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Aldolisation of unprotected ketoses to surfactants

Biwen Zhu

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Biwen ZHU

Préparation de tensioactifs par aldolisation de cétones non protégés

Devant le jury composé de :

BENVEGNO, Thierry
LEMAIRE, Marielle
CHEN, Guorong
GUEYRARD, David
LEMAIRE, Marc
DUGUET, Nicolas
POPOWYCZ, Florence

Professeur, E. N. S. C. de Rennes
Professeur, Université Clermont Auvergne
Professeur, ECUST
Maitre de Conférences, UCBL
Professeur Émérite, UCBL
Maitre de Conférences, UCBL
Professeur, INSA Lyon

Rapporteur
Rapporteur
Examinateur
Examinateur
Directeur de thèse
Co-directeur de thèse
Invitée

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Aldolisation of unprotected ketoses to surfactants

The research work presented in this manuscript fits in the frame of Green Chemistry and sustainable development and aims at using renewable resources to produce specialty chemicals such as surfactants. Surfactants are amphiphilic molecules that are widely encountered in cleaning and in detergency. For biodegradability reasons, most surfactants are esters or glycosides. As a result, these compounds could be subjected to hydrolysis under acid or basic conditions, thus limiting their range of applications.

In this context, we have studied the aldolisation of unprotected ketoses such as 1,3-dihydroxyacetone and D-fructose using a range of fatty aldehydes. The reaction occurs in a mixture of green solvents (EtOH/water) under mild conditions (20-60°C) under microwave irradiation to give aldol intermediates. These intermediates were reduced to the corresponding alkyl tetraols and heptaols to give C-C bond linked surfactants. The physicochemical properties (CMC, Kraftt point, Phase Inversion Temperature) of tetraols were also determined and the results have shown that some of these species are as efficient as commercially available surfactants. Overall, these new bio-based C-C bond linked surfactants are robust species that could be used for a wide range of applications.

Key words: aldolisation, C-C bond formation, ketoses, surfactants.

Préparation de tensioactif par aldolisation de cétooses non protégés

Les travaux de recherche décrits dans ce manuscrit s'inscrivent dans le cadre général de la chimie verte et du développement durable et visent l'utilisation de ressources renouvelables pour préparer des produits de spécialité comme les tensioactifs. Les tensioactifs sont des molécules amphiphiles largement rencontrées dans les domaines du nettoyage et de la détergence. Pour des raisons de biodégradabilité, la plupart des tensioactifs sont des esters ou des glycosides. Par conséquent, ces composés peuvent être hydrolysés dans des conditions acides ou basiques, limitant ainsi leur champ d'applications.

Dans ce contexte, nous avons étudié l'aldolisation de cétooses non protégés tels que la 1,3-dihydroxyacétone et le D-fructose en utilisant une gamme d'aldéhydes gras. La réaction est effectuée dans un mélange de solvants verts (EtOH / eau) dans des conditions douces (20-60 ° C) sous irradiation micro-ondes pour donner des intermédiaires de type aldols. Ces intermédiaires ont été réduits en alkyl tétraols et heptaols correspondants pour donner des tensioactifs à lien C-C. Les propriétés physico-chimiques (CMC, point de Kraftt, température d'inversion de phase) des tétraols ont également été déterminées et les résultats ont montré que certaines de ces espèces sont aussi efficaces que des tensioactifs commerciaux. Dans l'ensemble, ces nouveaux tensioactifs biosourcés à lien C-C sont des espèces robustes qui peuvent être utilisées pour un large éventail d'applications.

Mots clés: aldolisation, formation de liaisons C-C, cétooses, tensioactifs.

Institute de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS)

Laboratoire de Catalyse, Synthèse et Environnement (CASYEN)

UMR 5246 CNRS – Université Claude Bernard Lyon 1

1 Rue Victor Grignard – 69622 Villeurbanne cedex France

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Abbreviations

SDS	Sodium dodecyl sulfate	ABS	Alkylbenzene sulfonate
LAS	Alkylbenzene sulfonate	MAP	Monoammonium phosphate
DAP	Diammonium phosphate	DAC	Dodecyl ammonium chloride
CAPB	Cocamidopropyl betaine	EO	Ethylene oxide
PEF	Poly ethoxylated fatty ester	PEG	Poly ethoxylate glycol
SFAE	Sorbitol fatty acid ester	APG	Alkyl polyglucoside
DP	Degree of polymerization	SE	Sucrose ester
DMF	Dimethylformamide	DMSO	Dimethyl sulfoxide
HLB	Hydrophilic-hydrophobic balance	APE	Alkylphenol ethoxylate
AE	Alcohol ethoxylate	OPE	Octylphenol ethoxylate
NPE	Nonylphenol ethoxylate	ECH	epichlorohydrine
TMDS	1,1,3,3-tetramethyldisiloxane	PMB	<i>p</i> -methoxybenzyl chloride
CAN	Ceric ammonium nitrate	CPME	Cyclopentyl methyl ether
DHA	1,3-dihydroxyacetone	DHAP	Dihydroxyacetone phosphate
PP _i	Pyrophosphate	DHAAs	Dihydroxyacetone arsenate
FSA	D-fructose-6-phosphate aldolase	HCA	hydrocinnamaldehyde
DIPEA	<i>N,N</i> -diisopropylethylamine	CMC	Critical micelle concentration
PIT	Phase transfer temperature	HFS	High fructose syrup
5-HMF	5-hydroxymethylfurfural	PTC	Phase transfer catalysis
PTA	Phase transfer agent	TBPB	Tetrabutylphosphonium bromide
TBAI	Tetrabutylammonium iodide	TBAB	Tetrabutylammonium bromide
TBACl	Tetrabutylammonium chloride	HMDS	Hexamethyldisiloxane

TMSCI	Trimethylsilyl chloride	CTAB	Cetyltrimethylammonium bromide
FruA	D-fructose-1,6-bisphosphate aldolase		
RhaD	Rhamnulose-1-phosphate aldolase		
HWE	Horner-Wadsworth-Emmons reaction		
PTAB	Phenyl trimethylammonium bromide		
HMDS	1,1,1,3,3,3-Hexamethyldisilazane		
TMSCI	Trimethylsilyl chloride		

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General Introduction

Surfactants are fine chemicals with a wide range of useful properties such as moisturizing, emulsifying, dispersing, solublizing, foaming, infiltrating, lubricating and so on. They have found applications in almost every aspect in our daily life. In 2016, the annual worldwide production of surfactant has achieved 13 million tons with a total value of 31 billion USD, and the market is keeping on increasing at a rate around 3.1 % per year.¹ The surfactant market can be divided based on product types, major applications, and important regions. Depending on different classifications, ionic surfactants are more frequently consumed than nonionic surfactants especially the anionic surfactants, which take up to 49% of the global market share in 2016. The most frequently used applications of surfactants are detergents and cleaners for households, in 2016 around 55% of the overall market was registered in this area. Besides the household detergents and cleaners, surfactants are also used in numerous industrial applications listed below in Table 1. The Asia-Pacific region is by far the largest consumer of surfactants with a world market share of 38%.

Table 1. Surfactant applications and typical properties involved.

Applications	Properties
➤ Detergents and cleaners	Cleaning, wetting, foaming, emulsification, antistatic
➤ Personal care products	Cleaning, emulsification, lubricity, antistatic
➤ Food industry	Emulsification, cleaning, wetting, foaming
➤ Agrochemicals	Emulsification, wetting, foaming
➤ Pharmaceuticals	Emulsification, dispersing
➤ Textile industry	Wetting, dye leveling, lubricity, antistatic
➤ Oil field	Emulsifying/demulsifying, cleaning
➤ Paints and plastics	Emulsification, stabilizers, dispersing, antistatic

¹ Market Study: Surfactants (3rd edition), Ceresana, **2018**.

Market segment

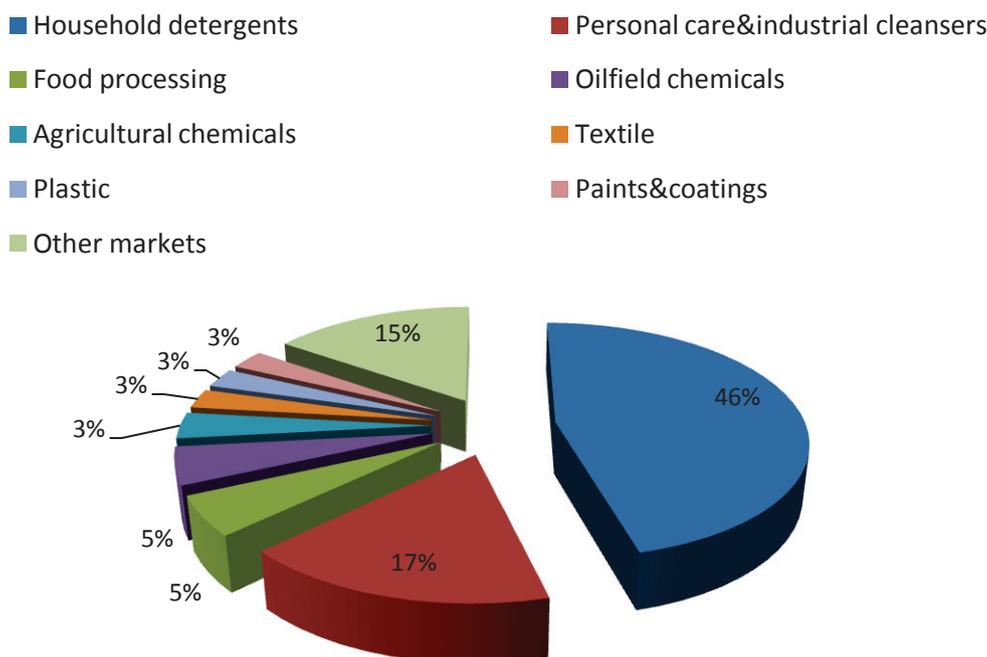


Figure 1. US surfactants market demand in 2007.²

With a large surfactant market demand and many different application requirements, numerous types of surfactants have been synthesized such as ionic/nonionic surfactants depending on whether the polar head is charged or not. Ionic surfactants can be divided into cationic, anionic and amphoteric surfactants depending on which kind of charge it carries. Currently, high-volume surfactants are commonly made from petroleum resources such as benzene, alpha-olefins and ethylene.³ Due to the realization that fossil fuel reserves are finite as well as the global warming caused by carbon dioxide emissions associated with the production and use of surfactants, the petroleum-based surfactants are gradually replaced. Efforts to reduce reliance on petroleum resources were also made due to the increasing public concerns about the green chemistry concept to utilize renewable feedstock. Patel *et al.* further estimated that if petrochemical surfactants were totally replaced by renewable-based surfactants in the EU, total CO₂ emissions could be reduced by as much as 37% due to the surfactant production.⁴

Most of these renewable-based surfactants are usually non-toxic and biodegradable such as glucosides or esters. However, they are not stable enough to be used in some special applications.

² R. Dwight, S. Wildes, <Surfactants-A Market Opportunity Study Update>, *OMNI TECH INTERNATIONAL, LTD.*, **2008**.

³ K. E. Joseph, C. Krumm, *INFORM*, **2017**, 28, 16-19.

⁴ V. Dornburg, I. Lewandowski, M. Patel, *J. Ind. Ecol.*, **2003**, 7, 93-116.

Particularly for extraction purposes, for example, the eco-extraction of natural products and for applications requiring medium-to-long-term stability upon storage such as in cosmetics. Finally, there is still a demand for robust surfactants which can resist low/high pH value.

Currently, a growing emphasis is placed on products made from renewable resources. More particularly, the nonionic surfactants have gained interest and are progressively occupying more and more market share with the strongest growth of revenues over the ionic surfactants. While the replacement of petrochemical surfactants by nonionic renewable-based surfactants may be desirable from a CO₂ standpoint, considerations such as cost and performance will ultimately determine the success of a surfactant. The nonionic surfactants offer many advantages over the ionic ones such as being less skin irritant, more biodegradable and stable, formulating flexibility and wider compatibility.⁵ From a physical chemistry point of view, the non-ionic surfactants have a lower Critical Micelle Concentration and are less sensitive to hard water.

In order to increase the stability of surfactants, many efforts have been devoted in our group to synthesize ether analogues instead of esters such as glycerol ethers, sorbitan ethers and methyl glycopyranoside alkyl ethers. Another option to increase the stability is to link the polar head and the non-polar part with a more robust C-C bond (Figure 2). This strategy is underdeveloped probably due to the difficulty to synthesize such species in a sustainable way.

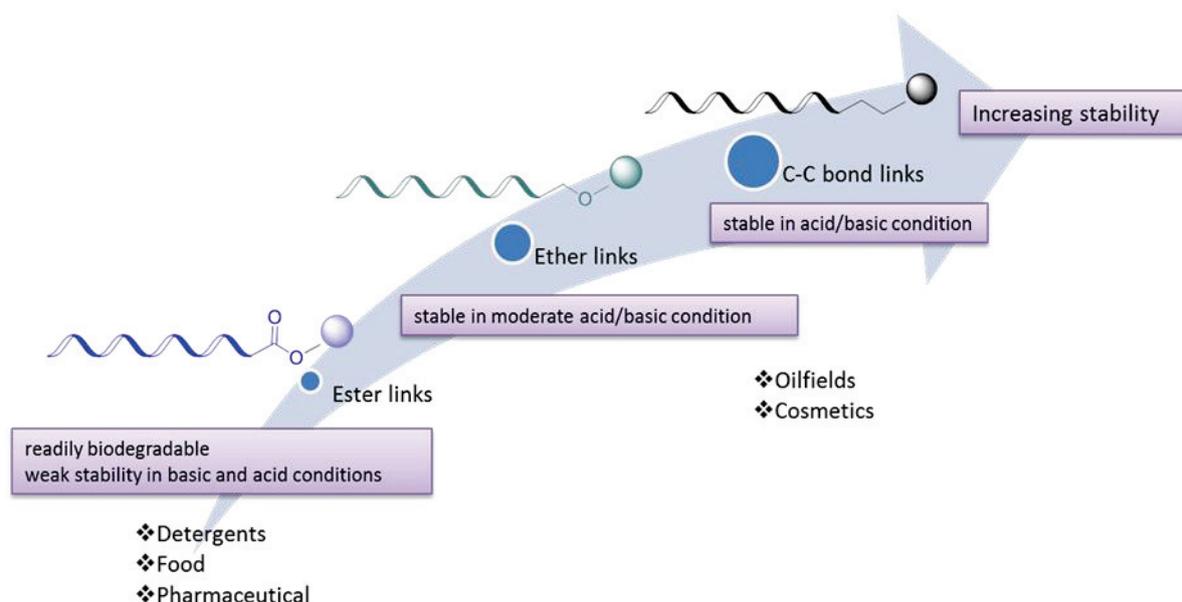


Figure 2. Increasing stability of different linkages.

⁵ C. Gozlan, E. Deruer, M.-C. Duclos, V. Molinier, J.-M. Aubry, A. Redl, N. Duguet, M. Lemaire, *Green Chem.*, **2016**, *18*, 1994-2004.

In this context, the aim of this Ph.D. thesis is to develop a robust surfactant derived from renewable resources. To reach this goal, the project focuses on how to construct a C-C bond linkage between the polar head and non-polar tail, more specifically, a two-step process of aldolisation and hydrogenation sequence without protection/deprotection steps has been developed to obtain a series of surfactants based on a stable C-C bond linkage.

The manuscript is divided into 5 parts. In the first part, a bibliographic introduction is given, illustrating the basic aspects of amphiphilicity, followed by the description of different carbohydrate heads/different linkage type of surfactants and their common synthetic routes.

Then, in the “result and discussion” part:

In Chapter 1, the synthetic route of aldolisation/hydrogenation sequence of unprotected 1,3-dihydroxyacetone has been described and the results of physico-chemical tests of these obtained potential tetraol surfactants were given.

In Chapter 2, the more abundant and cheaper starting material fructose has been selected as substrate, the optimization of its aldolisation/hydrogenation sequence has been described.

In Chapter 3, other substrates were used to explore new reactivities based on our previous findings.

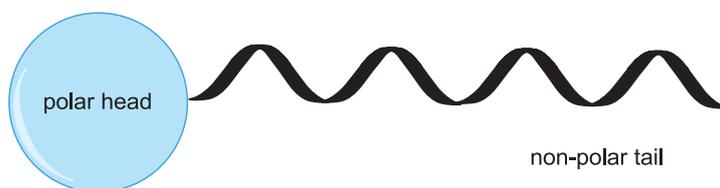
Then, a general conclusion of this thesis was summarized.

In the final part of this thesis, the experimental part, the experimental procedures, including spectroscopic data are documented.

Chapter 1 Literature review

1 Introduction

Surfactant is a compound typically consisting of two parts: a hydrophilic polar “head” and a hydrophobic non-polar “tail”. The hydrophilic head has more affinity towards polar media like water and the hydrophobic tail has more affinity towards the non-polar media like organic solvents. With only a low concentration of these surfactant molecules dissolved in water, they are rearranged in certain direction upon the surface of solution and generate a decreased surface tension on the interface.⁶ Scheme 1 is an illustration of these amphiphilic molecules.



Scheme 1. Illustration of amphiphilic surfactants.

Surfactants were used as the most important ingredients in detergents in their early period. Surfactants have taken up to 15-40% in detergent formulation due to their wetting and cleaning property. At first, soap was involved in people’s daily life around 2700 BC. The earliest soap was made by using caustic from wood ashes to hydrolyze the esters from fats.⁷ The first synthetic surfactant for general application was developed during World War I in Germany. Short-chain alkyl naphthalene sulfonates were prepared by sulfonation of alkyl-naphthalene and were used as detergents.⁸ Since then, huge progress in the surfactant area has been made since a variety of new surfactants has emerged during last several decades and their applications become diverse.

Since the chemical synthetic method has been used to design and manufacture surfactants, the detergent industry has witnessed a fast development. In 1947, the low-cost alkyl benzene sulfates (ABS) were first introduced and widely used. But later they were found to be poorly biodegradable and have caused environment problems. So a replacement for ABS was needed and a

⁶ Laurier L. Schramm, *Surfactants: Fundamentals and applications in the petroleum industry*, Cambridge University Press, 2009.

⁷ J. J. Scheibel, *J. Surfactants Deterg.*, 2004, 7, 319-328.

⁸ Drew Myers, *Surfactant science and technology*, 3rd ed., Wiley-Interscience, 2006.

more biodegradable linear alkyl benzene sulfate (LAS) was then developed. Until now, the detergent industry is still playing the most important role in surfactant applications.

Not only in detergents, nowadays non-ionic surfactants are more frequently used in textiles especially for the dyeing step,⁹ as non-toxic and safe ingredients in cosmetics¹⁰ and pharmaceuticals,¹¹ personal care products, food industry¹² and also in mining and flotation industry.¹³

1.1 Surfactant classifications.

According to different criteria, surfactants can be classified either in term of their properties or structures while the most important and commonly accepted way is to classify them by the nature of their hydrophilic heads. Generally speaking, the non-polar tail of most surfactants is quite similar, consisting of linear, branched or aromatic hydrocarbon chains. As shown in the Figure 3, non-ionic surfactant has no charge on its polar head. Cationic and anionic surfactants possess net positive or negative charge, respectively. When the polar head is charged with both two opposite charges, it is called zwitterionic or amphoteric surfactant.¹⁴ For each classification, it is possible to sub-classify according to the functional group of the hydrophilic head.

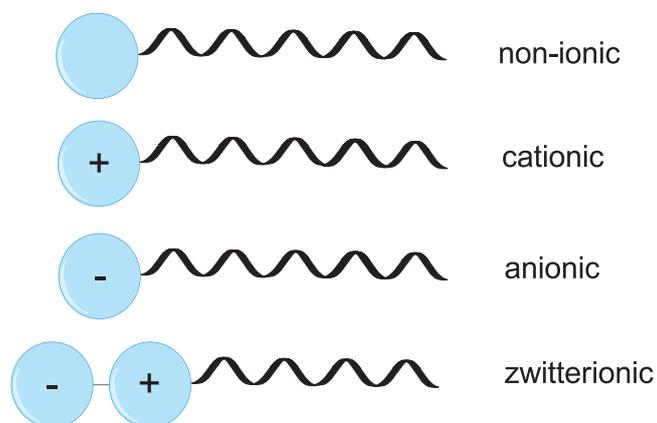


Figure 3. Classification of surfactants according to their polar heads.

⁹ a) X. F. Liu, *China Surfactant Deterg. Cosmet.*, **2006**, *36*, 99-102; b) A. Ozcan, C. Omeroglu, Y. Erdogan, A. S. Ozcan, *J. Hazard. Mater.*, **2007**, *140*, 173-179; c) A. S. Ozcan, B. Erdem, A. Ozcan, *J. Colloid Interf. Sci.*, **2004**, *280*, 44-54.

¹⁰ L. D. Rhein, A. O'Lenick, M. Schlossmann, P. Somasundaran, *Surfactants in Personal Care Products and Decorative Cosmetics*, 3rd ed., **2007**.

¹¹ J. Falbe, *Surfactants in Consumer Products: Theory, Technology and Application*, **2012**.

¹² a) G. Charlabous, G. Doxastakis, *Food emulsifiers: Chemistry, Technology, Functional Properties and Applications*, Amsterdam, Holland: Elsevier, **1989**; b) D. Guzey, D. J. McClements, *Adv. Colloid Interface Sci.*, **2006**, *128-130*, 227-248.

¹³ H. Q. Huang, *Modern Chemical Industry*, **2001**, *5*, 6-8.

¹⁴ G. Kume, M. Gallotti, G. Nunes, *J. Surfact Deterg.*, **2008**, *11*, 1-11.

1.1.1 Anionic surfactants.

Anionic surfactants are the earliest developed type in the field of detergency and compared to other types they have the largest production in market with mature industrialization. They are cheaper than non-ionic surfactants. Examples of anionic surfactant groups include four main types: sulfate esters, sulfonic acid salts, carboxylic acid salts, and phosphoric acid esters (Figure 4).¹⁵

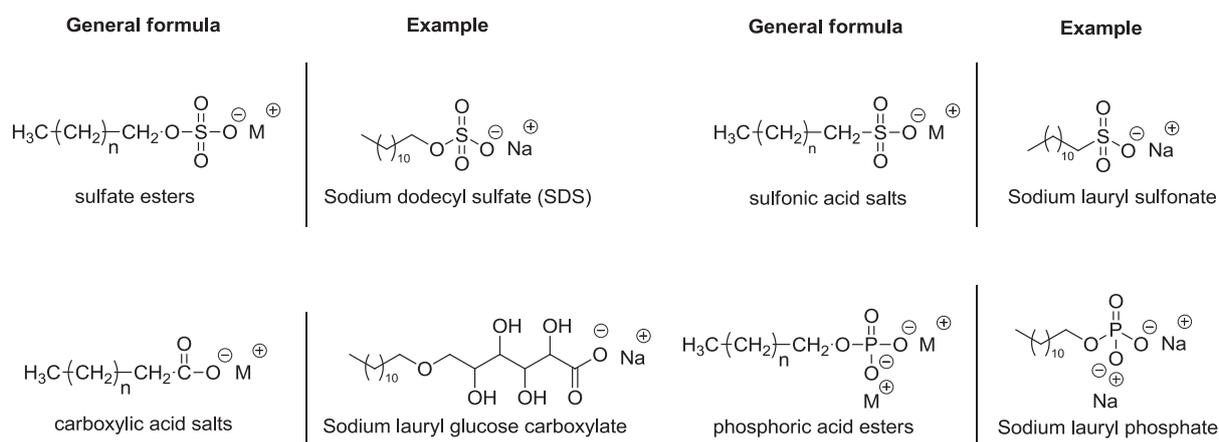


Figure 4. Four main types of anionic surfactants. (M could be alkali metal or ammonium ion.)

Sulfate ester (formula $\text{RO-SO}_3^- \text{M}^+$) surfactants are usually easy to synthesize with relatively low cost. The most used representative of this type is sodium dodecyl sulfate (SDS) with 12-carbon tail attached to a sulfate group, as a very important component in many domestic cleaning and hygiene products. Sulfonic acid salts (formula $\text{R-SO}_3^- \text{M}^+$) surfactants have good pH stability, good wetting properties and excellent water solubility with usually 8-20 carbons in its hydrocarbon chain, represented by alkylbenzene sulfonates (ABS) and linear alkylbenzene sulfonate (LAS). Carboxylic acid salts (formula $\text{R-COO}^- \text{M}^+$) are classical soaps which are less sensible to hard water and low pH. Phosphoric acid esters (formula $\text{RO-PO}_3^- \text{M}_2^+$) always have good compatibility with skin and inherent low-irritation characteristics, they find use in personal care applications and are often sold in mixture form of monoester (MAP) and diester (DAP)¹⁶.

¹⁵ J. Beringer, J. Kurz, *Handbook of Medical Textiles*, **2011**, 360-386.

¹⁶ D. J. Tracy, R. L. Reiersen, *J. Surfactants Deterg.*, **2002**, 5, 169-172.

1.1.2 Cationic surfactants.

Cationic surfactants can be sub-classified into two groups: neutral and acidic. They differ from each other on their molecular structures and physical properties. Neutral cationic surfactants can be further divided into two categories according to different nitrogen-containing group.¹⁷ One is quaternary ammonium-based surfactant, and the other one is heterocyclic amine-based surfactants (Figure 5). Cetyltrimethylammonium bromide (CTAB) is the most commonly used quaternary ammonium-based surfactant; it has no acidic proton on its cationic nitrogen and also no bonding electron pairs, so this kind of molecules is “neutral” in water. The acidic cationic surfactants bear at least one proton on the positive nitrogen, for example, dodecyl ammonium chloride (DAC). This could make the system extremely complex under different pH values. Compared to the anionic surfactant, they are more expensive and less efficient in detergency. However, they are often used for their antistatic and antimicrobial properties.¹⁸

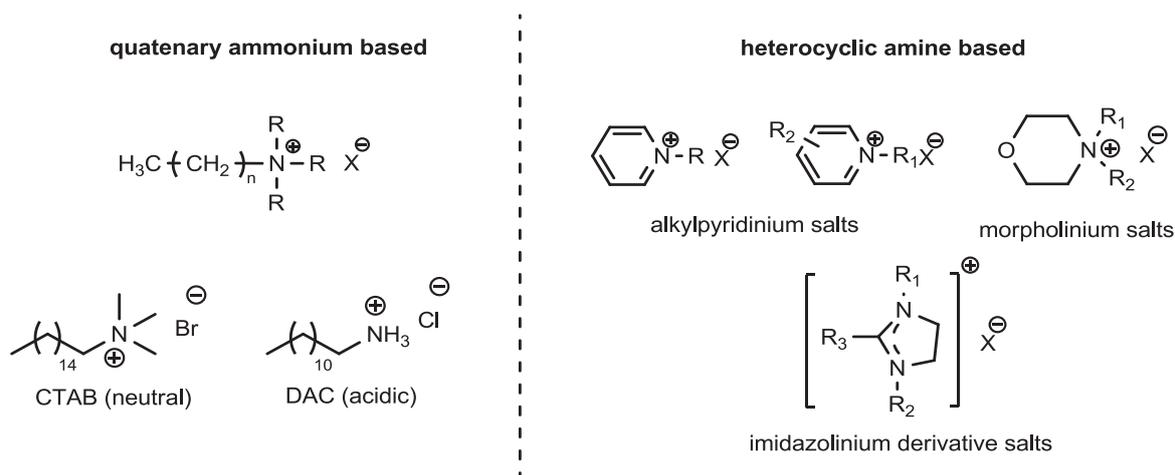


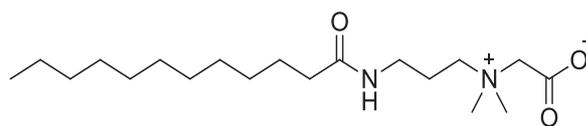
Figure 5. Classification and representatives of cationic surfactants.

1.1.3 Zwitterionic surfactants.

Zwitterionic surfactants (amphoteric surfactants) are those that neutrally have both positive and negative charges on the polar head. At neutral pH, these amphiphilic molecules are overall neutrally charged. PH changes in solution may somehow affect the zwitterionic molecule to become completely cationic or anionic in acidic or basic conditions. The positive charge is typically a quaternary ammonium or phosphonium ion, while the negative charge can be a sulfate, carboxylate or sulfonate ion.

¹⁷ D. Rubingh, *Cationic Surfactants: Physical Chemistry*, **1990**.

¹⁸ A.M. Carmona-Ribeiro, *Anti-Infect. Agents Med. Chem.*, **2006**, 5, 33-54.



cocamidopropyl betaine (CAPB)

Figure 6. Examples of zwitterionic surfactants.

One of the most commonly used zwitterionic surfactant is cocamidopropyl betaine (CAPB), derived from coconut oil and dimethylaminopropylamine,¹⁹ quite often used in personal care products for its gentle, effective cleaning properties (Figure 6). The overall neutrally charged molecule can diminish the ionic interactions with body and can be easily removed with minimum skin and eye irritation compared to other types. When used in association with anionic surfactant, they are able to enhance the foaming performance of the product.

1.1.4 Non-ionic surfactants.

Although today's surfactant market is still mostly consisting of synthetic surfactants prepared from petroleum resources, more and more energy has been put into synthesizing biomass-based surfactants. Not only because the petroleum resources is non renewable and getting more and more expensive, but also due to the toxicity of these petroleum-based surfactants deposited in the environment with accumulated damage to water and soil.²⁰ Efforts to reduce our reliance on petroleum resources were made also due to the increasing public concerns about using renewables. Solution for this problem might be to search for synthetic blocks for surfactants which are more nature-based (biomass) and with better degradability in nature.

Over the last decades in the surfactant industry, increasing attention has been turned into looking for natural raw materials to replace petrochemical based products, both for hydrophilic and hydrophobic materials.²¹⁻²² Many advantages with regard to performance, health of consumers, and environmental compatibility are obtained with these bio-based products compared to the others. Carbohydrate-based surfactants are based on the most accessible renewable resources and it has also attracted more and more attention in the surfactant industry. In this context, carbohydrate-based surfactants are better substitutes since they are biomass sourced.

¹⁹ C. Nitsch, H.-J. Heitland, H. Marsen, H.-J. Schlüssler, "Cleansing Agents" in Ullmann's Encyclopedia of Industrial Chemistry, **2005**.

²⁰ J. E. Pemberton, R. L. Polt, R. M. Maier, R. P. Pacheco, Tucson US 0121362 A1, **2017**.

²¹ I. Johansson, M. Svensson, *Curr. Opin. Colloid Interface Sci.*, **2001**, *6*, 178-188.

²² M. K. Adam, J. S. Poisson, Y. Hu, G. Prasannakumar, M. J. Pottage, R. N. Ben, B. L. Wilkinson, *RSC Adv.*, **2016**, *6*, 39240-39244.

Non-ionic surfactants usually consist of an uncharged polar head that is usually containing polyether or polyhydroxyl units. The class of non-ionic surfactants has the broadest structural diversity in its polar head compared to other types of surfactants. Generally, the non-ionic surfactants can be sub-classified into two main types: ethoxylate-based and carbohydrate-based (Figure 7).²³

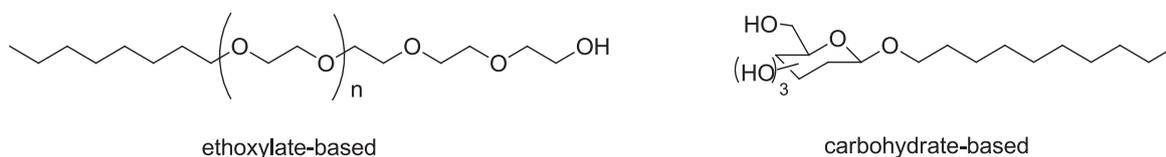


Figure 7. Examples of two main types of non-ionic surfactants.

The non-ionic surfactants offer many advantages over the ionic ones such as being less skin irritant, more biodegradable, formulating flexibility and wider compatibility.⁵ From a physical chemistry point of view, the non-ionic surfactants have a lower Critical Micelle Concentration and are less sensitive to hard water. This is the reason why currently non-ionic surfactants are more attractive for scientists to study. Among these commonly seen non-ionic surfactants, natural polyols or sugar sourced non-ionic surfactants are more attractive. Since most of them are biodegradable, some of them may have stability problems when used in harsh conditions such as strong acid/basic conditions.

1.2 Physico-chemical properties of surfactants.

Surfactants, or surface active agents, are able to decrease the surface tension of interface since they are diffused in solution and absorbed in interfaces. They have found applications in many fields such as detergents, foaming agents, wetting, dispersants, and emulsifiers. Specific applications of surfactants depend largely on their chemical structures and the ratio between their polar heads and non-polar tails, namely the hydrophilic-lipophilic balance (HLB value). By using different types of polar heads and non-polar tails, different HLB values can be achieved for several specific applications.²⁴ This diffusion based process also depends on the temperature.

1.2.1 Critical Micelle concentration.

Critical Micelle Concentration (CMC) is an important characteristic of a surfactant. It is defined as “the concentration of surfactants above which micelles form” and all additional surfactants added

²³ E. Olkowska, M. Ruman, A. Kowalska, Ż. Polkowska, *Ecol. Chem. Eng. S.*, **2013**, 20, 449-461.

²⁴ S. Sajjadi, F. Jahanzad, M. Yianneskis, B. W. Brooks, *Ind. Eng. Chem. Res.*, **2003**, 42, 3571-3577.

to the system becomes micelles.²⁵ The surfactant molecules are initially distributed on the interface of air and water and also in the solution (Figure 8, a). Upon increasing the surfactant concentration, the water surface is fully covered by a layer of surfactant molecules which decreases the surface free energy (surface tension). At this point the water-surfactant system reaches its critical micelle concentration. Above this concentration, theoretically all additional surfactant molecules added into the system will lead to these amphiphiles arrange themselves into micelles (Figure 8, b). Experimentally, above critical micelle concentration (CMC), both monomers and micelles of surfactant molecules are in dynamic equilibrium.²⁶

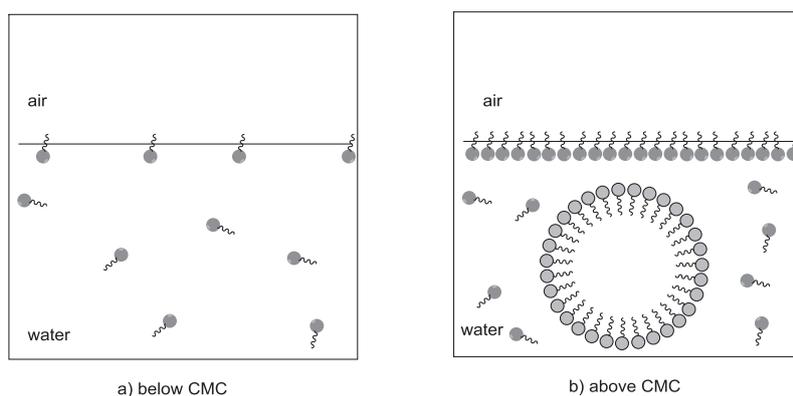


Figure 8. Surfactant concentration increasing leads to micelles forming in solution.

The physicochemical properties of the surfactant system could be dramatically changed after the micelles started forming in the solution system. Therefore, to determine the CMC value of surfactants and understand the parameters that could have influence on CMC value are essential when studying their physicochemical properties. From the point of view of application, it is more efficient for a surfactant to have a lower surface tension as well as a lower CMC value.

1.2.2 Krafft temperature (Krafft point).

The solubility of surfactants in solutions varies with temperature. The solubility of the surfactant improves gradually with increasing of temperature but increases dramatically, when temperature reaches a certain point (Krafft point). The Krafft point is the minimum temperature at which surfactants form micelles. Below the Krafft temperature, there is no value for the critical micelle concentration (CMC).

²⁵ A. D. McNaught, A. Wilkinson, IUPAC. Compendium of Chemical Terminology, 2nd ed, 1997.

²⁶ A. Domínguez, A. Fernández, N. González, E. Iglesias, L. Montenegro, *J. Chem. Educ.*, **1997**, 74, 1227-1231.

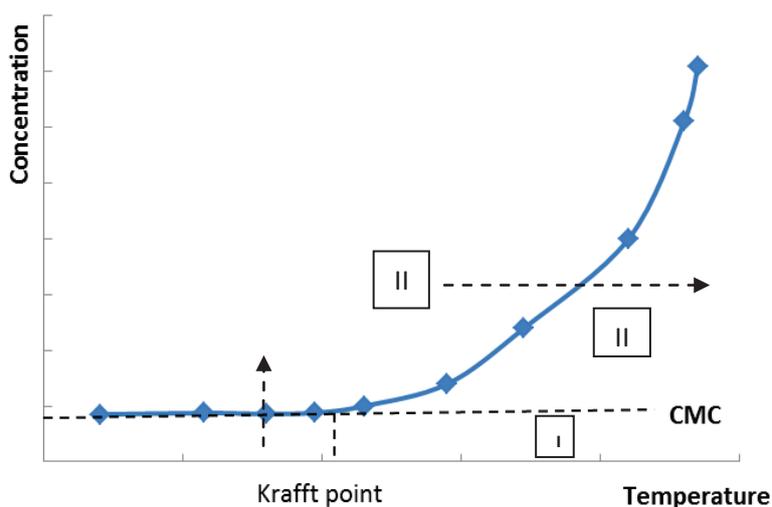


Figure 9. Surfactants solubility curve.

When the concentration is below the CMC, the surfactants remain in aqueous solution whatever the temperature (Figure 9, area I). If the concentration continues to increase, the surfactants will precipitate due to the already saturated solutions (Figure 9, area II). Then, if the temperature increases again, the solution will become transparent again (Figure 9, area III), while it is different with area I since surfactants form micelles in this area.

The Krafft temperature is a point of phase change below which the surfactant remains in crystalline form, even in aqueous solution. Surfactants in such a crystalline state will only solubilize and form micelles if another surfactant is added as assisting agent to help it in overcoming the forces that keep it crystallized for maintaining a better performance. It is also an important characteristic of a surfactant like CMC. It is the minimum application temperature of a surfactant, only when the temperature is above Krafft point the surfactant can be efficient enough. In general, longer alkyl chain will lead to a higher Krafft point due to the Van der Waals forces. This fact makes the Krafft point another glance into the hydrophilic-lipophilic property of the surfactant.

1.2.3 Hydrophilic-lipophilic balance and Phase Inversion Temperature.

The hydrophilic-lipophilic balance (HLB) of a surfactant is a calculation of surfactant whether it is more hydrophilic or more lipophilic. Griffin described a method to calculate the HLB value of non-ionic surfactants in 1954,²⁷ giving a value on a scale of 0 to 20.

²⁷ W. C. Griffin, *J. Soc. Cosmet. Chem.*, **1954**, *5*, 249-256.

$$\text{HLB} = 20 \times \frac{M(\text{hydrophilic portion})}{M(\text{surfactant})}$$

The higher the HLB value, the stronger the hydrophilicity. In general, surfactants with a HLB value less than 10 are more lipophilic while surfactants with a HLB value more than 10 are more hydrophilic. HLB value is relevant to interface tension, absorption, stability, and solubility, meanwhile surfactants with different HLB value can be used for different applications (Figure 23).²⁸

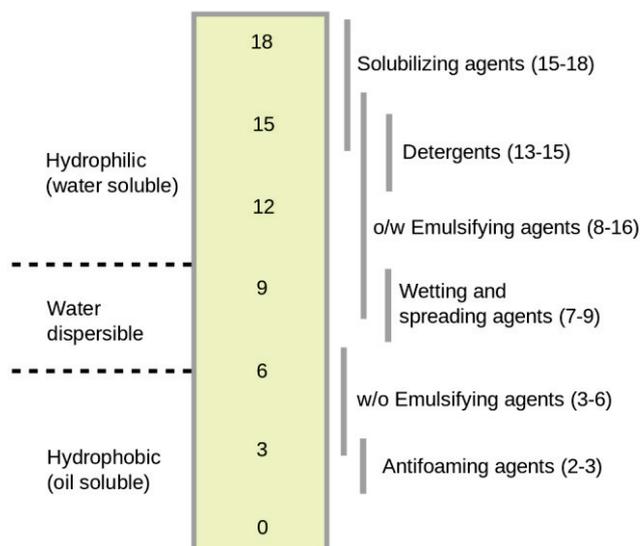


Figure 10. Application of surfactants based on HLB value.

Temperature can often affect the hydrophilic and lipophilic nature of surfactants, particularly nonionic surfactants. During the emulsifying process for a certain surfactant-oil-water system, there is a temperature below which the surfactant dissolves in water phase and above which the surfactant dissolves in oil phase. As the temperature increases oil-in-water (O/W) system will transfer to water-in-oil (W/O) system at a certain temperature which is called phase inversion temperature (PIT). In a particular system, PIT is the temperature at which the hydrophilic-lipophilic nature of the surfactant reaches equilibrium at the interface so it is also called HLB temperature.²⁹

1.3 Non-ionic surfactants based on different linkages.

The stability of non-ionic surfactants can be largely influenced by the type of linkages. Most of them have an ester linkage between their polar head and the non-polar tail such as sucrose esters and sorbitan esters, amongst others. Generally speaking, surfactants with ester linkages are readily biodegradable while they are sensitive to hydrolysis in both acidic and basic conditions.

²⁸ W. C. Griffin, *J. Soc. Cosmet. Chem.*, **1949**, *1*, 311-326.

²⁹ X. Y. Liu, C. X. Ma, W. H. Chu, Q. B. Li, J. G. Duan, *Journal of Daqing Petroleum Institute*, **2005**, *29*, 102-103.

Consequently, their applications are limited over a narrow range of pH. However, there is a demand for more robust surfactants which can be used in a broader range of pH such as some special detergents for protein or mineral grease, for some applications requiring long term stability upon storage in cosmetic industry and also for oil field extraction. Despite the ester linkages, more linkages such as amide, glucoside, ether and C-C bond linkages have been developed. In Figure 11, the linkages have been listed depending on their stability. In order to increase the stability of surfactants some other robust linkages have been explored such as ether function and C-C bond linkage.

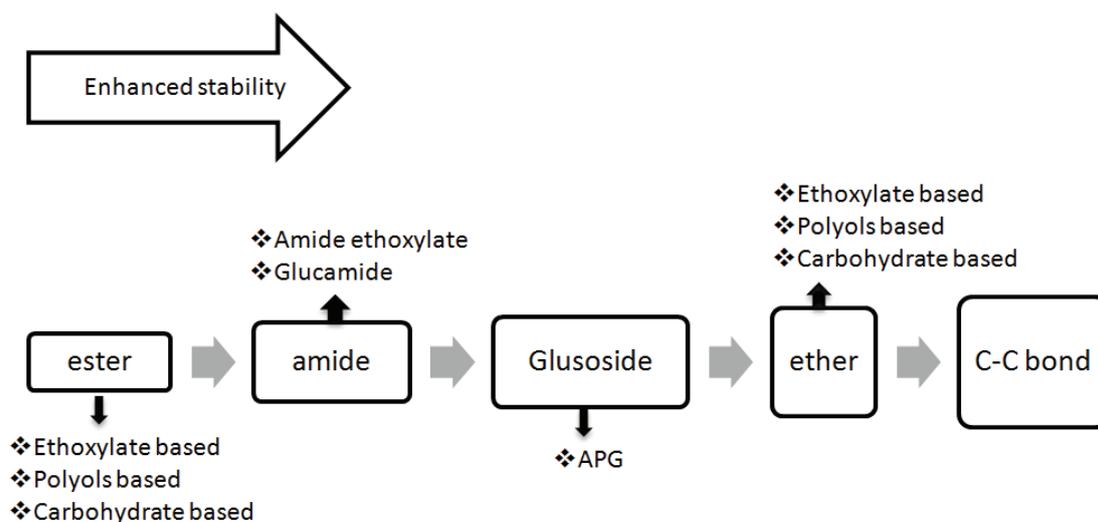


Figure 11. Stability of different linkages.

In this manuscript, different linkage types will be reviewed according to their polar heads and their synthetic routes will also be detailed.

1.3.1 Surfactants connected by ester linkage.

Surfactants connected by ester linkage are playing an important role in the surfactant industry. They usually exhibit a good biodegradability as they are usually prepared from polyols and fatty acids. They are accessible with great diversity for making ester functional group and they can be synthesized with relative simplicity through chemical or enzymatic catalysis.³⁰ Some typical ester-linked surfactants are listed in Figure 12.

³⁰ D. B. Samey, H. Kapeller, G. Fregapane, E. N. Vulfson, *JAACS*, **1994**, *71*, 711-714.

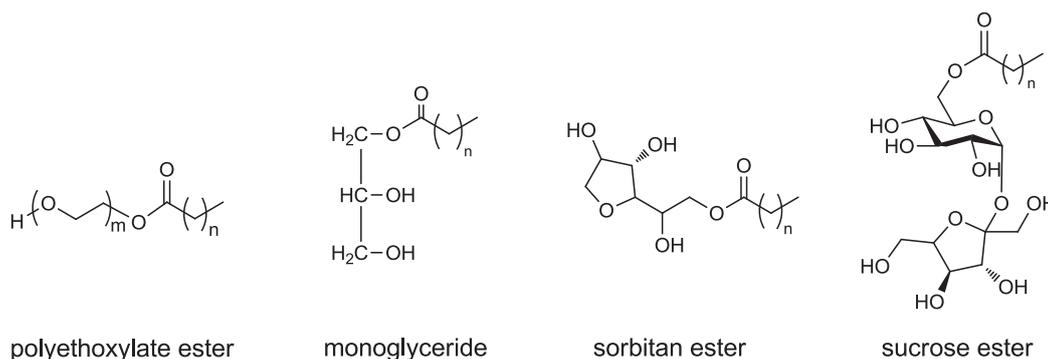


Figure 12. Some examples of ester-linked surfactants.

1.3.1.1 Ethoxylate-based ester surfactants.

Ethoxylate-based non-ionic surfactants possess several ethylene glycol units as hydrophilic head as they are able to form H-bond with water at room temperature. They are widely used in pulp and paper, textiles, coatings, agricultural pesticides, fuels and oils and plastics.³¹ Recently, people have put more attention about the use of ethoxylate-based non-ionic surfactants because of their relative stability and low biodegradability in the environment.³² Over three million metric tons of ethylene oxide (EO)-derived surfactants are consumed annually in the world today.³³

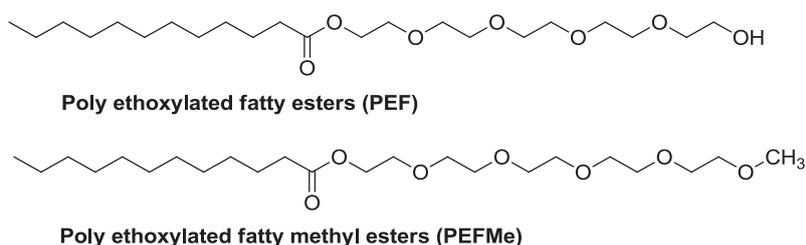


Figure 13. Typical examples of ethoxylate-based ester surfactants.

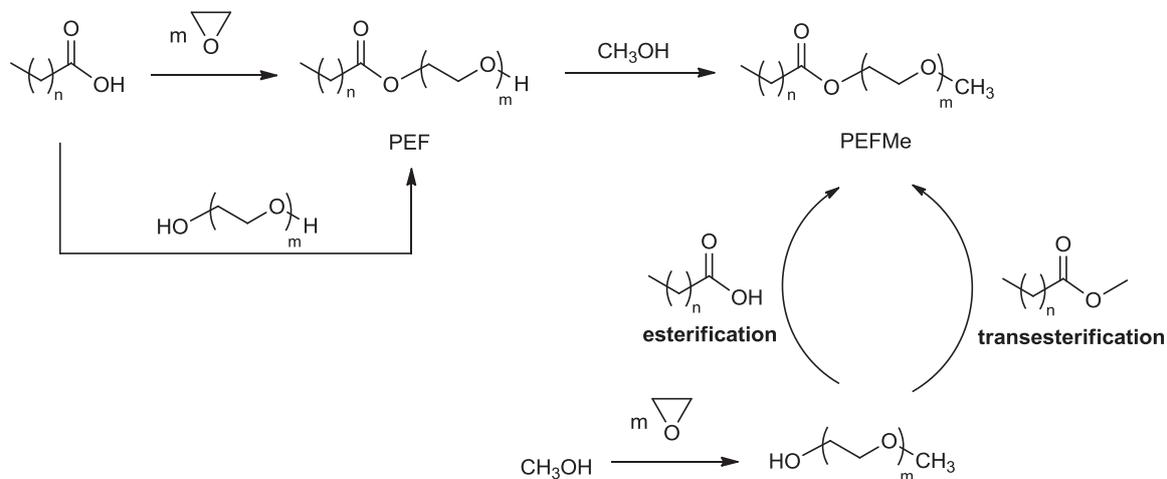
Polyethoxylated fatty esters (PEF) and polyethoxylated fatty methyl esters (PEFMe) are well known typical ethoxylate-based non-ionic surfactants. PEF can be directly obtained by reaction between fatty acids with ethylene oxide (EO) or polyethoxylate glycol (PEG) in the presence of a base (e.g. NaOH) or an acid (e.g. SbCl_5) catalyst. There are two conventional methods for synthesizing PEFMe. The first method is based on fatty acids through fatty acid ethoxylates, followed by an etherification under acid/base catalyst with methanol at high temperature/pressure to give PEFMe while with many by-products. Another method is through

³¹ G.-G. Ying, B. Williams, R. Kookana, *Environ. Int.*, **2002**, 28, 215-226.

³² C. J. Alexander, M. M. Richter, *Anal. Chim. Acta*, **1999**, 402, 105-112.

³³ M. F. Cox, Ethylene Oxide-Derived Surfactants, Proceedings of the 3rd World Conference on Detergents: Global Perspectives, edited by Arno Cahn, **1994**, 141-146.

methyl glycol ethers from methanol and followed by esterification with fatty acids or transesterification with fatty acid methyl esters (Scheme 2).³⁴

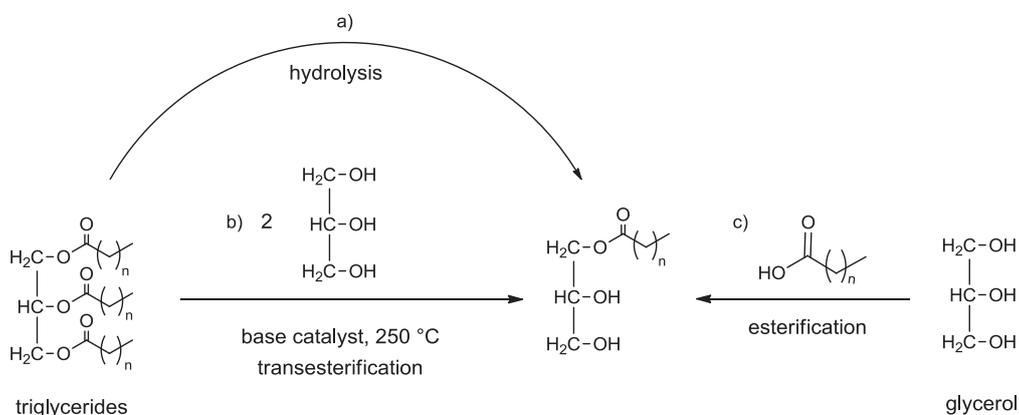


Scheme 2. Preparation of PEF and PEFMe.

This process is actually not very suitable for industrial applications due to tedious several steps at high temperature (>180 °C) to obtain numerous by-products such as polyethylene glycols. They are only capable to produce poor yields (10-30%) of the desired ethoxylated esters.³⁵

1.3.1.2 Glycerol-based ester surfactants.

Monoglycerides and polyglycerol esters are well known as surfactants or emulsifiers to find their applications in food, pharmaceutical and cosmetic industry. The monoglycerides are generally obtained by i) the hydrolysis of triglycerides (Scheme 3, a), ii) the transesterification of triglycerides with glycerol under base catalyst at high temperature (Scheme 3, b), iii) the direct esterification of glycerol with fatty acids (Scheme 3, c).

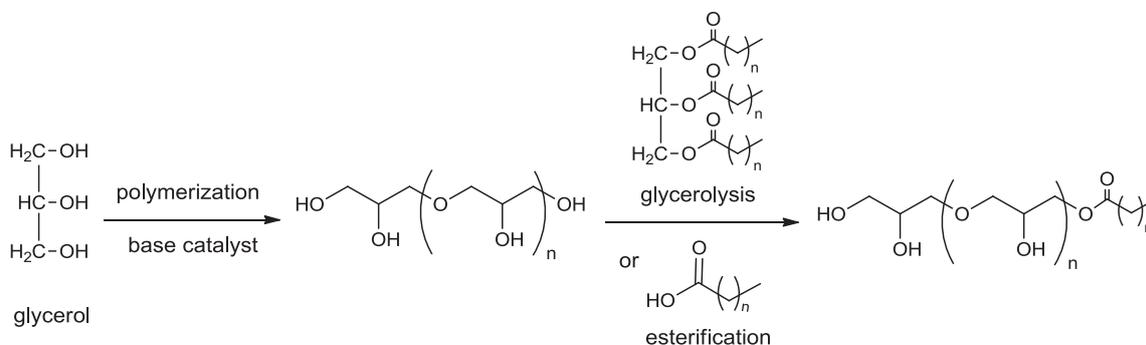


Scheme 3. Three general synthetic routes of monoglycerides.

³⁴ I. Hama, T. Okamoto, H. Nakamura, *JAACS*, **1995**, *72*, 781-784.

³⁵ M. F. Cox, U. Weerasooriya, *JAACS*, **1997**, *74*, 847-859.

Since glycerol is a trifunctional molecule, it may condense with itself to give polymers. Polyglycerol esters can be formed in the presence of base catalyst by random polymerization of glycerol and then followed by the esterification with fatty acids or transesterification with triglycerides (Scheme 4).



However, since the three hydroxyl groups almost have similar reactivities, the product obtained from the direct esterification with fatty acid or transesterification with triglyceride is a mixture of monoglyceride, diglycerides, triglycerides and glycerol, which typically contains 40-60% monoglyceride and 35-45% diglyceride.³⁶ Enzymatic routes have also been reported and some lipases have shown a better regioselectivity compared to the chemical route.³⁷

1.3.1.3 Sorbitan-based ester surfactants.

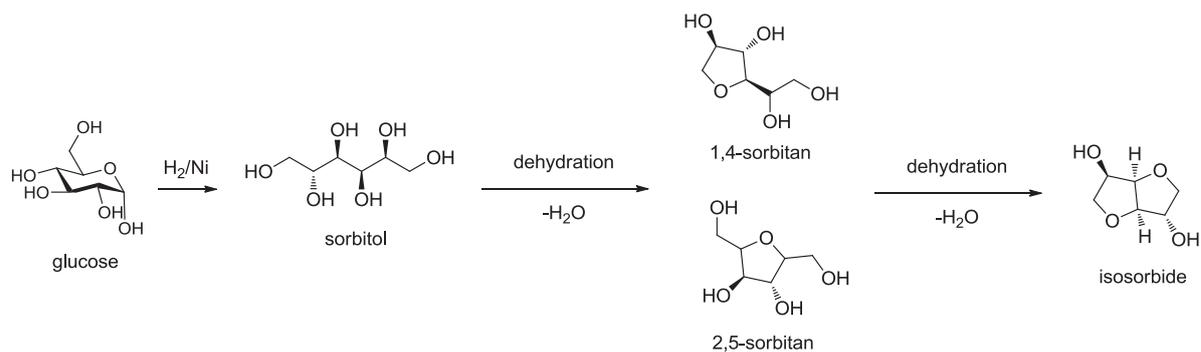
Sorbitol is a carbohydrate alcohol with a sweet taste which can be found from nature, for example, in apple, pear, peach or prunes, or can be obtained from reduction of glucose. The annual production of sorbitol is 1.70 million tons in 2011, and will surge to 2.15 million tons by the end of 2018 with relatively competitive raw material price of 0.80-1.70 US dollars per kilogram.³⁸ Now, the industrial production of sorbitan esters is quite stable and mature. They are mainly used as emulsifiers or stabilizers in food, cosmetics, and pharmaceuticals or as leather and textile auxiliaries.³⁹ The commercially manufactured sorbitol fatty acid esters (SFAEs) are obtained by reacting sorbitol with fatty acids and gives complex mixtures of fatty esters of several polyols derived from sorbitol, due to the rapid dehydration of sorbitol to sorbitan and isosorbide (Scheme 5). In this dehydration process, the formation rate of 1,4-sorbitan is faster than isosorbide and its counterpart 2,5-sorbitan which allows it to be the major product.⁴⁰

³⁶ C. H. Zhou, J. N. Beltramini, Y. X. Fana, G. Q. Lu, *Chem. Soc. Rev.*, **2008**, 37, 527-549.

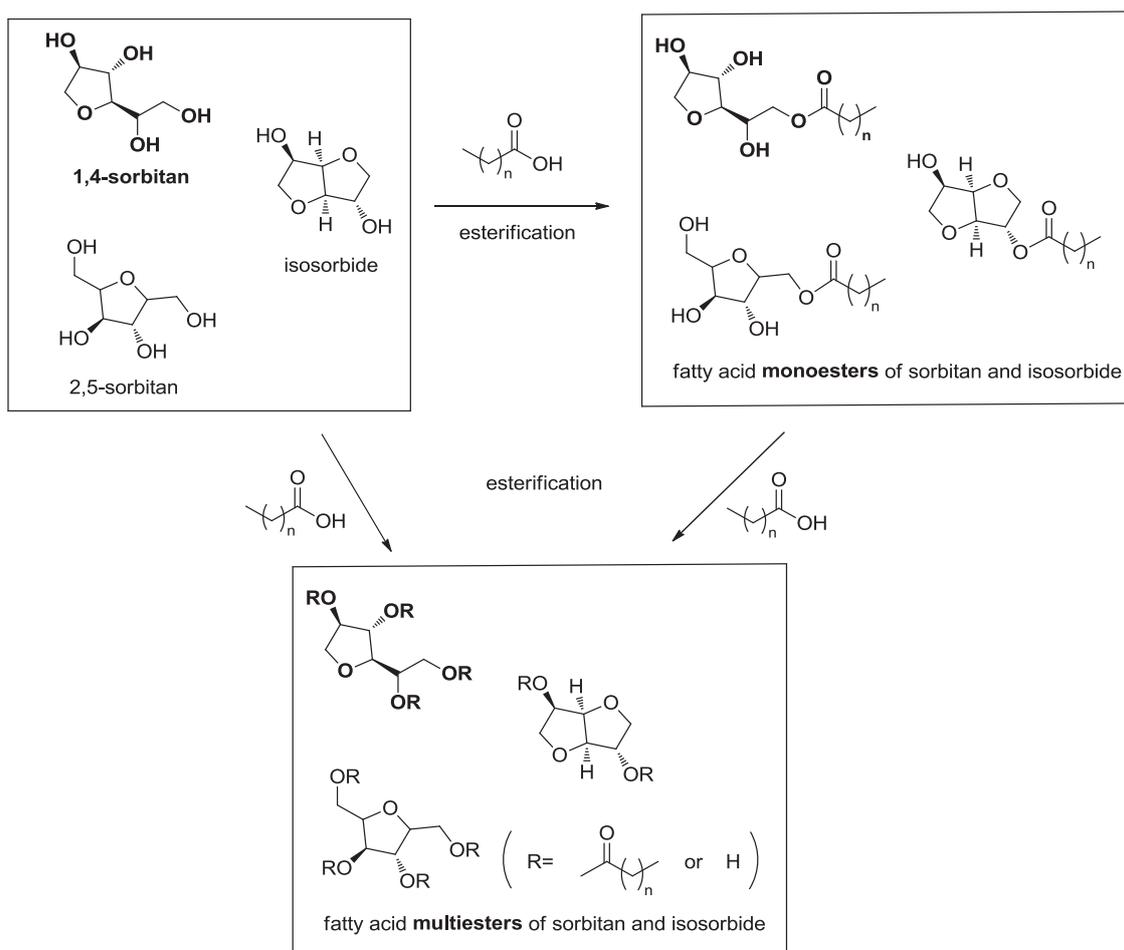
³⁷ Y. Tsujisaka, S. Okumura, M. Iwai, *Biochim. Biophys. Acta.*, **1977**, 489, 415-422.

³⁸ Global Sorbitol Market - Isosorbide, Propylene Glycol, Glycerol & Other Downstream Opportunities, Applications Size, Share, Growth, Trends And Forecast 2012-2018.

³⁹ K. Hill, O. Rhode, *Fett/Lipid*, **1999**, 101, 25-33.

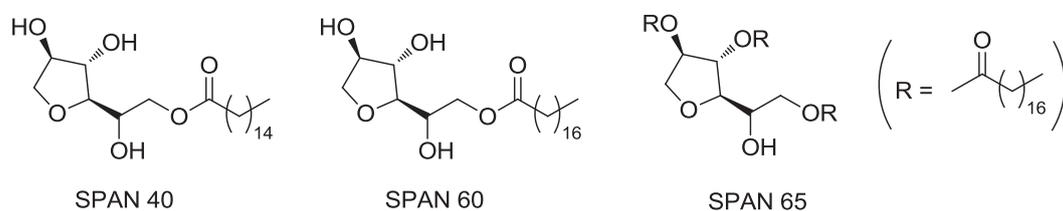


The synthetic route for SFAEs is often including two steps. In the first step, water is eliminated from sorbitol to form sorbitan and continued by the esterification with fatty acid in the second step (Scheme 6). These two steps can be carried out simultaneously for industry scale production.⁴⁰ Different types of sorbitan esters are produced when different types of fatty acid and starting material ratio is used (e.g. laurates, oleates, or stearates).



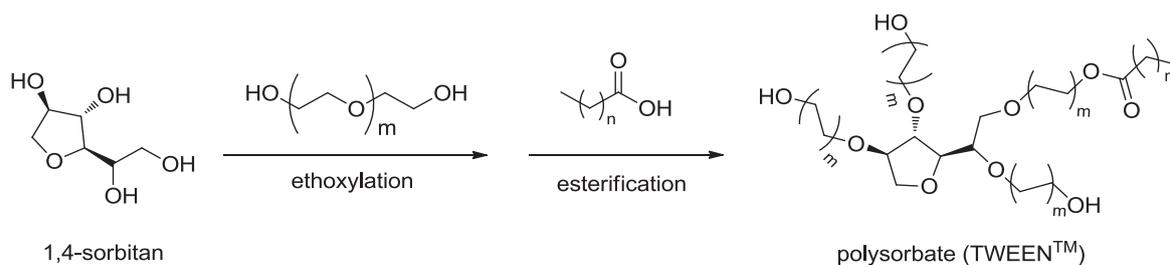
⁴⁰ A. Corma, S. B. A. Hamid, S. Iborra, A. Velty, *ChemSusChem*, **2008**, *1*, 85-90.

SPAN is a typical commercially available sorbitan esters widely applied as emulsifiers in oil field extraction, textiles, food, cosmetics and pharmaceuticals. Sorbitan laurate (SPAN 20), sorbitan monostearate (SPAN 60), sorbitan tristearate (SPAN 65), sorbitan oleate (SPAN 80) and sorbitan trioleate (SPAN 85) are the most used emulsifiers (scheme 7).



scheme 7. Some examples of SPAN surfactants.

After the ethoxylation of sorbitan with ethylene oxide, the fatty acid can be added to the reaction to produce sorbitan ester polyethoxylates or polysorbates⁴¹ commonly known as TWEENTM used as emulsifiers for oils, solvents and lubricants (scheme 8).



