup>[b]</sup>	<b>6</b> <sup>[b]</sup>	<b>7</b> <sup>[b]</sup>
1	7	10	40	93	17	41	-
2	15	40	20	97	46 (65)	18 (27)	4
3	15	40	10	98	47 (69)	5 (9)	3
4 <sup>[c]</sup>	8	50	20	98	73 (84)	3 (4)	8 (9)

Reactions were performed in a 300 mL stainless steel autoclave with mechanical stirrer, 1.09 mol of glycerol (40 equiv), 0.027 mol of methyl levulinate, 1 mol% of 5%-Pd/C, 140°C; [a] conversion of methyl levulinate; [b] Isolated yield after purification by silica gel chromatography, GC ratio gave in brackets; [c] 5 mol% of 5%-Pd/C, 120°C.

In the same way, the excess of glycerol was decrease to 20 equiv to promote this reduction by concentrating the medium (Table 1, entry 2). Hydrogenolysis of the acetals was more effective as 46% isolated yield was reached (65% of compound **5** in GC ratio), with 18% yield of acetals. In these conditions, a by-product appears,  $\gamma$ -valerolactone **7** (4%), arising from reduction of the ketone in alcohol, and lactonisation. Divided by two, the excess of glycerol (10 equiv) leads to a lower quantity of acetals after 15h (5%), for the same yield of ether **5** (47%) and formation of by-products, most probably the diether (Table 1, entry 3). We can notice that only traces of secondary position ether were obtained (< 2%). To improve this result, reaction time and temperature were decreased to 8h and 120°C respectively. To reduce the acetals, pressure and quantity of Pd/C were increased to 50 bar and 5mol% respectively (Table 1, entry 4). Almost complete conversion was reached (98%) with a good isolated yield toward ether **5** (73%). The quantity of acetal decreased to 3%, but  $\gamma$ -valerolactone **7** increased slightly (8%). These conditions allow to limit the transesterification as no weight loss was observed. Addition of the hydrophobic part was then accomplished by reductive alkylation of ether **5** and hexanal (Scheme 3). Due to the presence of the ester moiety, an experiment without acid co-catalyst was done, leading to a weak conversion and the formation of dihexyl ether.

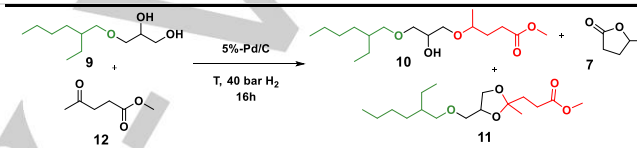


**Scheme 3.** Reductive alkylation of ether **5** and hexanal

With the addition of an acid co-catalyst (Amb 35), complete conversion of **5** was reached, but only 25% isolated yield was obtained for the product **8**. In view of the poor effectiveness of the reductive alkylation of **5** with aldehyde, reductive alkylation of glycerol mono-ether, such as 3-(2-ethylhexyloxy)-1,2-propanediol, and methyl levulinate were studied (Table 2). 3-(2ethylhexyloxy)

propanediol is obtained either by reductive alkylation of glycerol using carboxylic acid or aldehyde with good yield and selectivity.<sup>12</sup> An excess of glycerol mono-ether was used (5 equiv), with 1 mol% of 5%-Pd/C at 140°C under 40 bar of hydrogen (Table 2, entry 1). In these conditions, only 50% conversion was reached and 3% of the ether **10** was obtained, the main product being the acetal **11** (37%) and  $\gamma$ -valerolactone **7** (10%). The reactivity glycerol mono-ether is weaker compared to glycerol. This observation agrees with previous experimental data, indeed reductive alkylation between aldehyde and glycerol gave better results than with 1,2-butandiol demonstrating the important role of the free hydroxyl of the glycerol in such transformation. Reversing the ratio with a slight excess of methyl levulinate (1,2 equiv), the conversion was similar (52%) but hydrogenolysis of the acetal was faster and ether **10** was obtained in 25% yield (Table 2, entry 2). Higher quantity of  $\gamma$ -valerolactone **7** was obtained 18%.

**Table 2.** Reductive alkylation of methyl levulinate **12** and 3-(2-ethylhexyloxy)-1,2-propanediol.



Entry	<b>12</b> : <b>9</b> (equiv)	T (°C)	Conv (%) <sup>[a]</sup>	<b>10</b> <sup>[b]</sup>	<b>11</b> <sup>[b]</sup>	<b>7</b> <sup>[b]</sup>
1 <sup>[c]</sup>	1:5	140	50	3	37	10
2	1.2:1	140	52	25(18)	3(2)	18(13)
3	3:1	140	57	28	11	39
4 <sup>[d]</sup>	1.2:1	140	46	18	-	24
5 <sup>[e]</sup>	1.2:1	170	47	24	2	21

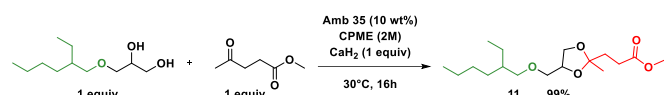
Reactions were performed in a 30 mL stainless steel autoclave with magnetically stirring, with 1 mol% of 5%-Pd/C, under 40 bar H<sub>2</sub> during 16h; [a] conversion of 3-(2-ethylhexyloxy)-1,2-propanediol determined by GC; [b] (%GC ratio, isolated yield gave in brackets; [c] conversion of methyl levulinate; [d] with 5 mol% 5%-Pd/C [e] CPME was added as solvent.

