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Trialkylamine-Catalyzed Aldolisation of Unprotected 1,3-Dihydroxyacetone (DHA) towards C-C Bond-Linked Tetraol Surfactants

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ABSTRACT. The aldolisation of unprotected 1,3-dihydroxyacetone (DHA) was studied under mild conditions (20°C) in a mixture of water/EtOH using hydrocinnamaldehyde as a model

substrate. It was shown that trimethylamine is the most effective base for this transformation giving the corresponding aldol with up to 98% selectivity and 82% yield. The method was extended to a range of (bio-based) aldehydes to give α-hydroxyketones with 29-70% isolated yields. These α-hydroxyketones were reduced under hydrogen using 5%-Ru/Al_2O_3 in EtOH at 100°C to give tetraols with 79-97% isolated yields. The physico-chemical properties of these tetraols were studied (CMC, Krafft point, PIT-slope method) and these studies revealed that this new class of C-C bond linked non-ionic surfactants exhibit high effectiveness reducing the surface tension of water.

KEYWORDS. Aldolisation, 1,3-Dihydroxyacetone, Surfactants, Tetraols, Trialkylamines

INTRODUCTION

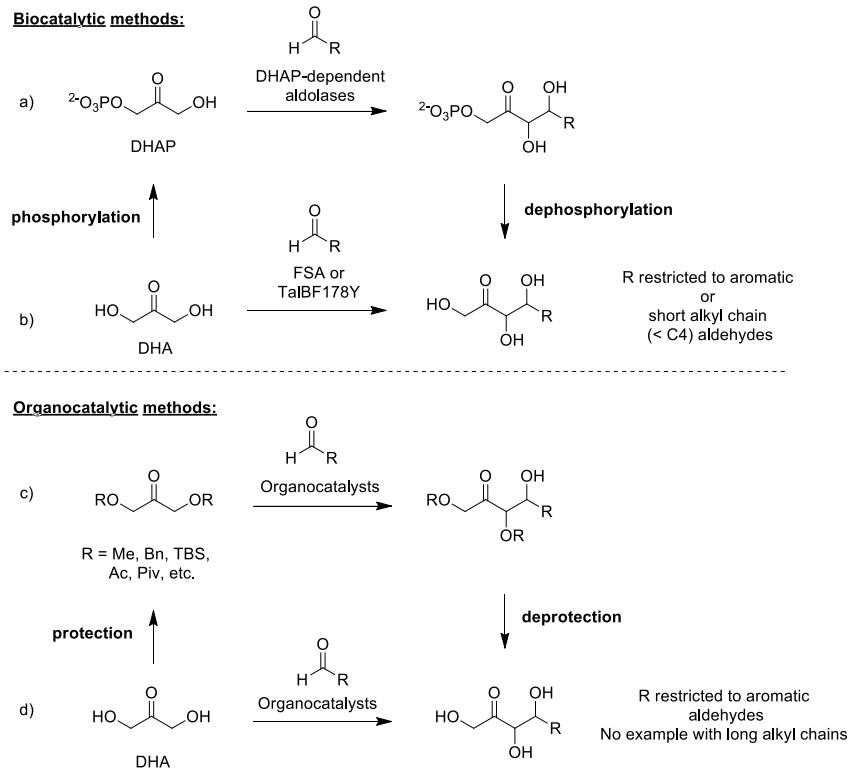
Surfactants are widely used in detergency, cosmetics, pharmaceuticals and as additives in paints, textiles and food. Among all surfactants developed so far, renewable surfactants are now occupying an increasingly important place.[1,2] In this context, carbohydrate-derived surfactants have attracted a lot of attention as they are inherently obtained from renewable resources (starch, hemicellulose, cellulose, saccharose).[3] Moreover, carbohydrates are available in bulk quantities at a very competitive price, that is particularly interesting for surfactants targeting industrial applications.[4] In addition, carbohydrates are generally non-toxic and biodegradable. For example, alkyl (poly)glycosides (APGs) are commercially available non-ionic surfactants that are widely used in detergency thanks to their good biodegradability.[5,6] Most of the other carbohydrate-based surfactants have an *ester* linkage between the polar head and the hydrophobic tail such as sucrose esters,[7] and sorbitan esters[8] amongst others. The ester functional

group is usually privileged for three reasons, that are: i) the wide availability and great diversity of polyols and carboxylic acids, ii) the relative simplicity of formation (through chemical or enzymatic catalysis) and iii) the good biodegradability properties. However, the *ester* group is sensitive to hydrolysis in acid or basic conditions, thus restricting their applications over a narrow range of pH. Still, there is a need of robust surfactants, particularly for extraction purposes (*e.g.*, eco-extraction of natural products), and for applications requiring medium-to-long-term stability upon storage (*e.g.*, cosmetics).

In order to increase the stability of surfactants, many efforts have been devoted to the preparation of *ether* analogues such as glycerol ethers.[9] However, they are only few examples of the preparation of carbohydrate-derived ethers. In this field, our group has recently reported the access to sorbitan[10,11] and methyl glycopyranoside[12,13] alkyl ethers through the reductive alkylation (reductive etherification) of the corresponding polyols. Another option to increase the stability is to link the polar head and the non-polar part with a robust C-C bond. Albeit very attractive from a synthetic point of view, this approach has been scarcely explored. To the best of our knowledge, there is only one report on carbohydrate derivatives. In 2011, Foley *et al.* have reported the access to linear and cyclic C-glycosides surfactants from Lubineau's nonulose[14] through enamine-catalysed aldol condensation using a range of alkyl aldehydes.[15]

Among the available renewable starting materials, 1,3-dihydroxyacetone (DHA) is a versatile C3-building-block for asymmetric synthesis[16] but it has barely been explored as starting material for surfactant applications. DHA is naturally present in sugar beets but only in small quantities, which are not sufficient for the targeted applications. However, DHA can be produced by direct oxidation of glycerol through organometallic[17] or enzymatic[18] catalysis. Glycerol is a renewable platform molecule (obtained from the hydrolysis or methanolysis of triglycerides) that is

available in bulk quantities and at a low price.[19,20] Therefore, glycerol-derived DHA presents similar assets, making it suitable for surfactants applications. The aldolisation of DHA has been previously investigated using aldolases as biocatalysts. However, most biocatalytic methods have been reported using dihydroxyacetone phosphate (DHAP) as starting material due to its ability to interact with enzyme active sites (Scheme 1, a).[21,22]

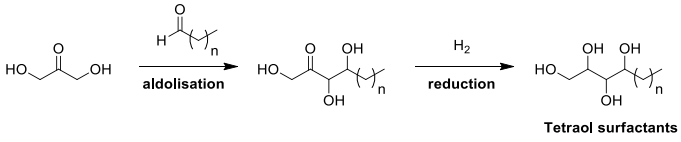


Scheme 1. Bio- and organocatalytic methods for the aldolisation of (protected) DHA.