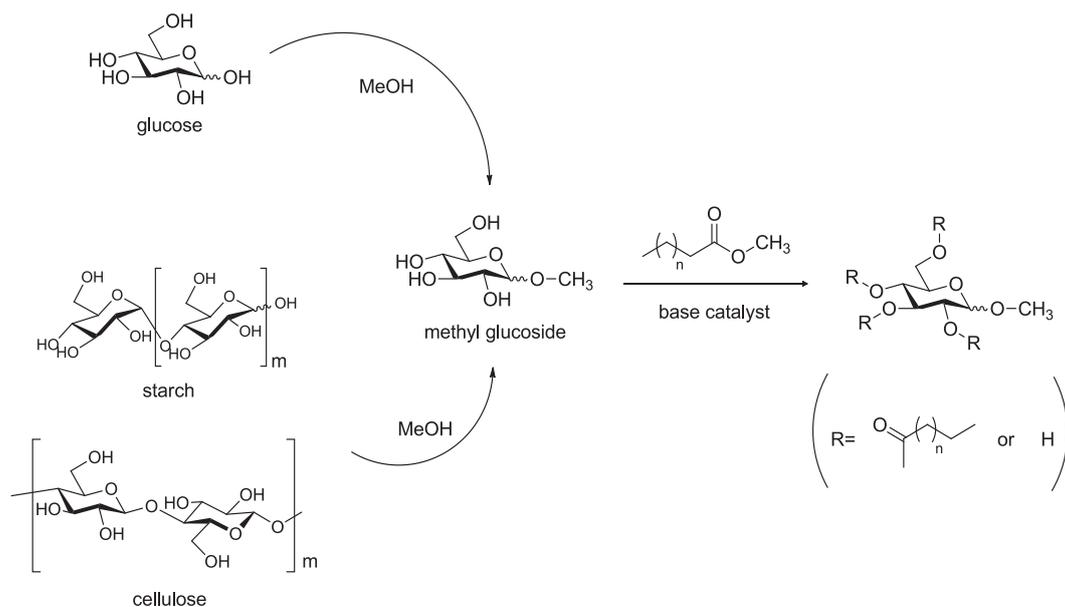
scheme 8. Modification of sorbitan to polysorbate (TWEENTM).

1.3.1.4 Glucose-based ester surfactants.

Since the alkyl polyglucosides (APGs) are quite abundant and available, with an estimated approximately 80,000 tons annual production capacity. A considerable interest has generated by using alkyl glucoside as starting material with some modification of its structure to enhance certain properties. Methyl glucoside is prepared by (trans)glycosylation from a) glucose, or directly from b) starch or cellulose (Scheme 9). Then, methyl glucoside ester is prepared by transesterification of methyl glucoside with fatty acid methyl esters (stearic or oleic acid) to improve its lipophilic properties.⁴²

⁴¹ Y. Wu, S. Iglauer, P. Shuler, Y. Tang, W. A. Goddard, *Tenside, Surfactants, Deterg.*, **2010**, 47, 280-287.

⁴² J. Texter, <Reactions And Synthesis In Surfactant Systems>, *CRC Press*, **2001**.



scheme 9. Synthetic routes for methyl glucoside esters.

Transesterification of methyl glucoside with stearic or oleic acid methyl esters is usually carried out under base catalyst (for example, K_2CO_3) at 120-160 °C to give a mixture of methyl glucoside mono-, di, tri- or tetra- fatty acid esters. Therefore, the industrial products are called alkyl polyglucosides. The average degree of polymerization (DP) can be characterized by the length of alkyl chain and the average number of glucose units connected to it. This value is largely influenced by the ratio of glucose to methyl glucoside ester in the reaction mixture. Although the existence of ester groups will decrease the solubility compared to the corresponding alkyl glucoside, they exhibit excellent emulsification ability to find application as emulsifying agents and thickeners in cosmetics.

Due to the moderate selectivity of chemical routes, the use of enzyme catalysts is favored because the enzymes have a better selectivity with a few by-products, require mild reaction conditions, recyclable and reusable. For example, Boures *et. al.* have developed a two-step enzymatic process consisting of a) the enzymatic synthesis of α -butylglucoside from a starch hydrolysate catalyzed by the α -transglucosidase from *Aspergillus sp.*, and b) the lipase-catalyzed esterification of α -butylglucoside to obtain a mixture of monoester and diester derivatives with better selectivity compared to the chemical routes.⁴³

⁴³ P. F. Monsan, F. Paul, V. Pelenc, E. Bourse, *Ann. N. Y. Acad. Sci.*, **1996**, 799, 633-641.

1.3.1.5 Disaccharide-based ester surfactants.

Disaccharides are formed of two molecules of monosaccharides with a glycosidic bond by eliminating a molecule of water. They are also abundant in nature, *e.g.* the most commonly seen disaccharides are sucrose, lactose and maltose. The annual production of sucrose is 130 million tons available at an average price of 0.65 €/kg.

Sucrose is a molecule composed of two monosaccharides, glucose and fructose. It can be obtained from sugar canes and sugar beets. Lactose is a disaccharide derived from the condensation of galactose and glucose. It is usually obtained from milk or whey as a by-product after the manufacturing of cheese in industry. Maltose is a disaccharide formed by two units of glucose. It is generated in the process of hydrolysis of amylose starch and is present in many staple foods such as potato, corn, cassava, wheat and rice. Their hydrophilic properties are quite similar to monosaccharide and are also used as biomass feedstock to manufacture surfactants (Figure 11).

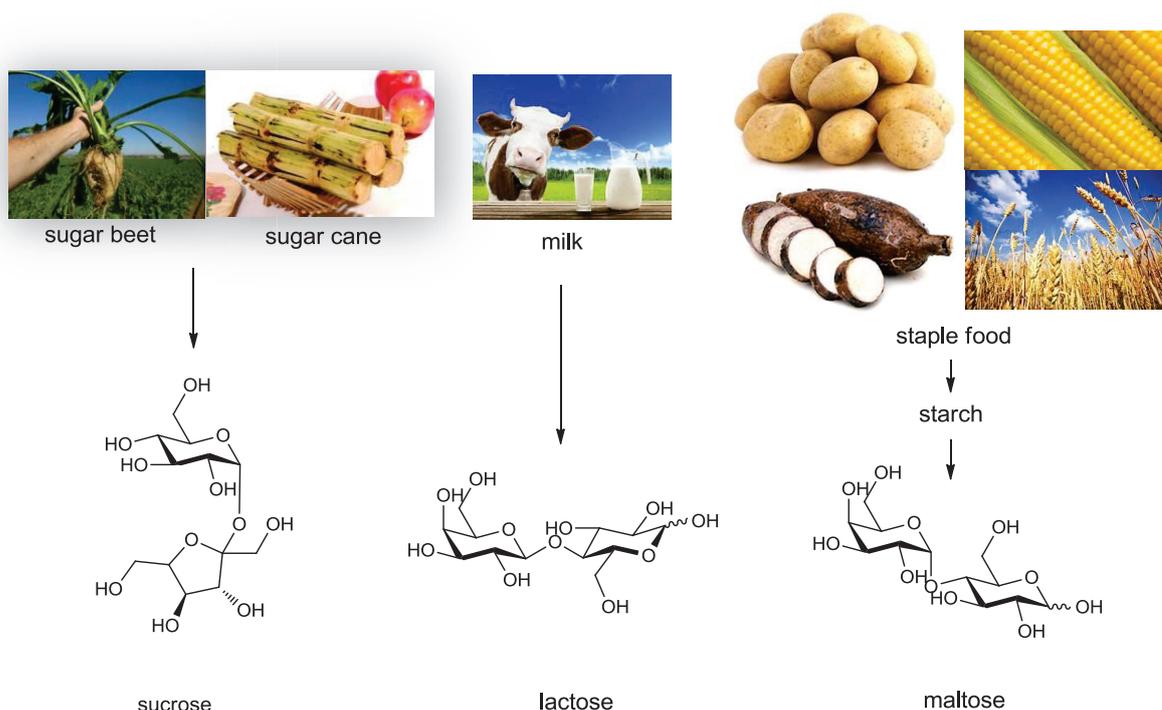
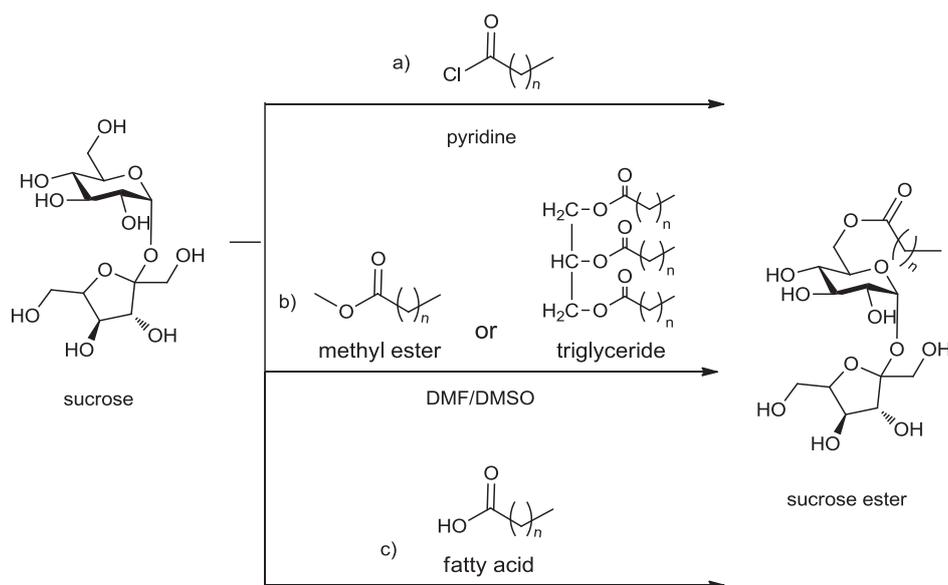


Figure 14. Structures of some common disaccharides.

Sucrose is one of the world's most abundantly produced organic compounds and it is available at a very low cost while with high purity (>89%). Sucrose esters (SEs) are widely used as emulsifiers in food and cosmetic industries, and recently more interest in their applicability in pharmaceutical fields has arisen due to their biodegradability.⁴⁴ Other disaccharides such as

⁴⁴ A. Szuts, P. Láng, R. Ambrus, L. Kiss, M. A. Deli, P. S. Révész, *Int. J. Pharm.*, **2011**, *410*, 107-110.

lactose, maltose and isomaltulose are also used as carbohydrate sources for disaccharide esters surfactant synthesis. There are several commercial routes to fatty acid sucrose monoesters. Sucrose esters or other sugar-based esters are usually prepared by transesterification between carbohydrates and alkyl ester of fatty acid.⁴⁵ Commercially synthetic route generally involves transesterification between these disaccharides with methyl ester of fatty acid or triglyceride from fat/oil (Scheme 10)⁴⁶ or through enzyme catalysis.⁴⁷



Scheme 10. Chemical synthetic route of sucrose esters.

Fatty acid chlorides were used for synthesis of these sucrose esters by condensing with sucrose in pyridine (Scheme 10, a).⁴⁸ They can be also prepared by transesterification with methyl ester fatty acid⁴⁹ or triglyceride⁴⁶ in dimethylformamide (DMF) or in a safer and less expensive solvent like dimethyl sulfoxide (DMSO) catalyzed by a base such as K₂CO₃ (Scheme 10, b). Unfortunately, these methods require the use of toxic solvents which are less green and the need of removal traces of these toxic solvents would also contribute to the slow advancement of this industry. Therefore, other routes have been reported by using volatile solvents or solvent-free method. Osipow and Rosenblatt have developed another process in which propylene glycol was used as solvent to dissolve sucrose and the methyl ester of fatty acid was emulsified into this

⁴⁵ H. E. Hoydonckx, D. E. De Vos, S. A. Chavan, P. A. Jacobs, *Top. Catal.*, **2004**, 27, 1-4.

⁴⁶ T. Polat, R. J. Linhardt, *J. Surfactants Deterg.*, **2001**, 4, 415-421.

⁴⁷ U. H. Zaidan, M. B. A. Rahman, S. S. Othman, M. Basri, E. Abdulmalek, R. N. Z. R. A. Rahman, A. B. Salleh, *Food Chem.*, **2012**, 131, 199-205.

⁴⁸ L. Rosenthal, W. Lenhard, *U.S. Patent*, 1739863, **1929**.

⁴⁹ L. Osipow, F. D. Snell, W. C. York, A. Finchler, *Ind. Eng. Chem.*, **1956**, 48, 1459-1462.

solution. Propylene glycol was then distilled off during the transesterification reaction.⁵⁰ Brown *et al.* have reported a solvent-free transesterification process of molten sucrose (120-170 °C) and fatty acid esters⁵¹ or triglyceride⁵² in the presence of lithium, sodium or potassium carbonate as catalyst and solubilizer.

These processes usually have some disadvantages such as heating at high temperature (120-170 °C) that generates various by-products and may cause unexpected coloring of the products. Since the hydroxyl groups on the carbohydrate almost have the same reactivity, the crude product is in fact a mixture of mono-ester, di-ester and even tri-ester without good selectivity. The product obtained usually contains >50% monoesters, >10% di- and higher esters, unreacted sucrose, and triglycerides. With suitable control of reaction conditions and ratio of starting materials, the formation of di-ester and tri-ester can be decreased which ends up with 85% monoester and 15% di-ester. Commercially sucrose monoesters including stearate (C18), behenate (C22), oleate (unsaturated C18), palmitate (C16), and myristate (C14) produced in Japan usually contain 70% of monoester and 30% of di-, tri-, and higher esters.⁵⁰

To avoid the use of high temperature and therefore to obtain a better regioselectivity and stereoselectivity of sugar esters, enzymatic esterification of carbohydrates has been explored in milder reaction conditions (Scheme 10, c). Recently, the synthesis of sugar esters with an enzyme in an organic solvent has become an increasingly attractive alternative.⁵⁰ Several lipases such as lipases from *Chromobacterium viscosum*, *Aspergillus niger*, and *Candida cylindracea* were found to catalyze the carbohydrate esterification to obtain both mono- or diesters in regiospecific esterification. Except the 6-O-acyl derivative obtained by acylation of primary hydroxyl group on the sugar, the esterification on the secondary hydroxyl group has also been investigated. When different lipases are used as catalysts, it is possible to prepare monoester derivatives of carbohydrate with regioselectivity at different expected positions.⁵³ Different lipases possess distinct, even sometimes opposite, regioselectivities in the esterifications, presumably due to different binding modes of the substrate with the enzymes' active centers. Most of them are in preferences of preparing C-2 or C-3 monoesters.⁵⁴ However, the solvents used for keeping the activity of these lipases (methylene chloride or tetrahydrofuran) are not capable of dissolving the carbohydrates. The polar solvents often used for carbohydrates such as pyridine or DMF are not

⁵⁰ L. Osipow, W. Rosenblatt, *JAACS*, **1967**, *44*, 307-309.

⁵¹ R. O. Feuge, H. J. Zeringue Jr., T. J. Weiss, M. Brown, *JAACS*, **1970**, 47-56.

⁵² K. J. Parker, K. James, J. Hurford, *Sucrochemistry*, **1977**, *41*, 97-114.

⁵³ F. Nicotra, S. Riva, F. Secundo, L. Zucchelli, *Tetrahedron Lett.*, **1989**, *30*, 1703-1704.

⁵⁴ M. Therisod, A. M. Klibanov, *J. Am. Chem. Soc.*, **1987**, *109*, 3977-3981.

capable of maintaining the bioactivity of these enzymes.⁵⁵ However, Therisod and Klubahov have found a porcine pancreatic lipase which is able to catalyze the esterification of monosaccharide with good regioselectivity to give 6-*O*-derivative in pyridine. The enzyme displays an overwhelming preference toward the primary hydroxyl group on the carbohydrates. Unfortunately, the poor catalytic ability of this lipase on the disaccharides and oligosaccharides has limited its application.⁵⁶ Riva has found a useful protease from *Bacilluslicheniformis* --- *subtilisin* which can esterify not only the monosaccharides (isolated yields around 60%) but also disaccharides (isolated yields around 50%), and oligosaccharides (isolated yields around 40%) with good activity and stability either in DMF or pyridine as solvent.⁵⁷

These enzymatic synthetic routes of sugar ester surfactants are more selective than chemical ones. However, the relatively high preparation costs of these biocatalysts are limitations for transformation at the industrial scale, and also with substrates such as disaccharides and oligosaccharides which have a large bulkiness, these moieties probably have difficulty to bind with these enzymes' active sites consequently leads to poor activities. Otherwise, most of them require toxic solvents, the reaction rate is quite slow (1 to 7 days) and the chain length of fatty acid esters is usually limited to less than 8 carbons.

1.3.1.6 Oligosaccharide-based ester surfactants.

Oligosaccharides are also used as feedstock for surfactant synthesis due to their abundant accessibility. Surfactants based on oligosaccharides may differ from monosaccharide-based surfactants due to their relatively large size of hydrophilic head. These could lead to an important change of their physic-chemical properties, such as hydrophilic-hydrophobic balance (HLB), which influences their practical applications. Oligosaccharide-derived surfactants are more soluble in water at room temperature when linked with same long chain hydrophobic part.⁴⁶ Better solubility at ambient temperature could help the surfactant to exert its best performance without the necessary to formulate with other hydrotropic agents. Some oligosaccharides show binding bioactivity with proteins which could be useful for medicine carrier in pharmaceuticals.⁵⁸

Raffinose is a tri-saccharide composed of galactose, glucose, and fructose. It can be found in beans, cabbage, brussels sprouts, broccoli, asparagus, and whole grains. Stachyose is a tetra-saccharide consisting of two units of galactose, one glucose unit, and one fructose unit, which is

⁵⁵ D. K. Allen, B. Y. Tao, *J. Surfactants Deterg.*, **1999**, 2, 383-390.

⁵⁶ M. Therisod, A. M. Klubanov, *J. Am. Chem. Soc.*, **1986**, 108, 5638-5640.

⁵⁷ S. Riva, J. Chopineau, A. P. G. Kieboom, A. M. Klubanov, *J. Am. Chem. Soc.*, **1988**, 110, 584-589.

⁵⁸ A. Ogura, A. Kurbangalieva, K. Tanaka, *Glycoconjugate J.*, **2014**, 31, 273-279.

similar with raffinose also occurs naturally in numerous vegetables such as green beans, soybeans, and other plants. It is mainly used as bulky sweeteners. Their fatty acid esters have been synthesized as surfactants (Figure 12).

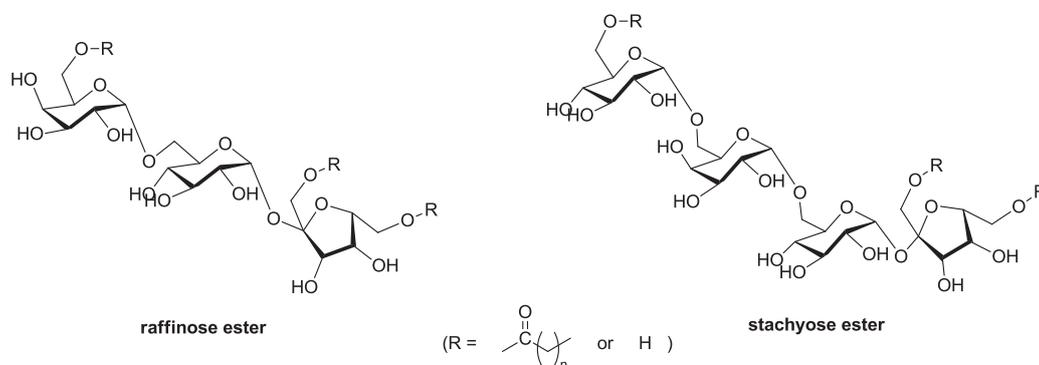
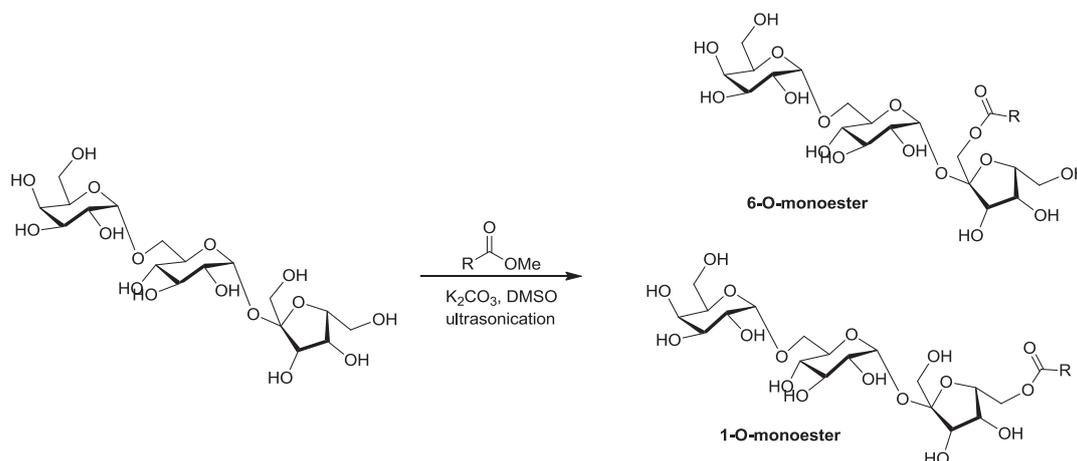


Figure 15. Examples of oligosaccharide-derived surfactants.

Lu *et al.* have reported a synthetic route to raffinose-derived surfactants by ultrasonic irradiation.⁵⁹ Raffinose was mixed with three different fatty acid methyl esters, including methyl caprylate, methyl laurate and methyl stearate. This process was done with controlled molar ratio (2:1) under base catalyst to obtain either 1-*O*-monoester or 6-*O*-monoester since the hydroxyl groups at these positions have the same reactivity. Following this procedure, a mixture with a high percentage of monoesters ($\geq 40\%$) was obtained with the ratio of 1-*O*-monoester/6-*O*-monoester 2.2 to 2.6 (scheme 11).



scheme 11. Preparation of raffinose esters.

In conclusion, these ester-linked surfactants can be easily synthesized through (trans)esterification using fatty acids or fatty acid methyl esters and biomass feedstocks such as triglycerides from animal fats or vegetable oils or abundant polyols and carbohydrates. However,

⁵⁹ Y. Lu, R. Yan, X. Ma, Y. Wang, *Eur. Food Res. Technol.*, **2013**, 237, 237-244.

some of them are not practical to be synthesized on the large scale for industrial use either due to their poor yield or selectivity. On the other hand, enzymatic synthetic methods offer better selectivity while they use costly biocatalysts and usually require longer reaction times. In addition, these ester-linked surfactants have good biodegradability which means they are relatively less stable which is not able to be applied to rigid conditions. The ester linkage tends to be hydrolyzed in both acidic and basic conditions, so they are not stable to be used for some special applications such as oil field extraction and for long-term storage. Due to this fact, surfactants based on other linkages have been explored by scientists for broader applications.

1.3.2 Surfactants connected by amide linkage.

Surfactants connected by an amide bond are also widely used as detergents and the role of amide bond can also contribute to additional properties of surfactants. Indeed, Bordes *et al.* have reported that amide-based surfactants are capable of forming intermolecular hydrogen bonds *via* the amide group which leads to tighter packing at the interface.⁶⁰ Hoque *et al.* have also reported that the amide functionality is able to improve the surfactant aggregation properties compared to the other surfactants having no amide bond.⁶¹ In conclusion, the amide bond is considered to be able to enhance the hydrophilicity of the surfactant molecules.

1.3.2.1 Ethoxylate-based amide surfactants.

As seen before, the ethoxylate-based surfactants usually consist of long polyoxyethylene chains which lead to a poor biodegradability. When an amide group is introduced into the surfactant molecule, the biodegradability can be significantly enhanced.⁶² Enzymes present in the sewage treatment plant are able to catalyze the hydrolysis of the fatty amide ethoxylate to give a fatty acid and an amino-terminated polyethylene glycol.⁶³ Ethoxylate-based fatty amides are already used in many practical applications such as personal-care products, detergents and as emulsifiers.

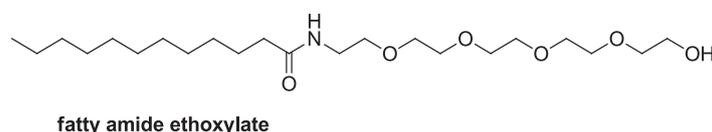


Figure 16. Ethoxylate-based amide surfactants.

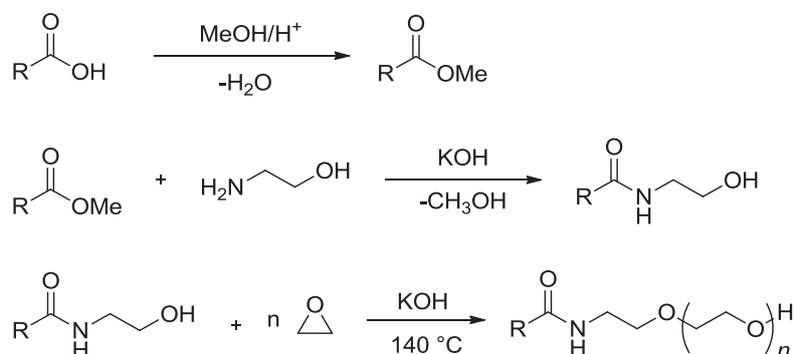
⁶⁰ R. Bordes, J. Tropsch, K. Holmberg, *Langmuir*, **2010**, *26*, 3077-3083.

⁶¹ J. Hoque, S. Gonuguntla, V. Yarlagadda, V. K. Aswal, J. Haldar, *Phys. Chem. Chem. Phys.*, **2014**, *16*, 11279-11288.

⁶² B. M. Folmer, K. Holmberg, E. G. Klingskog, K. Bergström, *J. Surfactants Deterg.*, **2001**, *4*, 175-183.

⁶³ C.G. van Ginkel, C. A. Stroo, A. G. M. Kroon, *Tenside, Surfactants, Deterg.*, **1993**, *30*, 213.

The ethoxylate fatty acid monoethanolamides are prepared by a three-step procedure including the synthesis of the methyl ester, the synthesis of the monoethanolamide then followed by the ethoxylation (Scheme 12).



Scheme 12. Preparation of ethoxylate-based amide surfactants.

This 3-step preparation method will also give access to the ethoxylated-esteramine derivatives. Thus, fatty acid monoethanolamide surfactants prepared by ethoxylation of the ethanolamide intermediate will contain side products such as fatty acid esters instead of amides, and also the by-product of two polyoxyethylene chains instead of one.

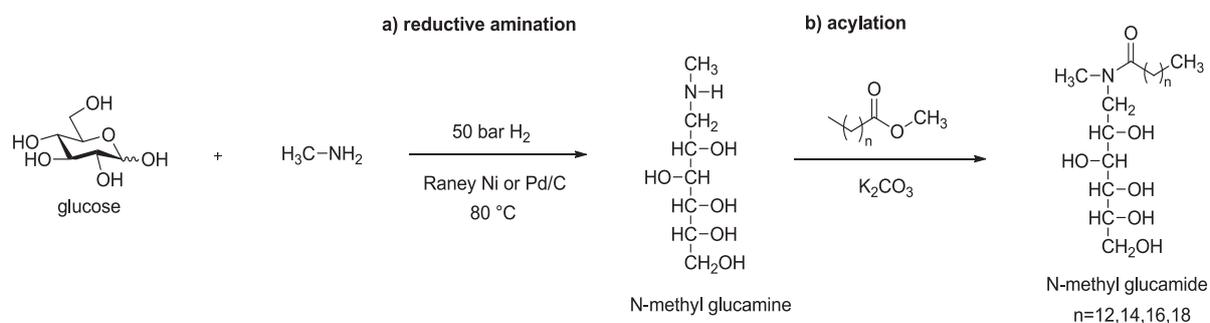
1.3.2.2 Monosaccharide-based amide surfactants.

Glucose is the most widely spread monosaccharide in nature, which can be easily accessed by hydrolysis of abundant saccharides (sucrose), cellulose and starch. *N*-methyl glucamide surfactants are widely used as detergents and the methyl group at the nitrogen contributes to the water solubility and foaming property.⁶⁴ Water solubility of the carbohydrate-based surfactants is not only dependent on the number of the molecule's hydroxyl groups on the hydrophilic moiety, but also largely dependent on the balance between intermolecular hydrogen bond formation of surfactant molecules and that with water molecules. The former decrease the water solubility, resulting in crystallization of surfactant from solution, while the latter increase the water solubility owing to the interaction between water molecules and hydroxyl groups of surfactant molecules. *N*-methyl glucamides, methyl group on the amide function, indicating strong intermolecular interaction due to less intermolecular hydrogen bond formation by hydroxyl groups, which may be responsible for higher water solubility.⁶⁵

⁶⁴ O. Soderman, I. Johansson, *Curr. Opin. Colloid Interface Sci.*, **2000**, *4*, 391-401.

⁶⁵ Y.-P. Zhu, M. J. Rosen, P. K. Vinson, S. W. Morrall, *J. Surfactants Deterg.*, **1999**, *2*, 357-362.

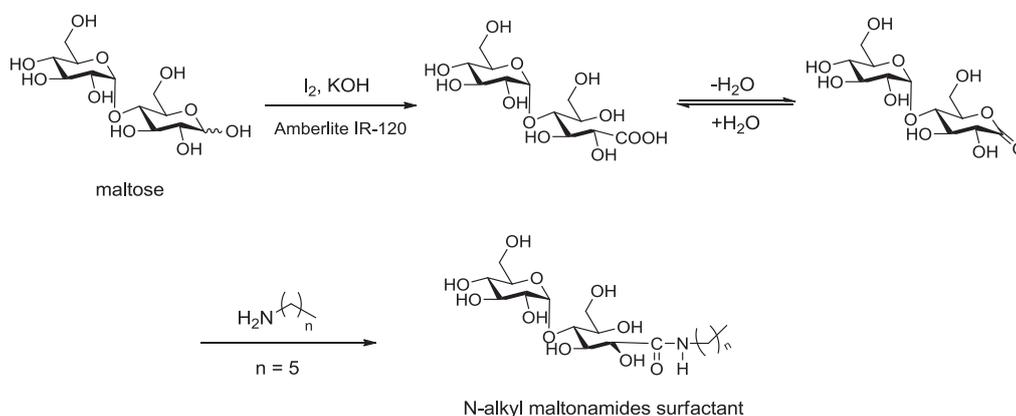
The synthetic route for *N*-methyl glucamide is presented below (scheme 13).⁶⁶ In the first step, glucose undergoes a reductive amination with of ammonia or short-chain primary amines (usually methyl amine) in the presence of hydrogen and Raney Nickel or palladium on carbon to give *N*-methyl glucamine. Then, in the second step, *N*-methyl glucamine is acylated with fatty acid methyl ester under base catalysis to give the final *N*-methyl glucamide surfactant.



scheme 13. Synthetic route for *N*-methyl glucamide.

1.3.2.3 Disaccharide-based amide surfactants.

Disaccharides can also be connected with hydrophobic moiety by an amide linkage. Zhang and Marchant have reported a *N*-alkyl maltonamide surfactant by oxidizing the masked aldehyde group of maltose to carboxylic acid, then followed with reversible cyclisation to lactone then reacted with alkylamine to form the amide surfactants.⁶⁷



Scheme 14. Amide linkage for maltose-derived surfactant.

An aqueous solution of I_2/KOH was used to oxidize the reducing end group of D-maltose and 98% of starting material D-maltose was found to be oxidized to maltonic acid after 2 hours of reaction and then followed by cyclisation to lactone. To achieve high conversion from lactone to

⁶⁶ D. Balzer, H. Luders, *Nonionic Surfactants: Alkyl Polyglucosides*, CRC Press, **2000**.

⁶⁷ a) T. Zhang, R. E. Marchant, *Macromolecules*, **1994**, *27*, 7302-7308. b) T. Zhang, R. E. Marchant, *J. Colloid Interface Sci.*, **1996**, *177*, 419-426.

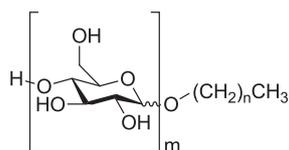
amide, excess hexylamine (molar ratio of lactone to amine = 1 to 10) was set at 60°C. In conclusion, in this process the linear structure of the polysaccharide surfactants was assured by the use of selective oxidation, lactonization, and aminolysis reactions.

1.3.3 Glucoside-based surfactants.

Many efforts have been devoted to attach the highly hydrophilic glucose (polyols structure) with a hydrophobic tail from fats or oil derivatives to synthesize glucose-based amphiphilic structures. In order to combine a hydrophobic alkyl chain with another hydrophilic glucose molecule, there are several methods such as Fischer glycosylation to form alkyl polyglucosides (APGs).

1.3.3.1 Alkyl polyglycosides (APGs) surfactants.

Alkyl polyglycosides (APGs) are available in the world market in large quantities (25 000 t annual production in 1992) with competitive price (approximately 1 €/kg). They are commonly used as surfactant in cosmetics, industrial cleaner or agricultural applications. According to the annual production report, they are considered as the most important sugar-surfactant today.⁶⁸ The first alkyl glucoside was synthesized by Emil Fischer⁶⁹ in 1894, and 40 years later their first application as detergents was patented in Germany.⁷⁰ Until the late 1970s, research groups in the world's biggest companies redirected their attention on APGs and developed technical process for APGs production.



alkyl polyglucosides (APGs)

Figure 17. Representatives of glucose-based surfactant.

There are lots of methods to prepare glucosides by attaching a sugar component with an alcohol. Enzyme catalysis could be a good choice to avoid protection-deprotection procedure with good regioselectivity.⁷¹ The main restriction in the enzymatic synthesis of surfactants is the extremely poor solubility of saccharides in the most appropriate organic solvents for such enzyme

⁶⁸ Alkyl Polyglycoside (APG) Industry 2017 Market Research Report, QY Research, **2017**.

⁶⁹ E. Fischer, *Ber. Dtsch. Chem. Ges.*, **1893**, 26, 2400-2412.

⁷⁰ H.Th. Böhme AG, DRP 593422, **1931**.

⁷¹ D. G. Drueckhammer, W. J. Hennen, R. L. Pederson, C. F. Barbas, C. M. Gautheron, T. Krach, C.-H. Wong, *Synthesis*, **1991**, 7, 499-525.

catalysis. Further, the enzyme based synthesis works well for the synthesis of lower chain length alkyl glycosides. With higher chain length alcohols (above C8) low yields are obtained due to poor miscibility of long chain alcohols with water. Although solubility can be improved by using higher temperature but that leads to denaturation of the enzymes.⁷²

Chemical methods have been preferred at the industrial scale for market requirements. In chemical synthetic routes, glucose can be catalyzed either by acid,⁷³ base⁷⁴ or by a leaving group such as halogen derivatives⁷⁵ or sulfonium group.⁷⁶

The fundamental approach to synthesize alkyl glucosides for industry is the well-known Fischer glycosylation of unprotected carbohydrates.⁶⁹ The fact that the reaction is an equilibrium and due to the polyfunctionality of glucose, the glycosylation leads to a complex mixture of randomly linked glycoside oligomers (disaccharide, trisaccharide...). Over the past decades, efforts have been made to control the ratio of alkyl monoglycosides to alkyl oligoglycosides by adjusting the amounts of glucose and fatty alcohol in the reaction mixture which successfully enable this synthesis route to be efficient enough for industrial process.

Depending on different source of glucose (starch/cellulose or glucose), there are three processes for alkyl polyglucoside manufacturing. When glucose is used as starting material, direct synthesis with long chain alcohol is carried out to obtain alkyl polyglucosides (scheme 15, a). Furthermore, when starch/cellulose is applied as carbohydrate source, the transglycosylation of them with short-chain alkyl alcohols occurs under acid catalyst at high temperature (200 °C). Among the different homogeneous acid catalysts tested, H₂SO₄ and heteropolyacids of the type H₃PW₁₂O₄₀ and H₄SiW₁₂O₄₀ were found to be most efficient. Longer alkyl alcohols usually have solubility problems with starch/cellulose, their glucosides are obtained by a cascade reaction, that is, by transglycosylation of starch/cellulose with short alkyl alcohols such as methanol and butanol followed by another transglycosylation with fatty alcohols such as *n*-octanol and dodecanol under acid catalyst such as Amberlyst 15 (scheme 15, b and c).⁷⁷ The yield of methyl D-glucosides produced was 84%, allowing *n*-octyl-D-glucosides to be produced in an overall yield of 73 %.

⁷² M. Y. Rather, S. Mishra, *Sustainable Chem. Processes*, **2013**, *1*, 7-22.

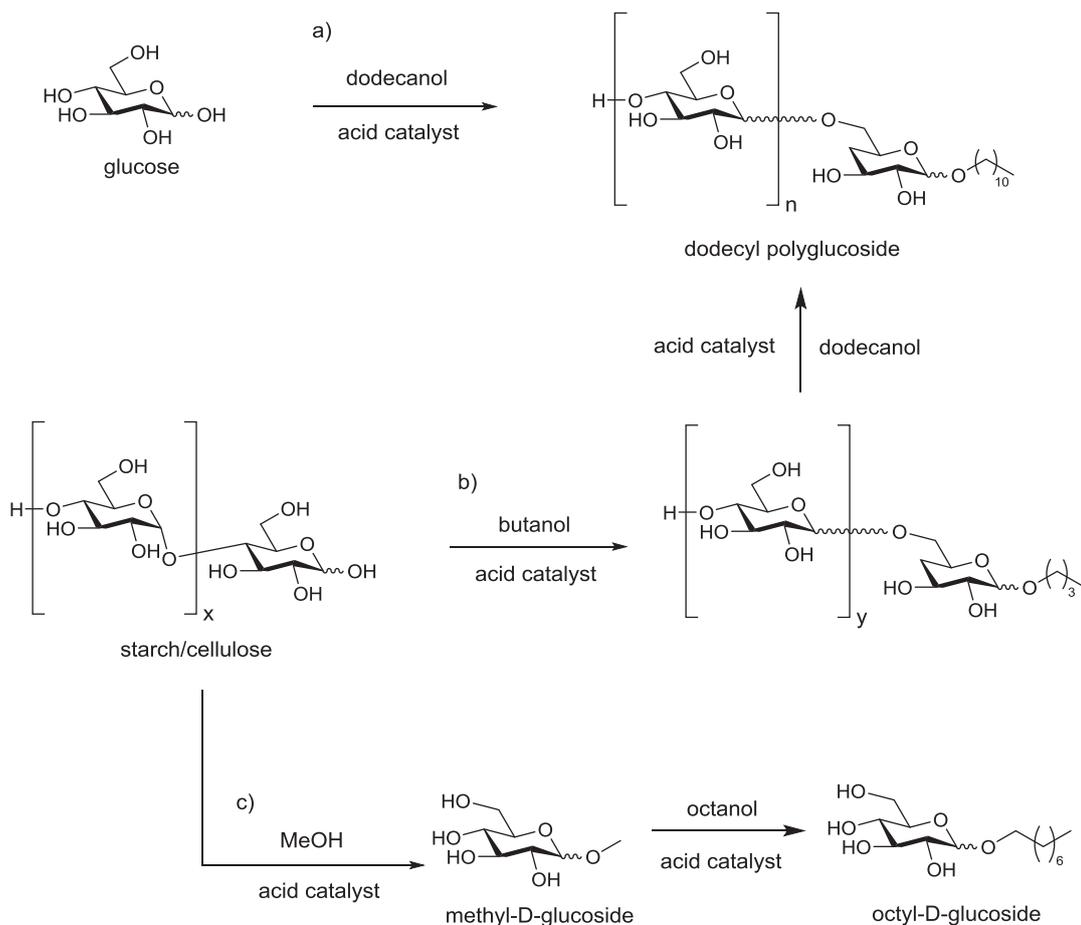
⁷³ C. Bosso, J. Defaye, A. Domard, A. Gadelle, C. Pedersen, *Carbohydr. Res.*, **1986**, *156*, 57-68.

⁷⁴ R. R. Schmidt, M. Reichrath, *Angew. Chem.*, **1979**, *18*, 466-467.

⁷⁵ W. Koenigs, E. Knorr, *Mitteilungen*, **1901**, *34*, 957-981.

⁷⁶ A. C. West, C. Schuerch, *J. Am. Chem. Soc.*, **1973**, *95*, 1333-1335.

⁷⁷ F. Jerome, S. Marinkovic, B. Estrine, *ChemSusChem*, **2018**, *11*, 1395-1409.



scheme 15. Reaction pathways for the industrial production of alkyl polyglucosides.

In the first step, the oligo- or polyglucose reacts with short chain alcohol and depolymerize at the same time. Then, in the second step, the short-chain alkyl glycoside is transacetalized with a long-chain alcohol such as dodecanol to form the final alkyl polyglucoside. After reaction, in the crude alkyl mono-, alkyl oligo- and alkyl polyglucoside are usually mixed together, the degree of polymerization can be calculated from the ratio of glucose to alcohol.⁷⁸

1.3.4 Surfactants connected by an ether linkage.

Surfactants connected by ether linkages are considered to be more stable and can be applied in a broader range of pH than esters. Some typical ether-linked surfactants are listed in Figure 18.

⁷⁸ N. Buschmann, F. Hulsbttter, A. Kruse, S. Wodarczak, *Fett/Lipid*, **1996**, *12*, 399-402.

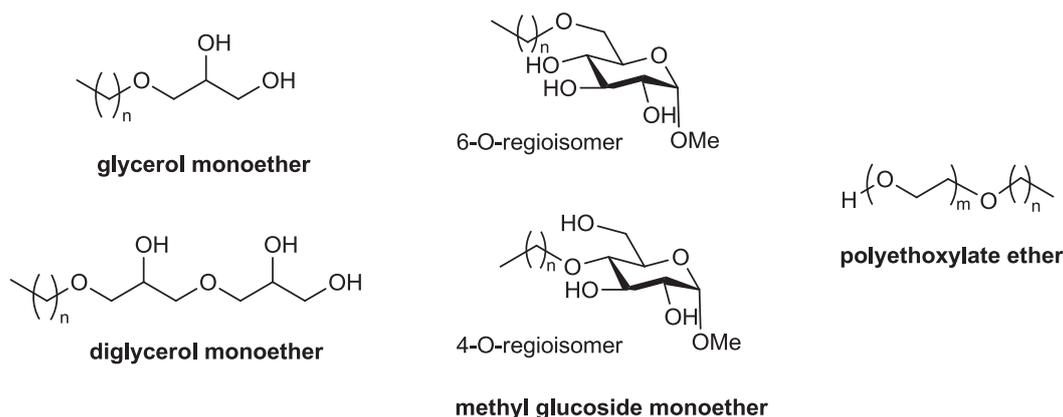


Figure 18. Examples of ether-linked surfactants.

In the last decades, their synthetic routes have been well investigated since the traditional Williamson etherification of these substrates is not practical for industrial process and it is not good enough from both the economic and environment point of views.

1.3.4.1 Ethoxylate-based ether surfactants.

Ethoxylate-based ethers are also synthesized in industry as emulsifiers and detergents. Alcohol ethoxylate (AE) and alkylphenol ethoxylate (APE) are the representatives mostly used among the non-ionic ethoxylate-based surfactants (Figure 19). They are manufactured by reacting alcohol or alkylphenol with ethylene oxide. Alkylphenol ethoxylates (APEs) are usually used with at least 8 ethoxylate (EO) units. Octylphenol ethoxylates (OPEs) and nonylphenol ethoxylates (NPEs) are two of the most common surfactants in the marketplace. NPEs represent approximately 80% to 85% of the volume of APEs. They are quite stable at high temperature, acid and base while they are less biodegradable than fatty alcohol ethoxylates (AEs). AEs usually perform their best properties when using a C12 to C15 alkyl chain and 9 to 10 ethoxylate (EO) units.

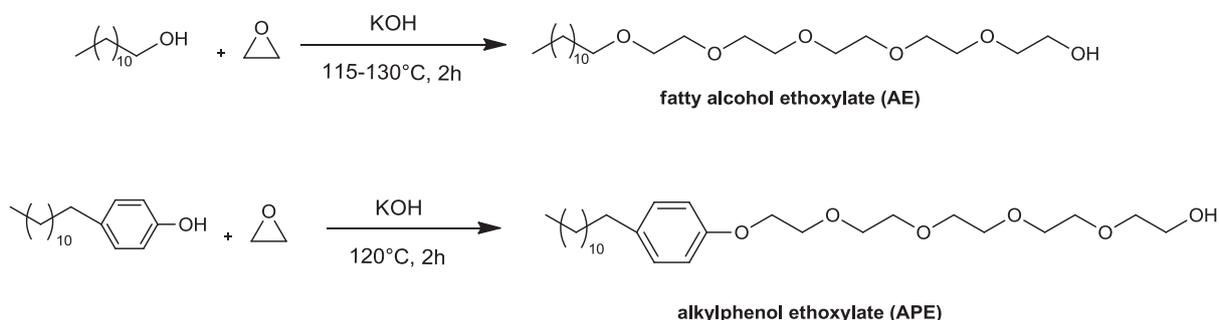


Figure 19. Examples of ethoxylate-based nonionic surfactant and their synthetic route.

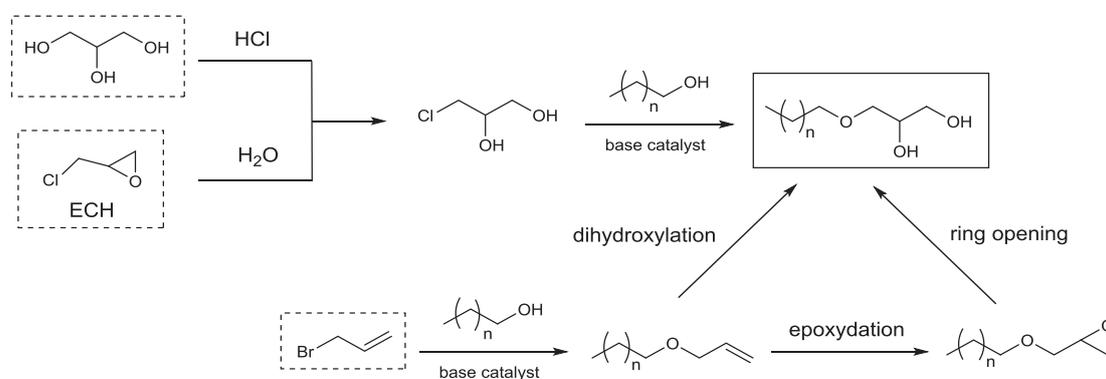
Polyethoxylate ether is usually prepared by addition of alcohol to ethylene oxide in the presence of a base catalyst.⁷⁹ The temperature of this process must be controlled (115-130 °C) to avoid explosion and lead to formation of a stoichiometric amount of salts. So other safer substrates and methods with higher atom economy have been investigated.

1.3.4.2 Glycerol-based ether surfactants.

Glycerol is formed as by-product from many different processes such as soap manufacture, fatty acid/ester production and microbial fermentation. The valorization of glycerol to value added derivatives has attracting more and more industrial interest. Glycerol monoethers (GME) are the most valuable glycerol derivatives which commonly find its application in detergents, cosmetics and pharmaceuticals.

Glycerol ethers can be synthesized by Williamson etherification from glycerol while due to the similar reactivity of the three hydroxyl groups of glycerol, protection and de-protection steps are required to obtain glycerol monoethers. It is also possible to start from modified substrates such as epichlorohydrine (ECH)⁸⁰ or allyl halide.⁸¹ However, as mentioned before, a stoichiometric amount of salts is formed in the process which leads to a low atom economy (

Scheme 16).



Scheme 16. Preparation of glycerol ethers by Williamson etherification from glycerol, ECH and allyl halide.

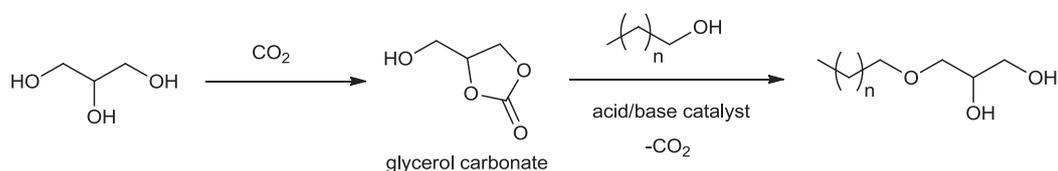
The use of toxic starting material (ECH), polar aprotic solvent such as DMSO and DMF when the substrate is long alkyl chain alcohol make this process with high ecological impact.

⁷⁹ a) F. Hulskotter, S. Scialla, B. J. Loughnane, A. E. Waun, S. Ebert, B. Ludolph, C. Wigbers, S. Maas, *US14919842*, **2014**. b) M. Kinoshita, K. Saito, *JP2014005185*, **2012**.

⁸⁰ W. H. Davies, I. M. Heilbron, W. E. Jones, *J. Chem. Soc.*, **1933**, 0, 165-167.

⁸¹ B. V. S. K. Rao, A. Gangadhar, R. Subbarao, G. Lakshminarayana, *Org. Prep. Proced. Int.*, **1991**, 23, 119-122.

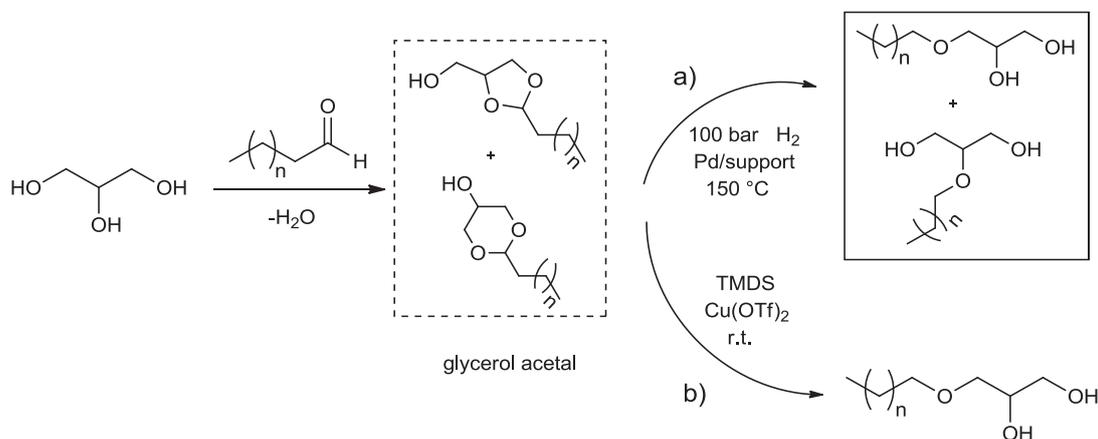
Our group has developed a process starting from glycerol, protected by CO₂ to glycerol carbonate intermediate then followed by etherification of alkyl alcohols to give desired glycerol monoethers with moderate to good yield.⁸² With the increase of chain length, this process becomes even less efficient due to the formation of dialkyl carbonate.



Scheme 17. Preparation through glycerol carbonate intermediate.

For selectivity reasons, it is also interesting to prepare glycerol acetals then followed by the reduction step. In the first step of preparing acetal by reacting glycerol with alkyl aldehydes, a mixture of both 5- and 6- membered glycerol acetal regioisomers were obtained.⁸³ This mixture was reduced under hydrogen and in the presence of supported palladium catalyst to give 75% of glycerol monoether (ratio 84:16) (Scheme 18, a).⁸⁴

Our group has developed another method using 1,1,3,3-tetramethyldisiloxane (TMDS) to open the ring of glycerol acetal mixture with a better selectivity under mild condition (room temperature) to give 1-*O*-glycerol monoether with 72% isolated yield (Scheme 18, b).⁸⁵



Scheme 18. Preparation through glycerol acetal intermediates.

⁸² G. Mignani, E. Da Silva, W. Dayoub, Y. Raoul, M. Lemaire, PCT Int. Appl. WO 2013139995, **2013**.

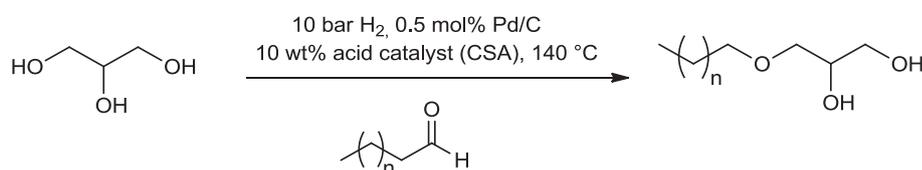
⁸³ S. Nakagawa, Y. Yokota, Patent EP 0624563, **1994**.

⁸⁴ A. Nagasawa, M. Okutsu, T. Kitsuki, Patent WO 132306, **2001**; Patent EP 1236511, **2001**.

⁸⁵ Y. J. Zhang, W. Dayoub, G. R. Chen, M. Lemaire, *Green Chem.*, **2011**, 13, 2737-2742.

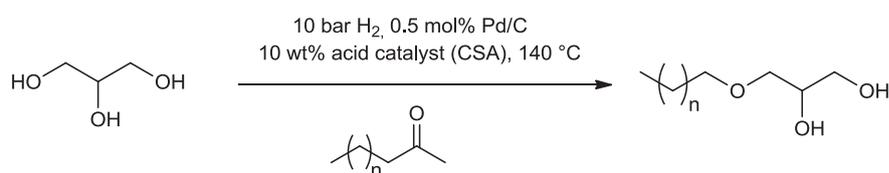
Although good isolated yield and high selectivity can be obtained in this process, the reagent TMDS, solvent and catalyst are relatively expensive and it leads to silicon waste. This method is still limited and is not suitable to be applied to large-scale industrial production.

Besides, direct reductive alkylation of glycerol has been carried out on a range of bio-sourced or readily available substrates such as aldehydes,⁸⁶ ketone,⁸⁷ carboxylic acid,⁸⁸ and fatty acid methyl esters,⁸⁹ especially with long alkyl chain, in a direct etherification by using a recyclable catalytic system. In this one-step synthesis (Scheme 19), glycerol was used directly as reagent and solvent with both linear and branched aldehydes and underwent reductive alkylation to give glycerol monoether with high GC yield (82-97%) and good selectivity (9 : 1 to 25 : 1).⁸⁶



Scheme 19. Direct etherification from glycerol with aldehyde.

Based on these successful results for the preparation of glycerol monoethers starting from aldehydes, catalytic etherification starting from ketone substrates were also investigated (Scheme 20). The synthesis of 1-O-alkyl glycerol monoethers by reductive alkylation of ketones is presented with good to excellent yields (42-87%) and good selectivity (8 : 1 to 9 : 1).⁸⁷



Scheme 20. Synthesis of glycerol monoethers directly from glycerol and ketones.

Unfortunately, there is only few industrial accesses to aldehydes and ketones from renewable starting materials. To prepare glycerol monoethers by an eco-efficient process, carboxylic acids were taken into consideration due to their bio-source, inexpensiveness and readily availability on a large scale. A large scope of carboxylic acids were investigated and moderate to good isolated

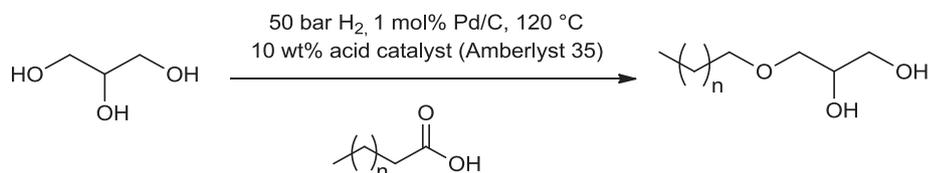
⁸⁶ a) Y. Shi, W. Dayoub, G. R. Chen, M. Lemaire, *Green Chem.*, **2010**, *12*, 2189-2195. b) Y. Shi, W. Dayoub, A. F. Réguillon, G. R. Chen, M. Lemaire, *Tetrahedron Lett.*, **2009**, *50*, 6891-6893.

⁸⁷ a) V. Bethmont, F. Fache, M. Lemaire, *Tetrahedron Lett.*, **1995**, *36*, 4235-4236. b) Y. Shi, W. Dayoub, G. R. Chen, M. Lemaire, *Sci. China: Chemistry*, **2010**, *53*, 1953-1956.

⁸⁸ M. Sutter, W. Dayoub, E. Metay, Y. Raoul, M. Lemaire, *ChemSusChem*, **2012**, *5*, 2397-2409.

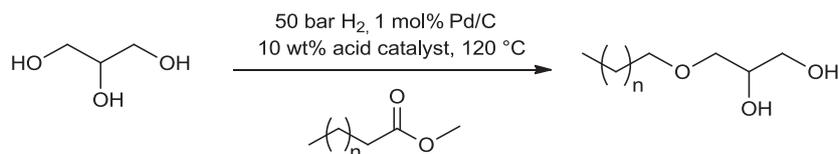
⁸⁹ M. Sutter, W. Dayoub, E. Metay, Y. Raoul, M. Lemaire, *Green Chem.*, **2013**, *15*, 786-797.

yields of 1-*O*-alkyl glycerol monoethers were obtained by using different chain length of linear fatty acids (28-73%), branched acids (47-72%) and also cyclic acids (71-74%) with good selectivity (80 : 20).⁸⁸ The reactivity of acids that contain longer alkyl chain was studied, consequently, the yields for 1-*O*-alkylglycerol monoethers with a longer chain decreased due to the less solubility of these substrates in glycerol.



Scheme 21. Reductive alkylation of glycerol with carboxylic acids.

In addition, methyl esters are obtained as products in the biodiesel industry, with a good accessibility and often a less expensive cost than the corresponding carboxylic acids. Thus the reductive alkylation of glycerol with methyl esters was explored (Scheme 22). Isolated yields of this direct preparation of 1-*O*-glycerol monoethers are 26-73% with good selectivity (85 : 15).⁸⁹



Scheme 22. Direct reductive alkylation through fatty acid methyl ester.

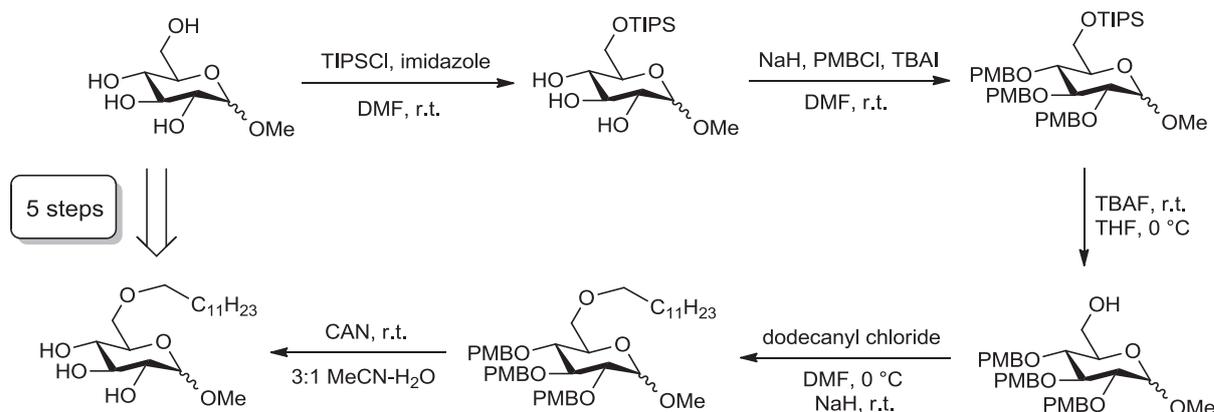
These processes usually require using a large excess of glycerol to obtain a good selectivity toward the primary glycerol ether and only generate water as by-product. However, the need for a high hydrogen pressure would limit its application due to safety reasons.

1.3.4.3 Carbohydrate-based ether surfactants.

Carbohydrate alkyl ethers have been proposed as an alternative for their corresponding esters for similar applications while with better stability since they have a better stability under acidic and basic conditions. However, due to the presence of several hydroxyl groups on the carbohydrate skeleton with similar reactivity, protection and de-protection steps are usually required to avoid the possibility formation of polysubstituted product.

Synthesis of these ether derivatives usually started from the protection of the primary hydroxyl group with a triisopropylsilyl group, then fully protected by using *p*-methoxybenzyl chloride (PMB). Next step is to remove the TIPS group to give the free primary hydroxyl to attach

with dodecanyl chloride. Finally, oxidative cleavage of the PMB groups with ceric ammonium nitrate (CAN) give the desired mono-dodecanyl carbohydrate (Scheme 23).



Scheme 23. Protection-deprotection steps of carbohydrate ether preparation.

This process would cause a low overall yield after several protection and deprotection steps and also lead to large amount of waste.⁹⁰

To avoid this large amount of waste, other synthetic routes were taken into account. Similar to the direct reductive alkylation of glycerol, the direct reductive alkylation of methyl glucoside was carried out with a range of aldehydes under previously optimized conditions (50 bar hydrogen with 0.5 mol% Pd/C catalyst and 10 wt% of an acid cocatalyst CSA). However, the yield of methyl glucoside ethers were very low (Scheme 24, a).

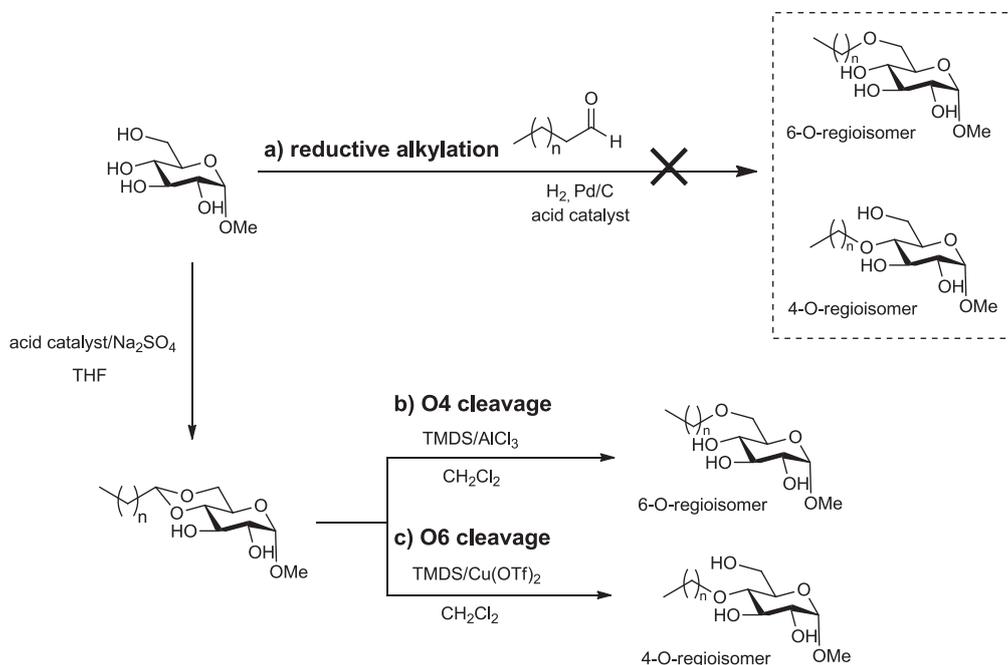
Reductive cleavage of the C-O bond of acetals is one of the major methods in ether synthesis which can also construct desired building blocks into carbohydrates. Acetals are often used to protect 4-O- and 6-O- position of pyranoside because they can be easily prepared and followed with selective cleavage to give primary or secondary ethers. Various hydride source such as LiAlH₄, NaH, DIBAL-H, NaBH₃CN, BH₃, Et₃SiH, PhSiH₃ are used in traditional methods to reduce 4,6-O-acetals.⁹¹ However, most of them are expensive, water sensitive and sometimes release toxic gas.

Our group has recently developed a regioselective cleavage of acetals in the presence of an efficient, water/air stable hydride source TMDS to obtain either 6-O- or 4-O- regioisomer with

⁹⁰ A. Smith, P. Nobmann, G. Henehan, P. Bourke, J. Dunne, *Carbohydr. Res.*, **2008**, *343*, 2557-2566.

⁹¹ a) H. M. Doukas, T. D. Fontaine, *J. Am. Chem. Soc.*, **1951**, *73*, 5917-5918. b) S. E. Denmark, N. G. Almstead, *J. Am. Chem. Soc.*, **1991**, *113*, 8089-8110. c) C. R. Shie, Z. H. Tzeng, S. S. Kulkarni, B. J. Uang, C. Y. Hsu, S. C. Hung, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1665-1668.

Cu(OTf)₂ and AlCl₃ respectively with moderate to good yields (Scheme 24, b and c).⁹² Unprotected methyl glucoside acetals were reduced using this direct and selective method to prepare carbohydrate-based long aliphatic chain ethers.