Therefore, the excess of methyl levulinate was increased to 3 equivalents (Table 2, entry 3) without change of conversion. Otherwise, higher quantity of acetal **11** and  $\gamma$ -valerolactone **7** was obtained (11% and 39% respectively). With 5 mol% of Pd/C (Table 2, entry 4) the yield in ether **10** (18%) was lower and the quantity of **7** was higher (24%). No trace of acetal **11** was detected. The increasing of the temperature to 170°C had not influence on the results (Table 2, entry 5).

#### Acetalisation/Hydrogenolysis sequence with methyl levulinate

As the reductive alkylation with mono-substituted glycerol led to a maximum yield of 25%, another strategy was proposed. Since a maximum of 50% conversion was observed, even when the intermediate acetal **11** was entirely reduced to ether **10**, the limiting step is the formation of acetal. To improve this step, a two steps synthesis of acetalisation and then hydrogenolysis was developed. The first step of acetalisation was accomplished using CaH<sub>2</sub> as desiccant. To avoid a purification step, CPME was chose as solvent and a heterogeneous acid resin as catalyst.

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**Scheme 4.** Acetalisation of methyl levulinate and 3-(2-ethylhexyloxy)-1,2-propanediol

A concentration of 2M in CPME with a resin acid catalyst (Amberlyst 35) and 1 equivalent of  $\text{CaH}_2$  were used at 30°C during 16h (Scheme 4). Complete conversion and selectivity were reached for the formation of acetal **11** in these conditions. At this end of the reaction the crude was filtrated.

**Table 3.** Hydrogenolysis of acetal **11**.

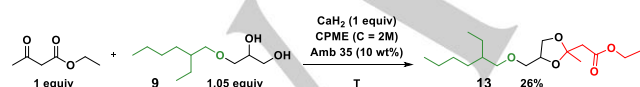
Entry	Pd/C (mol%)	Conv (%)	<b>10</b>	<b>12+7</b>	<b>9</b>
1	1	56	28	8	18
2	5	100	68 (55)	9 (7)	23 (20)

Reactions were performed in a 300 mL stainless steel autoclave with mechanical stirrer, with 30.72 mmol of **11**, 30.72 mL of CPME (1M), at 140°C under 40 bar of  $\text{H}_2$ , during 16h; GC ratio, isolated yield gave in brackets.

CPME (15.4mL) was added to wash the heterogeneous catalyst and to reach a 1M concentration, and the filtrate was directly introduced in the reactor for hydrogenolysis (table 3). Using 1mol% of 5%-Pd/C at 140°C under 40 bar of hydrogen, 56% conversion was obtained after 16h (Table 3, entry 1). Ether **10** was obtained in 28%, and hydrolyzed byproducts were observed with 18% of **9** and 8% of methyl levulinate and  $\gamma$ -valerolactone **7**. To improve conditions of hydrogenolysis, 5 mol% of Pd/C was used (Table 3, entry 2) leading to complete conversion. 55% isolated yield of ether **10** was noticed, but hydrolyzed products were still obtained (23%). This cascade reaction leads to 55% overall yield in ether **10**, compare to 25% in one step. In view of these results other ketoesters were tested in these conditions.

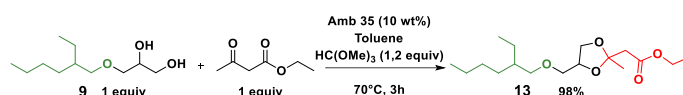
#### Acetalisation/Hydrogenolysis sequence with ethyl acetoacetate

Ethyl acetoacetate was then used to adjust the distance (number of carbons) of the ionic moiety from the glycerol moiety to evaluate the impact of such structural modification. Therefore, the best conditions of acetalisation applied for the methyl levulinate were tested (Scheme 5).



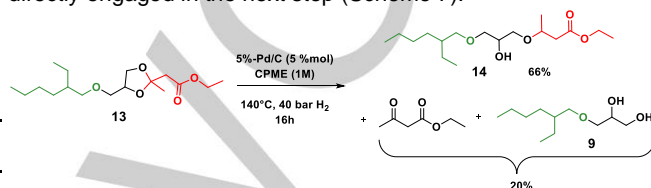
**Scheme 5.** Acetalisation with  $\text{CaH}_2$  of ethyl acetoacetate and 3-(2-ethylhexyloxy)-1,2-propanediol

At 30°C, only 26% conversion was reached with 98% selectivity for the acetal **13**. Increasing the temperature to 50°C and then 100°C led to a decrease of selectivity toward the acetal. Conditions were modified and trimethyl orthoformate was added (Scheme 6).



**Scheme 6.** Acetalisation with trimethyl orthoformate of ethyl acetoacetate and 3-(2-ethylhexyloxy)-1,2-propanediol

The reaction was carried out at 70°C in toluene to shift the equilibrium by evaporation of the azeotrope between the solvent and the methanol produced by the trimethyl orthoformate and the water. Usually in these conditions,  $p\text{-TsOH}^{29}$  or  $\text{BF}_3 \cdot \text{Et}_2\text{O}^{30}$  are used as acid catalyst, but heterogeneous catalyst is more interesting for reaction treatment. With Amberlyst 35 (10 wt.%) after 3h, quantitative yield was obtained with high selectivity toward acetal **13**. After filtration and evaporation, the crude was directly engaged in the next step (Scheme 7).



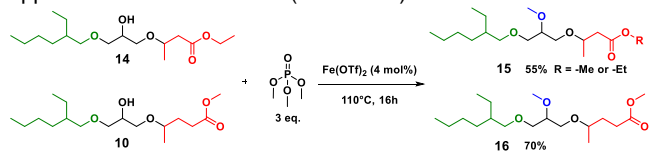
**Scheme 7.** Hydrogenolysis of acetal **13**

After 16h, 66% of ether **14** was obtained (50% isolated yield), with 20% of ethyl acetoacetate and **9**. Finally, an overall yield of 50% was obtained for this cascade reaction.