This requires two extra steps for preliminary phosphorylation of DHA and deprotection of the phosphate group at end-stage. Only a few enzymes such as D-fructose-6-phosphate aldolase (FSA)[23] from *Escherichia coli* or TalB^{F178Y}, a F178Y mutant of transaldolase B,[24] could accept unprotected DHA as substrate (Scheme 1, b). Unfortunately, the aldehyde substrate scope is

limited to aromatic aldehydes or short alkyl chain aldehydes (≤ C4) with electron withdrawing substituent.[25] Many organocatalytic methods have been developed for the aldolisation of DHA towards the formation of stereogenic centres. As a result, most of these methods use protected versions of DHA or cyclic analogues, mainly for selectivity reasons (Scheme 1, c).[26-28] In some cases, unprotected DHA could be used but the substrate scope is generally limited to aromatic aldehydes (Scheme 1, d).[29,30] In this context, there is a need to develop clean methodologies for the aldolisation of unprotected DHA using linear enolizable aldehydes under mild conditions.

Herein, we report the use of trialkylamines for the aldolisation of unprotected 1,3-dihydroxyacetone with a range of (bio-based) aromatic and linear aldehydes. The resulting α-hydroxyketones were reduced to the corresponding tetraols and their physico-chemical properties were studied in details (Scheme 2).



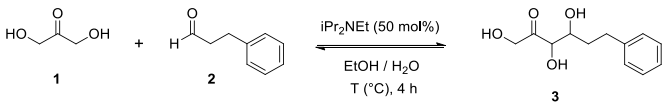
Scheme 2. Tetraol surfactants through an aldolisation/reduction sequence.

RESULTS AND DISCUSSION

Synthesis of tetraols through aldolisation/reduction

Initial screening was carried out to find appropriate conditions for the aldolisation of unprotected DHA using hydrocinnamaldehyde (HCA) as a model substrate (Table 1).

Table 1. Optimization of reaction conditions.[a]



Entry	**1** / **2** ratio	EtOH/ H_2O ratio	T (°C)	Conv.[b,c] (%)	Yield[c] (%)	Selec.[d] (%)
1	5 : 1	1 : 1	20	> 99	46	46
2	10 : 1	1 : 1	20	> 99	72	72
3	15 : 1	1 : 1	20	> 99	89	89
4	20 : 1	1 : 1	20	> 99	> 99	99
5[e]	5 : 1	1 : 1	20	73	65	89
6[e]	5 : 1	10 : 1	20	> 99	< 1	1
7[e]	5 : 1	1 : 10	20	98	11	11
8[e]	5 : 1	1 : 1	30	84	12	14
9[e]	5 : 1	1 : 1	50	74	8	11
10[f]	5 : 1	1 : 1	20	83	64	77

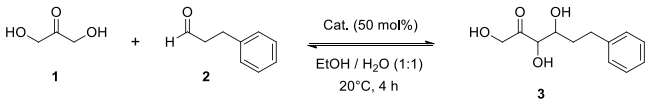
[a] Reaction conditions: sealed tube, dihydroxyacetone **1** (500 mg, 5.5 mmol), DHA (5-20 equiv.), iPr_2NEt (50 mol%), H_2O/EtOH (5 mL), T (20-50°C), 4 hours. [b] The conversion is based on the aldehyde. [c] Results were determined by HPLC using calibration curves. [d] Selectivity was calculated as follow: S = yield / conversion. [e] Dropwise addition of aldehyde **2** into a solution of DHA. [f] Reaction carried out with only 10 mol% of catalyst for 4 days.

First, the aldolisation of DHA **1** (5 equiv.) with hydrocinnamaldehyde **2** (1 equiv.) was carried out in a 1:1 mixture of EtOH/H_2O at room temperature (20°C) using iPr_2NEt (50 mol%). Satisfyingly, the conversion is complete after 4 hours and α-hydroxyketone **3** was obtained with 46% yield (Table 1, entry 1). However, a significant proportion (about 20%) of a heavier byproduct was formed under these conditions. This byproduct comes from the bis-aldolisation of

DHA with two equivalents of aldehyde **2** as confirmed by HRMS (see ESI). In order to prevent its formation, the amount of DHA was progressively increased from 5 to 20 equivalents (Table 1, entries 2-4). Gratifyingly, the yield of α-hydroxyketone **3** increased from 72 to 99% when using 20 equivalents and no di-aldol product has been detected under these conditions. Considering that the aldolisation is a reversible process, these results clearly indicate that a high DHA/HCA ratio should be employed to reach high yield and selectivity. However, in order to limit the quantity of DHA, the DHA/HCA ratio was set at 5 like in most reported literature procedures.[31] Consequently, the reaction was carried out by dropwise addition of aldehyde **2** to a DHA solution to maintain high concentration of DHA (Table 1, entry 5). Under these conditions, the yield of **3** reached 65% and the selectivity was 89%. Moreover, only traces (< 5%) of the bis-aldolisation product of DHA has been observed, thus confirming the high selectivity obtained. The proportions of EtOH and water were next investigated using a 10-fold of one of the solvent. With a 10:1 EtOH/water ratio, the conversion is high but the yield is poor (Table 1, entry 6). Only the self-aldolisation product of hydrocinnamaldehyde has been observed under these conditions. With a 1:10 EtOH/water ratio, once again the conversion is high but the yield is low (Table 1, entry 7). In that case, a large amount of the bis-aldolisation product was obtained. Finally, increasing the temperature to 30 or 50 °C did not improve the yield of the desired α-hydroxyketone **3** (Table 1, entries 8-9). It should be noted that similar results could be obtained using only 10 mol% of iPr_2NEt provided extended reaction times (4 days) (Table 1, entry 10). This is not surprising as most literature procedures using organocatalysts (10-30 mol%) require 1 to 7 days.[26-30] Consequently, the amine loading was set at 50 mol% in order to keep short reaction times for rapid optimization.