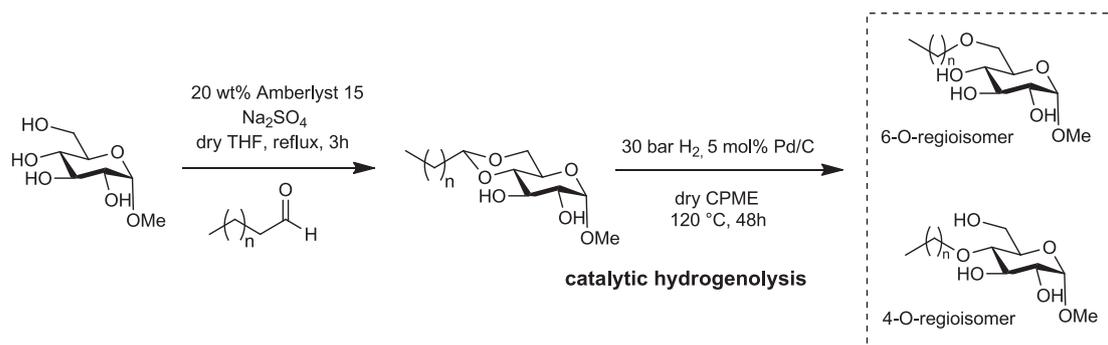
Scheme 24. Methods for preparation of glucoside monoether.

Even if it is safer to use TMDS as reducing agent, it is still expensive and the work-up is difficult. Later investigation has been carried on about catalytic hydrogenolysis of the unprotected methyl glucoside acetals by using environment benign hydrogen as a clean reducing agent in the presence of Pd/C in CPME which could give a better yield and higher selectivity to monoether with a 7:3 mixture of regioisomers (6-*O*- to 4-*O*- regioisomers). A two-step sequence has been developed started from unprotected methyl glucoside and other carbohydrate substrates⁹³ through acetal to obtain methyl glucoside monoethers.⁹⁴

⁹² Y. J. Zhang, W. Dayoub, G. R. Chen, M. Lemaire, *Eur. J. Org. Chem.* **2012**, 1960-1966.

⁹³ D. Belmessieri, C. Gozlan, M. C. Duclos, V. Molinier, J. M. Aubry, O. Dumitrescu, G. Lina, A. Redl, N. Duguet, M. Lemaire, *Eur. J. Med. Chem.*, **2017**, 128, 98-106.

⁹⁴ C. Gozlan, R. Lafon, N. Duguet, A. Redl, M. Lemaire, *RSC Adv.*, **2014**, 4, 50653-50661.



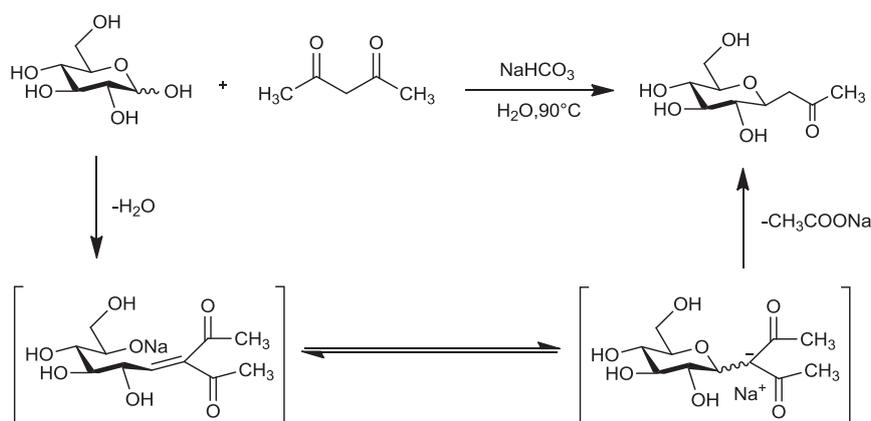
Scheme 25. Catalytic hydrogenolysis of methyl glucoside acetals to ethers.

1.3.5 Surfactants connected by C-C bond linkage.

The above linkages, either ester or ether link, they are *O*-glycosidic linkages. In carbohydrate chemistry, generally glycosides can be linked with *O*-, *N*-, *S*- and *C*- glycosidic bonds. Undoubtedly, the *C*- glycosidic linkage is the most stable connection to resist both acid and base hydrolysis and it can valorize the application of surfactants in harsh conditions. Y. Kishi. *et al.* has reported that *C*-glycoside could be expected to be similar in both structure and property with *O*-glycoside.⁹⁵ However, the replacement of exo-anomeric oxygen to a methylene group is still a challenge in carbohydrate chemistry. Significant attention has been focused on new routes for their synthesis.

1.3.5.1 Formation of *C*-glycosides.

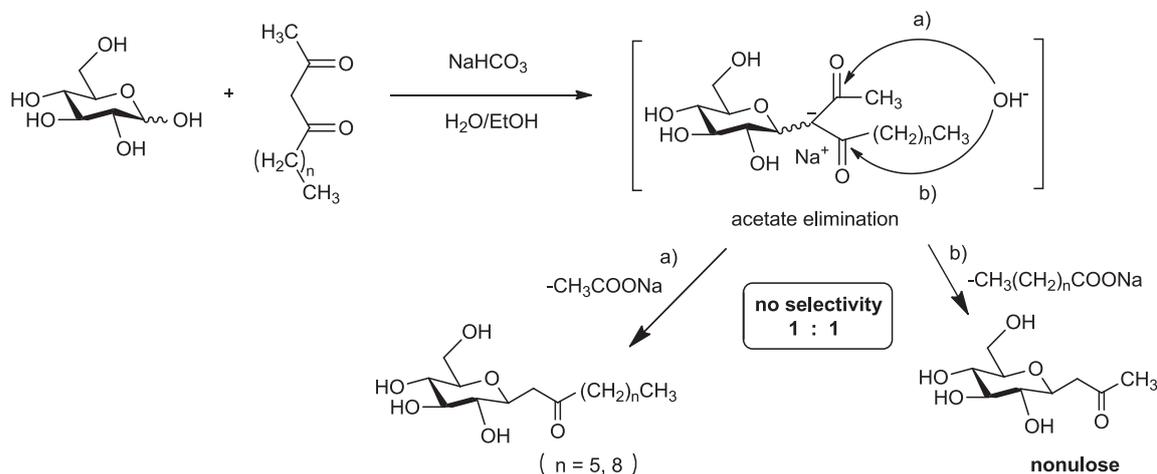
In 2000, Lubineau *et al.* have developed a convenient, one-step synthesis of β -*C*-glycosidic ketone in aqueous media.⁹⁶ The key synthetic step of this process relies on the Knoevenagel condensation of the carbanion of 1,3-diketone and the formyl group of an unprotected carbohydrate (Scheme 26).

Scheme 26. Preparation of *C*-glycosidic bond from unprotected carbohydrate and 1,3-diketone.

⁹⁵ T. C. Wu, P. G. Goekjian, Y. Kishi, *J. Org. Chem.*, **1987**, 52, 4819-4823.

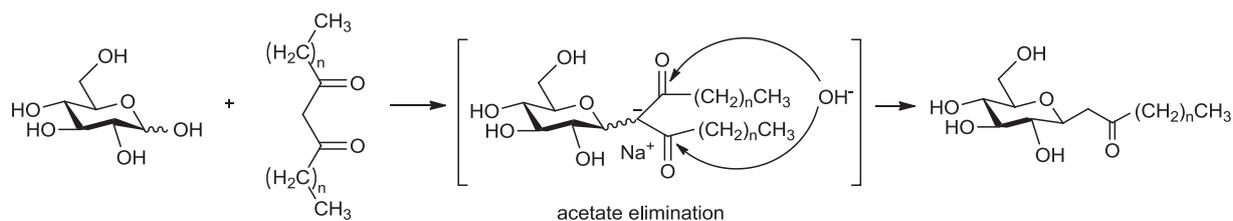
⁹⁶ F. Rodrigues, Y. Canac, A. Lubineau, *Chem. Commun.*, **2000**, 2049-2050.

In order to prepare carbohydrate-based surfactants by using this one-step direct method, nonsymmetrical ketones were used by Lubineau *et al.* expecting that the acetate elimination can be done with a preference towards the long chain C-glycoside rather than the short propanone C-glycoside. The nonulose and the long chain product were obtained at a ratio of 1:1 analyzed by ^{13}C NMR. Unfortunately, no selectivity was observed (Scheme 27).



Scheme 27. Preparation of C-glycosidic bond from unprotected carbohydrates with nonsymmetrical 1,3-ketones with no selectivity.

In order to obtain long chain based C-glycosides, symmetrical 1,3-ketones were used to synthesize these long chain based C-glycosides.⁹⁷ This method can also be used to prepare maltose derivatives bearing C-C bond linkage with 8 or 11 carbons (Scheme 28).



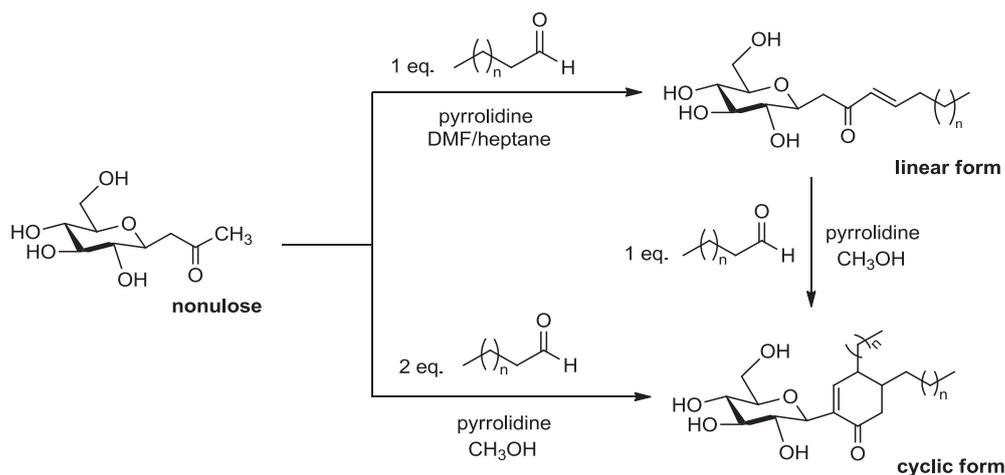
Scheme 28. Symmetrical 1,3-diketone based long chain C-glycosides preparation.

Anastas *et al.* have continued this work by treating the obtained nonulose with pyrrolidine in the presence of a fatty aldehyde under mild conditions (room temperature, with minimal solvent use) in one step.⁹⁸ Two types of C-glycosides (linear and cyclic form) can be accessed depending on

⁹⁷ Y. Hersant, R. A. Jneid, Y. Canac, A. Lubineau, M. Philippe, D. Semeria, X. Radisson, M. C. Scherrmann, *Carbohydr. Res.*, **2004**, 339, 741-745.

⁹⁸ P. M. Foley, A. Phimpachanh, E. S. Beach, J. B. Zimmerman, P. T. Anastas, *Green Chem.*, **2011**, 13, 321-325.

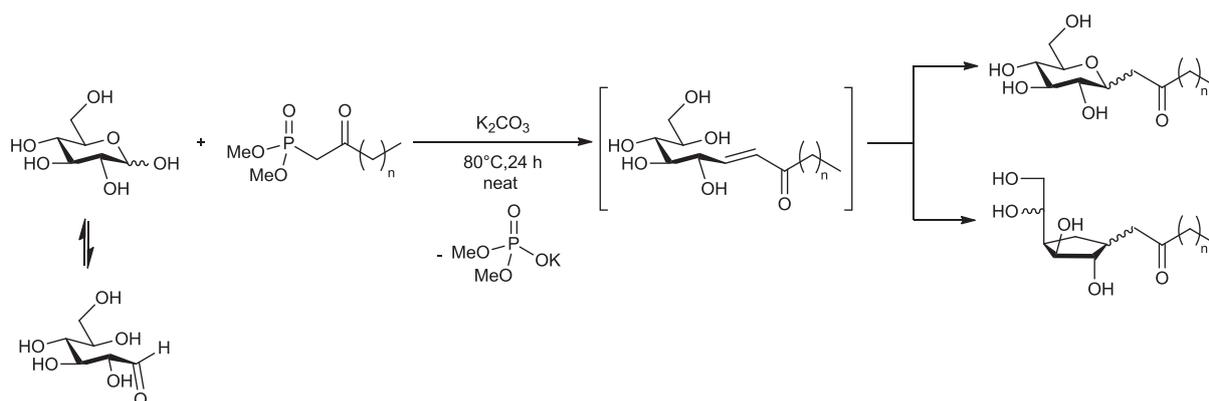
different equivalent of aldehyde/nonulose. The linear enones form generated by this approach can further undergo condensation with an additional fatty aldehyde to generate cyclic series enones (Scheme 29). The evaluation of these C-C bond linked surfactants has shown good physicochemical properties much like their *O*-glycoside counterparts in critical micelle concentration and interface tension decrease. They are able to reduce the water surface tension at very low concentrations (around 24 mN/m). In cooperation with anion surfactants, these C-C bond linkage surfactants appear to be able to enhance the foaming and stabilizing properties.



Scheme 29. General preparation for linear and cyclic C-glycoside surfactants from nonulose.

Besides using 1,3-diketones as nucleophiles, phosphonates were also used to react with unprotected sugars for the formation of the olefins through the Horner-Wadsworth-Emmons (HWE) reaction.⁹⁹ The unprotected carbohydrate is in equilibrium with its hemiacetal form and aldehydes or ketones in ring open form. The acyclic olefin can be obtained through HWE reaction when the carbohydrate is in the open form. They hydroxyl olefins can finally cyclize to give the expected C-glycosides.

⁹⁹ A. Ranoux, L. Lemiegre, M. Benoit, J. P. Guegan, T. Benvegna, *Eur. J. Org. Chem.*, **2010**, 1314-1323.



scheme 30. General route for both C-pyranoside and C-furanoside through the HWE reaction.

This HWE reaction developed by Benvegnu *et al.* was investigated in water or in solvent-free conditions. Unprotected carbohydrates were condensed with readily available β -keto phosphonates with various chain lengths (ranging from C3 to C19). The obtained C-glycosides are isomer mixtures of pyranoside and furanoside. With different chain lengths the yield obtained was moderate to good (48-64%) with 60:40 pyranoside/furanoside ratio. Treatment of the mixtures under basic conditions isomerizes to thermodynamically favored pyranosides.

The methods presented above are generally one-step synthesis of C-glycoside from unprotected carbohydrate and a nucleophile and give the desired product with moderate to good yields. However, there are some disadvantages for these processes: 1) the acetate elimination step leads to a low atom economy; 2) the β -keto phosphonates need to be prepared from corresponding fatty acids over additional two steps; 3) the C-glycoside precursor nonulose need to be synthesized by Lubineau's method, in a relatively green way.

According to the property tests, these C-C bond linked surfactants could be of potential interest. However, in most cases these procedures require specific or harsh reaction conditions; some of them even suffer from protection and deprotection steps which give unsatisfied low yields. Due to the difficulty of this C-C bond formation in a green way, surfactant connected by C-C bond linkage has been less reported despite the widespread attention. So, efforts should be continued to construct C-C bond linked surfactants from unprotected carbohydrates in a green way: green solvents or solvent-free, higher atom economy and mild reaction conditions.

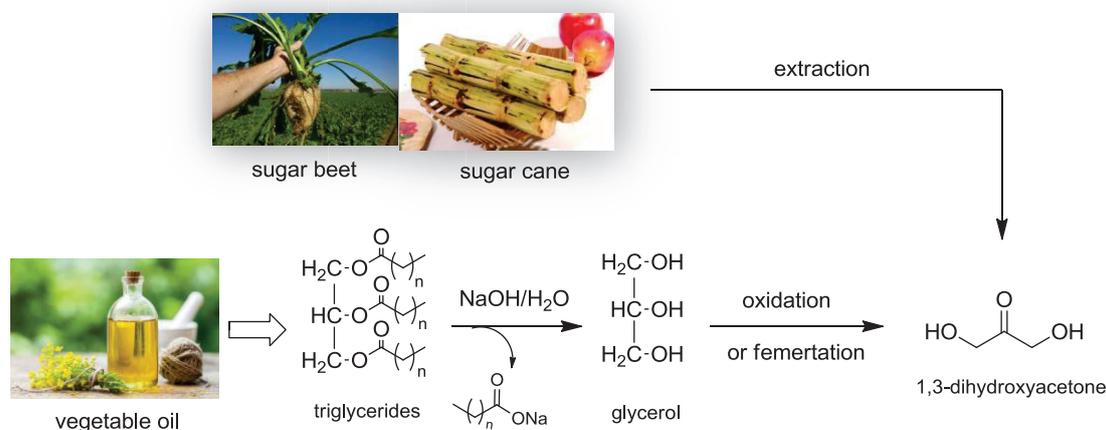
2 Result Part

Chapter 2 Aldolisation of 1,3-dihydroxyacetone (DHA) to C-C bond-linked tetraol surfactants

Based on the previous background, it is interesting for us to synthesize C-C bond linked surfactants directly from unprotected carbohydrates and a readily accessible long chain based starting material in a green way.

1 Introduction

1,3-Dihydroxyacetone (DHA) is a bio-based starting material that can be obtained from plant source such as sugar beets and sugar cane (Scheme 31).¹⁰⁰ It can also be prepared from glycerol by oxidation with some organometallic catalyst¹⁰¹ or by fermentation using enzymes.¹⁰² This production from glycerol is interesting due to the production of glycerol by the biodiesel industry.



Scheme 31. Bio-based 1,3-dihydroxyacetone preparation routes.

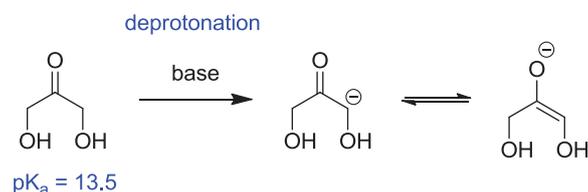
DHA is the simplest ketose (a triose) in nature. The normal form of DHA is a dimer that is slowly soluble in water and ethanol, when freshly prepared, the DHA dimer transfer rapidly into monomer. The monomer contains two hydroxyl groups and it can dissolve in water easily, so it can be used as a hydrophilic part for making non-ionic surfactants.

¹⁰⁰ C. G. Burkhart, C. N. Burkhart, *The Open Dermatology Journal*, **2009**, 3, 42-43.

¹⁰¹ R. M. Painter, D. M. Pearson, R. M. Waymouth, *Angew. Chem., Int. Ed.*, **2010**, 122, 9646-9649.

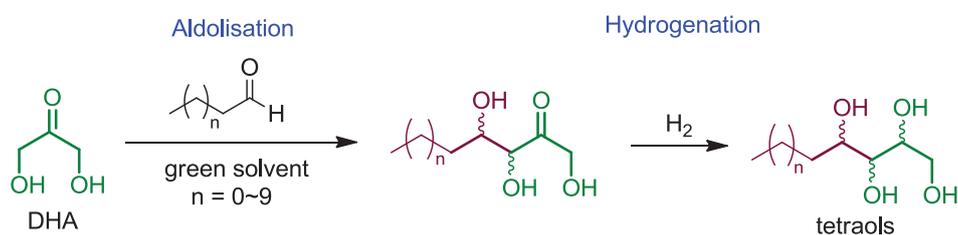
¹⁰² S. R. Lidia, B. Stanislaw, *Eur. Food Res. Technol.*, **2012**, 235, 1125-1132.

The structure of hydroxyl ketone makes 1,3-dihydroxyacetone (DHA) a readily carbonion precursor as nucleophile ($pK_a = 13.5$).¹⁰³ It can be used as a C3 building block in organic synthesis to build C-C bond via aldolisation with an aldehyde as electrophile.



scheme 32. Deprotonation of DHA to be a nucleophile.

The C-C bond connection between the hydrophilic part and hydrophobic part should be a better choice with the aim of building a series of robust surfactants. By using hydrophobic alkyl aldehydes as substrates, a series of different alkyl chain length hydroxyketones could be obtained. These α -hydroxyketone surfactants could be used as surfactants but considering the reversibility of the aldolisation, they can be further transformed to the corresponding tetraols. The reduction of these intermediates can be performed by catalytic hydrogenation to give the desired tetraol surfactants.



Scheme 33. Objective of synthesis of C-C bond-linked surfactant on the base of dihydroxyacetone.

Taking into account the physico-chemical property, with variety of chain lengths it is better to understand the effect between the properties and their structures. The results can also provide us an intelligent way to design a better surfactant for future work.

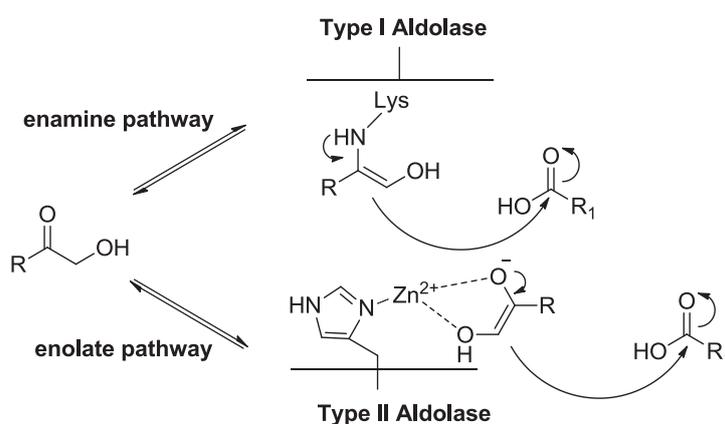
2 Aldolisation of hydroxyketone.

Aldol condensation with an electrophilic aldehyde substrate provides a good way to form C-C bond. Many biocatalysts and organocatalysts have been developed for this DHA aldol condensation.

¹⁰³ ChemAxon analysis predictor.

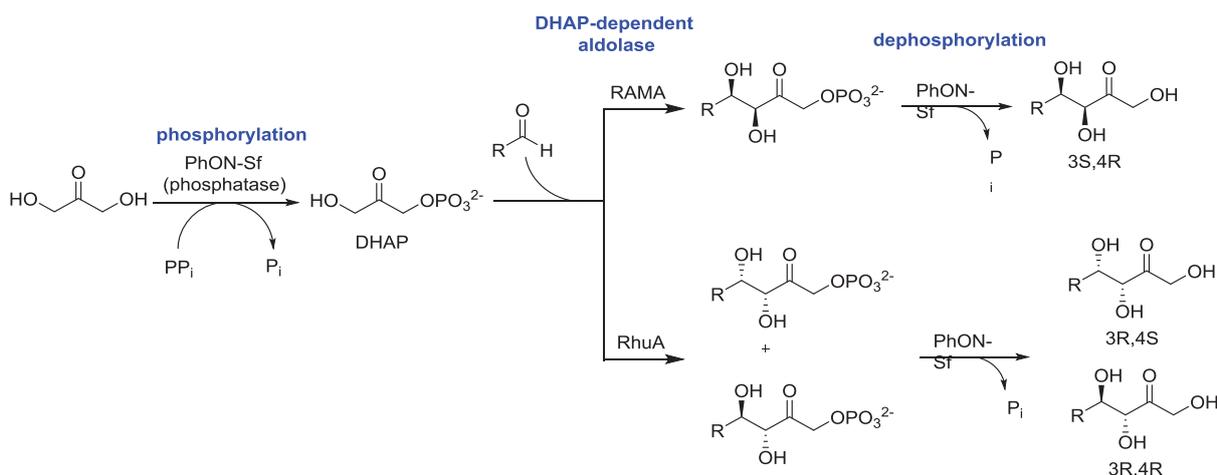
2.1 DHA aldolisation catalyzed by biocatalysts.

Enzymes are extensively used due to their mild reaction conditions and good regio and stereo selectivity. Several aldolases have been demonstrated to be efficient catalysts for the aldolisation of DHA with variety of aldehydes. In Nature, the aldol condensation is catalyzed by two types of aldolases in two different mechanisms either an enamine (Type I) or enolate (Type II) mechanism. Type I aldolase contains a lysine active site with formation of nucleophilic enamine intermediate, and Type II aldolase contains a Zn(II) cofactor active site with the formation of enolate intermediate by coordinating to the carbonyl oxygen of the ketone donor (Scheme 34).



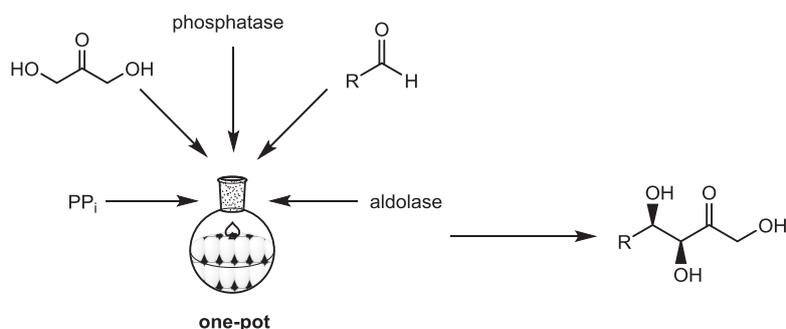
Scheme 34. Two different mechanisms of DHA aldol condensation.

However, most aldolases can not accept unprotected DHA as a substrate. They require dihydroxyacetone phosphate (DHAP) as a substrate.



scheme 35. Phosphatase-aldolase cascade reaction starting from dihydroxyacetone and different aldehydes.

Dihydroxyacetone (DHA) can be easily phosphorylated to DHAP by an acid phosphatase (PhoN-Sf) from a cheap donor (pyrophosphate, PP_i), then follow by an aldol reaction between DHAP and an aldehyde, by the DHAP-dependant aldolase such as RAMA and RhuA. RAMA is completely stereoselective to give (3*S*, 4*R*) product, while RhuA is not and with a linear aldehyde it gives a mixture of (3*R*,4*S*) and (3*R*,4*R*) products (scheme 35).¹⁰⁴



Scheme 36. One-pot synthesis starting from unprotected DHA to dephosphorylated product.

Furthermore, some practical DHAP preparation methods have been investigated by using PP_i in one-pot to obtain directly the dephosphorylated products.¹⁰⁵ DHAP was generated and coupled to propionaldehyde to give a yield of 53% of the isolated dephosphorylated end product.

Since the DHAP substrate is commercially available at a very expensive price (1900 €/g)¹⁰⁶ and instable¹⁰⁷, as well as the need to remove the phosphate ester from the product by phosphatase, makes this process less practical. Some efforts have been made to overcome the dependence on DHAP such as *in situ* formation of arsenate¹⁰⁸ or vanadate¹⁰⁹ esters of DHA.

The *in situ* formed dihydroxyacetone arsenate (DHAAs) was catalyzed by bacterial D-fructose-1,6-bisphosphate aldolase (FruA) with different aldehydes (scheme 37). The use of inorganic arsenate *via* DHAAs afforded higher yields with hydrophobic aldehydes than with hydrophilic aldehydes. Under the optimized conditions, the product of aldol reaction with butanal was separated in 86% yield. However, with the same amount of enzyme, hydrophilic aldehydes reacted 6 to 20 times slower with DHAAs than with DHAP. The use of DHAAs slightly reduces the

¹⁰⁴ L. Babich, A. F. Hartog, L. J. C. van Hemert, F. P. J. T. Rutjes, R. Wever, *ChemSusChem*, **2012**, *5*, 2348-2353.

¹⁰⁵ A. F. Hartog, T. van Herk, R. Wever, *Adv. Synth. Catal.*, **2011**, *353*, 2339-2344.

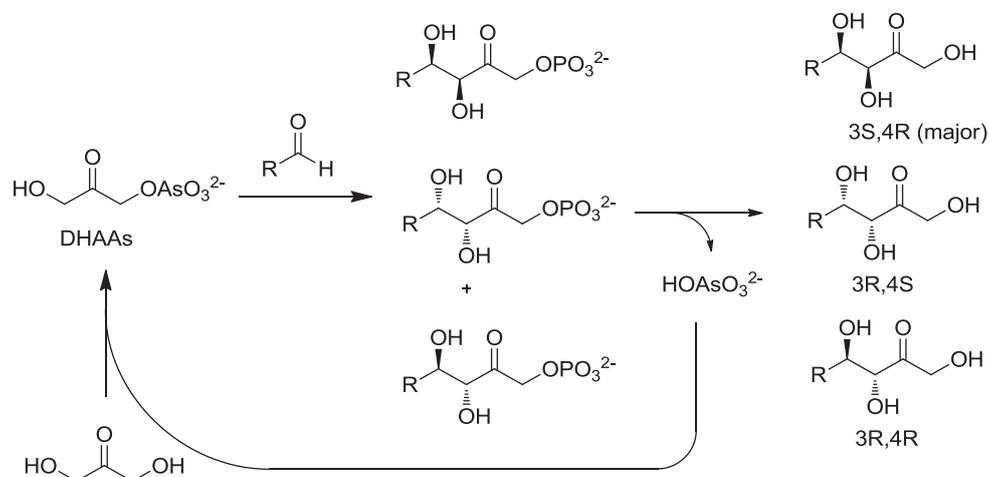
¹⁰⁶ Price from Sigma Aldrich.

¹⁰⁷ T. van Herk, A. F. Hartog, H. E. Schoemaker, R. Wever, *J. Org. Chem.*, **2006**, *71*, 6244-6247.

¹⁰⁸ a) R. Schoevaart, F. van Rantwijk, R. A. Sheldon, *J. Org. Chem.*, **2001**, *66*, 4559-4562. b) R. Lagunas, A. Solis, *FEBS Lett.*, **1968**, *1*, 32-34.

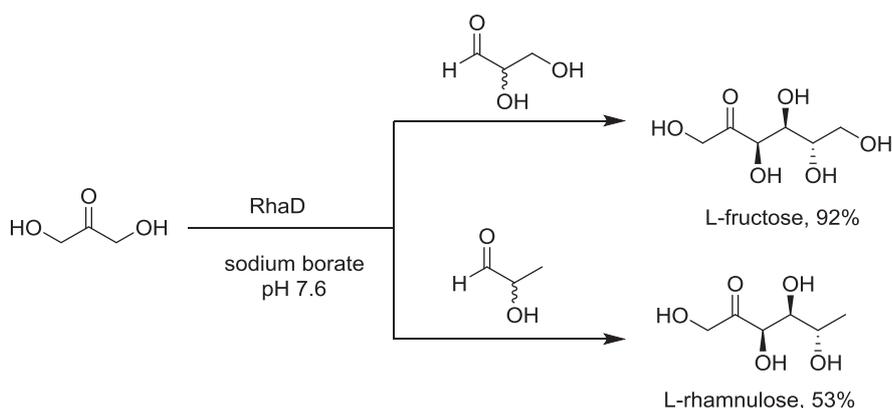
¹⁰⁹ D. C. Crans, K. Sudhakar, T. J. Zamborelli, *Biochemistry*, **1992**, *31*, 6812-6821.

stereoselectivity of the aldolisation. The major isomer obtained with propionaldehyde is (3*S*, 4*R*) at a ratio of 90%, while 100% selectivity observed with DHAP.



scheme 37. Arsenate esters act as a phosphorate mimics.

Arsenate and vanadate esters are mimics of DHAP, unlike the phosphate esters; they are formed spontaneously and reversibly. However, the high toxicity of arsenate and the cost of vanadate limit their practical use for synthetic applications. Moreover, inorganic borate buffer is used by forming a borate ester with DHA, which is also able to act as phosphate ester mimics, catalyzed by rhamnulose 1-phosphate aldolase (RhaD) (scheme 38), nevertheless boric derivatives are also known to be reprotoxic.¹¹⁰

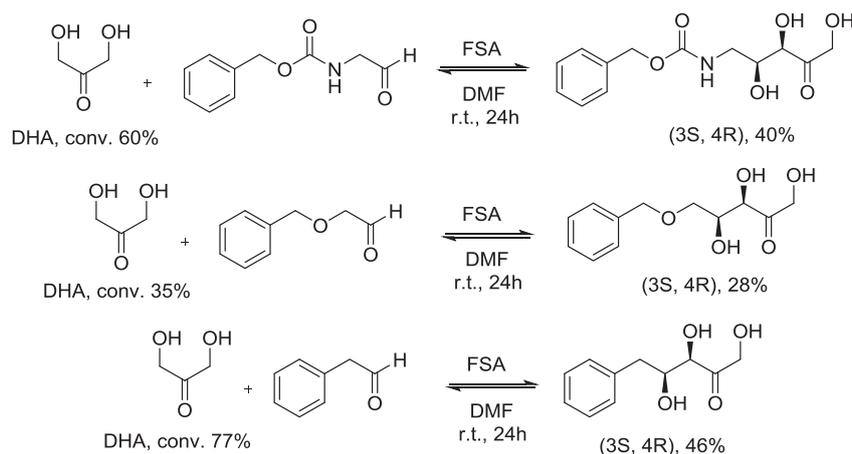


scheme 38. Aldol reaction catalyzed by RhaD in the presence of borate.

In order to avoid the use of DHAP or their mimics due to the synthetically laborious phosphorylation/dephosphorylation steps, D-fructose-6-phosphate aldolase (FSA) from *Escherichia*

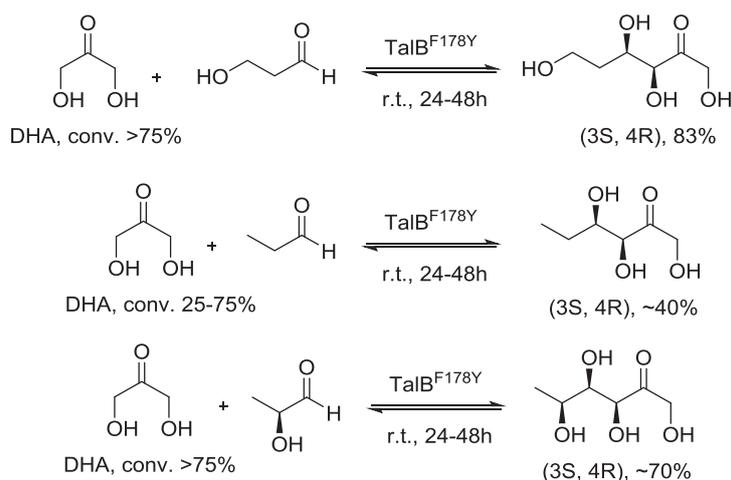
¹¹⁰ a) M. Sugiyama, Z. Hong, L. J. Whalen, W. A. Greenberg, C. H. Wong, *Adv. Synth. Catal.*, **2006**, 348, 2555-2559. b) J. Kjolholt, F. S. Lauridsen, A. S. Mogensen, S. Havelund, *Environmental Project*, **2003**.

coli has been studied due to its significant advantage of accepting unprotected DHA as a substrate. FSA has been shown to be a robust and stereoselective catalyst for DHA aldol condensation with a variety of aldehydes (scheme 39).¹¹¹ Due to reversibility of this aldol reaction, the conversion of DHA is not satisfying (35-77%), while attempts to improve the conversion by increasing the enzyme concentration or successive additions of the aldehyde both failed, leads to a moderate yield of product (28-46%). The FSA was stereoselective in the aldolisation only affording (3*S*, 4*R*) isomer.



scheme 39. FSA-catalyzed aldol addition reactions using unprotected DHA.

Fessner *et al.* have also demonstrated that another transaldolase B, TalB^{F178Y}, is able to accept DHA as direct substrate (scheme 40).¹¹² TalB^{F178Y} enzyme also affords good selectivity to (3*S*, 4*R*) isomer (NMR analysis dr. > 95%) with moderate to good yields (40-83%).



scheme 40. TalB^{F178Y}-catalyzed aldol addition reactions using unprotected DHA.

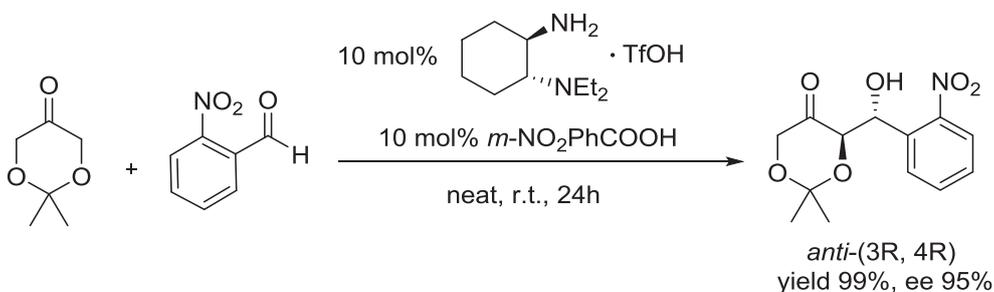
¹¹¹ A. L. Concia, C. Lozano, J. A. Castillo, T. Parella, J. Joglar, P. Clapes, *Chem. Eur. J.*, **2009**, *15*, 3808-3816.

¹¹² M. Rale, S. Schneider, G. A. Sprenger, A. K. Samland, W. D. Fessner, *Chem. Eur. J.*, **2011**, *17*, 2623-2632.

These two enzymes above, TalB^{F178Y} and FSA, have been shown to have the ability of using unphosphorylated DHA as a substrate. However, the aldehydes which can be used in this enzymatic process are limited to aromatic aldehydes or hydroxy short alkyl chain aldehydes. For the synthesis of surfactants, long alkyl chain aldehyde is required to be used as substrate which is still a challenge for biocatalyzed processes.

2.2 DHA aldolisation catalyzed by organocatalysts.

The difficulty of this aldol reaction is due to attaching the very polar DHA molecule to an unpolar aldehyde molecule. Cheng *et al.* have reported a protected cyclic DHA (2,2-dimethyl-1,3-dioxan-5-one) as donor in the presence of an organocatalyst (primary-tertiary diamine-Bronsted acid catalyst) with high yields (up to 99%) and excellent stereoselectivity (up to 97% ee) afforded major *anti*-aldol product (scheme 41).¹¹³



scheme 41. Aldol reaction of protected cyclic DHA by organocatalyst.

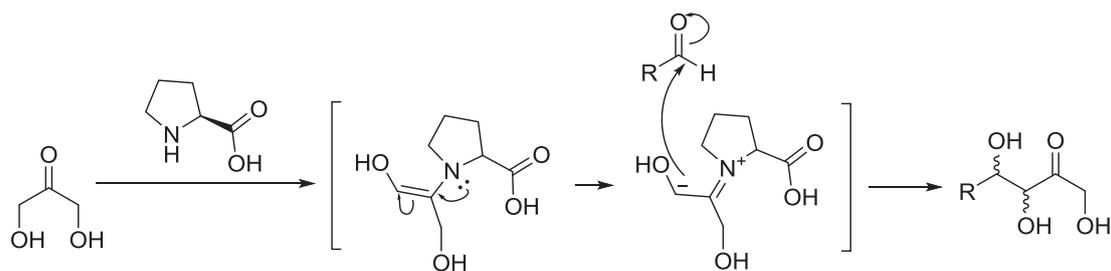
In order to develop organocatalysts which can catalyze this aldol reaction and accepting unprotected DHA, the mechanism of this aldolisation has been investigated.¹¹⁴ Organocatalysts have been investigated based on mimicking the two different types of aldolases in Nature.

2.2.1 Enamine pathway.

The mechanism was demonstrated in scheme 42. An enamine intermediate is forming by addition of L-proline to DHA, and then followed by addition onto the aldehyde.

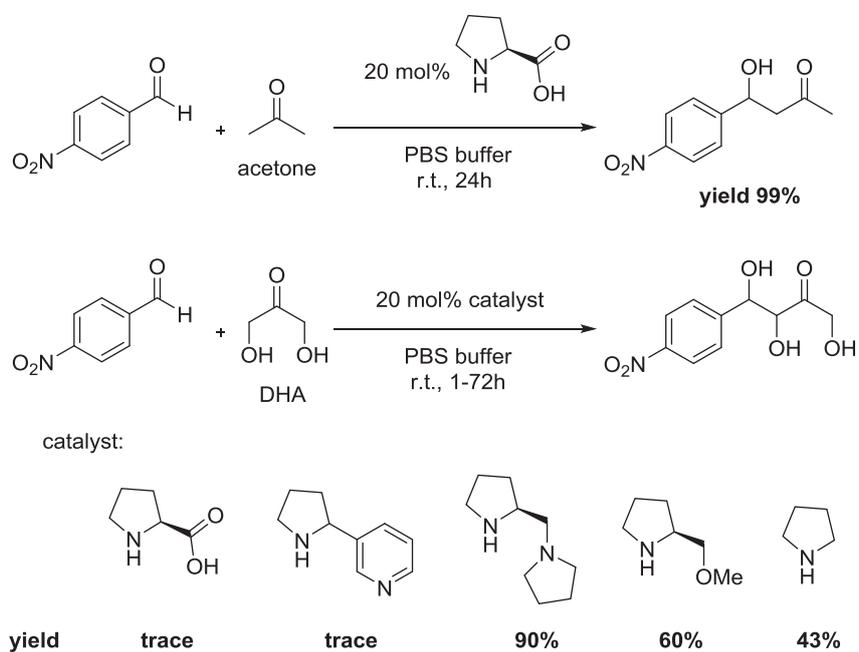
¹¹³ S. Luo, H. Xu, L. Zhang, J. Li, J. P. Cheng, *Org. Lett.*, **2008**, *10*, 653-656.

¹¹⁴ J. Kofoed, J. L. Reymond, T. Darbre, *Org. Biomol. Chem.*, **2005**, *3*, 1850-1855.



scheme 42. Enamine pathway mechanism.

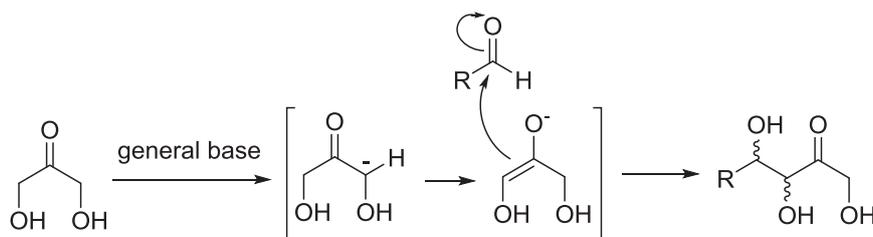
L-proline and short peptides containing *N*-terminal proline residues are capable of catalyzing direct aldol reactions on acetone donor operating *via* an enamine mechanism, while pyrrolidine-based catalysts were found to be more efficient on DHA donor.¹¹⁵

scheme 43. Organocatalysts operating *via* enamine pathway.

2.2.2 Enolate pathway.

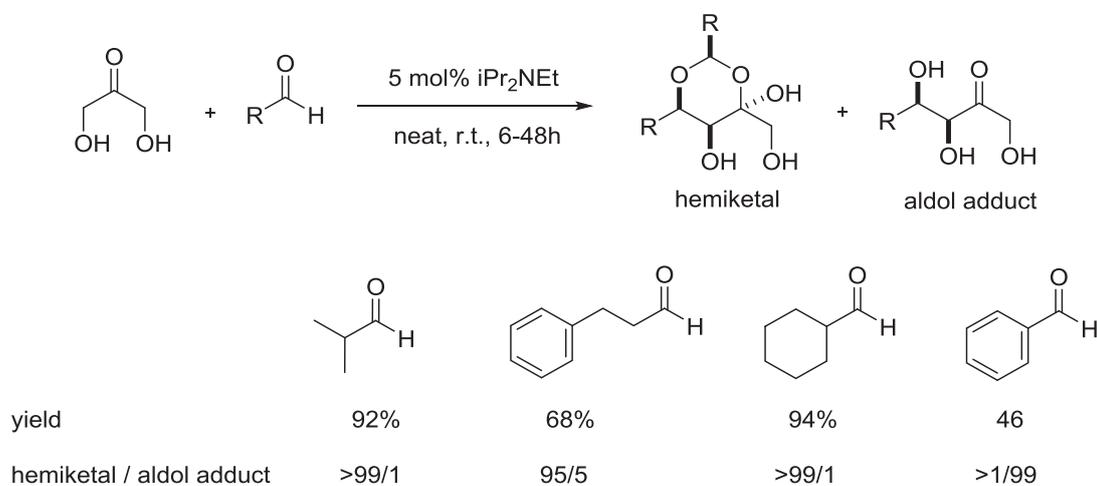
The mechanism was demonstrated in scheme 44. DHA is first deprotonated by a general base to form the enolate intermediate, then followed by the addition of aldehyde.

¹¹⁵ A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.*, **2002**, 3024-3025.



scheme 44. Enolate pathway mechanism.

Mahrwald *et al.* have realized a general amine-catalyzed aldol addition. The reaction was carried out at room temperature without any solvent in 6-48 hours. The products were observed to have an extremely high syndiastereoselectivity.¹¹⁶

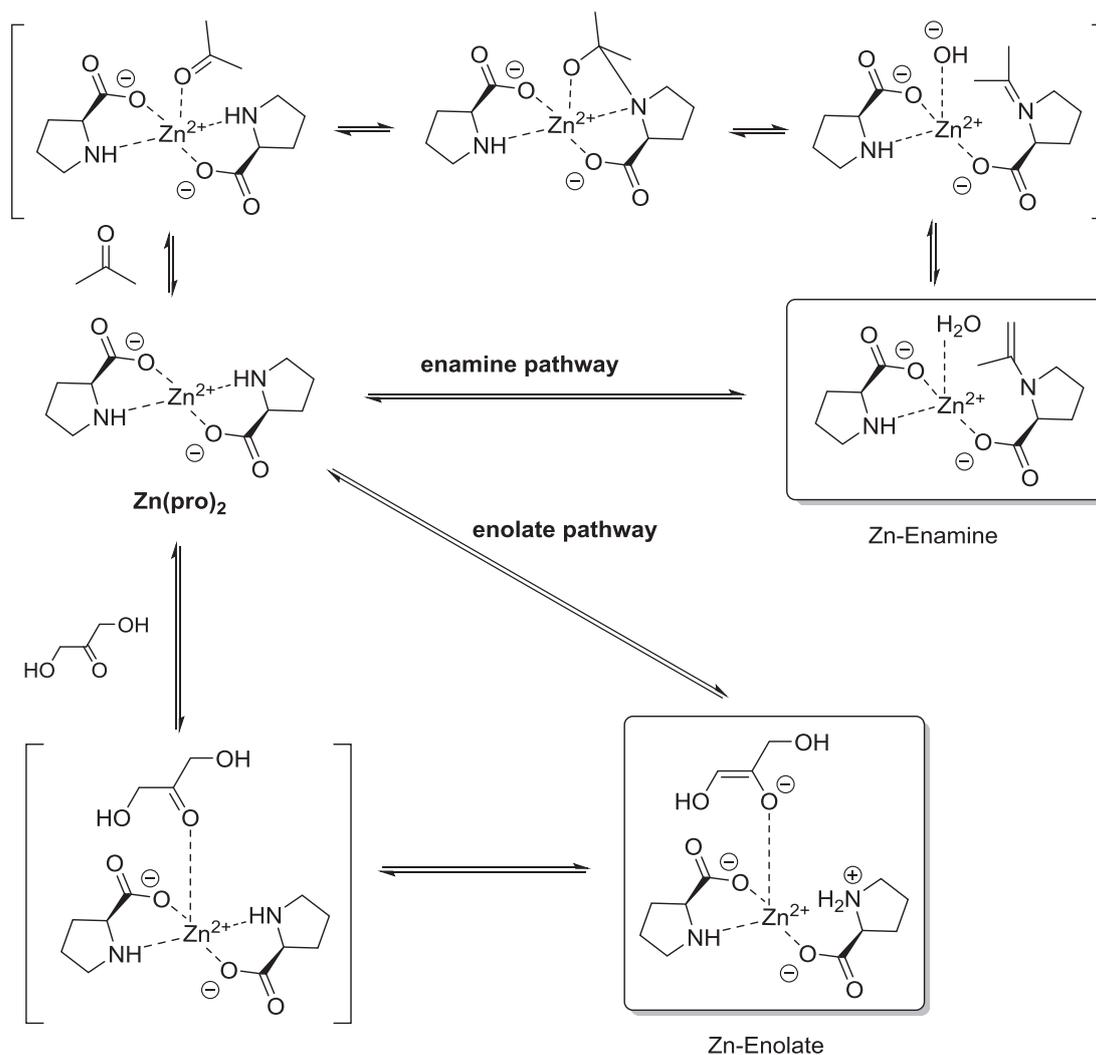
scheme 45. General base operating *via* enolate pathway.

2.2.3 Mixed enamine-enolate pathway.

Zinc is an abundant transition metal and it is found to be involved in the metabolism of carbohydrates in many metalloenzymes including aldolase. Zinc complex such as zinc-proline $Zn(pro)_2$ has been reported by Reymond *et al.* able to operate through both enamine and enolate mechanisms depending on different substrates. $Zn(Pro)_2$ is a watersoluble complex potentially capable of stabilizing an enolate intermediate under mild basic conditions, and contains two metal-coordinated secondary amines which could also form an enamine intermediate.¹¹⁷ The mechanism was drawn in scheme 46.

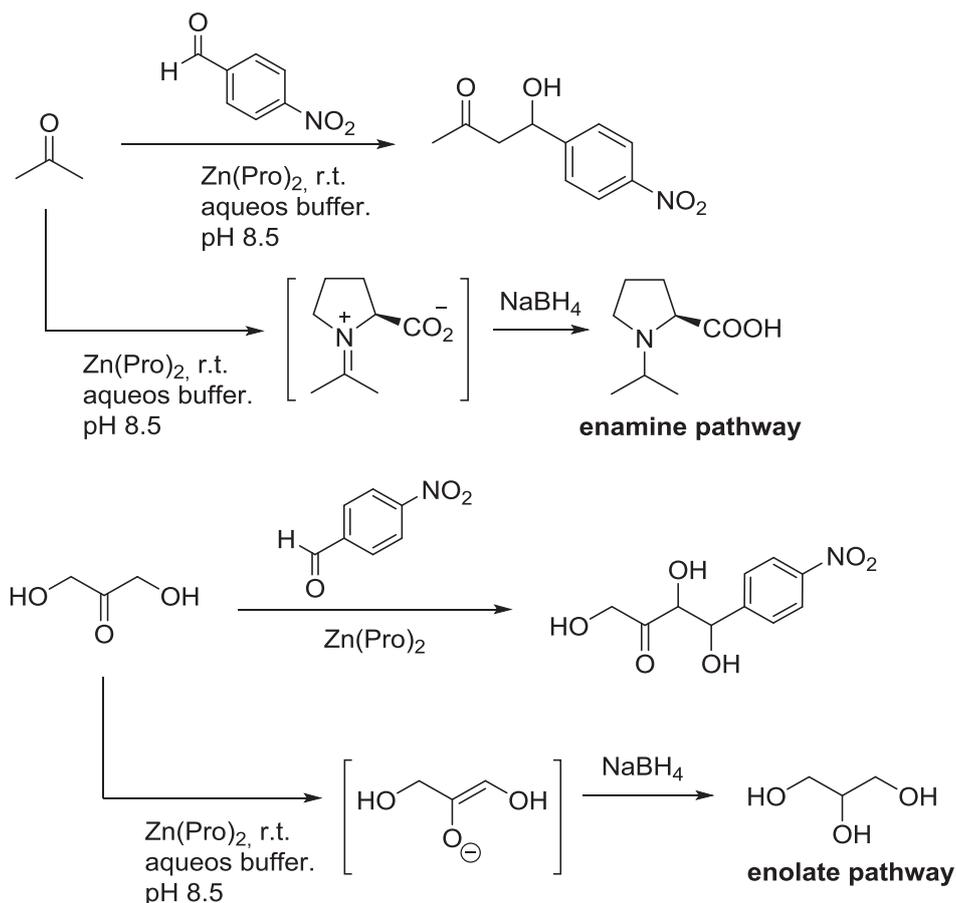
¹¹⁶ M. Markert, M. Mulzer, B. Schetter, R. Mahrwald, *J. Am. Chem. Soc.*, **2007**, *129*, 7258-7259.

¹¹⁷ J. Kofoed, T. Darbre, J. L. Reymond, *Chem. Commun.*, **2006**, 1482-1484.

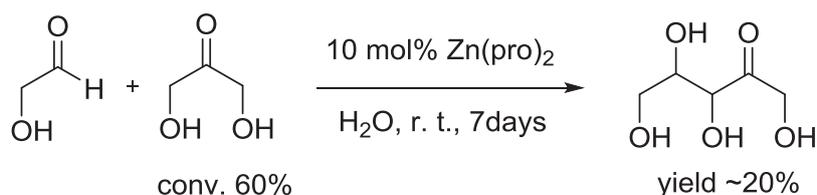


scheme 46. Zn(pro)₂ catalyzed aldol reaction *via* enamine and enolate pathways.

According to Reymond's work, both acetone and DHA have been used as substrates for aldol condensation with nitrobenzaldehyde under the Zn(Pro)₂ catalyst. On the one hand, reaction with acetone in the presence of catalyst Zn(Pro)₂ and reductive agent NaBH₄ led to the quantitative formation of *N*-isopropyl proline, implying that this aldol condensation follows mainly an enamine pathway. On the other hand, when DHA was reacted in the presence of Zn(Pro)₂ and NaBH₄, the reaction only produces glycerol and no traces of reductive alkylation of proline were detected. Meanwhile, L-proline shows almost no activity with DHA compared to Zn(Pro)₂ which suggests that DHA aldolisation follows an enolate pathway (Scheme 47). They have also claimed specific catalyst types for different mechanisms. For enamine pathway (type I), L-proline is one of the most common bases to use. And for enolate pathway (type II), most amines such as tertiary amines are used. Zinc-proline appears to be a particularly efficient catalyst for both enamine and enolate type.

Scheme 47. Reductive trapping of $\text{Zn}(\text{Pro})_2$ catalyzed aldol condensation.

The aldolisation catalyzed by $\text{Zn}(\text{pro})_2$ usually requires long reaction time and the products obtained are more stereo-complex depending on different structures.

scheme 48. $\text{Zn}(\text{pro})_2$ catalyzed aldolisation.

Unfortunately, the scope of these organocatalysts is also limited to aromatic aldehydes or hydroxy short chain aldehydes, which is not suitable and practical for the preparation of long chain surfactants.^{113, 118} Most of these DHA aldolisations require long reaction times (1 to 7 days) that is another drawback in surfactants industry.^{116, 119} In conclusion, DHA aldolisation can be catalyzed either by biocatalysts (DHAP-dependent aldolases/DHAP-independent aldolase/Transaldolase) and

¹¹⁸ B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.*, **2001**, 123, 3367-3368.

¹¹⁹ J. Kofoed, M. Machuqueiro, J. L. Reymond, T. Darbre, *Chem. Commun.*, **2004**, 1540-1541.

organocatalysts (*N*-terminal proline/tertiary amines/Zinc-proline). However, it still remains a challenge to introduce long chain aldehydes as electrophiles to react with unprotected DHA in a relatively green way (green solvent or solvent-free conditions, high atom efficiency and recyclable catalysts) to give C-C bond linked surfactants.

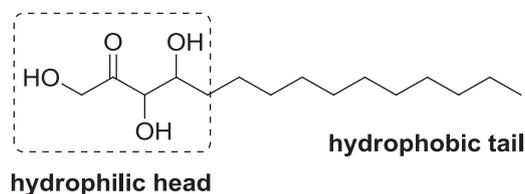
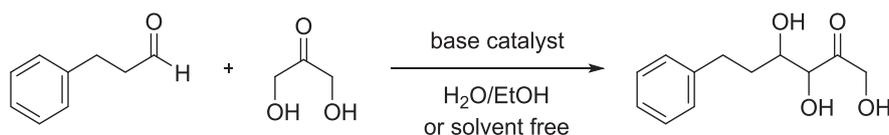


Figure 20. DHA-based surfactants.

3 Aldolisation process of 1,3-dihydroxyacetone

3.1 Optimisation of DHA aldolisation with hydrocinnamaldehyde as model substrate

From the previous literature about aldolisation between aldehyde and acetone or hydroxyketone, most of the substrate scope is based on aromatic aldehydes.^{113,120} We started our study by selecting hydrocinnamaldehyde (HCA) as substrate, for 2 reasons: i) the structure and activity of HCA is more similar to fatty aldehyde since there are two carbons between aromatic ring and aldehyde group, ii) the reaction can be monitored with HCA conversion by HPLC method under the UV lamp since the presence of phenyl group. This matches with our final objective – to build a fatty alkyl chain based surfactant by the means of aldolisation reaction.



Scheme 49. Model reaction for DHA aldolisation.

We started from the same conditions inspired by the work done by Mahrwald (Table 2).^{119a} *N,N*-diisopropylethylamine (DIPEA) base catalyst was added (5 mol%) to a mixture of DHA (1 equiv.) and hydrocinnamaldehyde (HCA, 2 equiv.) without solvent at room temperature, the reaction was kept for 15 hours (Table 2, entry 1). Unfortunately, DHA is not soluble in the reaction mixture, which has caused a bad stirring, and no new product was obtained.

¹²⁰ R. Martínez, L. Berbegal, G. Guillena, D. J. Ramón, *Green Chemistry*, **2016**, *18*, 1724-1730.

Table 2. Initial trial of model reaction.

Reaction scheme: 2 eq. of **1** (hydrocinnamaldehyde) + 1 eq. of **2** (dihydroxyacetone) $\xrightarrow[\text{EtOH/H}_2\text{O or solvent free}]{\text{X mol\% } i\text{Pr}_2\text{NEt}}$ **3** (α -hydroxyketone) + **4** (di-aldol) + **5** (self-condensation product).

Entry	Cat. Loading (mol%)	Solvent	Isolated yield ^c (%)		
			3	4	5
1 ^a	5	free	No reaction		
2 ^a	5	EtOH/H ₂ O (1:1)	No reaction		
3 ^b	50	EtOH/H ₂ O (1:1)	16	12	30

Reaction conditions: ^a 1M of DHA, r.t., 15 h. ^b 1M of DHA, r.t., 6 h. ^c Isolated by chromatography.

To improve the stirring situation caused by the low solubility of DHA, the reaction was carried out in 1:1 ratio of EtOH/H₂O (Table 2, entry 2). Unfortunately, after 15 hours the reaction does not occur. Then, the loading of *i*Pr₂NEt has been increased from 5 to 50 mol% (Table 2, entry 3). Under these conditions, the conversion of **2** was quantitative after 6h and the desired product **3** was isolated with 16% yield. Furthermore, product **4** and **5** have been isolated with respectively 12% and 30% yield. Compound **4** was formed due to the excess of HCA as a di-aldolisation product, and compound **5** was formed due to the self-condensation of HCA.

To screen this aldolisation process and avoid the tedious column separation, a convenient method for evaluation of the yields was developed. The calibration curves for both starting material hydrocinnamaldehyde and desired α -hydroxyketone were carried out by HPLC (Chapter Experimental Section, scheme 84).

3.2 Aldolisation process condition screening and optimization

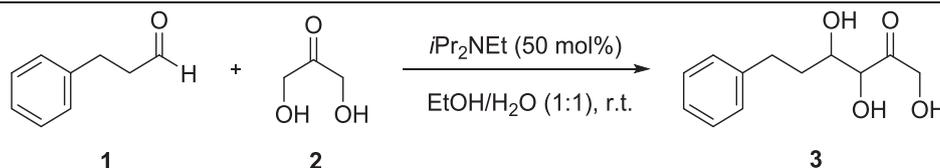
Based on the results in Table 2, for only 6 hours the isolated yield of aldol adduct α -hydroxyketone **3** (entry 3) is 16%. It has indicated that with 50 mol% of the base catalyst *N,N*-diisopropylethylamine loading, the aldolisation reaction rate is faster than the reaction time reported

in most of the literature (overnight or several days).¹²¹ It is necessary for us to seek a point when the aldolisation gets its highest yield since this is a reversible process.

3.2.1 Reaction time screening.

50 mol% *i*Pr₂NEt was added to a mixture of DHA (1 equiv.) and HCA (2 equiv.) without solvent at room temperature (Table 3). The reaction was tracked by HPLC at 2h, 3h, 4h, 6h, 7h and 24h.

Table 3. Reaction time screening.



Entry	Time / h	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	2	90	13	14
2	3	97	32	33
3	4	98	34	35
4	6	99	27	27
5	7	99	22	22
6	24	99	14	14

Reaction condition: ratio **1:2**=1:2; ^a Yields determined by calibration curves. ^b HPLC selectivity using Yield/Conversion.

From the curve below (Figure 21), the amount of α-hydroxyketone **3** is increasing fast at first. After 4 hours, it reaches the highest yield and if the reaction continues, the amount will decrease. Until 24 hours, the yield reaches a plateau around 15%. In conclusion, the aldol reaction needs to be stopped after 4 hours to maintain its highest yield.

¹²¹ N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.*, **2003**, 125, 2169-2178.

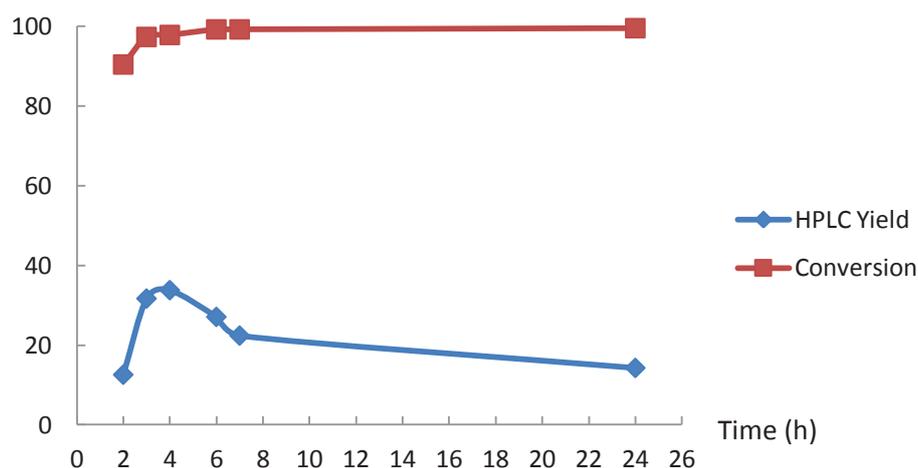
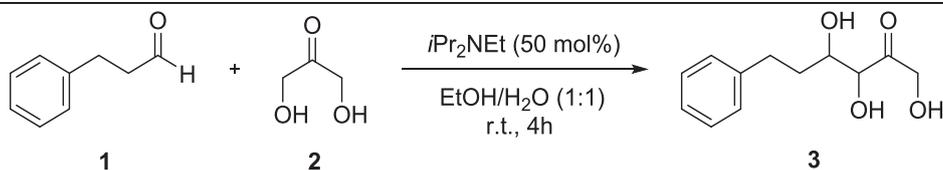
Conversion of **1** and yield of **3** (%)

Figure 21. Evolution of conversion and yield change with time.

3.2.2 Equivalent of starting material

To increase the yield of the desired α -hydroxyketone **3**, the amount of DHA needs to be increased. Different ratio of DHA (2 to 20 equiv.) was mixed with HCA (1 equiv.) under 50 mol% of *i*Pr₂NEt catalyst (Table 4).

Table 4. Starting material equivalent screening of model reaction.



Entry	Ratio 1 : 2	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	1 : 2	98	34	35
2	1 : 5	>99	46	46
3	1 : 10	>99	72	72
4	1 : 15	>99	89	89
5	1 : 20	>99	>99	>99

Reaction conditions: HCA **1** (5 mmol), *i*Pr₂NEt (50 mol%), 1 M DHA in EtOH/H₂O (1:1), 4 hours at r.t. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

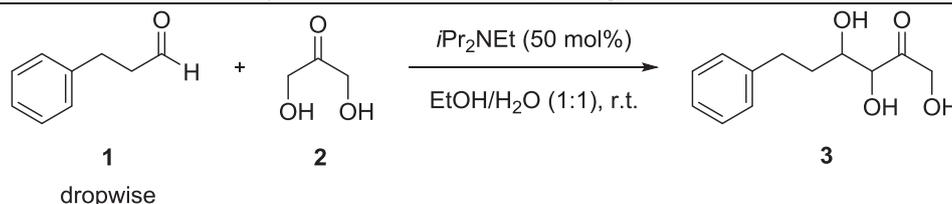
The reversible aldolisation process can be pushed to the desired direction when DHA was added in large excess, as well as to avoid the generation of di-aldolisation product **4** and self-condensation

product **5**. By adding excess of DHA, the yield of α -hydroxyketone **3** was dramatically improved from 34% to nearly 100% (Table 4, entries 1-5).