With the keto-ester methyl pyruvate, the acetylation/hydrogenolysis sequence turned out to be complicated by several side reaction including lactonization of the final product and makes our strategy poorly effective (see Supporting information).

#### Methylation of hydroxyl function

As we had previously discovered a considerable increase in salt-tolerance by methylating the glyceryl spacer of hydrotrope **3a**,<sup>[25]</sup> a methylation step was realized for the ethers **10** and **13**. Recently, Lemaire *et al.* have described a safe and eco-friendly methylation of alcohol using trimethyl phosphate. This methodology was applied to ethers **10** and **14** (Scheme 8).

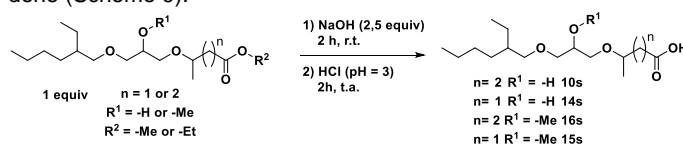


**Scheme 8.** Methylation of ether **10** and **14**

Using 3 equivalents of trimethyl phosphate, 4 mol% of iron (II) trifluoromethanesulfonate at 110°C during 16h, methylated products were obtained in 70% isolated yields for **15**, and 55% for **16**.

#### Saponification

To get the carboxylic moieties, saponification of ester groups was done (Scheme 9).



**Scheme 9.** Saponification of ethers **10**, **14**, **15** and **16**

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Quantitative yields were obtained for each products using 2.5 equivalents of NaOH at room temperature during 2h followed by addition of HCl to pH=3.

#### Physico-chemical analysis and application properties of hydrotropes

The hydrophilic/lipophilic ratio, the salt-tolerance and the solubilizing power of sodium 2-ethylhexyl glyceryl ether levulinates and acetoacetates (compounds **10s**, **14s**, **15s** and **16s**) were determined and compared with those of sodium 2-ethylhexyl and n-octyl glyceryl ether carboxylates **17** and **18** (Table 4). These latter compounds are obtained according to a known procedure<sup>[25]</sup> by condensation of sodium methoxide and sodium chloroacetate on 2-ethylhexyl and n-octyl glycidyl ether. The hydrophilic lipophilic ratio was assessed using the PIT-slope method.<sup>[31,32]</sup> This method is based on the perturbation of a well-defined Surfactant/Oil/Water (SOW) reference system comprising 3% of pure n-decyltetraethylene glycol ether (C<sub>10</sub>E<sub>4</sub>) in-Octane and 0.01 M aqueous NaCl with a W/O weight ratio = 1. This system was designed to be at the so-called "optimal formulation" at room temperature. Under these conditions the SOW system exhibits several specific phenomena, namely (i) the surfactant has an equal affinity for the aqueous and oil phases, (ii) it forms

at equilibrium a three-phase system (Winsor III) and (iii) the O/W interfacial tension is minimum. In addition, when this system is gradually heated under stirring, a phase inversion (O/W→W/O) occurring around 25°C can be detected by a sudden drop in the conductivity. To evaluate the hydrophilic/lipophilic ratio of a given amphiphile S2, small amounts of S2 must be added step by step to the reference system to modify the phase inversion temperature (PIT) of the emulsion. The evolution of the PIT is proportional to the concentration of the added amphiphile and the slope of the linear fit allows calculate its PIT-slope. If the PIT-slope is positive, the added amphiphile has a greater affinity for the aqueous phase than that of the reference surfactant (C<sub>10</sub>E<sub>4</sub>). On the contrary, when the PIT-slope is negative, the surfactant is more lipophilic than C<sub>10</sub>E<sub>4</sub>. It is important to specify that this method, based on the modification of the curvature of the interfacial film, "sees" only the amphiphiles present within this film and not the amphiphiles localized in the excess aqueous and oil phases. Table 4 shows the PIT-slope values of the four newly synthesized compounds **10s**, **14s**, **15s**, **16s** and for the related hydrotropes **17-20** already described<sup>[25]</sup> for comparative purposes. The interpretation of the absolute value of the PIT-slope of true surfactants and hydrotropes is different.

**Table 4.** PIT-slope (weight<sup>31</sup> and molar<sup>32</sup> basis) and salt-tolerance of the new sustainable hydrotropes **10s**, **14s**, **15s**, **16s** compared to hydrotropes **21-24** derived from sodium chloroacetate.<sup>33</sup>

N°	Precursor	Structure	dPIT/dC (°C/wt.%)	dPIT/dx (°C)	NaCl (wt.%)	CaCl <sub>2</sub> (wt.%)
<b>15s</b>	Ethyl acetoacetate		88	296	19	2.4
<b>14s</b>	Ethyl acetoacetate		100	284	15	0.8
<b>16s</b>	Methyl levulinate		110	340	17	1.3
<b>10s</b>	Methyl levulinate		113	334	18	1.3
<b>17</b>	Sodium chloroacetate		98	285	> 20	< 0.5
<b>18</b>	Sodium chloroacetate		152	422	> 20	1.2
<b>19</b>	Sodium chloroacetate		7.2	21.3	> 20	> 20
<b>20</b>	Sodium chloroacetate		8.6	24.0	> 20	< 0.4