Several traditional aldolisation catalysts such as $Zn(Pro)_2$,[32] *L*-proline,[33] cinchonidine, quinine and others were next screened under the optimized reaction conditions but they gave poor results (see Table S1 in ESI for details). Only trialkylamines with non-bulky substituents gave interesting results (Table 2).

Table 2. Catalyst screening.[a]



Entry	Catalyst	Conv. [b, c] (%)	Yield[c] (%)	Selec.[d] (%)
1	*i*-Pr_2NEt	94	54	57
2	Et_3N	53	51	96
3	$EtNMe_2$	78	73	93
4[e]	NMe_3	84	82	98
5	*n*-$C_{12}H_{25}NMe_2$	33	26	79

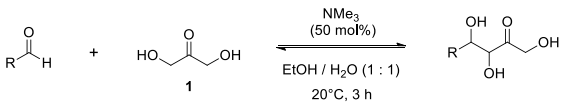
[a] Reaction conditions: sealed tube, 1,3-dihydroxyacetone **1** (500 mg, 5.5 mmol, 5 equiv), hydrocinnamaldehyde **2** (148 mg, 1.1 mmol), catalyst (50 mol%), H_2O/EtOH (1:1, 5 mL), 20°C, 4 hours. [b] The conversion is based on the aldehyde. [c] Results were determined by HPLC using calibration curves. [d] Selectivity was calculated as follow: S = yield / conversion. [e] Reaction was stopped after 3 hours.

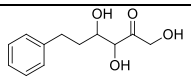
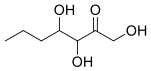
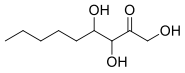
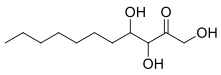
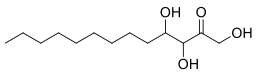
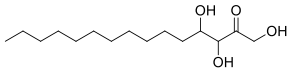
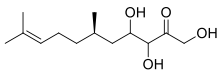
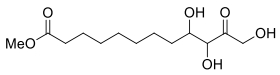
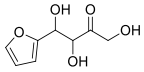
Hünig's base (^{i}Pr_2NEt) gave a high conversion but a moderate selectivity (Table 2, entry 1). Other trialkylamines were found particularly selective (93-98%) for the formation of α-hydroxyketone **3** (Table 2, entry 2-4). From these results, a trend can be identified: the smaller the substituents on trialkylamine, the better the yield. Indeed, the yield of **3** reached 82% when

using NMe_3 as catalyst (Table 2, entry 4). Finally, the catalytic activity of dodecyldimethylamine was tested as we envisaged that it could have a surfactant-like behaviour that could enhance the solubility of aldehyde **2** in water/EtOH solvent mixture. Unfortunately, only moderate results were obtained, thus refuting this hypothesis (Table 2, entry 5).

Consequently, the substrate scope was next extended to a range of (bio-based) aldehydes using NMe_3 as catalyst (Table 3). Repeating the reaction with hydrocinnamaldehyde **2** gave the corresponding α-hydroxyketone **3** with 65% isolated yield after purification by column chromatography (Table 3, entry 1). The product was obtained as a 95:5 mixture of diastereoisomers as determined by ^1H NMR (the 2 diastereoiomers could not be assigned unambiguously). A series of linear aldehydes, with increasing alkyl chain length from 4 to 12 carbons, were next considered. They could be obtained by reduction of the corresponding fatty acids which are accessible from vegetable oil derivatives. The corresponding α-hydroxyketone **4-8** were isolated with moderate yields (46-53%) (Table 3, entries 2-5). The use of dodecanal gave even a lower yield of α-hydroxyketone **8** due to the poor solubility of dodecanal in the reaction mixture (Table 3, entry 6). The use of citronellal as pine wood-derived aldehyde could also be used and the aldol product **9** was isolated with 42% yield (Table 3, entry 7). Conversely, bifunctional aldehyde, derived from the cleavage of fatty acid derivatives,[34-36] gave **10** with moderate yield but a high 95:5 d.r. (Table 3, entry 8). Finally, carbohydrate-derived[37] furfural gave **11** with a satisfying 70% yield (Table 3, entry 9).

Table 3. Scope for the aldolisation of DHA with a range of aldehydes.[a]



Entry	α-hydroxyketones		Yield[b] (%)	d.r.[c]
1		**3**	65 (57) [d]	95 : 5
2		**4**	46 (41)[d]	96 : 4
3		**5**	49 (42)[d]	96 : 4
4		**6**	48 (40)[d]	91 : 9
5		**7**	53 (48)[d]	90 : 10
6[e]		**8**	29	92 : 8
7		**9**	42	53 : 47
8		**10**	36	95 : 5
9		**11**	70	68 : 32

[a] Reaction conditions: sealed tube, aldehyde (2.2 mmol), DHA (1 g, 11 mmol, 5 equiv), Et_3N (50 mol%), H_2O/EtOH (1:1, 10 mL), 20°C. [b] Isolated yields after purification by column chromatography. [c] Diastereomeric ratios were determined by ^1H NMR. [d] Isolated yields in brakets were obtained using NEt_3 (50 mol%) for 7 hours. [e] Reaction was carried out at 32°C.

Contrary to most biocatalytic and organocatatylic methods reported so far, which require prolonged reaction times (up to several days), this method requires only short reaction times (3 hours) provided a high catalyst loading. Consequently, it is essential to recover the catalyst to

make this method attractive from economical and environmental points of view. We have first attempted to use heterogeneous catalysts to provide a recyclable system but the results were not satisfying (see Table S2 in ESI for details). Consequently, considering that the catalyst used (NMe_3) has a low boiling point (bp = 3-4°C), we decided to take advantage of this volatility to recover it. Hence, after reaction of DHA with aldehyde **2**, trimethylamine was evaporated at room temperature under vacuum (80 mbar) and the vapours were condensed into two consecutive dry ice/acetone traps. This distillation should be carried out at room temperature in order to avoid the degradation of the α-hydroxyketone **3** to the starting materials through a retro-aldolisation process. The collected catalyst was titrated with a 1M aqueous HCl solution. Unfortunately, the maximum yield of the recovered NMe_3 did not exceed 16% due to its extremely high volatility that makes the recycling difficult on a small scale using standard laboratory equipment. As a result, in order to validate this concept, trimethylamine was substituted by less volatile triethylamine (bp = 89°C) as it gave similar results than NMe_3 (see Table 3, entries 1-5, yields in brakets). In this case, the catalyst was recovered with 77% yield as a solution in EtOH/water without erosion of the reaction yield of the α-hydroxyketone **3** (Figure 1).

