

SUGAR -BASED SURFACTANTS WITH AMIDE LINKAGE

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Abstract

The first part deals with the synthesis and characterization of new sugar amide based surfactants from renewable materials via Staudinger reaction. The starting materials are carbohydrates (e.g. glucose and lactose) and fatty acid derivatives based on both straight and branched carboxylic acids with a total chain length of C₈ to C₁₆. Target applications of the surfactants focus on the stabilization of emulsions, in particular water-in-oil emulsions, as well as on life-science, e.g. drug delivery. The second part of the research deals with the study of the physical and chemical properties of the synthesized surfactants, especially with respect to phase and assembly behavior, focusing on potential applications as emulsifying agents.

Three series of surfactant were synthesized from various starting materials, i.e. methyl glucoside as well as glucose and lactose based diazides. The synthetic scheme applied a multi-step methodology, including protection, activation, functionalization, Staudinger based coupling with fatty acids and finally deprotection of the surfactants. The characterization, of the surfactants used ¹H and ¹³C NMR, IR, combustion analysis as well as high resolution mass spectroscopy. Physical properties were studied by optical polarizing microscopy (OPM), differential scanning calorimetry (DSC) and surface tension measurements. Lyotropic phases were investigated by contact penetration with water and oil under the OPM, while surface tension measurements used the DuNouy ring approach. The latter enables the determination of critical micelle concentrations.

Abstrak

Bahagian pertama merupakan sintesis dan pencirian struktur molekul surfaktan baru melalui tindak balas Staudinger dan berasaskan bahan-bahan yang boleh diperbaharui. Bahan-bahan pemula tersebut adalah karbohidrat (contohnya glukosa dan laktosa) dan terbitan asid-asid lemak daripada kumpulan asid karboksilik dengan rantai lurus dan bercabang serta dengan panjang rantai hidrokarbon berjumlah C_8 sehingga C_{16} . Sasaran aplikasi surfaktan ini adalah menumpu kepada penstabilan atau pengemulsian, khususnya emulsi air-dalam-minyak untuk kajian sains hayat, seperti penghantaran ubatan.

Bahagian kedua meliputi kajian sifat-sifat fizikal dan kimia terhadap surfaktan yang telah disintesis, terutamanya yang berkaitan dengan tingkah laku fasa dan susun atur, serta potensi aplikasi sebagai ejen pengemulsi.

Tiga siri surfaktan telah disintesis daripada pelbagai bahan pemula iaitu metil glukosida, glukosa dan diazida berasaskan laktosa. Skema sintesis menggunakan kaedah multi-langkah, termasuk penggunaan kumpulan perlindungan, pengaktifan, pertukaran kumpulan berfungsi, pepadanan melalui tindak balas di antara Staudinger dengan asid lemak dan akhirnya nyahperlindungan daripada surfaktan. Molekul surfaktan dianalisis menggunakan RMN 1H dan ^{13}C , infra-merah, analisis pembakaran serta spektroskopi jisim beresolusi tinggi. Sifat fizikal telah dikaji oleh mikroskop optik berpolar (OPM), perbezaan pengimbasan kalorimetri (DSC) dan ukuran ketegangan permukaan. Fasa liotropik dikaji menggunakan kaedah penembusan sentuhan oleh air dan minyak di bawah OPM, manakala pengukuran ketegangan permukaan adalah menggunakan pendekatan cincin DuNouy. Hasil pengukuran ketegangan permukaan tersebut seterusnya digunakan dalam penentuan kepekatan kritikal misel bagi surfaktan terpilih.

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List of Abbreviations

Cr	Crystalline phase`
[α] _D	Optical rotation
2-D	Two-dimensional
Ac	Acetate group
Ac ₂ O	Acetic anhydride
AcOH	Acetic acid
APGs	Alkylpolyglycoside
Ax	Axial
BF ₃ . Et ₂ O	Borontrifluoride-diethylether complex
CD ₃ OD	Deuterated methanol
CDCl ₃	Deuterated chloroform
CH ₃ Cl	Chloroform
CMC	Critical Micelle Concentration
D	Doublet
DCM	Dichloromethan
dd	Double doublet
ddd	Double double doublet
dd~t	Double doublet about triplet
dept	Distortion-less Enhancement by Polarization Transfer
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DSC	Differential Scanning Calorimetry
dt	Double triplet
Eq	Equatorial
G	Gram
Gal	Galactose
Glc	Glucose
Glc	Glycolipids
HCl	Hydrochloric acid

HMQC	Heteronuclear Multi-Quantum Correlation
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hrs	Hours
Hz	Hertz
H ₁	Hexagonal phase
Iso	Isotropic phase
J	Coupling constant
Kj	Kilo joule
L	Gel phase
M	Multiplet
mc	Center of multiplet
Mg	Milligram
Mmol	Millimole
Mol	Mole
NaOH	Sodium hydroxide
NaOMe	Sodium methoxide
NMR	Nuclear magnetic resonance
NCS	N-Chlorosuccinimide
°C	Degree Celsius
OPM	Optical polarizing microscopy
Pendant	Polarizaing enhancement nutured during attached nucleus testing
PTC	Phase transfer
R _f	Retention factor
S	Singlet
T	Triplet
tert-	Tertiary
TBAF	tert-butylammoniumfluoride
PPh ₃	Triphenylphosphine
TBDPSCl	Tert-Butylchlorodiphenylsilane

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TsOH	4-Toluene sulfonic acid monohydrate
TsCl	Tosyl chloride

Chapter 1: Introduction

1.1. Introduction

The Mediterranean cultures were the first users of natural surfactants (Myers, 2006). They produced alkali metal soaps from animal fat and ash wood, which contains potassium carbonate. The fat releases fatty acids upon saponification when boiled with ashes and subsequently forms the neutralized salts.

The first surfactants for general use were developed in Germany during the First World War in an attempt to overcome shortages of available animal and vegetable fat. They were based on short-chain alkyl-naphthalene sulfonates, which were prepared from propyl or butyl alcohol with naphthalene followed by sulfonation. The first synthetic material employed specifically for their surface-active properties was sulfated oil which was introduced in the nineteenth century as a dyeing aid. This material was obtained by treatment of castor oil with sulfuric acid. Nowadays the progress in the area of surfactants has no limitation. The availability of new chemical processes and raw material open the sky to develop a wide range of new surface-active compounds. Today, ecologic demands increasing amounts due to population growth and raw material resources are the driving forces for surfactants technology. Most of processes depend on petrochemical raw materials (Shinoda et al., 1996). Environmental issues and the shortage of latter, which is expected to increase, cause a continuous shift of chemical developments towards the utilization of renewable biological resources in order to ensure sustainable raw materials. The development of surfactants from carbohydrates and fatty acids is a strategy for the exclusive utilization of natural renewable resources. Three classes of sugar surfactant can be differentiated based on the chemical linkage of the two starting materials, i. e. glycoside, e.g. polyglucoside (APGs), alkyl glucamides and sugar esters. Each of these surfactants exhibit surface active properties, biodegradable and expected to show low

human toxicity based on the natural components and linkages. The glycosides are the most chemical resistant but expensive compared to sugar esters, which are significantly less stable. Sugar amide surfactants are reasonable chemically stable and economic. This work is aimed to:-

1. Synthesis new sugar amide
2. Study the Physiochemical properties of the synthesized surfactants

Chapter 2 : Background and literature survey

2.1. Surfactants

Surfactants or "surface-active agent" are a natural or synthetic compounds that stabilizes mixtures of two immiscible phases such as oil and water, by reducing the surface tension at the interface between them (Holmberg et al., 2002). Surfactants are usually organic compounds that are amphiphilic molecules .They possess a head group, which by itself would be soluble in water, and a hydrophobic tail that tends to minimize water contact. The head group can be anionic(sulfate, sulfonate, phosphate, carboxylate), cationic (ammonium, alkyl substituted ammonium, pyridinium), zwitterionic (betain), or nonionic (polyglycol, carbohydrate) (Hoffman and Ulbricht, 1995). The tail consists of one or more alkyl chains, which may be branched or straight as well as either saturated or unsaturated. Therefore, surfactant contains both a water insoluble (oil soluble) component and a water soluble component (figure 2-1). They are commonly used for cleaning applications and applied as emulsifier in cosmetics and pharmaceuticals (Mishra et al., 2009) as well as in food (Schramm et al., 2003) and paints industry (Bajpal and Tyagi, 2006). Besides, surfactants are used in the manufacturing of textiles (Lim et al., 2000), and plastics, in the paper industry, and in the oil production process (Schramm and Marangoni, 2000).

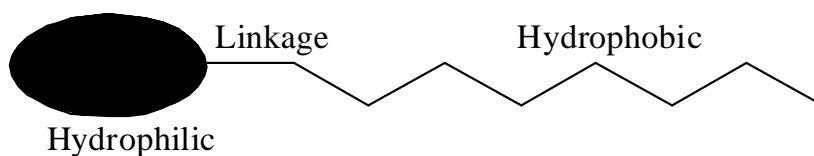


Figure 2-1: Schematic diagram of surfactant consist of hydrophilic and hydrophobic parts

2.1.1. Behaviour of Surfactants in Water

Surfactants diffuse in water and adsorb on the air surface or at the interface between oil and water, thus enabling the mixing of the two incompatible fluids. The insoluble hydrophobic group may be directed away from the water phase into the air or oil phase, while the water-soluble head group remains in the water phase (Garidel et al., 2008) figure 2-2A. This arrangement of surfactants at the surface modifies the surface properties of water at the water/air or water/oil interface. When surfactants are added to water, surfactant molecules adsorb at the surface or interface where the hydrophobic domain tries to avoid contact with water, as shown in figure 2-2B (Myers, 1999).

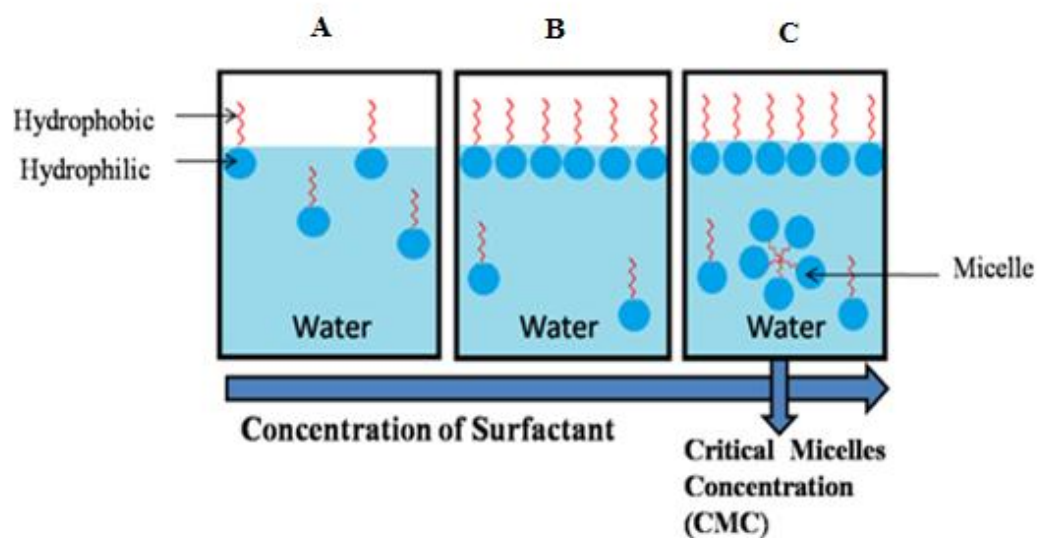


Figure 2-2: Behaviour of surfactants in water

The surfactant molecules will migrate to all available interfaces until these are blocked. After complete adsorption has taken place, additional surfactant starts to form aggregates (figure 2-2C).

Those initially formed associated aggregates of surfactants in aqueous medium are typically closed and spherical structures. Such structures are called micelles. Besides the spherical shape they can exist in other shapes, i.e. disk or rod (Zana, 1997), depending on some parameters such as the surfactant concentration, temperature, pH, ionic strength, etc. The self-association process starts at a defined concentration, which is called the critical micelles concentration, CMC.

2.1.2. Krafft Temperature T_k

The Krafft temperature, or critical micelle temperature, is the temperature at which the solubility of surfactants becomes high enough to form micelles. There is no possibility to form micelles below this temperature, whatever the quantity of surfactant may be. The Krafft temperature can be defined as the intersection of the solubility curve and the CMC curve as shown below in figure. 2-3 .The Krafft temperature depends on both the hydrophilic and the hydrophobic moieties of the surfactant (Holder et al., 2012).

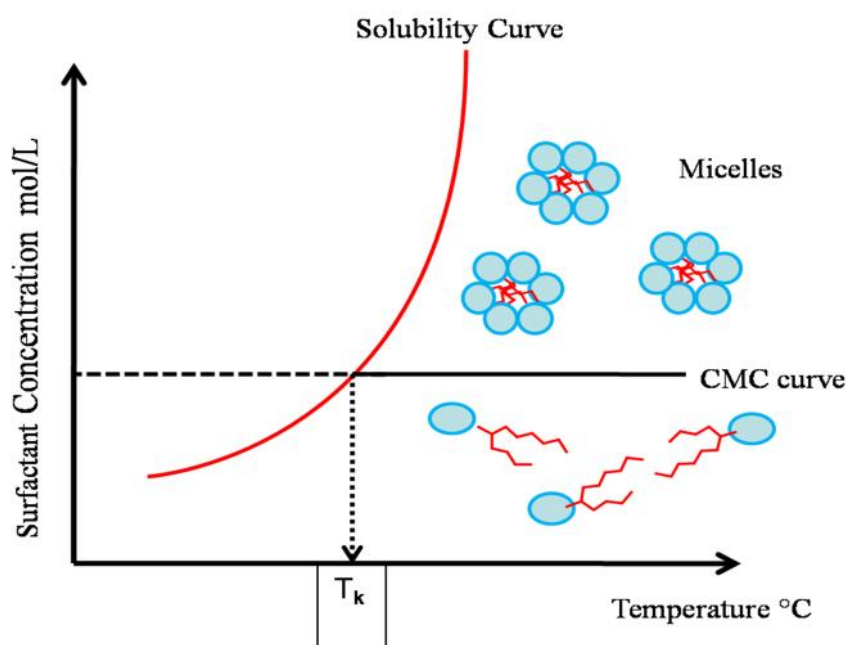


Figure 2-3: The relation between T_k and CMC

2.1.3. Surfactant and surface tension

Water molecules at the surface orientate each other's in order to maximize interaction with each other, so they look like holding hands due the hydrogen bonds. This force is relatively strong and is manifested in the high surface tension of water, about 72 mN/m. When surfactant adds to the water, the polar part of the surfactants associated with the surrounding molecules of water and ions by electrostatic interactions, especially hydrogen bonding. The non-polar domain on the other hand, associates with neighboring non-polar structures via Van Der Waals interaction. The disruption of the hydrogen bonds between the water molecules and the hydrophobic interaction of the hydrophobic domain of the surfactant reduce the surface tension of water (figure 2-4). Some surfactants can be reduced the surface tension below 30 mN/m (Rosen, 2004).

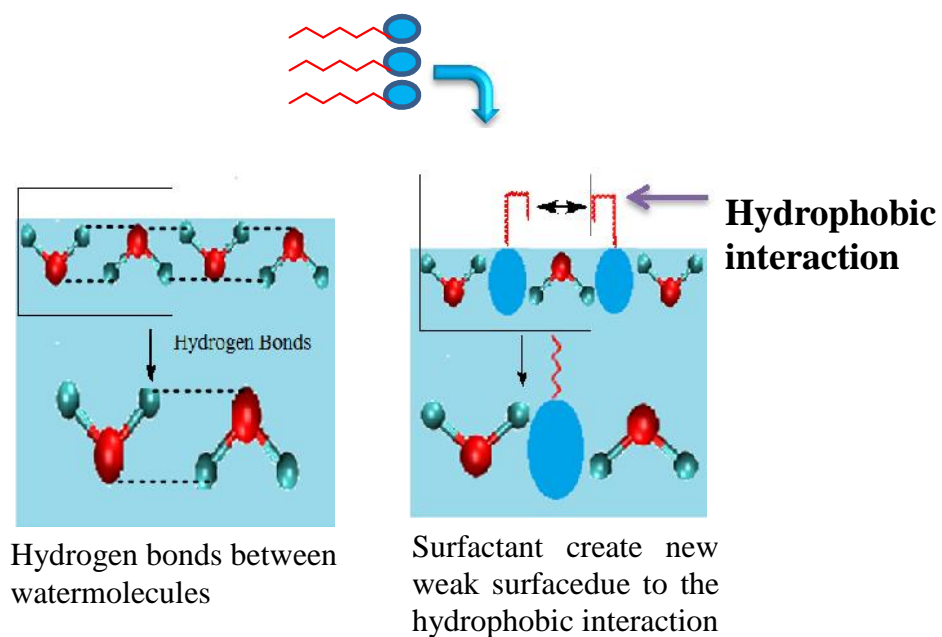


Figure 2-4: Effects of surfactants in water

2.1.4. Classification of Surfactants

Surfactants are usually classified according to the charge of their polar head group into four categories (Mishra et al., 2009).

2.1.4.1. Anionic surfactants

Anionic surfactants dissociate in water to form an amphiphilic anion and positively charge counter ion. They are the most commonly used surfactants, including carboxylic acids and salt, sulfuric and phosphoric acid derivatives and sulfonic acids. Some anionic surfactantsalts exhibit biological activity (Cserháti et al., 2002) an example is sodium dodecyl sulfate figure 2-5.

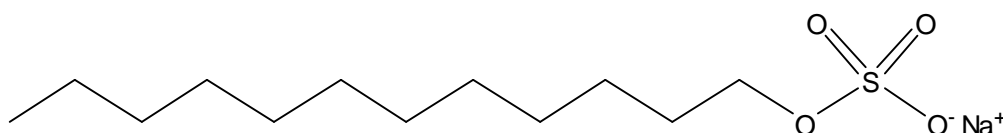


Figure 2-5: Sodium dodecyl sulfate

2.1.4.2. Cationic surfactants

Cationic surfactants are commonly long chain alkyl amines and their salts, especially quaternary ammonium salts, e.g. imidazolines (Bajpai and Tyagi, 2006, Kanga et al., 2011). Initially fatty amines are neutral and not cationic surfactants. However, they are generally classified under cationic because they are usually used at acidic pH, at which they form cationic salt (Salager, 2002). An example is dodecyltrimethylammonium chloride figure 2-6.

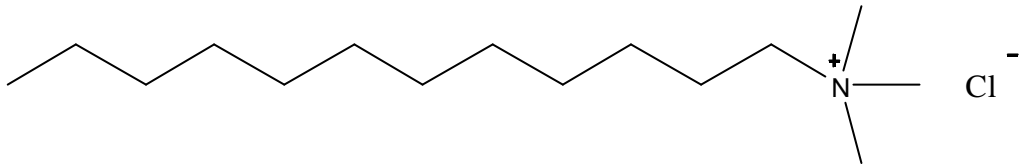


Figure 2-6: Dodecyltrimethylammonium chloride

2.1.4.3. Amphoteric surfactants

Amphoteric surfactants are characterized by the presence of both cationic and anionic charges on the surfactant. They can turn into either an anionic or a cationic surfactant, depending on the pH. Betaines are most common industrial examples of this type of surfactant as well as lauryldimethylamine oxide (LDAO) (Alargova et al., 1998). Some amphoteric surfactants are used as emulsifying agents, corrosion inhibitor and antibacterial agents (Gawish et al., 1981). An example is dipalmitoylphosphatidylcholine (DPPC), see figure 2-7.

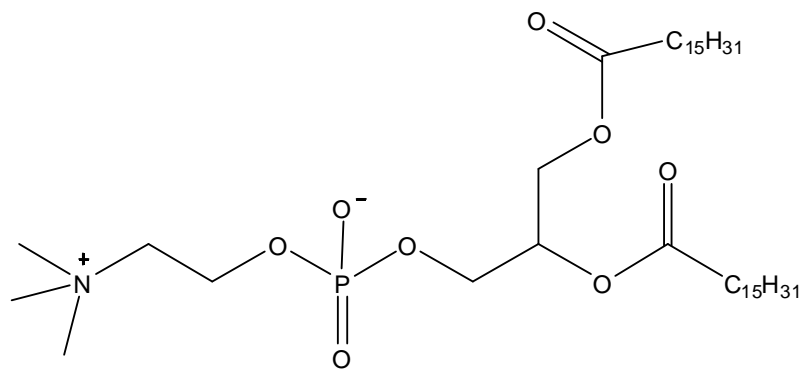


Figure 2-7: Dipalmitoylphosphatidyl choline

2.1.4.4. Nonionic surfactants

Nonionic surfactants have neutral form of polar head group. As a consequence, they are always compatible with other types of surfactants and are excellent candidates to enter complex mixtures. They are much less sensitive to electrolytes, particularly divalent cations, than ionic surfactants. They can be used at high salinity or hard water. Some of them exhibit a very low toxicity level that useful in pharmaceuticals, cosmetics (Bailey and Joseph, 1991) and food products. These surfactants involve alkylpolyglucosides, carbohydrate esters, polyethylene oxide based surfactants and sulphonamides (Ahmed, 2010) an example is Lauryl glucoside figure 2-8.

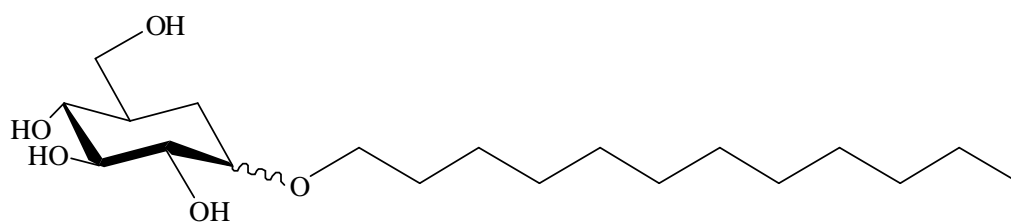


Figure 2-8: Lauryl glucoside surfactant

2.2. Carbohydrate Surfactants

In recent years, scientific and industrial institutions have a great focus on renewable sources for industrial medicinal and pharmacological substances in order to reduce their environmental pollution and depending on limited petrochemical resources. The development of surfactants based on carbohydrates and vegetable oils is the result of the concept of exclusive use of natural resources. Sugar based surfactants are gaining increasing attention due to advantages regarding to performance, biodegradability, low toxicity and environmental compatibility. They also exhibit surface-active properties due to the presence of the hydrophilic sugar moiety and the hydrophobic alkyl chain

originated from fatty acids or their derivatives. The selective attachment of an alkyl chain to a carbohydrate is a challenge due to the numerous hydroxyl groups present on the sugar moiety. However, chemists have found several ways to form such linkages at different positions of sugars and described many products on various carbohydrates. Not all carbohydrates fulfill the criteria of reasonable pricing and availability to become interesting raw materials. Interesting resources include sucrose, which is easily obtainable from sugar beet or sugar cane, glucose, which is derived from starch, and sorbitol as a hydrogenated derivative of glucose.

2.2.1. Classification of carbohydrate Surfactants

Carbohydrate surfactants can be classified according to the linkages between the carbohydrate and the hydrophobic domain into glycosides, sugar esters and sugar amides. The linkage affects the physical and chemical properties of the surfactant. Esters are quite sensitive toward hydrolysis (Soderman and Ingegard, 2000, Okumura et al., 2011), while amides are significantly more resistant toward hydrolysis in both neutral and alkaline medium (Laurent et al., 2011).

2.2.1.1. Sugar ester

Sugar esters are biocompatible nonionic surfactants, which are widely used in food industry (Watanabe, 1999, Nakamura, 1999), for cosmetics, medicine (Marshall and Bullerman, 1994) and insecticides (Chortyk, 1996). Sugar esters consist of a carbohydrate hydrophilic group and a fatty acid as lipophilic group. Plants materials are common source of low fatty acids ester of sucrose as well as for glucose (Chortyk, 1996). The synthesis of sugar esters can be carried out enzymatically (Yao et al., 2007, Neta et al., 2012, Kim et al., 2004) or chemically. Chemical synthesis usually exhibit low selectivity and leads to a mixture of sugar esters differing in the degree of esterification. By controlling the esterification degree and the nature of fatty acid and sugar it is possible to

prepare sugar esters with a wide range of hydrophilic-hydrophobic balance (HLB). The physicochemical properties depend on the average degree of substitution and the fatty acid chain length.

Bollenback and Parrish reported the synthesis of methyl 6-O-lauryl- α -D-glucopyranoside by trans esterification with fatty ester catalyzed by sodium methoxide in the absence of solvent (Bollenback and Parrish, 1970), see figure 2-9.

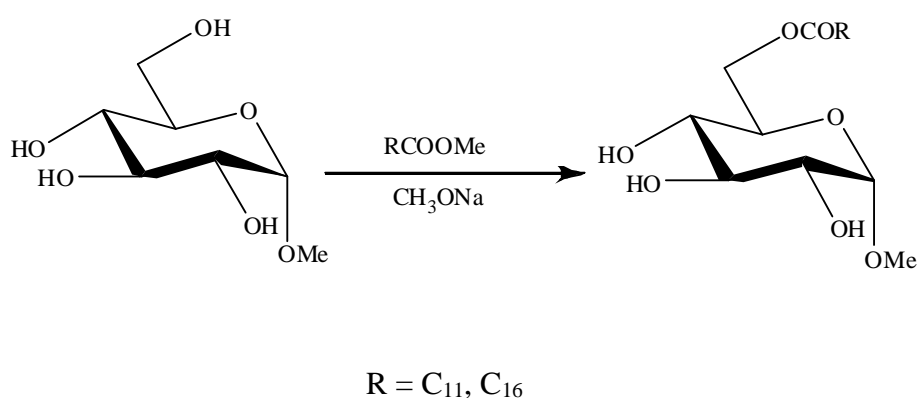


Figure 2-9: Esterification of methyl α -D-glucopyranoside

Cruces et al. have synthesized sucrose monoester by trans esterification of sucrose with corresponding vinyl esters using sodium hydrogen phosphate as catalyst and DMSO as solvent (Cruces et al., 2001). Regioselective benzylation of sucrose at the O-6 position can be obtained by exploiting a dibutylstannylene (Vlahov et al., 1996), see figure 2-10.

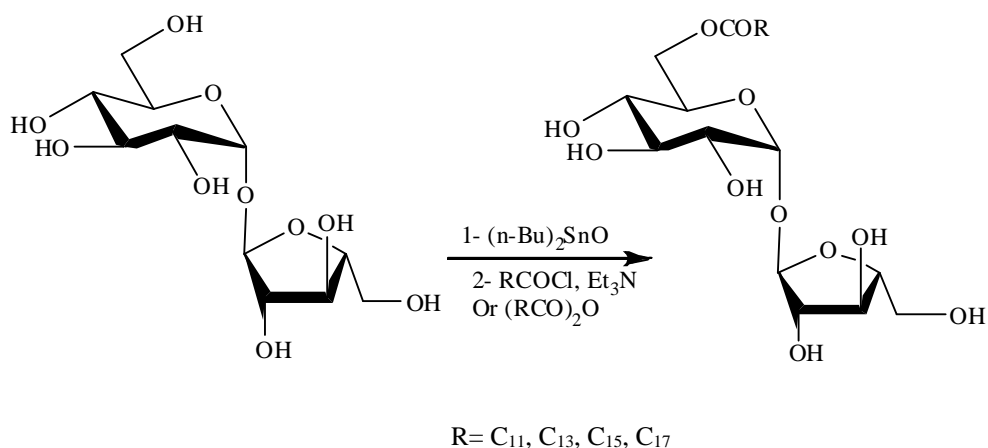


Figure 2-10: Regioselective synthesis of sucrose monoester

2.2.1.2. Glycoside

In a glycoside the carbohydrate residue is attached by an acetal linkage at the anomeric carbon to a non-carbohydrate alcohol. The non-sugar component is termed as the aglycone, while sugar component is called the glycone. If the carbohydrate portion is glucose, the resulting compound is a glucoside.

Alkyl glycosides have gained interest for industrial application such as cosmetics, food emulsifiers, lubricating (Hughes and Lew, 1970) drug carriers (Kiwada et al., 1985), solubilization of bacterial membrane protein (Baron and Thompson, 1975) and antimicrobial agents (Uchibori et al., 1990).

Glycosides can be synthesized enzymatically (Balogh et al., 2004) or chemically. The first synthesis of an alkyl glycoside was reported by Emil Fischer (Fischer, 1893). Later Koenigs and Knorr developed another synthesis approach (Koenigs and Knorr, 1901).

Milkereit and et al. synthesized long chain alkyl glycosides (C₁₂-C₁₄) by two methods. The first was applied a Lewis acid, i.e boron trifluoride diethyl etherate BF₃.OEt₂, on acetates (Helferich and Wedemeyer, 1949), while the second used a modified Koenigs and

Knorr approach and $\text{Hg}(\text{CN})_2/\text{HgBr}_2$ catalyzing, as shown in figure 2-11 (Miklkereit et al., 2004).

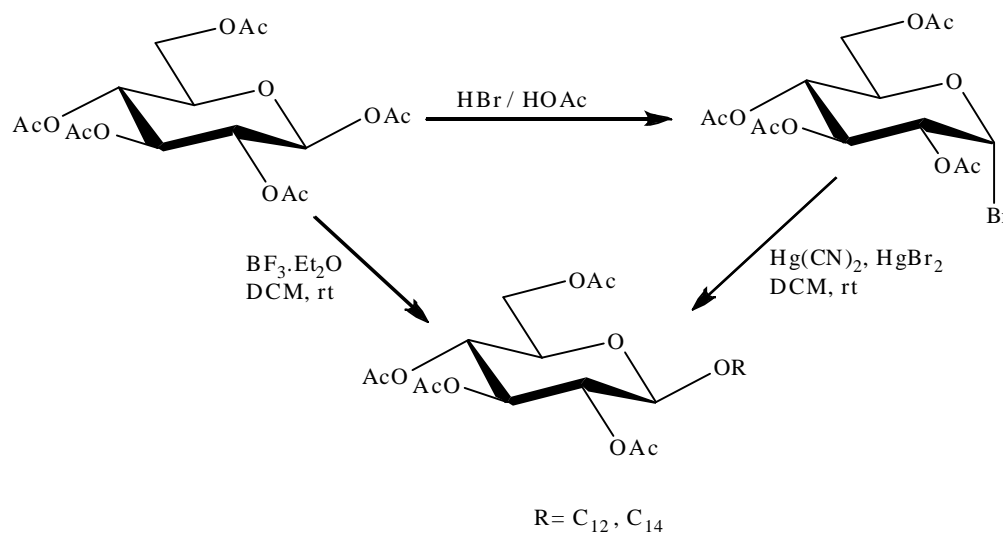


Figure 2-11: Synthesis of alkyl -D-glycopyranoside

Hashim and et al. have reported the synthesis of branched alkyl chain glycosides of both mono (figure 2-12A) and disaccharide (figure 2-12B) using $\text{BF}_3 \cdot \text{OEt}_2$. (Hashim et al., 2006a).