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As surfactants are essentially localized in the interfacial film of  $C_{10}E_4$ , their PIT-slope values are directly correlated with their hydrophilic-lipophilic ratios.<sup>32</sup> On the other hand, the hydrotropes have less affinity for the interfacial film and a significant part of the molecules partitions into the bulk aqueous and/or oily phase. The absolute value of the PIT-slope of hydrotropes therefore incorporates both its hydrophilic-lipophilic ratio and its affinity for the interfacial film. It's worth to note that this observed PIT-slope value is precisely the relevant data for the formulator who wishes to predict how a particular hydrotropes will modify the apparent hydrophilic-lipophilic ratio (i.e. the "effective" packing parameter) of a complex SOW system. Table 4 shows the values for the PIT-slope for the four synthesized compounds **10s**, **14s**, **15s**, **16s** and for the related hydrotropes **17-20** already described for comparative purposes.<sup>[25]</sup>

It is worth noting that the interpretation of the absolute value of the PIT-slope of true surfactants and hydrotropes is different. As surfactants are essentially localized in the interfacial film of  $C_{10}E_4$ , their PIT-slope values are directly correlated with their hydrophilic-lipophilic ratios.<sup>[32]</sup> On the otherhand, hydrotropes have less affinity for the interfacial film and a significant part of the molecules partitions into the bulk aqueous and/or oily phase. The absolute value of the PIT-slope of hydrotropes therefore incorporates both its hydrophilic-lipophilic ratio and its affinity for the interfacial film. It turns out that this observed PIT-slope value is precisely the relevant data for the formulator who wishes to predict how a particular hydrotropes will modify the apparent hydrophilic-lipophilic ratio (i.e. the "effective" packing parameter) of a complex SOW system.

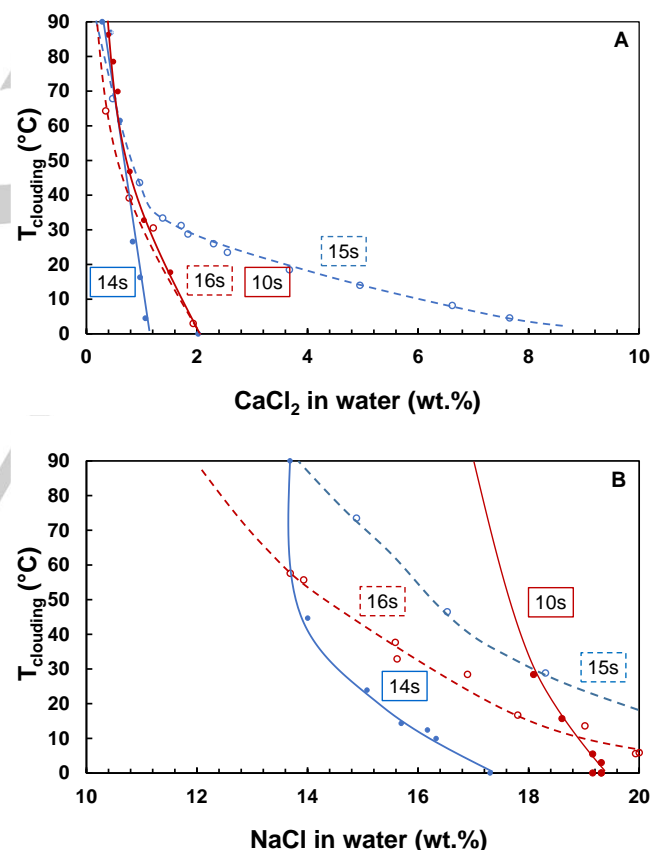
The positive sign of all PIT-slopes shows that all hydrotropes are significantly more hydrophilic than  $C_{10}E_4$  due to the presence of the very hydrophilic anionic group sodium carboxylate. However, the absolute values of these PIT-slopes do not follow the order of the hydrophilic-lipophilic ratios expected from their molecular structures. Thus compounds **19** and **20**, which have the shortest hydrophobic chain, are incontestably the most hydrophilic hydrotropes while the absolute values of the PIT-slopes are the lowest. In the same way, the PIT-slopes of sodium levulinates **10s** and **16s** are significantly higher than those of sodium acetoacetate derivatives **14s** and **15s**. This result may seem rather surprising since a simple glance at their molecular structures shows that acetoacetates derivatives are definitely more hydrophilic than levulinates derivatives, due to their shorter alkyl spacer between the glyceryl moiety and the carboxylate group.

These counter-intuitive experimental results can be explained by the more or less significant partitioning of these hydrotropes between the interfacial film of  $C_{10}E_4$  and the aqueous and oily compartments. In particular, most of the very short and very hydrophilic hydrotropes **19** and **20** are located in the aqueous phase and the minor part inserted within the interfacial film modifies very little its curvature and its effective packing parameter. These absolute values of PIT-slope are therefore very useful in practice because it allows predicting that hydrotropes **10s** and **16s** will be much more effective than all the other hydrotropes bearing the same ethylhexyl chain, including the reference hydrotrope **17** synthesized from potentially hazardous reagents.

The difference between the PIT-slope values of **14s** and **15s** on the one hand, and **10s** and **16s** on the other hand, is less than the experimental uncertainty. Therefore, the methylation of the free

hydroxyl group of the glyceryl spacer does not appear to have a major influence on the PIT-slope value. The effect of branching in the alkyl tail can be evaluated by comparing **17** and **18**. The packing parameter ( $v/ai$  = Hydrophobic tail volume/[Polar head area x Tail length]) of compound **17** with the i-octyl tail is significantly greater than that of compound **18** with the n-octyl tail. Actually, the volumes  $v$  and the surfaces  $a$  are almost identical for these two amphiphiles while the ethylhexyl chain length  $l$  is shorter than the n-octyl chain. As a result, compounds **18** and **17** are both very hydrophilic (positive PIT-slope) thanks to their sodium carboxylate function, but the 2-ethylhexyl chain decreases the hydrophilicity of the amphiphile more than the n-octyl chain.