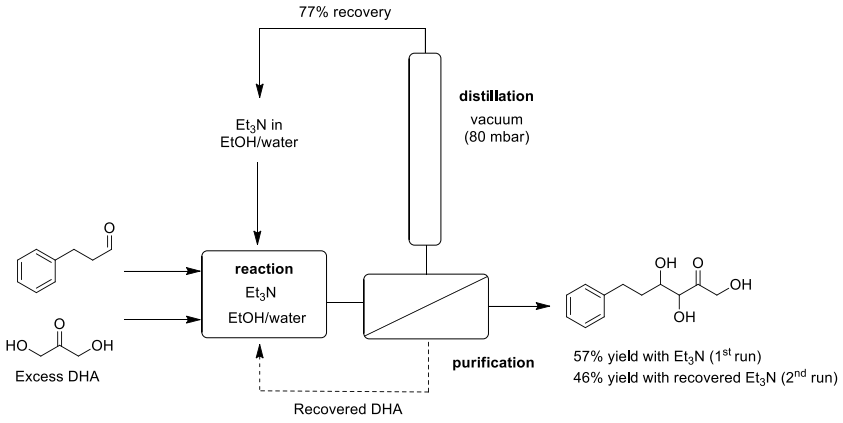
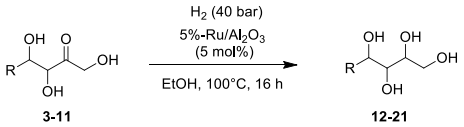


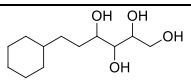
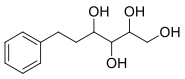
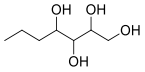
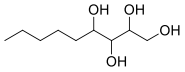
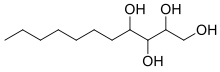
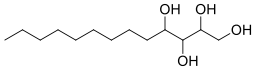
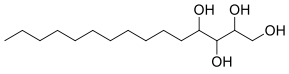
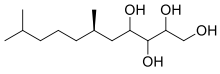
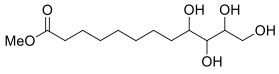
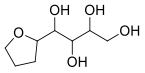
Figure 1. Process for the aldolisation of DHA including recycling of trialkylamine catalysts and recovery of excess DHA.

This EtOH/water solution containing the catalyst was directly re-used in another batch for the aldolisation of DHA with aldehyde **2** and the corresponding α-hydroxyketone **3** was recovered with 46% isolated yield. Overall, these results, with other recent works on the isomerization of glucose to fructose[38] and the hydrothermal liquefaction of algae residues,[39] highlight the potential of trialkylamines as recoverable organocatalysts for the valorization of biomass.

The hydrogenation of α-hydroxyketones to the corresponding tetraols was next investigated (Table 4). The hydrogenation of α-hydroxyketone **3** was first carried out under 40 bars of hydrogen using 5%-Ru/Al_2O_3 (5 mol%) in EtOH at 100°C. These conditions led to the reduction of the keto group but with concomitant reduction of the phenyl ring, giving tetraol **12** with 95% isolated yield (Table 4, entry 1). Almost no selectivity was detected as the product was obtained as a 56:44 mixture of diastereoisomers. In order to avoid the reduction of the phenyl ring, the hydrogen pressure was decreased to 5 bars and the temperature to 30°C to give the desired tetraol **13** with 94% isolated yield (Table 4, entry 2). The alkyl α-hydroxyketones **4-8** were also reduced to the corresponding tetraols **14-18** with excellent yields (92-97%) (Table 4, entries 3-7). The α-hydroxyketone **9**, bearing the citronellal chain, was also converted to the tetraol **19** with 96% yield, with concomitant reduction of the double bond (Table 4, entry 8). Finally, α-hydroxyketones **10-11** were also reduced to the corresponding tetraols **20-21** with good yields (Table 4, entries 9-10).

Table 4. Reduction of α-hydroxyketones to tetraols.[a]



Entry	Aldol	Tetraol		Yield[b] (%), d.r.
1	**3**		**12**	95 (56 : 44)
2[d]	**3**		**13**	94 (50 : 50)
3	**4**		**14**	97 (55 : 45)
4	**5**		**15**	93 (50 : 50)
5	**6**		**16**	94 (25 : 75)
6	**7**		**17**	92 (22 : 78)
7	**8**		**18**	94 (35 : 65)
8	**9**		**19**	96 (50 : 50)
9	**10**		**20**	79 (60 : 40)
10	**11**		**21**	87 (mixture of 8 isomers)

[a] Reaction conditions: 30 mL stainless steel autoclave, aldol (500 mg), hydrogen pressure (40 bar), 5%-Ru/Al_2O_3 (5 mol%), EtOH (12 mL), 100°C, 16 hours. [b] Isolated yields. [c] Diastereoisomer ratios were determined by NMR. [d] Reaction conditions: hydrogen pressure (5 bar), 30°C, 24 hours.

Overall, this two-step aldolisation/reduction procedure gave access to a range of tetraols with good atom-economy and satisfying yields considering the difficulty to isolate such species. So far, these methods do not present any diastereoselectivity, thus giving a mixture of products. In fact, this is not really a problem since nonionic surfactants are generally marketed as mixtures of oligomers or isomers since they exhibit better functional properties.[40] In particular, when a well-defined surfactant has a high Krafft point (T > 25°C), it does not behave as an amphiphile at room temperature. On the other hand, when mixed with oligomers or isomers, its apparent Krafft point decreases and the surfactant can then develop its surface-active properties at room temperature (*vide infra*).[41,42]

Physicochemical properties of tetraols

Alkyl 1,2,3,4-tetraols have only been reported for the preparation of natural product analogues[43] or for the synthesis of liquid crystals.[44] However, to the best of our knowledge, the amphiphilic properties of such compounds have never been investigated. Consequently, the physicochemical properties, *i.e.* Critical Micelle Concentration (CMC) and Krafft point, of these new amphiphilic tetraols were determined. Only the mixtures of isomers were considered for this study as the solubility of pure isomers is usually lower than those the mixtures. Their amphiphilicity was also assessed by using PIT-slope method and the results were used to formulate three phase microemulsion systems. The surface tension of all tetraols in aqueous solutions was measured by the Wilhelmy plate method using a platinum rod as probe. Tetraol **12** bearing a cyclohexyl group as hydrophobic chain and tetraol **13** bearing the corresponding phenyl group were first

compared. Their surface tension profiles are shown in figure 2 and the characteristic values are summarized in Table 5.