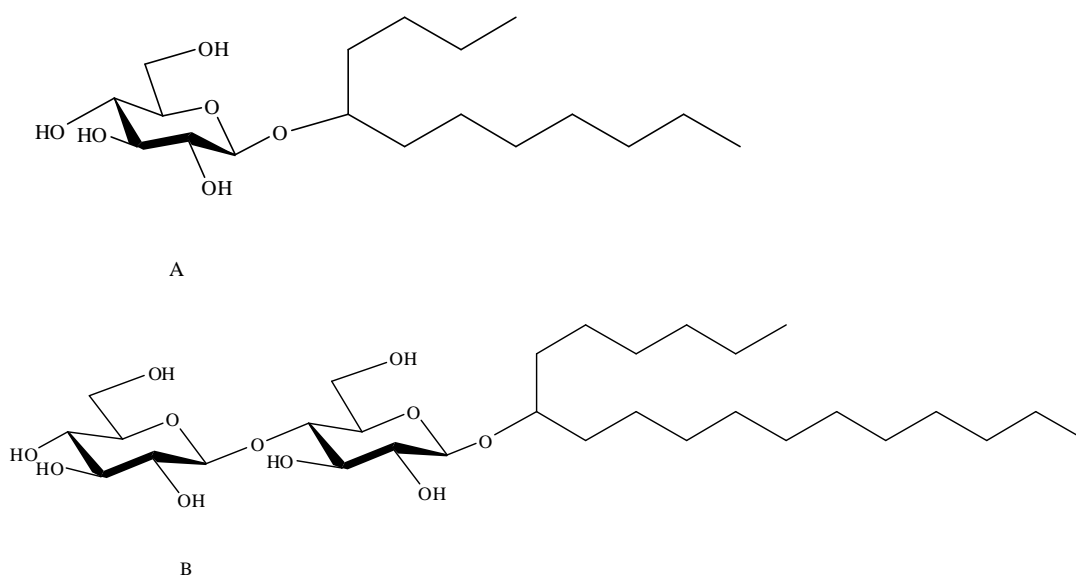


Figure 2-12: A) 2-Butyl-octyl -D-glucopyranoside b) 2-Hexy-decyl -cellobioside

Polakova and et al. have synthesized alkyl -D-mannopyranoside by using SnCl₄ treatment of the precursor in dichloromethane (Polakova et al., 2010).

2.2.1.3. Sugar amide

Sugar amides are nonionic biodegradable surfactants, in which the hydrophilic moiety is an amino sugar. The amino group is acylated by fatty acids to an amide linkage. The amide bond increases the hydrophobicity of the surfactant and is chemically stable under moderate alkaline conditions. Sugar amides can be prepared conventionally using the Schotten- Baumann reaction between an amino sugar and a fatty acid chloride (Kjellin and Johansson, 2010). Another synthesis method, which avoids salt by-products, is an enzymatic trans-acylation, e. g. by using a lipase enzyme (Maugard et al., 2001). Beside the indicated approaches, other syntheses of sugar amide have been reported. Wang have described the synthesis of *N*-lauroyl 2,3,4,6-tetra-O-acetyl-glucopyranosyl amine from glucose pentaacetate and dodecyl nitrile in the presence of AgClO₄ and TMSOTf (Wang, 2006), see figure 2-13.

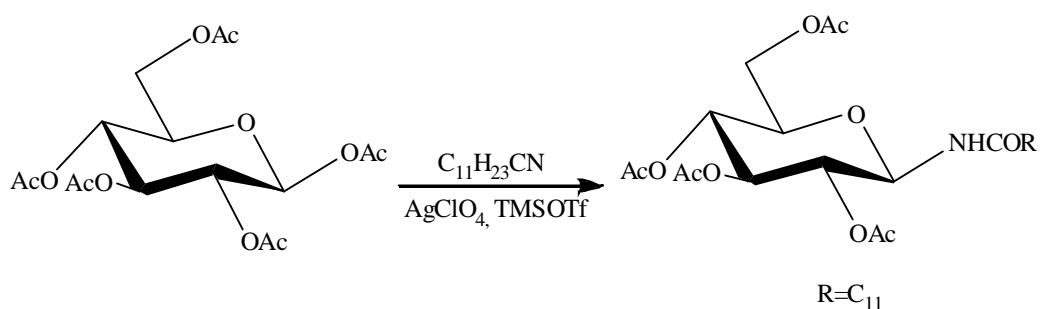


Figure 2-13: Synthesis *N*-lauroyl 2,3,4,6-tetra-O-acetyl-glucopyranosyl amine

Lubineau et al. applied an alternative three-step synthesis procedure to *N*-acyl- -D-glucopyranosylamines, as shown in figure 2-14 (Lunineau et al., 1995).

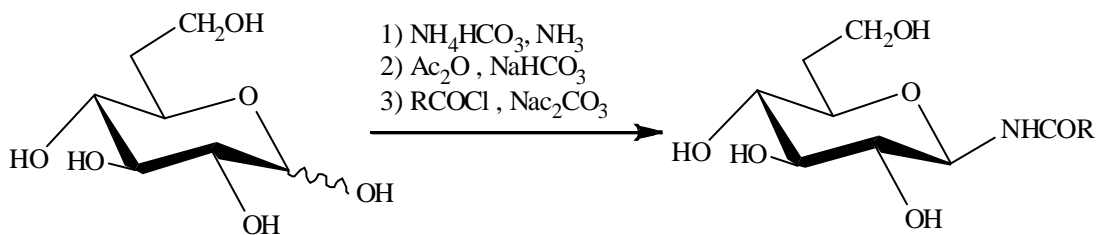


Figure 2-14: Synthesis of *N*-acyl- β -D-glucopyranosylamine

Bazito and Seoud used a Schotten–Baumann approach to synthesize 2-acylamido-2-deoxy-D-glucopyranose from 2-amino-D-glucose and dodecanoyl chloride (Bazito and Seoud, 2001b, Bazito and Seoud, 2001a), see figure 2-15.

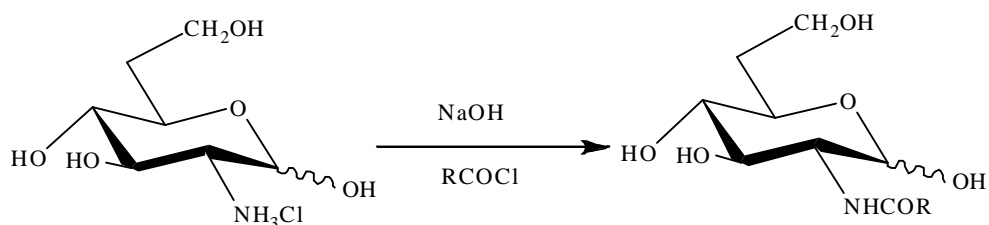


Figure 2-15: Synthesis of 2-acylamido-2-deoxy-D-glucopyranose

An alternative approach for the synthesis of sugar amides avoiding amino-sugar precursors is provided by the Staudinger reaction, which will be discussed later.

2.3. Synthesis

2.3.1. Protection groups

The biggest challenge in carbohydrate chemistry is regioselectivity because carbohydrates contain several hydroxyl groups with similar reactivity. Selective protecting groups with efficient temporary protecting became important (Dong, 2008). With recent protecting group developments there is potential for fulfilling every possible protection pattern, however efficient protecting group schemes still remain the main challenge in carbohydrate chemistry. Hydroxyl groups are commonly protected as ester, ether or acetal. The reactivity of carbohydrate hydroxyl groups differ depending on type, position and stereochemistry. In general the reactivity decrease from primary to secondary hydroxyl groups, and equatorial OH being more reactive than axial OH (Kondo, 1987). These differences in reactivity can be utilized to create a desired protection pattern. However, it may require several steps. (Kattnig and Albert, 2004, Kurahashi et al., 1999). Protection groups should satisfy several criteria; first they should only require cheap and readily available reagents, second their introduction should be in high yields, third they should be stable under the conditions and finally they should be readily removed under mild conditions. Typical carbohydrate protection schemes involve acetates, benzoates, isopropylidene and benzylidene acetals, benzyl and trityl ethers as well as silyl ethers.

2.3.1.1. Ester

Alcohols react readily with activated carboxylic acid derivatives, such as acid anhydrides or chlorides to produce the corresponding esters. Since esters are essentially non-nucleophilic they are frequently used as protecting groups in carbohydrate chemistry (Davis and Fairbanks, 2005).

Acetates are the most commonly used esters. Peracetylation of free sugar is usually undertaken in one of three ways. The first approach is using acetic anhydride in pyridine.

The reaction only requires room temperature and leads to mixture of α and β anomers, because the acetylation reaction is faster than the α / β equilibration via open chain form. The second approach applied acetic anhydride and sodium acetate at about 100 °C, which lead to pure β anomer, because the α / β equilibration is faster than acetylation. The third acetylation approach utilizes acetic anhydride and Lewis acid such as zinc chloride. This reaction leads to an anomeric mixture, However, since the β -anomer is thermodynamically favored by the anomeric effect, the dominant product is the β -anomer. Acetate groups are stable to acid conditions (Reese et al., 1975) and can easily be removed by Zemplén conditions, i.e. a catalytic amount of sodium methoxide in methanol (Mastelic et al., 2004, Zemplén et al., 1936), see figure 2-16.

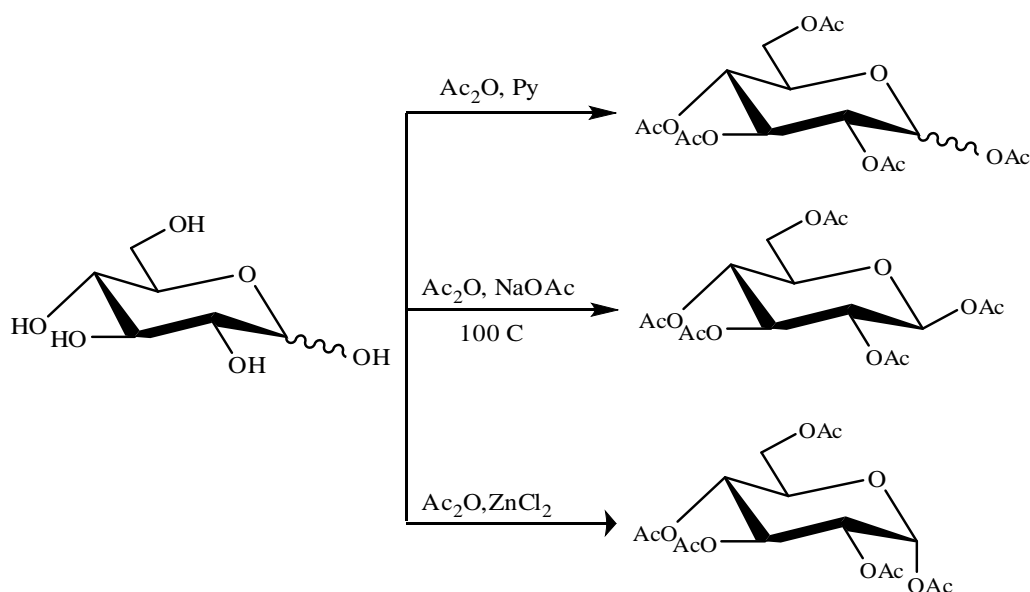


Figure 2-16: Peracetylation of sugar under various conditions

2.3.1.2. Acetals

The reaction of carbonyl groups with alcohols under acidic condition can lead to the formation of acetals. Since carbohydrates contain several hydroxyl groups, reaction of sugars with an aldehyde or ketone under acidic condition can result in the formation of cyclic acetals. Usually ketones prefer 5-ring cyclic acetal based on cis 1, 2-diols in order to prevent 1,3-diaxial repulsion between the carbon group of the ketone with the axial hydrogen atom of the sugar. Aldehydes, on other hand, prefer to form 6-ring cyclic acetals with the small (hydrogen) atom taking the axial position in a chair form.

2.3.1.2.1. Isopropylidene acetal

Cyclic acetals which results from the condensation of the two hydroxyl groups of a molecule with acetone are most commonly called acetonides (Wolefrom et al., 1974). They are extremely useful protecting groups in carbohydrate chemistry. Reactions with glycosides are usually straightforward. The simple rule is that only hydroxyl groups in cis orientation react to form cyclic 5-ring acetals. Common reagents for the protection are acetone and 2,2-dimethoxypropane $\text{Me}_2\text{C}(\text{OMe})_2$, which used under acidic catalysis. Common reagents for the deprotection are aqueous acidic, e. g. TsOH, TFA and HCl (Gelas and Horton, 1978, Gomez et al., 1999, Liptak et al., 1981).

2.3.1.2.2. Benzylidene acetal

The reaction of sugars with benzaldehyde or benzaldehyde dimethyl acetal under acidic catalysis (ZnCl_2 , TsOH) results in the formation of cyclic benzylidene acetals (Hall, 1980), figure 2-17. Aldehydes are preferentially forming 6-membered rings, which adopt a chair conformation with the bulky phenyl group in an equatorial position. Benzylidene is very selective to the 4- and 6-hydroxyl group of common carbohydrates to form either cis or trans fused bicyclic ring systems. Benzylidene can be removed either by acidic conditions

or by hydrogenation (DeNinno et al., 1995, Kojima et al., 2011). The acetals are very stable against bases.

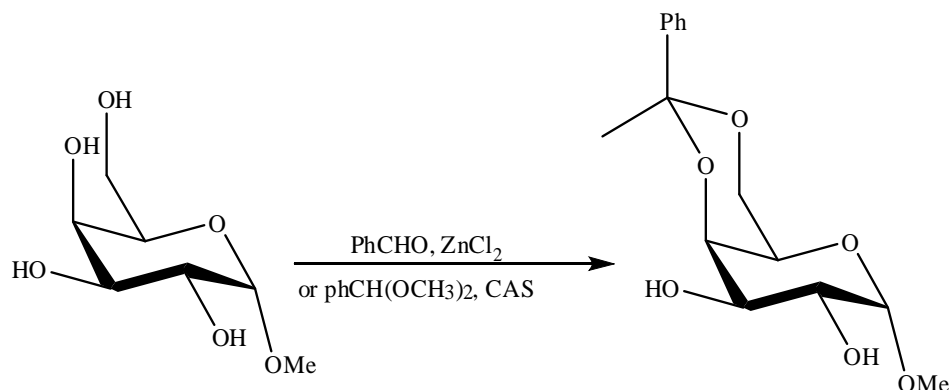


Figure 2-17: Acetal formation of methyl -D-galactopyranoside

Benzylidene acetals can be cleaved selectively under oxidative (Stevenin et al., 2010, Kumar et al., 2010, Chen and Wang, 2001, Hanessian and Plessas, 1969b) to give benzoyl ester halides, which are useful for the synthesis of deoxy sugar figure 2-18A. (Lemanski and Ziegler, 2000). Moreover benzylidene can also be cleaved also by using reducing conditions to form mono-benzyloxy alcohols (Brar and Vankar, 2006, Garegg and Hultberg, 1981), figure 2-18B. Santra reported the removal of benzylidene acetal using a mild, neutral reaction condition by combination of triethylsilane and 10% Pd/C (Santra et al., 2013), figure 2-18C.

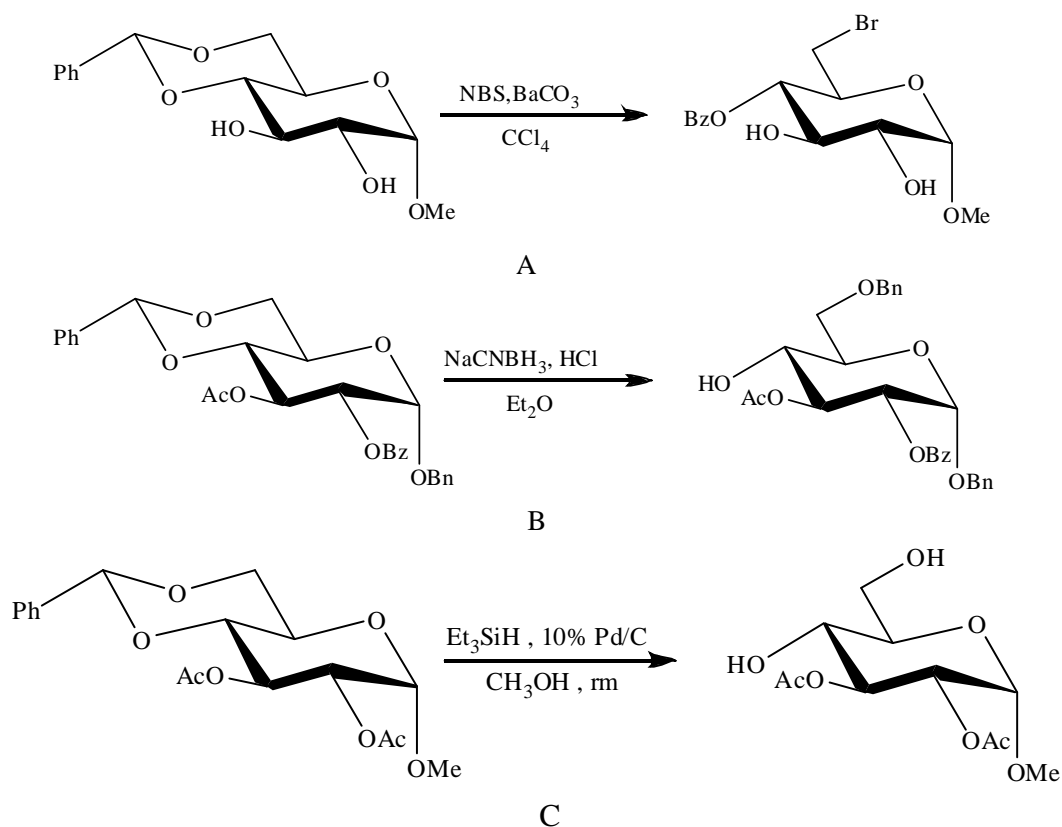


Figure 2-18: Selective cleavage of benzylidene in different conditions

2.3.1.2. Ethers

Alkyl ethers are particularly stable entities for both strong basic and strong acidic conditions. Their use as protecting groups is only limited by the requirements to selectively them. For protection groups only a few ethers can be employed, which are cleavable under mild reaction condition. Ethers are formed by the classical Williamson synthesis employing sodium hydride or sodium hydroxide as the base with respective alkyl halides.

2.3.1.2.1. Benzyl ethers

Benzyl ethers are the most common ether protecting groups used in carbohydrate chemistry. Benzyl ethers can be prepared easily by treatment of alcohols with benzyl halides, most commonly applied is benzyl bromide in the presence of a base, such as sodium hydride (Rao and Senthilkumar, 2001, Tennant-Eyles et al., 2000). Other

preparations involve treatment of alcohols with benzyl trichloroacetimidate and catalytic amount of acid, such as TfOH (Wessel et al., 1985). Benzyl ethers are most readily cleaved under very mild conditions of catalytic hydrogenation using palladium on carbon as catalytic (Colman and Shah, 1999, Smith and Notheisz, 1999) .

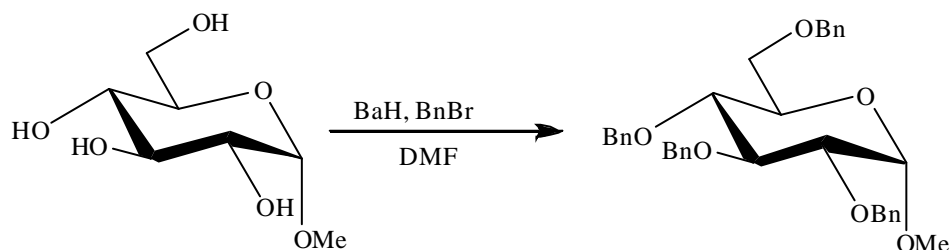


Figure 2-19: Benzylation of methyl -D-galactopyranoside

2.3.1.2.2. Trityl ethers

Trityl (triphenylmethyl) ethers are useful protecting groups as they are very selective for the primary hydroxyl groups. Trityl ethers are prepared by treatment of sugars with trityl chloride in pyridine (see figure 2-20) and cleavage under mild acidic conditions (Bessodes et al., 1986, Mazare et al., 2012).

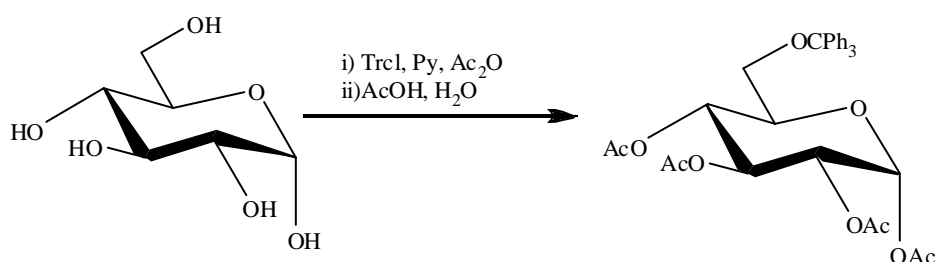


Figure 2-20: Trityl ether protection group

2.3.1.2.3. Silyl ethers

Silyl ethers are very common protecting groups. Silylations are easily achieved by using alkylated silyl chlorides under basic condition, usually pyridine and imidazole (Keliris et al., 2011, Ren et al., 2007, Xavier et al., 2009). Applying tert-butyldimethylsilyl (TMSCl)

chloride or tert-butyl diphenyldiphenylsilyl (TBDMSCl) in pyridine allows selective protection of primary hydroxyl group. Silyl ethers can be removed either by treatment with an acid (Chandra et al., 2009, Sharma et al., 2003) or treatment with a source of organic soluble fluoride, such as tertabutylammonium fluoride (TBAF).

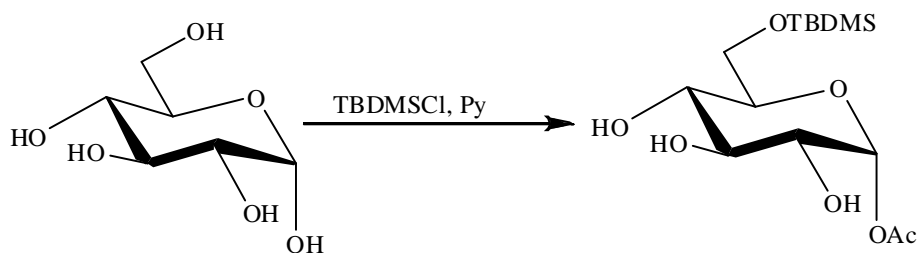


Figure 2-21: Selective protection with TBDMSCl

2.3.2. Reaction at the anomeric center

Acetylating is frequently the first step of a synthesis sequences involving sugars. The conversion of the hydroxyl group at the anomeric carbon into acetate is particularly useful since the acetate can readily act as a leaving group under the suitable reaction conditions, while at the same time enhances the solubility of sugar in solution. The substitution reaction of the leaving group at the anomeric center is enhanced by the presence of the ring oxygen. The reaction follows an S_N1 mechanism because the oxygen has lone pairs. That promotes the removal of the leaving group and stabilizes the carbonium ion intermediate by resonance (figure 2-22). The oxo-carbonium ion is attacked subsequently by the nucleophile. The incoming nucleophile can attack either face of the carbonium ion, thus leading to form of both and products (Ness and Fletcher, 1956, Ness et al., 1951).

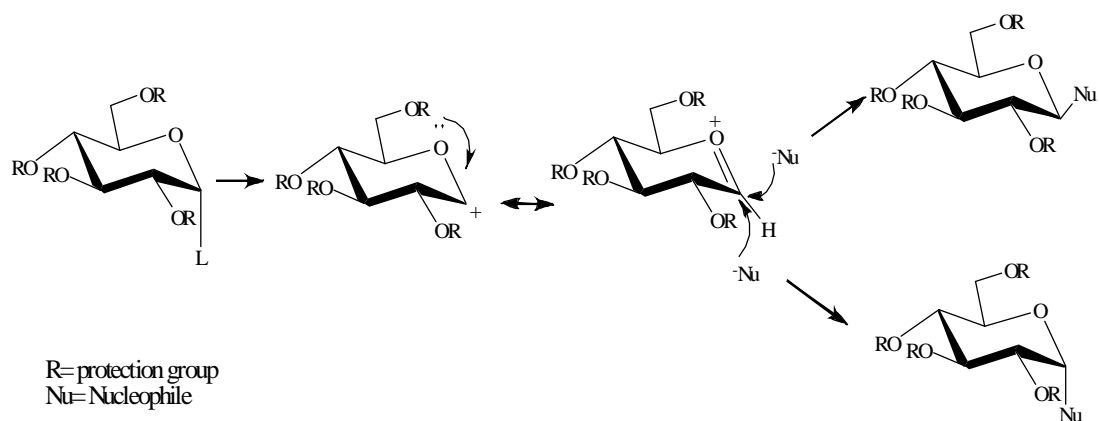


Figure 2-22: S_N1 mechanism of anomeric substitution reaction

In certain cases S_N2 type processes can occur competitively with the concomitant clean intersession of configuration at anomeric center (Boeckel et al., 1984).

One of the most effective ways to control the stereochemistry at the anomeric bond is by neighboring group participation of an ester protection group, such as acetate or benzoate, on the 2-hydroxyl group. The participation of the carbonyl oxygen can stabilize the intermediate glycosyl cation (figure 2-23) by forming a cyclic oxonium ion, which subsequently can then be opened by the external nucleophile in an S_N2 mechanism with the corresponding inversion of configuration (Davis and Fairbanks, 2005, Whitfield and Douglas, 1996, Baluja et al., 1960). The effect of the migration group are clean trans-1,2-glycosides see figure 2-23.

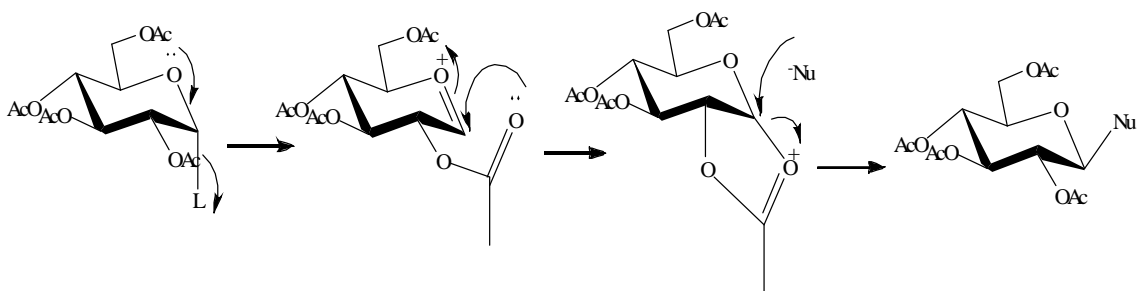


Figure 2-23: Nucleophilic reaction mechanism controlled by neighboring group

2.3.2.1. Glycosylation reaction

Glycoconjugates are compounds in which carbohydrate (glycosyl donor) is linked by an acetal at the anomeric center to another organic moiety (glycosyl acceptor) (Whitfield and Douglas, 1996) The construction of this linkages is called glycosylation (Bognar and Nansai, 1961) The stereochemistry of the glycosidic linkage can be controlled by the appropriate choice of solvent, donor (Schmidt et al., 1990) and acceptor (Spijker et al., 1993).

The first glycosylation reactions have been reported by Fischer in 1893, who reacted free sugar with alcohols under acidic condition figure 2-24 .This procedure is not stereo selective and therefore provides a mixture of anomers (Fischer, 1893).

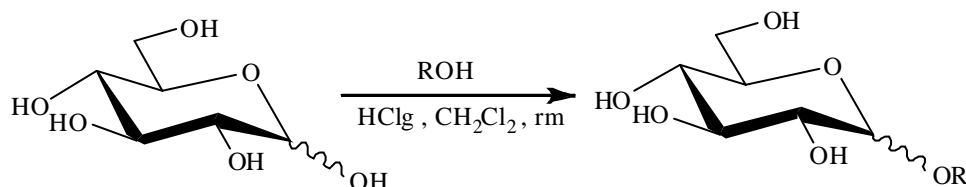


Figure 2-24: Fischer glycosylation

Koenigs and Knorr developed an alternative glycosylation in 1901 based on silver-ion catalyst. The stereochemistry of this reaction controlled by a neighboring group to yield α -glucosides (Koenigs and Knorr, 1901), see figure 2-25.

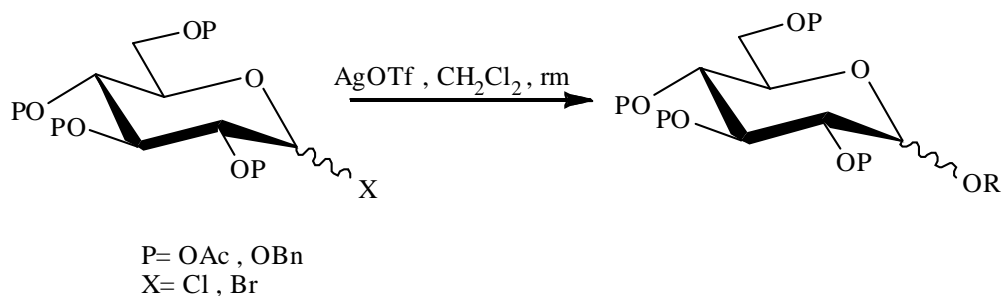


Figure 2-25: Koenigs-Knorr glycosylation

Many glycosylation reactions have been reported, Some of them apply unstable halides as glycosyl donor and heavy metal salt catalysts (Lemieux et al., 1975, Paulsen, 1984, Koto et al., 1983), While others use glycosyl fluorides as a donor with Lewis acid catalysts (Matsumoto et al., 1988, Suzuki et al., 1988, Nicolaou et al., 1984) Besides, several other glycosylations have been reported that apply non-halogen donors, such as trichloroacetimidates (Schmidt, 1994, Schmidt, 1986, Schmidt and Michel, 1980), thioglycosides (Veeneman et al., 1990, Veeneman and Boom, 1990), glycosyl acetate (Hanessian and Banoub, 1977), amino acid (Beljugam and Flitsch, 2004), glycosyl amine (Leon-Ruud et al., 1991) and n-pentenyl glycosides (Cristobal and Fraser-Reid, 1991).

2.3.3. Activation of sugar hydroxyl groups

As hydroxyl groups are poor leaving groups, the first step in the modification of carbohydrate OH group is activation, of the sugar hydroxyl into a good leaving group. This is mostly accomplished by forming sulfonates such as tosylates (Pellowska-Januszek et al., 2004, Baer and Hanna, 1982, Compton, 1938), mesylates

(Evans et al., 1968, Hanessian and Plessas, 1969a) , halogens (Hanessian et al., 1972, Giuliano, 1989, Aspinall et al., 1987). Displacement is easily performed on the primary carbon, but more difficult to handle secondary hydroxyl groups on sugars. They usually follow a S_N2 mechanism and with inversion of the configuration at the substitution center. As primary hydroxyl groups are more reactive than secondary alcohols, the 6-hydroxyl group of monosaccharaides can easily be selectively tosylated, mesylated or halogenated and subsequently converted to 6-deoxy derivative such as a 6-azido sugar (Blanco et al., 1997, Hanessian et al., 1978a) .

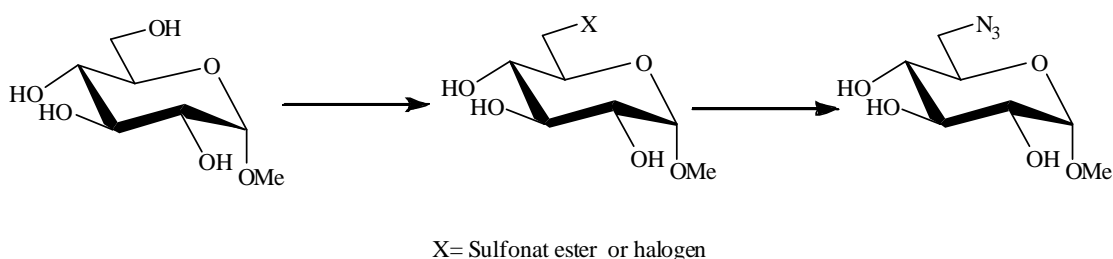


Figure 2-26: Activation of the primary hydroxyl group

The great reactivity of primary hydroxyl groups in carbohydrates and the use of bulky modifying reagent allows a great degree of flexibility and variety of modifying reactions to substitute the primary hydroxyl groups in the presences of secondary hydroxyl groups without the need of protection (Robyt, 1998) .