The salt tolerance of **10s**, **14s**, **15s**, **16s** in aqueous solutions as a function of the temperature has been determined at different salts concentrations of sodium and calcium chloride as shown in figure 1 and Table 4. The concentration of the amphiphiles was fixed at 5 wt.% as in previous publications<sup>[25,33]</sup> because this concentration is intermediate between that used in shampoos and detergents ( $\leq 30$  wt.%) and that used in Enhance Oil Recovery ( $\leq 1$  wt.%).



**Figure 1.** Evolution of the cloud points of biobased hydrotropes **15s** (○), **14s** (□), **16s** (△), and **10s** (●) at different concentrations of  $CaCl_2$  (A) or  $NaCl$  (B) and constant concentration of the hydrotropes (5 wt.%). The solutions are homogeneous under the limits and cloudy above.

Without salt, the four hydrotropes are fully water-soluble throughout the studied temperature range (5 – 85°C) and do not exhibit any Krafft point. But when the salt concentration increases, more and more water molecules bind to the electrolytes ions and are no longer available to hydrate the polar heads of the hydrotropes until causing a clouding phenomenon as observed previously for **18**<sup>[25]</sup> and other ionic amphiphiles with nonionic

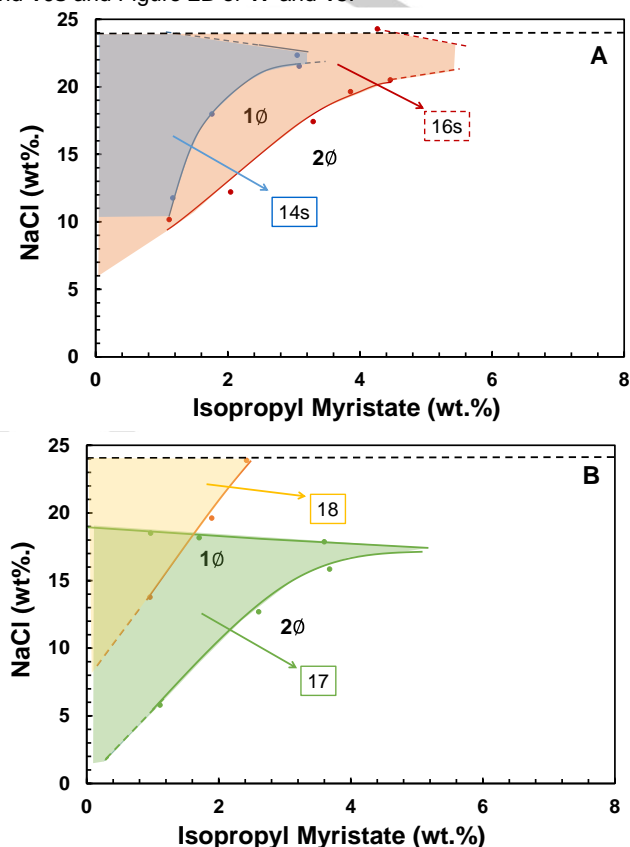
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spacers between the alkyl chain and the ionic head.<sup>[34]</sup> As expected, the salt tolerance is much higher towards NaCl ( $\approx$  15–18 wt.%) than towards CaCl<sub>2</sub> ( $\approx$  1–3 wt.%) because the divalent cation Ca<sup>2+</sup> can bind strongly to two carboxylate functions giving a calcium hydrotrope with two hydrophobic tails which self-associate to reduce their contact with water. Regarding the tolerance to CaCl<sub>2</sub>, the four amphiphiles behave similarly when the temperature is above 40 °C. However, at lower temperature (25°C) **14s** is clearly the least Ca<sup>2+</sup>-tolerant (0.8 wt.%) whereas its methylated counterpart **15s** exhibits a much higher Ca<sup>2+</sup>-tolerance (2.4 wt.%) while it is more hydrophobic according to its molecular structure. This paradoxical behaviour has already been reported by Illous et al.<sup>[25]</sup> who showed that the tolerance to CaCl<sub>2</sub> of the methylated compound **19** is much higher than that of the parent compound **20** whose OH group was left unmethylated. As pointed-out by these authors using molecular dynamics, the methyl group bound to the pendant glyceryl OH group impedes the bridging interaction of the methylglyceryl spacer with two Ca<sup>2+</sup> ions which is the first step towards precipitation of calcium hydrotrope. In addition, they confirm by <sup>1</sup>H NMR analyses that the complexation of Ca<sup>2+</sup> by the hydrophilic head of **19** does indeed take place in agreement with Mueller et al. to explain the salt tolerance of oligoether carboxylates.<sup>[35]</sup> In contrast, the salt tolerance towards CaCl<sub>2</sub> of **16s** and **10s** are similar. These different behaviours show that the methylation of the glyceryl spacer is not sufficient to confer a strong tolerance towards CaCl<sub>2</sub> to alkyl ether carboxylate hydrotropes, it is further necessary for the carboxylate function to be close to the ether groups of the spacer to allow complexation of one Ca<sup>2+</sup> ion by a single hydrotrope molecule.