3.2.3 Portion-wise addition of starting material HCA **1**.

From a green chemistry point of view, it is not strategic to use excess of reagent to improve the yield only if we recover the excess. While to increase the yield of α -hydroxyketone **3**, excess of DHA needs to be maintained in the reversible aldolisation system. One of the possible strategies is to make a portion-wise addition of HCA **1** to the mixture of DHA and base catalyst. This strategy was performed using a starting material **1:2** ratio at 1:1. HCA (1 equiv.) was added by a syringe pump dropwisely during 3 hours to a mixture of DHA (1 equiv.) and 50 mol% of catalyst *i*Pr₂NEt at room temperature. Dropwise addition of HCA could lead to a rate decrease of aldolisation, so the highest yield could be reached at some point after 4h. Due to this, several samples of the reaction crude have been prepared at every hour after 4h until the HPLC yield start to decrease (Table 5).

Table 5. Dropwise addition of HCA (change of reaction time).



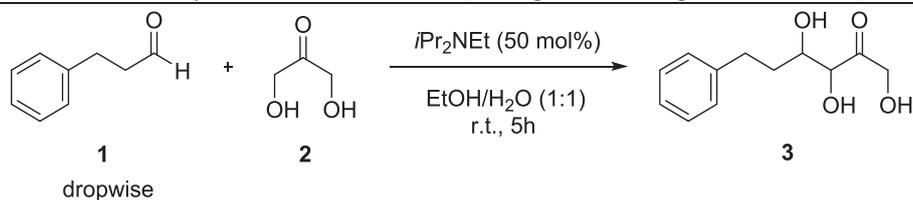
Entry	Reaction time / h	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	4	69	20	29
2	5	72	23	32
3	6	74	16	22

Reaction conditions: HCA (15 mmol), *i*Pr₂NEt (50 mol%), 1 M DHA (15 mmol) in EtOH/H₂O (1:1). ^aConv. and yields were determined by HPLC using calibration curves. ^bHPLC selectivity using Yield/Conversion.

When the starting material ratio **1:2** is set to 1:1 and dropwise addition of HCA, the highest yield of α -hydroxyketone **3** was obtained at 5h with 23% yield and 32% selectivity (Table 5, entry 2). Fewer yields were obtained with less or more reaction time (Table 5, entry 1 and 3). The result was obtained with same amount of HCA and DHA. So the amount of DHA was further increased to improve the yield. HCA (1 equiv.) was added dropwisely to a mixture of DHA (2 or 5 equiv.) and 50 mol% of catalyst *i*Pr₂NEt during 3 hours at room temperature. Sample was collected at 5h based on

the results (Table 6). The yield of HCA one-time addition under the same conditions was also listed for comparison.

Table 6. Dropwise addition of HCA (change of starting material ratio).



Entry	Ratio 1:2	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %	Yield of 3 ^c / %
1	1 : 1	72	23	32	---
2	1 : 2	77	27	35	35
3	1 : 5	73	65	89	46

Reaction conditions: HCA (10 mmol), $i\text{Pr}_2\text{NEt}$ (50 mol%), 1 M DHA (10, 20 or 50 mmol) in EtOH/H₂O (1:1), 5 hours at r. t. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion. ^c Results for the same ratio of starting material in the means of HCA one-time addition at 4h.

By increasing the amount of DHA from 1 to 5 equivalents, the yield of α -hydroxyketone **3** was improved from 23 to 65% (Table 6, entries 1-3). Compared to the result obtained from the HCA one-time addition, the selectivity has improved to 89% when the ratio increased to 1:5.

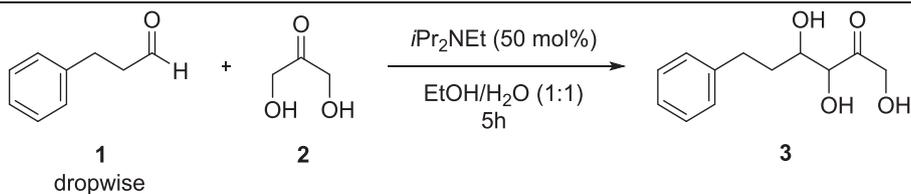
Now the best yield obtained is 65%, providing that the conversion is only 73%. It means that the yield could be further improved by modifying other parameters. Considering that the amount of DHA should be limited in this aldolisation process, the starting material ratio was set as 1:5 for further study like what was chosen in most reported literature procedures.¹²²

3.2.4 Influence of the temperature.

The influence of the temperature was studied using DHA (5 equiv.) and HCA (1 equiv.) with 50 mol% of catalyst $i\text{Pr}_2\text{NEt}$ in a 1:1 mixture of ethanol and water for 5 hours. The HCA addition was carried out dropwisely with a syringe pump during 3 hours (Table 7).

¹²² J. Fanton, F. Camps, J. A. Castillo, C. G. Héline, M. Lemaire, F. Charmantray, L. Hecquet, *Eur. J. Org. Chem.* **2012**, 203-210.

Table 7. Influence of temperature.



Entry	Temperature / °C	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	r.t.	73	65	89
2	30	84	13	15
3	50	75	9	12

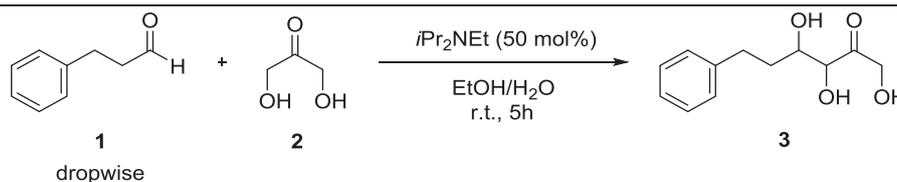
Reaction conditions: HCA (10 mmol), *iPr*₂NEt (50 mol%), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), 5 hours. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

When the temperature was increased from room temperature to 30°C, the conversion of aldehyde increased from 73% to 84%, but at the same time the yield decreased from 65% to 13% (Table 7, entries 1-2). If the temperature increased to 50°C, the yield decreased again to only 9% (Table 7, entry 3). From these results, the selectivity of α-hydroxyketone **3** is decreasing at higher temperature. Under these conditions, the HCA self-condensation adduct **5** is supposed to be easier formed at higher temperature. The desired aldol adduct **3** can also degrade to starting aldehyde due to the reversibility of this aldol reaction, then the aldehyde would make the self-condensation to give side product. Room temperature has been selected for future optimization.

3.2.5 Influence of solvent ratio.

The influence of solvent ratio was studied based on DHA (5 equiv.) and HCA (1 equiv.) in the presence of 50 mol% *iPr*₂NEt catalyst, in EtOH/H₂O (1:1) for 5 hours. HCA addition was carried out dropwisely with a syringe pump during 3 hours (Table 8). Instead of 1:1 EtOH/H₂O, 1:10 and 10:1 solvent ratio of EtOH/H₂O were studied and the corresponding HPLC chromatograms are listed in Chapter 5 Experiment section (Figure 40 and Figure 41). Under EtOH/H₂O (1:10) condition, the yield of desired α-hydroxyketone **3** is 11% with 99% HCA conversion. The di-aldol adduct **4** is the major side product (Table 8, entry 2). Under EtOH/H₂O (10:1) condition, no desired α-hydroxyketone **3** was formed even with nearly 100% HCA conversion. The major side product was confirmed to be the HCA self-condensation adduct **5** (Table 8, entry 3).

Table 8. Influence of solvent ratio.



Entry	Ratio EtOH/H ₂ O	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	1 : 1	73	65	89
2	1 : 10	99	11	11
3	10 : 1	>99	0	0

Reaction conditions: HCA (10 mmol), *i*Pr₂NEt (50 mol%), 1 M DHA (50 mmol) in EtOH/H₂O, 5h at r.t. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

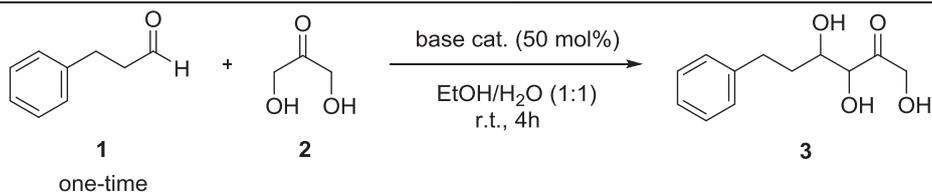
The fact is that HCA is soluble in ethanol while DHA is more soluble in water. The decrease of EtOH/H₂O ratio would limit the amount of DHA solubilized in ethanol and would lead to the formation of di-aldol adduct **4**. While an increase of EtOH/H₂O ratio can better solubilize HCA and would provide a better media for the formation of HCA self-condensation adduct **5**. In conclusion, a 1:1 mixture of EtOH/H₂O has been selected for further optimization to limit these side products.

3.2.6 Screening of base catalyst.

From these screening of reaction conditions, the best result has been obtained under these conditions, HCA (1 equiv.) was dropwisely added during 3h to DHA (5 equiv.) in the presence of 50 mol% base catalyst *i*Pr₂NEt in EtOH/H₂O (1:1) at room temperature after 5h whole reaction time. For further optimization of base catalysts, HCA one-time addition and 4h reaction time was used only for easier manipulation and for save of time (Table 9).

The screening work was started by trying these two types of base catalysts L-proline and Zn(pro)₂ (Table 9, entries 2-3). From these two entries, type I catalyst L-proline gives just 5% of desired α-hydroxyketone **3** while the dual-mechanism base catalyst zinc-proline can give 24% of desired product which means that our model aldol reaction goes through an enolate pathway instead of enamine pathway. This conclusion is in accordance with literature that they claimed DHA to be catalyzed under type II catalyst.¹¹⁷ In order to deprotonate the H⁺ in DHA, some bases with a relatively high pK_a have been used as catalyst (Table 9, entries 4-8). Their structures are shown in scheme 50. Cinchonidine and quinine are chiral amine catalysts with pK_a 12.98 and 12.80, respectively.

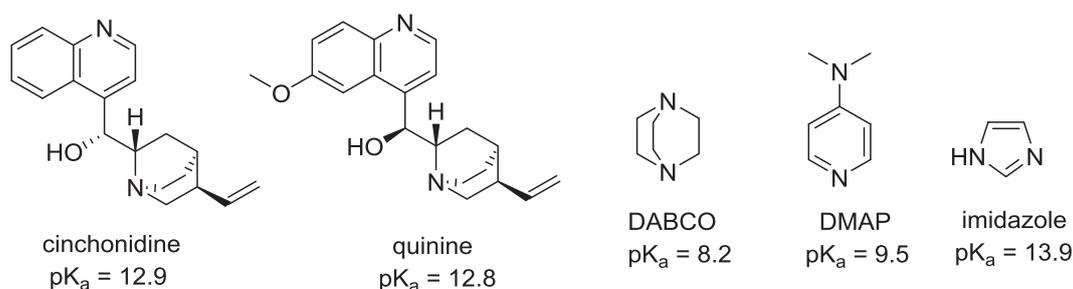
Table 9. Screening of bases.



Entry	Base cat.	pK _a	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	<i>i</i> Pr ₂ NEt	11.0	>99	46	46
2	L-proline	2.4	38	5	13
3	Zn(pro) ₂	-	45	24	53
4	cinchonidine	12.9	9	5	56
5	quinine	12.8	25	21	84
6	DABCO	8.2	9	6	67
7	DMAP	9.5	32	28	88
8	imidazole	13.9	0	0	0
9	Et ₃ N	10.6	53	51	96
10	EtNMe ₂	10.7	78	73	94
11	Et ₂ NC ₁₂ H ₂₅	10.6	33	26	79

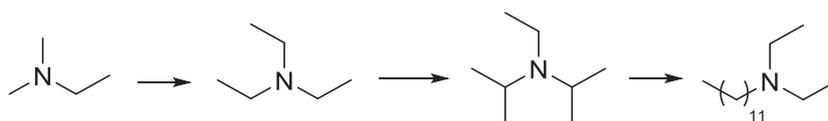
Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), 50 mol% of base catalyst, HCA one-time addition. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

DABCO (triethylenediamine), DMAP (4-dimethylaminopyridine) and imidazole are strong nucleophile with pK_a 8.19, 9.52, 13.89, respectively. Their performances are not very satisfying with conversion less than 35%, but their selectivities are higher compared to *i*Pr₂NEt.



scheme 50. Structures of base catalysts.

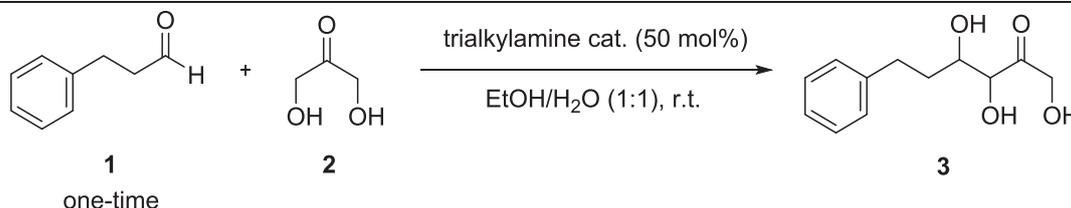
The Hunig's base $i\text{Pr}_2\text{NEt}$ gives a high conversion but a moderate yield and selectivity (Table 9, entry 1). Since the aldolisation was confirmed to operate through the enolate pathway, some amines similar to $i\text{Pr}_2\text{NEt}$ were also used (Table 9, entries 9-11). Other trialkylamines were found particularly selective for the formation of α -hydroxyketone **3** (selectivity 76-93%). A trend can be identified after comparing the structures of these amine catalysts with $i\text{Pr}_2\text{NEt}$, that the smaller the substituent on trialkylamine, the better the yield.



Scheme 51. The trend of substituent size of the amine catalyst.

In conclusion, base catalyst should be trialkylamines with smaller substituent. The most appropriate trialkylamine was found to be EtNMe_2 with 73% HPLC yield and 94% selectivity (Table 9, entry 11). However, the boiling point of EtNMe_2 is only 36.5°C . The HCA dropwise addition is not suitable due to the volatility of this amine catalyst. Sealed tube was introduced to solve this problem and trimethylamine (Me_3N , boiling point: 3°C), which is a gas at room temperature was also used as base catalyst in the form of 33 wt% Me_3N in ethanol solution (Table 10).

Table 10. One-time addition of HCA with volatile amine catalyst in sealed tube.



Entry	Base cat.	Time / h	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	EtNMe_2	4	84	78	93
2	Me_3N	2	68	65	96
3	Me_3N	3	84	82	98
4	Me_3N	4	80	67	84

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/ H_2O (1:1), 50 mol% of base catalyst, HCA one-time addition. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

With the help of sealed tube, both conversion and yield were improved in the presence of EtNMe₂ catalyst (Table 9, entry 10 and Table 10, entry 1). The yield was slightly improved from 73% to 78% with almost the same selectivity. Me₃N was used as base catalyst due to its low steric hindrance on substituent (Table 10, entries 2-4).

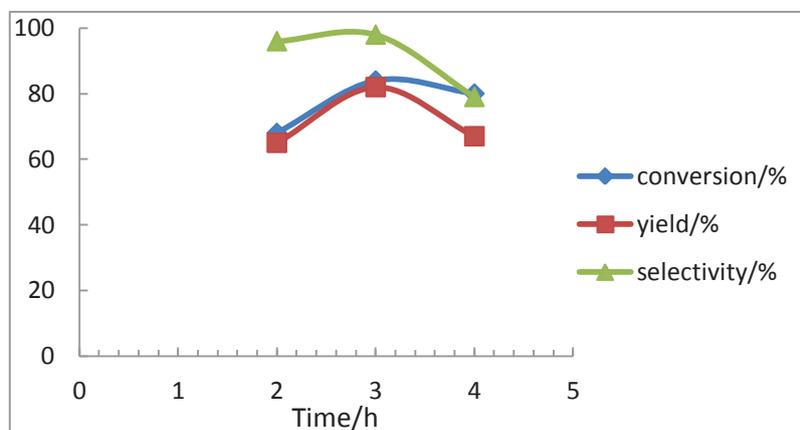


Figure 22. Reaction track of HCA one-time addition in the presence of Me₃N as base catalyst.

From 2 to 3 hours, the yield increased with higher selectivity. After 3 hours, the reaction started to form more side products than desired product and the yield decreased from 82% to 67%. The best reaction time is 3 hours, which is faster than the other trialkylamine catalysts.

Based on the previous results obtained after screening of base catalysts, when DHA (5 equiv.) and HCA (1 equiv.) were mixed in EtOH/H₂O (1:1) in the presence of 50 mol% Me₃N catalyst at room temperature after 3 hours, 82% yield of desired α -hydroxyketone **3** was formed with 98% selectivity. In conclusion, with a smaller substituent on the catalyst, the reaction rate was also improved.

3.2.7 Heterogeneous base catalyst.

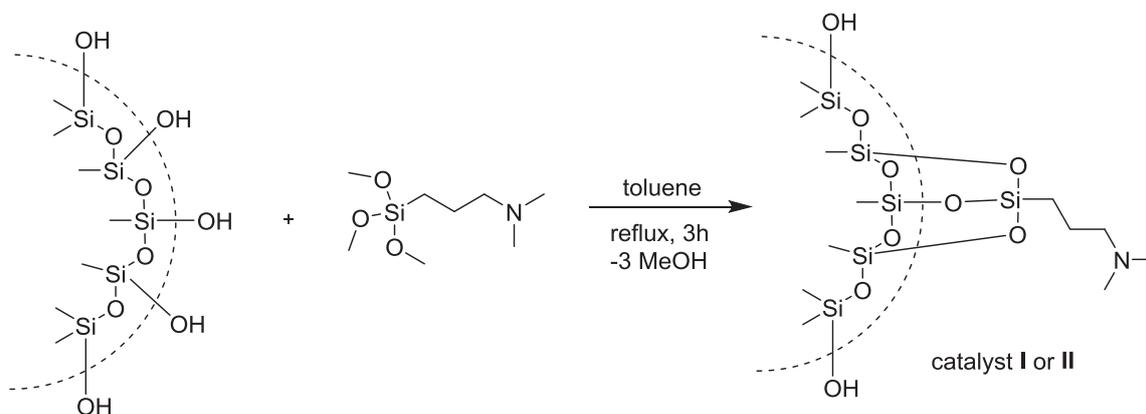
In this so-called “green” process 50 mol% of base “catalyst” was used, which can be improved by using heterogeneous catalyst in order to provide a recyclable system. As green chemistry has attracted more and more attention of scientists nowadays, in terms of making environment friendly reactions, heterogeneous catalysts have been studied. The heterogeneous catalysts are generally easy to separate and recycle. Due to their environment and economical advantages, heterogeneous

catalyst can be used in numerous applications. Fixed beds supported catalysts can be used to realize continuous column operations when reactions are fast enough.¹²³

Silica has been selected as a solid support among various materials such as alumina and montmorillonite clay because it is a nontoxic, inexpensive and available mesoporous material. It is also thermally stable (-70-350 °C) even under acidic conditions. On the other hand, due to the presence of silanol groups (Si-OH) on its surface, it is very active in chemical reactions. Meanwhile, the surface of silica can be easily functionalized with target groups to give the desired supported heterogeneous catalyst.

3.2.8 Silica-supported dimethylamine catalyst preparation.

Based on the screening results of bases, trialkylamine was selected as the most efficient catalyst. A silica-supported trialkylamine catalyst has been designed to serve as a heterogeneous catalyst for aldolisation process (Scheme 52). According to the work reported by Enrico,¹²³ the same procedure to prepare this type of catalyst was carried out. Silica (5 g) was suspended in anhydrous toluene (25 mL) with dropwisely addition of 3-(*N,N*-dimethylamino)propylmethoxysilane (1.5 g, 7 mmol) during 15 min, then refluxed for 2 hours. Solvents were removed by distilling after reaction. The crude was filtrated and dried to a constant weight.



Scheme 52. Silica supported dimethylamine catalyst I preparation.

¹²³ E. Angeletti, C. Canepa, G. Martinetti, P. Venturello, *J. Chem. Soc., Perkin Trans.*, **1989**, 1, 105-107.

From the weight increase, equivalent of $-N(CH_3)_2$ in the prepared supported dimethylamine catalyst **I** can be calculated following the equation below. The obtained catalyst **I** contains 1.24 mmol/g $-N(CH_3)_2$ as functional group.

$$\Delta m = \left[\begin{array}{c} \text{---O---} \\ | \\ \text{---O---Si---} \\ | \quad | \\ \text{---O---} \end{array} \text{---CH}_2\text{---CH}_2\text{---CH}_2\text{---N(CH}_3\text{)}_2 \right] - 3 \left[\text{H} \right] = 111 \text{ g/mol}$$

Catalyst **I** was used as a heterogeneous catalyst for model reaction. To a mixture of DHA (5 equiv.) and HCA (1 equiv.) in EtOH/H₂O (1:1), prepared silica-supported amine catalyst **I** was added at room temperature (Table 11).

Table 11. Aldolisation of DHA using supported amine catalyst **I**.

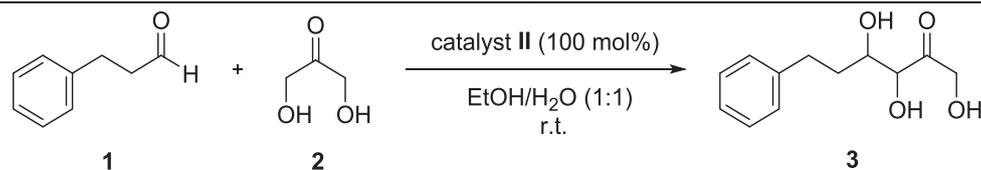
Entry	Equiv. of catalyst I /mol%	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	50	15	2	13
2	100	12	4	33

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1) at r. t. for 4h. ^aConv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

The conversion of HCA **1** is only 15% and yield is 2% when 50 mol% of the prepared catalyst was used (Table 11, entry 1). So another trial of 100 mol% catalyst **I** was used (Table 11, entry 2). But the conversion of HCA **1** is still very low and the yield slightly increased to 5%, which leads to a slightly higher selectivity too. In conclusion, the performance of catalyst **I** is not efficient.

From this result, we hypothesized that silica-supported amine catalyst **I** is not enough efficient due to low concentration of functional group $-N(CH_3)_2$. So, more equivalent of 3-(*N,N*-dimethylamino)propylmethoxysilane was added in the supported-amine catalyst preparation process. The same procedure has been repeated for preparing catalyst **II**. With 3-(*N,N*-dimethylamino)propylmethoxysilane (9 g, 42 mmol), the equivalent of functional group $-N(CH_3)_2$ supported on catalyst **II** was calculated to be 1.62 mmol/g. Catalyst **II** has been tested on the model reaction under the same condition than with catalyst **I**. To a mixture of DHA (5 equiv.) and HCA (1 equiv.) in EtOH/H₂O (1:1), 100 mol% of prepared silica supported amine catalyst **II** was added at room temperature (Table 12).

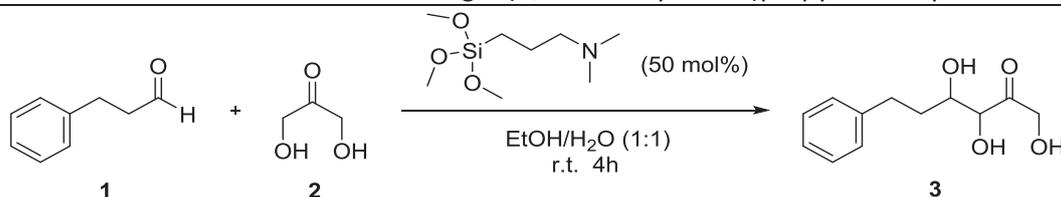
Table 12. Aldolisation of DHA using supported amine catalyst II.



Entry	Time/h	Conversion of 1 ^a /%	Yield of 3 ^a /%	Selectivity ^b /%
1	4	11	8	73
2	72	35	5	14

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), 100 mol% catalyst II at r.t. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

From these results, the performance of catalyst II is not satisfying too. After 4 hours, the conversion of HCA **1** is only 11% and the yield of compound **3** is 8%. After 72 hours, the conversion of HCA **1** is still very low and the yield decreased to 5% thus leading to a lower selectivity. To better understand the problem of our prepared silica-supported amine catalysts, 3-(*N,N*-dimethylamino)propylmethoxysilane was evaluated as base catalyst for model reaction (Table 13).

Table 13. Aldolisation of DHA using 3-(*N,N*-dimethylamino)propylmethoxysilane.

Entry	Time/h	Conversion of 1 ^a /%	Yield of 3 ^a /%	Selectivity ^b /%
1	4	10	8	80
2	72	48	7	15

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), 50 mol% base catalyst at r.t. for 4h. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

Results obtained from supported catalyst II (Table 12) are quite similar to that of non-supported amine precursor (Table 13). It reveals that the low conversion and yield is caused by the property of the functional group catalyst precursor 3-(*N,N*-dimethylamino)propylmethoxysilane. On the other hand, the way to immobilize the functional amine to silica was well performed according to the literature.

3.2.9 Screening and recycling of basic Amberlyst catalyst.

Since the attempt to immobilize trialkylamines to silica support did not work, some basic Amberlysts or solid bases which can be separated and recycled by filtration were used (Table 14). Hydroxyapatite is a natural mineral form of calcium apatite with hydroxyl endmember of the complex apatite group, with formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. It is not soluble in EtOH/H₂O, so it could be separated easily by filtration. Some Amberlysts have also been tried as catalysts.^{124,125,126}

Table 14. Screening of solid basic catalysts.

Reaction scheme: 3-phenylpropanal (1) + dihydroxyacetone (2) $\xrightarrow[\text{EtOH/H}_2\text{O (1:1), r.t., 4 h}]{\text{base catalyst (100 wt\%)}}$ 1,3-bis(3-phenylpropan-2-yl)propan-2-ol (3)

Entry	catalyst	Time / h	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	hydroxyapatite	4	7	2	29
2	Amber. IRA 400 Cl	4	42	2	5
3	Amber. IRA 400 Cl ^c	4	20	19	95
4	Amber. IRA 400 Cl ^c	8	25	23	92
5	Amber. 4200 Cl	4	20	5	25
6	Amber. 4200 Cl ^c	4	23	4	17
7	Amber. A26 (OH)	4	89	32	36
8	Amber. A26 (OH) ^c	4	53	45	85
9	Amber. A26 (OH) ^c	24	48	33	69

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), 100 wt% of base catalyst, at r.t. for 4h. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion. ^c Amberlyst was activated with Na(OH) solution.

Hydroxyapatite has been used as base catalyst but only 7% HCA conversion and 2% of α -hydroxyketone **3** was obtained (Table 14, entry 1). Amberlyst IRA400 Cl and Amber. 4200 Cl are two basic resins in chloride forms. All Amberlysts were added 100 wt% equivalent to DHA. Amber. IRA400 Cl was directly used and only 2% yield was obtained (Table 14, entry 2). So it was prepared as

¹²⁴ P. Costanzo, L. Cariati, D. Desiderio, R. Sgammato, A. Lamberti, R. Arcone, R. Salerno, M. Nardi, M. Masullo, M. Oliverio, *ACS Med. Chem. Lett.* **2016**, *7*, 470-475.

¹²⁵ M. M. Khodaei, K. Bahrami, A. Farrokhi, *Synth. Commun.*, **2010**, *40*, 1492-1499.

¹²⁶ G. Fogassy, C. Pinel, G. Gelbard, *Catal. Commun.*, **2009**, *10*, 557-560.

literature has reported for ion exchange, these resins were washed with 5% NaOH solution then dried at room temperature. The performance of Amber. IRA 400 Cl has improved a lot after activation, 19% yield obtained with very high selectivity 95% (Table 14, entry 3). So, it was continued to react for 8 hours but the result did not improve too much, only 23% yield with slightly decreased selectivity 92% (Table 14, entry 4). Amber. 4200 Cl was used and 20% conversion with 5% yield obtained without activation (Table 14, entry 5). Performance has not been improved even after the activation of resin (Table 14, entry 6). Amberlyst A26 (OH) is also a strong anionic basic resin with quaternary ammonium as functional group in hydroxide form. When it is used before activation, very high conversion (89%) of HCA was obtained while the yield is only 32% (Table 14, entry 7). Then, it was used after activation with enhanced performance, at 45% yield and 53% conversion (Table 14, entry 8). The reaction was continued for 24 hours while both the conversion and the yield decreased (Table 14, entry 9).

For conclusion, among these screened resins, the most efficient one is Amberlyst A26 (OH) with 45% yield and 85% selectivity. Although this result is not enough satisfying compared to that realized with homogeneous catalyst, it is quite a promising one as a heterogeneous catalyst. The reaction parameters were further optimized for achieving a better result with catalyst Amberlyst A26 (OH) by studying the loading of the resin catalyst (Table 15).

Table 15. Influence of the loading of Amberlyst A26 (OH).

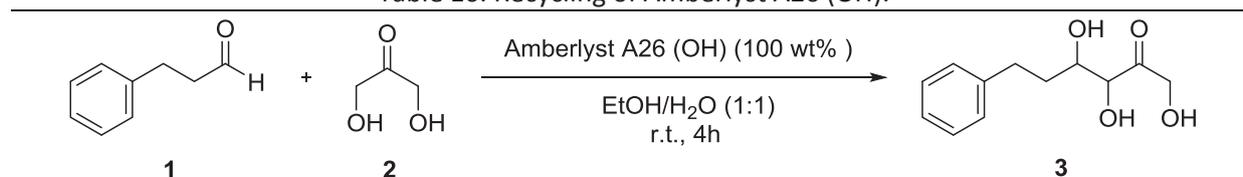
Entry	Catalyst Loading / wt%	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	10	13	9	69
2	50	19	17	89
3	100	53	45	85
4	300	99	6	6

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), Amberlyst A26 (OH) has been activated with 5% Na(OH) solution before use. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

Different amounts of Amberlyst A26 (OH) were added (Table 15, entries 1-4). When 10 wt% of resin was added, only 9% yield and 69% selectivity were obtained (Table 15, entry 1). Then, the loading of catalyst was increased to 50 wt%, and a high selectivity 89% has been obtained although the yield just increased from 9% to 17% (Table 15, entry 2). With 100 wt% of resin A26 (OH), the best performance obtained was 45% yield and 53% conversion (Table 15, entry 3). The yield was improved from 17% to 45% without loss of selectivity. If the amount of resin A26 (OH) was increased to 300 wt%, the result of 99% HCA conversion with only 6% yield of compound **3** shows that overloading of the basic resin catalyst leads almost all the HCA to self-condensation side product (Table 15, entry 4).

The most appropriate resin Amberlyst A26 (OH) has been selected as the best heterogeneous catalyst and loading of this resin has been optimized as 100 wt% to the amount of DHA. Next, the resin was recovered and reused to ensure its efficiency in recycling (Table 16). DHA (5 equiv.) and HCA (1 equiv.) were mixed in EtOH/H₂O (1:1) in the presence of 100 wt% Amberlyst A26 (OH) at room temperature for 4 hours, reactivated after each run with 5% NaOH solution before use.

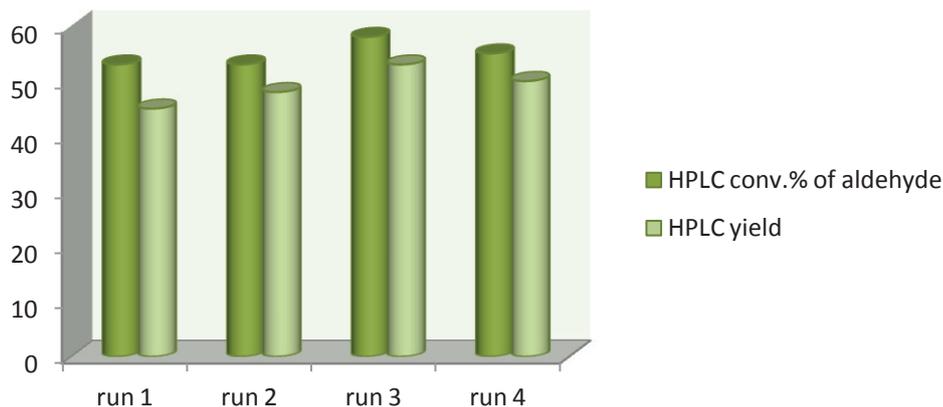
Table 16. Recycling of Amberlyst A26 (OH).



Entry	Catalyst	Conversion of 1 ^a / %	Yield of 3 ^a / %	Selectivity ^b / %
1	Amberlyst A26 (OH)	53	45	85
2	2 nd run Amberlyst A26 (OH)	53	48	91
3	3 rd run Amberlyst A26 (OH)	58	53	91
4	4 th run Amberlyst A26 (OH)	55	50	91

Reaction conditions: HCA (10 mmol), 1 M DHA (50 mmol) in EtOH/H₂O (1:1), Amberlyst A26 (OH) has been activated with 5% Na(OH) solution before use. ^a Conv. and yields were determined by HPLC using calibration curves. ^b HPLC selectivity using Yield/Conversion.

These results obtained by recycling are quite satisfying, from the 1st run to the 4th run, the yield maintained at 45% to 53% with high selectivity of 85% to 91% (Table 16, entries 1-4). In conclusion, Amberlyst A26 (OH) is able to keep its efficiency until its 4th run without any decrease in yield and selectivity.

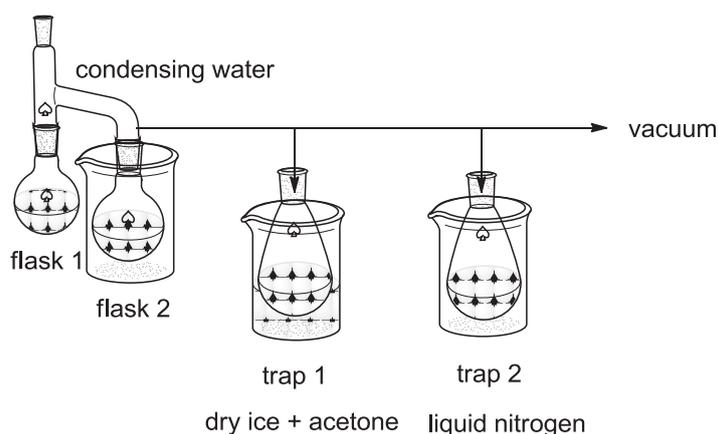


Scheme 53. Performances of recycled resin catalyst Amberlyst A26 (OH).

We have attempted to immobilize trialkylamine on silica as well as to use directly solid catalysts, the best result obtained is with Amberlyst A26 (OH), which is a strong basic anionic resin with quaternary ammonium functional group. However, even with this heterogeneous catalyst, the highest HPLC yield is approximately 45% with 85% selectivity.

3.2.10 Recycling of homogeneous base catalyst.

Since the boiling point of some homogeneous trialkylamine catalysts are quite low, we decided to take advantage of the volatile property of these trialkylamine catalysts by distilling them out of the reaction mixture and collecting them for reuse. The apparatus was set up for recycling the volatile trialkylamine catalyst (Scheme 54).



Scheme 54. Apparatus for distilling trialkylamine catalyst.

DHA and HCA were mixed together with trialkylamine catalyst in flask 1, connected with flask 2 and two additional traps to condense the amine gas. Me_3N was first recycled because it is the most volatile one with a boiling point only of 2.8 °C. To a mixture of DHA (5 equiv.) and HCA (1 equiv.) in

EtOH/H₂O (1:1), 50 mol% of Me₃N (33 wt% in EtOH) was added at room temperature for 3 hours. After reaction, the crude was distilled at 50 °C under 150 mbar vacuum for collecting amine catalyst. Based on the mass data, a balance was reached before and after distillation which means no losses of Me₃N gas due to the vacuum. Titration was carried out with 1M HCl solution by using pH meter. The Me₃N catalyzed aldol reaction has reached 82% yield and 98% selectivity before the distillation (Table 17, entry 1). With the help of this apparatus, 70% of the Me₃N catalyst was recovered in EtOH/H₂O solution. However, during the distillation at 50 °C, the reaction mixture changed and the selectivity went down from 98% to 27% (Table 17, entry 2).

Table 17. HPLC data before and after distillation of Me₃N.

Entry	Condition	Conversion of 1 / %	Yield of 3 / %	Selectivity / %
1	before distillation	84	82	98
2	after distillation	98	26	27

It is obvious from the result that after distillation at 50 °C, the yield was decreased from 82% to 26% while the conversion was improved from 84% to 98%. This is in accordance with our conclusion, high temperature makes it easier to form the HCA self-condensation product **5**. So, lower temperature for distillation has been tried to recover Me₃N (Table 18).

Table 18. Lower temperature for distillation of Me₃N.

Entry	Temperature / °C	Vacuum / mbar	Recycle rate / %
1	30	80	11
2	room temperature	no vacuum	3
3	room temperature	100	16
4	room temperature	200	3

At 30 °C and 80 mbar vacuum, only 11% of Me₃N has been collected after titration and based on the mass loss 90% has gone into the pump (Table 18, entry 1). Then, at room temperature and without vacuum Me₃N was still in the crude not able to be distilled out (Table 18, entry 2). When the distillation was carried out at 100 mbar, it ends up with 30% still in the residue and 50% into the pump (Table 18, entry 3). At 200 mbar, only 3% of Me₃N was collected (Table 18, entry 4). Unfortunately, the maximum yield of the recovered Me₃N is only 16% due to its extremely high volatility. This could make the recovery on small scale with the standard laboratory equipment very

difficult. So, next the less volatile triethylamine (Et_3N , boiling point = 89 °C) has been tried to be recovered by distillation.

The same apparatus and similar procedure were repeated to recover Et_3N . To a mixture of DHA (5 equiv.) and HCA (1 equiv.) in $\text{EtOH}/\text{H}_2\text{O}$ (1:1), 50 mol% Et_3N was dropwisely added at room temperature during 3 hours. The distillation was carried out at room temperature at 80 mbar after the addition finished. The reaction was continued to react 4 extra hours. In this case, 77% of Et_3N was recovered in the form of ethanol/water solution.

Two batches of the same reaction were set up and one of them was continued for distillation after 3h of HCA addition, the other one was continued to react for comparison. Both the reaction crudes of before and after distillation were separated to obtain the α -hydroxyketone **3**. The isolated yield was 57% (3 h HCA addition + 4 h reaction) and 53% (3 h HCA addition + 4 h distillation/reaction), respectively. In conclusion, it has been demonstrated that this volatile amine catalyst can be recovered without loss of yield.

Then, this recovered Et_3N in $\text{EtOH}/\text{H}_2\text{O}$ solution was directly reused in another batch for the aldolisation of DHA with HCA. Fortunately, 46% of α -hydroxyketone **3** has been isolated. Overall, these results have convinced us that the volatile trialkylamine catalyst is able to be recycled. The use of these volatile trialkylamines as recoverable organocatalysts for biomass valorization has also been reported before. The isomerization of glucose to fructose can be catalyzed by Et_3N with a better yield around 30% than by using inorganic bases (< 10%).¹²⁷ In the cleavage of cellulose process, Me_3N was also used and was more effective than other hydrothermal agents in breaking down cellulose under mild conditions. It was also recovered and reused up to 99%.¹²⁸ In our case, the recovery of Et_3N has been demonstrated again.

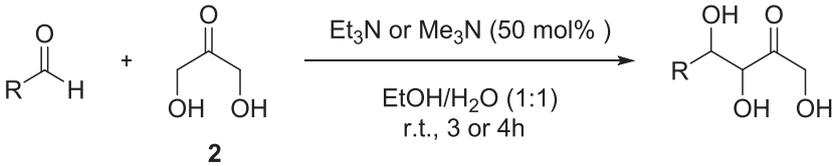
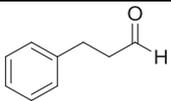
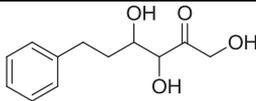
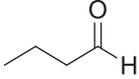
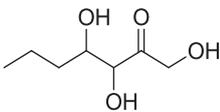
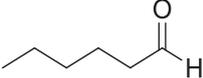
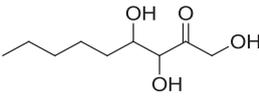
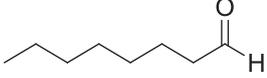
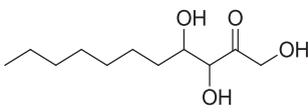
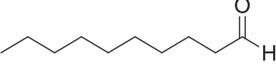
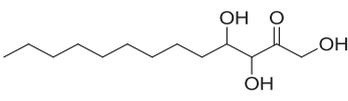
¹²⁷ C. Liu, J. M. Carraher, J. L. Swedberg, C. R. Herndon, C. N. Fleitman, J.-P. Tessonnier, *ACS Catal.*, **2014**, *4*, 4295-4298.

¹²⁸ Y. Chen, X. Ren, Q. Wei, *Bioresour. Technol.*, **2016**, *221*, 477-484.

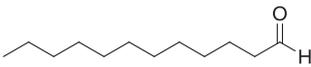
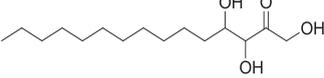
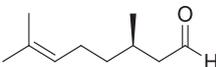
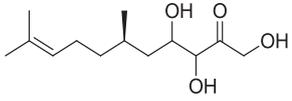
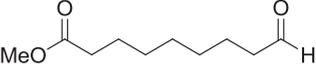
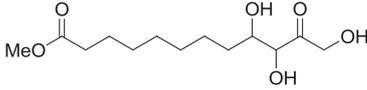
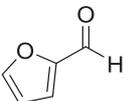
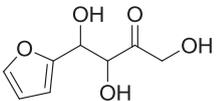
3.3 Aldolisation scope investigation.

The optimized conditions were next applied for the aldolisation of unprotected DHA with a series of alkyl aldehydes to give the corresponding α -hydroxyketone intermediates (Table 19).

Table 19. Aldolisation scope with a range of aldehydes ^a.

Entry	Aldehyde	α -hydroxyketone	Yield ^b / %		d.r. ^c
			Et ₃ N ^d	Me ₃ N ^e	
					
1	 1	 3	57	65	95 : 5
2	 6	 14	41	46	96 : 4
3	 7	 15	42	49	96 : 4
4	 8	 16	40	48	91 : 9
5	 9	 17	48	53	90 : 10

(to be continued in next page)

6			29	92 : 8
	10	18		
7			42	53 : 47
	11	19		
8			36	95 : 5
	12	20		
9			70	68 : 32
	13	21		

^a Reaction conditions: aldehyde (2.2 mmol), 1 M DHA (11 mmol) in EtOH/H₂O (1:1), Et₃N or Me₃N (50 mol%), room temperature. ^b Isolated yields obtained after purification by column chromatography. ^c Diastereoisomeric ratios were determined by ¹H NMR. ^d Reactions were in flask for 7h with dropwisely addition of aldehyde during 3h. ^e Reactions were in seal tubes for 3h.

When Et₃N and Me₃N were used as catalysts for HCA **1**, the desired α-hydroxyketone **3** was obtained with 57% and 65% isolated yields, respectively (Table 19, entry 1). A high d. r. of 95 : 5 was determined by the integration of –OH in *d*₆-DMSO from ¹H NMR (Figure 23).

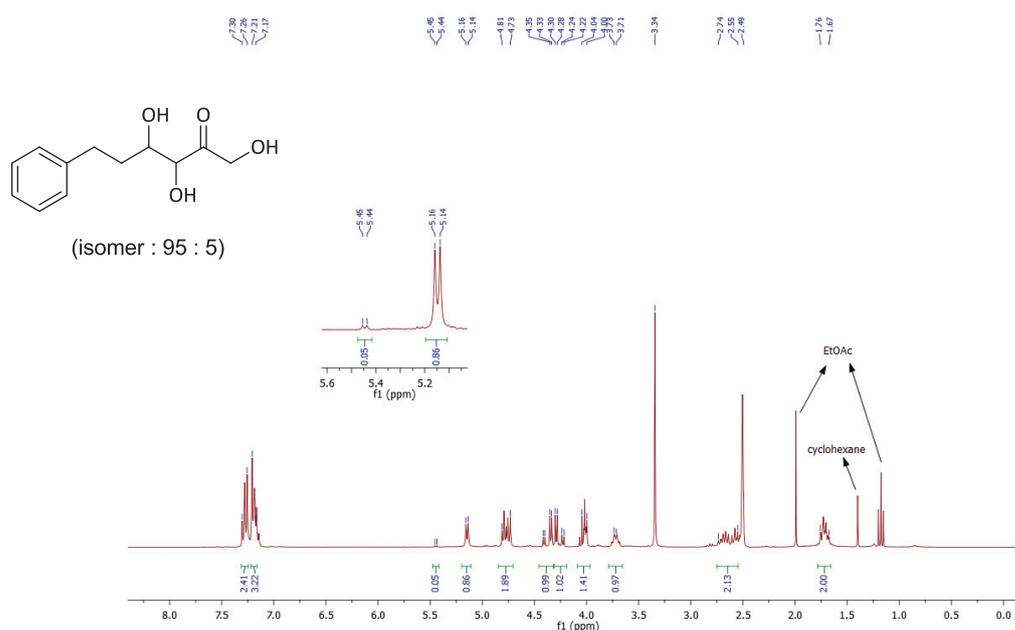


Figure 23. Determination of d.r. of α-hydroxyketone **3** by ¹H NMR.

The substrate scope was next extended to a range of linear aldehydes **6-10** with increasing alkyl chain length from 4 to 12 carbons (Table 19, entries 2-6). The corresponding α -hydroxyketones **14-18** were isolated with moderate yields (46-70%). The use of dodecanal **10** gave an even lower yield due to its poor solubility at room temperature. So, the reaction was carried out at 32 °C to slightly improve the solubility of the aldehyde in reaction mixture (Table 19, entry 6). The use of citronellal **11** (pine wood-derived aldehyde) gave 42% isolated yield of **19** while with a low d.r. of 53 : 47 (Table 19, entry 7). The reason for this low d.r. is not certain but it was supposed to be influenced by the already existed chiral center in the structure of citronellal. The bifunctional aldehyde **12** derived from cleavage of fatty acid derivatives¹²⁹⁻¹³⁰ was also used with a moderate yield of **20** and a high d.r. of 95:5 (Table 19, entry 8). Finally, carbohydrate-derived furfural **13** gave corresponding aldol product **21** with 70% yield (Table 19, entry 9).

3.4 Hydrogenation of α -hydroxyketones to tetraols.

3.4.1 Optimization of α -hydroxyketone hydrogenation conditions.

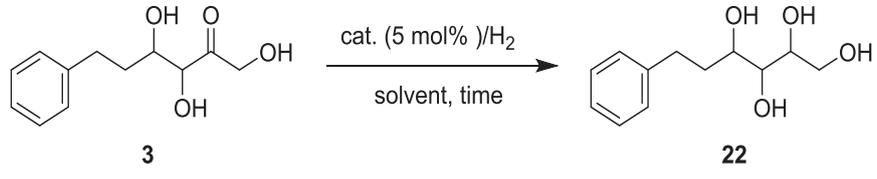
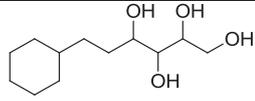
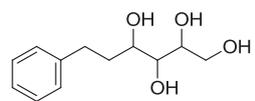
After these α -hydroxyketones have been obtained, the hydrogenation of these intermediates was next investigated. The hydrogenation of α -hydroxyketone **3** was first studied for optimizing the reaction conditions (Table 20). The hydrogenation of α -hydroxyketone **3** was first carried out under 40 bar of hydrogen using 5%-Ru/Al₂O₃ (5 mol%) in EtOH at 100 °C for 16 hours (Table 20, entry 1). Under these conditions, both carbonyl group and the phenyl ring were completely reduced and tetraol **23** was obtained with 95% yield. Some parameters were modified for obtaining the desired phenyl tetraol **22**. First, cyclopentyl methyl ether (CPME) was used as solvent (Table 20, entry 2) and 5% Pd/C was used as catalyst (Table 20, entry 3). Unfortunately in both entries, again tetraol **23** was obtained with 86% and 74% yield, respectively. Then, lower H₂ pressure and a lower temperature were used (Table 20, entries 4-7). The reaction was carried out using 10 bar H₂ at 100 °C and at 30 °C, but only a mixture of tetraol **22** and **23** was obtained (Table 20, entries 4-5). Their ratios were estimated by NMR, 40% and 72% of tetraol **22** was obtained in the mixture, respectively. Since these conditions are still too harsh for preparing tetraol **22**, the H₂ pressure was decreased to 5 bar and it gave a mixture of starting material **3** and tetraols **22** with 30:70 ratio (Table 20, entry 6). Finally, the reaction time was prolonged to 24 hours and tetraol **22** was obtained with 94% isolated yield (Table 20, entry 7). Almost no diastereoselectivity was obtained of the tetraol **22** estimated by ¹³C NMR

¹²⁹ K. Louis, L. Vivier, J.-M. Clacens, M. Brandhorst, J.-L. Dubois, K. De Oliveira Vigier, Y. Pouilloux, *Green Chem.*, **2014**, *16*, 96-101.

¹³⁰ T. S. Omonov, E. Kharraz, P. Foley, J. M. Curtis, *RSC Adv.*, **2014**, *4*, 53617-53627.

(diastereoisomer ratio around 50:50). Tetraol **22** and **23** were both prepared for further physicochemical investigation.

Table 20. Hydrogenation condition optimizing on model α -hydroxyketone **3**^a.

Entry	Catalyst	H ₂ pressure /bar	Temperature / °C	Time / h	Solvent	product ^b
						
1	5% Ru/Al ₂ O ₃	40	100	16	EtOH	 23 (95%)
2	5% Ru/Al ₂ O ₃	40	100	16	CPME	23 (86%)
3	5% Pd/C	40	100	16	CPME	23 (74%)
4	5% Ru/Al ₂ O ₃	10	100	16	EtOH	23 : 22 (60 : 40)
5	5% Ru/Al ₂ O ₃	10	30	16	EtOH	23 : 22 (28 : 72)
6	5% Ru/Al ₂ O ₃	5	30	16	EtOH	3 : 22 (30 : 70)
7	5% Ru/Al ₂ O ₃	5	30	24	EtOH	 22 (94%)

^a Reaction conditions: 30 mL stainless steel autoclave, α -hydroxyketone **3** (200 mg), catalyst (5 mol%). ^b Ratios were estimated by ¹H NMR and ¹³C NMR.

In conclusion, we have developed two complementary conditions for the hydrogenation of tetraol **22** in good yield (94-95%).

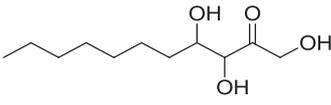
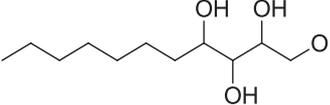
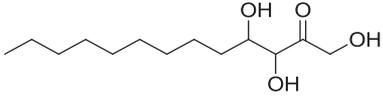
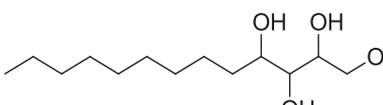
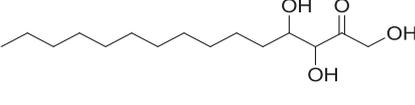
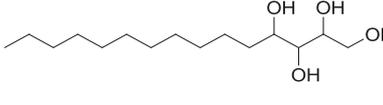
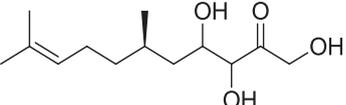
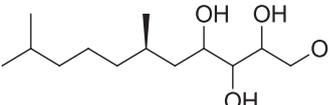
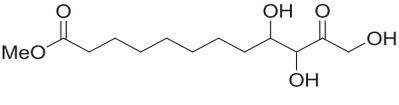
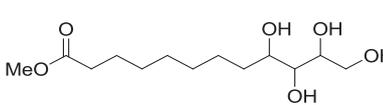
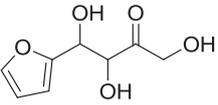
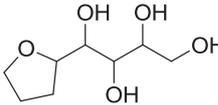
3.4.2 Scope for the hydrogenation of α -hydroxyketones.

The other α -hydroxyketones **14-21** were also reduced to the corresponding tetraols **24-31** with good to excellent yields 79-97% (Table 21). The phenyl α -hydroxyketone **3** can be reduced to tetraol **22** and **23** under different conditions (Table 21, entries 1-2). The alkyl chain based α -hydroxyketones **14-18** were reduced to desired tetraols **24-28** with excellent yields 92-97% (Table 21, entries 3-7). The α -hydroxyketone **19** bearing the citronellal chain was also converted to tetraol **29** with concomitant reduction of the double bond with 96% yield (Table 21, entry 8). Finally, furfural based α -hydroxyketone **21** was reduced to corresponding tetraol **31** as a mixture of 8 isomers. The hydrogenation step does not present any diastereoselectivity which only gave a mixture of isomers with d. r. around 50:50. All d. r. values were estimated based by ^{13}C NMR.

Table 21. Reduction scope of α -hydroxyketones to tetraols.^a

Entry	α -hydroxyketone	Tetraol	Yield ^b /%	d.r. ^c
1			95	56 : 44
	3	23		
2 ^d			94	50 : 50
	3	22		
3			97	55 : 45
	14	24		
4			93	50 : 50
	15	25		

(to be continued in next page)

5			94	25 : 75
	16	26		
6			92	22 : 78
	17	27		
7			94	35 : 65
	18	28		
8			96	50 : 50
	19	29		
9			79	60 : 40
	20	30		
10			87	mixture of 8 isomers
	21	31		

^a Reaction conditions: 30 mL stainless steel autoclave, α -hydroxyketone (500 mg), 5%-Ru/Al₂O₃ (5 mol%), H₂ pressure (40 bar), EtOH (12 mL), 100 °C, 16 h. ^b Isolated yields. ^c Diastereoisomer ratios were estimated by ¹³C NMR. ^d Reaction conditions: H₂ pressure (5 bar), 30 °C, 24 h.

Overall, this two-step aldolisation/reduction procedure gave access to a range of tetraols with good atom economy starting from renewable biomass and satisfying yields considering the difficulty to isolate such species. This sequence undergoes a relatively environment friendly method in green solvent and mild conditions (20 °C), could be very interesting for surfactant targeting industrial applications.

4 Physico-chemical properties of tetraols.

4.1 Critical micelle concentration of tetraols.

To measure the CMC of the synthesized tetraols, the surface tensions of the solutions at several surfactant concentrations are measured with a K100MK2 Krüss tensiometer using a platinum rod as probe.¹³¹ With increasing concentration of the surfactant, the surface tension of the solution decreases until it reaches a plateau. Then, a plot can be obtained by surface tension vs. surfactant concentration, the cross point of these two trendlines is the CMC value (Figure 24). All results were obtained at room temperature.

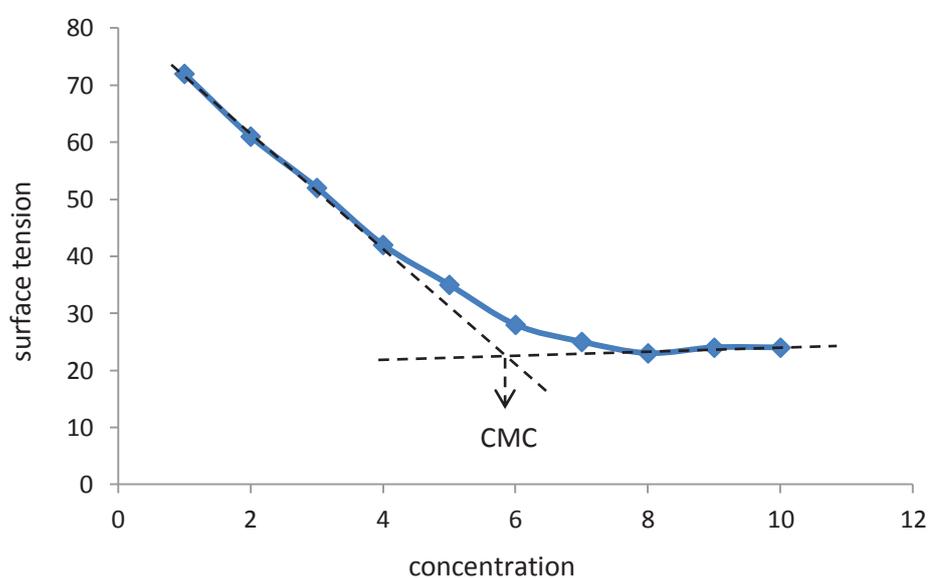


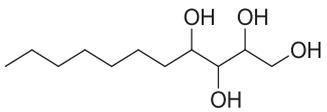
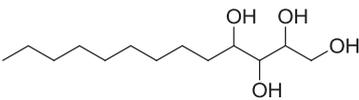
Figure 24. Measurement of CMC.

4.1.1 Mixture of isomers and pure isomer CMC test.

By taking advantage of the solubility, one of the isomers was able to be separated from the mixtures by recrystallisation in cold ethanol. For C7-tetraol **26** and C9-tetraol **27**, the surface tension of “pure” isomer and isomer mixtures were measured and their corresponding CMC values were calculated (Table 22).

¹³¹ In collaboration with Pr Jean-Marie Aubry from Lille University.

Table 22. CMC results comparison for isomer mixture and pure isomer.

Entry	Structure	Ratio ^a	CMC (mmol/L) ^b	γ_{sat} (mN/m) ^b	
1		"Pure"	6:94	0.67	54.1
2	26	Mixture	25:75	7.9	26.1
3		"Pure"	7:93	0.16	54.6
4	27	Mixture	22:78	1.6	24.0

^a Ratios were estimated by ¹³C NMR. ^b Determined by tensiometry.

On the one hand, for pure isomers of tetraol **26** and **27**, the lowest surface tension the system could achieve is approximately 54 mN/m, with only 0.67 and 0.16 mmol/L calculated CMC value, respectively (Table 22, entries 1 and 3). These obtained values are not CMC, since they are limited by the solubility of the pure isomers. Using higher concentration of these pure isomers, only suspensions were obtained and surface tension measured reached a plateau value. On the other hand, for isomer mixtures of tetraol **26** and **27**, the lowest surface tensions achieved were 26.1 and 24.0 mN/m, respectively (Table 22, entries 2 and 4). It is much lower and efficient than their corresponding pure isomers. From these results, with mixtures of isomers the system can reach a lower surface tension.

Moreover, to reach the same level of surface tension, lower CMC value means lower concentration of surfactant need to be used. So, it is more interesting for a surfactant to have a low CMC value. Both of them could reach a low plateau value of surface tension while the C9-tetraol **27** has a lower CMC (1.6 mmol/L) than the C7-tetraol **26** (7.9 mmol/L). This is due to their different chain length; with increasing carbon number in the hydrophobic tail the surfactant is able to reach a lower surface tension.

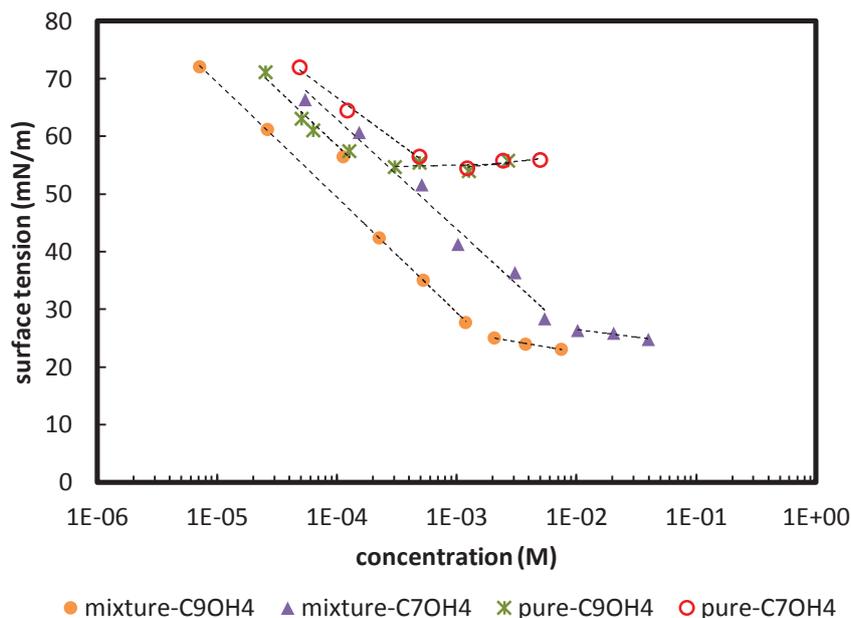


Figure 25. CMC measurements of C7-tetraol **26** and C9-tetraol **27**.

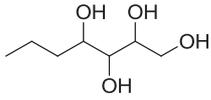
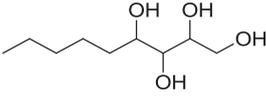
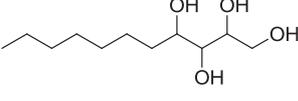
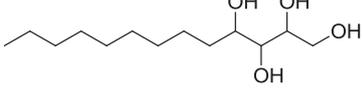
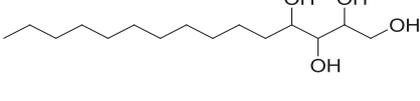
Therefore, in our case, both C7-tetraol **26** and C9-tetraol **27** isomer mixtures are more efficient than their pure isomers separated by recrystallisation. This is in accordance with experiences of industry. Commercial surfactants are usually marketed as mixtures of oligomers or isomers since their functional properties are usually better than pure isomers. For example, the trademark TWEEN[®] is marketed for a series of polyethylene glycol sorbitan monoesters used as detergents or emulsifiers.

4.1.2 Influence of alkyl chain length on CMC.

Based on the fact that the mixtures of isomers exhibit better performances than pure isomers, which are limited by their poor solubility in aqueous solution. Only the CMC values of the tetraol isomer mixtures were measured instead of the pure solid isomers.

A series of different alkyl chain length based tetraols have been obtained. By preparing samples of different concentrations of C3-tetraol **24** to C11-tetraol **28** and measuring their surface tension, their CMC curves can be obtained (Figure 26) and their CMC value, saturated surface tension were gathered (Table 23).

Table 23. CMC and surface tension values for different alkyl chain length.

Entry	Structure	Ratio ^a	CMC (mmol/L) ^b	γ_{sat} (mN/m) ^b
1	 24	55:45	100	26.5
2	 25	50:50	44	26.7
3	 26	25:75	7.9	26.1
4	 27	22:78	1.6	24.0
5	 28	35:65	0.26	23.7

^a Ratios were estimated by ¹³C NMR. ^b Determined by tensiometry.

All these linear surfactants show a decreasing trend of surface tension and reach a plateau value around 25 mN/m (Figure 26). Moreover, as expected, the CMC value of the tetraol decrease gradually with increasing number of carbon on the alkyl chain (Table 23, entries 1-5). The best results were obtained with the tetraol bearing a C11 alkyl chain, giving a CMC value of 0.26 mmol/L and lowest surface tension of 23.7 mN/m (Table 23, entry 5). It can be seen in the CMC curves of these alkyl chain tetraols that for a short chain length tetraol like C3-tetraol the surfactant displays a smoother decrease and reaches the surface tension plateau value at a relatively higher concentration than tetraols bearing longer chain length.

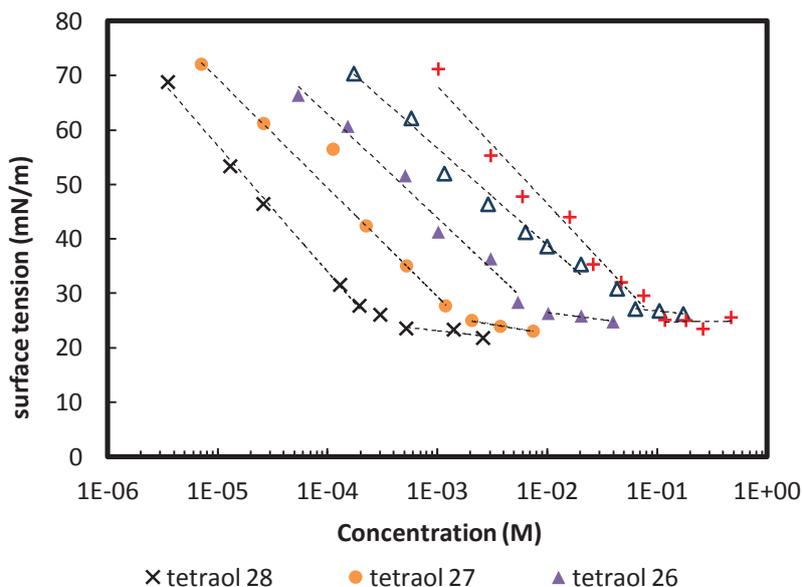


Figure 26. CMC measurements for tetraols of different alkyl chain length.