Sucrose has three primary hydroxyl group at C-1', C-6' and C-6. However the hydroxyl groups at C-1' is less reactive then the other two primary hydroxyl groups at C-6 and C-6' due to intermolecular hydrogen bonds with the oxygen atom of the glucose ring. Then 6,6'dideoxy sucrose derivatives of sucrose can be selectively synthesiszed (Zikopoulos et al., 1982 , Khan, 1984b) .

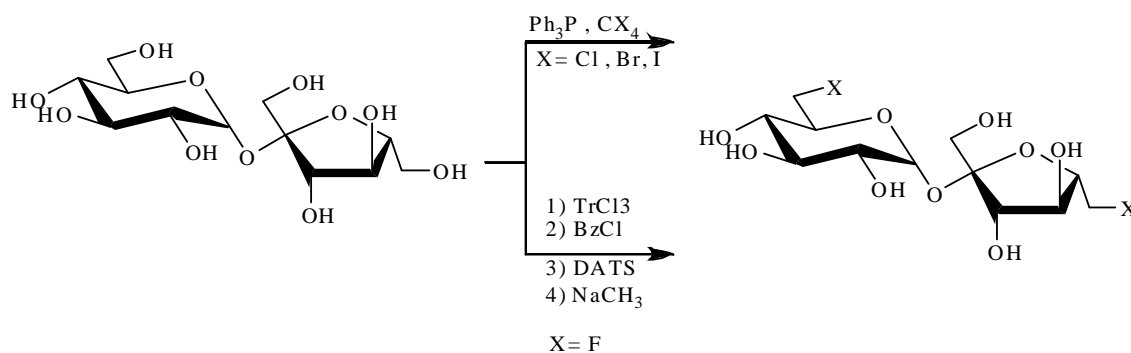


Figure 2-27: Activation of primary hydroxyl groups in sucrose

2.3.4. Staudinger reaction

The Staudinger reaction is an organic reaction used to convert an organic azide to a primary amine using a PR_3 compound and water (Vaultier et al., 1983, Amantini et al., 2002, Nyffeler et al., 2002). This reaction has since been used successfully to synthesize amines in countless organic compounds and still remains one of the most common reactions performed today. The Staudinger reaction was introduced in 1919 by Staudinger and Meyer (Staudinger and Meyer, 1919). It's a two-step process involving the initial electrophilic addition of azide to a p (III) center, followed by dinitrogen elimination from the intermediary phosphoazide to give the iminophosphoran (Gololobov and Kasukhin, 1992, Gololobov et al., 1981). The latter hydrolyzes spontaneously into a primary amine and the corresponding phosphine oxide in presence of water (Tian and Wang, 2004, Lin et al., 2005).

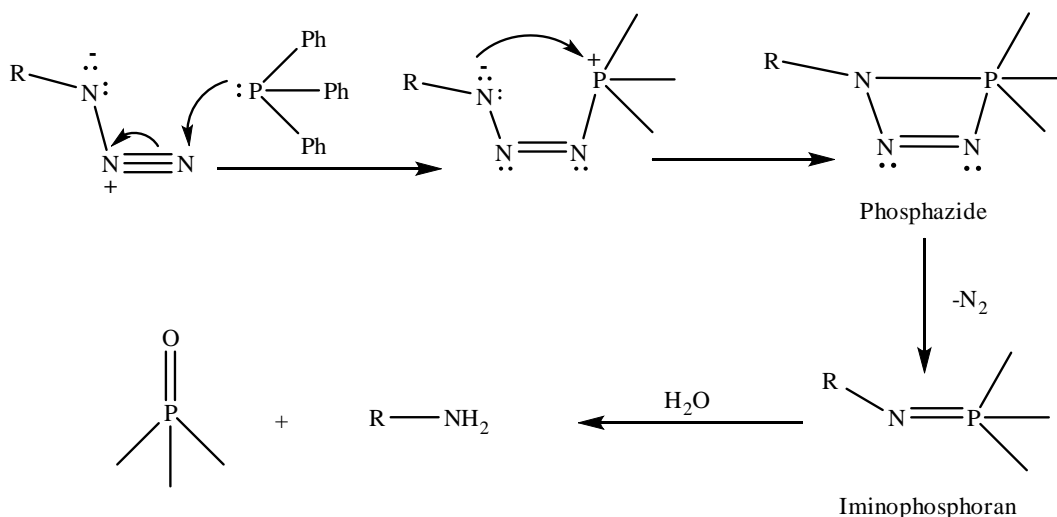


Figure 2-28: General mechanism for the Staudinger reaction

Many modifications to the Staudinger reaction have been reported within the past years, involving supported Staudinger reaction by using 2,2'-dipyridyl diselenide (PySeSePy) as catalyst (Bures et al., 2009b), and modified phosphines in order to avoid triphenylphosphine oxide impurities, which is hard to remove by-product in typical Staudinger reactions (Bianchi et al., 2005, Nisic et al., 2012, Nisic et al., 2009). Shalev and et al. have reported the combination of azides with acyl derivatives according to the mechanism shown in figure 2-29 (Shalev et al., 1996b, Boullanger et al., 2000). The reaction enables a direct access to amide without isolation of intermediary amines.

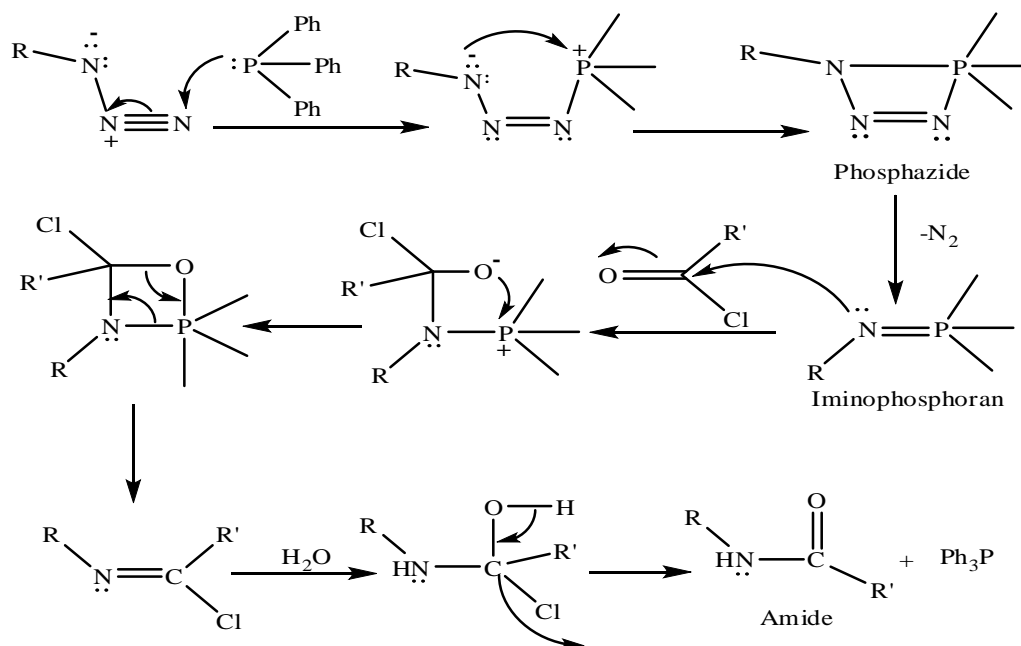


Figure 2-29: Synthesis of amide via Staudinger reaction

The reaction type have been applied by Maunier et al. to prepare α -glucopyranosyl and lactosyl amides from corresponding azide with triphenylphosphine and octanoyl chloride (Maunier et al., 1997a).

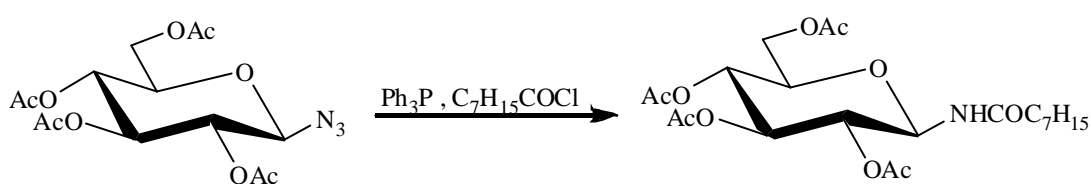


Figure 2-30: Synthesis of glycosyl amide via Staudinger reaction

Menger and Mbadugha used the modified Staudinger reaction to synthesized gemini surfactants from trehalose and long chain fatty acid chlorides (Menger and Mbadugha, 2001).

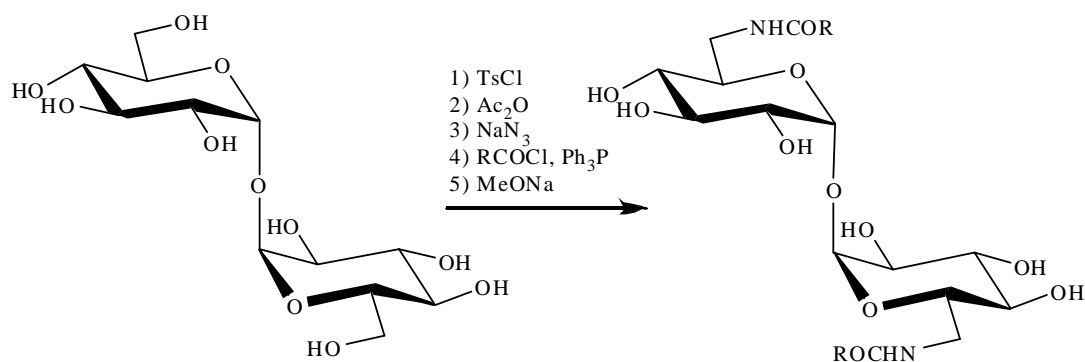


Figure 2-31: Synthesis of trehalose amide surfactant by Staudinger reaction

In order to avoid triphenylphosphine impurities Czifrak and et al. have been reported replaced triphenylphosphine with trialkyl analog to synthesize *N*-(β -D-glucopyranosyl) monoamide of dicarboxylic acids, which are potential inhibitors (Czifrak et al., 2006).

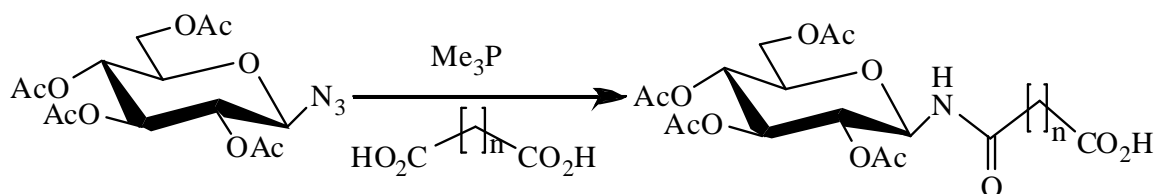


Figure 2-32: Coupling of β -D-glucopyranosyl with dicarboxylic acid via Staudinger reaction

Kovacs and et al. have reported similar synthesis of glycosyl amides from glycosyl azide by coupling with simple carboxylic acids such as benzoic acid, *p*-Chloro-, *p*-methyl-, and *p*-nitrobenzoic acid via Staudinger reaction in presence of trimethylphosphine (Kovacs et al., 2001).

Chapter 3 : Spectroscopic and physicochemical characterizations

3.1. NMR Spectroscopy

Nuclear magnetic resonance spectroscopy is a powerful analytical technique used to characterize organic molecules by identifying the carbon-hydrogen framework within molecules. One and two dimensional NMR spectra are used to characterize the organic structure.

One dimensional NMR spectroscopy is the chemist's most direct and general tool for identifying the structure of pure compounds and mixtures for both solid and liquids. It involves two common types i. e. ^1H NMR and ^{13}C NMR (Lambert and Mazzola, 2003).

^1H NMR is used to determine the type and number of hydrogen atoms in a molecule. There are three sets of information, which can be obtained from the ^1H NMR spectra of organic compounds; i. e. the chemical shift, the integration of the signal as well as the coupling pattern and the coupling constants J . Protons at a sugar ring encounter different environments and, therefore, absorb a slightly different energy. They are distinguishable by NMR and the frequency at which a particular proton absorbs is determined by its electronic environment. Magnetic shielding by the electrons around a proton determines its chemical shift. The chemical shift strongly depends on the number of oxygen atoms attached to a carbon, thus anomeric and non-anomeric hydrogens differ significantly. The anomeric proton is characterized by its extreme down-field shift and normally appears as a doublet, coupling with H-2. It is usually the most easily assigned hydrogen atom of the carbohydrate.

The H-1 proton in a β -anomer takes an axial position while in α -anomer it takes an equatorial position. They are in different environments and as a result the chemical shift and the value of the coupling constant $J_{1,2}$ differ significantly. Therefore it's easy to differentiate between α and β anomers by using ^1H NMR. For example, the coupling is 10 Hz

in α -D-(+)-glucose pentaacetate $J_{1,2}$ is 3.5 Hz, while in the anomeric analog it is 8.5 Hz of β -D-(+)-glucose pentaacetate. The differences in $J_{1,2}$ is caused by different dihedral angles between H-1 and H-2. The dihedral angle is 60° in the α - while 180° for the β -analog. (Lindhorst, 1999, Karplus, 1960), see figure 3-1.

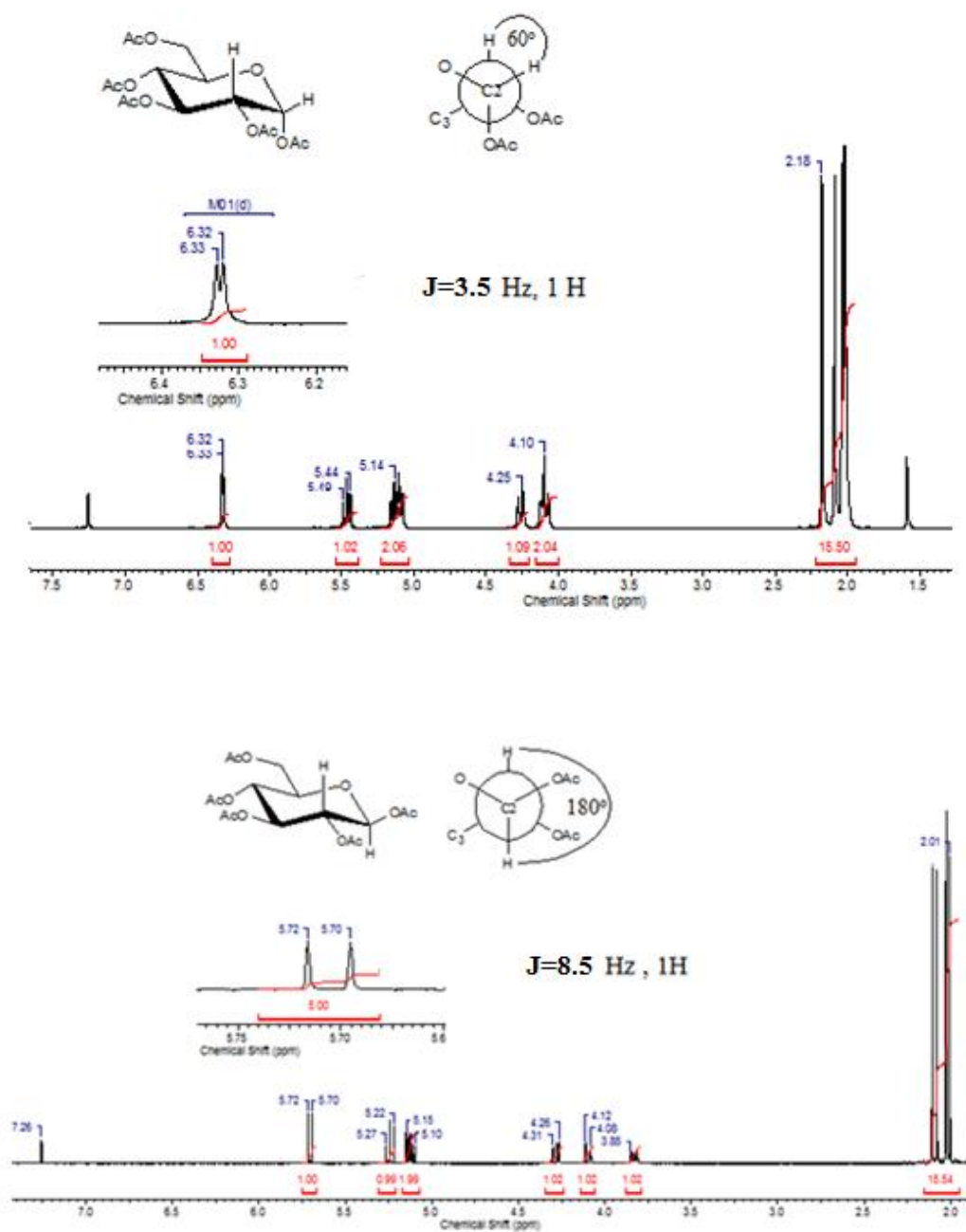


Figure 3-1: ^1H spectrum and dihedral angles for α & β -D-glucose pentaacetate anomers

^{13}C NMR was used to assign the carbon skeleton of the synthesized compounds. Due to the similarity of the environments of some carbons the PENDANT experiment (Polarization enhanced nutated during attached nucleus testing) was applied (see figure 3-2), which enable differentiating between carbon of different H- content (Homer and Perry, 1995). In practical it differentiates between the methylene (CH_2) and methine (CH) carbon signals. In a PENDANT spectra methyl (CH_3) and methine (CH) carbons appears as positive signals, while methylene (CH_2) and quaternary carbon (C) show negative signals.

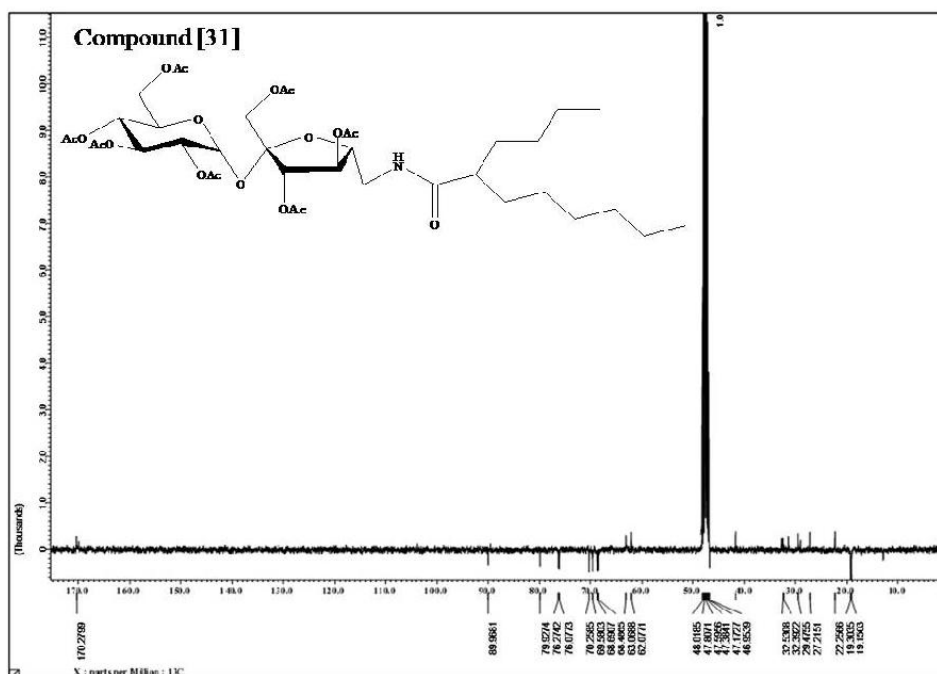


Figure 3-2: ^{13}C NMR PENDANT of Compound [31]

One-dimensional NMR is not sufficient to assign carbohydrate signals, especially with respect to ^{13}C . Two-dimensional NMR has been introduced to resolve this problem. One of the most common two-dimensional NMR spectra is the HMQC (Heteronuclear Multi-

Quantum Correlation), which can help to relate carbon and proton signals (Debenham et al., 1997, Rodebaugh et al., 1996), see figure 3-3.

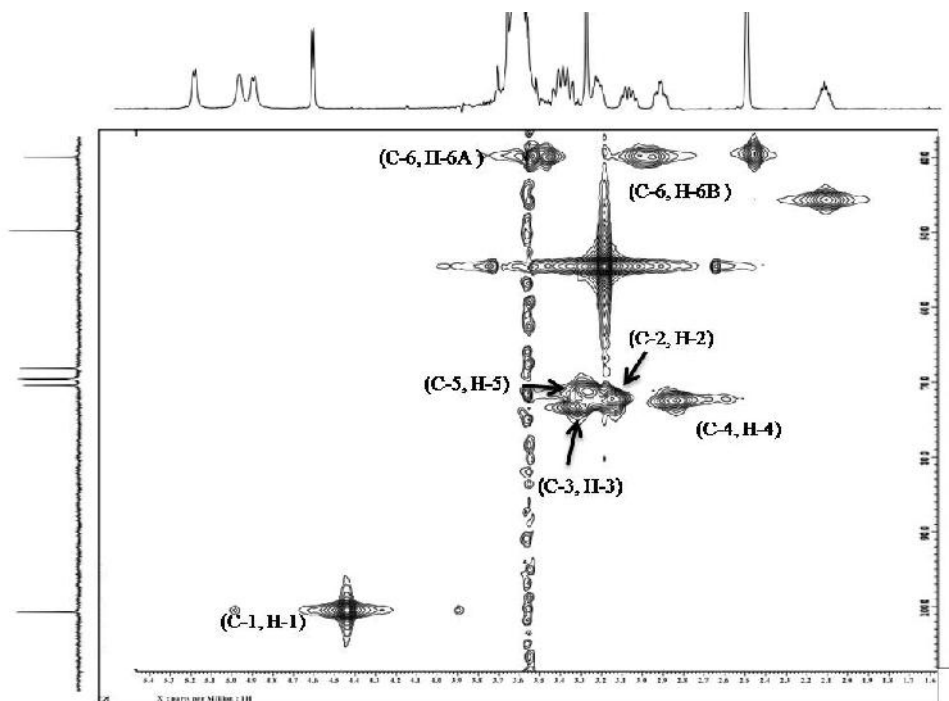


Figure 3-3: HMQC spectra for the compound [7c]

3.2. High Resolution Mass Spectra

High resolution mass spectra's were recorded on an LC-Mass (TOF modes) applying MeOH-Water in different ratios as an eluent. A gas flow of 250 °C hot nitrogen at 5 mL/min and electrospray ionization at 125 V was applied. With the high resolution mass spectra the identity of the surfactants would confirm due to the $[M+H]^+$, $[M+Na]^+$, $[2M+H]^+$ and $[2M+Na]^+$ as well as the isotope patterns.

3.3. Critical Micelle Concentration (CMC)

Critical micelle concentrations (CMC) were determined based on surface tension measurements carried out for the series of surfactant solution with different concentrations by The DuNouy ring method using a KSV Sigma 702 tensiometer at different temperature according to the Krafft temperature of the investigating surfactants (Noüy, 1919). The correction factor is calculated automatically by the equipment using Hun-Mason methods (Hoke and Chen, 1991). The critical micelle concentrations (CMC) were determined from the cross intersection between $\log C$ and the surface tension for the synthesized surfactants. See figure 3-5.

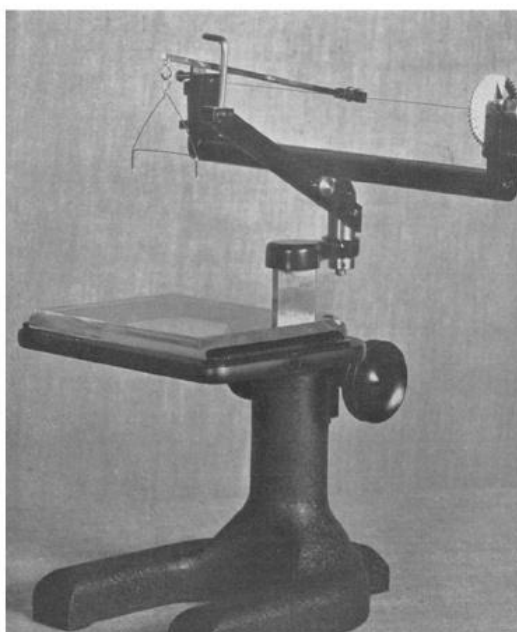


Figure 3-4: Du Nouy tensiometer 1919

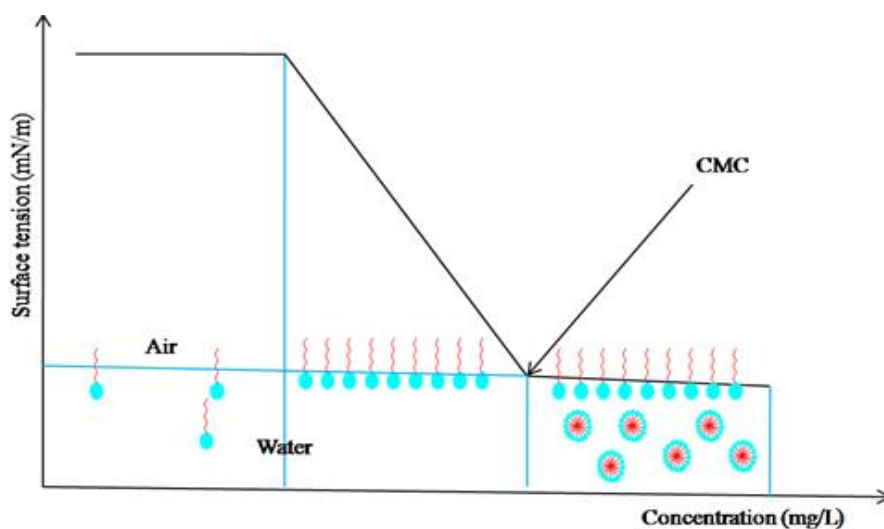


Figure 3-5: Surface tension curves as a function of log c

3.4. Optical Polarizing Microscope (OPM)

Liquid crystals phases were investigated by optical polarizing microscopy (OPM). A small amount of surfactant covered with a glass slip was put on a microscope slide and heated on a hot stage with a heating rate of about 2-5 °C per minute. When the surfactant was melted the glass covers was pressed carefully by a wooden stick to produce a thin film surfactant sample. The surfactant film was investigated under the optical polarizing microscope (OPM) by heating it up to the clearing temperature then allowing it to cool down to room temperature. Different phases were identified by their characteristic texture. Transition temperatures were determined on heating, while the textures were recognized on cooling mode.

For lyotropic investigations the surfactant films described above were cooled to room temperature and subsequently contacted with a solvent according to contact penetration technique (Minden et al., 2000, Milkereit et al., 2005). All surfactant were contacted with water. The surfactants films were cooled to room temperature and a very small amount of

water was added to the sample film using spatula and the sample slide was put in the hot stage under optical polarizing microscope (OPM). The sample was investigated under OPM while the temperature was raised up the Krafft temperature of each surfactant until we have got the textures.

Additionally for some surfactants the penetration experiment was repeated with methyl laurate to investigate the behavior of the surfactant in a reverse system.

3.5. Differential Scanning Calorimetry (DSC)

Differential scanning calorimeter was used to confirm thermotropic phase transitions previously determined optical polarizing microscope (OPM). Samples were dried over phosphorus pentoxide in vacuum oven at 50 °C. The dried sample was accurately weighted (4-8mg) in a standard aluminum pan of 40 µl size and sealed with a pinhole cover. The differential scanning calorimeter (DSC) was calibrated with an indium standard. Then the sample was placed in its position and a repeated heating/cooling cycle with a temperature range depending on the clearing temperature of the sample was recorded with a heating/cooling rate of 10 °C per minute.

3.6. Emulsifying test

Methyl laurate (5ml) was mixed with (0.25ml) of water and (15mg) of the methyl glycoside surfactant (C₁₄, C₁₆ and C₁₆ branched) and the mixture was heated gently in a sealed tubes, until the mixture became homogeneous. The tubes were left at room temperature and monitored on their appearance over a period up to 4 weeks (Yokoyama et al., 2001).

Chapter 4 : Results and discussions

4.1. Synthesis

4.1.1. Methyl glucoside surfactant

The target applications for the surfactants of this series focus on the stabilization for particularly water-in-oil emulsions. A potential application involves hydro-fuel, in which water contents reduce non-economic heat generation and increase the expansion of the fuel based on the generation of additional pressure due to evaporating water.

Methyl glucoside was chosen as starting material for this series for two reasons: first because of economy and accessibility and second based on its chemical stability as glycoside with reduce hydrophobicity compare to glucose because of the lower number of the hydroxyl groups, which potentially increase the surfactant's solubility in an oil-based medium.

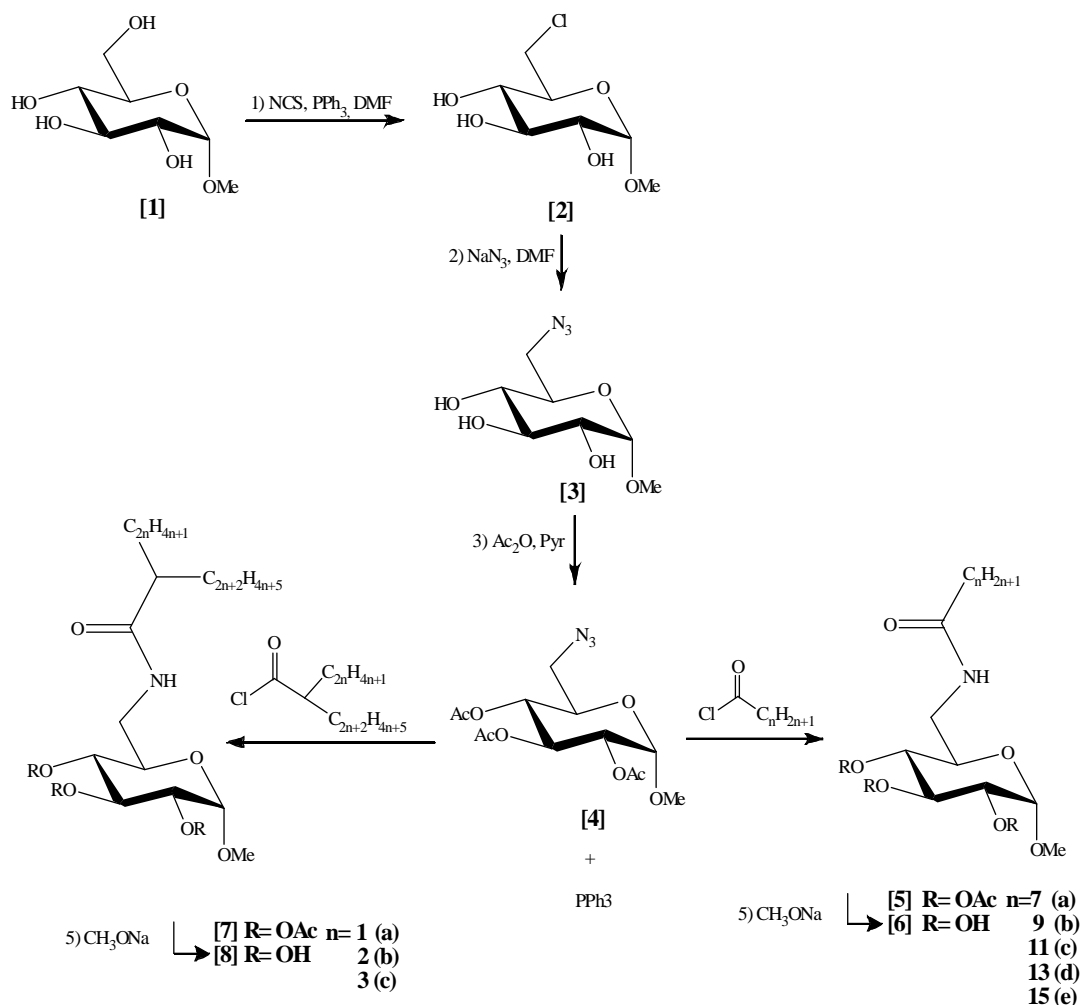


Figure 4-1: Synthesis of methyl glucoside surfactants

The synthesis of surfactants is based on methyl 6-azido-6-deoxy- β -D-glucopyranoside [3], which had been previously prepared by Hanessian and et al. (Hanessian et al., 1978b) in a one flask reaction. Methyl glucoside has only one primary hydroxyl group suitable for direct chlorination with *N*-chlorosuccinimide in the presence of triphenylphosphine in DMF. The reaction requires anhydrous conditions and furnishes methyl-6-deoxy-6-chloro- β -D-glucopyranoside [2] in good yield (Arcamone et al., 1976, Hanessian et al.,

1972). The chloride was substituted with sodium azide after the excess of chlorination reagent was destroyed by addition of methanol. Since the reaction medium remains the same no solvent exchange is required to obtain **[3]** (Marti et al., 1989, Beaupere et al., 1989). For better purification the latter was peracetylated with acetic anhydride in pyridine to produce methyl 2,3,4-tri-O-acetyl-6-deoxy-6-azido- β -D-glucopyranoside **[4]**.