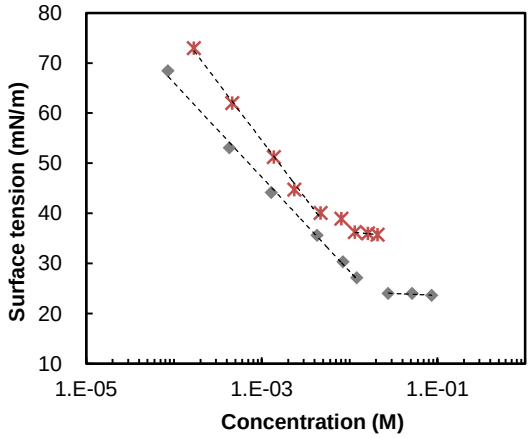


Figure 2. Surface tension vs. concentration of tetraol surfactants. (◆) tetraol **12** with cyclohexyl group, (✳) tetraol **13** with phenyl group.

Table 5. Critical Micelle Concentration (CMC) and surface tension (γ_{SAT}) values of tetraols.[a]

Entry	Tetraol		CMC[b] (mmol/L)	γ_{sat}[b] (mN/m)
1	cyclohexyl-C_2-tetraol	**12**	17	25.8
2	phenyl-C_2-tetraol	**13**	5.9	35.7
3	C_3-tetraol	**14**	100	26.5
4	C_5-tetraol	**15**	44	26.7
5	C_7-tetraol	**16**	7.9	26.1
6	C_9-tetraol	**17**	1.6	24.0
7	C_{11}-tetraol	**18**	0.26	23.7
8	iC_9-tetraol	**19**	3.6	23.3

9	Ester-C_7-tetraol	**20**	69	29.1
10	THF-tetraol	**21**	*nd*	*nd*

[a] Tetraols were used as mixtures of isomers as obtained through the aldolisation/reduction sequence. [b] Determined by tensiometry. nd: not determined.

The cyclohexane derivative **12** exhibits a higher CMC than its phenyl counterpart **13**, whereas, the surface tension of water could be decreased much lower (Table 5, entries 1-2). Hatzopoulos *et al.* reported this trend comparing very short phenyl and cyclohexyl n-alkanoates (n = 0 and 1).[45] For these molecules the hydrophobic contribution of the phenyl group is higher than the cyclohexyl compound, as observed for the compounds **12** and **13**. Tetraols **14-18** bearing linear alkyl chain with increasing length were next considered. All these linear surfactants show a decreasing trend of surface tension and a plateau value (γ_{sat}) around 25 mN/m (Figure 3) (Table 5, entries 3-7). The best results were obtained with tetraol **18** bearing a C11 alkyl chain, giving a CMC value of 0.26 mmol/L and a γ_{sat} of 23.7 mN/m (Table 5, entry 7).

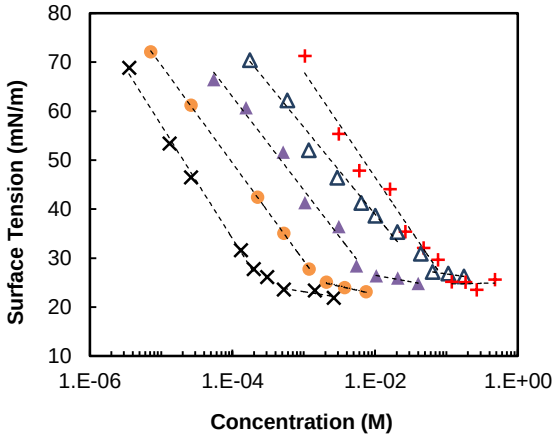


Figure 3. Surface tension vs. concentration of linear alkyl tetraol surfactants. (×) C_{11}-tetraol **18**, (●) C_9- tetraol **17**, (▲) C_7- tetraol **16**, (△) C_5- tetraol **15**, (+) C_3- tetraol **14**.

The CMC of tetraols **14-18** was plotted against the alkyl chain length (N) (Figure 4). The dotted line represents the linear behaviour described by the empirical equation proposed by Klevens:[46,47] log (CMC) = A – BN. In that case, coefficients A and B (calculated from figure 4) are 0.50 and 0.37, respectively. The shorter tetraol **14** does not follow the tendency observed for the longer tetraols **15-18**. Even if the tensiometric profile presents a clear brake, the structure of tetraol **14** matches better with an hydrotrope than with a surfactant.

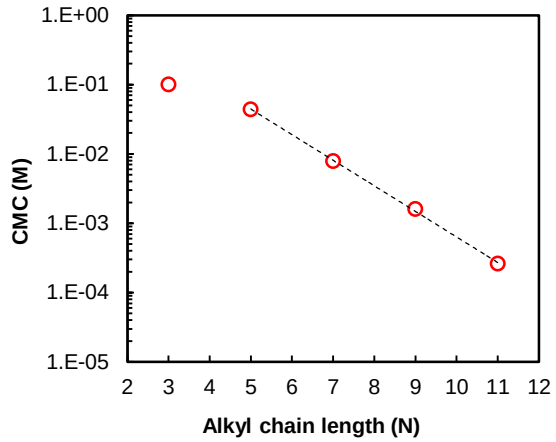


Figure 4. Critical Micelle Concentration of alkyl tetraols as function of the alkyl chain length (N).

Tetraol **19** bearing a branched alkyl chain exhibits a higher CMC than the linear compounds (Table 5, entry 8). Indeed, the surface tension profile of citronellal-derived tetraol **19** (Figure 5) is placed between the linear C_7–tetraol **16** and C_9–tetraol **17**. This phenomenon has already been reported and is explained by the steric hindrance of the branched structure that difficult the micelles formation. The CMC of linear C_8-tetraol was calculated using the Kleven's equation and was found to be approximately 3.4 mM, a very close value for iC_9-tetraol **19**. This result is fully in accordance with the rule proposed by Götte,[48] that each branched carbon appears to have "one-half" effect of a carbon in the alkyl linear chain.

The tensiometric profiles of tetraols **20** and **21** were compared with those of tetraol **17**, bearing a C_9 linear chain (Figure 5).