The CMC values have been plotted against their corresponding hydrophobic carbon numbers. The dotted line represents the linear behavior described by the empirical equation proposed by Klevens: $\log(\text{CMC}) = A - BN$ (Figure 27).¹³²

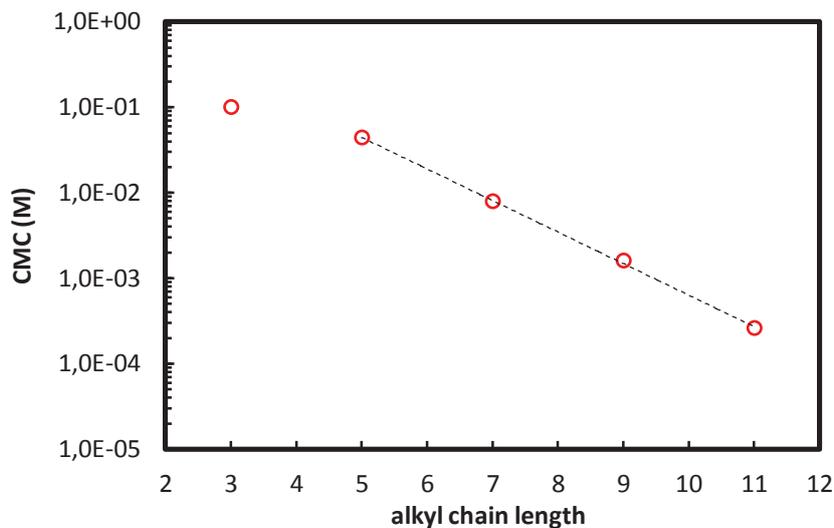


Figure 27. CMC value of alkyl chain tetraols as function of their corresponding alkyl chain length.

In our case, coefficients A and B (calculated from Figure 27) are 0.50 and 0.37, respectively. However, tetraol **24** does not follow the tendency observed for longer tetraols. It means that tetraol **24** is more similar to the behavior of a hydrotrope than of a surfactant. Hydrotrope is a type of compound like surfactant consists of both hydrophobic and hydrophilic part while compared to

¹³² Klevens, H. B., *J. Phys. Chem.*, **1948**, 52, 130-148.

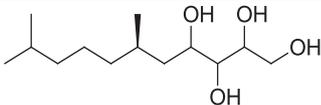
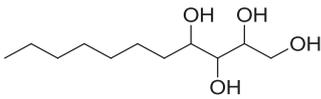
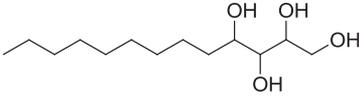
surfactant their hydrophobic part is often not long enough to form micelles in solutions. It is often used to improve the solubility of hydrophobic compounds in aqueous solutions.¹³³

4.1.3 Influence of branched chain on CMC.

The branched chain based tetraol is derived from a biomass aldehyde citronellal. Tetraol **26** (C7) and **27** (C9) were selected for comparison. Compared to tetraol **27**, which has the same amount of hydrophobic carbon, the branched tetraol **29** exhibits a higher CMC value (Table 24).

This phenomenon has already been reported and could be explained by the steric hindrance of the branched structure which may lead to micelles formation more difficult. However, compared to linear tetraol **27**, the branched tetraol **29** has a slightly lower CMC which is in accordance with the data obtained from Kleven's equation. The CMC of linear C8-tetraol was calculated using Kleven's equation and found to be approximately 3.4 mM. This value is very close to the CMC of branched tetraol **29** (Table 24, entry 1). This result is fully in accordance with the rule proposed by Götte: each branched carbon appears to have "one-half" effect of a carbon in the alkyl linear chain.¹³⁴

Table 24. CMC results for branched tetraol and two adjacent tetraols for comparison.

Entry	Structure	Ratio ^a	CMC (mmol/L) ^b	γ_{sat} (mN/m) ^b
1		50:50	3.6	23.3
	29			
2		25:75	7.9	26.1
	26			
3		22:78	1.6	24.0
	27			

^a Ratios were estimated by ¹³C NMR. ^b Determined by tensiometry.

¹³³ K. Nidhi, S. Indrajeet, M. Khushboo, K. Gauri, D. J. Sen, *Int. J. Drug Dev. Res.*, **2011**, 3, 26-33.

¹³⁴ M. J. Rosen, *J. Am. Oil Chem. Soc.*, **1972**, 49, 293-297.

The CMC curve of citronellal-derived tetraol **29** is placed in the middle of the linear tetraol **26** (C7) and tetraol **27** (C9) (Figure 28).

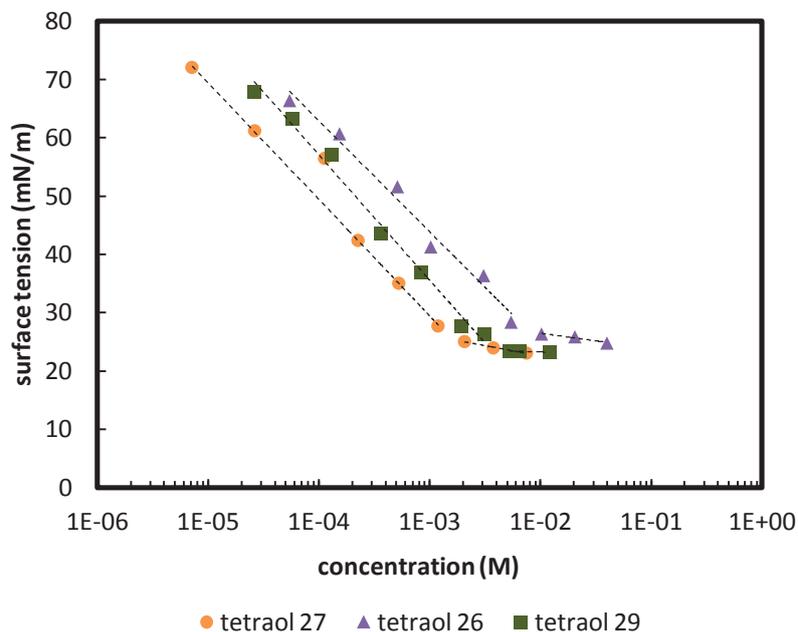
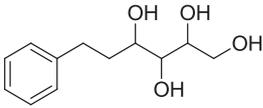
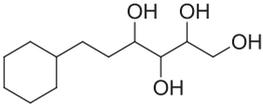


Figure 28. CMC measurements of branched chain tetraol **29** and tetraol **26**, **27**.

4.1.4 Influence of phenyl group and cyclohexane group on CMC.

Due to different reduction conditions, lower hydrogen pressure and temperature preserved the phenyl group which gave tetraol **22**, while harsher conditions (40 bar H₂, 100 °C) gave tetraol **23**.

Table 25. CMC results for tetraol **22** and its counterpart tetraol **23**.

Entry	Structure	Ratio ^a	CMC (mmol/L) ^b	γ_{sat} (mN/m) ^b
1		50:50	5.9	35.7
	22			
2		56:44	17	25.8
	23			

^a Ratios were estimated by ¹³C NMR. ^b Determined by tensiometry.

Tetraol **23** exhibits a higher CMC than its counterpart tetraol **22**, whereas the minimal surface tension of tetraol **23** solution is 25.8 mN/m, which decreased much lower than that of tetraol **22** (Table 25, entries 1-2). Dyer *et al.* have already reported this trend comparing very short phenyl and cyclohexyl *n*-alkanoates ($n = 0$ and 1).¹³⁵ For these molecules, the hydrophobic contribution of the phenyl group is higher than the cyclohexyl compound, as also observed with tetraol **22** and **23** (Figure 29).

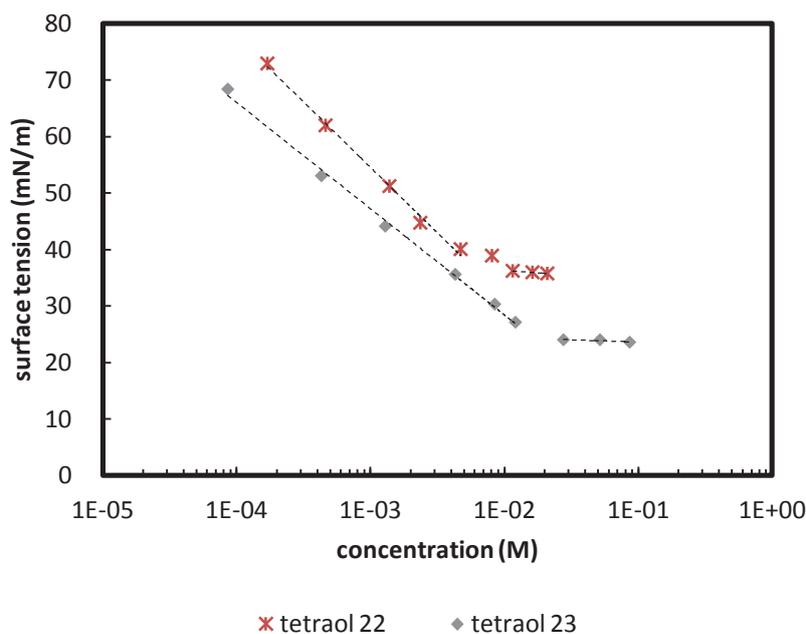


Figure 29. CMC measurements of tetraol **22** and **23**.

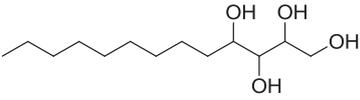
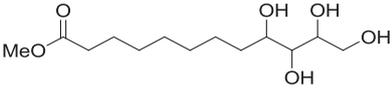
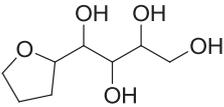
4.1.5 The CMC value measured with other tetraols.

Vegetable oil-derived tetraol **30** and furfural-derived tetraol **31** were also measured and compared with tetraol **27** (Table 26). Tetraol **30** has a much higher CMC value and surface tension due to the ester group at the end of hydrophobic tail which diminishes the lipophilic character compared to the linear tetraol **27**, in accordance with reported sodium monoalkyl dicarboxylates.¹³⁶ In conclusion, the ester group has a negative effect on surfactant performance.

¹³⁵ M. H. Hatzopoulos, J. Eastoe, P. J. Dowding, I. Grillo, B. Demé, S. E. Rogers, R. Heenan, R. Dyer, *Langmuir*, **2012**, *28*, 9332-9340.

¹³⁶ V. Nardello, N. Chailloux, G. Joly, J.-M. Aubry, *Colloids Surf., A*, **2006**, *288*, 86-95.

Table 26. Comparison between tetraol **30**, **31** and tetraol **27**.

Entry	Structure	Ratio ^a	CMC (mmol/L) ^b	γ_{sat} (mN/m) ^b
1		22:78	1.6	24.0
	27			
2		60:40	69	29.1
	30			
3		mixture of 8 isomers	nd	nd
	31			

^a Ratios were estimated by ¹³C NMR. ^b Determined by tensiometry.

Compared with the linear tetraol **27** (C9), tetraol **30** is not as efficient as the linear one. However, furfural-derived tetraol **31** is shown to be more similar to a hydrotrope since it decreased the surface tension smoothly only at higher concentration (10^{-2} M) (Figure 30).

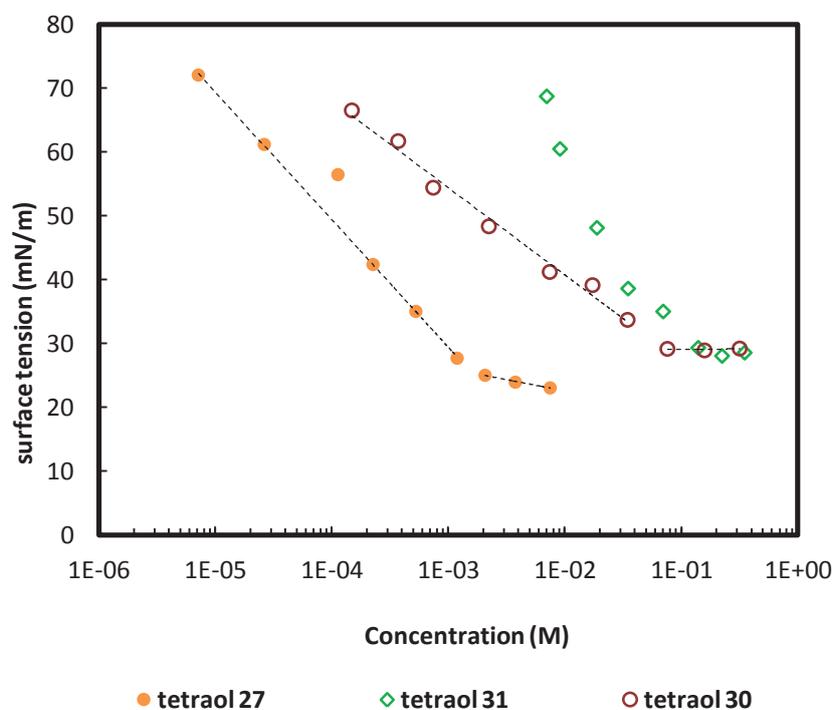
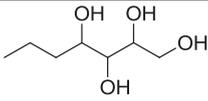
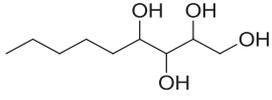
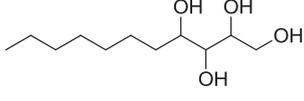
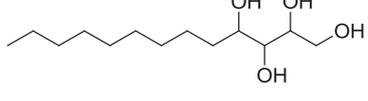
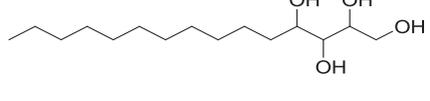


Figure 30. CMC curves of other substituent surfactants and comparison with tetraol **27**.

4.2 Determination of the Krafft point of tetraols.

The Krafft point was next determined for linear alkyl tetraols **24-28** (Table 27). All samples measured are mixtures of isomers. Krafft point is considered from a practical point of view as the temperature above which a 1 wt% aqueous solution of surfactant is soluble.¹³⁷

Table 27. Krafft point for different tetraols.			
Entry	Structure	Ratio ^a	Krafft point ^b / °C
1	 24	55:45	<5
2	 25	50:50	<5
3	 26	25:75	60
4	 27	22:78	65
5	 28	35:65	83

^a Ratios were estimated by ¹³C NMR. ^b Determined by constant temperature instruments.

This study shows that only short chain tetraol **24** (C3) and **25** (C5) are fully soluble at room temperature (Table 27, entries 1-2). On the contrary, other tetraols with an alkyl chain length more than 7 carbons have a limited solubility (Table 27, entries 3-5). High Krafft point (60-80 °C) means less soluble at room temperature which could also limit the application of these surfactants. One of the isomers is more soluble than the other and is able to facilitate its solubilization. To improve long

¹³⁷ Robert G. LAUGHLIN, Academic Press London, 1994, Vol 6.

chain surfactant application at room temperature, hydrotropes could be added into the formulation to reach a better performance of these tetraol surfactants.

4.3 Determination of HLB from the PIT-slope method.

The hydrophilic lipophilic balance value (HLB) for classifying surfactants were determined by using the PIT-slope method.¹³⁸ In this method, tetraethyleneglycol monodecyl ether ($C_{10}E_4$) was taken as a reference. A reference solution consisting of 3% $C_{10}E_4/n$ -octane/0.01M NaCl(aq) emulsion was prepared for determination of the phase inversion temperature (PIT). The conductivity of this emulsion was then followed with every quantified addition of alkyl tetraol **26-29**, and the influence of the PIT slope was measured at several concentrations of the added surfactant. The influence of addition of molar fraction x_2 of the tetraol surfactants into the mixture ($C_{10}E_4$ + alkyl tetraol **26-29**) to the PIT slope was demonstrated (Figure 31). The PIT slope of several n -alkyl tetraethoxylated surfactants are also shown for comparison. Longer alkyl tetraols **27-29** have a better linearity whereas the shorter tetraol **26** presents a less accurate linear match ($R_2=0.97$). The evolution of the PIT slope was obtained by the $dPIT/dx_2$ parameter that corresponds to the slope.

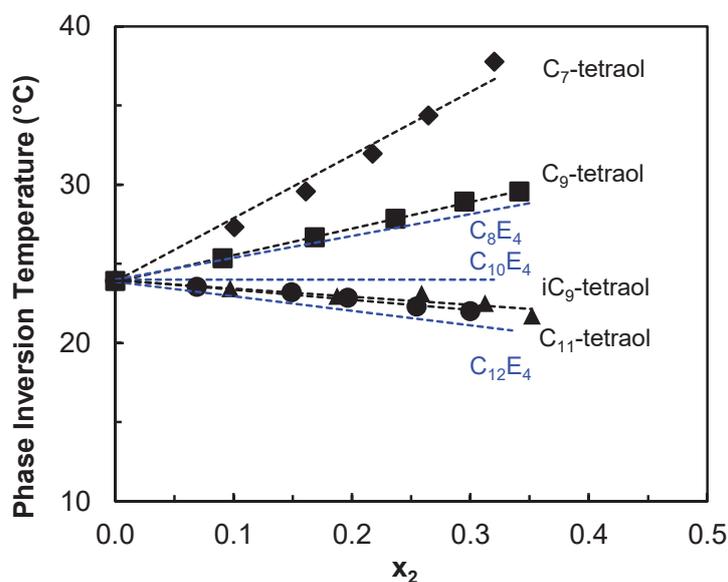
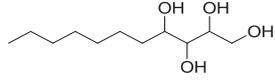
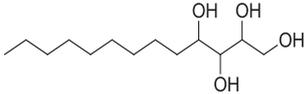
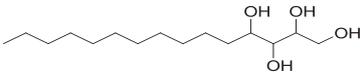
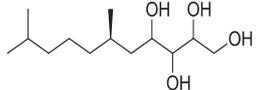


Figure 31. PIT slope of linear alkyl chain surfactants.

The obtained PIT-slope values were summarized (Table 28).

¹³⁸ J. F. Ontiveros, C. Pierlot, M. Catté, V. Molinier, J. L. Salager, J. M. Aubry, *J. Colloid Interface Sci.*, **2015**, *448*, 222-230.

Table 28. PIT-slope values expressed in °C (dPIT/dx₂) or °C/wt.% (dPIT/dC) for alkyl tetraols.

Entry	Structure	dPIT/dx ₂ (°C)	dPIT/dC (°C/wt.)
1	 26	43	14.8
2	 27	17	4.9
3	 28	-6.3	-1.7
4	 29	-5.1	-1.5

From these values, tetraol **28** and **29** are the only more lipophilic surfactants than the reference C₁₀E₄ while more hydrophilic than C₁₂E₄, however tetraol **26** and **27** tetraols are clearly more hydrophilic than C₁₀E₄ and C₈E₄.

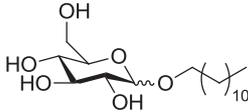
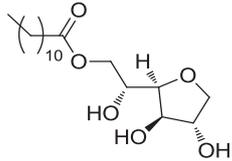
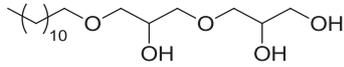
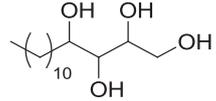
4.4 Comparison with other available polyol surfactants.

Finally, to evaluate the performance of the best tetraol surfactants **28** (C₁₁), the CMC and surface tension were compared with other polyol surfactants (Table 29).

Even with one carbon less than other surfactants, the CMC of tetraol **28** is near to the corresponding dodecylglucoside but 5-8 times higher than dodecanoylsorbitan (SPAN 20) or 1-*O*-dodecyl diglycerol (C₁₂Gly₂) (Table 29, entries 1-4). Interestingly, this tetraol surfactant is most efficient in decreasing the surface tension since it could reach as low as 23.7 mN/m. This could be proposed that the polar head of tetraol **28** bearing 4 hydroxyl groups in the first 4 carbons is shorter than the other surfactants and there is no heteroatom in linkage part.¹³⁹

¹³⁹ Rosen M. J., *Wiley Interscience: Hoboken, NJ, 2004*.

Table 29. Comparison with other available polyol surfactants.

Entry	Surfactant	CMC (mmol/L)	γ_{sat} (mN/m)
1	 C ₁₂ -glucosides (C ₁₂ Glu)	0.19 ¹⁴⁰	36 ¹⁴⁰
2	 C ₁₂ -sorbitan ester (Span 20)	0.041 ⁵	31 ⁵
3	 C ₁₂ -diglycerol (C ₁₂ Gly ₂)	0.031 ¹⁴¹	27 ¹⁴¹
4	 C ₁₁ -tetraol	0.26	23.7

In conclusion, the aldolisation of unprotected 1,3-dihydroxyacetone with a series of (bio-based) fatty aldehydes was developed. This process was catalyzed by trimethylamine under mild conditions in EtOH/H₂O mixture to give α -hydroxyketones with isolated yields of 29-70%. Then, these α -hydroxyketone intermediates were reduced under hydrogen to give the corresponding tetraols with 79-97% isolated yields. After obtaining these new C-C bond-linked tetraol surfactants, their physico-chemical properties were studied by measurements of CMC, Krafft point, PIT slopes and were compared to some commercially available surfactants to evaluate their performances. From these results, this new type of surfactant exhibits a high effectiveness to reduce the surface tension of water.

¹⁴⁰ S. Kozo, Y. Tokio, H. Ryohei, *Bull. Chem. Soc. Jpn.*, **1961**, 34, 237-241.

¹⁴¹ H. Sagitani, Y. Hayashi, M. Ochiai, *J. Am. Oil Chem. Soc.*, **1989**, 66, 146-152.

Chapter 3 Direct aldolisation of unprotected fructose to bio-based surfactants.

Sugar-based surfactants are the target objects of this work aiming at using renewable resources. Instead of the simplest ketose 1,3-dihydroxyacetone, other ketoses such as erythrulose (C4), ribulose/xylulose (C5) and fructose/sorbose (C6) can also be used as nucleophile substrates.

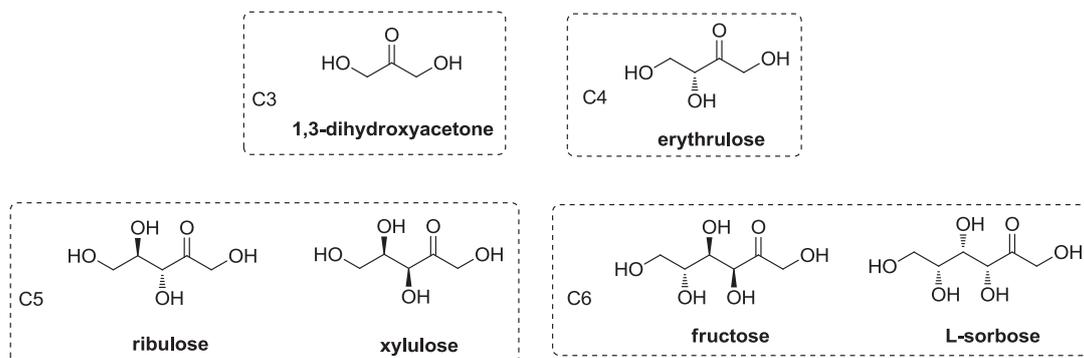


Figure 32. C3 to C6 ketoses.

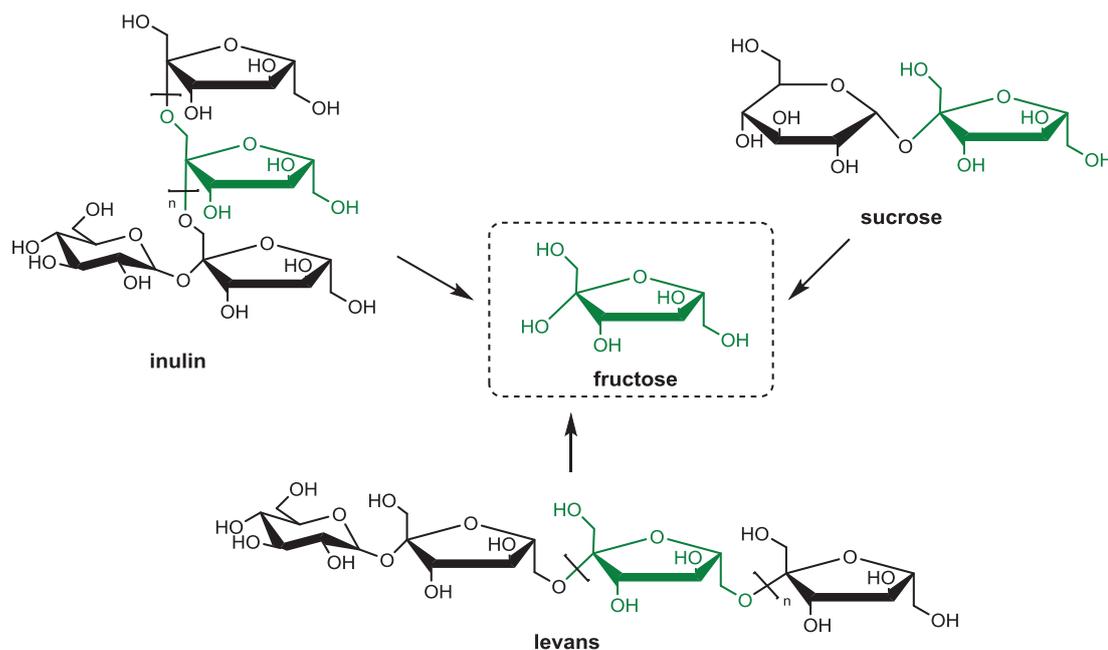
1 Introduction about fructose.

1.1 Natural occurrence.

D-Fructose is the most abundant ketoses in Nature where it is found as a monomer in inulin and levans or in association with glucose in sucrose (scheme 55). It can be commercially derived from sugar cane and sugar beets and also be produced by enzymatic hydrolysis of the disaccharides. Fructose is mainly produced as high fructose syrup (HFS) which is used as sweeteners in food and beverage industries. Moreover, due to its cheap price and renewable abundant accessibility, it is often used as raw material for the production of bio-based special chemicals (5-hydroxymethylfurfural¹⁴² and some biobased polymers¹⁴³). Fructose can also be used as a cheap renewable material for the production of bio-based chemicals for special use such as renewable surfactants.

¹⁴² a) A. A. Rosatella, S. P. Simeonov, R. F. M. Frade, C. A. M. Afonso, *Green Chem.*, **2011**, *13*, 754-793. b) R. Karinen, K. Vilonen, M. Niemelae, *Chemsuschem*, **2011**, *4*, 1002-1016.

¹⁴³ a) A. Gandini, T. M. Lacerda, A. J. F. Carvalho, E. Trovatti, *Chem. Rev.*, **2016**, *116*, 1637-1669. b) A. F. Sousa, C. Vilela, A. C. Fonseca, M. Matos, C. S. R. Freire, G. J. M. Gruter, J. F. J. Coelho, A. J. D. Silvestre, *Polym. Chem.*, **2015**, *6*, 5961-5983.



scheme 55. Fructose found as monomer in inulin, levans and sucrose.

1.2 Production and synthesis.

Most developments in the field of sugar-based surfactant industry have always been concentrated on feedstock such as sucrose, glucose and sorbitol due to their relatively low price and availability (Table 30). Among ketose starting materials, fructose is the most abundant with production of 240,000 t/year¹⁴⁴ and the cheapest price of 0.8 €/Kg.¹⁴⁵

Table 30. Availability of carbohydrate raw materials.		
	Production (t/year) ¹⁴⁶	Average price (€/Kg) ¹⁴⁷
sucrose	130,000,000	0.65
glucose	16,000,000	0.45-1
sorbitol	8,000,000	0.65-1.4
fructose	240,000	0.8

Industrial production of fructose is mostly obtained from the hydrolysis of sucrose and ends up with a mixture solution of fructose and glucose (HFS). To separate these two carbohydrates, usually calcium cation is added to form a fructose-Ca(OH)₂ complex that is separated by filtration,

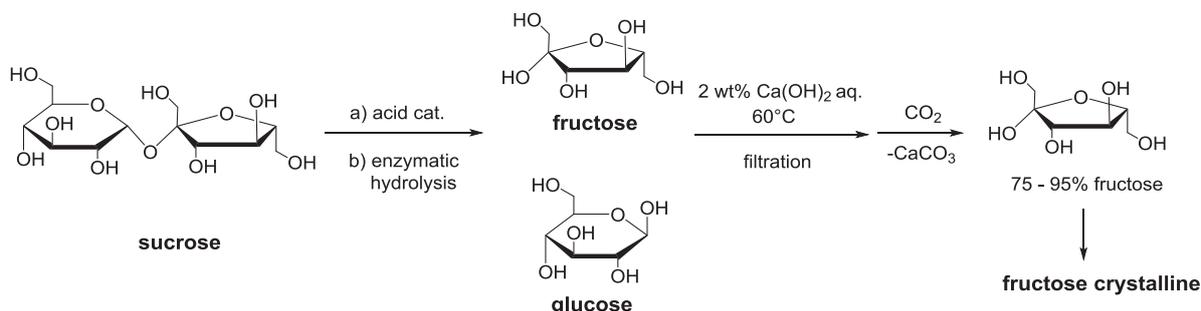
¹⁴⁴ Wolfgang Wach "Fructose" in Ullmann's Encyclopedia of Industrial Chemistry **2004**.

¹⁴⁵ Raw material price from Alibaba.

¹⁴⁶ Private communication (Cerestar, Henkel), **1996**.

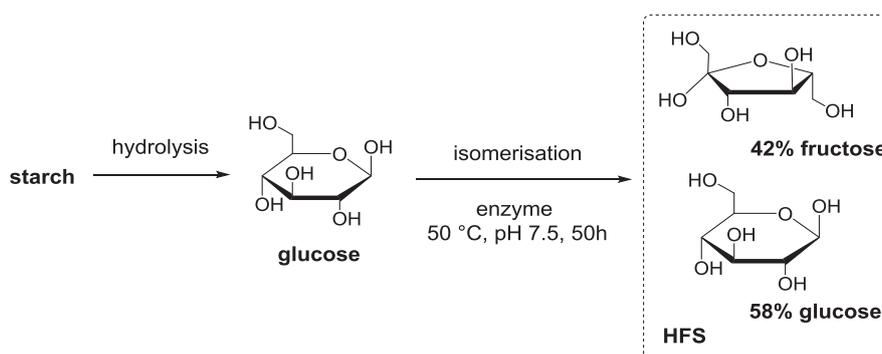
¹⁴⁷ acc. to Chem. Market Rep. 254 (**1998**), 20.

followed by introduction of CO_2 gas to remove CaCO_3 , to obtain a high concentration fructose syrup (75 to 95% fructose).¹⁴⁸ Further concentration can give crystalline fructose (scheme 56).



scheme 56. Fructose production from sucrose.

Fructose can also be produced by isomerization of glucose using starch as starting material (scheme 57). Conversion of this isomerisation is usually around 45% gave a mixture of 42% fructose and 58% glucose (HFS).¹⁴⁹



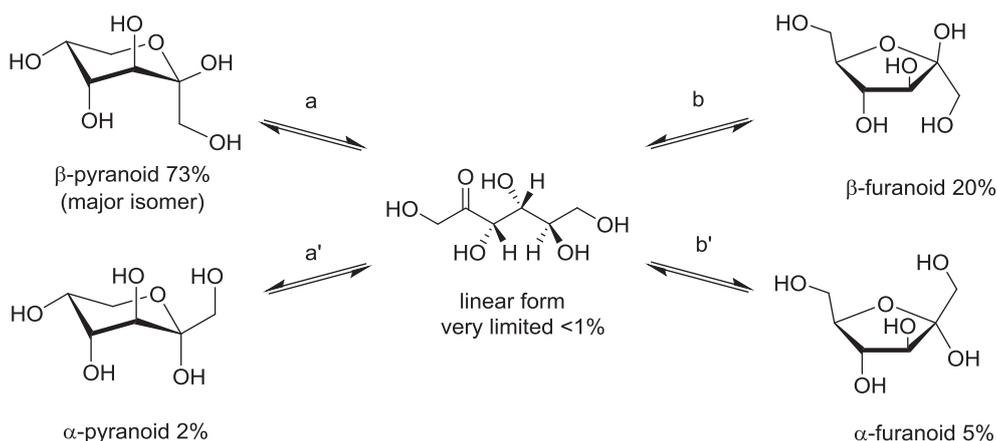
scheme 57. Fructose production from starch.

1.3 Fructose configuration properties.

The development of fructose chemistry was less explored than glucose despite its abundance in Nature. One of the causes maybe D-fructose exhibits a complex mutarotation behavior in aqueous solution leading to a mixture of five tautomeric forms. The proportion of each form mainly depends on solvent, time of equilibration, temperature and concentration.

¹⁴⁸ M. P. J. Kierstan, *Biotechnol. Bioeng.*, **1978**, *20*, 447-450.

¹⁴⁹ Y. Takasaki, O. Tanabe, US3616221A, **1965**.

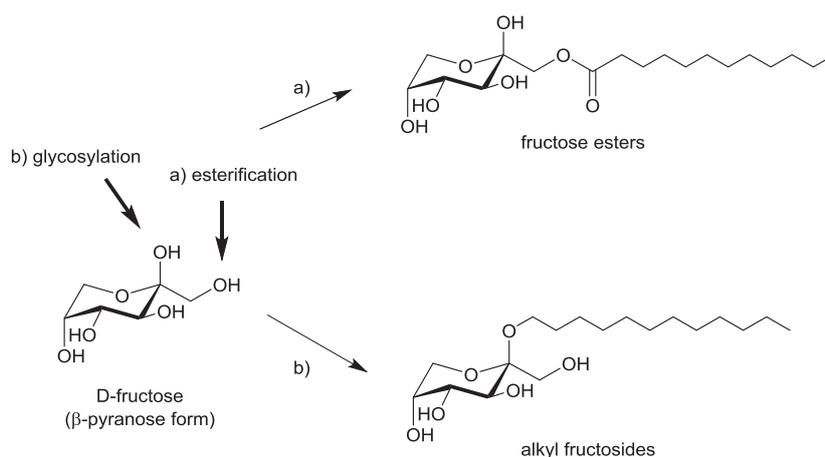


scheme 58. Fructose mutarotation in water (20 °C).

Schiweck *et al.* have reported that when D-fructose dissolved in water at 20 °C, at equilibrium and detected by ^{13}C NMR, the most occupying form is β -pyranoid which takes up around 73% of all forms. The second major isomer is β -furanoid representing around 20%. The other two cyclic forms (α -pyranoid and α -furanoid) almost take up the rest percentage. However, the acyclic hydroxyl keto-fructose is very limited in this aqueous solution. It is only detectable at higher temperatures and concentrations (scheme 58).¹⁵⁰

2 Fructose based surfactants.

To the best of our knowledge, fructose is less used as building block for carbohydrate-based surfactants compared to glucose, sucrose and sorbitan. To date, two families of fructose-based surfactants have been developed such as fructose esters and alkyl fructosides (scheme 59).



scheme 59. Alkylation of unprotected D-fructose to fructose esters and alkyl fructosides.

¹⁵⁰ B. Schneider, F. W. Lichtenhaler, G. Steinleb, H. Schiweck, *Liebigs Ann. Chem.*, **1985**, 2443-2453.

2.1 Fructose ester surfactants.

Sugar esters are of great interest because they can exhibit good surface-active properties. Ghoul *et al.* have established that fructose esters exhibit interesting surface-active properties, and at shorter chain length ever better than their sucrose counterparts. The lowest interfacial tension was obtained with Sisterna (SP70=30% sucrose palmitate and 70% sucrose stearate) at 38 mN/m, sucrose palmitate (P1670) at 37.5 mN/m and sucrose stearate (S1670) at 34 mN/m. While fructose esters exhibited generally lower surface tension, especially with short carbon chain length, with fructose monocaprate of 26 mN/m and fructose monostearate of 31.8 mN/m. Foamability and oil-water emulsion stability were largely depending on the carbon chain length and mono/diester ratio, with proper formulation, fructose esters could also be more advantageous than sucrose esters.¹⁵¹

2.1.1 Chemical synthesis route.

Sugar fatty acid esters are consisting of two abundant agricultural raw materials, sugars and fatty acids derived from fats or oils. These sugar esters obtained by chemical process are always with low selectivity since the existence of several hydroxyl groups with same reactivity which gives various by-products such as mixtures of mono-, di- and even higher degree esters. Moreover, their synthesis is often realized at high temperatures (120-170 °C) which may cause unexpected coloring of the products.⁴⁸ As a consequence, not all chemically produced sugar fatty acid esters are allowed for applications, and the chemical preparation methods were best studied with the commercial available sucrose esters. Therefore, fructose esters are mainly prepared by biocatalytic methods for better selectivity and mild conditions.

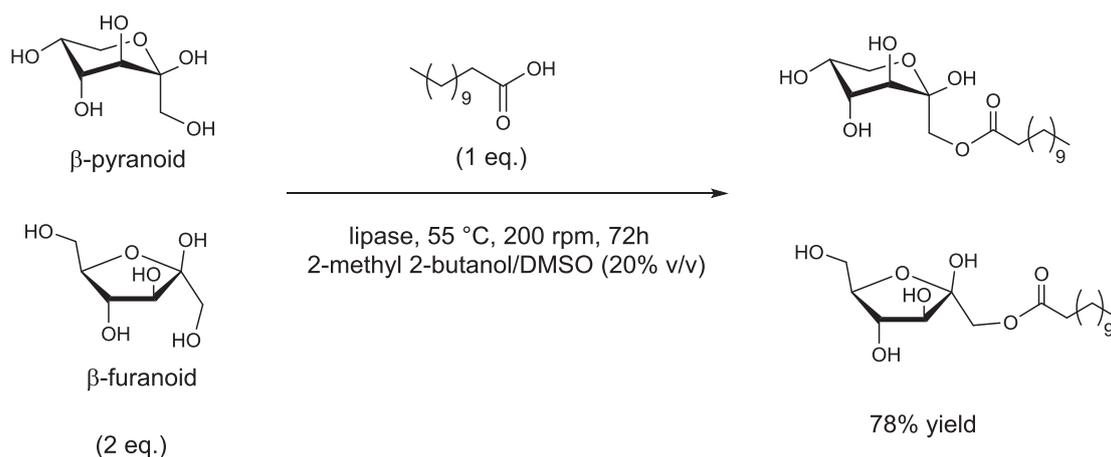
2.1.2 Enzymatic synthesis route.

In order to obtain a defined carbohydrate fatty acid monoester, enzymatic process of synthesizing sugar esters have been developed with several advantages: 1) better regioselectivity toward the monoester. 2) reaction performed under milder conditions than chemical process.¹⁵² Zheng *et al.* have reported a synthesis of fructose laurate esters catalyzed by a whole-cell biocatalyst from unprotected fructose and lauric acid in organic solvent. Under the best conditions, the yield of fructose laurate monoesters obtained was 78% (scheme 60).¹⁵³

¹⁵¹ S. Sultani, S. Ognier, J. M. Engasser, M. Ghoul, *Colloids Surf., A*, **2003**, 227, 35-44.

¹⁵² D. Coulon, M. Girardin, M. Ghoul, *Process Biochem.*, **1999**, 34, 913-918.

¹⁵³ Z. Jin, S. Liang, X. Zhang, S. Han, C. Ren, Y. Lin, S. Zheng, *Biotechnol. Bioprocess Eng.*, **2013**, 18, 365-374.



scheme 60. Enzymatic synthesis of fructose monolaurate ester.

Many efforts have been done in this field to optimize this bio-process. A green approach has been developed by Ye *et al.* to realize a solvent-free lipase catalyzed synthesis of fructose oleic acid ester. This process was carried out at 53 °C without solvent, yielding fructose oleate at 92.6 wt% within 132 hours.¹⁵⁴

Koo *et al.* have reported the application of ultrasound irradiation to enhance the activity of lipase. This bio-process was carried out with unprotected fructose and palmitic acid in ionic liquids. As a consequence, 1.44 times higher enzyme activity was achieved. Under optimized conditions of 60 °C, fructose to palmitic acid (1:2 molar ratio), after 14 hours, 75% of conversion was obtained, while only 64% conversion was obtained without ultrasound irradiation.¹⁵⁵

Fructose esters can be obtained by direct esterification of fructose with a wide range of fatty acids. Enzymatic methods are preferred due to their better selectivity towards monoesters over the chemical one.

¹⁵⁴ R. Ye, D. G. Hayes, *J. Am. Oil Chem. Soc.*, **2011**, *88*, 1351-1359.

¹⁵⁵ S. H. Ha, N. M. Hiep, Y. M. Koo, *Biotechnol. Bioprocess Eng.*, **2010**, *15*, 126-130.

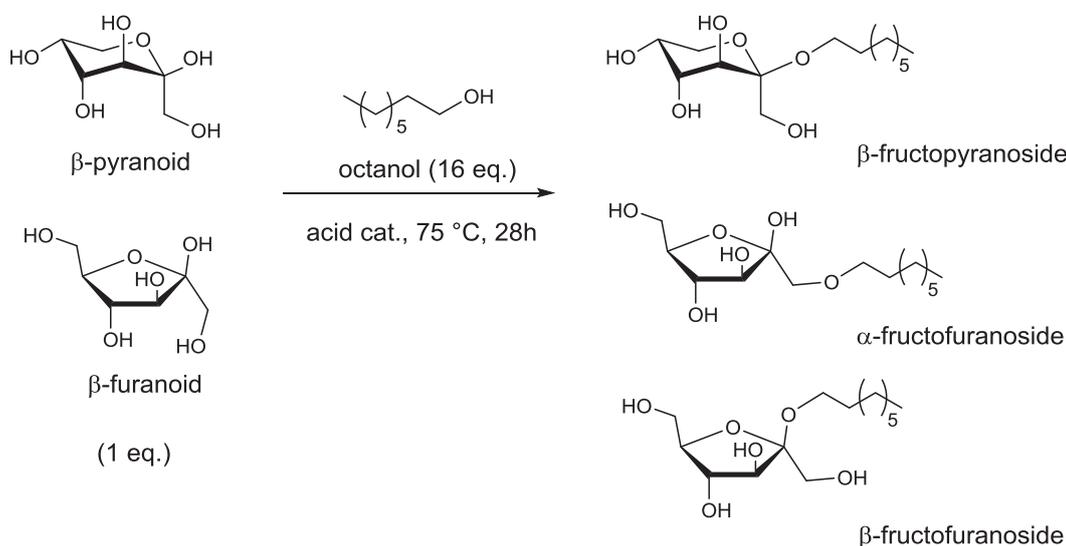
2.2 Alkyl fructosides.

Alkyl polyglucosides (APG) have shown great promise as surfactants due to their readily biodegradability and low toxicity.¹⁵⁶ Although the synthesis of APGs from glucose has been already well investigated,¹⁵⁷ *O*-alkyl fructosides are relatively less explored compared to their glucosides analogues.

2.2.1 From fructose.

Long chain alkyl fructosides have been prepared from fructose using a number of protection and deprotection steps.¹⁵⁸ To avoid these extra steps as well as the synthetic cost, unprotected fructose should be directly used as starting material. The mostly used preparation methods of alkyl fructosides starting from fructose are catalyzed by an acid catalyst with an alkyl alcohol.

Herman *et al.* have reported the reaction of unprotected D-fructose in 1-octanol with various acid catalysts (scheme 61).¹⁵⁹ Fructosides are usually obtained as a complex anomeric mixtures of α -/ β -fructose furanosides and α -/ β -fructose pyranosides due to the complexity of D-fructose isomers mixture. With oxalic acid as the best catalyst, this reaction can be obtained at the optimized conditions with a total yield of 54% was obtained for the three *O*-alkyl isomers, with β -fructopyranoside: α -fructofuranoside: β -fructofuranoside ratio at 9:61:30.



scheme 61. Fructosides prepared from alkylation of unprotected fructose and fatty alcohols.

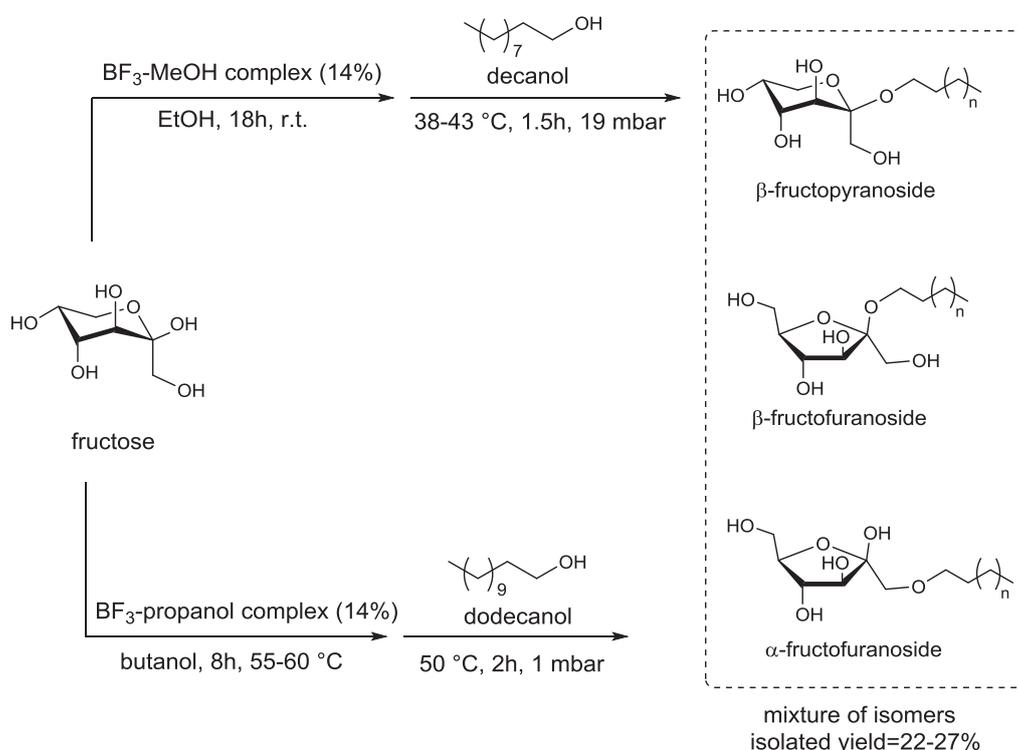
¹⁵⁶ T. Madsen, G. Petersen, C. Seiero, J. Torslov, *JAACS*, **1996**, 73, 929-933.

¹⁵⁷ M. M. A. El-Sukkary, N. A. Syed, I. Alad, W. I. M. El-Azab, *J. Surfact. Deterg.*, **2008**, 11, 129-137.

¹⁵⁸ F. W. Lichtenthaler, *Carbohydr. Res.*, **1998**, 313, 69-89.

¹⁵⁹ A. T. J. W. de Goede, F. van Rantwijk, H. van Bekkum, *starch*, **1995**, 47, 233-237.

However, this acid-catalyzed glycosidation is temperature dependent, in order to improve the yield with long chain alcohol substrate (>C10) higher temperatures are required. Unfortunately, this often leads to dehydration-degradation products such as 5-hydroxymethylfurfural (5-HMF) and levulinic acid. To obtain satisfying yield with longer chain alcohols, Gordon *et al.* have reported a glycosidation-transglycosidation sequence of preparing C10/C12-fructosides in by using BF₃-alcohol complex (scheme 62). These fructosides were isolated by column chromatography or recrystallisation, with decanol fructoside yield of 27% (β -fructopyranoside: β -fructofuranoside: α -fructofuranoside ratio 3%:14%:83%) and dodecanol fructoside of 22% (β -fructopyranoside: β -fructofuranoside: α -fructofuranoside ratio 64%:12%:24%).¹⁶⁰



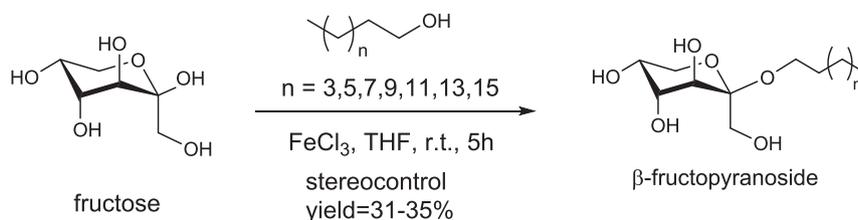
scheme 62. Preparation of C10/C12 fructosides by using BF₃-alcohol complex.

Bekkum *et al.* have also reported a mesoporous material MCM-41 catalyzed fructose glycosylation processes using long alkyl alcohol.¹⁶¹ The process was carried out at 80 °C after 24 hours with corresponding alcohol substrate (16 equiv.) as solvent and the products C10/C12 fructosides were obtained with 51% and 42% GC yield, respectively. Furthermore, with the help of another solvent such as *tert*-butyl alcohol or 1,2-dimethoxyethane to realize the glycosidation-transglycosidation sequence, the desired dodecyl fructosides can be obtained at 60% of GC yield in only 6 hours.

¹⁶⁰ H. Regeling, B. Zwanenburg, G. J. F. Chittenden, *Carbohydr. Res.*, **1998**, 314, 267-272.

¹⁶¹ A. M. van der Heijden, F. van Rantwijk, H. van Bekkum, *J. Carbohydr. Chem.*, **1999**, 18, 131-147.

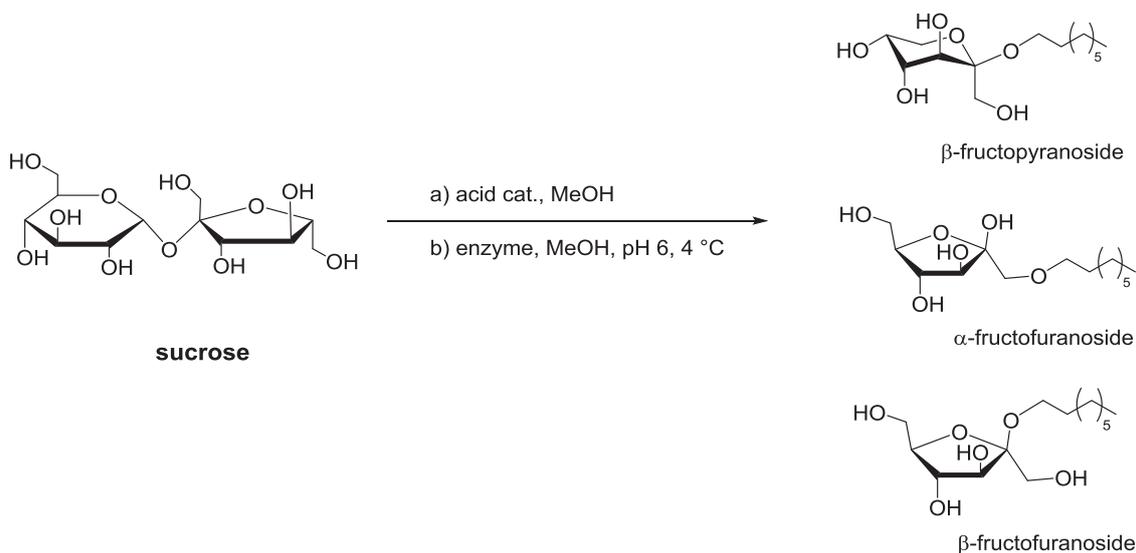
By using these mentioned methods, these fructosides are always obtained as mixtures of β -fructopyranosides and α - β -fructofuranosides. On the opposite, Durbin *et al.* have reported that, in the presence of FeCl_3 , the synthesis of alkyl β -fructopyranosides could be stereocontrolled from totally unprotected D-fructose by treatment with alcohol in yields of approximately 30% (scheme 63).¹⁶²



scheme 63. Stereocontrolled synthesis of alkyl β -fructopyranoside.

2.2.2 From sucrose.

Fructosides can be prepared from sucrose with organocatalysts or biocatalysts (scheme 64). However, these acid catalyzed methods have the same difficulty than with fructose of fatty alcohol substrates. To obtain a higher yield, usually high temperature is required which cause the formation towards 5-HMF by-product. Enzyme catalyzed process only suitable for short chain alcohol such as methanol or butanol and gives moderate yield (conversion 35%), while it is ineffective for fatty alcohols.¹⁶³



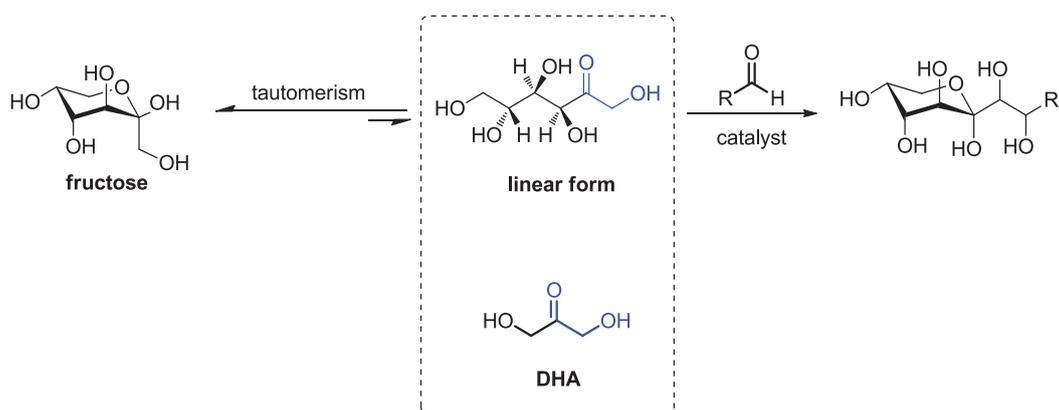
scheme 64. Fructosides prepared from sucrose.

¹⁶² V. Ferrières, T. Benvegnu, M. Lefeuvre, D. Plusquellec, G. Mackenzie, M. J. Watson, J. A. Haley, J. W. Goodby, R. Pindak, M. K. Durbin, *J. Chem. Soc., Perkin Trans.*, **1999**, 2, 951-959.

¹⁶³ a) G. Avigad, D. S. Feingold, *Arch. Biochem. Biophys.*, **1957**, 70, 178-184. b) M. Rodriguez, A. Gomez, F. Gonzalez, E. Barzana, A. L. Munguia, *Appl. Biochem. Biotechnol.*, **1996**, 59, 167-175.

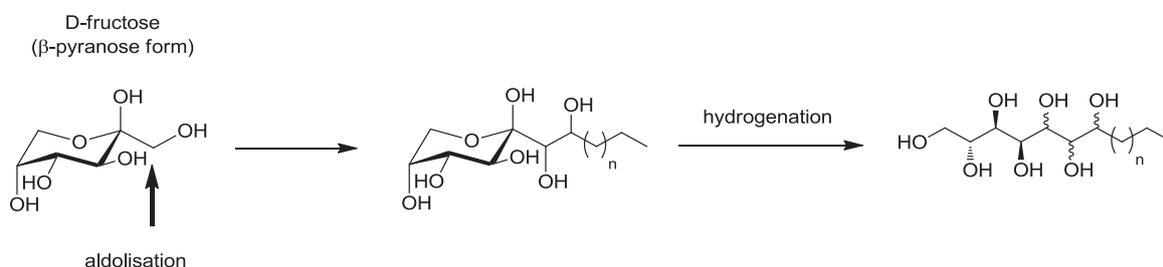
3 Aldolisation of unprotected fructose.

Based on the previous work of bio-based surfactants prepared by aldolisation of unprotected 1,3-dihydroxyacetone and fatty aldehydes, other ketoses can be used. Unprotected fructose can be used since the linear hydroxyketone moiety of D-fructose is very similar to that of DHA in the acyclic keto-form (scheme 65).



scheme 65. Preparation of fructose based surfactants.

However, due to the limited proportion of D-fructose linear form (< 1%), which is shown to be the only active specie reacting with aldehyde to give desired surfactant molecules, it remains a challenge to activate the fructose from cyclic β -pyranoid/furanoid to the linear keto-fructose form. Moreover, considering there are more hydroxyl groups on fructose structure compared to DHA, it could be a challenge to attach this highly hydrophilic carbohydrate molecule to a hydrophobic part such as fats or oil derivatives. This is a new approach for alkylation of fructose and the obtained adducts are further hydrogenated to give the corresponding sugar ring open form as alkylated heptaols (Scheme 66).



Scheme 66. Aldolisation/hydrogenation of unprotected D-fructose.

Unlike the other reported fructose-based surfactants preparation methods (esterification or glycosylation), surfactants prepared by this method should exhibit: 1) have a good regioselectivity only at the α -position of hydroxyl ketone. 2) to be able to create a C-C bond linkage from the

aldolisation with an alkyl chain aldehyde which is expected to be more robust than the other *O*-linkages (ester or ether).

In this context, a new approach of the abundant unprotected fructose valorisation to a value added robust C-C bond linkage surfactants will be investigated, through aldolisation with fatty aldehydes in a green way: green solvents or solvent-free, higher atom economy and mild reaction conditions.

3.1 Optimization of fructose aldolisation using Me₃N.

To test the hypothesis of aldolisation between limited keto-form fructose with aldehydes, a model reaction has been set up under the optimized condition for DHA by using the same substrate hydrocinnamaldehyde (HCA) (Table 31). However, only traces of the desired product **33** were obtained (Table 31, entry 1). No improvement was obtained even after 72 hours of reaction (Table 31, entry 2). These results were not surprising considering that fructose exists mainly as a mixture of four cyclic tautomers in solution and the only active formation of acyclic keto-form represents only 0.5-1% at room temperature.¹⁶⁴ In order to promote the formation of the linear keto-fructose in solution, microwave irradiation has been used. At 80 °C under microwave irradiation, 8% yield of product **33** was obtained and characterized by ¹H NMR and ¹³C NMR (Table 31, entry 3).

Table 31. Fructose aldolisation with hydrocinnamaldehyde under the optimized condition for DHA. ^a

Reaction scheme: Fructose (32) + Hydrocinnamaldehyde (1) $\xrightarrow[\text{EtOH/H}_2\text{O} = 1/1]{\text{Me}_3\text{N (50 mol\%)}}$ Product 33

Entry	Temperature/ °C	Time/ h	Isolated yield (%)
1	room temperature	4	traces
2	room temperature	72	traces
3	microwave, 80	2	8

^a Reaction conditions: fructose : HCA = 5 : 1, 50 mol % Me₃N as catalyst in EtOH/H₂O=1/1.

¹⁶⁴ F. W. Lichtenthaler, *Carbohydr. Res.*, **1998**, 313, 69-98.

Based on the ^{13}C NMR spectrum, there is no signal for the ketone group (around 210 ppm) and there are two peaks for the anomeric carbon on the carbohydrate skeleton (100 and 104 ppm), which means that almost no linear ketone form was produced and at least two isomers were obtained, namely, pyranoid or furanoid tautomers (Figure 33).

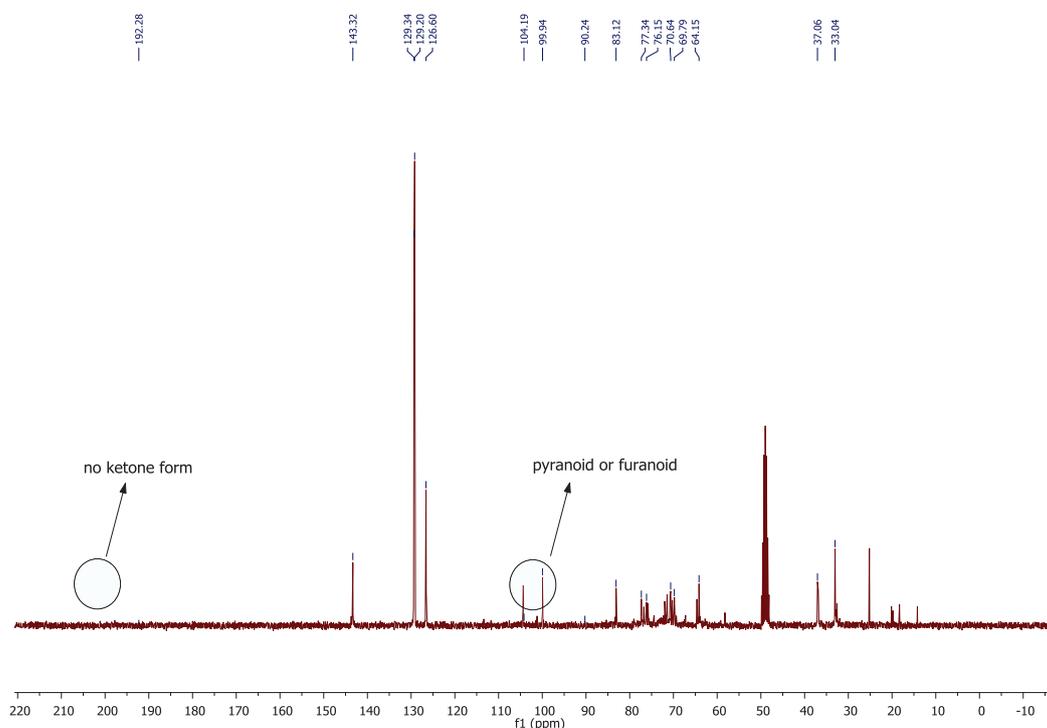
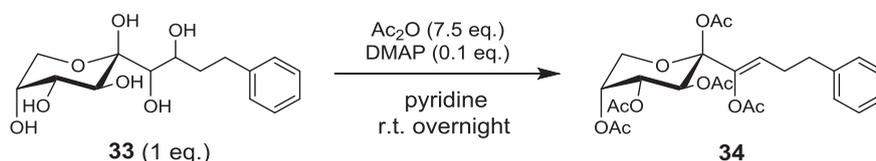


Figure 33. ^{13}C NMR (CD_3OD , 300 MHz) spectrum of product **33**.

To verify how many isomers were obtained, the isolated product **33** has been acetylated. The acetylation step was performed in pyridine with Ac_2O (7.5 equiv.) and catalyst DMAP (0.1 equiv.) at room temperature overnight (scheme 67). After purification by column chromatography, the given product was proven to be the eliminated product **34** of the expected acetylated product by NMR spectrum.



scheme 67. Acetylation of product **33**.

Although the acetylation process may change the ratio between each isomer, this equilibrium only changes slightly when the solvent is pyridine and reacts at room temperature as reported by B. Schneider.¹⁵⁰ Figure 34 was obtained after the injection of product **34**. GC

chromatograph of **34** has shown that the acetylated product contains at least three types of isomers with a ratio of 13:14:74 (Figure 34). By comparison with results reported by Schneider, it was possible to assign each peak with the help of NMR spectra as α -furanoid/ β -furanoid/ β -pyranoid with the ratio of 13/14/74.

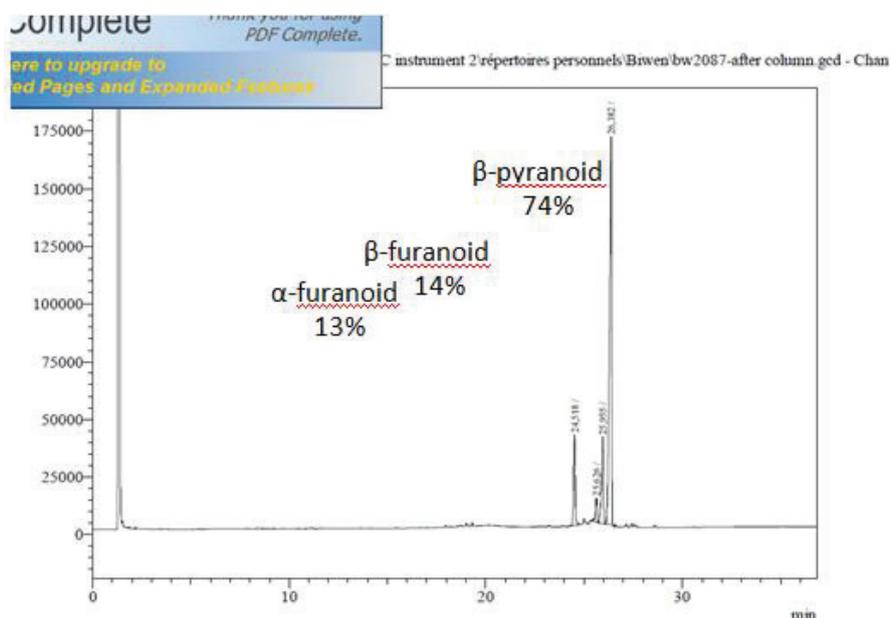


Figure 34. GC chromatograph of acetylated product **34**.