In order to reduce the reaction steps for the surfactant without missing the opportunity for chromatography purification a Staudinger based coupling (Staudinger and Hauser, 1921) of azide **[4]** with acid chloride ranging from C₈ to C₁₆ was performed. This process avoids a possible acetyl migration, which could happen if a two-step procedure passing the amino sugar was applied. Straight (C₈-C₁₆) and branched (C₆₋₂, C₈₋₄, C₁₀₋₆) fatty acid chloride were applied. The latter is accessible by a simple treatment of the acid with oxalyl chloride (Daubert et al., 1943). The Staudinger coupling used triphenylphosphine in dichloromethane to afford the acetylated sugar amide with straight hydrocarbon chain **[5a , 5b, 5c , 5d , 5e]** and acetylated branched analogs **[7a, 7b, 7c]** respectively. Chromatography purification was required, in particular to remove the phosphineoxide formed during the initial substitution of the hydroxyl group at C-6 as well as in the coupling. Deacetylation under Zemplen condition with sodium methoxide in methanol (Zemplen et al., 1936) gave the free straight clean amide surfactants **[6a,6b ,6c ,6d , 6e]** as well as the branched compounds **[8a , 8b, 8c]**, respectively in an overall yields of almost 50% based on methyl glycoside. Combustion analysis of the acetylated intermediates **[5]** and **[7]** confirmed high purity of the material, as both carbon and nitrogen contents matched the calculated values, whereas the NMR-spectra of the final surfactants **[6]** and **[8]**, respectively proved complete removal of the protecting groups. The NMR data were in good agreement with previously reported values for lower homologues. (Maunier et al., 1997b).

The coupling of fatty acids and azide was performed using two different procedures, i.e. 6.4.7A, 6.4.7B. The results of both procedures were approximately the same. Coupling of fatty acid instead of the fatty acid chloride as described by Czifrak and et al (Czifrak et al., 2006) failed.

All surfactants were spectroscopically analyzed in both acetylated as well as the deprotected form. Structural identities are based on NMR spectra (^1H & ^{13}C) and high-resolution mass spectrometry. Chemical purities were confirmed by elemental composition analysis (CHN), since the pure surfactants are hygroscopic, which cause significant deviations due to instrumental limitations and high environmental humidity the hydrogen data were consistently too high, whereas both carbon and nitrogen contents reflect the calculated data of the compounds.

^1H NMR of the acetylated surfactants shows the signals of the amide proton at about 5.78. The protons for the sugar at acetylated oxygens (H-2 to H-4) appear between 5.50 and 4.80, while the anomeric signal (H-1) is found around 5.00. The non-acetylated sugar signal (H-5) is found around 3.85, while the primary CH_2 (H-6a/b) appears between 3.58 and 3.30. All coupling constants in the sugar ring are in the range of 8-10 Hz, referring trans-diaxial arrangements of the protons, referring to a $^4\text{C}_1$ conformation for the glucose. A singlet at around 3.36 refers to the methyl group, while acetate protons are found at about 2.0. The protons of the alkyl chain appear between 2.16 ($-\text{CH}_2$) and 0.8 (terminal CH_3). The integration of the bulk methylene signals at around 1.25 reflects the respective chain length of the surfactant ($\text{C}_8 - \text{C}_{12}$). The ^{13}C NMR spectra show the signal of the amide carbon at about 173 and the signals of acetyl carbonyl at about 170. The anomeric carbon is found around 97 while other methyne carbons appear between 71.00 and 67.70. The position of the primary carbon (C-6) around 39 (upfield shift compared to about 65 for the oxygen compound) reflects the nitrogen

substitution. The methyl group is found at 55 while the alkyl chain carbons appear in between 36.5 (-CH₂) and 13.5 (CH₃).

The deacetylated surfactants show the completely removal of the acetyl groups signals mentioned above. Due to the absence of the ester, the sugar hydrogens at C-2 to C-4 are shifted upfield and appear between 3.33 and 2.89. Besides, in DMSO the hydroxyl groups are found between 5.00 and 4.80. The amide proton shifts due to the different solvent and is found at about 7.80. The anomeric signal (H-1) appears around 5.50, while the sugar protons (H-2 to H-5) are located between 3.40 and 3.20. The primary CH₂ (H-6a/b) appears between 3.50 and 3.00 and the methyl group at the anomeric center at about 3.24. The protons of the alkyl chain remain as before in between 2.07 (-CH₂) and 0.85 (terminal CH₃). The ¹³C NMR spectra show the signal of the amide carbon at about 173 and the anomeric carbon at around 100. Other sugar carbons appear between 72 and 70.50. The position of the primary carbon (C-6) is around 40, while the methyl group is found at 54. The alkyl chain carbons appear in between 35 (-CH₂) and 14 (CH₃). For detailed data analysis see chapter 6.

4.1.2. Bisamide sugar surfactants

The major amphiphilic compounds of the cell membrane are characterized by a biantennary lipid structure comprising a single hydrophilic head group and two hydrophobic alkyl chains, which commonly are derived from fatty acids. A typical glycolipid structure involves a glycerol spacer linking two fatty acids and the carbohydrate (Mannock et al., 1990, Mannock et al., 2001, Sauvageau et al., 2012) , example structure A as shown in figure 4-2 utilizes a lactose head group, as saccharides with this core structure are frequently found in the nature (Choi et al., 1999, Gil et al., 2003) . Unlike the glycosidic linkage between the glycerol and sugar, the ester bonds between the polyol and the fatty acids are easily affected by hydrolysis under both acid

and basic conditions. This sensitivity renders natural glycolipids non-favorable for delivery applications.

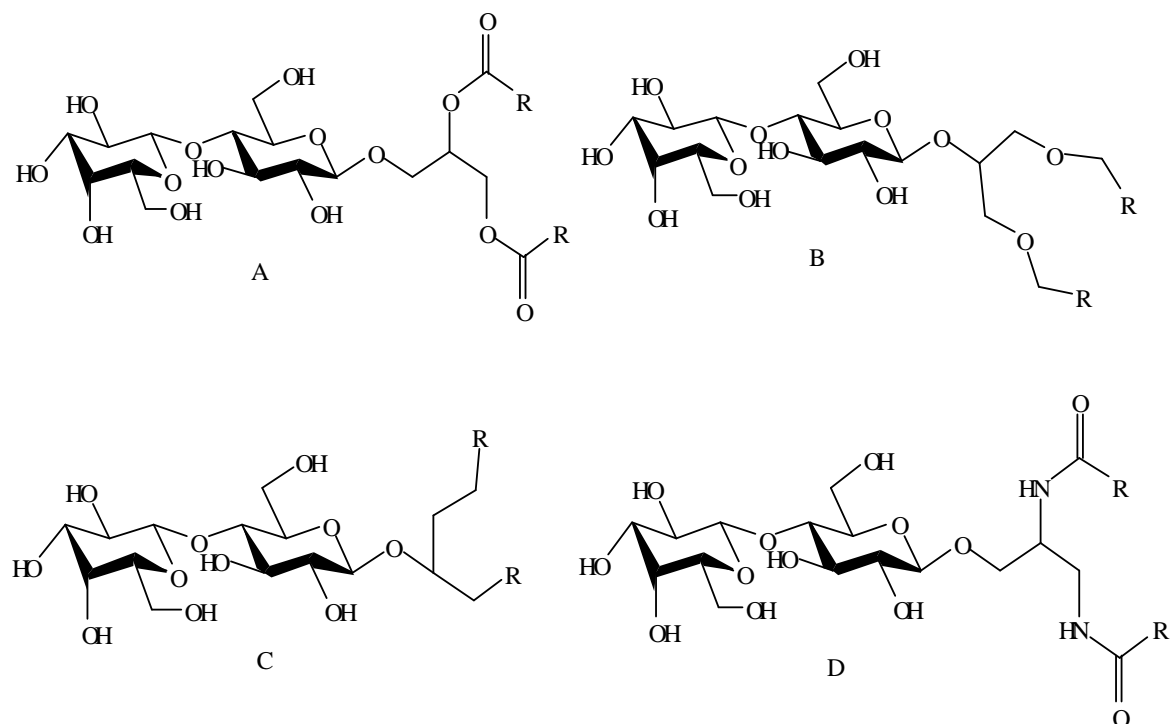


Figure 4-2: Structure comparison of natural and synthetic biatennary glycolipids

Several modifications have been suggested to increase the chemical stability of biatennary glycolipids. Examples involve replacement of the ester linkage by ethers (Minamikawa et al., 1994), figure 4-2B or replacement of the entire diacylglycerol by a branched alcohol chain (Hashim et al., 2006b), figure 4-2C. In both approaches the branching domain rather attributes the hydrophobic region than to the hydrophilic, as it is in glyco-glycerolipid. This difference is not expected to alter the generic assembly behavior of lipids, which can be understood based on packing theory based considerations (Nguan et al., 2010). However, it may affect the water profile around a delivery vesicle and, thus, has implication on the fusion of the vesicle with a cell membrane. In the desire

to optimize the glycolipid structure for a vesicular delivery system, therefore, the replacement of ester linkages with amide analogs appear to be a suitable concept.

The aim of this series is to synthesize new glycolipid with enhanced chemical stability and close structural similarity to natural cell membrane lipids by replacement of the ester linkage with amide analogs for the development of a drug delivery system.

4.1.2.1. Bisamide surfactant on glucose

The synthesis concept was developed on glucose figure 4-3, prior to application on the more interesting lactose core. Peracetylation of glucose [9] with acetic anhydride and sodium acetate gave α -glucose pentaacetate [10]. Kinetic glycosylation applied with 1,3-dichloro-2-propanol and boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) in dichloromethane over a period of less than 3h in order to control the stereoselectivity at the anomeric center to give exclusively the dichloride [11]. The latter was converted into diazide [12] by sodium azide in DMF at 80 °C. Final coupling of compound [12] with three straight chain fatty acid chlorides (C_8 , C_{10} , C_{12}) applied triphenylphosphine in dichloromethane by Staudinger reaction and furnished the three binary glycolipids **13a**, **13b** and **13c**, respectively. The reaction follows the Staudinger mechanism suggested by Shalev (Shalev et al., 1996a). The final compounds were deacetylated with sodium methoxide in methanol to the final surfactants **14a**, **14b**, and **14c**, respectively (Sani et al., 2012).

Both acetylated and deacetylated surfactants were spectroscopically analyzed. Structural identities are based on NMR spectra (^1H & ^{13}C) and high-resolution mass spectrometry. Chemical purities were confirmed by elemental composition analysis (CHN) peracetylation on the stage of peracetylates. Due to instrumental limitations and high environmental humidity the hydrogen data were consistently too high, whereas both carbon and nitrogen contents conformed the purity of the surfactants.

^1H NMR of the acetylated surfactants for this series show the signals of the two amide protons at about 6.58 and 6.19. The anomeric proton appears at about 4.60. The vicinal coupling constant of 8 Hz indicates a dihedral angle of 180° , which identifies the product as β -anomer. The protons for the sugar at acetylated oxygens (H-2 to H-4) are found between 5.00 and 4.90. The non-acetylated sugar signal (H-5) is found at around 3.00, while the primary CH_2 (H-6a/b) appears between 4.23 and 3.20. The protons of the acetyl groups are located at about 2.0 and the protons of the linker at about 3.05 (OCH) and 3.66 (CH_2N). Alkyl chain protons appear between 2.20 ($-\text{CH}_2$) and 0.86 (CH_3). ^{13}C NMR spectra show the signal of the two amide carbons at about 175 and 174.50 and the acetyl carbonyls at about 170. The anomeric carbon is found around 101, while other methyne carbons appear between 74.5 and 68. The position of the primary carbon (C-6) is around 61.5. The carbons of the linker appear between 39.60 and 38.60 (CH_2N) and at 78 (OCH). Alkyl chain protons are found between 36.50 ($-\text{CH}_2$) and 13.5 (terminal CH_3).

^1H NMR of the deacetylated surfactants shows the removal of the acetyl groups and the previously reported upfield shift of the corresponding sugar protons. Due to the applied solvent (CD_3OD) no hydroxyl groups are found. Instead these protons increase the water peak inside the solvent. The amide protons appear at a similar location than in DMSO, i.e. at 7.95 and 7.80. The anomeric signal (H-1) is found around 4.36, while other sugar protons (H-2 to H-5) appear between 3.50 and 3.22. The primary sugar protons (H-6a/b) appears between 3.90 and 3.70 and the protons of the linker between 3.22 and 2.80 (CH_2N) and at 3.80 (OCH), respectively. Alkyl chain protons appear in between 2.20 ($-\text{CH}_2$) and 0.90 (terminal CH_3). The ^{13}C NMR spectra show the signal of the two amide carbon at about 175. The anomeric carbon is found around 105, while other methyne carbons appear between 78 and 71.5. The position of the primary carbon (C-6) is around 63. The methylene carbons of the linker appear between 42.7

and 42, while the methyne proton (OCH) is found at 80. Alkyl chain carbons appear between 37 (-CH₂) and 14 (terminal CH₃). For detailed data analysis see chapter 6.

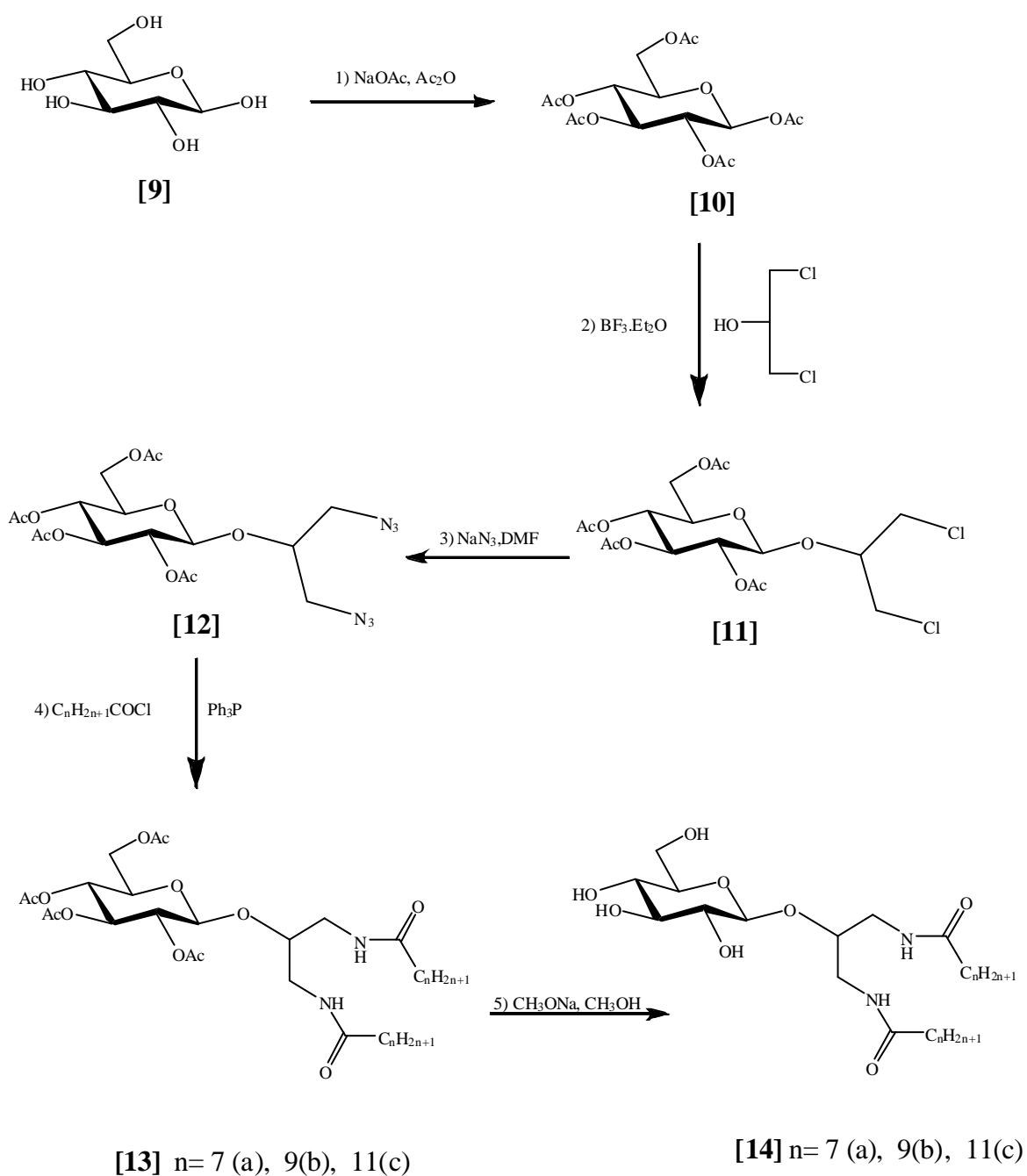


Figure 4-3: Synthesis of bisamide glucose surfactants

4.1.2.2. Coupling of lactose diazide with fatty acid

The application of the previous synthetic scheme on lactose is shown in figure 4-4.

Lactose [15] was peracetylated with acetic anhydride and sodium acetate (general procedure 3.4.1) to furnish α -lactose octaacetate [16] (contain% 10). The latter used for the glycosylated of 1,3-dichloro-2-propanol, following the same approach that reported before for glucose. 1,3-Dichloro-2-propyl 2,3,4,2',3',4',6'-hepta-O-acetyl- β -D-lactopyranoside [17] was obtain as white crystals NMR pure compound. It was azidated with sodium azide in DMF at 80 °C to furnished the precursor 1,3-diazido-2-propyl 2,3,4,2',3',4',6'-hepta-O-acetyl- β -D-lactopyranoside [18] in 48% yield based on lactose acetate.

Azide [18] was coupled with three fatty acid chlorides, varying in chain length from C₈ to C₁₂ via Staudinger reaction in the same manner and using the same conditions that were previously applied for the glucose analog. However the expected double chained lactose surfactant [19] was not obtained. Instead a (1,4,5,6-tetrahydropyrimidine) ring was formed and compounds **20a**, **20b**, and **20c**, was isolated in 70% yield. Upon deacetylation the monoantennary surfactants **21a**, **21b** and **21c** were obtained.

The non-symmetric structure of the tetrahydro-pyrimidine ring gives rise to diastereomers; this is reflected in the NMR spectra of the compounds [20] and [21], which indicate two products in different ration as 3:2 for [**20 a**, **21a**], 4:1 for [**20b**, **21b**] and 1:1 for [**20c**, **21c**]. The varying ratios are an indicator that unknown reaction parameter may have significant effects.

All surfactants were spectroscopically analyzed in both acetylated as well as the deprotected form. Structural identities are based on NMR spectra.

^1H NMRs of the acetylated surfactants of this series show two signals of the (NH) of the ring at about 5.98, 5.59 with one integration, which indicate to two diastereomers for these surfactants as ,that confirm the formation of the 1,4,5,6-tetrahydropyrimidine ring as it has a chiral center and two diastereomers. The anomeric protons(H-1, H-1') appear at about 4.61 and 4.46 , the protons for the sugar rings appear between 5.32 for (H-4') and 3.85 for (H-5/5'), the primary protons of the rings (H-6/6') appear at 4.5 and 4.15. The protons of the acetyl groups at about 2.0 and the protons of the (CH₂) of the ring at about 3.67 - 3.25 and at 3.90 for the chiral proton, the difference in chemical shift for the two (CH₂) confirm the formation of thetetrahydropyrimidine. While the protons of the alkyl chain appear between 1.6 for (-CH₂) and 0.7 for the (CH₃), the integration of the (bulk-CH₂) at 1.25 indicate the formation of only one alkyl chain in structure of the surfactants . The ^{13}C NMR spectra show the signal of the two amide carbons at about 174, 171, The anomeric carbons (C-1, C-1') appear at about 101.22 (101.10) and 100.68. , the carbons for the sugar rings appear between 5.32 for (C-4) and 66.5 for (C-4'), the primary carbons of the rings (C-6/6') appear at 61.50 and 60.68. The carbons of the (-CH₂N) of the ring at about 40.30, 43.54, and 79 for the chiral carbon (OCH). Signal of the alkyl chain carbons in between 36.35, 36.13 for (-CH₂) and 13,70 for (-CH₃).

^1H NMRs of the deacetylated surfactants show the removal of the acetyl groups and appearance the anomeric protons at (4.48)/ 4.45 and 4.36 /(4.35) for (H-1 , H-1'). the protons sugar ring in between 4.02- 3.25, while the protons of the alkyl chain appear between 2.38)/2.21 for (-CH₂) and 0,90 forthe terminal (-CH₃).

^{13}C NMR spectra shows the two signals of the (CH₂N) at about 177.50, the anomric carbons at about 105.51, 105.33 for (C-1, C-1') and the carbons of the sugars ring at 80.71 and 61.96 for (C-6, C6'), the carbons of the linker at about 45.50. for (CH₂N)

and (CH₂NH), and the signal of the alkyl chain carbons in between 37.14 for (-CH₂) and 14.24 for the terminal carbon. Detailed data analysis see chapter 6.

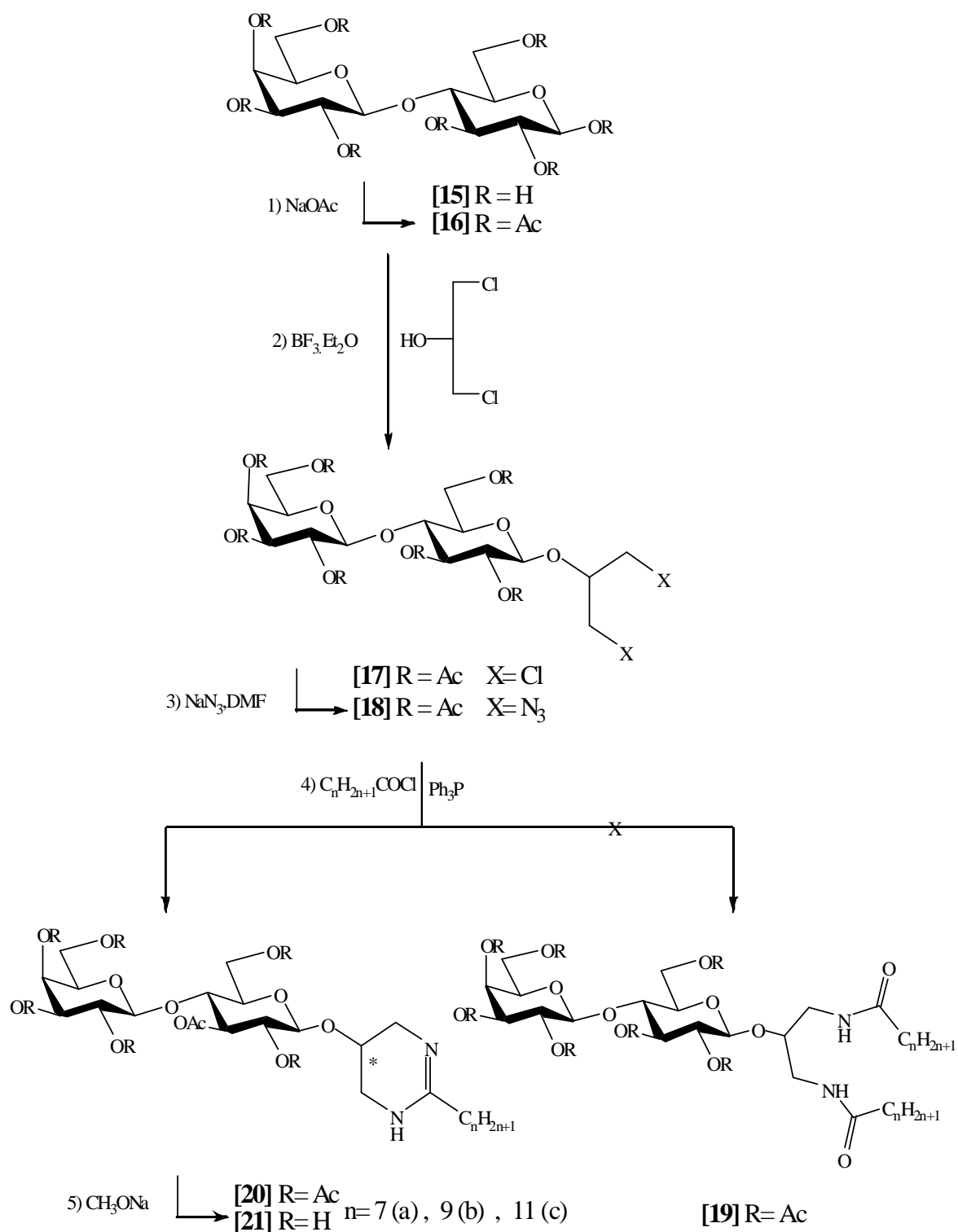
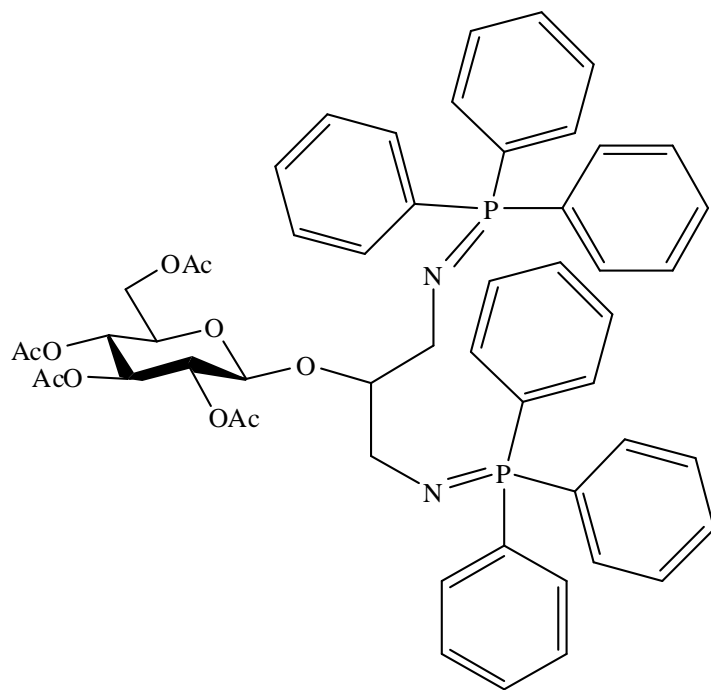


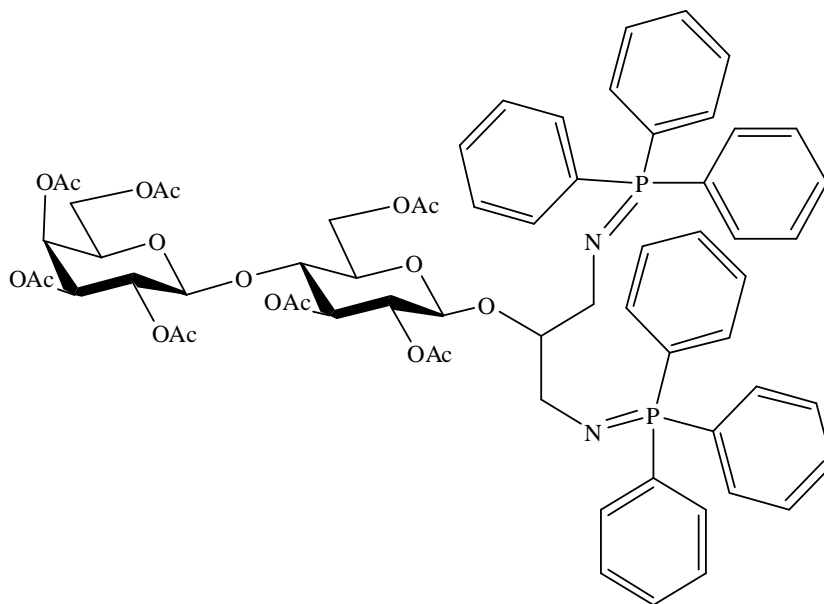
Figure 4-4: Synthesis of lactose surfactants

Although phosphine mediated cyclizations of azide-amides have been reported previously (Gololobov et al., 1985, Takeuchi et al., 1989, Wu and Burgess, 2008) the reaction output is rather unexpected. This does not only refer to the formation of tetrahydropyrimidines, which so far have been accessed by different strategies (Aspinall, 1940, Skinner and Wunz, 1951, Brimblecombe et al., 1969) but particularly relates to the different behaviour of glucose and lactose, despite identical stereochemistry at the reducing sugar.

In an attempt to explain the different behavior of glucose di azide [12] and the lactose diazide [18] in Staudinger reaction, a molecular modeling study was performed. Structure optimization for the glucose bis-iminophosphorane intermediate [22] and lactose bis-iminophosphorane intermediates [23] figure 4-5, led to the conformations depicted in figure 4-6. While both nitrogen atoms of glucose bis-iminophosphorane [12] are easily accessible for reaction with the fatty acid chloride, the corresponding lactose bis-iminophosphoran [18] is partially blocked by the non-reducing sugar of the lactose. Hence only one of the reaction centers of lactose can easily reacts with fatty acid chlorides , while the second reaction center of sterically hindered. This steric hindrance appears to be sufficient to block the intermolecular reaction, thus promoting the competing cyclization based on the coupling of the remaining iminophosphoran with the initially formed first amide. The glucose-based bis-iminophosphoran, on the other hand, does not exhibit sterical hindrance. The higher reactivity of the fatty acid chloride compared to the intermolecular amide explains the formation of the bisamide surfactants type [13] instead of the tetrahydropyrimidine.