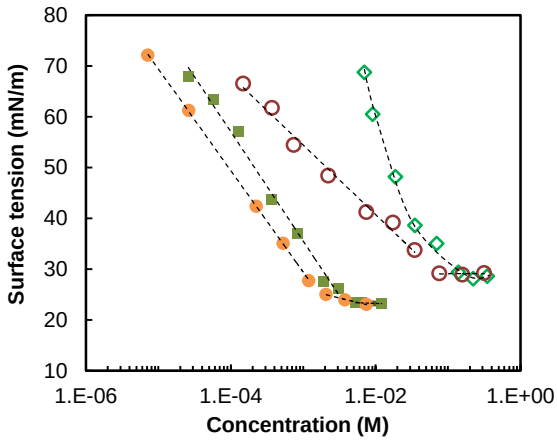


Figure 5. Surface tension vs. concentration of alkyl tetraol surfactants. (●) C_9-tetraol **17,** (■) iC_9-tetraol **19,** (○) ester-C_7-tetraol **20,** (◇) THF-tetraol **21.**

The presence of an ester group in **20** diminishes dramatically the lipophilic character at the end of the alkyl chain, thus increasing its CMC compared to the surfactant with the same alkyl chain, as described by Nardello *et al.*[49] for sodium monoalkyl dicarboxylates. For furfural-derived tetraol **21**, the decrease of the surface tension is weak and starts only a high concentration (10^{-2}M), a typical behaviour for hydrotropes.

The Krafft point was next determined for tetraols **14-18** (Table 6). This parameter is considered of a practical point of view as the temperature above which a 1%wt. aqueous solution of surfactant is soluble.[50] All these samples are mixtures of diastereomers and their behavior is complex,[51] *i.e* the Krafft point of the two isomers (α and β) of alkyl glucopyranosides presents even 20°C of difference.[52]

Table 6. Krafft temperature for different tetraols. [a]

Entry	Tetraol		Krafft Temperature (°C)
1	C_3-tetraol	**14**	< 5
2	C_5-tetraol	**15**	< 5
3	C_7-tetraol	**16**	60
4	C_9-tetraol	**17**	65
5	C_{11}-tetraol	**18**	83

[a] Determined by observation.

This study shows that only short chain tetraols **14** and **15** are fully soluble at room temperature (Table 6, entries 1-2). However, other tetraols **16-18** with an alkyl chain length >7 carbons have a limited solubility (Table 6, entries 3-5). The sudden increase in Krafft temperature when the hydrophobic chain passes from C_5 to C_7 is probably due to relative proportions of the diastereoisomers which are equal to 50:50 and 25:75, respectively. Results from figure 3 reflect the typical surface tension profiles; however, several of the most concentrated solutions were indeed stable dispersions. One of the diastereoisomers is more soluble than the other and facilitates its solubilisation. When increasing the total concentration, the mixture partially precipitates. To improve its use at room temperature, hydrotropes could be added into the formulation.

The hydrophilic lipophilic balance of some of these surfactants was assessed by using the so-called PIT-slope method.[53] This method allows classifying surfactants taking tetraethyleneglycol monodecyl ether ($C_{10}E_4$) as reference. The phase inversion temperature (PIT) of a reference 3%$C_{10}E_4$/n-octane/0.01M $NaCl_{(aq)}$ emulsion is followed by conductivity and the influence of adding an alkyl tetraol is quantified by the slope of the PIT values measured at several

concentrations of the second surfactant. Figure 6 shows the increase or decrease of the PIT with the molar fraction x_2 of the second surfactant in the mixture ($C_{10}E_4$ + alkyl tetraol). The slope of several n-alkyl tetraethoxylated surfactants are also shown for comparison. Longer alkyl tetraols show a linear behavior whereas the shortest compound (C_7-tetraol **16**) presents a less accurate linear match (R^2=0.97). The evolution of the PIT when adding the tetraols was quantified by the $dPIT/dx_2$ parameter that corresponds to the slope obtained from figure 6. The PIT-slope values are summarized in Table 7.

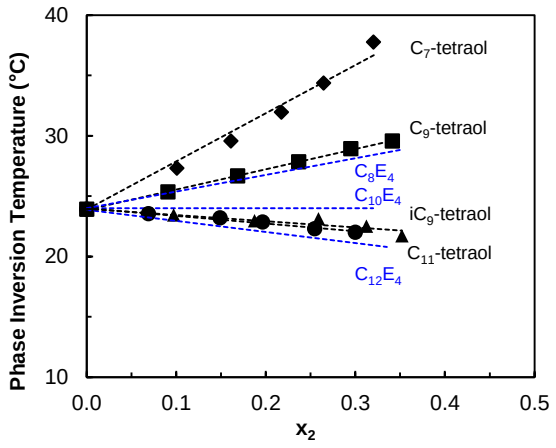


Figure 6. Phase inversion Temperature (PIT) vs. molar fraction x_2 of added surfactant for the 3% $C_{10}E_4$/n-octane/0.01M $NaCl_{(aq)}$ emulsion. S_2= (◆) C_7-tetraol, (■) C_9-tetraol, (▲) iC_9-tetraol and (●) C_{11}-tetraol. The dotted lines indicate the linear fitting. C_8E_4 [54] and $C_{12}E_4$ [8] are shown for comparative purposes.

Table 7. PIT-slope values expressed in °C ($dPIT/dx_2$) or °C/wt.% (dPIT/dC) for alkyl tetraols and C_iE_j.

Entry	Surfactant		$dPIT/dx_2$ (°C)	dPIT/dC (°C/wt.)
1	C_7-tetraol	**16**	43	14.8
2	C_9-tetraol	**17**	17	4.9
3	C_8E_4		13.8	2.2
4	$C_{10}E_4$	(reference)	0	0
5	iC_9-tetraol	**19**	-5.1	-1.5
6	C_{11}-tetraol	**18**	-6.3	-1.7
7	$C_{12}E_4$		-9.2	-1.8

From the PIT-slope values, C_{11}-tetraol **18** and iC_9-tetraol **19** are the only surfactants more lipophilic than the $C_{10}E_4$ and more hydrophilic than $C_{12}E_4$, however the C_9 and C_7 tetraols **16** and **17** are clearly more hydrophilic than $C_{10}E_4$ and C_8E_4, respectively. In order to evaluate if the synthesized surfactants are able to give microemulsions without co-surfactant or salt, an oil scan was carried out. The alkanes are characterized by the number of carbons in the molecule (*i.e.* 8 for octane). For other oils such as esters, ethers or chloro-alkanes, the oil is characterized by an equivalent alkane carbon number EACN whose experimental determination is described elsewhere.[55,56] The oil that allows obtaining a three phase behavior (Winsor III)[57] for a non-ionic Surfactant/Oil/Water system at 25°C provides the so-called Preferred Alkane Carbon Number (PACN)[58] of the surfactant. This parameter is a scientifically founded version of the HLB empirical scale. Hydrophilic surfactants have low PACN, *i.e.* they need somewhat polar oils such as chloro or di-chloro alkanes to provide three phase behaviour.