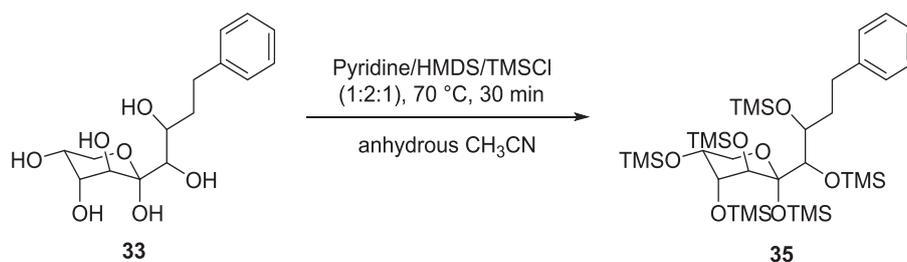
3.2 GC methods and calibration curve.

In order to better optimize this fructose-based aldolisation process, a more convenient analysis method was built. Due to the polyhydroxy groups of the product, a derivatisation step was required to obtain a more volatile compound which can be tracked by GC. Most of the derivatisation methods are to prepare silylated derivatives.¹⁶⁵ The isolated product **33** obtained from the model reaction was then silylated in the presence of 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 6 equiv.) and TMSCl (trimethylsilyl chloride) following a protocol reported in the literature (scheme 68).¹⁶⁶ Unlike the acetylation process, no elimination product was detected. With the help of an internal standard, calibration curve of both starting material HCA and obtained product **33** (mixture of isomers) have been constructed for subsequent study.

¹⁶⁵ a) C. C. Sweeley, R. Bentley, M. Makita, W. W. Wells, *Gas Chromatography of Sugars*, **1963**, *85*, 2497-2507.

b) M. Becker, T. Zweckmair, A. Forneck, T. Rosenau, A. Potthast, F. Liebner, *J. Chromatogr. A*, **2013**, *1281*, 115-126. c) S. Moldoveanu, W. Scott, Jeff Zhu, *J. Sep. Sci.*, **2015**, *38*, 3677-3686.

¹⁶⁶ C. C. Sweeley, R. Bentley, M. Makita, W. W. Wells, *J. Am. Chem. Soc.*, **1963**, *85*, 2497-2507.

scheme 68. Trimethylsilylation of isolated product **33**.

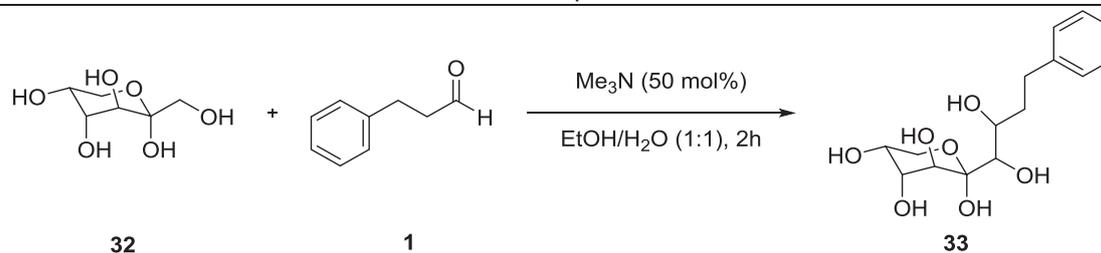
3.3 Aldolisation condition screening and optimization.

Based on our preliminary result, only 8% yield was obtained from this fructose aldolisation. The yield should be improved by screening reaction conditions.

3.3.1 Influence of the temperature.

To improve the percentage of linear keto fructose, the temperature should be increased. The influence of the temperature was studied based on the unprotected D-fructose (5 equiv.) and HCA (1 equiv.) using Me₃N catalyst (50 mol%) in EtOH/H₂O (1:1) for 2 hours under microwave. The reaction was carried out in a sealed tube to avoid the loss of volatile amine catalyst (Table 32).

Table 32. The influence of temperature on model reaction.



Entry	(μW) T / °C	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	40	34	3	9
2	60	49	31	63
3	80	56	28	50
4	100	68	25	37

Reaction conditions: sealed tube, D-fructose (5.6 mmol, 5 equiv.), Me₃N (0.56 mmol, 50 mol%), HCA (0.28 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 4 mL) for 2h. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

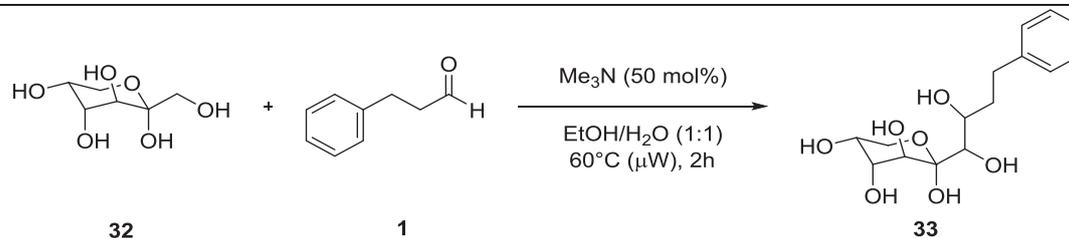
When the temperature increased from 40 to 100 °C, the conversion of HCA increased from 34% to 68% (Table 32, entries 1-4). At first when temperature increased from 40 to 60 °C, the yield increased dramatically from 3 to 31% (Table 32, entries 1-2). It means in this process the temperature increase can promote the equilibrium to increase the percentage of active linear keto form of fructose. If the temperature increased to 80 °C and 100 °C, the yield will slightly decreased in spite of higher conversion (Table 32, entries 3-4). The yield of byproducts (HCA self-condensation) has exceeded the formation of desired product **33**. The highest yield was obtained at 60 °C with 63% selectivity (Table 32, entry 2).

In conclusion, 60 °C was selected. In order to improve the yield, other parameters need to be studied to shift the equilibrium towards the formation of the active acyclic fructose.

3.3.2 Influence of the aldehyde concentration.

The influence of the HCA concentration was studied at 60 °C under microwave, based on the D-fructose/HCA (5:1) using Me₃N (50 mol%) in EtOH/H₂O (1:1) for 2 hours (Table 33). Higher HCA concentrations can lead to higher selectivity (Table 33, entries 1-3). However, 1.12 M HCA would decrease the conversion and yield (Table 33, entry 3).

Table 33. The influence of HCA concentration.

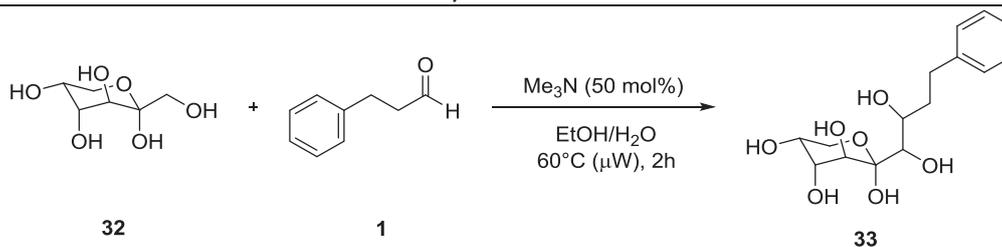


Entry	C(HCA)/ M	Conversion of 1 ^a /%	Yield of 33 ^a /%	Selectivity ^b /%
1	0.28	49	31	63
2	0.56	58	42	72
3	1.12	50	36	72

Reaction conditions: sealed tube, D-fructose (5.6 mmol, 5 equiv.), Me₃N (0.56 mmol, 50 mol%), HCA (1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 1, 2, 4 mL) with microwave irradiation for 2h. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

0.56 M was selected to be the best concentration of HCA with 42% GC yield and 72% selectivity (Table 33, entry 2).

Table 35. Study of the solvent mixture.



Entry	EtOH/H ₂ O (v:v) ratio	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	1/1	58	42	72
2	1/9	51	34	67
3	9/1	49	11	22

Reaction conditions: sealed tube, D-fructose (5.6 mmol, 5 equiv.), Me₃N (0.56 mmol, 50 mol%), HCA (0.56 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 2 mL) with 60 °C microwave irradiation for 2h. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

EtOH/H₂O (1:1) gave the highest conversion 58% and 42% yield (Table 35, entry 1). When EtOH/H₂O ratio (1:9) and (9:1) were used, the yield and selectivity were less (Table 35, entries 2-3). This could be explained by the solubility of fructose in EtOH/H₂O system as reported by Crestani.¹⁶⁷ In this work, the solubility of fructose in EtOH/H₂O mixture was determined over a temperature range from 25 to 60 °C. The solubility decreases with the increasing of EtOH proportion and increases with the increasing of temperature. Based on this work, fructose reaches its saturated mass fraction at 60 °C in EtOH/H₂O (1:1). This is in accordance with our experimental results (EtOH/H₂O 1:1 at 60 °C).

3.3.5 Influence of the fructose/aldehyde ratio.

Since this fructose aldolisation is a reversible process, excess of fructose could be used to push this equilibrium to obtain more desired product **33**. In that case, the abundant and cheap starting material fructose is more accessible to be used in large excess.

The study of fructose/aldehyde ratio was carried out based on D-fructose and HCA (1 equiv.) using Me₃N (50 mol%) in EtOH/H₂O (1:1) for 2 hours under microwave at 60 °C (Table 36).

¹⁶⁷ C. E. Crestani, A. Bernardo, B. B. C. Caliane, M. Giulietti, *J. Chem. Eng. Data.*, **2013**, *58*, 3039-3045.

Table 36. Influence of the fructose/aldehyde ratio.

Reaction scheme: Fructose (32) + 3-phenylpropanal (1) $\xrightarrow[\text{EtOH/H}_2\text{O (1:1), 60}^\circ\text{C } (\mu\text{W}), 2\text{h}]{\text{Me}_3\text{N (50 mol\%)}}$ Product 33

Entry	Fructose/HCA ratio	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	1 : 1	62	8	13
2	5 : 1	58	42	72
3	10 : 1	60	47	78
4	20 : 1	75	63	84

Reaction conditions: sealed tube, D-fructose (1-20 equiv.), Me₃N (0.56 mmol, 50 mol%), HCA (0.56 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 2 mL) with 60 °C microwave irradiation for 2h. ^aResults were calculated by GC calibration curve. ^bSelectivity=Yield/Conversion.

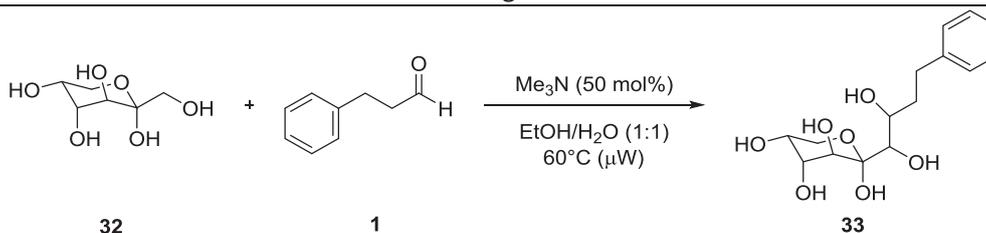
Fructose equivalent was enhanced from 1 to 5 equiv. and the yield of product **33** has been dramatically increased from 8% to 42% (Table 36, entries 1-2). Advantageously, excess of fructose can diminish the formation of HCA self-condensation by-product. The ratio was continued to be increased to 10 and 20 equiv., the best result was obtained when 20 equiv. of fructose was added which gave 63% yield and 84% selectivity (Table 36, entries 3-4). No higher fructose ratio was tested due to the limitation of fructose solubility in this solvent mixture and to avoid the stirring problem.

In conclusion, excess of fructose in this aldolisation can lead to higher yield and selectivity of product **33**.

3.3.6 Influence of the reaction time.

Kinetic study has been done on fructose (5 and 20 equiv.) with HCA (1 equiv.) in the presence of catalyst Me₃N (50 mol%) for 2 hours under microwave (Table 37).

Table 37. Screening of reaction time.



Entry	Fructose/HCA ratio	Time / h	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1		0.5	13	9	69
2		1	34	12	35
3	5 : 1	2	49	31	63
4		3	54	23	43
5		3 ^c	45	16	36
6		1	32	26	81
7	20 : 1	2	75	63	84
8		3	61	47	77

Reaction conditions: sealed tube, D-fructose (5.6 or 22.4 mmol, 5 or 20 equiv.), Me_3N (0.56 mmol, 50 mol%), HCA (0.56 M, 1.1 mmol, 1 equiv.) in $\text{EtOH}/\text{H}_2\text{O}$ (1:1, 2 mL) with 60°C microwave irradiation for 2h. ^aResults were calculated by GC calibration curve. ^bSelectivity=Yield/Conversion. ^cAldolisation is done without microwave irradiation.

The study was done first with 5 equivalents of fructose and in these cases fructose is not saturated in the solvent mixture yet. From 0.5 to 2 hours, the conversion increased from 13% to 49%, as well as the yield of product **33** increased from 9% to 31% (Table 37, entries 1-3). If the reaction time continued to be prolonged to 3 hours, the conversion of **1** still increased to 54% while the corresponding yield decreased to 23% due to the formation of HCA self-condensation by-product (Table 37, entry 4). When the reaction was carried out without microwave, it works but not so effective compared with the same condition under microwave and the yield and conversion were both slightly lower (Table 37, entry 5). Furthermore, 20 equivalents of fructose were used as a saturated solution. From 1 to 2 hours, the conversion and yield obey the same trend than with 5 equiv., that the conversion and yield both increased (Table 37, entries 6-7). However, after 3 hours the conversion decreased to 61% with 47% yield (Table 37, entry 8). Kinetic curve of the saturated fructose (20 equiv.) was made to better understand this fructose aldolisation process (Figure 35).

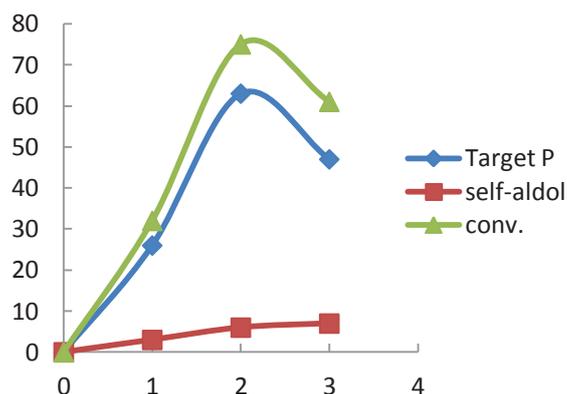


Figure 35. Kinetic curve in the case of saturated fructose (20 equiv.).

From this kinetic curve, at first the formation of desired product **33** is the dominant process until 2 hours. However, at 2 hours the yield reached its peak value at 63%. And if the reaction continues, the aldolisation yield decreases due to the HCA self-condensation by-product meanwhile the conversion decreases due to the reversible reaction. In conclusion, this fructose aldolisation should be stopped after 2 hours to obtain the best yield.

3.3.7 Model reaction under optimized conditions.

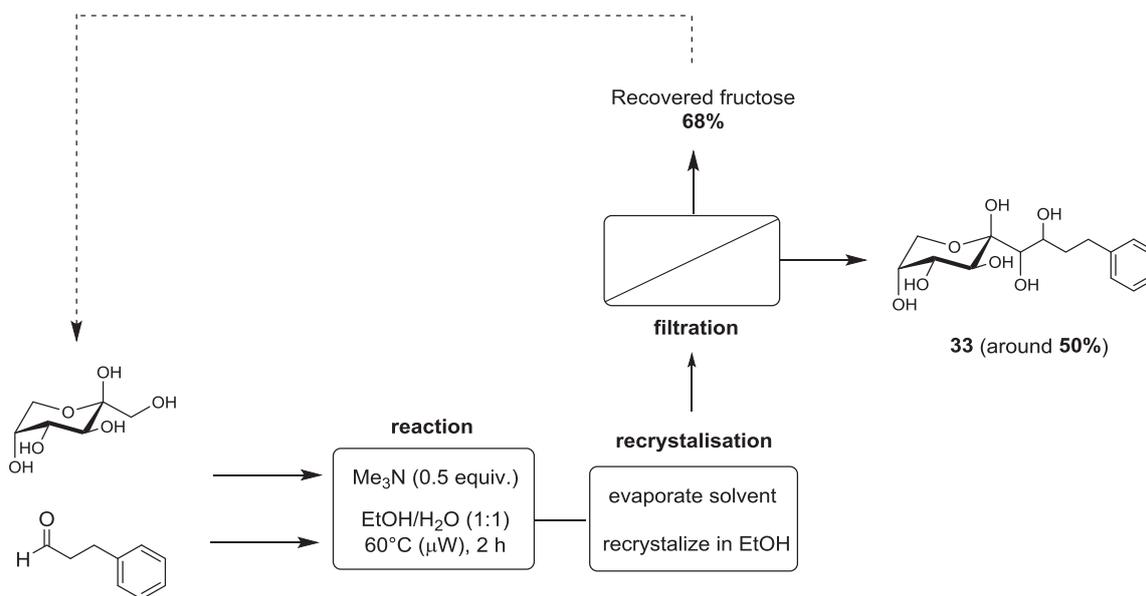
After this parametric study, a reaction has been set up to confirm the optimization result. Fructose/HCA (20:1) was mixed in the presence of Me₃N (50 mol%) in EtOH/H₂O (1:1) under 60 °C microwave irradiation for 2 hours. Three samples from different batches have been taken from the crude and were analyzed by GC (Table 38).

Table 38. Fructose aldolisation under optimized conditions.

Entry	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %	Iso. Yield ^c / %
1	76	71	93	51
2	77	64	83	---
3	71	67	94	48

Reaction conditions: sealed tube, D-fructose (22.4 mmol, 20 equiv.), Me₃N (0.56 mmol, 50 mol%), HCA (0.56 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 2 mL) under 60 °C microwave for 2h. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion. ^c Isolated yield were obtained by column chromatography.

From these results, the optimized GC yield of HCA substrate is 64-71%. However, considering the difficulty to separate this type of products, isolated yield around 50% were obtained. However, for this optimized condition, 20 equivalents of fructose were used which is not interesting from economic point of view if excess of fructose is wasted. The recycling of fructose has been studied (Scheme 69).



Scheme 69. Recycling of excess fructose.

Fructose was recovered after removal of water by evaporation then followed by recrystallization in ethanol at 0°C . From 4 grams of fructose, up to 68% of fructose was recovered by this process. This recovered fructose was next used as starting material to confirm its reusability and their corresponding GC yield of 1st run was listed for comparison (Table 39).

Table 39. Recycling of fructose.

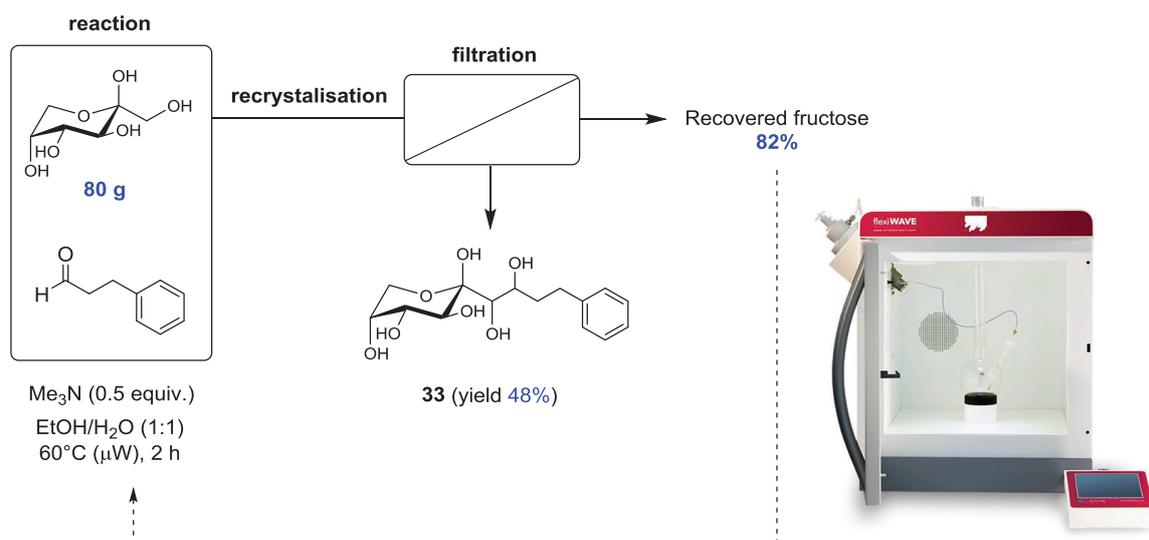
Entry	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %	1 st cycle. GC yield ^a / %
1	57	51	89	64
2	62	57	92	67

Reaction conditions: sealed tube, recycled D-fructose (15 mmol), Me_3N (0.38 mmol, 50 mol%), HCA (0.56 M, 0.75 mmol, 1 equiv.) in $\text{EtOH}/\text{H}_2\text{O}$ (1:1, 2 mL) under 60°C microwave for 2h. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

The GC yields obtained from this recovered fructose were 51-57% (Table 39, entries 1-2). Both conversion and yield have decreased slightly compared to the 1st run yield obtained from natural fructose but these results are still acceptable.

3.4 Scale up of fructose aldolisation.

With the help of FlexiWAVE Microwave Synthesis Platform from Milestone, a large scale of the model reaction was carried out in the scale of 80 grams of fructose (scheme 70). Fructose (80 g, 20 equiv.)/HCA (1 equiv.) were mixed with catalyst Me₃N (50 mol%) in 40 mL EtOH/H₂O (1:1) at 60 °C under microwave irradiation for 2 hours. Fortunately, a higher recoverability was obtained compared to the 4-gram scale, 82% of fructose can be recovered without significant loss of the isolated yield of the product **33** (48%).

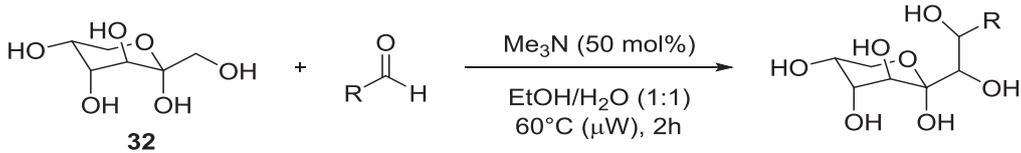
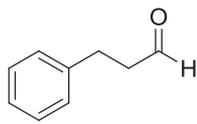
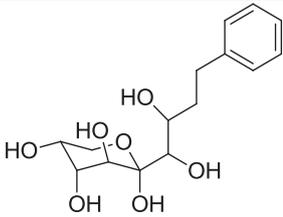
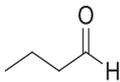
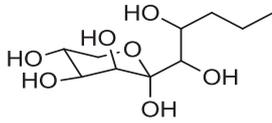
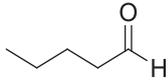
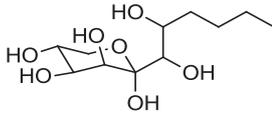
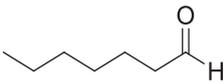
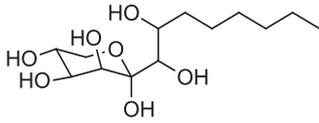
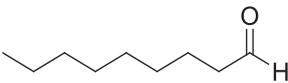
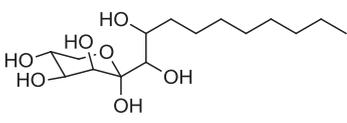


scheme 70. Scale up of the aldolisation.

3.5 Scope of aldehydes.

A scope of fructose aldolisation was investigated with a range of fatty chain aldehydes under optimized conditions (Table 40). Alkyl aldehydes such as butanal and pentanal were used, and isolated yield of their corresponding product **34**, **36** were 44% and 49%, respectively (Table 40, entries 2-3). When bio-based aldehydes such as heptanal or nonanal, prepared from vegetable oils, were used as substrates, only 16% isolated yield of product **38** and 11% of product **40** were obtained (Table 40, entries 4-5).

Table 40. Aldolisation scope with series of aldehydes ^a.

Entry	Aldehyde	Alkyl-fructose product	Yield ^b /%
			
1	 1	 33	51
2	 6	 34	44
3	 35	 36	49
4	 37	 38	16
5	 39	 40	11

^a Reaction conditions: sealed tube, D-fructose (22.4 mmol), Me₃N (0.56 mmol, 50 mol%), aldehyde (0.56 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 2 mL) at 60 °C under microwave for 2 hours. ^b Isolated yields after purification by column chromatography.

For short chain aldehydes the aldolisation yield is moderate, however, for long chain aldehydes the aldolisation yield is very low. The increase of the alkyl chain length leads to a lower

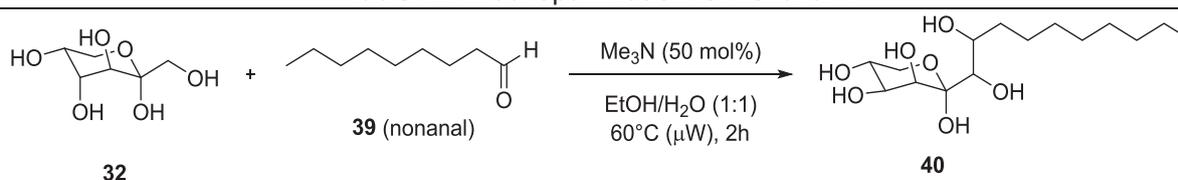
yield of the fructose aldolisation. This is due to the difficulty of mixing between the highly hydrophilic fructose and highly hydrophobic fatty aldehydes.

Overall, this method allows the direct alkylation of unprotected fructose through aldolisation using aldehydes as alkylating agents. However, the main limitation is that only poor yields were obtained when using fatty aldehydes which is disappointing as surfactant applications are targeted. So, some parameters of the system need to be modified under the optimized conditions to enhance the aldolisation yield with long chain aldehydes.

3.6 Optimization of reaction with long chain aldehydes.

Nonanal was selected as model substrate to study the aldolisation with fatty aldehydes. In order to improve the yield, meanwhile to improve the low solubility of fatty aldehydes in the EtOH/H₂O solvent system, initially temperature enhancement and other solvents have been introduced to provide a better miscible system (Table 41).

Table 41. Initial optimization for nonanal ^a.



Entry	Condition	Isolated yield ^b / %
1	100 °C (μW)	12
2	methanol/water=1/1	5
3	isopropanol/water=1/1	3
4	butanol/water=1/1	traces

^a Reaction conditions: sealed tube, D-fructose (22.4 mmol), Me₃N (0.56 mmol, 50 mol%), nonanal (0.56 M, 1.1 mmol, 1 equiv) in EtOH/H₂O (1:1, 2 mL) at 60 °C under microwave for 2 hours. ^b Isolated yields after purification by column chromatography.

When the temperature increased to 100 °C, only 12% isolated yield of product **40** was obtained (Table 41, entry 1). Then, solvent system was changed to methanol, isopropanol or butanol with water, but the isolated yield was less than 5% (Table 41, entries 2-4).

The results showed that none of these modifications were able to improve the yield of this aldolisation. During these reactions, it was noticed that there were two phases existing in this EtOH/H₂O solvent system. As a result, the fatty aldehyde on the top layer has little opportunity to react with fructose in the bottom aqueous layer and the self-condensation product of the aldehyde was the main by-product (Figure 36).

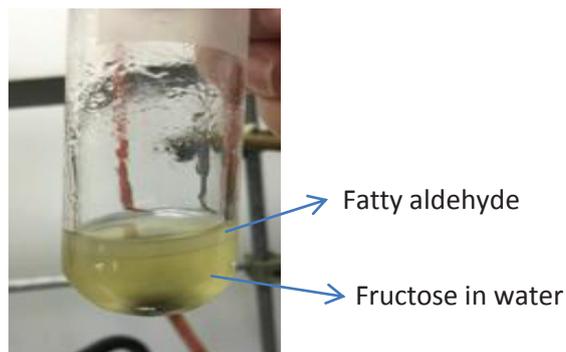


Figure 36. Two-phase mixture of reagents.

Due to the formation of two-phase mixture, the use of a phase transfer agent was investigated. Phase transfer catalysis (PTC) uses catalytic amounts of phase transfer agents which facilitate inter-phase transfer of species. By this way, reactions are made possible by bringing reagents together which are originally in two immiscible phases.¹⁶⁸

Many commercially available chemicals are used as PTA (phase transfer agent) such as onium salts (ammonium and phosphonium salts), macrocyclic polyethers (crown ethers), aza-macrobicyclic ethers (cryptands), open chain polyethers (polyethylene glycols, PEGs, and their dimethyl ethers, glymes).¹⁶⁹ Ammonium and phosphonium salts are relatively cheap with moderate activity compared to other types PTA while phosphonium salts are more thermally stable than their corresponding ammonium salts. Crown ethers and cryptands are highly toxic and quite expensive for industrial use. PEG is very cheap but its activity is much generally lower than the others.

Various phase transfer agents have been screened on the model reaction. The mixture of fructose/HCA (20:1) in the presence of Me₃N (50 mol%) and PTA (100 mol%) in EtOH/H₂O (1:1) was reacted at 60 °C under microwave for 2 hours (Table 42). For this model reaction, without any PTA, the GC yield is still moderate around 63% (Table 42, entry 1). When ammonium salts such as TBAI and TBAB were used, it even leads to decrease of the GC yield to 45% and 42%, respectively (Table 42, entries 2-3). Lower concentrations have been set up for PTA screening (Table 42, entries 4-10). The GC yield of HCA (0.28 M) in absence of PTA is 47% with a very high selectivity at 98% (Table 42, entry 4). Some of these PTA were able to slightly improve the GC yield to 56% and 53% still with good selectivity more than 90% (Table 42, entries 5 and 7) while others were not able (Table 42, entries 6 and 8).

¹⁶⁸ A. W. Herriott, D. Picker, *J. Am. Chem. Soc.*, **1975**, *97*, 2345-2349.

¹⁶⁹ S. D. Naik, L. K. Doraiswamy, *AIChE J.*, **1998**, *44*, 612-646.

Table 42. Initial screening of phase transfer agents.

Reaction scheme: **32** + **1** $\xrightarrow[\text{EtOH/H}_2\text{O (1:1), 60}^\circ\text{C } (\mu\text{W}), 2\text{h}]{\text{PTA (1 eq.)}, \text{Me}_3\text{N (50 mol%)}}$ **33**

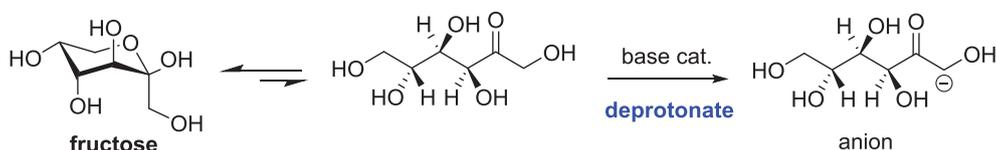
Entry	C(HCA) / M	PTA	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1		---	75	63	84
2	0.56	Tetrabutyl ammonium iodide (TBAI)	47	45	96
3		Tetrabutyl ammonium bromide (TBAB)	77	42	54
4		---	48	47	98
5		TBAI	61	56	92
6	0.28	TBAB	50	36	72
7		Tetrabutyl phosphonium bromide (TBPB)	54	53	98
8		18-crown-6	45	42	93
9	0.14	---	48	45	94
10		TBAI	44	37	84

Reaction conditions: sealed tube, D-fructose (16.8 mmol, 20 equiv.), Me₃N (0.42 mmol, 50 mol%), HCA (0.84 mmol, 1 equiv.) and PTA (0.84 mmol, 1 equiv.) in EtOH/H₂O (1:1, 1.5/3/6 mL) at 60 °C under microwave for 2 hours. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

Further decrease of HCA concentration to 0.14 M without any PTA almost gave the same yield of 45% (Table 42, entries 4 and 9). With HCA (0.14 M), the addition of PTA will not help to improve the yield (Table 42, entry 10). In conclusion, these initial trials of PTA applications in the fructose aldolisation have shown some positive results. Moreover, to avoid the generation of the aldehyde self-condensation by-product in the organic phase, organic base (Me₃N) was replaced by inorganic bases which only stay in water phase. Based on this fact, we have re-investigated the reaction by screening different PTAs and different inorganic bases.

3.6.1 Screening of inorganic base.

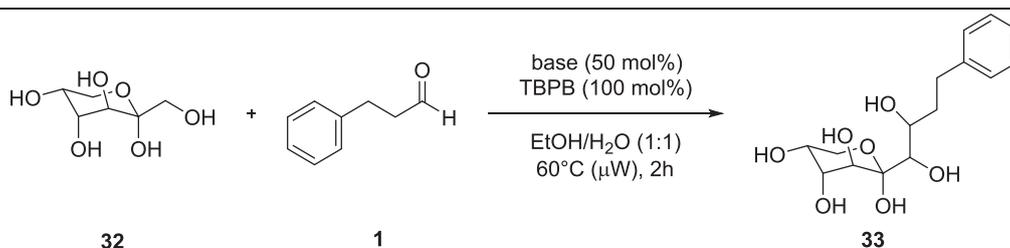
The role of the base catalyst is to deprotonate fructose to give an anion (scheme 71). Since fructose is soluble in water phase, the use of an inorganic base instead of an organic amine may be better to avoid the self-condensation of fatty aldehydes in the organic phase.



scheme 71. Deprotonation of D-fructose.

Several of inorganic bases were next screened using tetrabutylphosphonium bromide (TBPB) as PTA (Table 43).

Table 43. Screening of inorganic bases.



Entry	base	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	Li ₂ CO ₃	65	42	66
2	Na ₂ CO ₃	57	35	61
3	K₂CO₃	70	61	87
4	Cs ₂ CO ₃	60	25	42
5	KHCO ₃	51	44	86
6	KOH	92	26	28
7	KOAc	45	0	0
8	t-BuOK	70	32	46
9	NaOH	63	52	83

Reaction conditions: sealed tube, D-fructose (16.8 mmol, 20 equiv.), inorganic base (0.42 mmol, 50 mol%), HCA (0.84 mmol, 1 equiv.) and TBPB (0.84 mmol, 1 equiv.) in EtOH/H₂O (1:1, 3 mL) at 60 °C under microwave for 2 hours. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

A range of inorganic carbonates was first screened (Table 43, entries 1-4). The best yield/selectivity was achieved by using K_2CO_3 (Table 43, entry 3). Consequently, other potassium bases were also investigated (Table 43, entries 5-8). $KHCO_3$ also promotes the reaction with similar selectivity than K_2CO_3 but was found to be slightly less active (Table 43, entry 5). Other bases such as KOH, KOAc and KO^tBu gave lower selectivities due to their ability to promote the competitive self-aldolisation of the aldehydes. NaOH was also used but the result was not satisfied (Table 43, entry 9).

3.6.2 Phase transfer agent screening.

Based on the initial screening of PTA, a broader scope of PTA was next investigated with inorganic base K_2CO_3 (50 mol%) (Table 44).

Table 44. Screening of phase transfer agents.

Entry	PTA	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	Aliquat 336	74	19	26
2	CTAB	80	53	66
3	PTAB	80	54	68
4	TBAI	74	43	58
5	TBAB	72	54	75
6	TBACl	68	53	78
7	TBPB	70	61	87
8	SDS	68	37	67

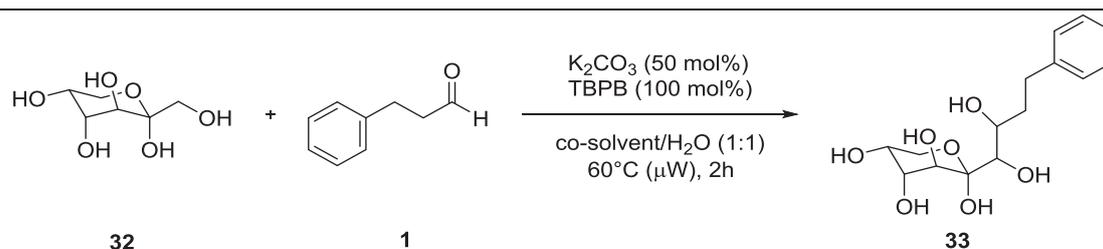
Reaction conditions: sealed tube, D-fructose (16.7 mmol, 20 equiv.), K_2CO_3 (0.42 mmol, 50 mol%), HCA (0.84 mmol, 1 equiv.) and PTA (0.84 mmol, 1 equiv.) in EtOH/H₂O (1:1, 3 mL) at 60 °C under microwave irradiation for 2 hours. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion. Aliquat 336: methyltrioctyl(decyl)ammonium chloride, CTAB: cetyltrimethylammonium bromide, PTAB: phenyltrimethylammonium bromide, TBAI: tetrabutylammonium iodide, TBAB: tetrabutylammonium bromide, TBACl: tetrabutylammonium chloride, TBPB: tetrabutylphosphonium bromide, SDS: sodium dodecyl sulfate.

Aliquat 336 was first used but gave a poor yield of 19% (Table 44, entry 1). CTAB and PTAB gave improved results with about 53-54% yield (Table 44, entries 2-3). Tetrabutylammonium salts (iodide, bromide, chloride) gave similar yields but the selectivity was improved to 78% by using TBACl (Table 44, entries 4-6). Finally, tetrabutylphosphonium salt (TBPB) showed the best result giving 61% yield and a high 87% selectivity for the desired product **33** (Table 44, entry 7). The anionic surfactant SDS only gave 37% yield (Table 44, entry 8).

3.6.3 Solvent screening.

The aldolisation takes place in water and ethanol mixtures providing that fructose is more soluble in water phase and ethanol acting as an organic co-solvent to facilitate the fatty aldehydes solubility. The nature of this organic co-solvent was studied as a 1:1 (v:v) mixture with water for formation of a better miscible reaction solution (Table 45).

Table 45. Screening of organic co-solvent.



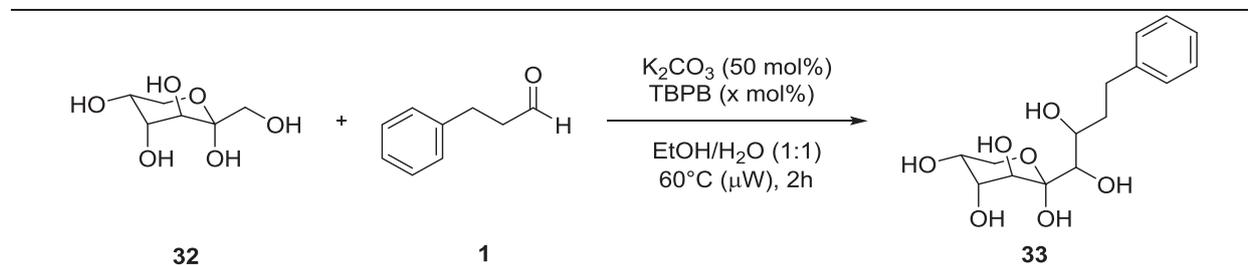
Entry	co-solvent	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	MeOH	62	42	68
2	EtOH	70	61	87
3	BuOH	83	5	6
4	<i>i</i> PrOH	64	31	48
5	THF	42	23	55
6	2-MeTHF	21	16	76
7	CPME	47	8	17
8	Toluene	7	2	29
9	---	77	8	10

Reaction conditions: sealed tube, D-fructose (16.7 mmol, 20 equiv.), K_2CO_3 (0.42 mmol, 50 mol%), HCA (0.84 mmol, 1 equiv.) and TBPB (0.84 mmol, 1 equiv.) in organic co-solvent/ H_2O (1:1, 3 mL) at $60^\circ C$ under microwave irradiation for 2 hours. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

3.6.5 Loading of phase transfer agent.

The loading of the phase transfer agent was next studied (Table 47).

Table 47. Loading of phase transfer agent.



Entry	Loading of TBPB / mol%	Conversion of 1 ^a / %	Yield of 33 ^a / %	Selectivity ^b / %
1	100	70	61	87
2	50	68	37	67

Reaction conditions: sealed tube, D-fructose (16.7 mmol, 20 equiv.), HCA (0.84 mmol, 1 equiv.) and K₂CO₃ (0.42 mmol, 50 mol%) with different loading of TBPB, in EtOH/H₂O (1:1, 3 mL) at 60 °C under microwave irradiation for 2 hours. ^a Results were calculated by GC calibration curve. ^b Selectivity=Yield/Conversion.

If the loading of TBPB was used 50 mol%, the yield decreased almost a half from 61% to 37% (Table 47, entries 1-2). In conclusion, 100 mol% of TBPB was selected.

3.6.6 Proposed mechanism.

To better understand the aldolisation process, a mechanism has been proposed (Scheme 72).

At first, fructose and the inorganic base K₂CO₃ are totally soluble at 60 °C in the EtOH/H₂O solvent mixture as one phase. The fatty aldehydes and TBPB are staying in the layer upon this EtOH/H₂O phase. A large excess of fructose **I** is used to produce more open-chain form **II** that only presents less than 1% in solution. This α -hydroxyketone could be deprotonated, similarly as dihydroxyacetone, with K₂CO₃ to give the corresponding potassium enolate **III**. This intermediate could form ion metathesis with TBPB (phase transfer agent) to generate the phosphonium enolate **IV** along with one equivalent of KBr. This species could probably stay at the interphase to react with the hydrophobic aldehydes, giving phosphonium alcoholate **V**. In this process, EtOH could enhance the solubility of hydrophobic aldehydes in water phase like a hydrotrope. Finally, the protonation of **V** generated aldolisation product **VI**, at the same time it cyclized to give a mixture of tautomers.

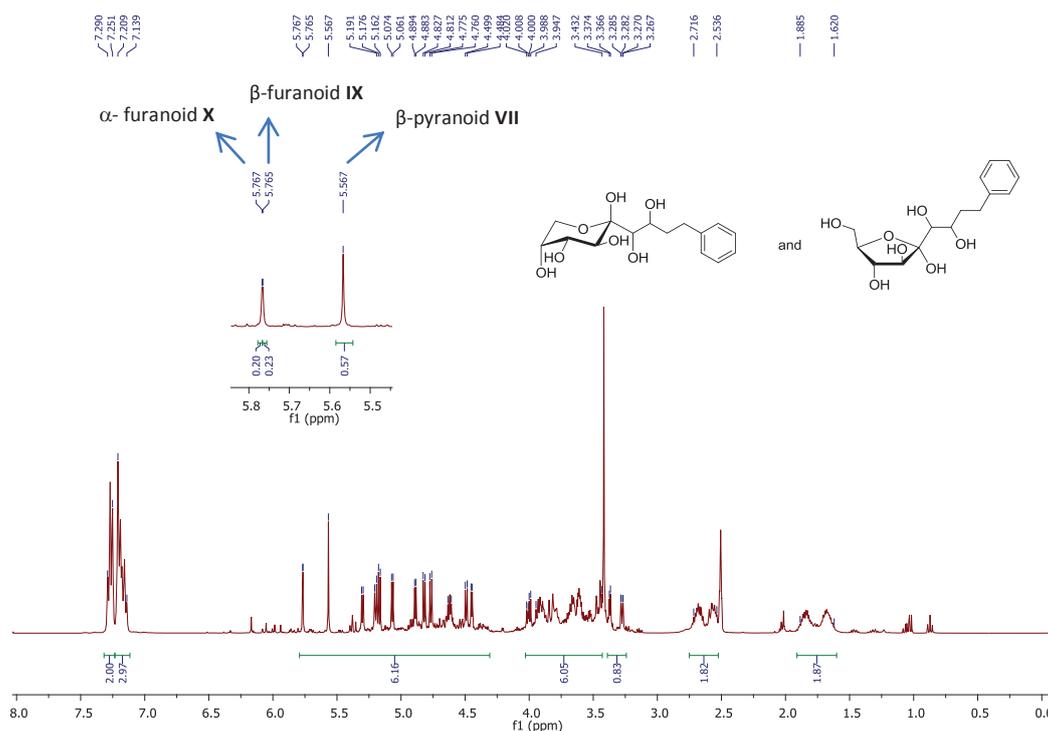


Figure 37. ^1H NMR spectrum of product **33** (400 MHz, d_6 -DMSO).

3.8 Scope of long chain aldehydes.

The scope of the aldolisation of fructose has been re-investigated using fatty aldehydes under the optimized conditions. The results were compared with those obtained with organic base catalyst Me_3N without PTAs (Table 48).

When the substrate is HCA, the yield obtained with/without PTA is almost the same, around 50% (Table 48, entry 1). However, when using longer chain aldehyde such as heptanal (C7) and nonanal (C9), the yield of their corresponding aldolisation products **38** and **40** were significantly improved to 43 and 37%, respectively (Table 48, entries 4-5). Decanal (C10) and dodecanal (C12) were also used and aldolisation product **41** and **42** were obtained with 39 and 31% yield, respectively (Table 48, entries 6-7). Considering the difficulty of reacting highly hydrophilic unprotected fructose with highly hydrophobic fatty aldehydes, these isolated yields are satisfying although they are just moderate. For comparison, the reaction of decanal and dodecanal with unprotected fructose led to the corresponding decyl and dodecyl fructosides with 33% and 35% isolated yields.

Table 48. Re-investigation of aldolisation scope ^a.

Entry	Aldehyde	Alkyl-fructose product	Yield ^b /%	Yield ^c /%	Ratio (α-p/α-f/β-f/β-p)
1			46	51	0/20/24/56
2			---	44	0/15/16/70
3			---	49	0/24/25/51
4			43	16	0/22/22/56
5			37	11	0/18/22/60
6			39	---	7/17/25/51
7			31	---	9/11/17/60

^a Reaction conditions: sealed tube, D-fructose (22.4 mmol, 20 equiv.), K₂CO₃ (0.56 mmol, 50 mol%), TBPB (1.1 mmol, 1 equiv.), aldehyde (0.28 M, 1.1 mmol, 1 equiv.) in EtOH/H₂O (1:1, 4 mL) at 60 °C under microwave for 2 hours. ^b Isolated yields obtained by column chromatography in the presence of PTAs. ^c Isolated yields obtained by column chromatography without PTAs.

The GC chromatogram after derivatization by trimethylsilylation using HMDS/TMSCl gave a mixture of 3 isomers. The ratio between the obtained 3 tautomers was then estimated according to their corresponding ^1H NMR spectra for each substrate. Generally, only 3 tautomers were obtained (α -furanoid/ β -furanoid/ β -pyranoid), while for decanal and dodecanal the minority existing α -pyranoid has been detected also at 7% and 9% respectively (Table 48, entries 6-7).

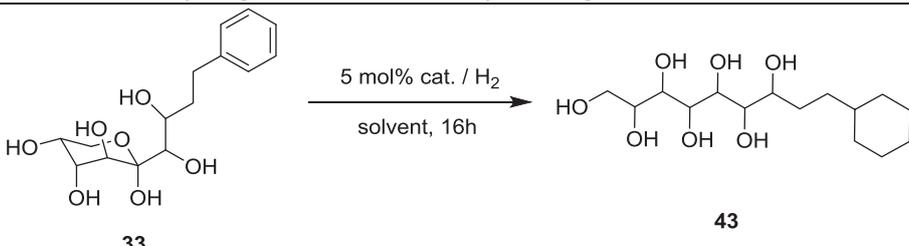
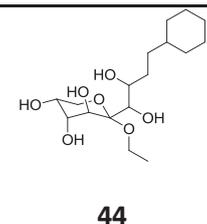
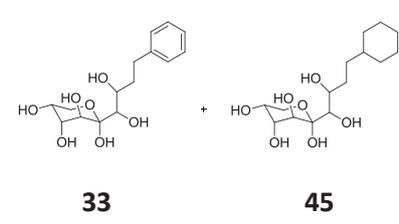
3.9 Hydrogenation of obtained fructose alkyl chain derivatives.

The reduction of the fructose aldolisation products was carried out in order to extend the scope of the new compounds that could be used as non ionic surfactants.

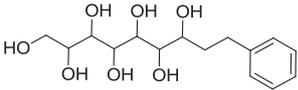
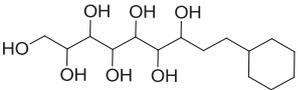
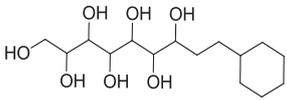
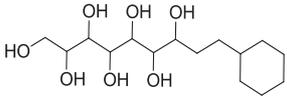
3.9.1 Hydrogenation reaction condition screening.

The aldolisation product **33** was then reduced under hydrogen with catalyst (Table 49).

Table 49. Hydrogenation condition optimizing on model aldolisation^a.

Entry	Catalyst	H ₂ pressure /bar	Temperature/°C	Solvent	product ^b
					
1	5% Ru/Al ₂ O ₃	40	100	EtOH	
2	5% Ru/Al ₂ O ₃	20	80	EtOH	
3	5% Ru/Al ₂ O ₃	10	30	EtOH	No reaction

(to be continued in next page)

4	5% Ru/Al ₂ O ₃	20	80	water		46
						43
5 ^c	5% Ru/Al ₂ O ₃	40	100	water		43, iso. yield 94%
6 ^c	Raney Nickel	40	100	water		43, iso. yield 89%

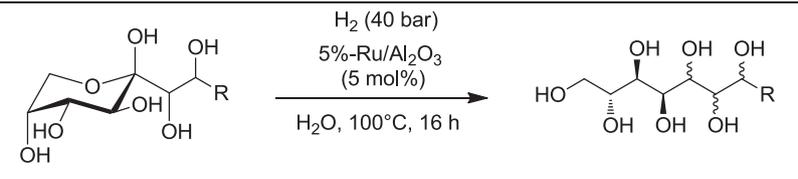
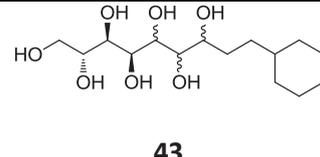
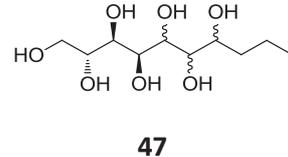
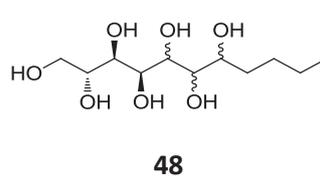
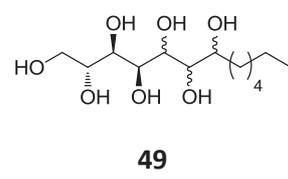
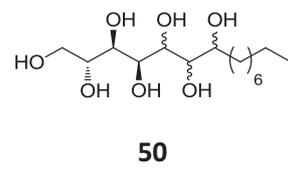
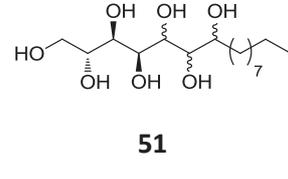
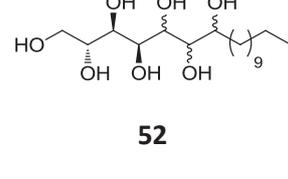
^a Reaction conditions: 30 mL stainless steel autoclave, aldolisation product **33** (200 mg), catalyst (5 mol%). ^b Ratios were estimated by ¹H NMR and ¹³C NMR. ^c Isolated yield was obtained after direct filtration.

The phenyl ring was completely reduced and reacted with ethanol thus giving product **44** (Table 49, entry 1). Milder conditions (e.g., lower hydrogen pressure or lower temperature) were also used, but led to a complex mixture of product **45** and starting material **33** (Table 49, entry 2). Reaction could not happen with 10 bar hydrogen at 30 °C (Table 49, entry 3). Water has been selected as solvent instead of ethanol. Product **33** was hydrogenated under 20 bar and 80 °C however the phenyl group was partially reduced to give a mixture of product **43** and **46** (Table 49, entry 4). Product **33** can be totally reduced to cyclic heptaols **43** under 40 bar at 100 °C with 5% Ru/Al₂O₃ or with Raney Nickel catalyst, with 94% and 89% isolated yield, respectively (Table 49, entries 5-6).

3.9.2 Scope of obtained fructose alkyl chain derivatives.

The other aldolisation products were hydrogenated under the same conditions to give the corresponding heptaols with 84-95 yields (Table 50). These reduced species could be very interesting as they could not cyclize in solution.

Table 50. Reduction scope of fructose based aldolisation products to heptaols.^a

Entry	R/aldolisation product	heptaols	Yield ^b /%
			
1	CH ₂ CH ₂ Ph 33	 43	94
2	n-C ₃ H ₇ 34	 47	94
3	n-C ₄ H ₉ 36	 48	95
4	n-C ₆ H ₁₃ 38	 49	86
5	n-C ₈ H ₁₇ 40	 50	89
6	n-C ₉ H ₁₉ 41	 51	84
7	n-C ₁₁ H ₂₃ 42	 52	87

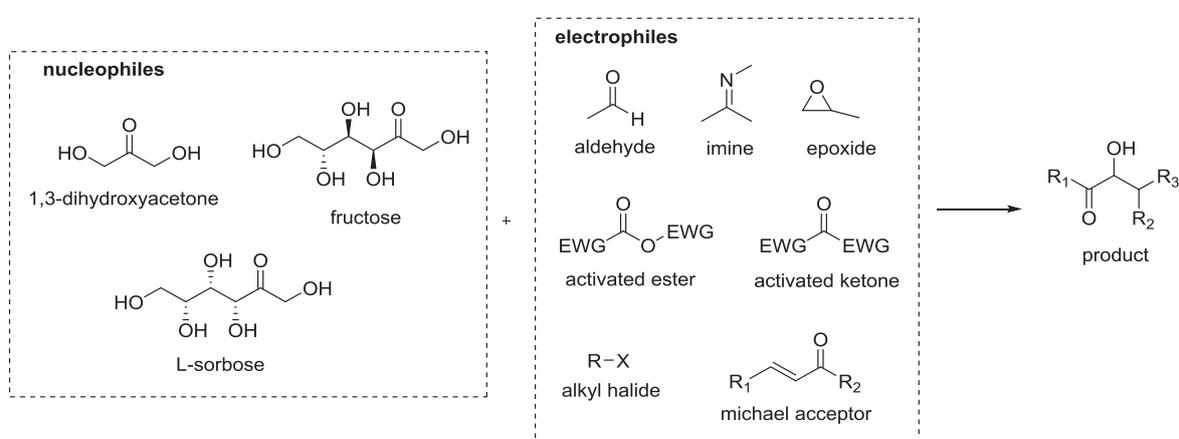
^a Reaction condition: 30 mL stainless steel autoclave, aldolisation products (200 mg), 5%-Ru/Al₂O₃ (5 mol%), hydrogen pressure (40 bar), water (6 mL), 100 °C, 16 h. ^b Isolated yields after direct filtration.

Overall, fatty aldehydes can be attached to unprotected fructose by aldolisation on the basis of C-C bond linkage. The reaction occurs in benign solvents (1:1 mixture of EtOH/H₂O) at 60°C under microwave irradiation. Under these conditions, the corresponding alkylated fructoses were isolated with 31-46% yields, which is satisfactory given the difficulty to react highly polar fructose with hydrophobic aldehydes. These obtained aldol products can be consequently reduced to heptaols under hydrogen to give the corresponding alkylated heptaols with 84-95% isolated yields. Further studies will focus upon studying in details the physico-chemical properties of all these new amphiphilic species.

Chapter 4 Reaction of ketoses with various electrophiles.

1 Introduction.

A methodology of base catalyzed aldolisation of ketoses as nucleophiles with alkyl aldehydes as electrophiles has been developed by employing renewable, cheap and abundant substrates such as 1,3-dihydroxyacetone and fructose in green solvents EtOH/H₂O.¹⁷⁰ Instead of using different ketoses as nucleophiles, other electrophiles rather than aldehydes can be used for further extending the scope of this method (scheme 73).



scheme 73. Possible substrates for the extension of the method.

2 Use of other ketoses as nucleophiles.

L-Sorbose is a readily available natural sugar that occurs in plant fruits such as apple, pear and grape. The annually production of L-sorbose is approximately 60,000 tons.¹⁷¹ It is mainly produced by biochemical oxidation of D-sorbitol through regiocontrolled dehydrogenation by *Gluconobacter oxydans*.¹⁷² It can be also prepared by purely chemical transformations from D-glucose with catalyst at high temperature (scheme 74).¹⁷³

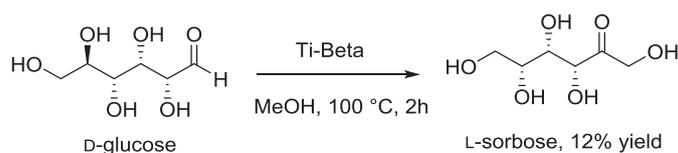
¹⁷⁰ B. Zhu, D. Belmessieri, J. F. Ontiveros, J.-M. Aubry, G.-R. Chen, N. Duguet, M. Lemaire, *ACS Sustainable Chem. Eng.*, **2018**, *6*, 2630-2640.

¹⁷¹ I. Zebiri, S. Balieu, A. Guilleret, R. Reynaud, A. Haudrechy, *Eur. J. Org. Chem.*, **2011**, *16*, 2905-2910.

¹⁷² M. Rosenberg, J. Svitel, I. Rosenbergova, E. Sturdik, *Acta. Biotechnol.*, **2004**, *13*, 269-274.

¹⁷³ R. Gounder, M. Davis, *ACS Catal.*, **2013**, *3*, 1469-1476.

C1 reduction/C5 oxidation



scheme 74. L-Sorbose prepared from D-glucose through chemical method.

L-sorbose can exist in an open form and also in pyranose/furanose forms. All those forms are in equilibrium and mainly existed as only one isomer α -sorbofuranose at room temperature in water which can make the product structure less complex than fructose.¹⁷⁴

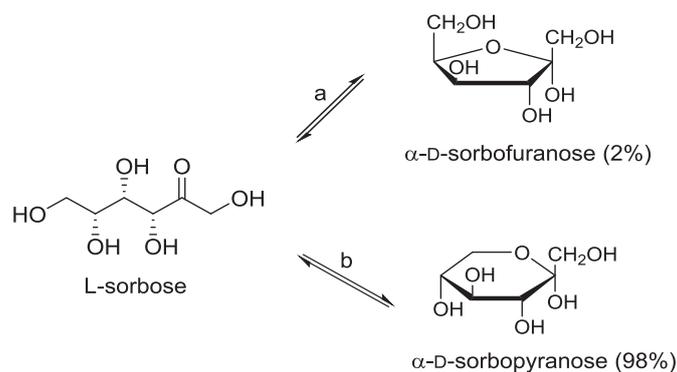
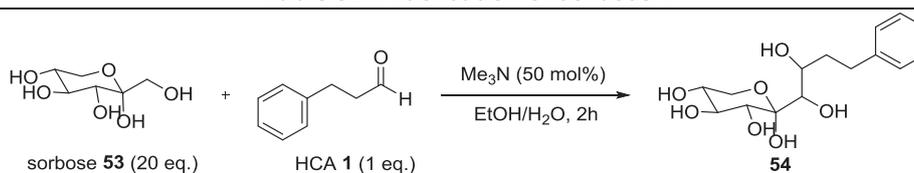


Figure 38. L-Sorbose and its isomers.

As a ketose, L-sorbose is supposed to react in the same mechanism like fructose. L-sorbose has been utilized instead of 1,3-dihydroxyacetone and D-fructose (Table 51).

Table 51. Aldolisation of sorbose^a.

Entry	Solvent (H ₂ O/EtOH, v:v, mL)	Temperature / °C	Time / h	Result ^b
1	2/2	60, μ	2	Not soluble
2	4/4	60, μ	2	Not soluble
3	8/6	80, μ	2	traces, 7%

^a Reaction conditions: sealed tube, L-sorbose (22.4 mmol, 20 equiv.), Me₃N (1.1 mmol, 50 mol%), HCA (2.2 mmol, 1 equiv.) in solvent for 2 hours. ^b Isolated yield after column chromatography.

¹⁷⁴ P. M. Collins, *Dictionary of carbohydrates*, CRC Press, **2005**, 1282.

At first, sorbose was treated under the optimized conditions of fructose aldolisation (Table 51, entry 1). However, the less solubility of sorbose (2.35 g/mL) than fructose (3.75 g/mL) in water makes this mixture not soluble and the reaction more difficult. More solvent was added for better solubilization while it is still not enough (Table 51, entry 2). To better improve the yield, ratio of EtOH/H₂O and temperature has been modified. Finally, the ratio of solvents was adjusted since water is a better solvent for sorbose, and temperature has been increased to 80 °C, the desired adduct was obtained by column with 7% yield (Table 51, entry 3).

Due to the limitation of L-sorbose solubility, less active open-ring form is available in reaction mixture. By modification of some parameters, the yield of desired product has been improved. On this basis, the ratio of solvent and temperature could be further screened to obtain a better yield.

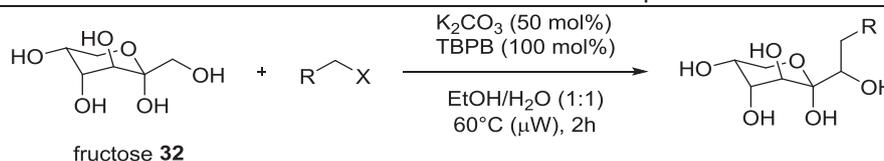
3 Use of other electrophiles.

In this context, a range of electrophiles such as alkyl halide, imine, epoxide, activated ester/ketone and Micheal acceptors have been tested. Although from the application point of view, it is less interesting compared to these already obtained fatty aldehydes-based polyols, it is still worthy to test their reactivity on the developed methodology of aldolisation from the view of investigating new organic synthetic method.

3.1 Alkylation with alkyl Halides.

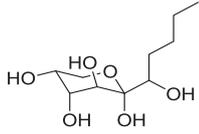
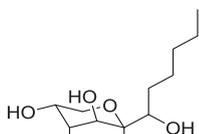
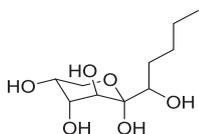
Halides have been selected because of 1) their relatively cheap price (2-4 €/kg); 2) the formation of surfactants. Benzyl halides and alkyl halides have been used as electrophiles (Table 53).

Table 52. Halides substrates as electrophile^a.



Entry	Halide	Expected product	Result
1	PhCH ₂ Br 55	 56	No reaction

(to be continued in next page)

2	$n\text{-C}_4\text{H}_9\text{Cl}$ 57	 58	No reaction
3	$n\text{-C}_5\text{H}_{11}\text{Br}$ 59	 60	No reaction
4	$n\text{-C}_4\text{H}_9\text{I}$ 61	 58	No reaction

^a Reaction conditions: sealed tube, D-fructose (22.4 mmol, 20 equiv.), K_2CO_3 (0.56 mmol, 50 mol%), TBPB (1.1 mmol, 1 equiv.), halides (0.28 M, 1.1 mmol) in EtOH/ H_2O (1:1, 4 mL) at 60 °C under microwave for 2 hours.

These reactions were carried out under the optimized conditions of fructose. Benzyl bromide was used but no reaction occurs (Table 53, entry 1). The chloride substrate was considered to be not active enough so bromide and iodide substrates have been used however it gave the same result (Table 53, entries 2-4).

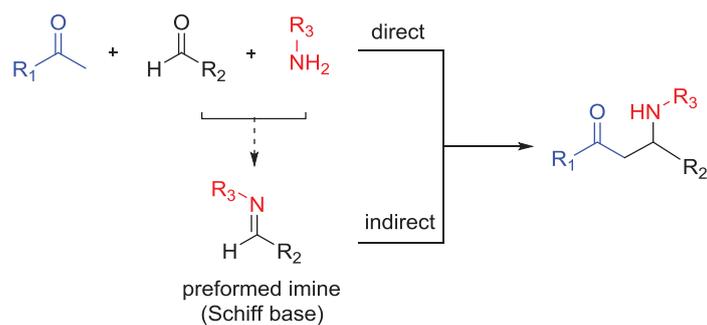
When halides are used as electrophiles, the reaction also depends on the leaving group. In conclusion, the chlorinated, brominated and iodinated halides substrates are not active enough.