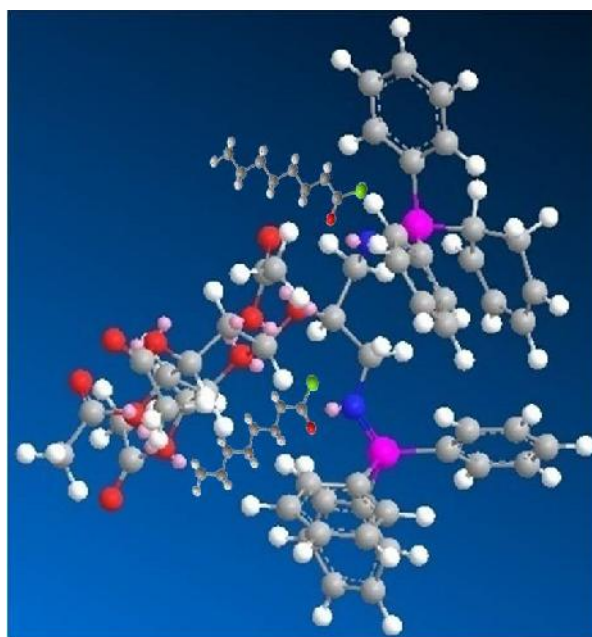


Glucose bis-iminophosphoran intermediate [22]



Lactose bis-iminophosphoran intermediate [23]

Figure 4-5: Structures of the Staudinger bis-iminophosphorane intermediates



Glucose iminophosphoran intermediate [22]



Lactose iminophosphoran intermediate [23]

Figure 4-6: Molecular modeling of bis-iminophosphorann intermediates for both glucose and lactose

A suggestion for a mechanism of the tetrahydropyrimidine formation shown in figure 4-7.

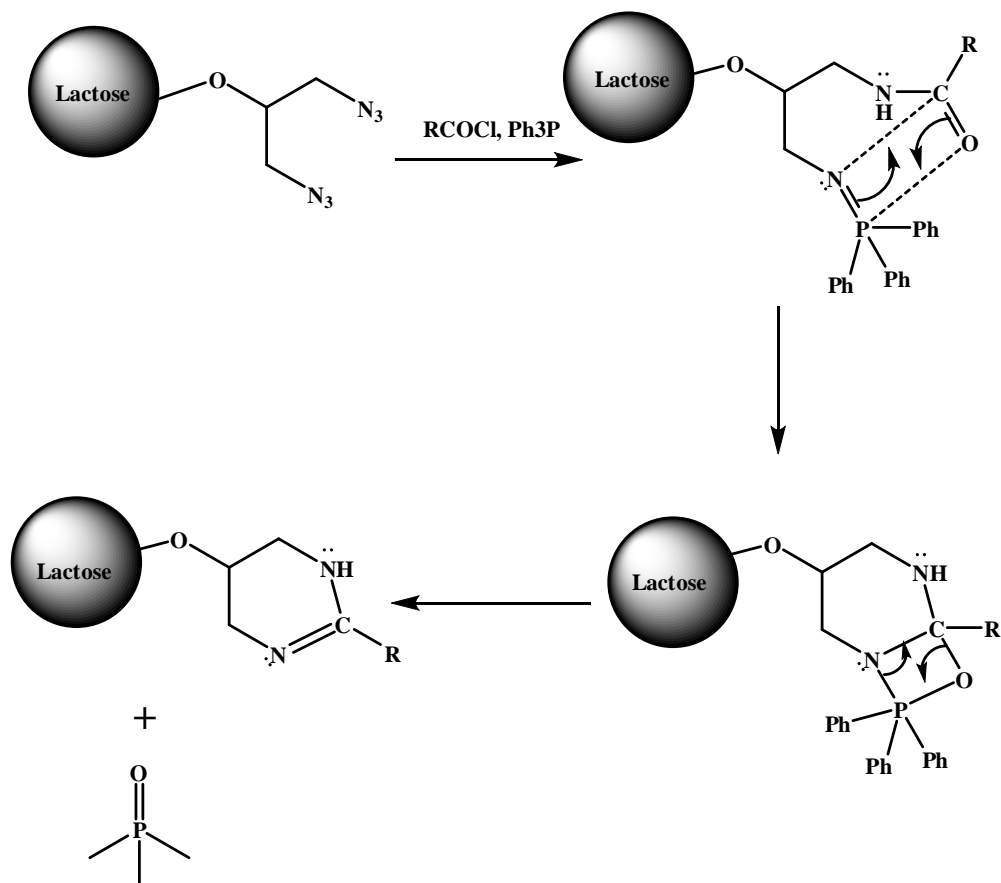


Figure 4-7: Suggested mechanism for the tetrahydropyrimidine formation

4.1.3. Sucrose amide surfactant

Sucrose is a non-reducing disaccharide that occurs naturally in most fruit and vegetable. It is produced in large quantities, e. g. in sugar cane and sugar beets, from which it is isolated for commercial use. The annual production of sucrose is about 168 million tons, (Blauer, 2011). Sucrose is the less expensive carbohydrate with a price about £160 per ton on the world market. Sucrose production exceed world market demand by over

million tons (Khan, 1984a). Because of that, more application of sucrose are needed. The aim of this series is to synthesize sucrose monoamides by replacement of the hydroxyl group at position 6 of fructose with straight and branched C₁₂ alkyl chains via Staudinger reaction. The target application of sucrose surfactants are an oil-in water emulsifier.

Due to the number of hydroxyl groups on the sugar head, sucrose is good candidate for oil-in-water emulsifier. However the chemical conversion a single hydroxyl group in sucrose is a big challenge. The subtle reactivity differences of primary and secondary hydroxyl groups have been mentioned before, indicating that primary ones can be selectively alkylated, acylated, oxidized and displaced by halogen. The reactivity order for the primary follows 6-OH glucose ~ 6-OH fructose >>1-OH fructose. This order, however, is only accessible by using bulky reagents , which necessarily favor reactions at the 6-OH , 6'OH groups (Lichtenthaler and Peters, 2004).

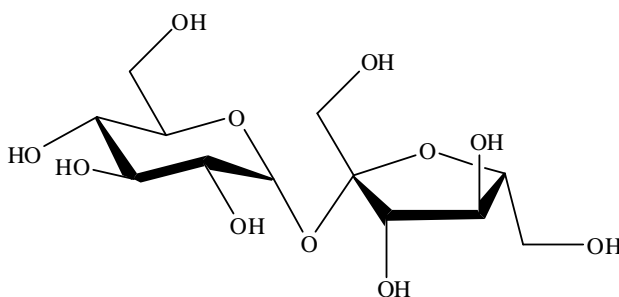


Figure 4-8: Chemical structure of sucrose

The reaction of sucrose with 1.10 eq. of the bulky reagent tert-butyldiphenylsilyl chloride (TBDPSCI) led to the sole protect of the hydroxyl group at position 6 of the fructose moiety by yield 6'-O-tert-butyldiphenylsilyl sucrose [25]. Afterword remaining hydroxyl groups can be easily acylated with acetic anhydride in pyridine to form the fully protected sucrose compounds 1',2,3,3',4,4',6-hepta-O-acetyl-6'-tert-butyldiphenylsilyl-

sucrose [26]. The hydroxyl group at position 6 of fructose can be selectively deprotection with tert-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) to obtain the partially protected 1',2,3,3',4,4',6-hepta-O-acetyl-6'-sucrose [27]. Activation of 6'-OH applied in pyridine to furnish 1',2,3,3',4,4',6-hepta-O-acetyl-6'-tosyl-sucrose [28]. The tosyl was substituted with sodium azide in *N,N*-dimethylformamide DMF at 80 °C to give the surfactant precursor 1',2,3,3',4,4',6-hepta-O-acetyl-6'-azido-sucrose [29]. Coupling of the latter with dodecanoyl chloride and 2-butyloctanoyl chloride via Staudinger reaction in presence of triphenylphosphine furnished the acetylated surfactants 1',2,3,3',4,4',6-hepta-O-acetyl-6'-dodecanamido-sucrose [30] and 1',2,3,3',4,4',6-hepta-O-acetyl-6'-2-butyl-octanamido-sucrose [32] respectively. Final deacetylation under Zemplén conditions led to NMR pure surfactants 6'-dodecanamido-sucrose [31] and 6'-2-butyl-octanamido-sucrose [33]. The synthetic scheme is pictured in figure 4-9.

¹H NMRs of the acetylated surfactants of this series shows the signals of the amide proton at about 6.15. The sugar protons appear between 5.62 (H-1) and 4.40 (H-5). The primary proton of fructose domain found at 3.32 (H-6'B), which indicate the replacement of the oxygen with amide. Acetyl groups are found at about 2.1. The alkyl chain protons appear between 2.2 (-CH₂) and 0.85 (terminal -CH₃). In ¹³C NMR the signal for the amide carbon appears at about 173.54, whereas acetyl carbons of the pyranose are found between 170.66 and 170.11, while for furanose found between 196.98 and 196.56, Sugar carbons appear between 89.80 for (C-1) 103 and 61, but (C-6') found at 41 which indicate the replacement of oxygen with amide. The signal of the alkyl chain carbons in between 36.50 for (-CH₂) and 14.09 for (-CH₃).

The deacetylated surfactants show the signals of the amide proton in about 7.83, the protons of the sugar ring in between 4.08 and 3.32, while the protons of the alkyl chain appear between 2.21 (-CH₂) and 0.91 (terminal -CH₃). The ¹³C NMR spectra

show the signal of the amide carbon at about 175.58, the signals of sugar ring in between 92.16 (C-1) and acetylated 61.4 (C-1'), The primary carbon of the fructose demine found at acetylated 42.29 (C-6'), and the signal of the alkyl chain carbons in between 35.75 (-CH₂) and 13.08 (terminal-CH₃).

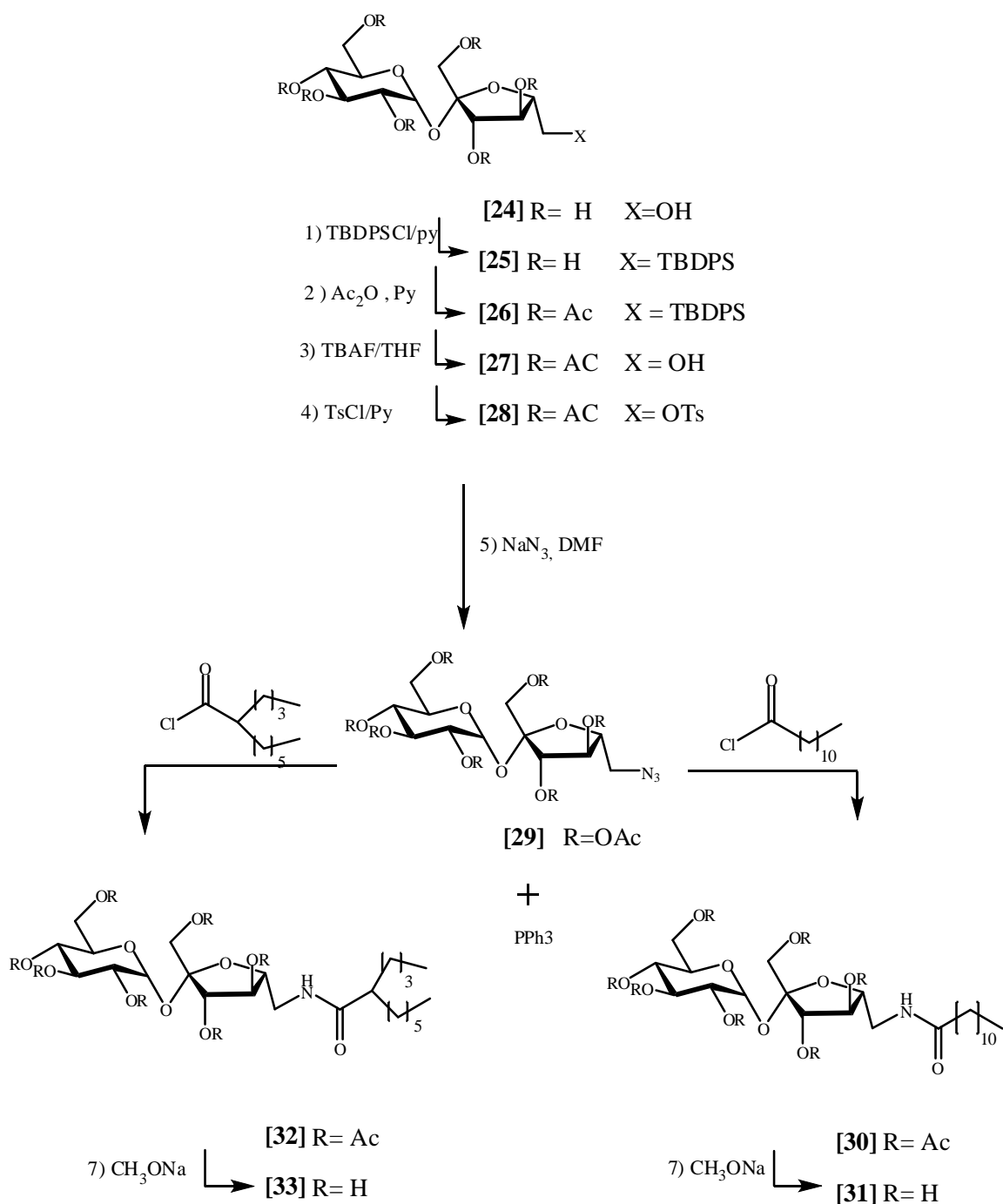


Figure 4-9: synthesis of sucrose monoamide surfactants

4.2. Physicochemical properties

The physicochemical properties of the synthesized surfactants are summarized in table 4-1.

Com. No.	Chain Length	OPM investigation		CMC investigation			Mp °C	H KJ/mol
		Thermotropic Phases	Lyotropic Phases	CMC mmol/L	Surface tension mN/m	T _k °C		
6a	C ₈	Cr	H ₁			65	131	32
6b	C ₁₀	Cr	H ₁			70	139	27
6c	C ₁₂	Cr	H ₁	0.5	31	80	144	37
6d	C ₁₄	Cr	H ₁			95	147	42
6e	C ₁₆	Cr	H ₁			100	147	43
8a	C ₆₋₂	Cr	H ₁			55	185	30
8b	C ₈₋₄	Cr	H ₁	0.5	32	75	171	31
8c	C ₁₀₋₆	Cr	H ₁			100	154	25
14a	C ₈	Cr	L , Q ₁ , H ₁			75	119	19
14b	C ₁₀	Cr	L , H ₁			85	120	23
14c	C ₁₂	Cr	L , H ₁			95	119	22
21a	C ₇	Cr	L ₁			45	184	22
21b	C ₉	Cr	H ₁			50	190	19
21c	C ₁₁	Cr	H ₁	0.4	29	55	190	13
31	C ₁₂	Cr	H ₁ , L ₁	0.7	36	25	158	66
33	C ₈₋₄	Cr	H ₁			25	148	2

Table 4-1: Physicochemical properties of the synthesized surfactant

4.2.1 Methyl glycoside surfactant

4.2.1.1. Krafft temperature

The surfactants of methyl glycoside amide showed low solubility in water at room temperature and high Krafft temperature. That is in good agreement with the result of the high resolution mass spectrum, which besides the expected molecules ion $[M+H]^+$, $[M+Na]^+$ shows an intense peak for $[2M+Na]^+$, see figure. 4-1. The existing of the latter demonstrates the high interaction of surfactants molecules by hydrogen bonding e. g. figure 4-11, which is considered as the main reason for the high Krafft temperature of this surfactants series. Table 4-1 shows an increase of the Krafft temperature for both straight and branched methyl glycoside surfactants compounds **[6a-8c]** with the number of the carbon atoms in the alkyl chain. This is a common surfactants behavior and reflects increasing the hydrophobicity.

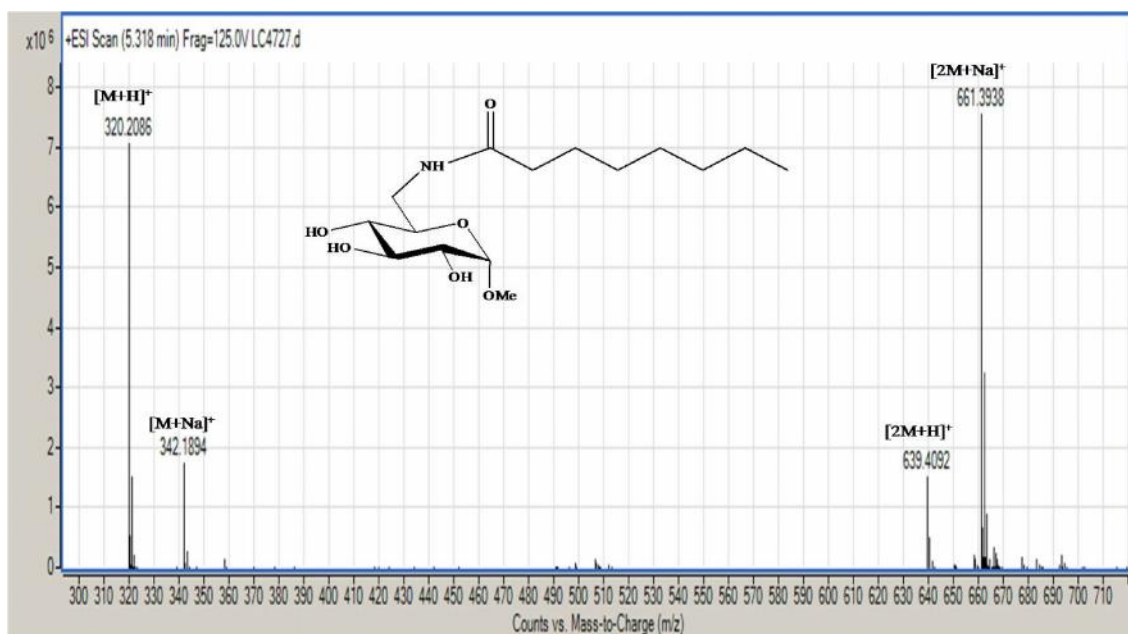


Figure 4-10: An example of the high resolution mass spectrum for methyl glycoside surfactant

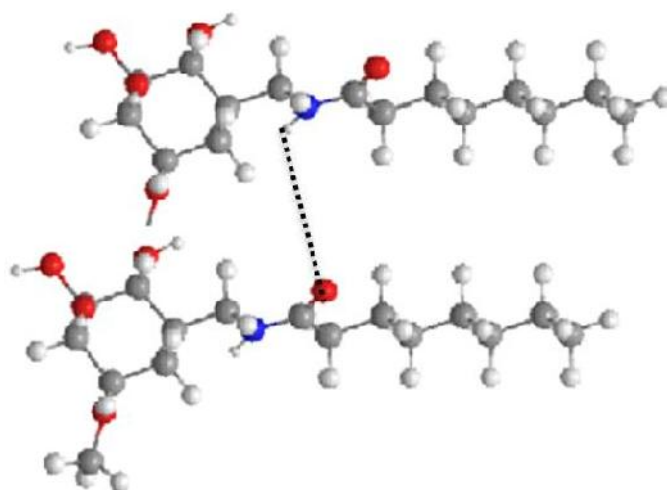
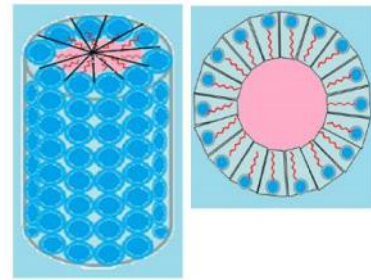
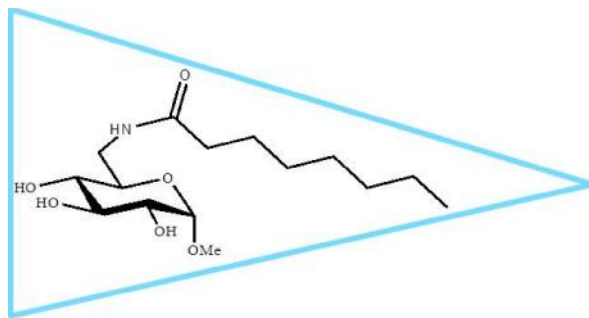


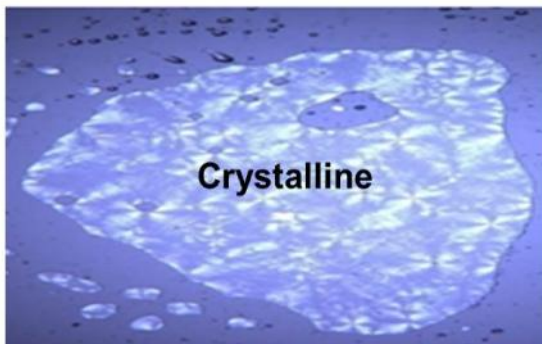
Figure 4-11: Cohesion of the glucoside surfactant molecules by hydrogen bonding

4.2.1.2. Phase behaviour

Non surfactant shows a liquid crystals phase, but all surfactants exhibit a crystalline phase and isotropic liquid. In contact with water hexagonal phases H_1 were found. The curved lyotropic phase is expected based on the shapes of the surfactant molecule, which appears trapezoidal shape. In contact with water the surfactant molecules assemble in order to avoid contact with water for the alkyl chain. The trapezoidal shape leads to a curvature, which results in a hexagonal phase. Optical polarizing microscope images for the straight chain surfactants methyl 6-deoxy-6-octanamido- β -D-glucopyranoside [**6d**] and branched analog methyl 6-deoxy-6-(2-hexyl-dodecanamido)- β -D-glucopyranoside [**8e**] are displayed in figure 4-12 and 2-13, respectively.

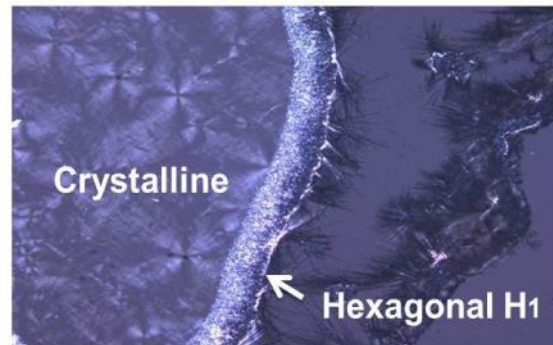


Thermotropic



Crystalline

Lyotropic

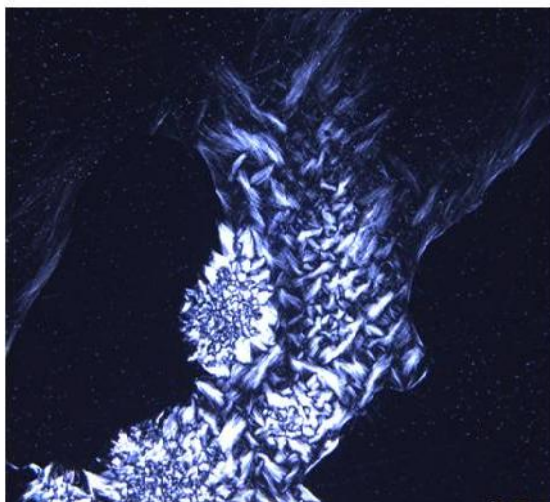


Crystalline

Hexagonal H₁

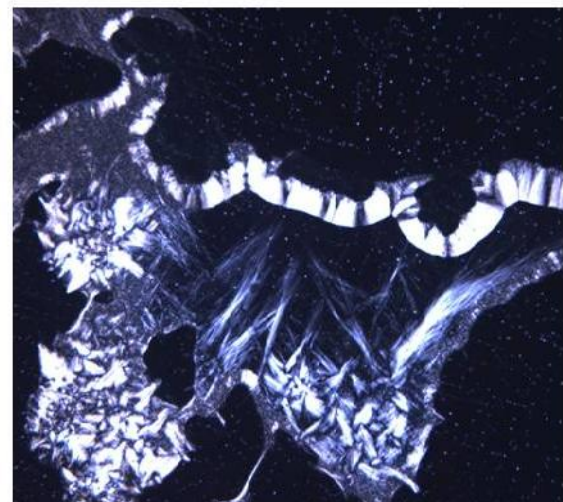
Figure 4-12: Thermotropic and lyotropic phases of methyl 6-deoxy-6-octanamido-β-D-glucopyranoside surfactant.

Thermotropic



Crystalline Phase

Lyotropic



Hexagonal H₁ Phase

Figure 4-13: Thermotropic and lyotropic phases of methyl-6-deoxy-6-(2-butyl-octanamido-β-D-glucopyranoside

The absence of thermotropic liquid crystalline of methyl glycoside monoamide surfactant was confirmed by differential scanning calorimetry (DSC). The values of the enthalpy indicate low temperature phase as a crystalline ones. The DSC spectrum of methyl 6-deoxy-6-dodecanamido- β -D-glucopyranoside [6c] figure 4-14, which shows a melting enthalpy of 37KJ/mol. At the first heating an additional phase transition was found, which refers the evaporation of water at 119 °C as the compound was not dried in a vacuum oven before running the DSC due to the shortage of drying reagent. The second peak at 144 °C, which was confirmed in the second heating, refers to the melting of a crystalline phase. A similar behaviour was observed for the branched surfactant methyl 6-deoxy-6-(2-hexyl-decanamido- β -D-glucopyranoside [8c], which exhibit a melting enthalpy of 25 KJ/mol. Due to the application of vacuum drying no water peak was observed in figure 4-15.

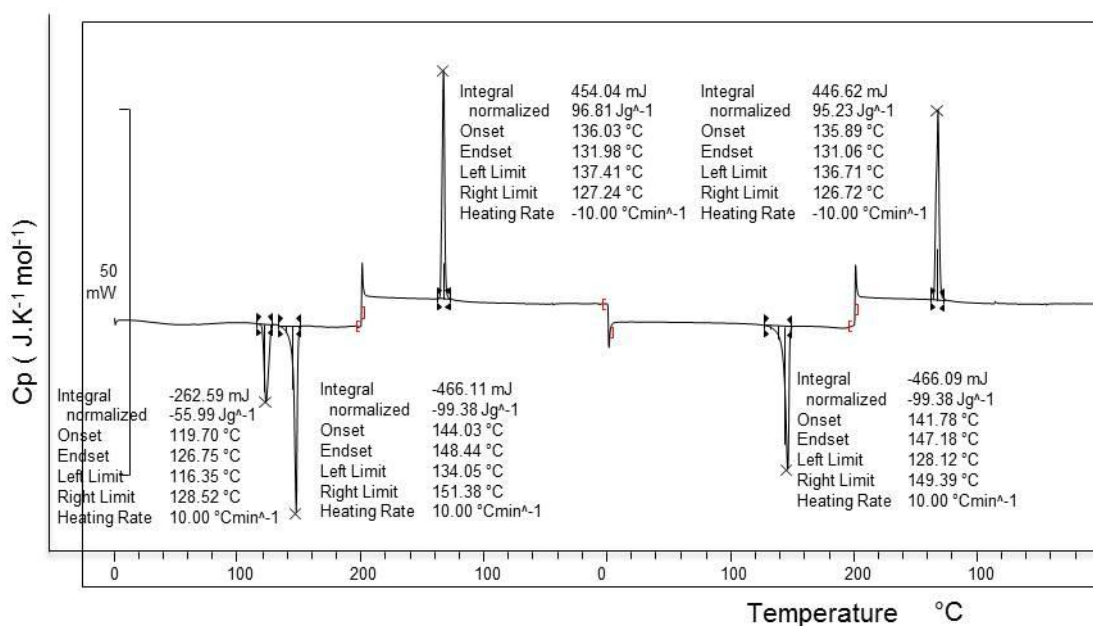


Figure 4-14: DSC spectrum of methyl 6-deoxy-6-dodecanamido- β -D-glucopyranoside [6c]

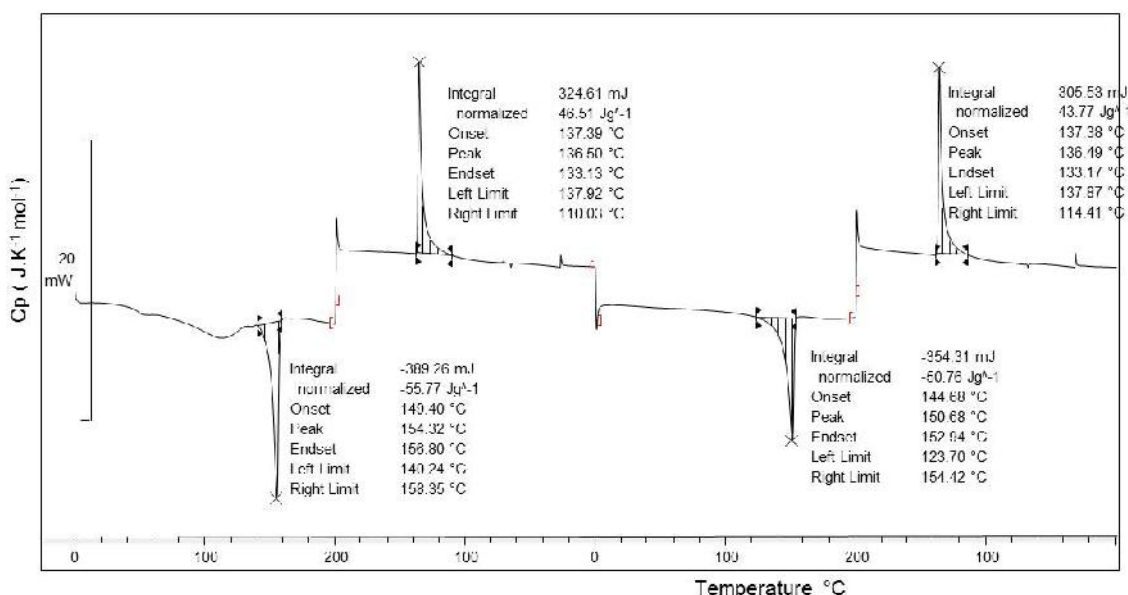


Figure 4-15: DSC spectrum of methyl 6-deoxy-6-(2-hexyl-decanamido)-D-glucopyranoside [8c]

4.2.1.3. Critical micelle concentrations by surface tension

The critical micelle concentrations (CMC) were determined based on surface tension measurements carried out for the series of surfactant solutions with different concentrations. The CMC investigation was limited to the C₁₂ surfactants, both straight and branched, as the shorter chained surfactants are neither expected to exhibit good performance of an oil based media, nor economically due to low contents in renewable resources. Longer chained homologues, on the other hand, are extremely difficult to measure, due to the high Krafft temperature.

The surface tensions and CMC for both C₁₂ surfactants are consistent with previously reported mono saccharides of this chain links (Abe et al., 2004), (31 mN/m at CMC 0.5 mmol/L) for straight surfactants [6c], figure 4-16 and (32 mN/m at CMC 0.5 mmol/L) for C₁₂ branched surfactants [8b], figure 4-17 , both are slightly below that previously reported for [6a] (Maunier et al., 1997b).