The phase behavior towards NaCl is quite different even if, at temperature lower than 90°C, **15s** is still more salt-tolerant than **14s**. Furthermore, the cloud point curve for both amphiphiles with the methylated glyceryl spacer have the same shape and the two with the alcohol free are also similar to each other. For **16s** and **10s**, the cloud point curves intersect in the vicinity of 18.8 wt.% NaCl and 11°C. The intersection also occurs for **15s** and **14s** in the vicinity of 14.5 wt.% NaCl and 90°C. Under these conditions their salt tolerance is identical. The effect of the methylation of glyceryl spacer methylation on the salt tolerance depends on the structure of the polar ionic head. Methylated amphiphiles are more salt tolerant than the corresponding free -OH in a higher range of NaCl concentrations (and temperature) when the ionic polar head is shorter as in the acetoacetate case. The last two columns of table 4 shows the salt concentrations needed to reach the cloud point of 5 wt.% solutions of amphiphiles at 25°C. Compared to **17**, the salt tolerance of hydrotropes **15s**, **14s**, **16s** and **10s** is lower towards NaCl but significantly higher for all of them towards CaCl<sub>2</sub> and even reaches 2.4 wt.% for **15s** with the distinct advantage of being synthesized by a sustainable route.

The salt tolerance of hydrotropes **15s**, **14s**, **16s** and **10s** makes it possible to change the salinity on a wide range to tune their effective hydrophilic/lipophilic ratio. In particular, by suitably adjusting the salinity of the aqueous phase, it is possible to maximize their solubilizing power with respect to a given oil or a fatty soil. To illustrate this interesting application, we have studied the solubilization in aqueous phase of isopropyl myristate (IPM) which is an oil widely used in cosmetics. Thus, the binary phase diagrams shown in Figure 2A were constructed at 25°C while maintaining a constant concentration of the hydrotropes **14s** and **16s** equal to 5 wt.%. The two hydrotropes **14s** and **16s** were

chosen because they have the lowest (284°C) and the highest (340°C) PIT-slope respectively. In the absence of NaCl, or at very low concentrations, the addition of IPM to the amphiphile aqueous solution produces a two-phase system (2 $\emptyset$ ). Then, by gradually increasing the concentration the concentration of NaCl, a monophasic zone appears over a large zone of salinity and, at a very specific optimum salinity, the solubility of IPM reaches a maximum value, between 2 and 5% depending on the structure of the hydrotrope. Figure 2A shows the phase diagrams of **14s** and **16s** and Figure 2B of **17** and **18**.



**Figure 2.** Influence of salinity (wt.%) on the solubilization of isopropyl myristate (wt.%) at 25°C and 5 wt.% of hydrotrope. A) Bio-based hydrotropes **14s** and **16s**. B) Hydrotropes derived from chloroacetic acid **17** and **18**. The upper horizontal dotted line indicates the NaCl solubility limit in water.

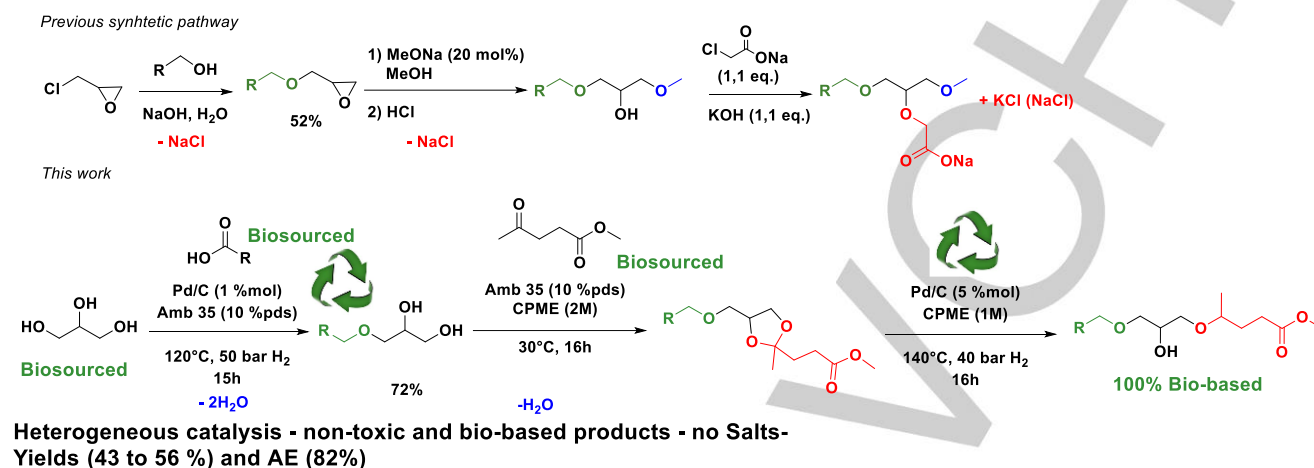
This 2 $\emptyset$ →1 $\emptyset$  behavior is analogous to the WI→WIV<sup>36</sup> typical transition for anionic surfactants, in which the effective hydrophilicity decreases significantly by addition of electrolytes such as NaCl. Indeed, the counter-cation Cl<sup>-</sup> partially screens the anionic charge and progressively improves the solubilization of the oil until a maximum value is reached. The monophasic region is more extensive for **16s** than for **14s** (Fig. 2A) because of its stronger amphiphilicity. These results are promising for solubilizing oils in saline aqueous media. For the related amphiphiles derived from chloroacetic acid **17** and **18**, the phase behaviours are different. The compound with a linear tail **18** requires higher salinity to achieve monophasic behaviour for a given IPM content in accordance with its higher hydrophilicity. As the polar ionic head are the same, the change into the salinity is the consequence of the branched alkyl chain that increases the lipophilicity of the compounds as previously discussed.

### Sustainability analysis

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Molecules **18**, **19**, **20** with optimal salt resistance described by J.M Aubry were obtained using epichlorohydrin as a key raw material (scheme 10). This chemical is widely used in industry for many applications. It could be bio-based however it is toxic and is identified as a CMR product. In our knowledge sodium

chloroacetate is not bio-based. Moreover, for each step, salts are generated. The global yield reaches only 11% and the atom economy is 62%.