3.2 Mannich reaction with imines.

3.2.1 Introduction.

Mannich reaction is an important type of C-C bond forming reaction in organic chemistry. It consists of three components, a ketone, an aldehyde, and an amine, reacting to form a β -amino-ketone (scheme 75). It is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base.¹⁷⁵

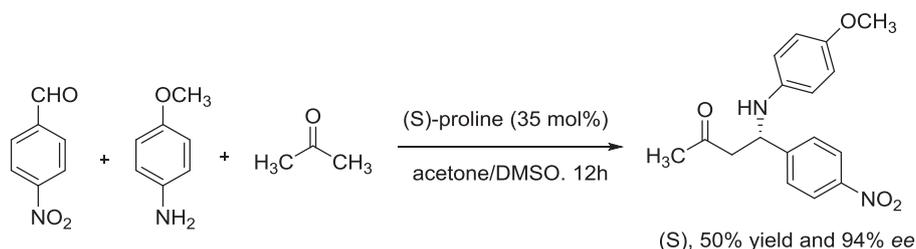
¹⁷⁵ B. List, *J. Am. Chem. Soc.*, **2000**, *122*, 9336-9337.



scheme 75. General scheme of Mannich reaction.

When imines are preformed, generally they are much less electrophilic than the corresponding aldehyde, and it allows the reaction to proceed under very mild conditions and also can avoid the aldol-type self-condensation by-product caused by the aldehyde.¹⁷⁶

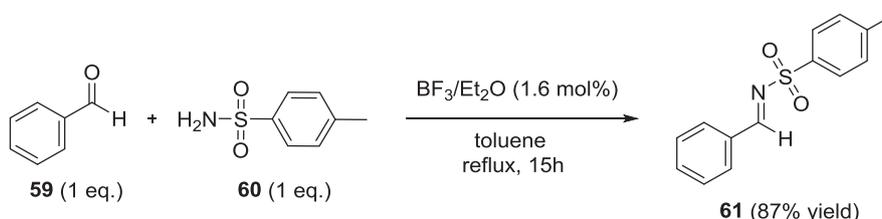
Organic catalysts such as chiral amines (chiral proline, chiral pyrrolidines) and chiral Bronsted acids can stereochemically control the Mannich reaction product in one-pot. List has reported (S)-proline as catalyst for three-component Mannich reaction, the corresponding Mannich product was formed in 50% yield and 94% ee.¹⁷⁷



scheme 76. Chiral amine catalyzed Mannich reaction.

3.2.2 Preparation of tosyl imine.

Imines present similar reactivity of C=N functional group than C=O group in aldehydes. Tosyl imine was first prepared from *p*-toluenesulfonamide and benzaldehyde according to literature.¹⁷⁸

scheme 77. Preparation of imine **61**.

¹⁷⁶ M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed.*, **1998**, 37, 1044-1070.

¹⁷⁷ A. Ting, S. E. Schaus, *Eur. J. Org. Chem.*, **2007**, 35, 5797-5815.

¹⁷⁸ K. Yoshida, N. Akashi, A. Yanagisawa, *Tetrahedron: Asymmetry*, **2011**, 22, 1225-1230.

3.2.3 Mannich-type reaction of prepared imines.

Then, imine **61** has been used to react with 1,3-dihydroxyacetone and fructose under amine catalyst (Table 53).

Table 53. Mannich-type reaction of DHA and fructose using imines.

Entry	ketose	T / °C	Time / h	Solvent	Product	Yield ^d / %
1 ^a		80 (μW)	2	EtOH/H ₂ O (1:1)		40
2 ^b		80	1	neat		12
3 ^c		120 (μW)	2	neat		2
4 ^c	32	80 (μW)	3	CPME	No reaction	---

^a Reaction conditions: sealed tube, DHA (5.56 mmol, 5 equiv.), Me₃N (0.56 mmol, 50 mol%), tosylimine **61** (1.1 mmol, 1 equiv.) in solvent (4 mL) under microwave. ^b Traditional heating. ^c D-fructose (22.4 mmol, 20 equiv.). ^d Isolated yields after purification by column chromatography.

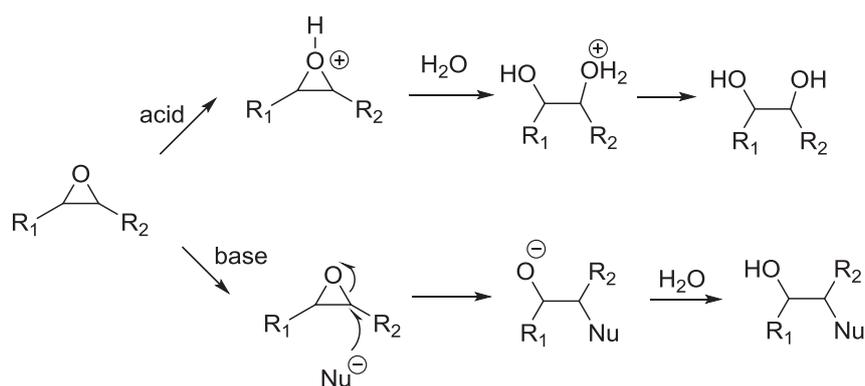
When EtOH/H₂O was used as solvent, the product obtained was hydroxyketone **62** with 40% yield as aldolisation product of DHA and benzaldehyde. This is due to the hydrolysis of imine to aldehyde in the solvent (Table 53, entry 1). The reaction was under neat condition with traditional heating for 1 hour and the desired imine adduct **63** was obtained with 12% isolated yield (Table 53, entry 2). On the basis of this result, fructose was also used as starting material (Table 53, entries 3-4). To avoid the difficulty of stirring under solvent free conditions, the reaction temperature was

improved above the melting point of fructose (103 °C). Under these conditions, only 2% of 5-hydroxymethylfurfural was obtained as byproduct (Table 53, entry 3). The reaction was carried out at 80 °C in CPME while no product was obtained (Table 53, entry 4). Fructose is less reactive compared to DHA substrate. On the other hand, high temperature also leads to the dehydration of fructose to form 5-HMF as a byproduct. In conclusion, imines can be used as electrophiles for this amine catalyzed mannich-type reaction. The yield could be further improved by optimizing parameters.

3.3 Ring-opening of epoxides.

3.3.1 Introduction.

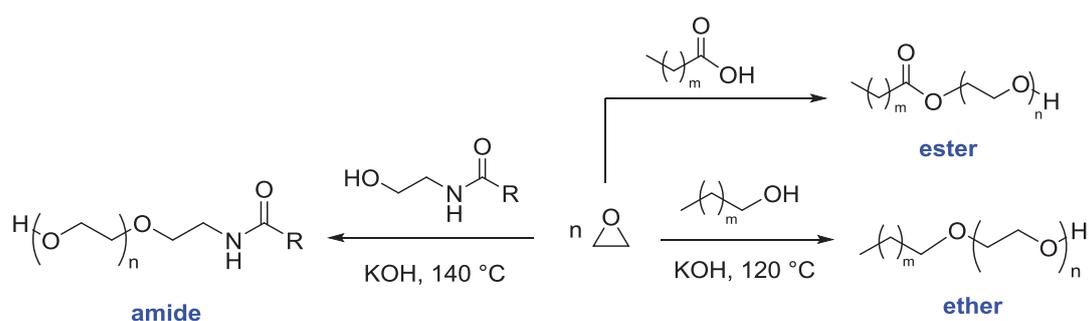
Epoxides are quite reactive as electrophiles in ring opening reactions. They can serve as electrophiles under both acidic and basic conditions. Under acid conditions, the epoxide was first protonated and was attacked by water as nucleophile to open the ring. Under basic conditions, the nucleophile attacks the least substituted carbon in epoxide ring then followed by a S_N2 (scheme 78).



scheme 78. Ring opening of epoxide under acidic and basic conditions.

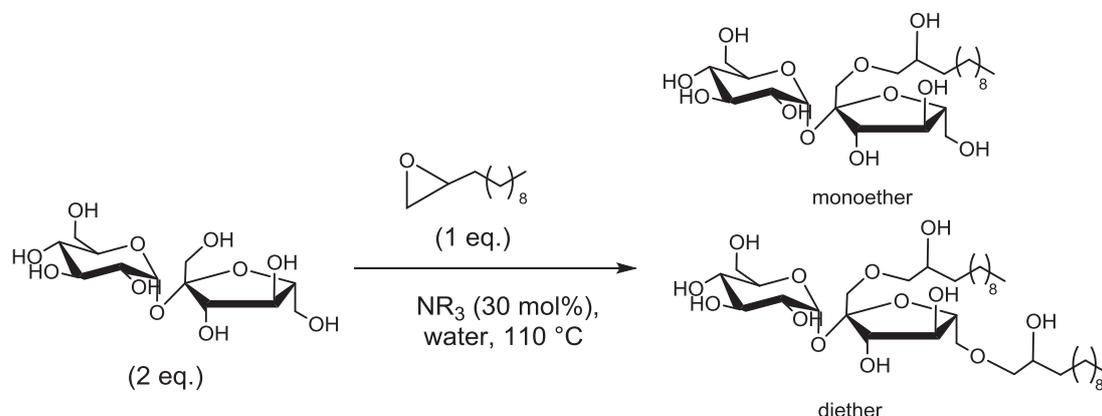
3.3.2 Surfactants prepared from ring-opening of epoxides.

Many ethoxylated-based surfactants such as polyethoxylated ester, ether and amide can be prepared from ring-opening of epoxides (scheme 79).



scheme 79. Ethoxylated-based surfactant preparation.

Moreover, Queneau *et al.* have reported a sucrose-based surfactant prepared by opening the epoxide ring. The reaction of sucrose with 1,2-epoxydodecane was carried out in water, and sucrose monoethers, sucrose diethers were obtained at a moderate yield 42-52% (scheme 80).¹⁷⁹

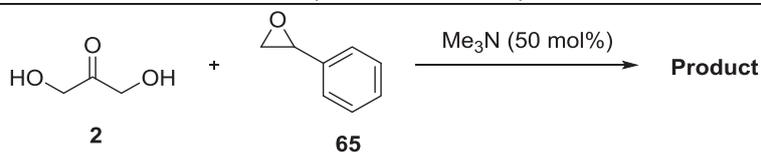


scheme 80. Sucrose-based surfactant prepared from epoxide ring-opening.

3.3.3 Styrene oxide used as electrophile.

Styrene oxide was selected as a model substrate due to its high reactivity and DHA was first used as nucleophile (Table 54).

Table 54. Epoxide as electrophile.

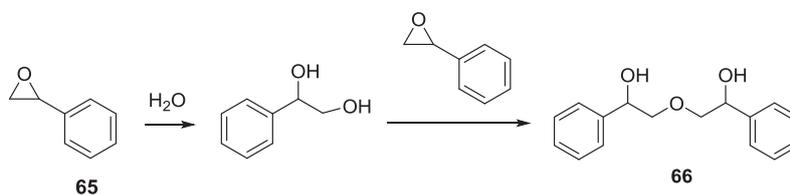


Entry	T / °C	Time / h	Solvent	Product	Yield ^c / %
1 ^a	60 (μW)	2	EtOH/H ₂ O (1:1)		---
2 ^b	60	3	neat		20
3 ^b	80	4	CPME	66	---

^a Reaction conditions: sealed tube, DHA (11.1 mmol, 5 equiv.), Me₃N (1.1 mmol, 50 mol%), styrene oxide (2.2 mmol, 1 equiv.) in solvent 4 mL at 60 °C under microwave for 2 hours. ^b Traditional heating. ^c Isolated yields obtained after purification by column chromatography.

¹⁷⁹ J. Gagnaire, A. Cornet, A. Bouchu, G. Descotes, Y. Queneau, *Colloids Surf., A*, **2000**, 172, 125-138.

Under the optimized standard conditions, styrene oxide **65** was hydrolyzed in water to give diol and then the diol further attacks another molecule of **65** to give product **66** (scheme 81). Even if this reaction was done under neat condition, this hydrolysis can not be avoided (Table 54, entry 2).



scheme 81. The formation of product **66**.

In conclusion, epoxides are too sensitive to water, and they are easily to form product **66**. They are not ideal substrates for this reaction which is usually done under mild conditions. But maybe strict anhydrous conditions for this reaction could be further studied in the future.

3.4 Use of activated esters as electrophiles.

Although the ester group is not as reactive as aldehydes, with electron withdrawing group linking to ester group may help to enhance its reactivity. Some ester substrates were used to react with DHA (Table 55).

Table 55. Activated esters as substrates^a.

Entry	R ₁	R ₂	Expected product	Result
1	CH ₃	CH ₃		No reaction
2	CH ₃ CH ₂	CF ₃		No reaction
3	CN	CH ₃		No reaction

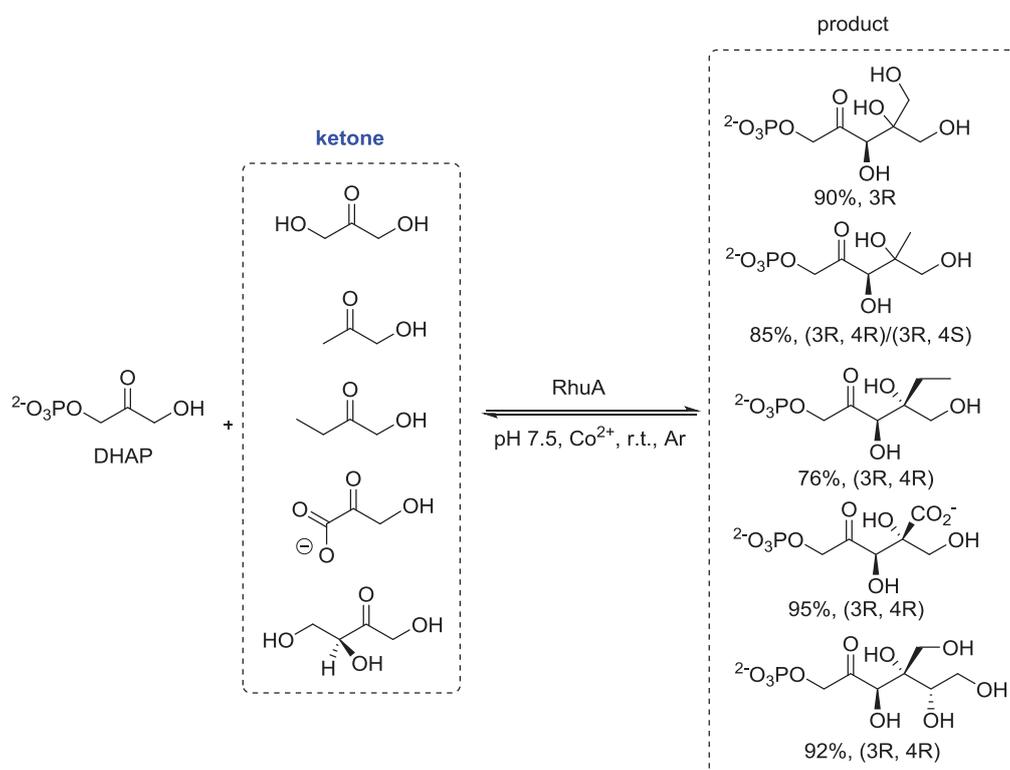
^a Reaction conditions: sealed tube, DHA (11.1 mmol, 5 equiv.), Me₃N (1.1 mmol, 50 mol%), ester (2.2 mmol, 1 equiv.) in EtOH/H₂O (4 mL) at room temperature for 4 hours.

When there is no electron withdrawing group on the ester, the reaction can not occur (Table 55, entry 1). Unfortunately, even with electron withdrawing group the activated ester is not able to react with DHA as an electrophile (Table 55, entries 2-3).

3.5 Use of activated ketones as electrophiles.

3.5.1 Introduction.

The ketones can also be used as electrophiles as aldehydes. Laurent *et al.* have already reported some α -hydroxylated ketones used as electrophiles with dihydroxyacetone phosphate (DHAP) in enzymatic route.¹⁸⁰ This reaction was stereoselective and products were readily obtained in good to excellent yields (76%-95%) (scheme 82). This work provides new access for activated ketones to be electrophilic substrates for RhuA on DHAP.



scheme 82. Ketones used as electrophiles for DHAP.

¹⁸⁰ V. Laurent, E. Darii, A. Aujon, M. Debacker, J.-L. Petit, V. Helaine, T. Liptaj, M. Breza, A. Mariage, L. Nauton, M. Traikia, M. Salanoubat, M. Lemaire, C. G.-Helaine, V. de Berardinis, *Angew. Chem. Int. Ed.*, **2018**, *57*, 5467-5471.

3.5.2 Results.

An activated ketone such as trifluoroacetophenone was used as a model substrate (Table 56).

Table 56. Activated ketones as substrates.

Entry	R (nucleophile)	Product	Yield ^c /%
1 ^a	 2	 68	36
2 ^b	 32	 69	15

^a Reaction conditions: sealed tube, DHA (11.1 mmol, 5 equiv.), Me₃N (1.1 mmol, 50 mol%), ketone (2.2 mmol, 1 equiv.) in EtOH/H₂O (4 mL) at room temperature for 4 hours. ^b D-fructose (22.2 mmol, 20 equiv.), at 80 °C under microwave for 2 hours. ^c Isolated yield after column chromatography.

At first, DHA was used as nucleophile with trifluoroacetophenone and product **68** was obtained with 36% yield (Table 56, entry 1). Then, D-fructose was also used as nucleophile. The reaction works while since the fructose is less active compared to DHA, even if 20 equivalents of fructose was used, the isolated yield of product **69** is only 15% (Table 56, entry 2).

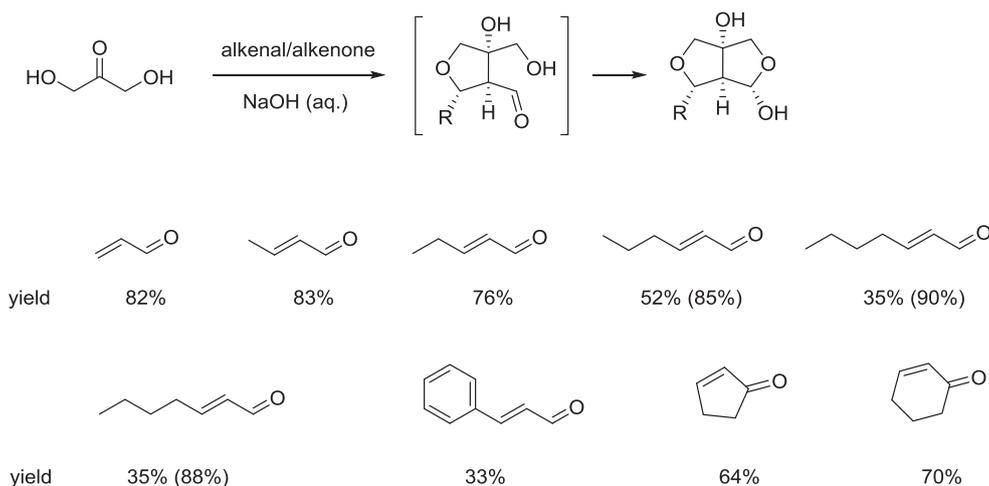
In conclusion, activated ketones bearing CF₃ group could be used as electrophiles in this reaction. The nucleophile can be both DHA as well as D-fructose. For future study, more activated ketones with other electron withdrawing groups can be developed as electrophiles and also activated alkyl chain ketones can be used for more practical application such as fluorinated surfactants.

3.6 Use of Michael acceptors as electrophiles.

3.6.1 Introduction.

The Michael addition reaction is a commonly used synthetic methodology for efficient coupling. It is a C-C bond forming reaction of a nucleophile such as a carbanion (Michael donor) to an α,β -unsaturated carbonyl containing compound (Michael acceptor).¹⁸¹ Michael acceptors are typically activated olefins, and the reactivity of the acceptor increases if the substituent is electron withdrawing group. Michael acceptor could be a good choice for electrophile substrates with DHA.

Shigemasa *et al.* have reported a reaction of C3 and C4 ketoses (DHA and erythrulose) with alkenals and alkenones under base catalyst in water. In the cases of long chain alkenals, an organic co-solvent (1,4-dioxane) was used for better yield (in the brackets). This reaction gave bicyclic tetrahydrofuran derivatives by Michael addition of the hydroxyl group of DHA to alkenals, intramolecular aldolisation, and hemiacetal formation (scheme 83).¹⁸²



scheme 83. Reaction of DHA with α,β -unsaturated carbonyl compounds under base catalyst.

Michael addition could occur with unprotected ketoses and α,β -unsaturated carbonyl compounds either by Stetter reaction under NHC-catalysis or by formation of hemiacetal under aqueous basic conditions.

3.6.2 Results.

Some Michael acceptors such as ethyl cinnamate and chalcone have been used (Table 57).

¹⁸¹ B. D. Mather, K. Viswanathan, K. M. Miller, T. E. Long, *Prog. Polym. Sci.*, **2006**, *31*, 487-531.

¹⁸² H. Saimoto, T. Onitsuka, H. Motobe, S. Okabe, Y. Takanori, M. Morimoto, Y. Shigemasa, *Tetrahedron Lett.*, **2004**, *45*, 8777-8780.

Ethyl cinnamate **70** was first used as electrophile with DHA, however, no reaction occurred even at 80 °C (Table 57, entries 1-3). Then, chalcone was used as electrophile. Unfortunately, no reaction happened with traditional heating (Table 57, entries 4-6). With microwave heating at 80 °C, the conversion was very low (Table 57, entry 7). The temperature was improved to 120 °C but without significant improvement of conversion. Many byproducts were formed under these conditions (Table 57, entry 8).

Table 57. Michael acceptors as substrates.^a

Entry	R-	Temperature / °C	Time / h	Expected product	Result
1		20	4		No reaction
2		20	20		No reaction
3	70	80	4	71	No reaction
4		20	2		No reaction
5		80	3		No reaction
6		80	24		No reaction
7 ^b	72	80 (μW)	2	73	Low conversion
8 ^b		120 (μW)	2		Too many byproducts

^a Reaction conditions: sealed tube, DHA (11.1 mmol, 5 equiv.), Me₃N (1.1 mmol, 50 mol%), Michael acceptor (2.2 mmol, 1 equiv.) in EtOH/H₂O (4 mL). ^b Microwave heating for 2 hours.

For further study, other Michael acceptors with electron withdrawing groups can be used as substrates such as maleic anhydride and 2-phenylmethylene malononitrile (Figure 39).¹⁸³

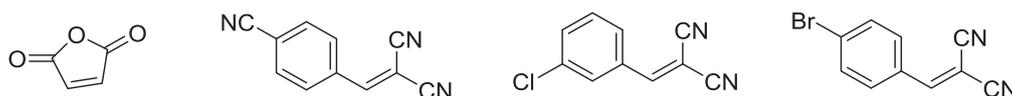


Figure 39. Possible Michael acceptors.

¹⁸³ L. R. Domingo, P. Perez, R. Contreras, *Tetrahedron*, **2004**, *60*, 6585-6591.

4 Conclusion.

For the aldolisation process developed for DHA and D-fructose, both nucleophiles and electrophiles can be substituted by other substrates. In this chapter, alkyl halides, epoxides, imines, Michael acceptors, activated esters and activated ketones have been used as electrophiles, some of them show positive results. The most interesting electrophiles could be the imines and the activated ketones which could be further improved. On the other hand, sorbose has been used as nucleophile as well. These results give us a general view of reactivity for this reaction. For future research, some new substrates (more activated with electron withdrawing group) could be used and also some screening work could be done for obtaining better yields.

General Conclusion

The aldolisation of bio-sourced unprotected ketoses, such as 1,3-dihydroxyacetone and D-fructose, has been developed with fatty aldehydes to prepare C-C bond linked surfactants under mild reaction conditions.

This study started from the simplest triose 1,3-dihydroxyacetone in the presence of trimethylamine catalyst in a mixture of ethanol and water at room temperature to give the aldol intermediates with moderate isolated yields (29%-70%). Then, the more complex and available ketose fructose was used as substrate under microwave irradiation at 60 °C. In order to improve the yields with long alkyl chain aldehydes, tetrabutylphosphonium bromide was used as a phase transfer agent to facilitate the reaction at the interphase, and inorganic base K_2CO_3 was also used to replace trimethylamine to limit the generation self-condensation byproduct of aldehydes. The corresponding alkylated fructose was obtained with 31%-49% isolated yields. After obtaining the aldol intermediates, a catalytic hydrogenation step with Ru/Al_2O_3 catalyst under H_2 pressure gave access to the alkylated polyols with high yield (79%-97%).

This aldolisation-reduction sequence is advantageous, due to: 1) the direct use of unprotected ketoses that avoids protection and deprotection steps; 2) the formation of C-C bond provides a route for constructing robust surfactants that could be applied more broadly; 3) the 100% atom economy and recyclable amine catalyst makes this process more sustainable.

The physico-chemical properties of the alkylated dihydroxyacetone-based tetraol surfactants were also studied. The critical micelle concentration is lower of these surfactants bearing longer alkyl chains. The C-C bond linked surfactants are efficient in reducing the surface tension of water compared to those available commercial surfactants.

In addition, other electrophiles/nucleophiles were used as substrates to check the reactivity of this reaction. Sorbose was used as another ketose but the yield was limited due to its lower solubility than fructose in the solvent system. Alkyl halides, epoxides, imines, Michael acceptors, activated esters and activated ketones have been used as electrophiles, and the imines and activated ketones could be further optimized for better yield.

Overall, a new method of unprotected ketoses alkylation by aldehydes has been developed. The obtained C-C bond linked surfactants are found to be efficient in physico-chemical properties. This process could be promisingly used in industrial production of robust surfactants in future.

Experiment Section

Chapter 5 Experiment section.

1 Experiment part for chapter 2.

1.1 General information

All reagents were used as received from the chemical company. 1,3-Dihydroxyacetone (dimer, 97 % purity) was purchased from Alfa-Aesar. Butyaldehyde, hexanal, octanal, decanal, dodecanal and hydrocinamaldehyde were supplied by Sigma-Aldrich or Alfa-Aesar, and were purified by distillation before use. Amberlyst A26 (OH), ion exchange resin, A17361 was bought from Alfa-Aesar. Pd (5 % on activated wood carbon, reduced, dry, EscatTM 1431), Ruthenium (5 % on carbon), Ruthenium (5 % on alumina) were purchased from Strem Chemicals. Reactions were monitored by TLC (thin-layer chromatography) using aluminium silica gel (60F₂₅₄) and chromatography was performed using silica 60M (0.04–0.063 mm). ¹H and ¹³C NMR spectra were recorded on a Brüker DRX 300 or Brüker ALS 300 in CDCl₃, DMSO-*d*₆ or CD₃OD solutions using tetramethylsilane (TMS) as an internal standard. HPLC was carried out on an PerkinEimer Series 200 HPLC system. Electrospray ionization (ESI), High resolution mass spectra (HRMS) were recorded on a MicroTOFQ-II, Bruker Daltonics spectrometer instrument using standard conditions (ESI, 70 eV). Melting points were measured using a Kofler system (type WME).

1.2 General procedure for the aldolisation.

To a sealed tube, 1,3-dihydroxyacetone (DHA) **2** (1.0 g, 11.1 mmol, 5 equiv.) was dissolved in 5.5 mL ethanol and 5.5 mL distilled water. The aldehydes (2.2 mmol, 1 equiv.) was added to the tube, followed by the homogeneous catalyst (1.1 mmol, 0.5 equiv.) or heterogeneous catalyst Amberlyst A26(OH) (100 wt %/DHA). The mixture was stirred (800 rpm) at room temperature (20 °C) for 3 hours. Then, solvent was removed in vacuum, and the residue was purified by column chromatography. (eluent: dichloromethane-methanol : 40 : 1 ~ 25 : 1) to obtain the ketone intermediate.

1.3 General procedure for the hydrogenation.

To a 30 mL steel autoclave, the ketone intermediate (5 mmol, 1 equiv.) was dissolved in 25 mL ethanol (0.2 M). Then Ru/Al₂O₃ (5 % Ru, 0.25 mmol, 0.05 equiv.) was added. The autoclave was first flushed with 10 bar hydrogen for 3 times. The solution was stirred (800 rpm) under 40 bar hydrogen

at 100°C for 16 h. The reaction mixture was then filtered (Millipore Durapore filter 0.01 μm) with ethanol. Then, solvent was removed in vacuum to obtain the tetraol products.

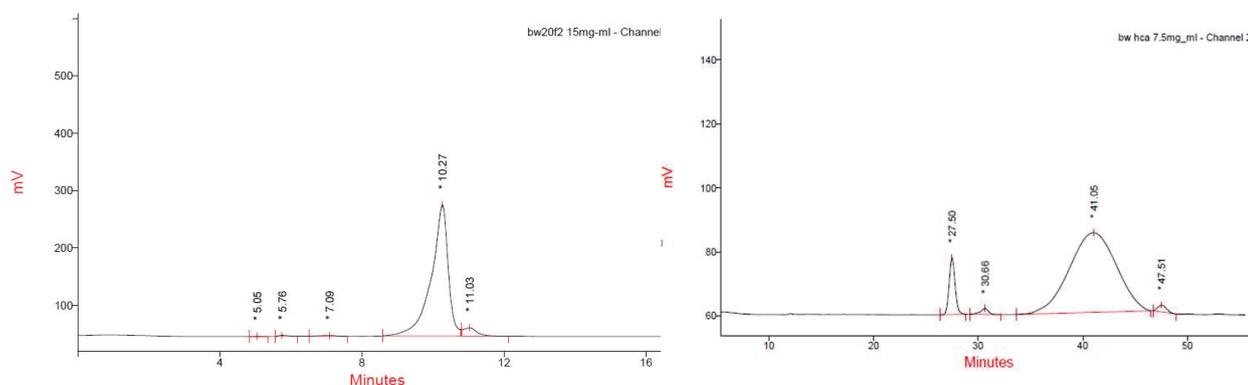
1.4 General procedure for CMC test and Krafft point.

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), record the value as the first result. Repeat it 2 or 3 times to get an average value of each sample. For each compound, the measurement was stopped once the surface tension reaches a plateau. The Krafft point was determined by increasing the temperature of a 1% wt. surfactant solution and it corresponds to the temperature at which the solution of precipitated surfactant became soluble.

1.5 HPLC condition selecting and calibration curve

HPLC was carried out on an PerkinEimer Series 200 HPLC system. The column is reverse phase RP-C18 column and the wavelength of UV detector is 254 nm. After optimization of the HPLC condition, the mobile phase has been prepared with 30% of acetonitrile and 70% of distilled water (mixed with 0.1% phosphoric acid). Mobile phase flow is 0.6 mL/min.

Solutions of hydrocinnamaldehyde **1** and α -hydroxylketone **3** has been prepared in 5 different concentrations. These samples have been successively injected in HPLC and for each injection, retention time and curve area has been recorded. The optimized condition allows to obtain the peak of hydrocinnamaldehyde **1** at the retention time of 10 min and the peak of α -hydroxylketone **3** at the retention time of 41 min (the peak at 27 min is the corresponding acid by oxidation).



scheme 84. HPLC curve of α -hydroxylketone **3** and hydrocinnamaldehyde **1**.

1.6 Corresponding HPLC spectrums of solvent ratio study.

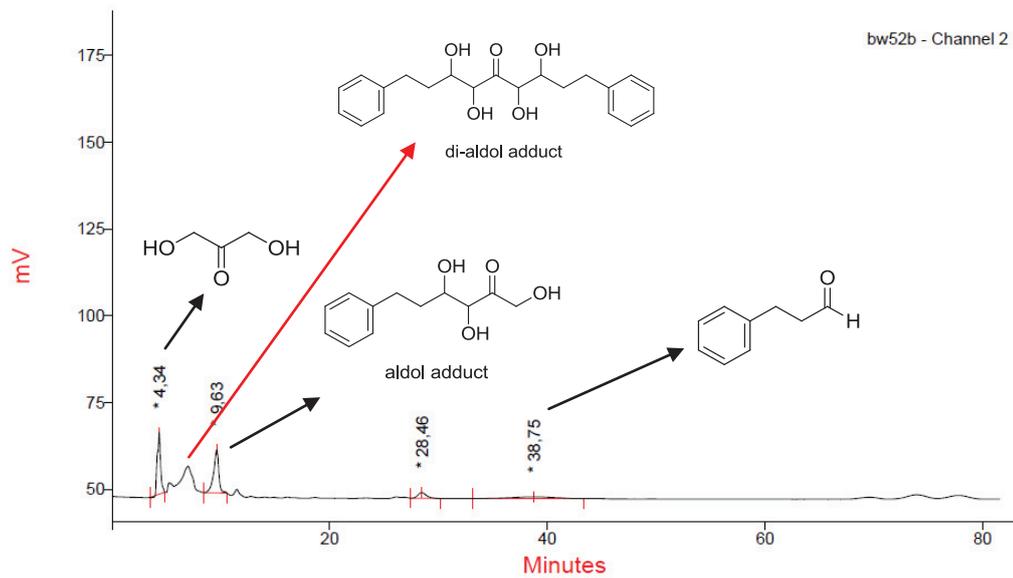


Figure 40. HPLC spectrum of Table 8, entry 2.

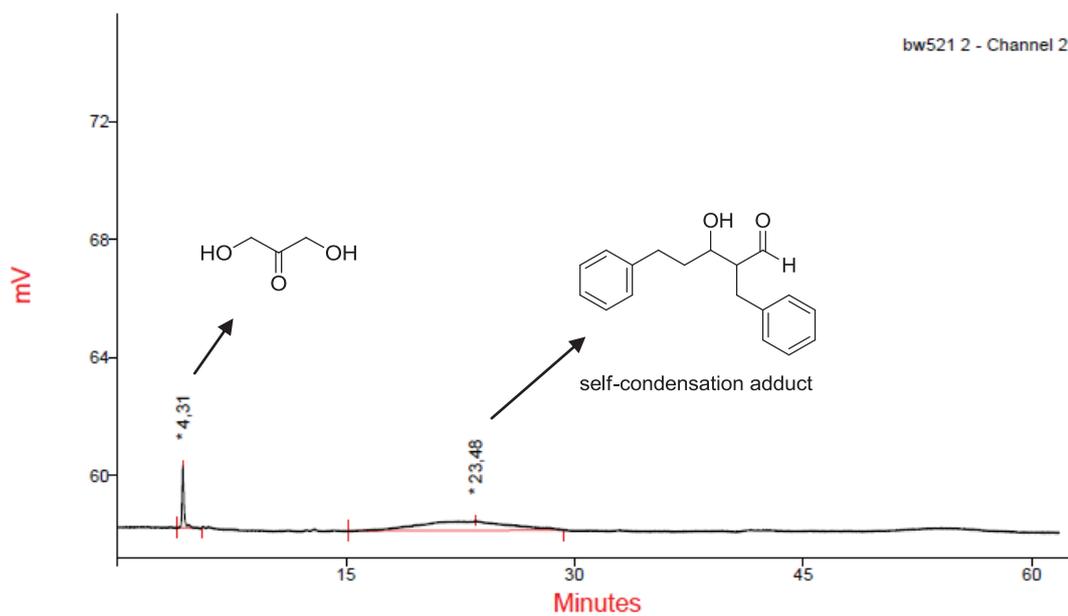
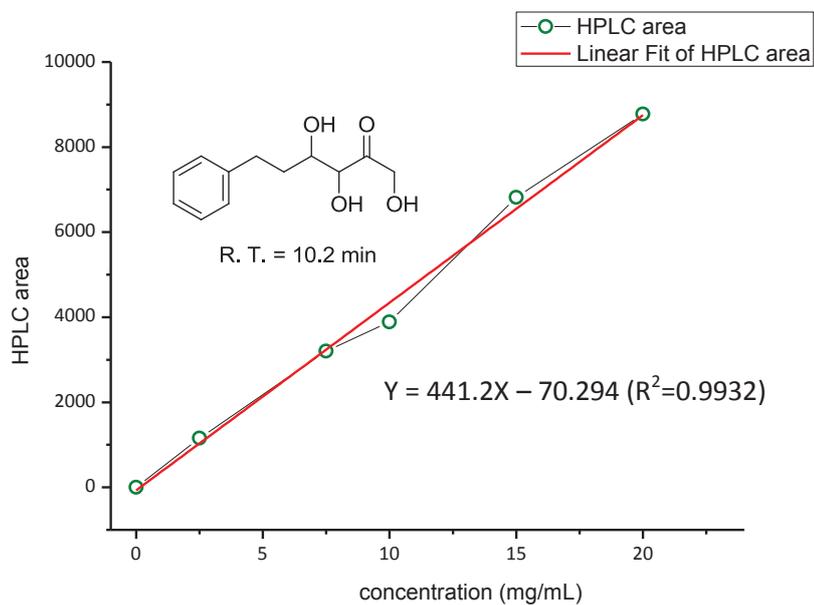
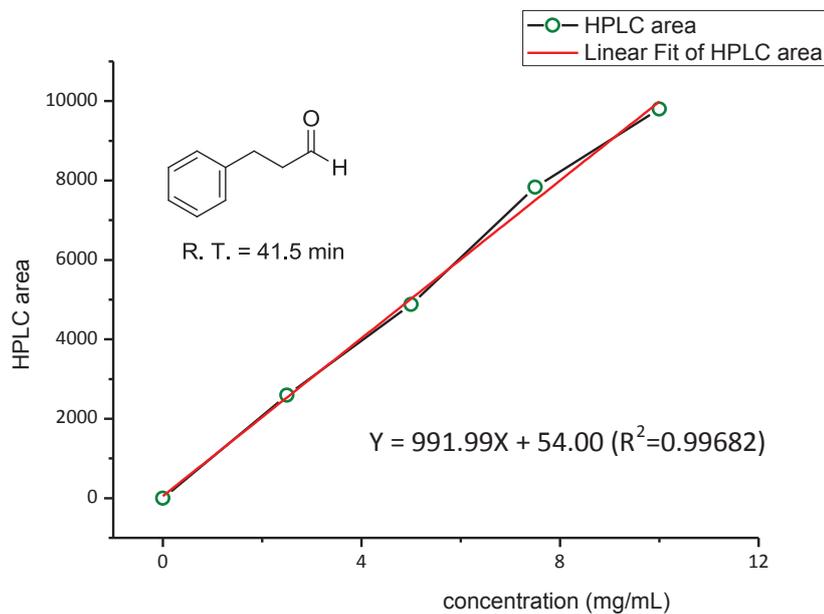


Figure 41. HPLC spectrum of Table 8, entry 3.

The calibration curve has been made based on concentration and the corresponding HPLC area. The equation has been listed below for further calibration and screening for model reaction. See Scheme 85 and Scheme 86.

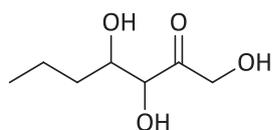


Scheme 85. Calibration curve for α -hydroxyketone **3**.

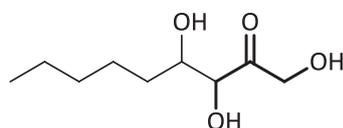


Scheme 86. Calibration curve for hydrocinnamaldehyde **1**.

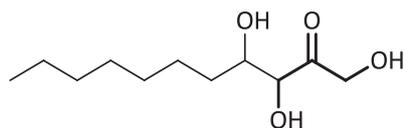
1.7 NMR Spectrum data.



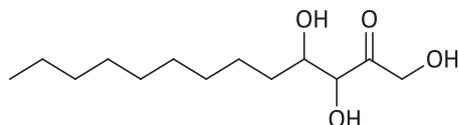
1,3,4-Trihydroxyheptan-2-one (14). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and butanal (0.10 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 25 : 1 v/v) to give α -hydroxyketone (83 mg, 46%) as a transparent oil. The product was obtained as a 96:4 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group, δ for the major isomer 4.13, for the minor isomer 4.06). $R_f = 0.5$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3404 (br, O-H), 2957, 2873 (C-H stretching), 1722 (C=O ketone), 1066 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 4.54 (d, $J = 19.2$, 1 H, CH_2OH), 4.43 (d, $J = 19.2$, 1H, CH_2OH), 4.13 (d, $J = 2.4$, 1H, CHOH), 3.90 (td, $J = 6.8$, 2.4, 1H, CHOH), 1.62-1.52 (m, 2H, CH_2CHOH), 1.52-1.29 (m, 2H, CH_2), 0.96 (t, $J = 7.2$, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ for the major isomer: 213.82 (C=O), 79.30 (CHOH), 73.22 (CHOH), 67.84 (CH_2OH), 36.36 (CH_2), 20.01 (CH_2), 14.30 (CH_3); MS (ESI^+): $m/z = 185.2$ ($[\text{C}_7\text{H}_{14}\text{O}_4 + \text{Na}]^+$), 347.3 ($[2 \text{C}_7\text{H}_{14}\text{O}_4 + \text{Na}]^+$); HRMS (ESI^+): calcd. for $\text{C}_7\text{H}_{14}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$, 185.0790, found 185.0785.



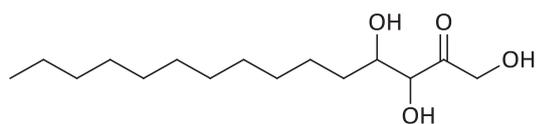
1,3,4-Trihydroxynonan-2-one (15). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and hexanal (0.13 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 30 : 1 v/v) to give α -hydroxyketone (103 mg, 49%) as a white solid (mp = 64°C). The product was obtained as a 96:4 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group, δ for the major isomer 3.88, for the minor isomer 3.78). $R_f = 0.5$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3249 (br, O-H), 2952, 2918, 2851 (C-H stretching), 1725 (C=O ketone), 1074 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 4.54 (d, $J = 19.2$, 1H, CH_2OH), 4.43 (d, $J = 19.2$, 1H, CH_2OH), 4.14 (d, $J = 2.4$, 1H, CHOH), 3.88 (td, $J = 6.9$, 2.4, 1H, CHOH), 1.62-1.50 (m, 2H, CH_2CHOH), 1.49-1.24 (m, 6H, 3 CH_2), 0.92 (t, $J = 6.7$, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ for the major isomer: 213.81 (C=O), 79.23 (CHOH), 73.48 (CHOH), 67.81 (CH_2OH), 34.13 (CH_2), 32.88 (CH_2), 26.56 (CH_2), 23.62 (CH_2), 14.37 (CH_3); MS (ESI^+): $m/z = 213.1$ ($[\text{C}_9\text{H}_{18}\text{O}_4+\text{Na}]^+$), 403.0 ($[2 \text{C}_9\text{H}_{18}\text{O}_4+\text{Na}]^+$).



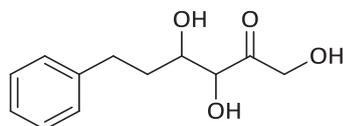
1,3,4-Trihydroxyundecan-2-one (16). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and octanal (0.17 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 30 : 1 v/v) to give α -hydroxyketone (115 mg, 48%) as a white solid (mp = 77°C). The product was obtained as a 91:9 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group, δ for the major isomer 4.20, for the minor isomer 4.29). R_f = 0.5 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3343 (br, O-H), 2916, 2850 (C-H stretching), 1725 (C=O ketone), 1075 (C-O stretching); ^1H NMR (300 MHz, CDCl_3): δ for the major isomer: 4.59 (d, J = 19.4, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.43 (d, J = 19.3, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.20 (d, J = 2.1, 1H, $\underline{\text{CHOH}}$), 3.97-3.90 (m, 1H, $\underline{\text{CHOH}}$), 1.69-1.53 (m, 2H, $\underline{\text{CH}_2\text{CHOH}}$), 1.28 (brs, 10H, 5 CH_2), 0.88 (t, J = 6.0, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): δ for the major isomer: 211.07 (C=O), 77.64 (CHOH), 72.49 (CHOH), 66.52 (CH_2OH), 33.69 (CH_2), 31.89 (CH_2), 29.52 (CH_2), 29.31 (CH_2), 25.87 (CH_2), 22.77 (CH_2), 14.23 (CH_3); MS (ESI $^+$): m/z = 241.3 ($[\text{C}_{11}\text{H}_{22}\text{O}_4+\text{Na}]^+$), 459.4 ($[2 \text{C}_{11}\text{H}_{22}\text{O}_4+\text{Na}]^+$).



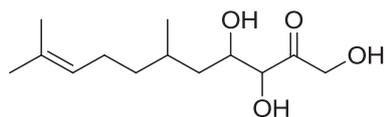
1,3,4-Trihydroxytridecan-2-one (17). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and decanal (0.20 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 35 : 1 v/v) to give α -hydroxyketone (145 mg, 53%) as a white solid (mp = 82°C). The product was obtained as a 90:10 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group, δ for the major isomer 4.12, for the minor isomer 4.06). R_f = 0.6 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3337 (br, O-H), 2912, 2846 (C-H stretching), 1725 (C=O ketone), 1077, 1052 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 4.53 (d, J = 19.2, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.43 (d, J = 19.2, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.12 (d, J = 2.4, 1H, $\underline{\text{CHOH}}$), 3.88 (td, J = 6.8, 2.4, 1H, $\underline{\text{CHOH}}$), 1.62-1.50 (m, 2H, $\underline{\text{CH}_2\text{CHOH}}$), 1.30 (brs, 14H, 7 CH_2), 0.90 (t, J = 6.8, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ for the major isomer: 213.84 (C=O), 79.30 (CHOH), 73.54 (CHOH), 67.86 (CH_2OH), 34.23 (CH_2), 33.06 (CH_2), 30.73 (CH_2), 30.70 (2 CH_2), 30.46 (CH_2), 26.94 (CH_2), 23.73 (CH_2), 14.44 (CH_3); MS (ESI $^+$): m/z = 269.2 ($[\text{C}_{13}\text{H}_{26}\text{O}_4+\text{Na}]^+$), 514.9 ($[2 \text{C}_{13}\text{H}_{26}\text{O}_4+\text{Na}]^+$).



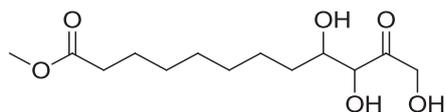
1,3,4-Trihydroxypentadecan-2-one (18). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and dodecanal (205 mg, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 40 : 1 v/v) to give α -hydroxyketone (90 mg, 29%) as a white solid (mp = 90°C). The product was obtained as a 92:8 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group, δ for the major isomer 4.12, for the minor isomer 4.06). R_f = 0.6 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3240 (br, O-H), 2913, 2846 (C-H stretching), 1725 (C=O ketone), 1078, 1056 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 4.53 (d, J = 19.2, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.43 (d, J = 19.2, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.12 (d, J = 2.4, 1H, $\underline{\text{CHOH}}$), 3.88 (td, J = 8.9, 6.9, 1H, $\underline{\text{CHOH}}$), 1.64-1.50 (m, 2H, $\underline{\text{CH}_2\text{CHOH}}$), 1.30 (brs, 18H, 9 CH_2), 0.90 (t, J = 6.7, 3H, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ for the major isomer: 213.84 (C=O), 79.31 (CHOH), 73.55 (CHOH), 67.86 (CH_2OH), 34.24 (CH_2), 33.07 (CH_2), 30.78 (CH_2), 30.75 (CH_2), 30.73 (2 CH_2), 30.71 (CH_2), 30.47 (CH_2), 26.94 (CH_2), 23.73 (CH_2), 14.43 (CH_3); MS (ESI $^+$): m/z = 297.3 ($[\text{C}_{15}\text{H}_{30}\text{O}_4 + \text{Na}]^+$), 571.0 ($[2 \text{C}_{15}\text{H}_{30}\text{O}_4 + \text{Na}]^+$).



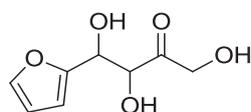
1,3,4-Trihydroxy-6-phenylhexan-2-one (3). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and hydrocinnamaldehyde (0.15 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 40 : 1 v/v) to give α -hydroxyketone (162 mg, 65%) as a white solid (mp = 156°C). The product was obtained as a 95:5 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{OH}$ group, δ for the major isomer 5.14, for the minor isomer 5.22). R_f = 0.5 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3312 (br, O-H), 1706 (C=O ketone), 1602, 1496, 1454 (aromatic ring), 1398, 1294, 1067 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ for the major isomer: 7.31-7.23 (m, 2H, Ar-H), 7.23-7.12 (m, 3H, Ar-H), 5.14 (d, J = 6.5, 1H, $\underline{\text{CHOH}}$), 4.79 (t, J = 5.9, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.73 (d, J = 7.3, 1H, $\underline{\text{CHOH}}$), 4.38 (dd, J = 19.2, 5.7, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.26 (dd, J = 19.2, 6.1, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.01 (dd, J = 6.5, 2.6, 1H, $\underline{\text{CHOH}}$), 3.78-3.67 (m, 1H, $\underline{\text{CHOH}}$), 2.75-2.52 (m, 2H, CH_2), 1.83-1.61 (m, 2H, CH_2); ^{13}C NMR (75 MHz, d_6 -DMSO): δ for the major isomer: 212.70 (C=O), 142.17 (Cq), 128.29 (2 CH), 128.26 (2 CH), 125.63 (CH), 78.02 (CHOH), 71.04 (CHOH), 66.46 (CH_2OH), 34.94 (CH_2), 31.55 (CH_2); HRMS (ESI $^+$): calcd. for $\text{C}_{12}\text{H}_{16}\text{NaO}_4$ [$M + \text{Na}$] $^+$, 247.0946, found 247.0942.



1,3,4-Trihydroxy-6,10-dimethylundec-9-en-2-one (19). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (1 g, 11.1 mmol) and citronellal (0.4 mL, 2.2 mmol), following the general procedure. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 40 : 1 v/v) to give α -hydroxyketone (228 mg, 42%) as a yellow oil. The product was obtained as a 53:47 mixture of diastereoisomers as determined by ^{13}C NMR (integration of the carbon on the carbonyl group, δ for the major isomer 213.94, for the minor isomer 213.74). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1, v/v). IR (ν_{max}): 3413 (br, O-H), 2917 (C-H stretching), 1722 (C=O ketone), 1070, 1024 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 5.12 (t, $J = 6.6$, 1H, $\underline{\text{CH}}=\text{C}$), 4.54 (d, $J = 19.2$, 1H, $\underline{\text{CH}}_2\text{OH}$), 4.43 (d, $J = 19.2$, 1H, $\underline{\text{CH}}_2\text{OH}$), 4.10 (d, $J = 8.6$, 1H, $\underline{\text{CHOH}}$), 4.06-3.97 (m, 1H, $\underline{\text{CHOH}}$), 2.10-1.92 (m, 2H, CH_2), 1.67 (s, 3H, $\underline{\text{CH}}_3\text{C}=\text{}$), 1.61 (s, 3H, $\underline{\text{CH}}_3\text{C}=\text{}$), 1.73-1.52 (m, 1H, CH), 1.50-1.31 (m, 2H, CH_2), 1.31-1.08 (m, 2H, CH_2), 0.93 (d, $J = 6.6$, 3H, $\underline{\text{CH}}_3\text{CH}$); δ for the minor isomer: 5.12 (t, $J = 6.6$, 1H, $\underline{\text{CH}}=\text{C}$), 4.53 (d, $J = 19.2$, 1H, $\underline{\text{CH}}_2\text{OH}$), 4.43 (d, $J = 19.2$, 1H, $\underline{\text{CH}}_2\text{OH}$), 4.11 (d, $J = 8.4$, 1H, $\underline{\text{CHOH}}$), 4.06-3.97 (m, 1H, $\underline{\text{CHOH}}$), 2.10-1.92 (m, 2H, CH_2), 1.67 (s, 3H, $\underline{\text{CH}}_3\text{C}=\text{}$), 1.61 (s, 3H, $\underline{\text{CH}}_3\text{C}=\text{}$), 1.73-1.52 (m, 1H, CH), 1.50-1.31 (m, 2H, CH_2), 1.31-1.08 (m, 2H, CH_2), 0.96 (d, $J = 6.7$, 3H, $\underline{\text{CH}}_3\text{CH}$); ^{13}C NMR (75 MHz, CD_3OD): δ for the major isomer: 213.94 (C=O), 131.82 (C=), 125.79 (CH=), 79.14 (CHOH), 71.51 (CHOH), 67.84 (CH_2OH), 41.39 ($\underline{\text{CH}}_2\text{CHOH}$), 37.86 (CH_2), 30.26 ($\underline{\text{CH}}\text{CH}_3$), 26.38 (CH_2), 25.91 (CH_3), 20.43 (CH_3), 17.74 (CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ for the minor isomer: 213.74 (C=O), 131.85 (C=), 125.79 (CH=), 79.92 (CHOH), 71.15 (CHOH), 67.84 (CH_2OH), 41.35 ($\underline{\text{CH}}_2\text{CHOH}$), 38.85 (CH_2), 29.74 ($\underline{\text{CH}}\text{CH}_3$), 26.29 (CH_2), 25.91 (CH_3), 20.43 (CH_3), 17.74 (CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{13}\text{H}_{24}\text{NaO}_4$ [$\text{M} + \text{Na}$] $^+$, 267.1572, found 267.1564.

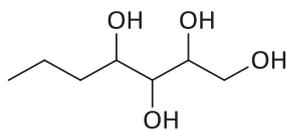


Methyl-9,10,12-trihydroxy-11-oxododecanoate (20). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (1 g, 11.1 mmol) and methyl azelaaldehyde (413 mg, 2.2 mmol), following the general procedure. The residue was purified by column chromatography (CH₂Cl₂/MeOH, 20 : 1 v/v) to give α -hydroxyketone (220 mg, 36%) as a yellow oil. The product was obtained as a 95:5 mixture of diastereoisomers as determined by ¹H NMR (integration of the proton on the –CH next to the carbonyl group, δ for the major isomer 4.13, for the minor isomer 4.06). R_f = 0.3 (CH₂Cl₂/MeOH, 15:1, v/v). IR (ν_{\max}): 3403 (br, O-H), 2926 (C-H stretching), 1719 (br, C=O ketone & C=O ester), 1068 (C-O stretching); ¹H NMR (300 MHz, CD₃OD): δ for the major isomer: 4.53 (d, J = 19.2, 1H, CH₂OH), 4.43 (d, J = 19.2, 1H, CH₂OH), 4.13 (d, J = 2.4, 1H, CHOH), 3.88 (td, J = 6.9, 2.4, 1H, CHOH), 3.65 (s, 3H, OCH₃), 2.32 (t, J = 7.4, 2H, CH₂C=O), 1.72-1.51 (m, 4H, 2 CH₂), 1.47-1.21 (m, 8H, 4 CH₂); ¹³C NMR (75 MHz, CD₃OD): δ for the major isomer: 213.81 (C=O ketone), 176.02 (C=O ester), 79.29 (CHOH), 73.49 (CHOH), 67.85 (CH₂OH), 51.97 (OCH₃), 34.77 (CH₂), 34.16 (CH₂), 30.45 (CH₂), 30.28 (CH₂), 30.09 (CH₂), 26.82 (CH₂), 25.98 (CH₂); HRMS (ESI⁺): calcd. for C₁₃H₂₄NaO₆ [M + Na]⁺, 299.1465, found 299.1459.

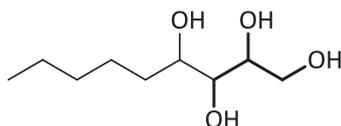


4-(Furan-2-yl)-1,3,4-trihydroxybutan-2-one (21). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (1 g, 11.1 mmol) and furfural (0.18 mL, 2.2 mmol), following the general procedure. The residue was purified by column chromatography (CH₂Cl₂/EtOAc, 1 : 2 v/v) to give α -hydroxyketone (290 mg, 70%) as a yellow oil. The product was obtained as a 68:32 mixture of diastereoisomers as determined by ¹³C NMR (integration of the carbon on the –CH₂OH next to the carbonyl group, δ for the major isomer 66.45, for the minor isomer 66.33).. R_f = 0.5 (CH₂Cl₂/MeOH, 6:1, v/v). IR (ν_{\max}): 3359 (br, O-H), 1248 (Ar-O stretching), 1723 (C=O ketone), 1008 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the major isomer: 7.58-7.53 (m, 1H, CH=), 6.41-6.35 (m, 1H, CH=), 6.33-6.27 (m, 1H, CH=), 5.59 (d, J = 6.5, 1H, CHOH), 5.38 (d, J = 6.9, 1H, CHOH), 4.94-4.87 (m, 1H, CHOH), 4.87-4.84 (m, 1H, CH₂OH), 4.41-4.14 (m, 3H, CHOH, CH₂OH); δ for the minor isomer: 7.58-7.53 (m, 1H, CH=), 6.41-6.35 (m, 1H, CH=), 6.33-6.27 (m, 1H, CH=), 5.70 (d, J = 5.8, 1H, CHOH), 5.59 (d, J = 6.5, 1H, CHOH), 4.94-4.87 (m, 1H, CHOH), 4.67 (t, J = 6.1, 1H, CH₂OH), 4.41-4.14 (m, 3H, CHOH, CH₂OH); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the major isomer: 211.49 (C=O), 154.99 (Cq), 141.76 (O-CH=CH), 110.35 (CH=), 106.98 (CH=), 77.35 (CHOH), 68.29 (CHOH), 66.45 (CH₂OH); δ for the minor

isomer: 210.50 (C=O), 154.99 (Cq), 141.89 (O-CH=CH), 110.31 (CH=), 107.33 (CH=), 76.20 (CHOH), 68.26 (CHOH), 66.33 (CH₂OH); HRMS (ESI⁺): calcd. for C₈H₁₀NaO₅ [M + Na]⁺, 209.0420, found 209.0412.

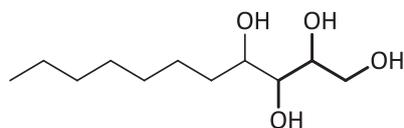


Heptane-1,2,3,4-tetraol (24). The title compound was obtained from C3- α -hydroxyketone (200 mg, 1.2 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give C3-tetraol (196 mg, 97%). The product was obtained as a 55:45 mixture of diastereoisomers as determined by ¹³C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 131°C). IR (ν_{\max}): 3350, 3237 (br, O-H), 2954, 2910, 2868 (C-H stretching), 1091, 1061, 1038 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the solid: 4.44 (d, *J* = 5.3, 1H, CHOH), 4.30 (t, *J* = 5.7, 1H, CH₂OH), 4.18 (d, *J* = 7.2, 1H, CHOH), 3.99 (d, *J* = 6.9, 1H, CHOH), 3.69-3.54 (m, 2H, CH₂OH), 3.49-3.41 (m, 1H, CHOH), 3.41-3.34 (m, 1H, CHOH), 3.11 (td, *J* = 7.6, 2.0, 1H, CHOH), 1.50-1.21 (m, 4H, CH₂), 0.87 (t, *J* = 7.0, 3H, CH₃); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 73.03 (CHOH), 71.69 (CHOH), 68.91 (CHOH), 63.73 (CH₂OH), 35.65 (CH₂CHOH), 18.80 (CH₂), 14.13 (CH₃); HRMS (ESI⁺): calcd. for C₇H₁₆NaO₄ [M + Na]⁺, 187.0946, found 187.0942.

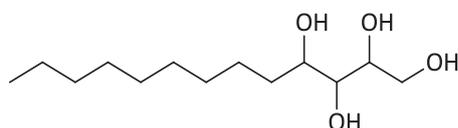


Nonane-1,2,3,4-tetraol (25). The title compound was obtained from C5- α -hydroxyketone (200 mg, 1.1 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give C5-tetraol (188 mg, 93%). The product was obtained as a 50:50 mixture of diastereoisomers as determined by ¹³C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 142°C). IR (ν_{\max}): 3349, 3249 (br, O-H), 2950, 2856 (C-H stretching), 1078 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the solid: 4.44 (d, *J* = 5.3, 1H, CHOH), 4.30 (t, *J* = 5.6, 1H, CH₂OH), 4.17 (d, *J* = 7.2, 1H, CHOH), 4.00 (d, *J* = 6.9, 1H, CHOH), 3.66-3.53 (m, 2H, CH₂OH), 3.48-3.41 (m, 1H, CHOH), 3.38 (d, *J* = 10.5, 5.6, 1H, CHOH), 3.12 (td, *J* = 7.6, 2.0, 1H, CHOH), 1.51-1.17 (m, 8H, 4 CH₂), 0.86 (t, *J* = 6.7, 3H, CH₃); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 72.98 (CHOH), 71.70 (CHOH), 69.25 (CHOH), 63.73 (CH₂OH),

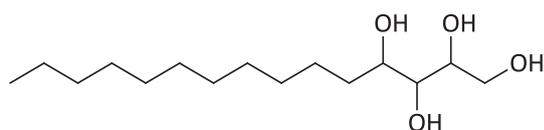
33.39 (CH₂), 31.48 (CH₂), 25.33 (CH₂), 22.18 (CH₂), 13.97 (CH₃); HRMS (ESI⁺): calcd. for C₉H₂₀NaO₄ [M + Na]⁺, 215.1259, found 215.1255.



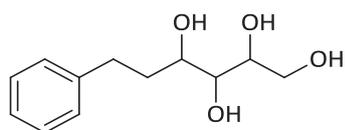
Undecane-1,2,3,4-tetraol (26). The title compound was obtained from C7- α -hydroxyketone (200 mg, 0.8 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give C7-tetraol (190 mg, 94%). The product was obtained as a 72:25 mixture of diastereoisomers as determined by ¹³C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 138°C). IR (ν_{\max}): 3346, 3242 (br, O-H), 2953, 2915, 2847 (C-H stretching), 1084, 1022 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the solid: 4.43 (d, *J* = 5.3, 1H, CHOH), 4.30 (t, *J* = 5.6, 1H, CH₂OH), 4.17 (d, *J* = 7.2, 1H, CHOH), 3.99 (d, *J* = 6.8, 1H, CHOH), 3.65-3.52 (m, 2H, CH₂OH), 3.49-3.41 (m, 1H, CHOH), 3.41-3.33 (m, 1H, CHOH), 3.11 (td, *J* = 7.6, 2.0, 1H, CHOH), 1.51-1.13 (m, 12H, 6 CH₂), 0.86 (t, *J* = 7.0, 3H, CH₃); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 72.97 (CHOH), 71.69 (CHOH), 69.24 (CHOH), 63.72 (CH₂OH), 33.43 (CH₂), 31.30 (CH₂), 29.18 (CH₂), 28.79 (CH₂), 25.67 (CH₂), 22.11 (CH₂), 13.96 (CH₃); HRMS (ESI⁺): calcd. for C₁₁H₂₄NaO₄ [M + Na]⁺, 243.1572, found 243.1567.



Tridecane-1,2,3,4-tetraol (27). The title compound was obtained from C9- α -hydroxyketone (500 mg, 1.9 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give C9-tetraol (463 mg, 92%). The product was obtained as a 78:22 mixture of diastereoisomers as determined by ¹³C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 140°C). IR (ν_{\max}): 3346 (br, O-H), 2954, 2914, 2847 (C-H stretching), 1086, 1065, 1050 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the solid: 4.44 (d, *J* = 5.3, 1H, CHOH), 4.30 (t, *J* = 5.6, 1H, CH₂OH), 4.17 (d, *J* = 7.2, 1H, CHOH), 3.99 (d, *J* = 6.8, 1H, CHOH), 3.65-3.52 (m, 2H, CH₂OH), 3.48-3.41 (m, 1H, CHOH), 3.41-3.35 (m, 1H, CHOH), 3.11 (td, *J* = 7.6, 1.9, 1H, CHOH), 1.47-1.16 (m, 16H, 8 CH₂), 0.86 (t, *J* = 6.7, 3H, CH₃); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 72.98 (CHOH), 71.70 (CHOH), 69.25 (CHOH), 63.73 (CH₂OH), 33.43 (CH₂), 31.32 (CH₂), 29.23 (CH₂), 29.15 (CH₂), 29.03 (CH₂), 28.74 (CH₂), 25.67 (CH₂), 22.11 (CH₂), 13.97 (CH₃); HRMS (ESI⁺): calcd. for C₁₃H₂₈NaO₄ [M + Na]⁺, 271.1880, found 271.1875.