Hydrophobic surfactants have higher PACN and they could need oils as hexadecane to obtain a WIII behavior. Figure 6 showed that C_9-tetraol has a hydrophilic-lipophilic balance close to the C_8E_4 behavior and their PACN must be equivalent. However, the high Krafft temperature of alkyl-tetraols does not allow the formulation of Alkyl Tetraol/Oils/Water microemulsion systems at 25°C. The oil scan for the C_9-tetraol was therefore carried out at 75°C (Figure 7). The lighter 1-chlorohexane is able to promote a Winsor II behavior in which the surfactant is preferentially in the oily phase in equilibrium with an excess water phase (Figure 7, left). For 1-chlorooctane and 1-chlorodecane, a third microemulsion phase is obtained in equilibrium with both, aqueous and oil excess phases (Figure 7, middle). Heavy oils decrease the affinity of the surfactant for the oily phase and promote Winsor I system (Figure 7, right).

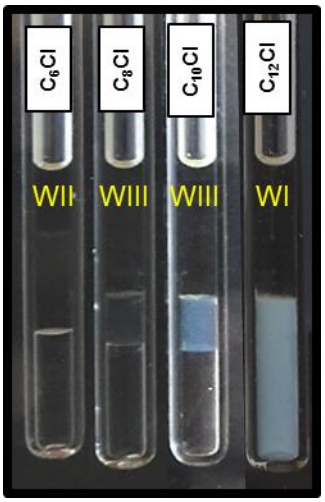


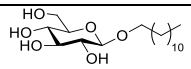
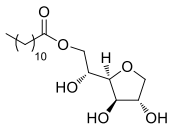
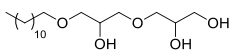
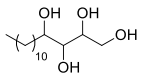
Figure 7. Oil scan performed for 3% C_9-tetraol/1-Chloro-alkane/Water systems after 2 days equilibration period at 75°C.

When the temperature is increased up to 85°C the phase behavior changes since 1-chlorododecane provides a Winsor III system. The alkyl tetraols hydrophilicity decreases when the temperature increases. Such as behavior was described by Stubenrauch *et al.*[59] for alkyl

glucosides. As these surfactants, C_9-tetraol **17** allows formulate microemulsions at higher temperatures without adding cosurfactants for polar oils. However, to be used at room temperature or with linear alkanes, cosurfactants are required.

Finally, the CMC and the PIT-slope for C_{11}-tetraol **18** was compared with of other polyol surfactants (Table 8).

Table 8. Comparison with other available polyol surfactants.

Entry	Surfactant	CMC[a] (mmol/L)	γ_{sat}[a] (mN/m)	dPIT/dC[b] (°C/wt.%)
1	 C_{12}-glucoside (C_{12}Glu)	0.19[60]	36[60]	5.9[53]
2	 C_{12}-sorbitan ester (Span 20)	0.041[10]	31[10]	-12.1[61]
3	 C_{12}-diglycerol ($C_{12}Gly_2$)	0.031[62]	27[62]	1[53]
4	 C_{11}-tetraol	0.26	23.7	-1.7

[a] Determined by tensiometry. [b] Determined by the PIT-slope method.

Even with one carbon less than other surfactants, **18** is as efficient as the corresponding dodecylglucoside in terms of its CMC, but 5-8 times less efficient than dodecanoylsorbitan (SPAN 20) or 1-*O*-dodecyldiglycerol ($C_{12}Gly_2$). Interestingly, the tetraol surfactant has the highest effectiveness since it decreases the surface tension as low as 23.7 mN/m. In 1,2,3,4-tetraols, the polar head bearing 4 hydroxyl groups in the first 4 carbons is shorter than the other ones and there is no heteroatom between the alkyl chain and the polar head. This difference could be at the origin of its enhanced effectiveness.[63] From the PIT-slope values, the hydrophilicity ranking is C12Glu > C12Gly2 > C11-tetraol > Span 20. These results are fully consistent with the structure of these surfactants.

CONCLUSIONS

In conclusion, we have developed a method for the aldolisation of unprotected 1,3-dihydroxyacetone (DHA) with a range of (bio-based) non-aromatic aldehydes. The reaction is promoted by trimethylamine under mild conditions (20°C) in a mixture of water/EtOH to give α-hydroxyketones with 29-70% isolated yields. The α-hydroxyketones were reduced under hydrogen to give the corresponding tetraols with 79-97% isolated yields. The amphiphilic properties of these new C-C bond linked tetraol surfactants have been studied by the measurement of their CMC and Krafft point and their hydrophilicy has been evaluated using the PIT-slope method. These studies have shown that this new type of surfactants exhibits a high effectiveness to reduce the surface tension of water. Finally, C_9-tetraol is able to produce a microemulsion with three phase behaviour at high temperatures.

EXPERIMENTAL SECTION

General information

All reagents were used as received from the chemical company. 1,3-Dihydroxyacetone (DHA, dimer, 97 % purity) was purchased from Alfa-Aesar. Butyaldehye, hexanal, octanal, decanal, dodecanal and hydrocinamaldehyde were supplied by Sigma-Aldrich or Alfa-Aesar, and were purified by distillation before use (except dodecanal). Amberlyst A26 (OH), ion exchange resin, A17361 was bought from Alfa-Aesar. Pd (5 % on activated wood carbon, reduced, dry, Escat^{TM} 1431), ruthenium (5 % on carbon), ruthenium (5 % on alumina) were purchased from Strem Chemicals.

General procedure for the aldolisation of DHA.

In a sealed tube, 1,3-dihydroxyacetone (DHA) **1** (1.0 g, 11.1 mmol, 5 equiv.) was dissolved in a mixture of EtOH (5.5 mL) and distilled water (5.5 mL). The aldehyde (2.2 mmol, 1 equiv.) was added, followed by the homogeneous catalyst (1.1 mmol, 0.5 equiv.) or the heterogeneous catalyst Amberlyst A26(OH) (100 wt %/DHA). The mixture was stirred (800 rpm) at room temperature (20 °C) for 4 hours. After reaction, the solvent was removed in vacuum, and the residue was purified by column chromatography (CH_2Cl_2/MeOH 40:1 → 25:1) to give α-hydroxyketones **3-11**. All details of the chemical characterizations (^{1}H NMR, ^{13}C NMR, MS) are given in the ESI.