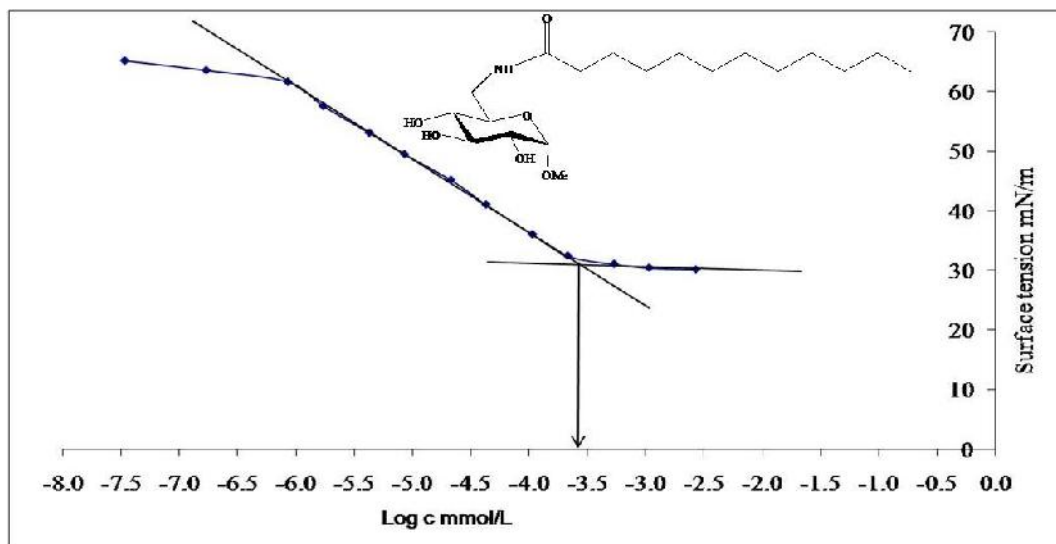


Figure 4-16: CMC investigation of methyl 6-deoxy-dodecanamido-β-D-glucopyranoside surfactant [6c]

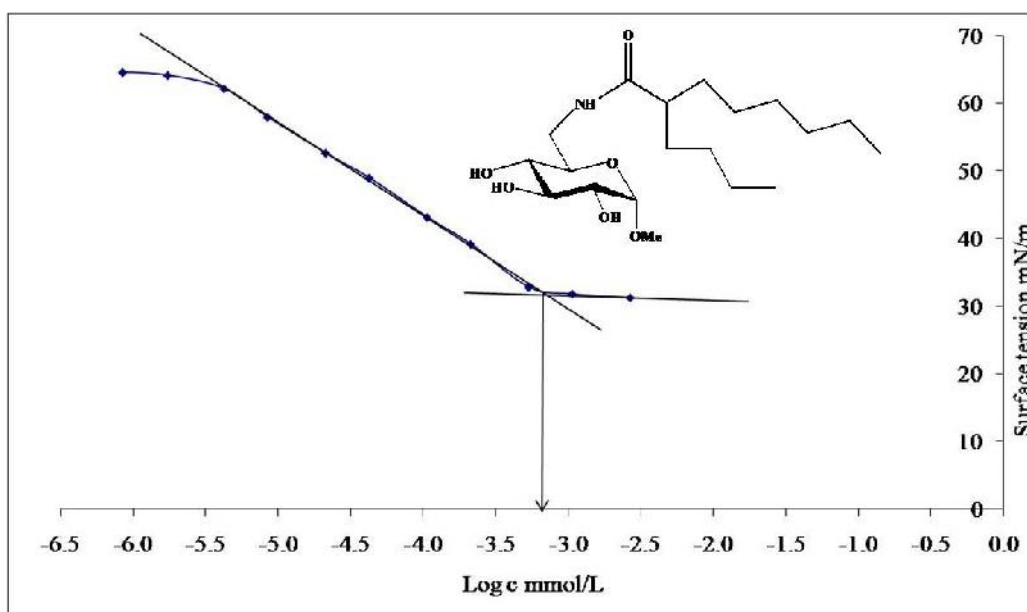


Figure 4-17: CMC investigation of methyl 6-deoxy-6-(2-butyl-octanamido)-β-D-glucopyranoside [8b]

4.2.1.4. Emulsions properties

Two experiments were performed to evaluate the potential of the surfactants as stabilizer for water-in-oil emulsions. The results summarized in table 2-1. The initial experiment was contact penetration with methyl laurate. The hydrophobic solvent was selected based on potential application for hydro-fuel from renewable sources, i.e. biodiesel. Two surfactants were chosen for this experiment, i. e. C₁₂ straight [6c] and C₁₆ branched [8c]. The OPM images in figure 4-18 show that both surfactants are growing into the oil phase and the growing of the surfactants in the oil increase with the chain length. This suggests a good interaction of the surfactant, especially the C₁₆ compound with oil and a potential for the intended application.

The second experiment applied a preliminary formulation study according to the general procedures (3.2.4). The formulation consists of (5 ml) methyl laurate, (0.25 ml) water and (15mg) of the methyl glycoside surfactant (C₁₄, C₁₆ and C₁₆ branched). The surfactants were chosen based to the highest expected solubility in oil. Table 4-2 shows the straight hydrocarbon surfactants led to phase separation within a week (3 days for C₁₄ surfactant, while the C₁₆ analog required about 7 days). The best result we obtained with the C₁₆ branched, which did not separate within the observation period of several weeks. However, the initial fluid emulsion forms a gel after about three weeks, which requires heating above 40 °C to liquefy again.

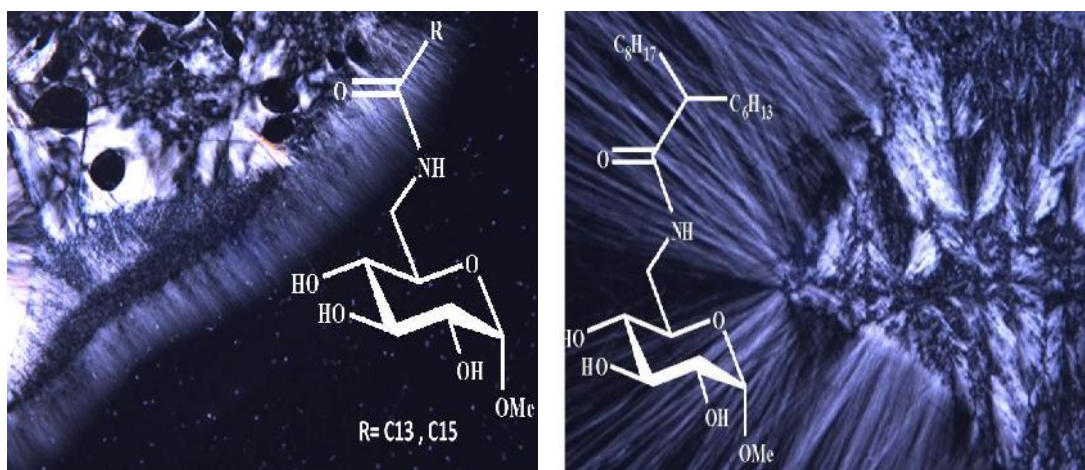


Figure 4-18: OPM investigation of methyl glycoside surfactant with methyl laurate

Surfactant	Chain length	Phase separation time
	R= C ₁₃	3 days
	R= C ₁₅	7 days
	C ₁₀ C ₆	< a month

Table 4-2: Emulsions properties of methyl glycoside surfactants

4.2.2. Bisamide on glucose surfactant

The glucose bis-amide surfactants exhibit high melting temperature, see table 4-1. That can be explained by strong intermolecular hydrogen bonding involving the amide groups. The surfactants only form a crystalline or gel solid as indicated by differential scan calorimetry (DSC), which shows only single phase with an enthalpy that is outside the range of liquid crystalline phase termination (19, 22 and 23 kg/mol). The DSC spectrum of 1,3-didodecanoyl-2-propyl- β -D-glucopyranoside [**14c**] figure 4-19 does not show a phase transition upon cooling, instead an exothermic peak was observed upon reheating closely before the melting point. This indicates a kinetically hindered crystallization and, therefore, identifies the low temperature phase as a crystalline solid. All the compounds of this series exhibit practically identical phase transition data, which suggests that the crystallization is entirely driven by the hydrophilic domain.

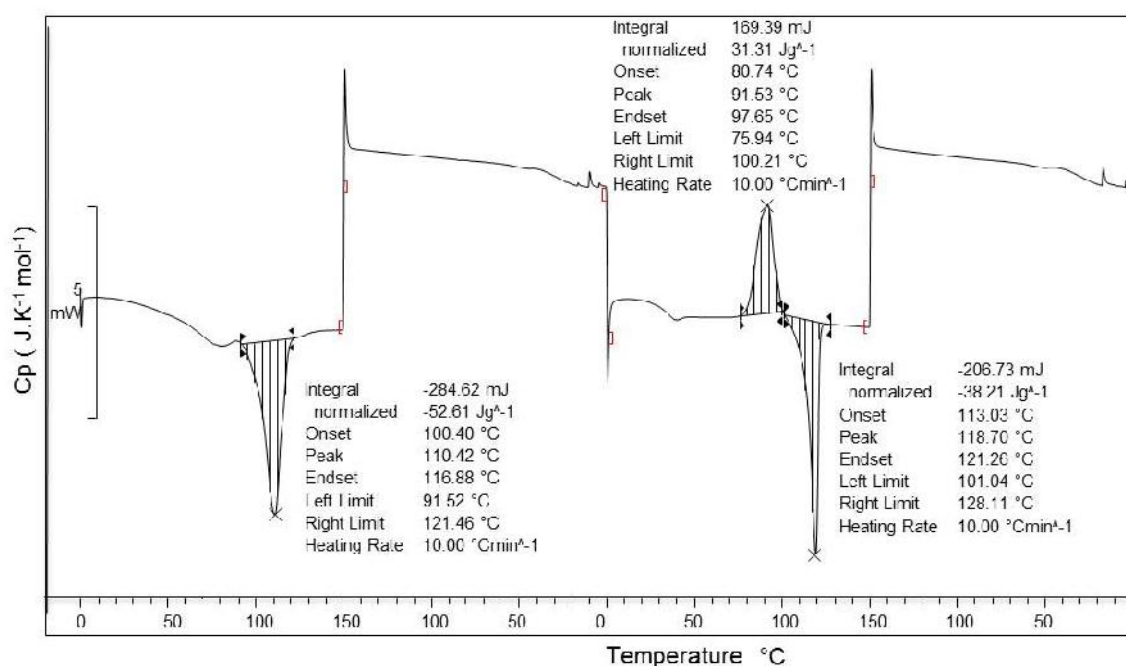


Figure 4-19: DSC thermogram for 1,3-didodecanamido-2-propyl- β -D-glucopyranoside [14c]

The water penetration study of the biantennary glycolipids of glucose exhibit particular the hexagonal phase, H_1 , which is expected based on the shapes of the surfactant molecules; the hydrophobic domain is bigger than the hydrophilic head. Besides this lyotropic phase, the optical polarizing microscope (OPM) image of [14a] in figure 4-20, shows bicontinuous cubic phase Q_1 and lamellar phases L_α on the low water concentration side. For the higher homologs [14b] and [14c] the lyotropic texture is significantly reduced in size, thus less clear. The reason is the low water solubility of the surfactant, which is reflected in the Krafft temperature.

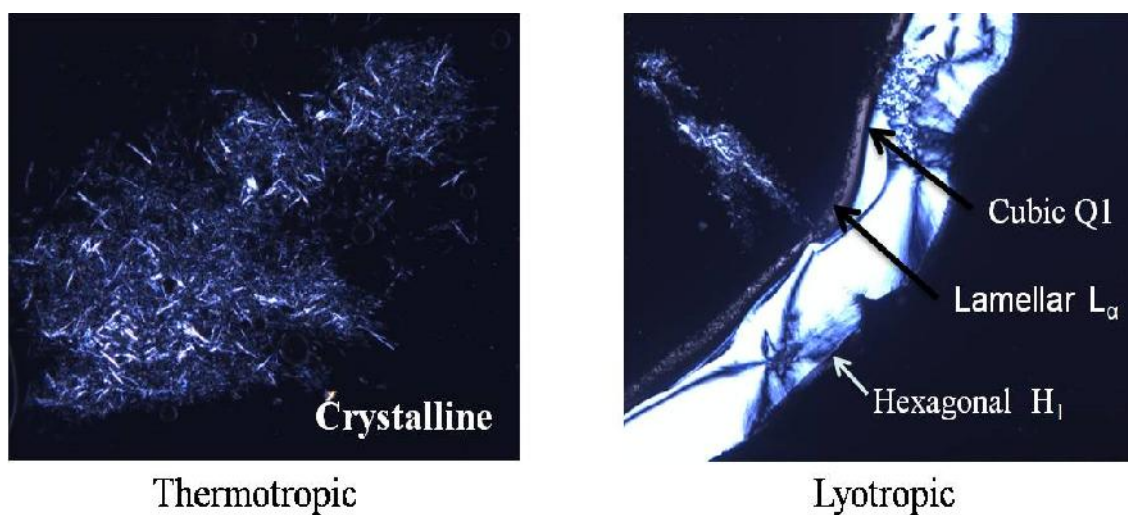


Figure 4-20: Thermotropic and lyotropic phases of the [14a]

4.2.3. Lactose tetrahydropyrimidine surfactant

The mono-antennary surfactants [21a, 21b and 21c] exhibit significantly lower Krafft temperatures than the biantennary surfactants see table 4-1. This is expected based on the reduced size of the overall hydrophilic domain. However, the Krafft temperatures are comparably high, thus indicating strong intermolecular interactions. It is expected that hydrogen bonds involving the tetrahydropyrimidine NH are considerably contributing.

The mono-antennary surfactants [21a, 21b and 21c] did not show a reversible phase transition from a solid to a liquid phase. A phase transition could only be observed for the first heating cycle. The DSC spectrum of [21a] Figure 4-21 shows that the reformation of a solid appears to be strongly kinetic hindered. A closer look revealed two transitions at 183 °C and 185 °C with enthalpies of 16 J/g and 37 J/g, referring to 8 KJ/ mol and 19 KJ/mol, respectively. These two phases-transitions may refer to the different diastereomers of [21a], due to the non-symmetric tetrahydropyrimidine ring. While the longer chained lipids [21b] and [21c] turned into liquid phase at about 190 °C, but the transition coincides with significant degradation, which may be the reason for the non-reversible phase.

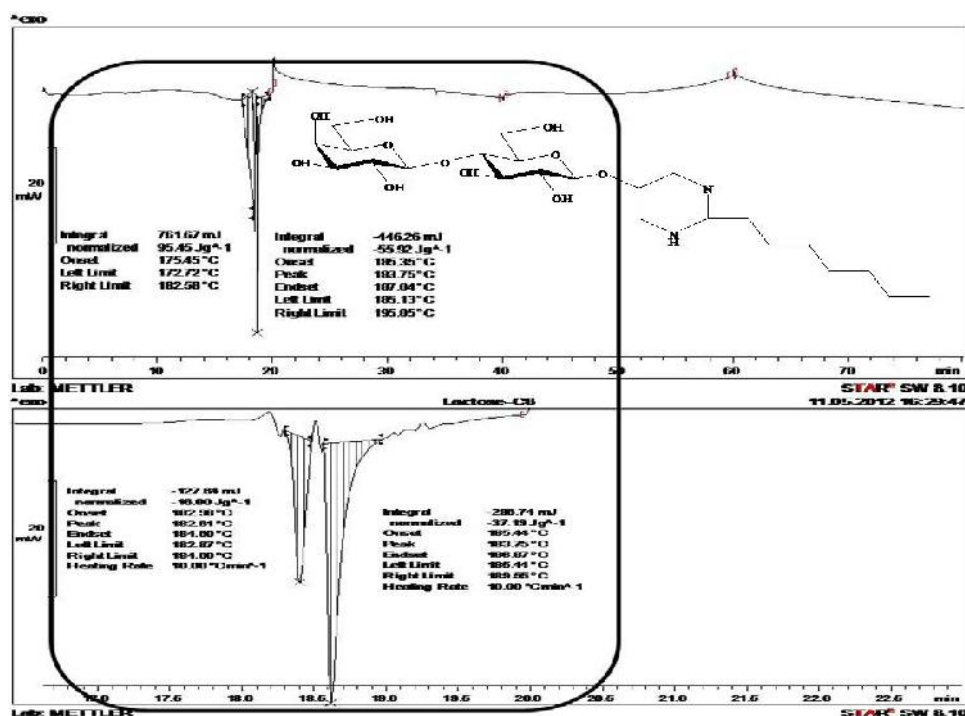


Figure 4-22 : The DSC spectrum of [21a]

In contact with water the mono-antennary surfactants [21b] and [21c] show only a hexagonal H_1 as shown in figures 4-22 and figure 4-23. This reflects a significantly larger molecular surface area for the hydrated sugar compared to the single alkyl chain. The mono-antennary C_7 -chained surfactant [21a] only show amicellar solution, L1. The absence of the hexagonal phase of the latter can be explained with its high solubility.

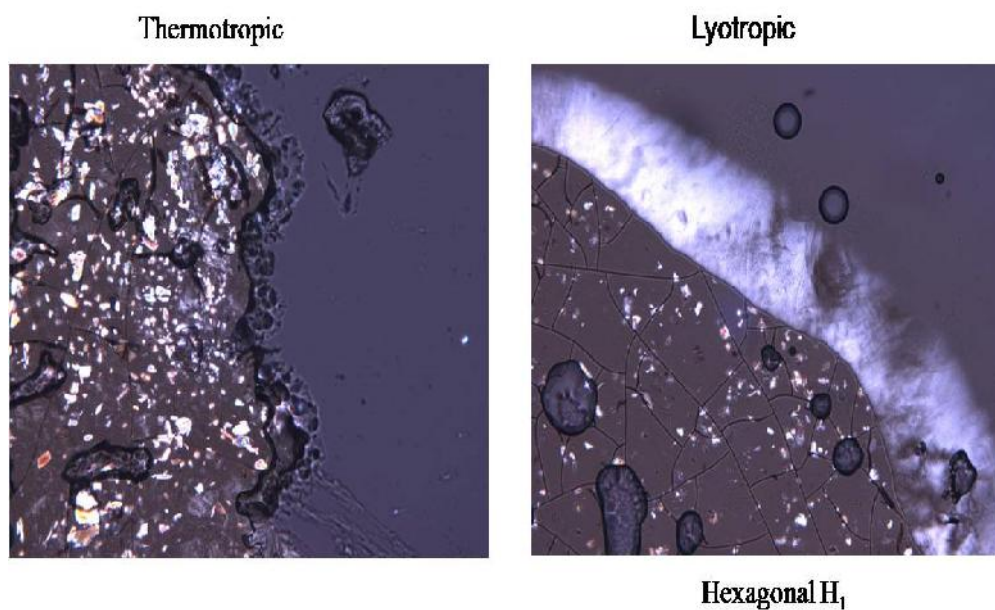


Figure 4-23: Thermotropic and lyotropic phases of surfactant [21b]

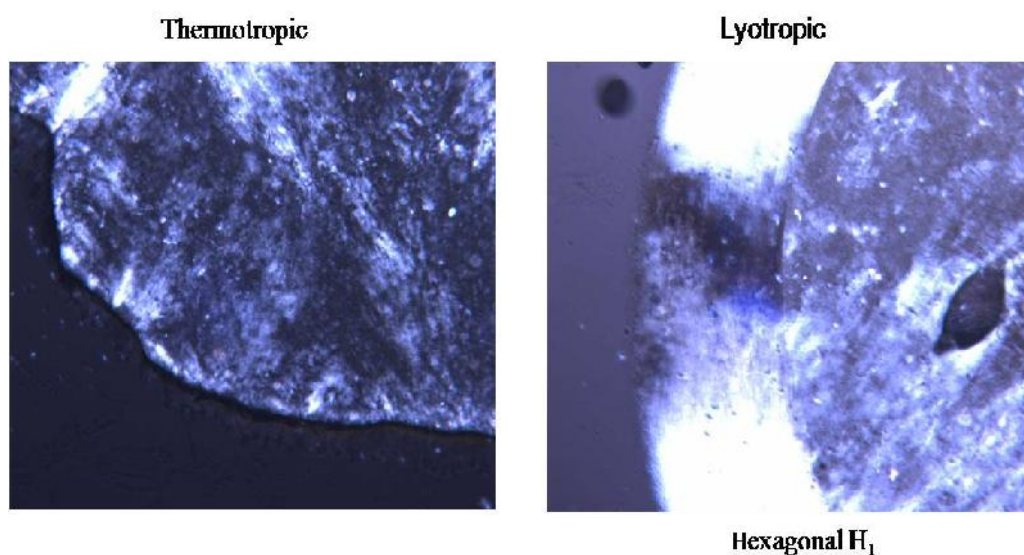


Figure 4-24: Thermotropic and lyotropic phases of surfactant [21c]

The CMC of the C₁₁-surfactant [21c] was determined at 60 °C as 0.41 mmol/L, see figure 4-24. This value is in agreement with those for other surfactants of similar chain length. The correlated surface tension of 29 mN/m suggested good emulsifying ability.

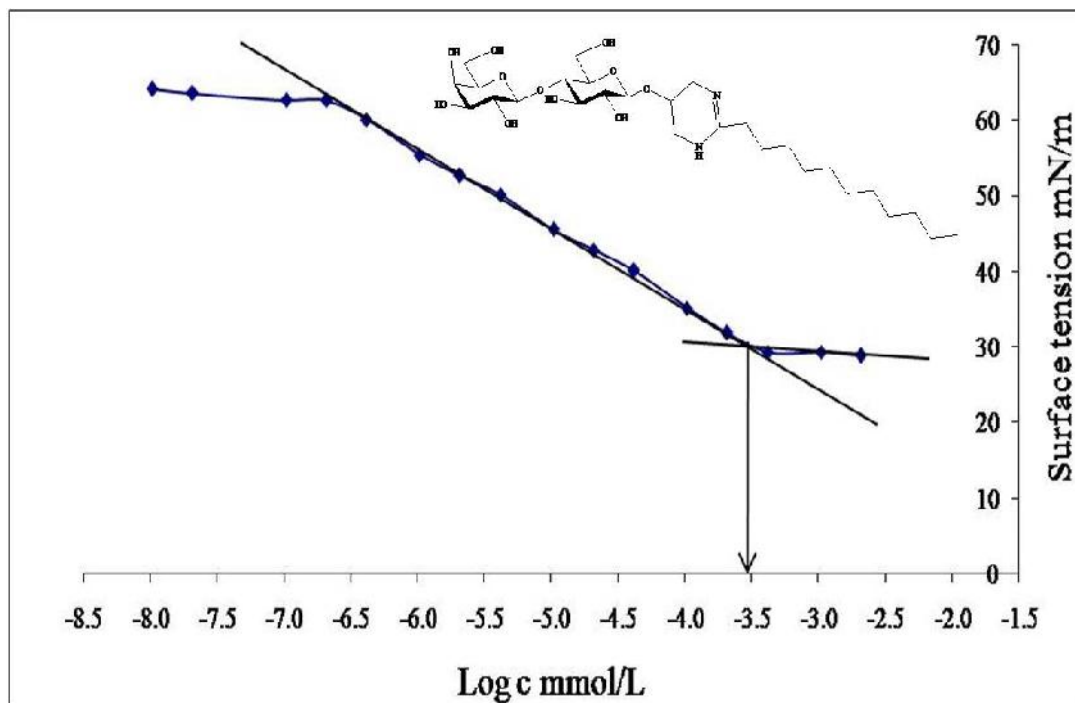


Figure 4-25: CMC investigation of [21c]

4.2.4. Sucrose amide surfactant

Both sucrose amide surfactants both C₁₂straight and corresponding branched are soluble in water at room temperature. The surfactants only exhibit crystalline as a thermotropic phase. The straight surfactant melts at 158 °C with an enthalpy of 66 KJ/mol, figure 4-26. The compound does not crystalline upon cooling. OPM investigations suggest a (partial) decompose of the compound at about 190 °C. In contact with water the micellar phase, L₁ is followed by strong birefringent phase refers to hexagonal phase, H₁, see figure 4-25.

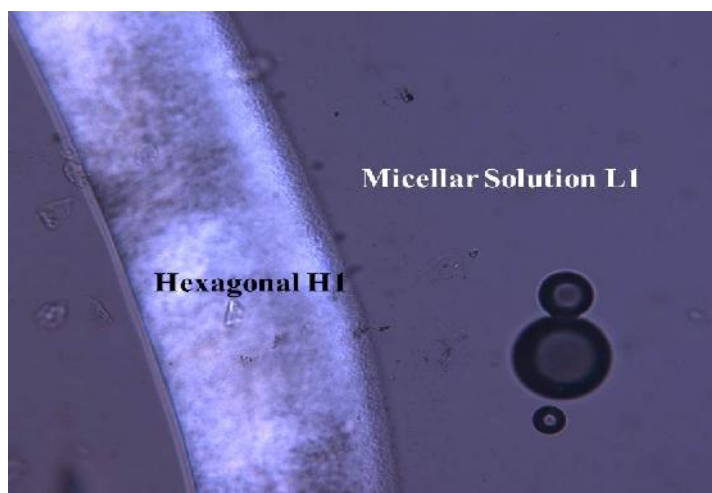


Figure 4-26: Lyotropic phase of the surfactant [31]

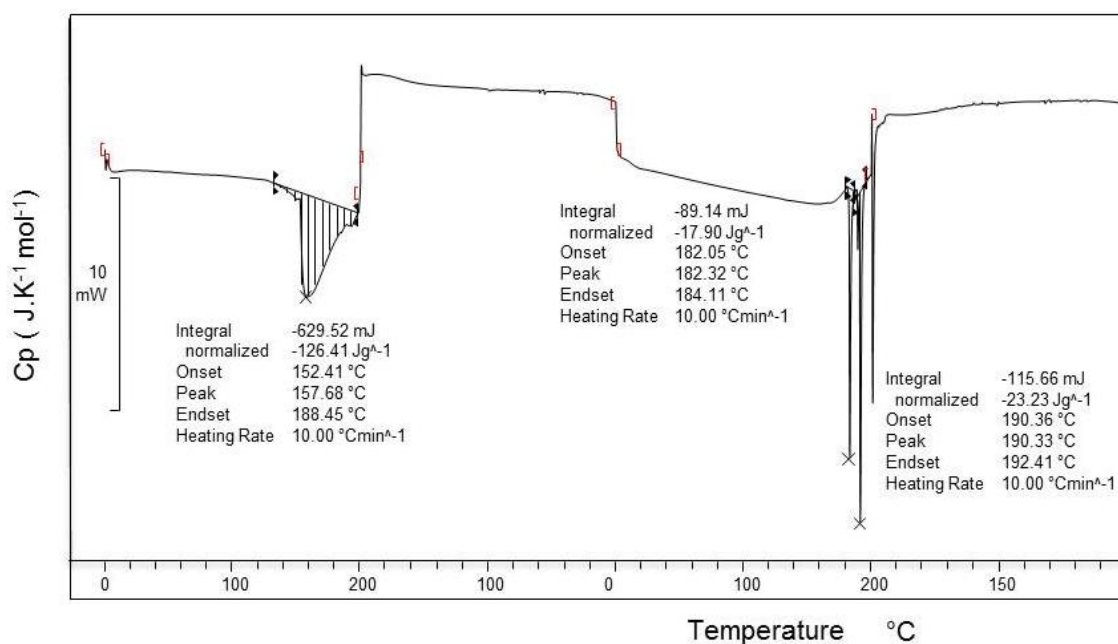


Figure 4-27: DSC spectrum of the surfactant 6'-dodecanamido-sucrose [31]

The CMC of the C₁₂-straight sucrose mono amide surfactants [31] was determined at room temperature as 0.7 mmol/L, see figure 4-27. This value is in good agreement with other di-saccharide surfactants of similar chain length. The correlated surface tension of 36

mN/m suggested good emulsifying ability. Although less than corresponding glycosides, (Polat and Linhard, 2001).

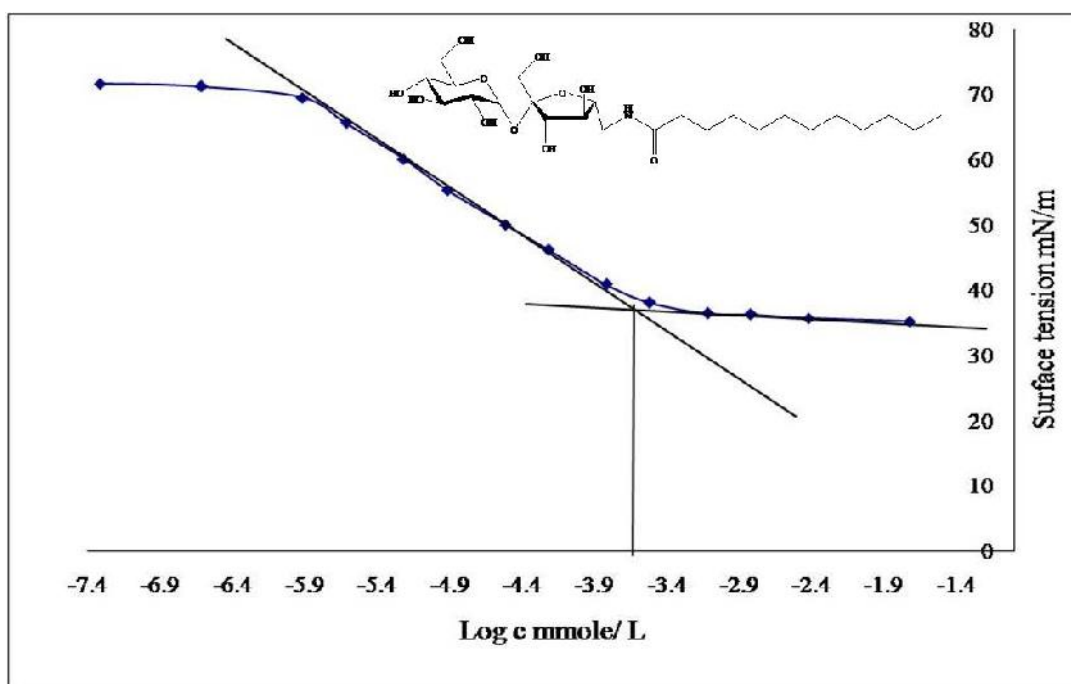


Figure 4-28: CMS investigation of the surfactant 6'-dodecanamido-sucrose [31]

Chapter 5 : Conclusion

Four series of surfactants were synthesized by coupling of sugar azide with fatty acid chloride using the Staudinger reaction. Four different sugars were used, i.e. the monosaccharides methyl glucoside and glucose as well as the disaccharides lactose and sucrose. Applied fatty acids involve straight hydrocarbon chains (C_8 , C_{10} , C_{12} , C_{14} and C_{16}) and branched analogues (C_6C_2 , C_8C_4 and $C_{10}C_6$). While straight fatty acid chlorides were acquired from commercial resources, branched acid chlorides were obtained from the fatty acids by treatment with oxalyl chloride. The physicochemical properties of these surfactants were investigated by optical polarizing microscope (OPM), differential scanning calorimetry (DSC) systematic surface tension measurements.

The Staudinger reaction enables an easy access to sugar amide glycolipids including monoamide and bisamide at different substitution positions. Amide linked sugar based surfactants are easily accessed as chemically pure compounds based on natural renewable resources, and they are reasonable economic.