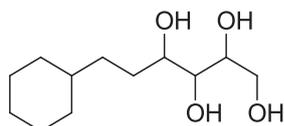


Pentadecane-1,2,3,4-tetraol (28). The title compound was obtained from C11- α -hydroxyketone (500 mg, 1.8 mmol), following the general procedure. The residue was filtered and evaporated at reduced pressure to give C11-tetraol (473 mg, 94%) as a white solid (mp = 91°C). The product was obtained as a 35:65 inseparable mixture of diastereoisomers as determined by ^1H NMR on the crude product. IR (ν_{max}): 3387, 3292 (br, O-H), 2954, 2914, 2847 (C-H stretching), 1090, 1068, 1036 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ for the major isomer: 4.43 (t, J = 5.4, 1H, CH_2OH), 4.34 (d, J = 5.1, 1H, CHOH), 4.23 (d, J = 5.4, 1H, CHOH), 4.05 (d, J = 6.3, 1H, CHOH), 3.68-3.33 (m, 4H, 2 CHOH , CH_2OH), 3.23 (dt, J = 6.4, 4.0, 1H, CHOH), 1.55-1.15 (m, 20H, 10 CH_2), 0.85 (t, J = 6.6, 3H, CH_3); δ for the minor isomer: 4.43 (d, J = 5.2, 1H, CHOH), 4.30 (t, J = 5.6, 1H, CH_2OH), 4.16 (d, J = 7.2, 1H, CHOH), 3.99 (d, J = 6.8, 1H, CHOH), 3.68-3.33 (m, 4H, 2 CHOH , CH_2OH), 3.11 (td, J = 7.6, 1.8, 1H, CHOH), 1.55-1.15 (m, 20H, 10 CH_2), 0.85 (t, J = 6.6, 3H, CH_3); ^{13}C NMR (75 MHz, d_6 -DMSO): δ for the major isomer: 72.63 (CHOH), 72.40 (CHOH), 71.25 (CHOH), 62.75 (CH_2OH), 33.11 (CH_2), 31.29 (CH_2), 29.25 (CH_2), 29.13 (CH_2), 29.08 (CH_2), 29.06 (CH_2), 29.03 (CH_2), 28.71 (CH_2), 25.43 (CH_2), 22.09 (CH_2), 13.95 (CH_3); ^{13}C NMR (75 MHz, d_6 -DMSO): δ for the minor isomer: 72.97 (CHOH), 71.69 (CHOH), 69.24 (CHOH), 63.72 (CH_2OH), 33.42 (CH_2), 31.29 (CH_2), 29.23 (CH_2), 29.13 (CH_2), 29.08 (CH_2), 29.06 (CH_2), 29.03 (CH_2), 28.71 (CH_2), 25.66 (CH_2), 22.09 (CH_2), 13.95 (CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{15}\text{H}_{32}\text{NaO}_4$ [$\text{M} + \text{Na}$] $^+$, 299.2193, found 299.2180.

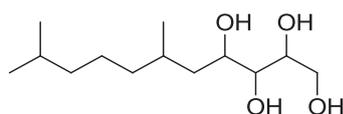


6-Phenylhexane-1,2,3,4-tetraol (22). The title compound was obtained from phenyl- α -hydroxyketone (100 mg, 0.4 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give phenyl-C2-tetraol (95 mg, 94%). The product was obtained as a 50:50 mixture of diastereoisomers as determined by ^{13}C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 164°C). IR (ν_{max}): 3341 (br, O-H), 2920 (C-H stretching), 1685, 1605 (aromatic ring), 1089 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ for the solid: 7.30-7.23 (m, 2H, Ar-H), 7.22-7.11 (m, 3H, Ar-H), 4.45 (d, J = 5.4, 1H, CHOH), 4.32 (t, J = 5.6, 1H, CH_2OH), 4.30 (d, J = 7.1, 1H, CHOH), 4.15 (d, J =

7.0, 1H, CHOH), 3.70-3.54 (m, 2H, CH₂OH), 3.51-3.43 (m, 1H, CHOH), 3.39 (dd, $J = 10.6, 5.6$, 1H, CHOH), 3.17 (td, $J = 7.9, 1.9$, 1H, CHOH), 2.78-2.65 (m, 1H, CH₂-Ar), 2.63-2.53 (m, 1H, CH₂-Ar), 1.78-1.62 (m, 2H, CH₂); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 142.63 (Cq), 128.32 (2 CH), 128.21 (2 CH), 125.50 (CH), 73.12 (CHOH), 71.67 (CHOH), 68.80 (CHOH), 63.76 (CH₂OH), 35.60 (CH₂), 31.90 (CH₂); HRMS (ESI⁺): calcd. for C₁₂H₁₈NaO₄ [M + Na]⁺, 249.1097, found 249.1095.

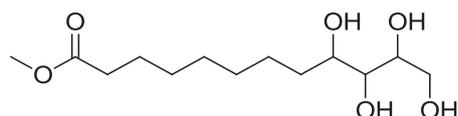


6-Cyclohexylhexane-1,2,3,4-tetraol (23). The title compound was obtained from phenyl- α -hydroxyketone (100 mg, 0.4 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give cyclohexyl-C2-tetraol (98 mg, 95%). The product was obtained as a 56:44 mixture of diastereoisomers as determined by ¹³C NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 180°C). IR (ν_{max}): 3359 (br, O-H), 2950 (C-H stretching), 1008 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the solid: 4.43 (d, $J = 5.3$, 1H, CHOH), 4.30 (t, $J = 5.6$, 1H, CH₂OH), 4.16 (d, $J = 7.3$, 1H, CHOH), 4.00 (d, $J = 6.8$, 1H, CHOH), 3.61-3.52 (m, 2H, CH₂OH), 3.49-3.41 (m, 1H, CHOH), 3.38 (dd, $J = 10.5, 5.7$, 1H, CHOH), 3.12 (td, $J = 7.6, 2.0$, 1H, CHOH), 1.74-1.57 (m, 5H), 1.50-1.34 (m, 2H, CH₂), 1.29-1.09 (m, 6H, CH₂), 0.97-0.70 (m, 2H, CH₂); ¹³C NMR (75 MHz, *d*₆-DMSO): δ for the solid: 72.95 (CHOH), 71.71 (CHOH), 69.63 (CHOH), 63.74 (CH₂OH), 37.24 (CH), 33.48 (CH₂), 33.10 (CH₂), 32.92 (CH₂), 30.71 (CH₂), 26.27 (CH₂), 25.91 (CH₂), 25.90 (CH₂); HRMS (ESI⁺): calcd. for C₁₂H₂₄NaO₄ [M + Na]⁺, 255.1567, found 255.1559.

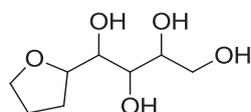


6,10-Dimethylundecane-1,2,3,4-tetraol (29). The title compound was obtained from citro- α -hydroxyketone (1.19 g, 4.9 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give citro-C9-tetraol (1.16 g, 96%) as yellow oil. The product was obtained as a 50:50 mixture of diastereoisomers as determined by ¹³C NMR. IR (ν_{max}): 3346, 3247 (br, O-H), 2952, 2912 (C-H stretching), 1090, 1076, 1029 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ for the mixture of isomers: 4.45 (d, $J = 5.3$, 1H, CHOH isomer 1) and 4.45 (d, $J = 5.3$, 1H, CHOH isomer 2), 4.30 (t, $J = 5.6$, 1H, CH₂OH), 4.20 (d, $J = 7.2$, 1H, CHOH isomer 1) and 4.16 (d, $J = 7.4$, 1H, CHOH isomer 2), 3.93 (d, $J = 7.1$, 1H, CHOH), 3.81-3.69 (m, 1H, CHOH), 3.63-3.52 (m, 1H, CHOH),

3.49-3.34 (m, 2H, $\underline{\text{CH}_2\text{OH}}$), 3.13-3.02 (m, 1H, $\underline{\text{CHOH}}$), 1.60-1.44 (m, 2H, 2 CH), 1.37-0.93 (m, 8H, 4 CH_2), 0.85 (d, $J = 6.6$, 6H, 2 CH_3), 0.83 (d, $J = 6.6$, CH_3); ^{13}C NMR (75 MHz, d_6 -DMSO): δ for the mixture of isomers: 73.84 and 72.94 (CHOH), 71.71 and 71.61 (CHOH), 67.12 and 66.93 (CHOH), 63.76 and 63.75 (CH_2OH), 41.00 and 40.80 (CH_2), 38.87 and 38.81 (CH_2), 37.72 and 36.41 (CH_2), 28.93 and 28.52 (CH), 27.42 and 27.40 (CH), 24.17 and 24.08 (CH_2), 22.65 and 22.60 (CH_3), 22.52 and 22.46 (CH_3), 20.33 and 19.23 (CH_3); HRMS (ESI⁺): calcd. for $\text{C}_{13}\text{H}_{28}\text{NaO}_4$ [M + Na]⁺, 271.1880, found 271.1873.



Methyl 9,10,11,12-tetrahydroxydodecanoate (30). The title compound was obtained from ester- α -hydroxyketone (1.2 g, 4.35 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give ester-tetraol (948 mg, 79%). The product was obtained as a 60:40 mixture of diastereoisomers as determined by ^1H NMR on the crude product. One of the diastereoisomers could be separated by recrystallisation from EtOH to give a white solid (mp = 128°C). IR (ν_{max}): 3344, 3252 (br, O-H), 2912, 2848 (C-H stretching), 1736 (C=O ester), 1076, 1028 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ 4.45 (d, $J = 5.3$, 1H, $\underline{\text{CHOH}}$), 4.31 (t, $J = 5.6$, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.18 (d, $J = 7.3$, 1H, $\underline{\text{CHOH}}$), 4.01 (d, $J = 6.9$, 1H, $\underline{\text{CHOH}}$), 3.57 (s, 3H, OCH_3), 3.65-3.52 (m, 2H, $\underline{\text{CH}_2\text{OH}}$), 3.49-3.41 (m, 1H, $\underline{\text{CHOH}}$), 3.41-3.35 (m, 1H, $\underline{\text{CHOH}}$), 3.11 (td, $J = 7.6$, 1.9, 1H, $\underline{\text{CHOH}}$), 2.28 (t, $J = 7.4$, 2H, $\underline{\text{CH}_2\text{C=O}}$), 1.58-1.46 (m, 2H, CH_2), 1.44-1.17 (m, 10H, 5 CH_2); ^{13}C NMR (75 MHz, d_6 -DMSO): δ 173.41 (C=O ester), 72.98 (CHOH), 71.69 (CHOH), 69.23 (CHOH), 63.75 (CH_2OH), 51.19 (OCH_3), 33.43 ($\underline{\text{CH}_2\text{C=O}}$), 33.30 (CH_2), 29.08 (CH_2), 28.80 (CH_2), 28.49 (CH_2), 25.63 (CH_2), 24.48 (CH_2); HRMS (ESI⁺): calcd. for $\text{C}_{13}\text{H}_{26}\text{NaO}_6$ [M + Na]⁺, 301.1622, found 301.1626.



1-(Tetrahydrofuran-2-yl)butane-1,2,3,4-tetraol (31). The title compound was obtained from fural- α -hydroxyketone (250 mg, 1.34 mmol), following the general procedure. The residue was filtered and evaporated under reduced pressure to give furfural-tetraol (226 mg, 87%) as dark yellow oil. The product was obtained as a mixture of 8 diastereoisomers as determined by ^{13}C NMR. IR (ν_{max}): 3390 (br, O-H), 2947 (C-H stretching), 1029 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ 4.23-3.46 (m, 8H), 2.11-1.65 (m, 4H, 2 CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ for the 8 diastereoisomers (only visible peaks are reported): 82.30, 81.45, 80.97, 80.89, 80.03, 79.90, 79.68, 79.31 ($\underline{\text{CH-O}}$), 74.87, 74.81,

74.57 73.70, 73.33, 72.99, 72.87, 72.74, 72.52, 71.80, 71.65 (3 CHOH), 69.50, 69.34, 69.23, 69.04, 68.97 ($\text{CH}_2\text{-O}$), 64.99, 64.87, 64.85, 64.71, 64.57, 64.27, 64.17, 64.02 (CHOH), 29.35, 28.76, 28.71, 28.60, 28.50, 28.47 (CH_2), 27.12, 26.95, 26.78, 26.76, 26.55, 26.48 (CH_2); HRMS (ESI⁺): calcd. for $\text{C}_8\text{H}_{16}\text{NaO}_5$ [$\text{M} + \text{Na}$]⁺, 215.0890, found 215.0882.

2 Experiment part for chapter 3.

2.1 General information.

All reagents were used as received from the chemical companies. D-Fructose (>99 % purity) was purchased from sigma-Aldrich. Hydrocinamaldehyde, butanal, pentanal, heptanal, nonanal, decanal and dodecanal were supplied by Sigma-Aldrich or Alfa-Aesar, and were purified by distillation before use (except dodecanal). $\text{Ru}/\text{Al}_2\text{O}_3$ (5%) was purchased from Strem Chemicals. Reactions were monitored by TLC (thin-layer chromatography) using aluminium silica gel (60F₂₅₄) and chromatography was performed using silica 60M (0.04–0.063 mm). ¹H and ¹³C NMR spectra were recorded on a Brüker DRX 300, DRX 400 or Brüker ALS 300 in $\text{DMSO-}d_6$ or CD_3OD solutions using tetramethylsilane (TMS) as an internal standard. Electrospray ionization (ESI), High resolution mass spectra (HRMS) were recorded on a MicroTOFQ-II, Bruker Daltonics spectrometer instrument using standard conditions (ESI, 70 eV). Melting points were measured using a Kofler system (type WME).

2.2 GC method.

Gas chromatography (GC) analyses for the starting material hydrocinamaldehyde and the corresponding fructose aldol were performed using a Shimadzu GC (GC-2025) apparatus equipped with a ZB-5-MS capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness). The carrier gas was N_2 , at a flow rate of 1.19 mL/min and the injection mode is split (ratio 1:40). The column temperature was initially at 100°, and then was gradually increased to 240°C (8°C/min) and the temperature was kept at 240°C during 3 min. Finally, the temperature was increased to 280°C (3°C/min) and kept at 280°C during 3 min. The injector and FID temperature were respectively set at 240°C and 315°C.

2.3 General procedures A and B for the aldolisation of D-fructose.

Method A (organic base)

In a sealed tube, D-fructose (4.00 g, 22.2 mmol, 20 equiv.) was dissolved in a 1:1 mixture of EtOH (1 mL) and water (1 mL). Then trimethylamine (0.13 mL, 0.56 mmol, 0.5 equiv.) and aldehydes (1 equiv.) was added into the solution. The mixture was heated at 60°C for 2 hours under microwave

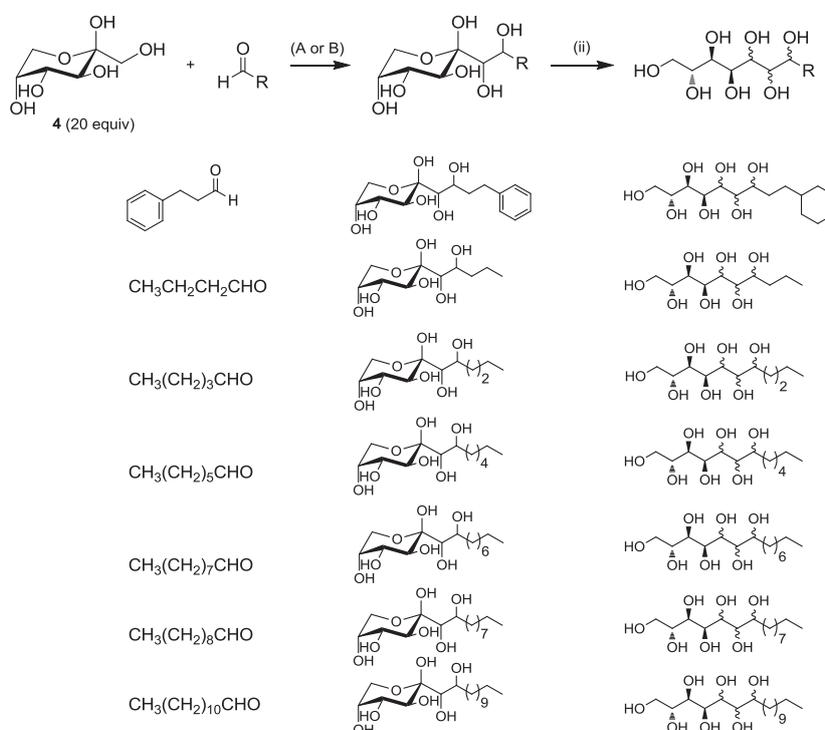
irradiation. After reaction, the solvent was removed in vacuum, and the residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 15:1 \rightarrow 12:1) to give aldolisation products.

Method B (inorganic base)

In a sealed tube, D-fructose (4.00 g, 22.2 mmol, 20 equiv.) and K_2CO_3 (77 mg, 0.56 mmol, 0.5 equiv.) were dissolved in a 1:1 mixture of EtOH (2 mL) and water (2 mL). Then aldehyde (1 equiv.) and tetrabutylphosphonium bromide (TBPB, 377 mg, 1.11 mmol, 1 equiv.) were added to give an organic phase on top of the water phase. The mixture was heated at 60°C for 2 hours under microwave irradiation. After reaction, the solvent was removed in vacuum, and the residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 15:1 \rightarrow 12:1) to give aldolisation products.

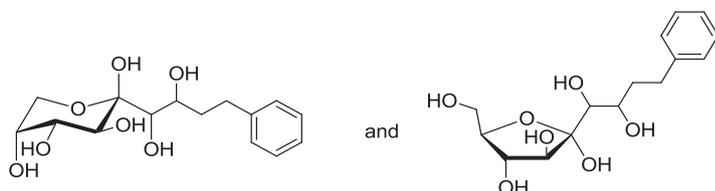
2.4 General procedure C for the hydrogenation of aldolisation products to heptaols.

In a 30-mL stainless steel autoclave, the aldolisation products (200 mg, 1 equiv.) was dissolved in water (6 mL). 5%-Ru/ Al_2O_3 (5 mol% in Ru) was added. The autoclave was flushed with hydrogen (10 bar) for 3 times. The solution was stirred (600 rpm) under 40 bar hydrogen at 100°C for 16 hours. After cooling to room temperature, the reaction mixture was filtered (Millipore Durapore filter 0.01 μm) and washed with EtOH. The filtrate was concentrated under vacuum to give heptaol products.

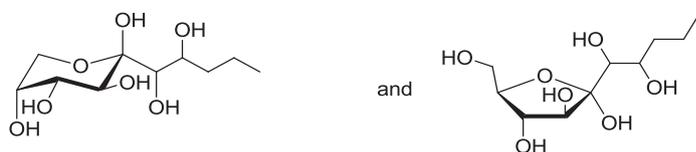


Scheme 87. Reagents and conditions: (A), 50 mol% Me₃N, EtOH/H₂O=1/1, 60°C (μW), 2 hours; (B), 50 mol% K₂CO₃, tetrabutylphosphonium bromide (1 equiv.), EtOH/H₂O=1/1, 60°C (μW), 2 hours; (ii), 5 mol% Ru/Al₂O₃, 40 bar H₂, 100 °C, H₂O, 16 h.

2.5 NMR Spectrum data.

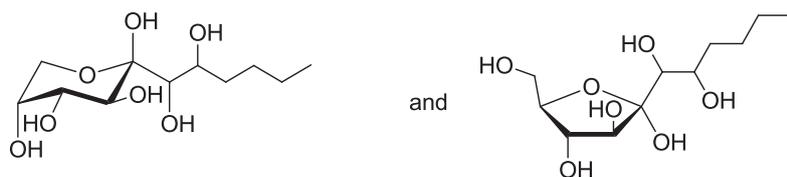


2-(1,2-dihydroxy-4-phenylbutyl)tetrahydropyran-2,3,4,5-tetraol and **2-(1,2-dihydroxy-4-phenylbutyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (33)**. The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and hydrocinnamaldehyde **2** (0.15 mL, 1.1 mmol), following the general method A. The residue was purified by column chromatography. (CH₂Cl₂/MeOH, 15:1 → 12:1 v/v) to give the aldol adduct (178 mg, 51%) as a light yellow oil. Ratio of isomers can be estimated by ¹H NMR (α-furanoid, β-furanoid, β-pyranoid=20%, 24%, 56%). R_f = 0.4 (CH₂Cl₂/MeOH, 6:1, v/v). IR (ν_{max}): 3270 (br, O-H), 2917 (C-H stretching), 1602, 1637 (aromatic ring), 1022 (C-O stretching); ¹H NMR (400 MHz, d₆-DMSO): δ 7.29-7.25 (m, 2H, Ar-H), 7.21-7.14 (m, 3H, Ar-H), 5.77-4.44 (m, 6H, -OH), 4.02-3.27 (m, 7H, 5 CHOH, CH₂O), 2.72-2.54 (m, 2H, CH₂Ph), 1.89-1.62 (m, 2H, CH₂CH₂Ph); ¹³C NMR (101 MHz, d₆-DMSO): δ 142.93 (Cq), 142.80 (Cq), 128.77 (2 CH), 128.71 (2 CH), 128.69 (2 CH), 126.04 (2 CH), 126.00 (CH), 103.78 (anomeric C), 98.93 (anomeric C), 82.44 (CHOH), 76.38 (CHOH), 75.47 (CHOH), 75.19 (CHOH), 74.89 (CHOH), 70.43 (CHOH), 69.98 (CHOH), 69.63 (CHOH), 69.34 (CHOH), 68.94 (CHOH), 63.54 (CH₂O), 63.32 (CH₂O), 36.13 (CH₂CH₂Ph), 36.06 (CH₂CH₂Ph), 32.25 (CH₂Ph), 32.06(CH₂Ph); HRMS (ESI⁺): calcd. for C₁₅H₂₂NaO₇ [M + Na]⁺, 337.1263, found 337.1245.

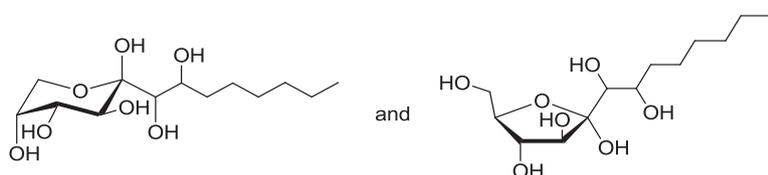


2-(1,2-dihydroxypentyl)tetrahydropyran-2,3,4,5-tetraol and **2-(1,2-dihydroxypentyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (34)**. The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and butanal (0.1 mL, 1.1 mmol), following the general method A. The residue was purified by column chromatography. (CH₂Cl₂/MeOH, 15:1 → 12:1 v/v) to give the aldol adduct (123 mg, 44%) as a light yellow oil. Ratio of isomers can be estimated by ¹H NMR (α-furanoid,

β -furanoid, β -pyranoid=15%, 15%, 70%). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 6:1, v/v). IR (ν_{max}): 3264 (br, O-H), 2957, 2915, 2873 (C-H stretching), 1072, 1029 (C-O stretching); ^1H NMR (400 MHz, d_6 -DMSO): δ 5.77-4.12 (m, 6H, -OH), 3.97-3.16 (m, 7H, 5 CHOH , CH_2O), 1.54-1.22 (m, 4H, 2 CH_2), 0.87 (t, $J = 7.1$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.46 (anomeric C), 98.55 (anomeric C), 82.05 (CHOH), 75.83 (CHOH), 74.98 (CHOH), 74.82 (CHOH), 74.32 (CHOH), 70.07 (CHOH), 69.57 (CHOH), 69.42 (CHOH), 68.96 (CHOH), 68.68 (CHOH), 63.15 (CH_2O), 63.05 (CH_2O), 35.81 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 35.79 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 18.87 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 18.68 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 14.19 (CH_3), 14.13 (CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{10}\text{H}_{20}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 275.1107, found 275.1093.

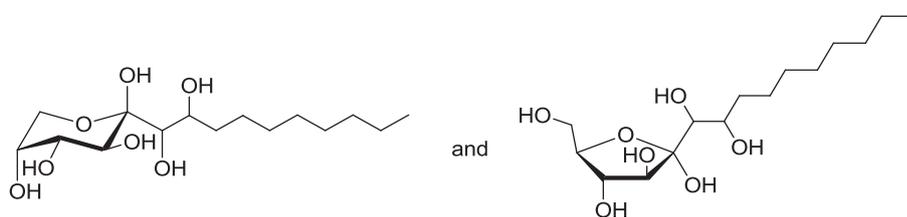


2-(1,2-dihydroxyhexyl)tetrahydropyran-2,3,4,5-tetraol and **2-(1,2-dihydroxyhexyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (36)**. The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and pentanal (0.12 mL, 1.1 mmol), following the general method A. The residue was purified by column chromatography. ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1 \rightarrow 12:1 v/v) to give the aldol adduct (145 mg, 49%) as a light yellow oil. Ratio of isomers can be estimated by ^1H NMR (α -furanoid, β -furanoid, β -pyranoid=24%, 25%, 51%). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 6:1, v/v). IR (ν_{max}): 3249 (br, O-H), 2916, 2848 (C-H stretching), 1023 (C-O stretching); ^1H NMR (400 MHz, d_6 -DMSO): δ 5.77-4.44 (m, 6H, -OH), 3.97-3.16 (m, 7H, 5 CHOH , CH_2O), 1.52-1.17 (m, 6H, 3 CH_2), 0.86 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.45 (anomeric C), 98.54 (anomeric C), 82.05 (CHOH), 75.77 (CHOH), 74.98 (CHOH), 74.82 (CHOH), 74.28 (CHOH), 70.07 (CHOH), 69.69 (CHOH), 69.56 (CHOH), 68.97 (CHOH), 68.95 (CHOH), 63.15 (CH_2O), 63.05 (CH_2O), 33.26 (2 CH_2CHOH), 27.96 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 27.76 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 22.32 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 22.28 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 14.16 (CH_3), 14.13 (CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{11}\text{H}_{22}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 289.1263, found 289.1247.

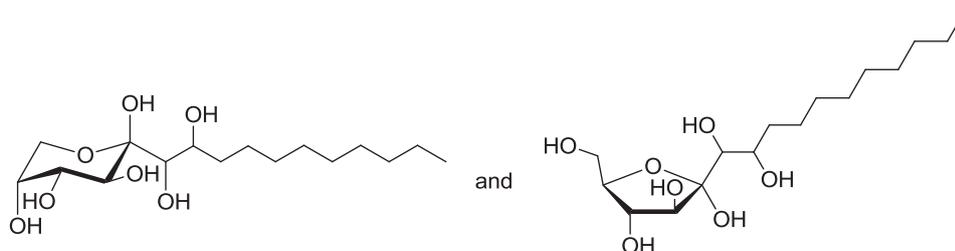


2-(1,2-dihydroxyoctyl)tetrahydropyran-2,3,4,5-tetraol and **2-(1,2-dihydroxyoctyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (38)**. The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and heptanal (0.16 mL, 1.1 mmol), K_2CO_3 (77 mg, 0.55 mmol) and tetrabutylphosphonium bromide (377 mg, 1.1 mmol), following the general method B. The residue

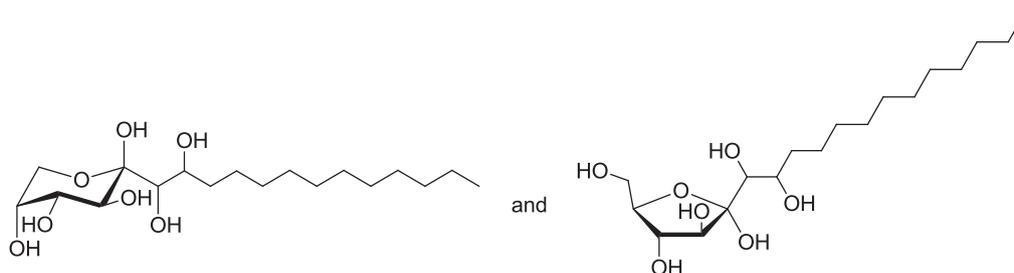
was purified by column chromatography. ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1 \rightarrow 12:1 v/v) to give the aldol adduct (140 mg, 43%) as a light yellow oil. Ratio of isomers can be estimated by ^1H NMR (α -furanoid, β -furanoid, β -pyranoid=22%, 22%, 56%). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 6:1, v/v). IR (ν_{max}): 3251 (br, O-H), 2916, 2849 (C-H stretching), 1022 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ 6.23-3.90 (m, 6H, -OH), 3.98-3.19 (m, 7H, 5 $\text{CHOH}, \text{CH}_2\text{O}$), 1.49-1.25 (m, 10H, 5 CH_2), 0.87 (t, $J = 6.5$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.38 (anomeric C), 98.47 (anomeric C), 82.01 (CHOH), 75.71 (CHOH), 75.06 (CHOH), 74.83 (CHOH), 74.29 (CHOH), 70.12 (CHOH), 69.63 (CHOH), 69.54 (CHOH), 68.95 (CHOH), 68.90 (CHOH), 63.10 (CH_2O), 62.96 (CH_2O), 33.53 (CH_2CHOH), 31.40 (CH_2CHOH), 28.83 (CH_2), 25.60 (CH_2), 23.48 (CH_2), 23.32 (CH_2), 22.71 (CH_2), 22.12 (CH_2), 17.60 (CH_2), 17.13 (CH_2), 14.01 (CH_3), 13.31 (CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{13}\text{H}_{26}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 317.1571, found 317.1566.



2-(1,2-dihydroxydecyl)tetrahydropyran-2,3,4,5-tetraol and 2-(1,2-dihydroxydecyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (40). The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and nonanal (0.19 mL, 1.1 mmol), K_2CO_3 (77 mg, 0.55 mmol) and tetrabutylphosphonium bromide (377 mg, 1.1 mmol), following the general method B. The residue was purified by column chromatography. ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 15:1 \rightarrow 12:1 v/v) to give the aldol adduct (132 mg, 37%) as a light yellow oil. Ratio of isomers can be estimated by ^1H NMR (α -furanoid, β -furanoid, β -pyranoid=18%, 22%, 60%). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 6:1, v/v). IR (ν_{max}): 3284 (br, O-H), 2919, 2851 (C-H stretching), 1029 (C-O stretching); ^1H NMR (400 MHz, d_6 -DMSO): δ 6.15-4.30 (m, 6H, -OH), 3.97-3.19 (m, 7H, 5 $\text{CHOH}, \text{CH}_2\text{O}$), 1.49-1.25 (m, 14H, 7 CH_2), 0.86 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.39 (anomeric C), 98.47 (anomeric C), 82.02 (CHOH), 75.71 (CHOH), 75.02 (CHOH), 74.81 (CHOH), 74.25 (CHOH), 70.06 (CHOH), 69.63 (CHOH), 69.52 (CHOH), 68.94 (CHOH), 68.90 (CHOH), 63.10 (CH_2O), 62.96 (CH_2O), 33.53 (2 CH_2CHOH), 31.36 (2 CH_2), 29.18 (CH_2), 29.16 (CH_2), 29.12 (CH_2), 29.10 (CH_2), 28.74 (2 CH_2), 25.63 (CH_2), 25.46 (CH_2), 22.15 (2 CH_2), 14.00 (2 CH_3); HRMS (ESI $^+$): calcd. for $\text{C}_{15}\text{H}_{30}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 345.1884, found 345.1871.

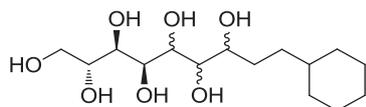


2-(1,2-dihydroxyundecyl)tetrahydropyran-2,3,4,5-tetraol and 2-(1,2-dihydroxyundecyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (41). The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and decanal (0.21 mL, 1.1 mmol), K_2CO_3 (77 mg, 0.55 mmol) and tetrabutylphosphonium bromide (377 mg, 1.1 mmol), following the general method B. The residue was purified by column chromatography. ($CH_2Cl_2/MeOH$, 15:1 v/v) to give the aldol adduct (146 mg, 39%) as a light yellow oil. Ratio of isomers can be estimated by 1H NMR (α -pyranoid, α -furanoid, β -furanoid, β -pyranoid= 7%, 17%, 25%, 51%). $R_f = 0.5$ ($CH_2Cl_2/MeOH$, 6:1, v/v). IR (ν_{max}): 3264 (br, O-H), 2927, 2873 (C-H stretching), 1022 (C-O stretching); 1H NMR (400 MHz, d_6 -DMSO): δ 6.23-4.07 (m, 6H, -OH), 3.98-3.41 (m, 6H, 4 \underline{CHOH} , $\underline{CH_2O}$), 3.31-3.19 (m, 1H, \underline{CHOH}), 1.49-1.40 (m, 2H, CH_2), 1.25 (brs, 14H, 7 CH_2), 0.86 (t, $J = 6.7$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.42 (anomeric C), 98.50 (anomeric C), 82.03 (\underline{CHOH}), 75.76 (\underline{CHOH}), 74.96 (\underline{CHOH}), 74.79 (\underline{CHOH}), 74.26 (\underline{CHOH}), 70.06 (\underline{CHOH}), 69.67 (\underline{CHOH}), 69.53 (\underline{CHOH}), 68.97 (\underline{CHOH}), 68.92 (\underline{CHOH}), 63.13 ($\underline{CH_2O}$), 63.01 ($\underline{CH_2O}$), 33.55 (2 $\underline{CH_2CHOH}$), 31.40 (CH_2), 29.22 (CH_2), 29.09 (CH_2), 28.83 (CH_2), 25.68 (2 CH_2), 23.52 (CH_2), 23.37 (CH_2), 22.73 (CH_2), 22.69 (CH_2), 22.19 (2 CH_2), 17.60 (CH_2), 17.12 (CH_2), 14.05 (CH_3), 13.36 (CH_3); HRMS (ESI $^+$): calcd. for $C_{16}H_{32}NaO_7$ [$M + Na$] $^+$, 359.2040, found 359.2029.

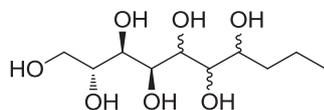


2-(1,2-dihydroxytridecyl)tetrahydropyran-2,3,4,5-tetraol and 2-(1,2-dihydroxytridecyl)-5-(hydroxymethyl)tetrahydrofuran-2,3,4-triol (42). The title compound was obtained from D-fructose **4** (4 g, 22.2 mmol, 20 eq.) and dodecanal (204 mg, 1.1 mmol), K_2CO_3 (77 mg, 0.55 mmol) and tetrabutylphosphonium bromide (377 mg, 1.1 mmol), following the general method B. The residue was purified by column chromatography. ($CH_2Cl_2/MeOH$, 15:1 v/v) to give the aldol adduct (125 mg, 31%) as a transparent oil. Ratio of isomers can be estimated by 1H NMR (α -pyranoid, α -furanoid, β -

furanoid, β -pyranoid=9%, 11%, 17%, 60%). $R_f = 0.4$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 6:1, v/v). IR (ν_{max}): 3259 (br, O-H), 2927, 2872 (C-H stretching), 1025 (C-O stretching); ^1H NMR (400 MHz, d_6 -DMSO): δ 5.74-4.28 (m, 6H, -OH), 3.97-3.16 (m, 7H, 5 CHOH , CH_2O), 1.50-1.24 (m, 20H, 10 CH_2), 0.85 (t, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 103.38 (anomeric C), 98.45 (anomeric C), 82.01 (2 CHOH), 75.71 (CHOH), 75.02 (CHOH), 74.80 (CHOH), 74.24 (CHOH), 70.07 (CHOH), 69.63 (CHOH), 69.51 (CHOH), 68.94 (CHOH), 63.09 (CH_2O), 62.94 (CH_2O), 33.53 (2 CH_2CHOH), 31.34 (2 CH_2), 29.16 (2 CH_2), 29.13 (2 CH_2), 29.09 (2 CH_2), 29.07 (2 CH_2), 28.76 (2 CH_2), 25.63 (2 CH_2), 25.45 (2 CH_2), 22.13 (2 CH_2), 13.98 (2 CH_3); HRMS (ESI^+): calcd. for $\text{C}_{18}\text{H}_{36}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 387.2353, found 387.2344.

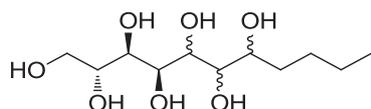


9-Cyclohexylnonane-1,2,3,4,5,6,7-heptaol (43). The title compound was obtained from aldol adduct **5** (200 mg, 0.64 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (193 mg, 94%) as a white solid isomer (mp = 125°C). IR (ν_{max}): 3254 (br, O-H), 2917, 2848 (C-H stretching), 1087, 1021 (C-O stretching); ^1H NMR (300 MHz, d_6 -DMSO): δ 4.79-4.12 (m, 7H, -OH), 3.84-3.15 (m, 8H, 6 CHOH , 1 CH_2OH), 1.65-1.14 (m, 13H, 6 CH_2 , 1CH), 0.86-0.84 (m, 2H, CH_2); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 74.60 (CHOH), 73.58 (2 CHOH), 73.54 (CHOH), 73.36 (CHOH), 72.92 (CHOH), 72.75 (CHOH), 72.11 (CHOH), 71.90 (CHOH), 71.79 (CHOH), 71.65 (2 CHOH), 71.62 (2 CHOH), 71.41 (CHOH), 71.21 (CHOH), 70.81 (CHOH), 70.72 (CHOH), 70.27 (CHOH), 70.14 (CHOH), 69.49 (CHOH), 69.31 (CHOH), 68.62 (CHOH), 67.44 (CHOH), 64.03 (CH_2OH), 63.83 (CH_2OH), 63.52 (CH_2OH), 63.35 (CH_2OH), 37.48 (CH), 37.42 (CH), 37.40 (CH), 37.37 (CH), 33.62 (2 CH_2), 33.51 (2 CH_2), 33.38 (2 CH_2), 33.26 (2 CH_2), 33.23 (2 CH_2), 33.17 (2 CH_2), 33.04 (2 CH_2), 32.92 (2 CH_2), 30.94 (CH_2), 30.86 (CH_2), 30.54 (CH_2), 30.40 (CH_2), 26.37 (4 CH_2), 26.01 (4 CH_2); HRMS (ESI^+): calcd. for $\text{C}_{15}\text{H}_{30}\text{NaO}_7$ [$\text{M} + \text{Na}$] $^+$, 345.1884, found 345.1876.

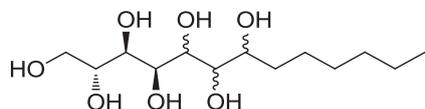


Decane-1,2,3,4,5,6,7-heptaol (47). The title compound was obtained from aldol adduct (200 mg, 0.79 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (190 mg, 94%) as a white solid isomer (mp = 108°C). IR (ν_{max}): 3257 (br, O-H), 2955, 2871 (C-H stretching), 1072, 1021 (C-O stretching); ^1H NMR (300 MHz, CD_3OD): δ 4.10-3.56 (m, 8H, 6 CHOH , 1 CH_2OH), 1.63-1.40 (m, 4H, 2 CH_2), 0.96 (t, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (101 MHz, d_6 -DMSO): δ 76.09 (CHOH), 74.57 (CHOH), 74.16 (CHOH), 73.67 (CHOH), 73.39 (CHOH),

73.18 (CHOH), 73.03 (CHOH), 72.82 (CHOH), 72.34 (CHOH), 72.08 (CHOH), 71.95 (CHOH), 71.84 (CHOH), 71.79 (CHOH), 71.66 (CHOH), 71.56 (CHOH), 71.45 (CHOH), 71.24 (CHOH), 71.02 (CHOH), 70.82 (CHOH), 70.76 (CHOH), 70.47 (CHOH), 70.19 (CHOH), 70.07 (CHOH), 70.03 (CHOH), 69.80 (CHOH), 69.60 (CHOH), 69.54 (CHOH), 69.35 (CHOH), 68.99 (CHOH), 68.67 (CHOH), 64.07 (CH₂OH), 63.88 (CH₂OH), 63.56 (CH₂OH), 63.01 (CH₂OH), 62.95 (CH₂OH), 35.81 (CH₂CHOH), 35.77 (CH₂CHOH), 35.70 (CH₂CHOH), 35.51 (CH₂CHOH), 35.38 (CH₂CHOH), 18.90 (CH₂), 18.85 (CH₂), 18.67 (CH₂), 18.61 (CH₂), 18.59 (CH₂), 14.43 (CH₃), 14.39 (2 CH₃), 14.31 (CH₃), 14.27 (CH₃); HRMS (ESI⁺): calcd. for C₁₀H₂₂NaO₇ [M + Na]⁺, 277.1258, found 277.1249.

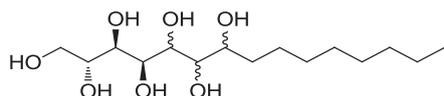


Undecane-1,2,3,4,5,6,7-heptaol (48). The title compound was obtained from aldol adduct (200 mg, 0.75 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (191 mg, 95%) as a white solid isomer (mp = 114°C). IR (ν_{\max}): 3258 (br, O-H), 2953, 2913, 2871 (C-H stretching), 1077, 1016 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ 4.80-3.90 (m, 7H, -OH), 3.78-3.37 (m, 8H, 6CHOH, 1CH₂OH), 1.45-1.25 (m, 6H, 3CH₂), 0.86 (t, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, *d*₆-DMSO): δ 74.64 (CHOH), 73.89 (CHOH), 73.65 (CHOH), 73.59 (CHOH), 73.46 (CHOH), 72.83 (CHOH), 72.67 (CHOH), 72.61 (CHOH), 71.97 (CHOH), 71.88 (CHOH), 71.77 (CHOH), 71.74 (CHOH), 71.68 (CHOH), 71.48 (CHOH), 71.36 (CHOH), 71.27 (CHOH), 70.89 (CHOH), 70.78 (CHOH), 70.21 (CHOH), 69.94 (CHOH), 69.82 (CHOH), 69.56 (CHOH), 69.39 (CHOH), 68.71 (CHOH), 64.09 (CH₂OH), 63.90 (CH₂OH), 63.58 (CH₂OH), 63.22 (CH₂OH), 33.43 (CH₂CHOH), 33.30 (CH₂CHOH), 32.99 (CH₂CHOH), 32.87 (CH₂CHOH), 28.16 (CH₂), 28.04 (CH₂), 27.79 (CH₂), 27.72 (CH₂), 22.60 (CH₂), 22.54 (CH₂), 22.51 (CH₂), 22.48 (CH₂), 14.29 (CH₃), 14.28 (CH₃), 14.24 (2 CH₃); HRMS (ESI⁺): calcd. for C₁₁H₂₄NaO₇ [M + Na]⁺, 291.1414, found 291.1408.

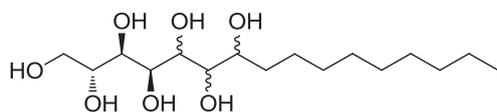


Tridecane-1,2,3,4,5,6,7-heptaol (49). The title compound was obtained from aldol adduct (200 mg, 0.68 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (173 mg, 86%) as a light yellow solid isomer (mp = 132°C). IR (ν_{\max}): 3242 (br, O-H), 2953, 2910, 2871, 2855 (C-H stretching), 1076, 1015 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ 4.78-3.87 (m, 7H, -OH), 3.79-3.29 (m, 8H, 6CHOH, 1CH₂OH), 1.44-1.26 (m, 10H, 5CH₂), 0.86 (t, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, *d*₆-DMSO): δ 73.88 (CHOH), 73.65 (CHOH), 73.42 (CHOH), 73.12 (CHOH), 72.75 (CHOH), 72.62 (CHOH), 72.58 (CHOH), 72.39 (CHOH),

71.93 (CHOH), 71.76 (CHOH), 71.73 (CHOH), 71.52 (CHOH), 71.39 (CHOH), 71.20 (CHOH), 70.73 (CHOH), 70.61 (CHOH), 70.52 (CHOH), 70.32 (CHOH), 70.15 (CHOH), 69.85 (CHOH), 69.75 (CHOH), 69.28 (CHOH), 68.91 (CHOH), 66.09 (CHOH), 63.96 (CH₂OH), 63.51 (CH₂OH), 63.14 (CH₂OH), 62.89 (CH₂OH), 33.56 (CH₂CHOH), 33.48 (CH₂CHOH), 33.26 (CH₂CHOH), 32.85 (CH₂CHOH), 31.50 (CH₂), 31.49 (CH₂), 29.04 (CH₂), 29.00 (CH₂), 25.74 (CH₂), 25.69 (CH₂), 25.48 (CH₂), 25.44 (CH₂), 23.54 (CH₂), 23.39 (CH₂), 22.79 (CH₂), 22.75 (CH₂), 22.25 (CH₂), 22.22 (CH₂), 17.68 (CH₂), 17.21 (CH₂), 14.08 (2 CH₃), 13.37 (2 CH₃); HRMS (ESI⁺): calcd. for C₁₃H₂₈NaO₇ [M + Na]⁺, 319.1727, found 319.1722.

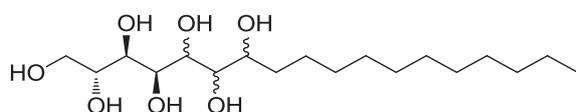


Pentadecane-1,2,3,4,5,6,7-heptaol (50). The title compound was obtained from aldol adduct (200 mg, 0.62 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (180 mg, 89%) as a light yellow solid isomer (mp = 158°C). IR (ν_{\max}): 3288(br, O-H), 2913, 2848 (C-H stretching), 1067, 1024 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ 4.78-3.90 (m, 7H, -OH), 3.79-3.36 (m, 8H, 6CHOH, 1CH₂OH), 1.41-1.25 (m, 14H, 7CH₂), 0.85 (t, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (101 MHz, *d*₆-DMSO): δ 74.58 (CHOH), 73.58 (CHOH), 73.52 (CHOH), 73.37 (CHOH), 72.71 (CHOH), 72.59 (CHOH), 71.99 (CHOH), 71.92 (CHOH), 71.74 (CHOH), 71.66 (CHOH), 71.59 (CHOH), 71.38 (CHOH), 71.25 (CHOH), 71.18 (CHOH), 70.79 (CHOH), 70.70 (CHOH), 70.13 (CHOH), 69.84 (CHOH), 69.47 (CHOH), 69.23 (CHOH), 69.19 (CHOH), 68.90 (CHOH), 68.59 (CHOH), 67.40 (CHOH), 64.00 (CH₂OH), 63.81 (CH₂OH), 63.50 (CH₂OH), 63.33 (CH₂OH), 33.66 (CH₂CHOH), 33.54 (CH₂CHOH), 33.24 (CH₂CHOH), 33.11 (CH₂CHOH), 31.41 (2 CH₂), 29.50 (CH₂), 29.45 (CH₂), 29.40 (CH₂), 29.36 (CH₂), 29.34 (CH₂), 29.33 (CH₂), 29.20 (2 CH₂), 28.82 (2 CH₂), 25.81 (CH₂), 25.70 (CH₂), 25.46 (CH₂), 25.40 (CH₂), 23.51 (CH₂), 23.36 (CH₂), 22.75 (CH₂), 22.71 (CH₂), 22.20 (2 CH₂), 17.64 (CH₂), 17.17 (CH₂), 14.03 (2 CH₃), 13.33 (2 CH₃); HRMS (ESI⁺): calcd. for C₁₅H₃₂NaO₇ [M + Na]⁺, 347.2040, found 347.2033.



Hexadecane-1,2,3,4,5,6,7-heptaol (51). The title compound was obtained from aldol adduct (200 mg, 0.60 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (169 mg, 84%) as a light yellow solid isomer (mp = 180°C). IR (ν_{\max}): 3263 (br, O-H), 2914, 2848 (C-H stretching), 1068, 1025 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ 4.78-3.91 (m, 7H, -OH), 3.79-3.35 (m, 8H, 6CHOH, 1CH₂OH), 1.39-1.25 (m, 16H, 8CH₂), 0.86 (t, *J* = 6.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, *d*₆-DMSO): δ 74.57 (CHOH), 73.57

(CHOH), 73.51 (CHOH), 73.35 (CHOH), 72.70 (CHOH), 72.58 (CHOH), 71.91 (CHOH), 71.73 (CHOH), 71.64 (CHOH), 71.59 (CHOH), 71.37 (CHOH), 71.24 (CHOH), 71.18 (CHOH), 70.78 (CHOH), 70.70 (CHOH), 70.39 (CHOH), 70.30 (CHOH), 70.12 (CHOH), 69.83 (CHOH), 69.46 (CHOH), 69.22 (CHOH), 68.89 (CHOH), 68.58 (CHOH), 67.39 (CHOH), 64.00 (CH₂OH), 63.80 (CH₂OH), 63.49 (CH₂OH), 63.33 (CH₂OH), 33.66 (CH₂CHOH), 33.54 (CH₂CHOH), 33.23 (CH₂CHOH), 33.10 (CH₂CHOH), 31.39 (4 CH₂), 29.43 (CH₂), 29.38 (CH₂), 29.32 (2 CH₂), 29.23 (2 CH₂), 29.11 (2 CH₂), 28.82 (4 CH₂), 25.80 (CH₂), 25.69 (CH₂), 25.46 (CH₂), 25.40 (CH₂), 23.50 (CH₂), 23.35 (CH₂), 22.73 (CH₂), 22.69 (CH₂), 22.18 (2 CH₂), 17.62 (CH₂), 17.15 (CH₂), 14.01 (2 CH₃), 13.32 (2 CH₃); HRMS (ESI⁺): calcd. for C₁₆H₃₄NaO₇ [M + Na]⁺, 361.2197, found 361.2192.



Octadecane-1,2,3,4,5,6,7-heptaol (52). The title compound was obtained from aldol adduct (200 mg, 0.55 mmol), following the general procedure C. The residue was filtrated with EtOH and evaporated at reduced pressure to give heptaol (175 mg, 87%) as a white solid isomer (mp = 202°C). IR (ν_{\max}): 3286 (br, O-H), 2916, 2848 (C-H stretching), 1068, 1023 (C-O stretching); ¹H NMR (300 MHz, *d*₆-DMSO): δ 4.77-3.76 (m, 7H, -OH), 3.71-3.34 (m, 8H, 6CH₂OH, 1CH₂OH), 1.43-1.24 (m, 20H, 10CH₂), 0.86 (t, *J* = 6.0 Hz, 3H, CH₃); ¹³C NMR (101 MHz, *d*₆-DMSO): δ 73.60 (CHOH), 73.36 (CHOH), 72.70 (CHOH), 72.59 (CHOH), 72.53 (CHOH), 71.91 (CHOH), 71.80 (CHOH), 71.70 (CHOH), 71.58 (CHOH), 71.50 (CHOH), 71.37 (CHOH), 71.24 (CHOH), 71.17 (CHOH), 70.70 (CHOH), 70.45 (CHOH), 70.11 (CHOH), 69.81 (CHOH), 69.21 (CHOH), 63.48 (CH₂OH), 63.12 (CH₂OH), 62.72 (CH₂OH), 33.54 (CH₂CHOH), 33.24 (CH₂CHOH), 32.60 (CH₂CHOH), 31.38 (3 CH₂), 29.45 (2 CH₂), 29.37 (CH₂), 29.33 (CH₂), 29.28 (CH₂), 29.24 (3 CH₂), 29.18 (3 CH₂), 29.12 (3 CH₂), 29.04 (CH₂), 28.81 (3 CH₂), 25.70 (CH₂), 25.57 (CH₂), 25.47 (CH₂), 22.17 (3 CH₂), 14.00 (3 CH₃); HRMS (ESI⁺): calcd. for C₁₈H₃₈NaO₇ [M + Na]⁺, 389.2510, found 389.2495.

3 Experiment part for chapter 4.

3.1 General information

All reagents were used as received from the chemical company. Hydrocinamaldehyde were supplied by Sigma-Aldrich or Alfa-Aesar, and were purified by distillation before use. Reactions were monitored by TLC (thin-layer chromatography) using aluminium silica gel (60F₂₅₄) and chromatography was performed using silica 60M (0.04–0.063 mm). ¹H and ¹³C NMR spectra were recorded on a Brüker DRX 300 or Brüker ALS 300 in CDCl₃, DMSO-*d*₆ or CD₃OD solutions using tetramethylsilane (TMS) as an internal standard. Electrospray ionization (ESI), High resolution mass spectra (HRMS) were recorded on a MicroTOFQ-II, Bruker Daltonics spectrometer instrument using standard conditions (ESI, 70 eV).

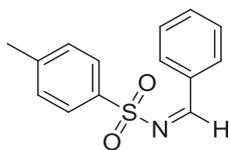
3.2 General procedures for the aldolisation.

In a sealed tube, D-fructose (4.00 g, 22.2 mmol, 20 equiv.) or 1,3-dihydroxyacetone (500 mg, 5.6 mmol, 5 eq.) was dissolved in a 1:1 mixture of EtOH (2 mL) and water (2 mL). Then trimethylamine (0.13 mL, 0.56 mmol, 0.5 equiv.) and other substrates (1 equiv.) were added into the solution. The mixture was heated with traditional heating or under microwave irradiation at 60 °C/80 °C for 2 hours. After reaction, the solvent was removed in vacuum, and the residue was purified by column chromatography (CH₂Cl₂/MeOH or cyclo/EtOAc) to give aldolisation products.

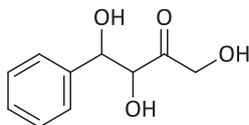
3.3 General procedures for tosylimine preparation.

In a 100 mL round flask, benzaldehyde (5 g, 47.2 mmol, 1 eq.) and p-toluenesulfonamide (8 g, 46.8 mmol, 1 eq.) were mixed together and heated to reflux (100-110 °C). Boron trifluoride etherate (0.11 g, 0.75 mmol, 0.016 eq.) was added into the reaction then. The reaction was left over night and the solvents were removed under decreased pressure. Extraction was done with CH₂Cl₂ and water for three times. Then cyclohexane/EtOAc was used to make recrystallisation. Filtration to obtain the desired tosylimine product.

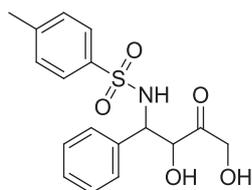
3.4 NMR Spectrum data.



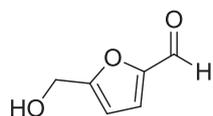
N-benzylidene-4-methylbenzenesulfonamide (61). The title compound was obtained from *p*-toluenesulfonamide (8 g, 46.8 mmol) and benzaldehyde (5 g, 47.2 mmol), boron trifluoride etherate (0.11 g, 0.75 mmol), following the general procedure. The residue was extracted with 3×50 mL CH₂Cl₂/water and then recrystallized by cyclo/EtOAc to give tosylimine (10.6 g, 87%) as a white solid. $R_f = 0.3$ (cyclo/EtOAc, 6:1, v/v). ¹H NMR (300 MHz, CD₃OD): δ : 9.06 (s, 1H, N=C-H), 7.99-7.25 (m, 9H, Ar-H), 2.45 (s, 3H, CH₃); ¹³C NMR (75 MHz, CD₃OD): δ : 170.80 (N=C), 143.09, 139.46, 138.64, 130.86, 129.65, 129.09, 128.99, 128.03, 127.95, 127.71, 126.53, 125.88 (Ar-C), 20.20, 20.05 (CH₃); MS (ESI⁺): $m/z = 260.0$ ([C₁₄H₁₃NO₂S + H]⁺), 282.0 ([C₁₄H₁₃NO₂S + Na]⁺).



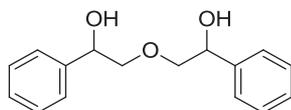
1,3,4-trihydroxy-4-phenylbutan-2-one (62). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and tosylimine (288 mg, 1.1 mmol), following the general procedure. The residue was purified by column chromatography (CH₂Cl₂/MeOH, 25 : 1 v/v) to give α -hydroxyketone (88 mg, 40%) as a transparent oil. The product was obtained as a 66:34 mixture of diastereoisomers as determined by ¹H NMR (integration of the proton on the -CH next to the carbonyl group). $R_f = 0.5$ (CH₂Cl₂/MeOH, 8:1, v/v). ¹H NMR (300 MHz, CD₃OD): δ : 8.06-7.99 (m, 2H, Ar-H), 7.69-7.60 (m, 1H, Ar-H), 7.57-7.50 (m, 2H, Ar-H), 5.31 (d, $J = 1.9$ Hz, 1H, CHOH), 5.14 (d, $J = 5.9$ Hz, 1H, CHOH), 4.02-3.93 (m, 1H, CHCHOH), 3.81-3.60 (m, 2H, CH₂OH); ¹³C NMR (75 MHz, CD₃OD): δ : 200.90, 200.50 (C=O), 136.10, 134.60, 133.27, 133.07, 128.45, 128.25 (Ar-H), 73.62, 73.39 (CHOH), 73.26, 72.75 (CHOH), 65.40, 62.46 (CH₂OH); MS (ESI⁺): $m/z = 219.1$ ([C₁₀H₁₂O₄ + Na]⁺), 415.1 ([C₁₀H₁₂O₄ + Na]⁺).



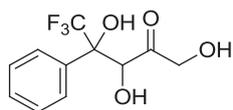
N-(2,4-dihydroxy-3-oxo-1-phenylbutyl)-4-methylbenzenesulfonamide (63). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (500 mg, 5.6 mmol) and tosylimine (288 mg, 1.1 mmol), following the general procedure. The residue was purified by column chromatography (cyclo/EtOAc, 2 : 1 v/v) to give desired product (45 mg, 12%) as a transparent oil. $R_f = 0.1$ (cyclo/EtOAc, 1:2, v/v). ^1H NMR (300 MHz, CD_3OD): δ : 7.75 (d, $J = 8.3$ Hz, 1H, NH), 7.57-7.54 (m, 2H, Ar-H), 7.40-7.31 (m, 2H, Ar-H), 7.25-7.21 (m, 5H, Ar-H), 4.37 (d, $J = 7.0$ Hz, 1H, $\underline{\text{CHOH}}$), 4.23-4.08 (m, 2H, $\underline{\text{CH}_2\text{OH}}$), 3.90-3.87 (m, 1H, $\underline{\text{CHNH}}$), 2.39 (s, 3H, CH_3); MS (ESI $^+$): $m/z = 372.0$ ($[\text{C}_{17}\text{H}_{19}\text{O}_5\text{S} + \text{Na}]^+$), 721.1 ($[\text{2 C}_{17}\text{H}_{19}\text{O}_5\text{S} + \text{Na}]^+$).



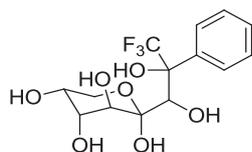
5-hydroxymethylfurfural (64). The title compound was obtained as a byproduct from D-fructose (4 g, 22.2 mmol) and tosylimine (288 mg, 1.1 mmol), following the general procedure. The residue was purified by column chromatography (cyclo/EtOAc, 1 : 1 v/v) to 5-HMF (55 mg, 2%) as a white solid. $R_f = 0.5$ (cyclo/EtOAc, 1:4, v/v). ^1H NMR (300 MHz, CD_3OD): δ : 9.55 (s, 1H, CHO), 7.40 (d, $J = 3.6$ Hz, 1H, Ar-H), 6.60 (dt, $J = 3.6, 0.6$ Hz, 1H, Ar-H), 4.91 (s, 2H, CH_2OH); ^{13}C NMR (75 MHz, CD_3OD): δ : 178.16 (C=O), 161.65, 152.57, 123.42, 109.60 (4 Ar-H), 56.21 (CH_2OH); MS (ESI $^+$): $m/z = 149.0$ ($[\text{C}_6\text{H}_6\text{O}_3 + \text{Na}]^+$), 298.0 ($[\text{2 C}_6\text{H}_6\text{O}_3 + \text{2Na}]^+$).



2,2'-oxybis(1-phenylethanol) (66). The title compound was obtained as a byproduct from 1,3-dihydroxyacetone (1 g, 11.1 mmol) and styrene oxide (267 mg, 2.2 mmol), following the general procedure. The residue was purified by column chromatography (DCM/MeOH, 60: 1 v/v) to the hydrolysis product (60 mg, 20%) as light yellow oil. $R_f = 0.3$ (DCM/MeOH, 20 : 1 v/v). ^1H NMR (300 MHz, CD_3OD): δ : 7.41-7.37 (m, 5H, Ar-H), 7.35-7.24 (m, 5H, Ar-H), 4.70 (dd, $J = 6.9, 5.2$ Hz, 2H, 2 $\underline{\text{CHOH}}$), 3.64 (d, $J = 0.5$ Hz, 2H, $\underline{\text{CH}_2\text{O}}$), 3.62 (d, $J = 2.6$ Hz, 2H, $\underline{\text{CH}_2\text{O}}$); ^{13}C NMR (75 MHz, CD_3OD): δ : 141.90, 127.83, 127.10, 125.99 (12 Ar-H), 74.56 (2 CH_2O), 67.36 (2 $\underline{\text{CHOH}}$); MS (ESI $^+$): $m/z = 281.09$ ($[\text{C}_{16}\text{H}_{18}\text{O}_3 + \text{Na}]^+$).



5,5-trifluoro-1,3,4-trihydroxy-4-phenylpentan-2-one (68). The title compound was obtained from 1,3-dihydroxyacetone (DHA) (1 g, 11.1 mmol) and trifluoroacetophenone (0.31 mL, 2.2 mmol), following the general procedure. The residue was purified by column chromatography (cyclo/EtOAc, 2 : 1 v/v) to give desired product (210 mg, 36%) as a transparent oil. The product was obtained as a 70:30 mixture of diastereoisomers as determined by ^1H NMR (integration of the proton on the $-\text{CH}$ next to the carbonyl group). $R_f = 0.6$ (cyclo/EtOAc, 1:4, v/v). ^1H NMR (300 MHz, CD_3OD): δ for the major isomer: 7.72-7.58 (m, 2H, Ar-H), 7.45-7.35 (m, 3H, Ar-H), 5.53 (d, $J = 4.4$ Hz, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.64 (d, $J = 5.2$ Hz, 1H, $\underline{\text{CH}_2\text{OH}}$), 4.08 (s, 1H, $\underline{\text{CHOH}}$); ^{13}C NMR (75 MHz, CD_3OD): δ : 207.27 (C=O), 135.04 (CF_3), 128.48, 127.95, 127.60, 126.15 (6 Ar-H), 77.37 ($\underline{\text{CHOH}}$), 66.17 ($\underline{\text{CH}_2\text{OH}}$); MS (ESI $^+$): $m/z = 287.0499$ ($[\text{C}_{11}\text{H}_{11}\text{F}_3\text{O}_4 + \text{Na}]^+$), 551.1111 ($[2 \text{C}_{11}\text{H}_{11}\text{F}_3\text{O}_4 + \text{Na}]^+$).



(2R,3S,4R,5R)-2-(3,3,3-trifluoro-1,2-dihydroxy-2-phenylpropyl)tetrahydro-2H-pyran-2,3,4,5-tetraol (69). The title compound was obtained from D-fructose (4 g, 22.2 mmol) and trifluoroacetophenone (0.16 mL, 1.1 mmol), following the general procedure. The residue was purified by column chromatography (DCM/MeOH, 12 : 1 v/v) to give desired product (60 mg, 15%) as a yellow oil. $R_f = 0.4$ (DCM/MeOH, 4:1, v/v). ^1H NMR (300 MHz, d_6 -DMSO): δ : 7.80-7.67 (m, 2H, Ar-H), 7.37-7.30 (m, 3H, Ar-H), 6.62-6.18 (m, 1H, OH), 5.81 (dd, $J = 10.9, 5.6$ Hz, 1H, OH), 5.18 (dd, $J = 11.4, 6.6$ Hz, 1H, OH), 4.87 (t, $J = 8.5$ Hz, 1H, OH), 4.64-4.37 (m, 2H, 2OH), 4.10-3.43 (m, 6H, 4 $\underline{\text{CHOH}}$, 1 $\underline{\text{CH}_2\text{OH}}$); ^{13}C NMR (75 MHz, d_6 -DMSO): δ : 140.59 (Ar-C), 134.75 (CF_3), 128.45, 128.21, 127.95, 127.42, 126.86 (5 Ar-C), 104.38, 103.94 (q- $\underline{\text{COH}}$), 82.38 (q- $\underline{\text{CCF}_3}$), 74.99, 72.68, 69.38, 63.88, 56.49 (5 $\underline{\text{CHOH}}$, 1 $\underline{\text{CH}_2\text{OH}}$); HRMS (ESI $^+$): $m/z = 377.0818$ ($[\text{C}_{14}\text{H}_{17}\text{F}_3\text{O}_7 + \text{Na}]^+$).