General procedure for the hydrogenation of α-hydroxyketones to tetraols.

In a 35-mL stainless steel autoclave, the α-hydroxyketone (5 mmol, 1 equiv.) was dissolved in EtOH (25 mL). Ru/Al_2O_3 (5wt% Ru, 0.25 mmol, 5 mol% in Ru) was added. The autoclave was

flushed with hydrogen (10 bar) for 3 times. The solution was stirred (800 rpm) under 40 bar hydrogen at 100°C for 16 hours. After cooling to room temperature, the reaction mixture was filtered (Milllipore Durapore filter 0.01 μm) and washed with EtOH. The filtrate was concentrated under vacuum to give tetraol products **12-21**. All details of the chemical characterizations (^{1}H NMR, ^{13}C NMR, MS) are given in the ESI.

General procedure for measuring the CMC and the Krafft Point

The surface tensions were measured at room temperature with a K100MK2 Krüss tensiometer using a platinum rod as probe. Measurements were made on 2 mL samples. The surface tension of pure water was first measured to calibrate and then different concentrations of the same sample were measured. When the surface tension was stable (standard deviation of the 5 final measurements lower than 0.15 mN m−1), record the value as the first result. The measurement was repeated twice or 3 times to get an average value for each sample.

The Krafft point was determined by increasing the temperature of a 1% wt. surfactant solution. It corresponds to the temperature at which the precipitated surfactant became soluble.

PIT-slope method

Before the experiment, 10 mL of the $C_{10}E_4$/n-Octane/Water system was prepared in a 20 mL vial (d=2.5 cm, h=5.5 cm) by pouring a mass m_w (4.25 g) of NaCl 10^{-2}M aqueous brine, a mass m_o (4.25 g) of *n*-octane, and then a mass of surfactant $S_1 = C_{10}E_4$ (0.263 g). This system was hand-shaken during a few seconds and left to pre-equilibrate 24 h at room temperature. A first heating-cooling cycle was performed and then the second surfactant S_2 was added (mass m_{S2}). The amount of $C_{10}E_4$ was then adjusted to m_{S1} so that the proportion of S_1 surfactant remains constant

at 3 wt. % of the whole system in all experiments. Equation 1 defines S_2 surfactant molar fraction in the surfactant mixture.

$$x_2 = \frac{m_{S2}/MW_2}{m_{S1}/MW_1 + m_{S2}/MW_2} \quad (1)$$

The water weight fraction f_w defined by equation 2 is 0.5 in all systems.

$$f_w = \frac{m_w}{m_w + m_o} \quad (2)$$

During the whole experiment, the system was kept under continuous stirring using a cross-shaped magnetic stirrer (1.8 cm diameter) at 500 rpm. The sample was then subjected to two heating-cooling cycles at a rate of 1°C/min. Temperature-controlled water from a HUBER Ministat 125 bath circulated through the vessel in which the vial was introduced. The conductivity and temperature were simultaneously measured by a Radiometer Analytical CDM 210 conductimeter fitted with a CDC741T platinized platinum probe. The software used was custom written in a Labview 7.1 National Instruments platform. Temperature and conductivity profiles for two heating-cooling cycles were obtained as a function of time. The parallel tangent method was used to determine the PIT. The reported value is the average of the four determined temperatures.

Oil scan

1g-samples were prepared in 2-mL vials by weighting successively water (W), oil (O) and surfactant (S). In all samples, the water/oil ratio equals 1, *i.e.* the water weight fraction f_w equals 0.5. The surfactant/oil/water systems are then gently mixed to favour the contact of phases while avoiding emulsification. The vials are then placed in a thermostatic bath HUBER Ministat 125 at

75°C ± 0.1°C until phase separation and equilibrium are reached. The determination of the phase behaviour is determined by visual inspection in order to classify the systems according to Winsor nomenclature.

ASSOCIATED CONTENT

Supporting Information. The supporting information contains the general procedures, the characterization data of α-hydroxyketones and tetraols, as well as ^{1}H and ^{13}C NMR spectra of all compounds.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DHA, 1,3-dihydroxyacetone; APG, alkyl (poly)glycoside; FSA, D-fructose-6-phosphate aldolase; HCA, hydrocinnamaldehyde; 4-DMAP, 4-dimethylaminopyridine, DABCO, 1,4-diazabicyclo[2.2.2]octane; CMC, Critical Micelle Concentration; PIT, phase inversion temperature; EACN, equivalent alkane carbon number; PACN, Preferred Alkane Carbon Number.

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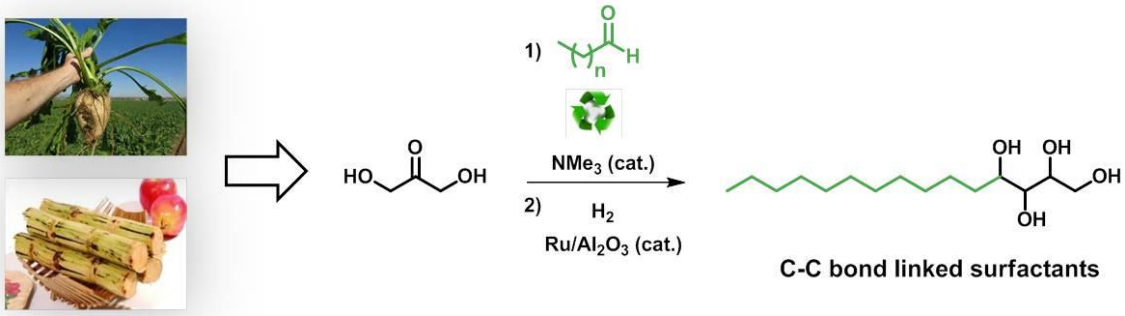
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C-C bond linked 1,2,3,4-tetraol surfactants were prepared from unprotected 1,3-dihydroxyacetone (DHA) through aldolisation/reduction.


1)
2)
NMe3 (cat.)
H2
Ru/Al2O3 (cat.)
HO
OH
OH
OH
OH
C-C bond linked surfactants