Amide based glycolipids from methyl glucoside exhibit good interaction with lipid-based oil, like methyl laurate. However, only the alkyl-branched type, namely Methyl-6-deoxy-6-(2-hexyl-decanoyl)- β -D-glucopyranoside, enables the formation of a stable water-in-oil emulsion. The reason lies in the large, carbohydrate-dominated surface area of the surfactant, which originated from a tilting of the hydrocarbon chain towards the cyclic carbohydrate due to the intermolecular H-bonding of the 4-hydroxyl-hydrogen to the amide carbonyl. This curvature, however, does not match the requirements of a reverse phase, which forms the basis for oil-based emulsions, thus formulated emulsions separate. Only chain branching combined with longer chain lengths enables a balance of the surface areas of the surfactant antipodes, leading to stable water-in-oil emulsions. Strong intermolecular interactions of the head group, which are related to the primary amide

structure, lead to high Krafft temperatures causing emulsions to solidify into a gel. Therefore, application of the emulsifier for bio-diesel based hydro-fuel would require preheating of the fuel.

The Staudinger reaction enables easy access to bisamide linked biantennary surfactants with close structural similarity to natural glycol-glycerolipids, provided the carbohydrate does not give rise to sterical hindrance. In case of the latter, an intra-molecular cyclization of a monoamide leads to a tetrahydropyrimidine linked mono-antennary surfactant instead. Amide analogs of glyco-glycero lipids exhibit very high Krafft temperatures. This may affect their potential use in a vesicular delivery system, as formulation requires high temperature treatments. The problem might, however, be solved by applying surfactant blends rather than single compounds. The phase behaviour of the biantennary amide surfactants in contact with water indicates the material as promising for the target application, due to the expression of a cubic phase, which is an important feature for supposed fusion of the vesicle with a cellular membrane.

Monoamide surfactants are also accessible from sucrose, which is considered as the cheapest natural carbohydrate resource. These surfactants exhibit very good solubility in water at room temperature. CMC and surface tension indicate them as a good candidate for oil-in-water emulsifiers.

Chapter 6: Experimental details

6.1. Chemicals

All solvents and reagent were purchased from commercial sources and reagent used without further purification

6.2. General techniques

Thin layer chromatography was performed on silica gel (Merck GF₂₅₄) coated on aluminum plates. The detection applied UV light and dipping of the plates into diluted sulfuric acid H₂SO₄:H₂O: EtOH (2:8:90) or 2% ethanoic ninhydrin solution respectively followed by heating. Compounds were purified either by recrystallization or by flash column chromatography on silica gel 0.035-0.074 μm using either hexane/ethyl acetate or hexane/acetone mixtures in varying ratios. The pressure was generated by a hand bellow. Samples were dried at 50 C in a vacuum oven over phosphorus pentoxide prior to physical investigations.

6.3. Instruments

¹H and ¹³C NMR spectra were recorded in CDCl₃, CD₃OD and DMSO-d₆ on JEOL INM-LA 400, JNM-ECA 400 and Bruker avance 400 spectrometers at 400 and 100 MHz, respectively. Internal calibration of the spectra used the solvent signals, i.e. 7.26 ppm for ¹H-NMR and 77.0 ppm for ¹³C-NMR in CDCl₃ and 3.30 ppm for ¹H-NMR and 49.0 ppm for ¹³C-NMR in CD₃OD (Silverstein et al., 2005). High resolution mass spectra were recorded on an LC-Mass Agilent 6530 Q-TOF mass spectrometer. Elemental analyses were record on Perkin-Elmer series II 2400-CHNS Analyzer. Optical rotations were determined on a Jasco P-1020 digital polarimeter using a 10 cm cell.

IR spectra were recorded on a FT-IR Perkin-Elmer 1600 Series spectrophotometer.

Optical texture of liquid crystal phases and their transition temperatures were investigated using an Olympus BX52 polarizing microscope combined with a Mettler FP82 hot stage (heating stage). Images were captured and stored using analySIS® Imager software by Soft Imaging System GmbH.

Differential scanning calorimetry measurements were carried out on a Mettler Toledo; DSC 822^e equipped with a Haake EK90/MT intra-cooler applying heating rates between 5-10°C/min.

6.4. General procedures

6.4.1. Peracetylation: Synthesis of α -peracetylated anomers.

In a two necked round bottom flask, a suspension of 10 g sodium acetate and 100 mL acetic anhydride was heated to reflux by using a heat gun. A small fraction from 20 g sugar about (2-3g) was then added into the solution and the mixture stirred until the sugar dissolved and the solution became clear before adding more sugar in small fractions. After complete the addition the reaction was heated to ~ 120 °C for about 1.5 hours before being cooled down to room temperature. Then it was poured into ice water slowly and stirred until a sticky white solid compound appeared. It was filtered and recrystallized from ethanol (Fischer, 1916).

6.4.2. Activation of primary hydroxyl groups.

6.4.2.1. Chlorination.

A solution of methyl α -D-glucopyranoside (1.0 eq.), triphenylphosphine (2.0 eq) and N-chlorosuccinimide (2.0 eq.) in dry *N,N*-dimethylformamide (20 mL per gram) was heated to 60 °C with stirring for about 2 hours. When the TLC (ethyl acetate hexane 4:1) showed the consumption of the starting material the solution was cooled and 10 ml of methanol was added in order to decompose unreacted chlorinating agent (NCS).*N,N*-

dimethylformamide was evaporated and triphenylphosphine oxide was removed by added water and extraction with dichloromethane. The filtrate was evaporated to yield methyl 6-chloro-6-deoxy- α -D-glucopyranoside, which subjected to azidation without further purification (Dziedzic et al., 1984).

6.4.2.2. Tosylation

To the solution of sugar derivatives (1.0 eq.) in pyridine (25 ml per gram) was added tosyl chloride (1.0 eq.). After about 24 hours TLC (hexane- ethyl acetate 3:1) showed consumption of the starting material. The mixture was poured into ice water and extracted with dichloromethane for three times. The combined extracts were evaporated and the residue was subjected to azidation without further purification (Suami et al., 1975).

6.4.3. Protection

6.4.3.1. Acetylation

Acetic anhydride (2 mL per one hydroxyl group) was added to sugar derivatives (1.0 eq.) in pyridine. The mixture was stirred at room temperature and monitored by TLC using hexane-ethyl acetate 3:1 as an eluent. When the TLC showed the consumption of the starting materials, the solvent was removed at reduced pressure. The residue was dissolved in dichloromethane and washed with sodium hydrogen carbonate solution and water, dried over magnesium sulfate and concentrated. The compound was used for the next reaction without further purification (Khan et al., 1978).

6.4.3.2. Tert-butyldiphenylsilylation

4-Dimethylaminopyridine (0.026 eq.) was added to the mixture of sucrose (1.0 eq.) and tert-butyldiphenylsilyl chloride (1.1 eq.) in pyridine (25 mL per one gram). The mixture was stirred at room temperature and monitored by TLC using (ethyl acetate- acetone- water, 10:10:1) as eluent. When the TLC showed consumption of the starting materials,

the mixture was concentrated and used for the next reaction without further purification (Barros et al., 2004, Jarosz et al., 2000, Karl et al., 1982).

6.4.4. Glycosidation

A solution of peracetylated sugar -acetate (1.0 eq.) and 1,3-dichloro-2-propanol (1.2 eq.) in dry dichloromethane (25 mL per one gram) was placed in a double necked round bottom flask fitted with a dropping funnel. Boron trifluoride diethyl etherate (1.2 eq) was added drop wise over period of 30 min using syringe. The reaction mixture was then stirred for about 3 hours at room temperature diluted with dichloromethane (10 ml) and poured onto ice water (100 ml). The organic layer was separated and washed with water and saturated sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate, concentrated on a rotary evaporator and the resulting residue was recrystallized from ethanol to yield NMR pure dichloride (Dahmén et al., 1983).

6.4.5. Azidation

A suspension of chloro deoxy sugar (1.0 eq.) or sugar tosylate and sodium azide NaN_3 (6.0 eq) in *N,N*-dimethylformamide DMF (20 ml per gram) was heated to 80 °C for 24 hours. The solution was cooled to room temperature, diluted with water and extracted with dichloromethane. The organic layer was washed with water, saturated NaHCO_3 solution and water, dried over MgSO_4 and concentrated under reduced pressure. After acetylation with acetic anhydride (2.0 eq.) in pyridine (20 mL per gram) and recrystallization with ethanol NMR pure white azide was obtained in very good yield (Carvalho et al., 2010, Li et al., 2006).

6.4.6. Activation of fatty acid

The saturated or unsaturated fatty acids (1.0 eq) and oxalyl chloride (1.4 eq.) were mixed together in 100 mL of chloroform and heated to reflux for 3 hours. The solvent was

removed by evaporation under vacuum to yield NMR pure yellow liquid of the fatty acid chloride in approximately quantitative yield (Quinn et al., 1967, Bauer, 1946).

6.4.7. Staudinger Reaction

Procedure A: Fatty acid chloride (1.6 eq.) in (5 ml) of dichloromethane was added drop wise at room temperature to a mixture of acetylated sugar azide (1 eq.) and triphenylphosphine (1.2 eq) in (20 ml) of dichloromethane. Stirring was continued for about 15 hours at room temperature to obtain a cloudy solution. The solid was filtered off and the solution was washed with 5% solution of sodium hydrogen carbonate, dried over magnesium sulfate and evaporated to dryness. The resulting syrup was chromatographed on silica gel with 6:1 ethyl acetate- acetone as eluent to afford the protected derivatives as white NMR pure crystals (Maunier, Boullanger et al. 1997; Dedola, Hughes et al. 2010).

Procedure B: Triphenylphosphine (1.2 eq.) in dichloromethane was added to the solution of azide (1.0 eq.) in the same solvent. The reaction mixture was stirred at room temperature and monitored by TLC (ethyl acetate: hexane 4:1) , immediately after the nitrogen bubbles were ceased (about 15 mins), fatty acid chloride (1.6 eq.) in dichloromethane, was added drop wise to the mixture and stirring was continued about 15 hours at room temperature (rt). When TLC (ethyl acetate: hexane 4:1) showed the consumption of the starting materials, the solution was filtered off and washed with 5% solution of sodium hydrogen carbonate, dried over magnesium sulfate and evaporated to dryness. The resulting syrup was chromatographed on silica gel with (6:1 ethyl acetate- acetone) as eluent to afford the protected derivatives as white NMR pure crystals.

3.4.8. Deprotection

The acetylated amide derivatives were dissolved in methanol (25 mL per one gram) and treated with a catalytic amount of sodium methoxide to obtain a basic medium. The mixture was stirred for 24 hours at room temperature and monitored by TLC

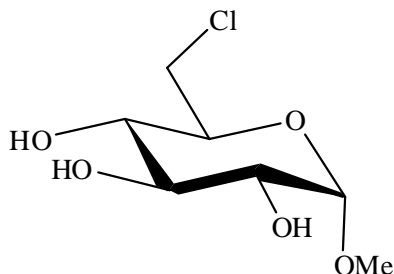
(dichloromethane: ethanol 9:1). The basic catalyst was removed with Amberlite IR 120 (H^+), the solid was filtered and methanol was evaporated to furnish the surfactant in approximately quantitative yield (Hough and Mufti, 1972, Neto et al., 2010).

6.4.9. Desilylation

The solution of tert-butyldiphenylsilyl-sucrose peracetate (1.0 eq.) in tetrahydrofuran (25 mL per one gram) was treated at room temperature with tetra-butylammonium fluoride (1.1eq. 1 M solution in THF). The reaction was monitored by TLC (hexane- ethyl acetate, 3:1), When the starting material was consumed (about 5 hours), the solvent was evaporated and the residue was dissolved in dichloromethane (DCM).The organic solution was washed with water, dried over magnesium sulfate and concentrated. The compound was utilized for the next reaction without further purification (Barros et al., 2000).

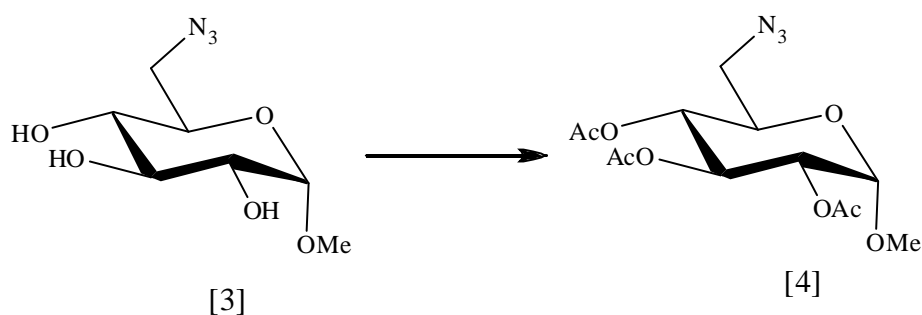
Synthesized surfactants details

Methyl-6-deoxy-6-chloro- -D-glucopyranoside [2]



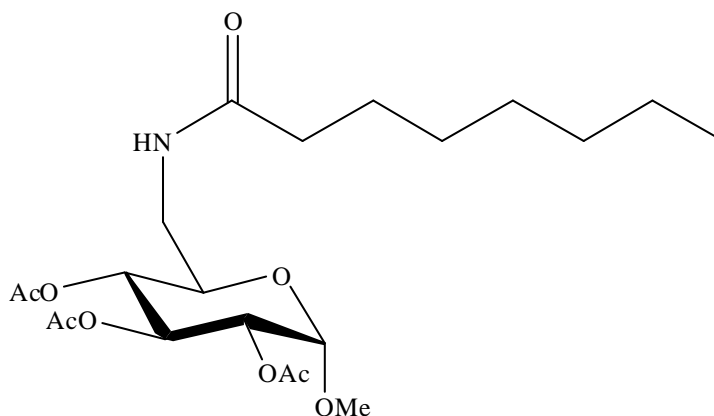
Methyl -D-glucopyranoside [1] (10.00 g , 51.50 mmol) triphenylphosphine (27.00g, 103.00 mmol) and N-chlorosuccinimide (13.75g, 103.00 mmol) were reacted in dry DMF (200 mL) according to general procedures 6.4.2.1 to yield (7.00 g, 64%) of methyl-6-deoxy-6-chloro- -D-glucopyranoside[2], (Dziedzic et al., 1984.)

Methyl 2, 3, 4-tri-O-acetyl-6-deoxy-6-azido- -D-glucopyranoside [4]



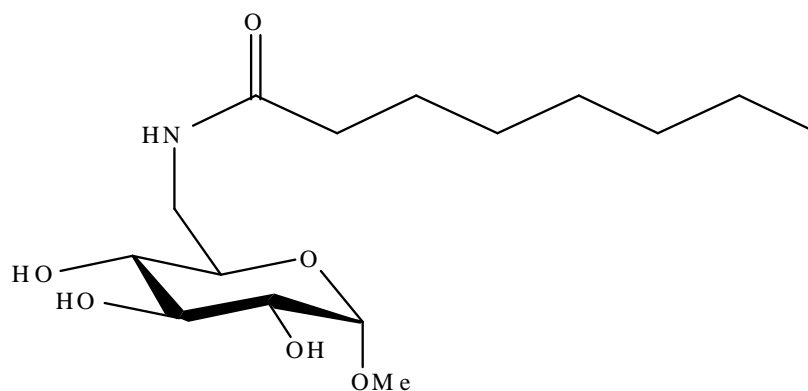
Methyl 6-deoxy-6-chloro- -D-glucopyranoside [2] (5g , 23.52 mmol) and sodium azide NaN₃ (9.20 g, 141.10 mmol) were reacted in (100 mL) of DMF according to the general procedures 6.4.5 to yield methyl -6-deoxy-6-azido- -D-glucopyranoside [3]. The latter was treated with acetic anhydride (4.5 mL,45.62 mmol) in (100 mL) of pyridine to furnished methyl 2,3,4-tri-O-acetyl -6-deoxy-6-azido- -D-glucopyranoside [4](5.7, 70%) as NMR pure white crystals after recrystallization from ethanol,(Carvalho et al., 2010).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-octanamido- β -D-glucopyranoside[5a]:



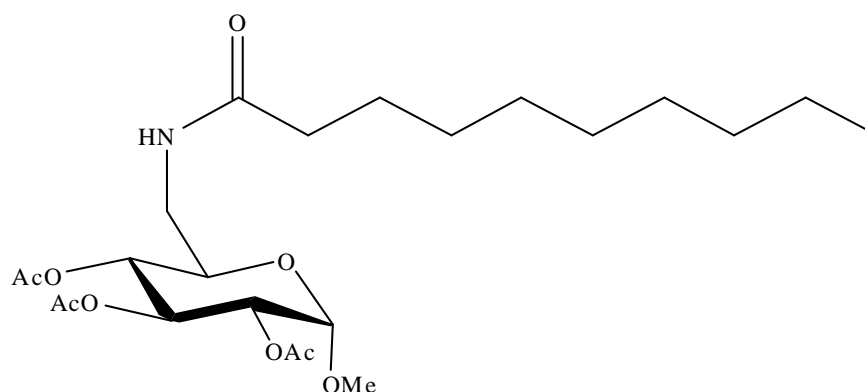
Compound [4] (1.00 g, 2.90 mmol) , octanoyl chloride (0.8 mL, 4.7 mmol) and triphenylphosphine PPh₃ (0.9g ,3.5 mmol) were reacted according to general procedure 6.4.7.A to yield compound [5a] (0.92 g, 71%) as white crystals. ¹H NMR (400 MHz, CDCl₃) = 5.80(dd~t, NH), 5.44 (dd~t, H-3), 4.89 (d, H-1), 4.82 (dd~t, H-4), 4.82 (dd, H-2), 3.84 (ddd, H-5), 3.58 (ddd, H-6A), 3.36 (s, 3H, Me), 3.30 (ddd, H-6B), 2.16 (mc, 2H, -CH₂), 2.05 , 2.03,1.98 (3s, 3x3H, Ac), 1.59 (mc, 2H, -CH₂), 1.31-1.22 (m, 8H, bulk-CH₂), 0.85 (t, 3H, CH₃); ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=9.5, ³J_{4,5}=10.0, ³J_{5,6A}=2.5, ³J_{5,6B}=5.5, ²J₆= 14.5 , ³J_{6A,NH}=6.0 , ³J_{6B,NH}=6.5 Hz. ¹³C NMR (100MHz, CDCl₃) 173.60 (CONH), 170.70, 170.45, 170.43 (COAc), 96.74 (C-1), 70.92 (C-3), 69.82 (C-4), 69.28 (C-2), 67.76 (C-5), 55.23 (CH₃), 38.54 (C-6), 36.49 (-CH₂), 31.40 (-2), 28.94, 28.69 (bulk-CH₂), 25.31 (-CH₂), 22.26 (-1), 20.37, 20.33x2 (Ac),13.67 (). Elemental anal. For C₂₁H₃₅NO₉: C, 56.62; H, 7.92; N, 3.14. Found: C, 56.81; H, 9.56; N, 3.18.

Methyl-6-deoxy-6-octanamido- -D-glucofuranoside [6a]:



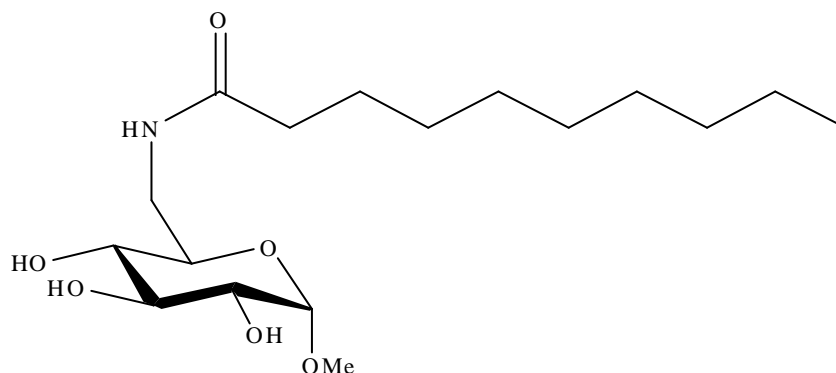
Compound [5a] (0.92 g, 2.07 mmol) was deacetylated according to general procedure 6.4.8.1 to produce compound [6a] (0.61g, 95.6%) as white crystals. mp 131 °C (32 KJ mol⁻¹). ¹H NMR (400 MHz, DMSO) 7.84 (dd~t, NH), 5.03, 4.01, 4.80 (3bs, 3OH), 4.50 (d, H-1), 3.52 (ddd, H-6A), 3.39-3.30 (m, H-5), 3.33 (dd~t, H-3), 3.23 (s, 3H, Me), 3.19 (dd, H-2), 3.02 (ddd~dt, H-6B), 2.89 (dd,~t, H-4), 2.07 (t, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), 1.22 (mc, 8H, bulk-CH₂), 0.85 (t, 3H, CH₃; ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=9.5, ³J_{4,5}=9.0, ³J_{5,6A}=2.0, ³J_{5,6B}=7.0, ²J₆= 14.0 , ³J_{6A,NH}=6.0 , ³J_{6B,NH}=6.0 Hz. ¹³C NMR (100 MHz , DMSO) 173.23 (CONH), 99.91 (C-1), 72.98 (C-2), 72.09x2 (C-3 & C-5), 70.57 (C-4), 54.24 (CH₃), 39.93 (C-6), 35.15 (-CH₂), 31.07 (-), 28.49, 28.34 (bulk-CH₂), 25.25 (-CH₂), 21.90 (-1), 13.73 (). HRMS [M+H]⁺calcd. For C₁₅ H₃₀NO₆: 320.2073, 321.2107 (17%) found, 320.2086 (100%), 321.2107 (22%); [M+Na]⁺: calcd. For C₁₅H₂₉NO₆Na: 342.1893, 343.1926 (17%) found 342.1893 (100%), 343.1927 (20%); [2M+H]⁺ calcd. For C₃₀H₅₉N₂O₁₂: 639.4068, 640.4102 (33%), found, 639.4090 (100%), 640.4126 (34%); [2M+Na]⁺: calcd. for C₃₀ H₅₈ N₂O₁₂Na: 661.3887, 662.3921 (33%), found 661.3935 (100%), 662.3952 (44%).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-decanamido- β -D-glucopyranoside [5b]



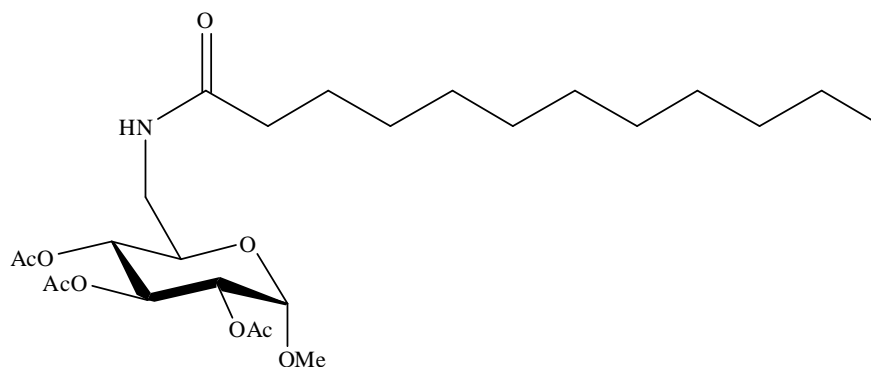
Compound [4] (1.0g, 2.9 mmol) was reacted with decanoyl chloride (1.0 mL, 4.8 mmol) and triphenylphosphine PPh_3 (0.9g 3.5 mmol) according to general procedure 6.4.7.A to furnish compound [6b] (0.98g, 72 %) as white crystals. $[\alpha]_{\text{D}}^{25} = +114$ (c 0.15, CHCl_3). ^1H NMR (400 MHz, CDCl_3) = 5.78 (dd~t, NH), 5.44 (dd~t, H-3), 4.90 (d, H-1), 4.84 (dd~t, H-4), 4.81 (dd, H-2), 3.85 (ddd, H-5), 3.58 (ddd, H-6A), 3.36 (s, 3H, Me), 3.30 (ddd, H-6B), 2.16 (mc, 2H, $-\text{CH}_2$), 2.05, 2.03, 1.97 (3s, 3x3H, Ac), 1.59 (mc, 2H, $-\text{CH}_2$), 1.32-1.18 (m, 12H, bulk- CH_2), 0.85 (t, 3H, CH_3); $^3\text{J}_{1,2}=3.5$, $^3\text{J}_{2,3}=10.0$, $^3\text{J}_{3,4}=9.5$, $^3\text{J}_{4,5}=9.5$, $^3\text{J}_{5,6A}=2.5$, $^3\text{J}_{5,6B}=6.0$, $^2\text{J}_6=14.5$, $^3\text{J}_{6A,\text{NH}}=5.5$, $^3\text{J}_{6B,\text{NH}}=5.5$ Hz. ^{13}C NMR (100MHz, CDCl_3) 173.60 (CONH), 170.72, 170.45, 170.43 (COAc), 96.73 (C-1), 70.92 (C-3), 69.80 (C-4), 69.28 (C-2), 67.76 (C-5), 55.22 (CH_3), 38.54 (C-6), 36.50 ($-\text{CH}_2$), 31.56 ($-\text{CH}_2$), 29.14, 29.04, 29.00, 28.96 (bulk- CH_2), 25.31 ($-\text{CH}_2$), 22.31 ($-\text{CH}_2$), 20.37, 20.33x2 (Ac), 13.71 ($-\text{CH}_3$). Elemental anal. For $\text{C}_{23}\text{H}_{39}\text{NO}_9$: C, 58.33; H, 8.30; N, 2.97; Found: C, 58.25; H, 9.86; N, 2.98.

Methyl-6-deoxy-6-decanamido- β -D-glucopyranoside [6b]



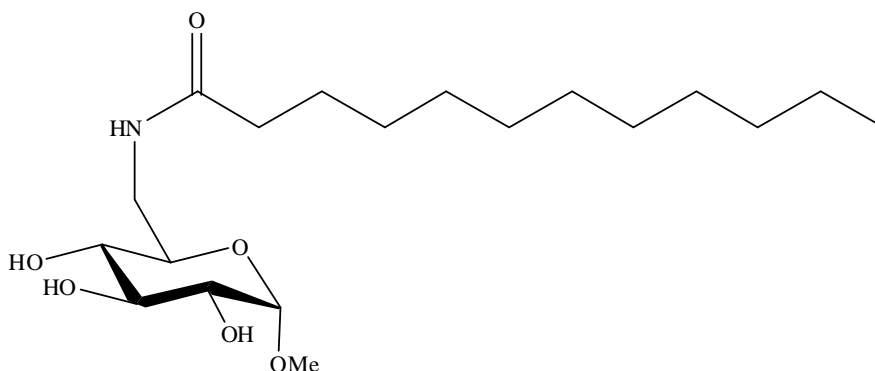
Compound [5b] (0.98g, 2.07 mmol) was deacetylated according to general procedure 6.4.8.1 to produce (0.69g, 95.8%) of compound [6c] as white crystals. mp 139 °C (27 KJ mol⁻¹. [α]_D²⁵ = + 108 (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.83 (dd~t, NH), 5.01, 4.87, 4.77 (3d, 3OH), 4.50 (d, H-1), 3.52 (ddd, H-6A), 3.40-3.29 (m, 2H, H-3 & H-5), 3.24 (s, 3H, Me), 3.19 (dd, H-2), 3.01 (ddd~dt, H-6B), 2.89 (dd,~t, H-4), 2.07 (t, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), 1.22 (mc, 12H, bulk-CH₂), 0.85 (t, 3H, CH₃; ³J_{1,2}=3.5, ³J_{2,3}=9.0, ³J_{3,4}=9.0, ³J_{4,5}=9.0, ³J_{5,6A}=2.0, ³J_{5,6B}=7.5, ²J₆= 13.5, ³J_{6A,NH}=6.0, ³J_{6B,NH}=6.0 Hz. ¹³C NMR (100 MHz , DMSO) 173.23 (CONH), 99.92 (C-1), 72.99 (C-2), 72.09x2 (C-3 & C-5), 70.58 (C-4), 54.24 (CH₃), 39.92 (C-6), 35.14 (-CH₂), 31.17 (-2), 28.79, 28.69, 28.56, 28.53 (bulk-CH₂), 25.24 (-CH₂), 21.93 (-1), 13.75 (). HRMS [M+H]⁺calcd. For C₁₇H₃₄NO₆: 348.2386, 349.2420 (19%), found, 348.2374 (100%), 349.2412 (26%); [M+Na]⁺: calcd. For C₁₇H₃₃NO₆Na: 370.2206, 371.2239 (19%), found 370.2199 (100%), 371.2232 (18%); [2M+H]⁺ calcd. For C₃₄H₆₆N₂O₁₂: 695.4694, 696.4728 (38%); found, 695.4705 (100%), 696.4744 (39%); [2M+Na]⁺: calcd. for C₃₄ H₆₆N₂O₁₂Na: 717.4513, 718.4547 (38%); found 717.4549 (100%), 718.4570 (50%).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-dodecanamido- β -D-glucopyranoside [5c]



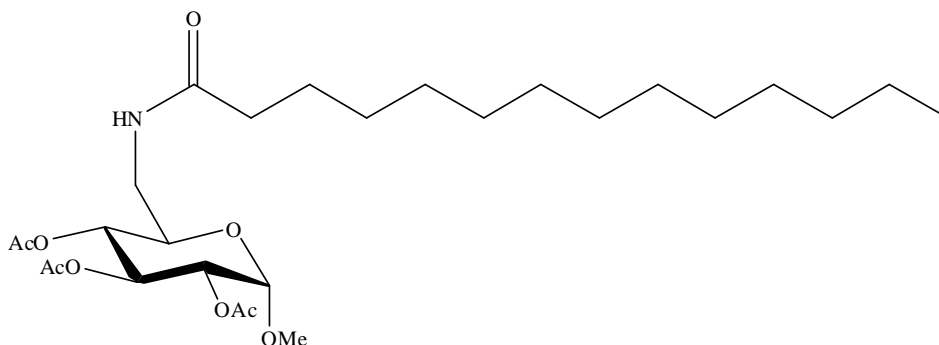
Compound [4] (1.0g, 2.9 mmol) was reacted with dodecanoyl chloride $C_{11}H_{23}COCl$ (1.1 mL, 4.6 mmol) and triphenylphosphine PPh_3 (0.9 g 3.5 mmol) according to general procedure 6.4.7.A to furnish of compound [5d] (1.00g, 69 %) as white crystals. $[\alpha]_D^{25} = +110$ (C 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 5.76 (dd~t, NH), 5.44 (dd~t, H-3), 4.90 (d, H-1), 4.84 (dd~t, H-4), 4.82 (dd, H-2), 3.85 (ddd, H-5), 3.59 (ddd, H-6A), 3.37 (s, 3H, Me), 3.31 (ddd, H-6B), 2.17 (mc, 2H, $-CH_2$), 2.06, 2.04, 1.98 (3s, 3x3H, Ac), 1.60 (mc, 2H, $-CH_2$), 1.32-1.19 (m, 16H, bulk- CH_2), 0.85 (t, 3H, CH_3); $^3J_{1,2}=3.5$, $^3J_{2,3}=10.0$, $^3J_{3,4}=9.5$, $^3J_{4,5}=10.0$, $^3J_{5,6A}=2.5$, $^3J_{5,6B}=6.0$, $^2J_6=14.0$, $^3J_{6A,NH}=6.0$, $^3J_{6B,NH}=6.0$ Hz. ^{13}C NMR (100MHz, $CDCl_3$) 173.61 (CONH), 170.73, 170.46x2 (COAc), 96.78 (C-1), 70.97 (C-3), 69.85 (C-4), 69.32 (C-2), 67.80 (C-5), 55.27 (CH_3), 38.59 (C-6), 36.56 ($-CH_2$), 31.67 ($-CH_2$), 29.41, 29.39, 29.38, 28.25, 29.09x2, 29.06 (bulk- CH_2), 25.36 ($-CH_2$), 22.39 ($-CH_2$), 20.42, 20.38x2 (Ac), 13.77 ($-CH_3$). Elemental anal. For $C_{25}H_{43}NO_9$: C, 59.86; H, 8.64; N, 2.79; Found: C, 59.92; H, 10.41; N, 2.84