**Scheme 10.** Comparison between classical and sustainable synthetic methodologies

Both strategies allow the formation of soluble salt-resistant amphiphiles in a similar manner, but the pathway proposed in this paper takes care of the sourcing of the starting material. More precisely, the first step supposes the reductive alkylation of bio-based carboxylic acid with glycerol affording only water as by-product. The excess of glycerol, used to favour the formation of the monoether, can be recycled as well as both catalysts. During the second step the carboxylic moieties is added thanks to the use of bio-based levulinic acid derivative. The same solvent is used for the two-last steps to limit wastes and purification. Heterogeneous catalysts allow the formation of the products with good yields. In the case below the global yield reach 50% with 88% atom economy.

## Conclusion

Simple glycerol mono-ethers (MEGs) already have interesting hydrotropic properties. However, the hydrophilicity of the polar head is too small, making MEGs not very tolerant to saline media. Addition of a carboxylic acid as close as possible to the glycerol unit, as well as the methylation of the hydroxyl, significantly increase the salt tolerance. Different strategies were studied using MEGs obtained by reductive alkylation of glycerol with a carbonyl derivative. In this case, the use of ketoesters was considered.

A two-step sequential synthesis of acetalization followed by hydrogenolysis provides access to the target ethers in good yields (60%). This strategy was extended to ethyl acetoacetate with similar yields. Low yields are however observed when methyl pyruvate is used. Indeed, a side reaction during hydrogenolysis leads to the formation of the lactone (see supporting information). The methylation of the hydroxyl was then carried out with trimethyl

phosphate with yields of 55% to 72%. Saponification was performed quantitatively to obtain the desired carboxylic acid function. The general synthesis of these compounds was performed in a sustainable way using as much as possible heterogeneous catalyst avoiding the formation of salts.

The hydrophilic/lipophilic behaviour, the salt-tolerance and the oil solubilization of biobased sodium ethyl hexyl glyceryl ether levulinates (**16s** and **10s**) and acetoacetates (**15s** and **14s**) were determined and compared with the hydrotropes derived from chloroacetic acid (**17** and **18**). All new hydrotropes are water soluble in the 5°C - 85°C range at 5 wt.%. When increasing the salinity, no precipitation occurs but a cloud temperature appears and it diminishes when salt concentration increases. At 25°C, the new hydrotropes (5 wt.%) present a high salt tolerance to NaCl (15-19 wt.%) and CaCl<sub>2</sub> (0.8-2.4 wt.%), a concentration high enough to be entirely soluble in very hard water. The methylation of the glyceryl spacer enhances the tolerance to the CaCl<sub>2</sub> for acetoacetates. Concerning the salt-tolerance towards NaCl, the methylated hydrotropes **15s** and **16s** are more salt-tolerant than the non-methylated hydrotropes **14s** and **10s**.

Phase diagrams at constant 5 aq. wt.% of hydrotrope showed that complete solubilization of 3-5 wt.% of isopropyl myristate can be achieved into high salinity aqueous media. The relevant properties of these biobased hydrotropes make them serious sustainable candidates for industrial applications in high salinity environments.

## Experimental Section

### General information

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Glycerol ( $\geq 99\%$  purity), trimethyl phosphate (97% purity), trimethyl orthoformate ( $\geq 99\%$  purity) and methyl levulinate ( $\geq 98\%$  purity) were purchased from Sigma-Aldrich. 3-(2-ethylhexyloxy)-1,2-propanediol ( $>98\%$  purity), methyl pyruvate ( $>97\%$  purity) were supplied from TCI. Ethyl acetoacetate ( $\geq 99\%$  purity) was purchased from ACROS. Hexanal was supplied by Sigma-Aldrich. Amberlyst 35 was bought from Rohm and Haas. Pd/C (5% Pd on activated carbon, reduced and dry, Escat 1431) and iron (III) trifluoromethanesulfonate (98% purity) were purchased from Strem Chemicals. All other reagents and solvents were used as received without further purification. Reactions were monitored by TLC and chromatographic separations were performed over silica gel 60H (40-63 $\mu$ ). Direct reductive alkylations were undertaken in a 300 mL steel Parr autoclave equipped with a mechanic stirrer.

#### General procedure for the reductive alkylation.

In a 300 mL steel Parr autoclave equipped with a mechanical stirrer, Glycerol (1.08 mol, 100.0 g, 40 equiv) and the corresponding carbonyl (27.2 mmol, 1 equiv) were mixed at room temperature. Next, Amberlyst 35 dry (10 wt.%) and Pd/C (1 mol% Pd, 0.58 g) were added to the mixture. The autoclave was flushed with argon then with hydrogen four times. The solution was stirred (800 rpm or more) at 120°C under 50 bar hydrogen for 16 h (for the acids or esters compounds), or 140°C under 10 bar hydrogen for 24 h (for aldehyde compounds). The medium was then dissolved in absolute ethanol and filtered (Millipore Durapore filter 0.1  $\mu$ m). The solvent was evaporated under reduced pressure and the organic products were extracted four times with dichloromethane. The crude products were finally purified by silica column chromatography to afford glycerol monoethers (eluent: cyclohexane/ethyl acetate 4:1 ~ 1:0).

#### Acetalisation and hydrogenolysis sequence of methyl levulinate and glycerol mono ether.

In a round bottom flask equipped with a condenser fitted with a CaCl<sub>2</sub> guard, methyl levulinate (4 g, 30.7 mmol, 1 equiv.) and the corresponding glycerol mono ether (30.7 mmol, 1 equiv.) were mixed in CPME (15.4 mL, 2 mol/L). Then, Amberlyst 35 (400 mg, 10 wt.%) and the CaH<sub>2</sub> (1.3 g, 30.7 mmol, 1 equiv.) were added. The mixture was magnetically stirred at room temperature for 10 to 16 hours (the conversion was followed by GC). The solution was filtered off with CPME (15.4 mL) and directly put in a 300 mL stainless steel autoclave purged under argon. Then, 5%-Pd/C (3.26 g, 5 mol% Pd) was added and the reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (40 bar). The system was heated at 140°C and mechanically stirred for 16 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in EtOAc (100 mL), filtered (Millipore Durapore filter 0.01  $\mu$ m), and washed two times with 20 mL of EtOAc. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography to give corresponding ethers (eluent: 70:30~30:70 cyclohexane/EtOAc).

#### Acetalisation and hydrogenolysis sequence of ethyl acetoacetate and glycerol mono ether.

In a two-neck round bottom flask flushed under argon, ethyl acetoacetate (4 g, 30.7 mmol, 1 equiv.) and trimethyl orthoformate (4.0 mL, 36.9 mmol, 1.2 equiv.) were added in toluene (61.4 mL, 0.5 mol/L). Then, Amberlyst 35 (400 mg, 10 wt.%) and the corresponding glycerol mono ether (30.7 mmol, 1 equiv.) were added. The mixture was magnetically stirred at 75-80°C for 1 to 8 hours (the conversion was followed by GC). The methanol formed by the reaction of the water and the trimethyl orthoformate was distilled off by distillation. The solution was filtered off and washed with EtOAc (2 times 20 mL), and the solvents are evaporated under reduced pressure. The solution obtained was put in a 300 mL stainless steel autoclave containing CPME (30.8 mL, 2 mol/L) under argon. Then, 5%-Pd/C (3.26 g, 5 mol% Pd) was added and the reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (40 bar). The system was heated at 140°C and mechanically stirred for 16

hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in EtOAc (100 mL), filtered (Millipore Durapore filter 0.01  $\mu$ m), and washed two times with 20 mL of EtOAc. The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography to give corresponding ethers (eluent: 70:30~30:70 cyclohexane/EtOAc)

#### General procedure for methylation.

In a sealed tube flushed under an argon atmosphere, the corresponding glycerol diether (10 mmol) was mixed in trimethyl phosphate (30 mmol, 4.2 g). Then, iron (III) trifluoromethanesulfonate (141.6 mg, 4 mol%) was added and the tube was sealed. The solution was magnetically stirred and heated to 110°C for 16 hours. After cooling to room temperature, the mixture was extracted three times with 40 mL of pentane. The extracted solution was concentrated under vacuum, and the residue was purified by flash chromatography to give the corresponding dimethylated acetal (eluent: 100:0~90:10 cyclohexane/EtOAc).

#### General procedure for saponification.

In a round bottom flask kept at 5°C, a solution of 2 mol/L of NaOH in water (8.25 mL, 2.5 equiv.) was added dropwise to the corresponding ester (6.6 mmol). The solution was magnetically stirred and kept 1 hour at 5°C, and then 1 hour at room temperature. Then, a solution of 1 mol/L of HCl (8 mL) was added dropwise still pH = 3-4. The solution was magnetically stirred during 30 min at room temperature. The aqueous solution was extracted three times with EtOAc (20 mL), the organic phase was then dried with MgSO<sub>4</sub>, filtrated and solvent was evaporated under vacuum. The corresponding acid was obtained in quantitative yield without any purification.

#### PIT-slope.

The procedure previously reported in the literature was strictly followed<sup>31,32</sup>

#### Salt-tolerance.

Concentrated solutions were prepared by introducing 5 aq. wt.% of the hydrotrope in an aqueous solution with 20 wt.% of NaCl or 5 wt.% CaCl<sub>2</sub>. The cloud temperature of these solutions has been measured at different salt concentrations. The cloud point was determined by decreasing the temperature and corresponds to the temperature at which the turbid solution becomes perfectly clear (maximum uncertainty of 0.5°C). The salt concentration was reduced by adding the required amount of an aqueous solution of hydrotrope at 5 wt.%.

#### Solubility of Isopropyl Myristate.

Concentrated solutions containing 5 wt.% of hydrotrope and different concentrations of NaCl were prepared. An increasing amount of isopropyl myristate (previously dyed yellow by the hydrophobic dye D8C Yellow 11 W1201) is added to different tubes. After introducing the same amount of stock solutions into each tube, they are slowly shaken and placed in a thermoregulated bath at 25°C. The solutions were observed after one hour of equilibration. The solution was considered homogeneous if no excess phase, cloud, or suspended oil drops were observed.

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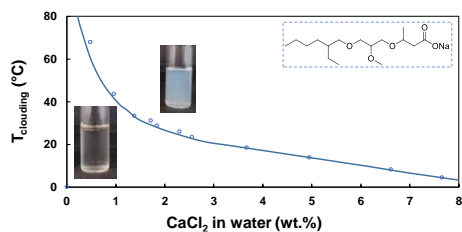
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**Keywords:** Hydrotrope • reductive alkylation • Salt-tolerance • glyceryl spacer • levulinic acid

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## Entry for the Table of Contents

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Insert text for Table of Contents here. An eco-compatible access to new alkyl ether carboxylates with glyceryl spacer is described and the evaluation of their physico-chemical properties. The targeted application is hydrotrope which can be used in numerous domains such as extraction, detergency, solubilization, etc... The interesting properties of these biobased hydrotropes make them serious sustainable candidates for high salinity applications.

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