Methyl-6-deoxy-6-dodecanamido- -D-glucopyranoside [6c]



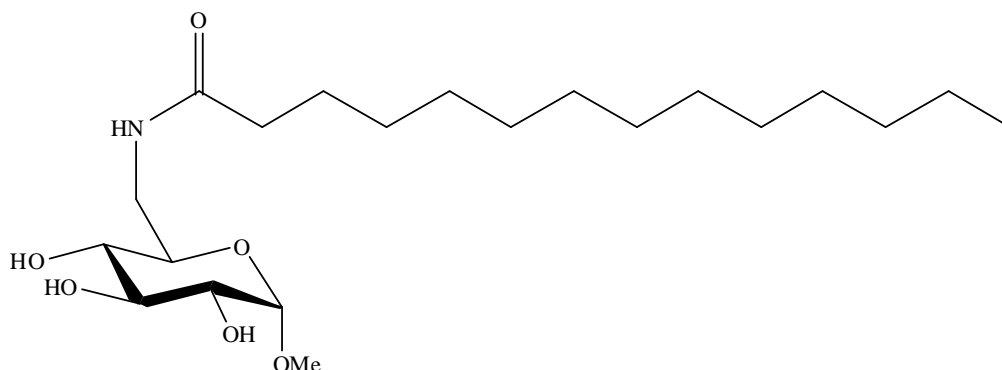
Compound [5d] (0.96g, 1.91 mmol) was deacetylated according to general procedure 6.4.8.1 to provide compound [6d] (0.72g, 96 %) as white crystals.. mp 144 °C (37 KJ mol⁻¹. [α]_D²⁵ = + 110 (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.84 (dd~t, NH), 4.98, 4.81, 4.74 (3d, 3OH), 4.50 (d, H-1), 3.52 (ddd, H-6A), 3.43-3.25 (m, 2H, H-3 & H-5), 3.21 (s, 3H, Me), 3.19 (dd, H-2), 3.01 (ddd~dt, H-6B), 2.89 (dd,~t, H-4), 2.07 (t, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), 1.23 (mc, 16H, bulk-CH₂), 0.85 (t, 3H, CH₃; ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=9.5, ³J_{4,5}=9.5, ³J_{5,6A}=2.0, ³J_{5,6B}=7.0, ²J₆= 14.5 , ³J_{6A,NH}=6.0 , ³J_{6B,NH}=6.0 Hz. ¹³C NMR (100 MHz , DMSO) 173.59 (CONH), 101.58 (C-1), 74.84 (C-2), 73.81 (C-3), 73.41 (C-5) , 71.93 (C-4), 55.64 (CH₃), 41.45 (C-6), 37.10 (-CH₂), 33.04 (-), 30.70x2, 30.60, 30,43x2, 30.31 (bulk-CH₂), 27.08 (-CH₂), 23.65 (-), 14.30 (). HRMS [M+H]⁺calcd. For C₁₉ H₃₈NO₆: 376.2699, 377.2733 (21%), found 376.2688 (100%), 377.2720 (22%); [M+Na]⁺: calcd. For C₁₉H₃₇NO₆Na: 398.2919, 399.2552 (21%); found 398.2506 (100%), 399.2538 (20%); [2M+Na]⁺: calcd. for C₃₈ H₇₄N₂O₁₂Na: 773.5139, 7174.5173 (42%); found 773.5156 (100%), 774.5193 (46%).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-tetradecanoyl- β -D-glucopyranoside [5d]



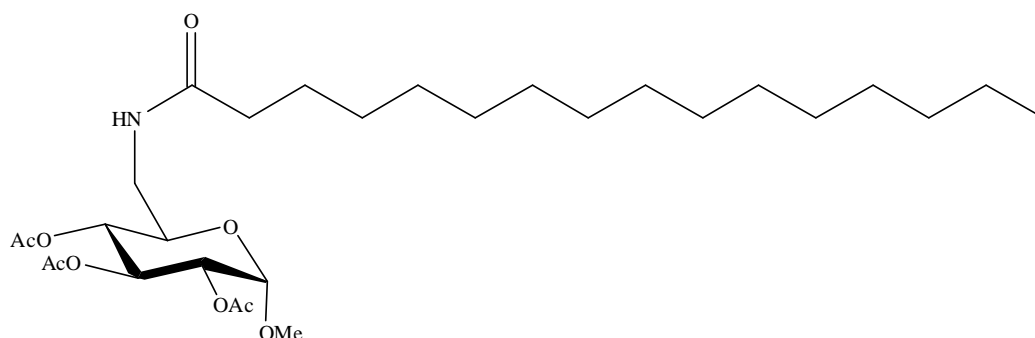
Compound [4] (1.0g, 2.9 mmol) was reacted with tetradecanoyl chloride $C_{13}H_{27}COCl$ (1.3 mL, 3.5 mmol) according to general procedure 6.4.7.A to furnish [5d] (1.05g, 68.62 %) as white crystals. $[\alpha]_D^{25} = +106$ (C 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 5.76 (dd~t, NH), 5.46 (dd~t, H-3), 4.91 (d, H-1), 4.86 (dd~t, H-4), 4.82 (dd, H-2), 3.85 (ddd, H-5), 3.60 (ddd, H-6A), 3.37 (s, 3H, Me), 3.31 (ddd, H-6B), 2.17 (mc, 2H, $-CH_2$), 2.06, 2.04, 1.99 (3s, 3x3H, Ac), 1.61 (mc, 2H, $-CH_2$), 1.32-1.19 (m, 20H, bulk- CH_2), 0.86 (t, 3H, CH_3); $^3J_{1,2}=3.5$, $^3J_{2,3}=10.0$, $^3J_{3,4}=9.5$, $^3J_{4,5}=10.0$, $^3J_{5,6A}=2.5$, $^3J_{5,6B}=6.0$, $^2J_6=14.5$, $^3J_{6A,NH}=6.0$, $^3J_{6B,NH}=6.0$ Hz. ^{13}C NMR (100MHz, $CDCl_3$) 173.59 (CONH), 170.73, 170.46x2 (COAc), 96.78 (C-1), 70.97 (C-3), 69.85 (C-4), 69.32 (C-2), 67.80 (C-5), 55.27 (C-3), 38.59 (C-6), 36.56 ($-CH_2$), 31.67 ($-$), 29.41, 29.39, 29.38, 28.25, 29.09x2, 29.06 (bulk- CH_2), 25.36 ($-CH_2$), 22.39 ($-$), 20.42, 20.38x2 (Ac), 13.77 ($-$). Elemental anal. For $C_{27}H_{47}NO_9$: C, 61.23; H, 8.94; N, 2.64; Found: C, 61.21; H, 10.51; N, 2.70.

Methyl-6-deoxy-6-tetradecanoyl- β -D-glucopyranoside [6d]



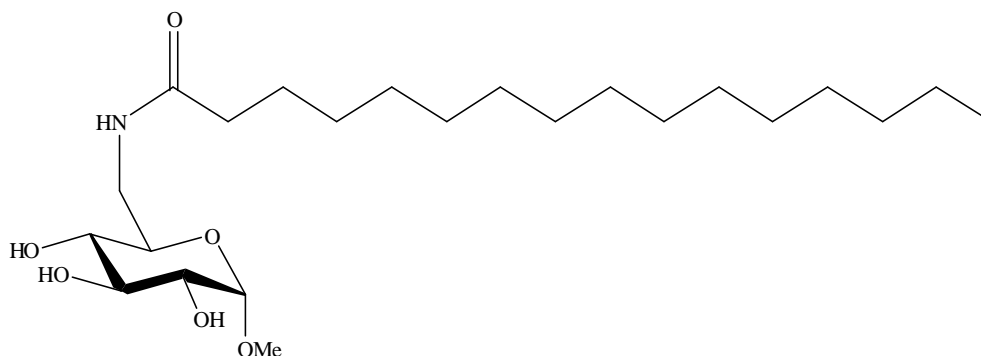
Compound [5d] (0.96g, 1.91 mmol) was deacetylated according to general procedure 6.4.8.1 to provide compound [6d] (0.72g, 96 %) as white crystals. mp 147 °C (42 KJ mol⁻¹. [α]_D²⁵ = + 106 (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.83 (dd~t, NH), 4.96 (d, 4-OH), 4.80 (3-OH), 4.73 (d, 2-OH), 4.51 (d, H-1), 3.52 (ddd, H-6A), 3.36 (ddd, , H-3), 3.37-3.33 (m, H-5), 3.24 (s, 3H, Me), 3.19 (ddd, H-2), 3.01 (ddd~dt, H-6B), 2.89 (ddd, H-4), 2.07 (t, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), 1.23 (mc, 20H, bulk-CH₂), 0.85 (t, 3H, CH₃); ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=9.5, ³J_{4,5}=9.5, ³J_{5,6A}=2.0, ³J_{5,6B}=7.0, ²J₆= 14.0, ³J_{2-OH}=6.5, ³J_{3-OH}=4.5, ³J_{4-OH}=6.5, ³J_{6A,NH}=6.0, ³J_{6B,NH}=6.0 Hz; ¹³C NMR (100 MHz, DMSO) 173.17 (CONH), 99.88 (C-1), 72.97 (C-2), 72.06x2 (C-3 & C-5), 70.54 (C-4), 54.22 (CH₃), 39.90 (C-6), 35.13 (-CH₂), 31.16 (-2), 28.89x4, 28.81, 28,67, 28.56, 28.51 (bulk-CH₂), 25.23 (-CH₂), 21.91 (-1), 13.73 (). HRMS [M+H]⁺calcd. For C₂₁H₄₂NO₆: 404.3012, 405.3046 (23%); found, 404.999 (100%), 405.3042 (25%); [M+Na]⁺ calcd. for C₂₁H₄₂NO₆Na: 426.2832, 427.2865 (23%), found 426.2829 (100%), 427.2854 (22%); [2M+H]⁺ calcd. For C₄₂H₈₅N₂O₁₂: 807.5946, 808.5980 (47%); found, 807.5926 (100%), 808.5978 (42%); [2M+Na]⁺ calcd. for C₄₂ H₈₄N₂O₁₂Na: 829.5765, 830.5799 (47%); found 829.5762 (100%), 830.5792 (50%).

Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-hexadecanoyl- β -D-glucopyranoside [5e]



Compound [4] (1.0g, 2.9 mmol) was reacted with hexadecanoyl chloride $C_{15}H_{31}COCl$ (1.4 mL, 4.6 mmol) according to general procedure 6.4.7.A to furnish compound [5e] (1.1 g, 68%) as white crystals. $[\alpha]_D^{25} = +128$ (C 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 5.77 (dd~t, NH), 5.45 (dd~t, H-3), 4.91 (d, H-1), 4.85 (dd~t, H-4), 4.82 (dd, H-2), 3.86 (ddd, H-5), 3.59 (ddd, H-6A), 3.37 (s, 3H, Me), 3.31 (ddd, H-6B), 2.17 (mc, 2H, $-CH_2$), 2.08, 2.04, 1.98 (3s, 3x3H, Ac), 1.60 (mc, 2H, $-CH_2$), 1.34-1.17 (m, 24H, bulk- CH_2), 0.86 (t, 3H, CH_3); $^3J_{1,2}=3.5$, $^3J_{2,3}=10.0$, $^3J_{3,4}=10.0$, $^3J_{4,5}=10.0$, $^3J_{5,6A}=3.0$, $^3J_{5,6B}=6.0$, $^2J_{6,5}=14.0$, $^3J_{6A,NH}=6.0$, $^3J_{6B,NH}=6.0$ Hz; ^{13}C NMR (100MHz, $CDCl_3$) 173.65 (CONH), 170.53, 170.50x2 (COAc), 96.76 (C-1), 70.94 (C-3), 69.82 (C-4), 69.29 (C-2), 67.77 (C-5), 55.26 (C-3), 38.55 (C-6), 36.54 ($-CH_2$), 31.63 ($-CH_2$), 29.41, 29.37, 29.34, 28.23, 29.07x2, 29.04 (bulk- CH_2), 25.34 ($-CH_2$), 22.39 ($-CH_3$), 20.40, 20.36x2 (Ac), 13.76 ($-CH_3$). Elemental anal. For $C_{27}H_{47}NO_9$: C, 61.23; H, 8.94; N, 2.64; Found: C, 61.94; H, 9.90; N, 2.92.

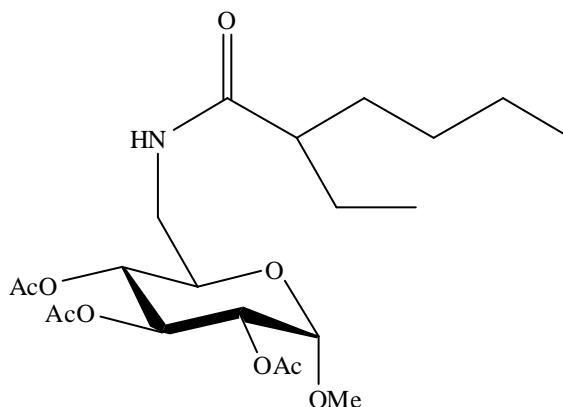
Methyl-6-deoxy-6-hexadecanoyl- β -D-glucopyranoside [6e]



Compound [5e] (1.1 g, 1.97 mmol) was deacetylated according to general procedure 6.4.8.1 to give compound [6e] (0.82 g, 96.5, %) as white crystals. mp 147 °C (44 KJ mol⁻¹). $[\alpha]_D^{25} = +109$ (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.83 (dd~t, NH), 4.98, 4.82, 4.74 (3d, 3OH), 4.50 (d, H-1), 3.52 (ddd, H-6A), 3.39- 3.29 (m, 2H, H-3 & H-5), 3.24 (s, 3H, Me), 3.19 (ddd, H-2), 3.01 (ddd~dt, H-6B), 2.89 (ddd, H-4), 2.07 (t, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), 1.23 (mc, 24H, bulk-CH₂), 0.85 (t, 3H, CH₃); ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=9.5, ³J_{4,5}=9.5, ³J_{5,6A}=2.0, ³J_{5,6B}=7.0, ²J₆= 14.0, ³J_{6A,NH}=6.0, ³J_{6B,NH}=6.0 Hz; ¹³C NMR (100 MHz, DMSO) 180.26 (CONH), 101.62 (C-1), 74.76 (C-2), 73.82 (C-3), 73.55 (C-5), 72.22 (C-4), 55.82 (CH₃), 41.33 (C-6), 34.25 (-CH₂), 33.00, 32.90, 30.75x2, 30.60x2, 30.45, 30.42, 30, 39, 30.37, 28,29x2 (bulk-CH₂), 25.64 (-1), 14.29 (). HRMS [M+H]⁺ calcd. For C₂₃ H₄₆NO₆: 432.3325, 433.3359 (26%); found, 432.3335 (100%), 433.3373 (30%); [2M+H]⁺ calcd. For C₄₆H₉₁N₂O₁₂: 863.6572, 864.6606 (51%); found, 863.6583 (100%), 864.6627 (53%); [2M+Na]⁺: calcd. for C₄₆ H₉₀N₂O₁₂Na: 885.6391, 886.6425 (51%); found 885.6403 (100%), 886.6433 (58%).

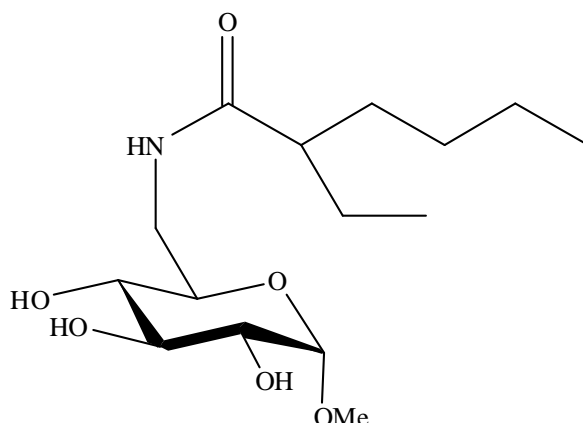
Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-(2-ethyl-hexanamido)- β -D-glucopyranoside

[7a]



Compound [4] (1.00 g, 2.90 mmol), 2-ethylhexanoyl chloride (0.75, 4.6 mmol) and triphenylphosphine PPh₃ (0.9g, 3.5 mmol) were reacted according to general procedure 6.4.7.A to yield compound [7a] (0.90g, 70%) as white crystals. $[\alpha]_D^{25} = +125$ (c 0.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) = 5.80 (dd~t, NH), 5.46 (dd~t, H-3), 4.91 (d, H-1), 4.84 (dd~t, H-4), 4.80 (dd, H-2), 3.84 (ddd, H-5), 3.70 (ddd, H-6A), 3.38 (s, 3H, Me), 3.19 (ddd, H-6B), 2.06, 2.05, 1.98 (3s, 3x3H, OAc), 1.93 (mc, 2H, -CH₂), 1.59 (mc, 2H, -CH₂), 1.45 (mc, 2H), 1.31-1.20 (m, 4H), 0.91-0.84 (m, 6H, CH₃); ³J_{1,2}=3.5, ³J_{2,3}=10.0, ³J_{3,4}=10.0, ³J_{4,5}=9.5, ³J_{5,6A}=2.5, ³J_{5,6B}=6.0, ²J₆=14.5, ³J_{6A,NH}=5.5, ³J_{6B,NH}=5.5 Hz. ¹³C NMR (100MHz, CDCl₃) 176.34/176.31 (CONH), 170.72, 170.45x2 (COAc), 96.78 (C-1), 70.98 (C-3), 69.77 (C-4), 69.71/69.63 (C-2), 66.13/68.10 (C-5), 55.32 (CH₃), 49.76/49.72 (-CH₂), 38.64/38.56 (C-6), 32.17/32.12 (-), 29.67/29.45 (-), 25.70/25.68 (-1), 22.46 (-1), 20.40, 20.35x2 (Ac), 13.61 (-), 11.77 11.70 (-'). Elemental anal. For C₂₁H₃₅NO₉: C, 56.62; H, 7.92; N, 3.14. Found: C, 56.93; H, 8.63; N, 3.56.

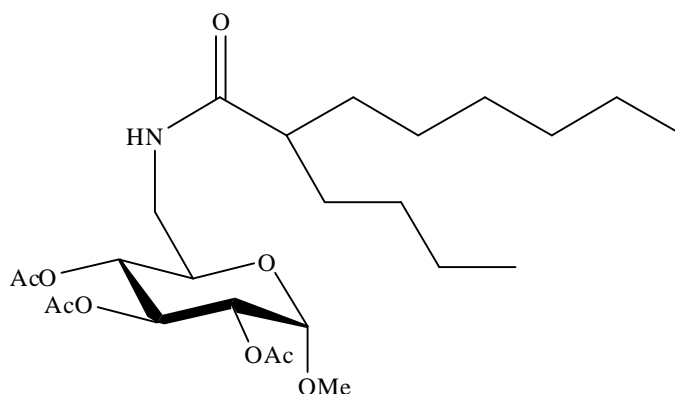
Methyl-6-deoxy-6-(2-ethyl-hexanamido)- α -D-glucopyranoside [8a]



Compound [7a] (0.90g, 2.02 mmol) was deprotected according to general procedure 6.4.8.1 to yield compound [8b] (0.62g, 95.38 %) as white crystals. mp. 185 °C (30 KJ mol⁻¹), [α]_D²⁵ = +121 (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.86 (dd~t, NH), 4.98, 4.83, 4.74 (3s, 3OH), 4.50 (d, H-1), 3.55 (ddd~mc, H-6A), 3.37 (dd~t, H-3), 3.36- 3.28 (m, H-5), 3.25 (s, 3H, Me), 3.18 (dd, H-2), 3.06 (ddd~mc, H-6B), 2.90 (dd, ~t, H-4), 2.10 (mc, -CH), 1.43 (mc, 2H, -CH₂), 1.34-1.10 (m, 8H, bulk-CH₂), 0.82, 0.77 (2xt, 6H, CH₃; ³J_{1,2}=3.5, ³J_{2,3}=9.5, ³J_{3,4}=9.5, ³J_{4,5}=9.0, ³J_{6A,NH}=5.5, ³J_{6B,NH}=5.5 Hz. ¹³C NMR (100 MHz, DMSO) 175.86 / 175.82 (CONH), 99.99 / 99.97 (C-1), 72.84 / 72.82 (C-2), 72.15x2 (C-3 & C-5), 70.93 (C-4), 54.39 (CH₃), 47.19. / 47.16 (-CH), 39.80 (C-6), 31.94 / 31.90 (-2), 29.15 (), 25.49x2 ('-1), 22.03 / 22.01 (-1) 13.72, 13.67 (), 11.68 / 11.64('), . HRMS [M+H]⁺ calcd. For C₁₅ H₃₀NO₆: 320.2073, 321.2107 (17%) found, 320.2095 (100%), 321.2191 (33%); [M+Na]⁺: calcd. For C₁₅H₂₉NO₆Na: 342.1893, 343.1926 (17%) found 342.1872 (100%), 343.1913 (17%); [2M+H]⁺ calcd. For C₃₀H₅₉N₂O₁₂: 639.4068, 640.4102 (33%), found, 639.4073 (100%), 640.4109 (37%); [2M+Na]⁺: calcd. for C₃₀H₅₈N₂O₁₂Na: 661.3887, 662.3921 (33%), found 661.3955 (100%), 662.3946 (44%).

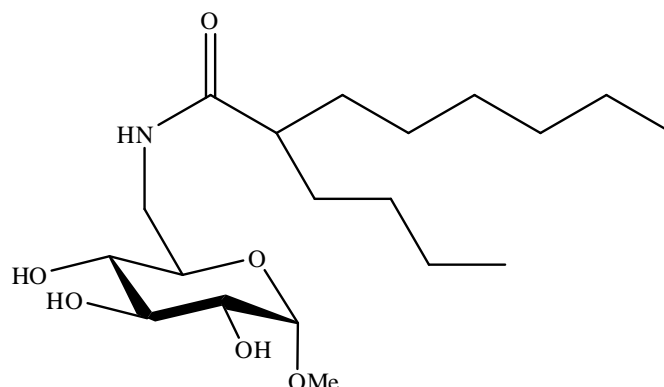
Methyl 2,3,4-tri-O-acetyl-6-deoxy-6-(2-butyl-octanamido)- β -D-glucopyranoside

[7b]



Compound [4] (1.0g, 2.9 mmol) was reacted 2-butyl-octanoyl chloride (1.0, 4.6 mmol) and triphenylphosphine PPh_3 (0.9 g, 3.5 mmol) according to general procedure 6.4.7.A to furnish compound [7b] (0.95g, 65.5 %) as white crystals. $[\alpha]_{\text{D}}^{25} = +105$ (c 0.2, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ = 5.80 (dd~t, NH), 5.46 (dd~t, H-3), 4.91 (d, H-1), 4.84 (dd~t, H-4), 4.80 (dd, H-2), 3.83 (ddd, H-5), 3.76 (ddd~mc, H-6A), 3.38, (s, 3H, Me), 3.16 / 3.14 (ddd, H-6B), 2.06, 2.05, 1.99 (3s, 3x3H, OAc), 1.97 (mc, ,), 1.56 (mc, 2H), 1.40 (mc, 2H) 1.32-1.20 (mc, 12H), 0.86-0.85 (2t, 6H, CH_3); $^3\text{J}_{1,2}=3.5$, $^3\text{J}_{2,3}=10.0$, $^3\text{J}_{3,4}=10.0$, $^3\text{J}_{4,5}=10.0$, $^3\text{J}_{5,6A}=2.5$, $^3\text{J}_{5,6B}=6.0$, $^2\text{J}_6=14.5$, $^3\text{J}_{6A,\text{NH}}=6.0$, $^3\text{J}_{6B,\text{NH}}=6.0$ Hz. ^{13}C NMR (100 MHz, CDCl_3) 176.84 (CONH), 170.71, 170.47x2 (COAc), 96.73 (C-1), 70.97 (C-3), 69.73, 69.71 (C-2, C-4), 68.11 (C-5), 55.30 (CH_3), 48.13 (C-6), 38.61 (-CH), 32.80, 32.54, 31.50, 29.69, 27.34 (bulk- CH_2), 22.47, 22.33 (-1, '-1), 20.42, 20.37x2 (Ac), 13.73, 13.63 (, '). Elemental anal. For $\text{C}_{21}\text{H}_{35}\text{NO}_9$: C, 56.86; H, 8.64; N, 2.79. Found: C, 59.91; H, 10.62; N, 2.79.

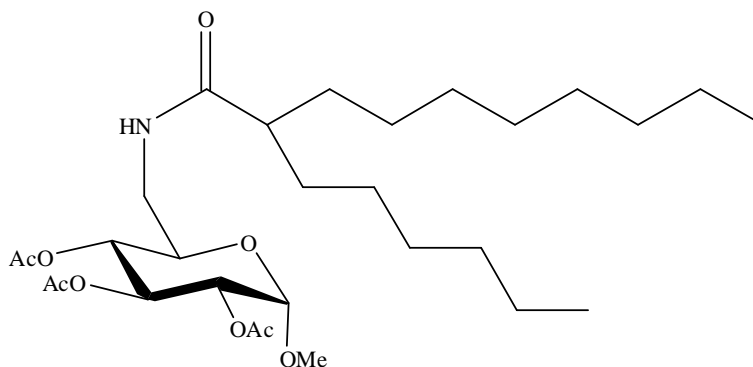
Methyl-6-deoxy-6-(2-butyl-octanamido)- α -D-glucopyranoside [8b]



Compound [7b] (0.95g, 1.89 mmol) was deacetylated according to general procedure 6.4.8.1 to provide compound [8b] (0.68g, 95.77%) as white crystals. mp 171 °C (31 KJ mol⁻¹), $[\alpha]_D^{25} = +125$ (c 0.2, CH₃OH). ¹H NMR (400 MHz, DMSO) 7.88 (dd~t, NH), 5.06, 4.93, 4.81 (3bs, 3OH), 4.50 (d, H-1), 3.56 (ddd~mc, H-6A), 3.37 (dd~t, H-3), 3.32 (ddd, H-5), 3.28 (s, 3H, Me), 3.18 (dd, H-2), 3.04 (ddd~mc, H-6B), 2.89 (dd, ~t, H-4), 2.16 (mc, -CH), 1.41 (mc, 2H, -CH₂), 1.20 (m, 14H, bulk-CH₂), 0.84, 0.82 (2x2s, 6H, CH₃; ³J_{1,2}=3.5, ³J_{2,3}=9.5, ³J_{3,4}=9.5, ³J_{4,5}=9.5, ³J_{5,6A}=2.0, ³J_{5,6B}=7.5, ²J₆=14.0, ³J_{6A,NH}=6.0, ³J_{6B,NH}=6.0 Hz. ¹³C NMR (100 MHz, DMSO) 176.02 (CONH), 100.00 (C-1), 72.84 (C-2), 72.21x2 (C-3 & C-5), 70.96 (C-4), 54.34 (CH₃), 45.49 (-CH), 39.80 (C-6), 32.64, 32.32 (-2, '-2), 31.15 / 31.12, 29.17, 28.66 / 28.63 (bulk-CH₂), 26.86 (-CH₂), 22.05 / 22.04, 21.91 (-1, '-1) 13.75, 13.72 (, '). HRMS [M+H]⁺ calcd. For C₁₉H₃₈NO₆: 376.2699, 377.2733 (21%) found, 376.2771 (100%), 377.2782 (34%); [M+Na]⁺ calcd. For C₁₉H₃₇NO₆Na: 398.2919, 399.2552 (21%) found 398.2558 (100%), 399.2597 (20%); [2M+H]⁺ calcd. For C₃₈H₇₅N₂O₁₂: 751.5320, 752.5354 (42%), found, 751.5412 (100%), 752.5434 (50 %); [2M+Na]⁺ calcd. for C₃₈H₇₄N₂O₁₂Na: 773.5139, 774.5173 (42%), found 773.5274 (100%), 774.5281 (60%).

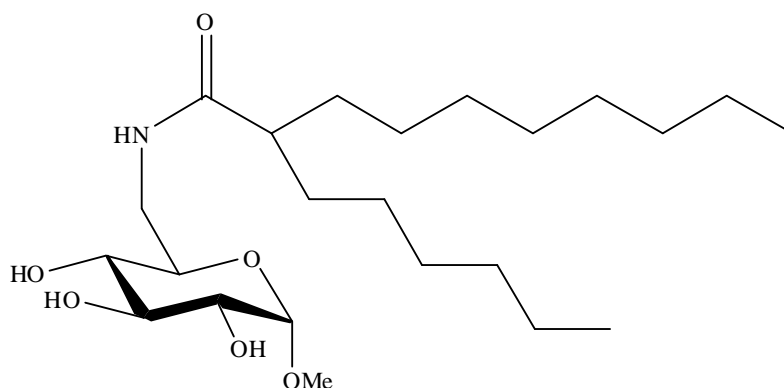
Methyl 2, 3, 4-tri-O-acetyl-6-deoxy-6-(2-hexyl-decanoyl)- β -D-glucofuranoside

[7c]



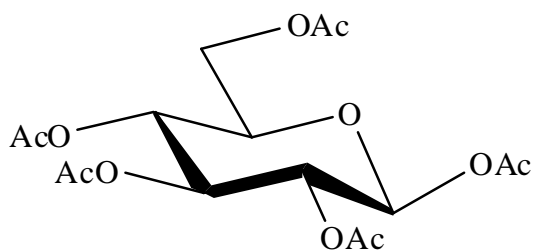
Compound [4] (1.0g, 2.9 mmol) was reacted with 2-hexyldecanoyl chloride $C_8H_{17}CH(COCl)C_6H_{13}$ (1.3 g, 4.7 mmol) and triphenylphosphine PPh_3 (0.9 g, 3.5 mmol) according to general procedure 6.4.7.A to furnish compound [7a] (1.1 g, 68%) as white crystals. $[\alpha]_D^{25} = +109$ (c 0.2, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) δ = 5.81 (dd~t, NH), 5.44 (dd~t, H-3), 4.90 (d, H-1), 4.82 (dd~t, H-4), 4.78 (dd, H-2), 3.81 (ddd, H-5), 3.74 (ddd, H-6A), 3.36 (s, 3H, Me), 3.14 (ddd, H-6B), 2.04, 2.03, 1.97 (3s, 3x3H, OAc), 2.02-1.93 (mc, ,), 1.55 (mc, 2H), 1.38 (mc, 2H), 1.22 (mc, 16H), 0.84 (t, 6H, CH_3); $^3J_{1,2}=3.5$, $^3J_{2,3}=10.0$, $^3J_{3,4}=10.0$, $^3J_{4,5}=9.5$, $^3J_{5,6A}=2.5$, $^3J_{5,6B}=5.0$, $^2J_6=14.0$, $^3J_{6A,NH}=5.5$, $^3J_{6B,NH}=5.5$ Hz. ^{13}C NMR (100 MHz, $CDCl_3$) 176.47 (CONH), 170.65, 170.45x2 (COAc), 96.69 (C-1), 70.94 (C-3), 69.72, 69.67 (C-2, C-4), 68.07 (C-5), 55.24 (CH_3), 48.07 (C-6), 38.60 (C-6), 32.77, 32.74 (C-2, C-2), 31.45, 29.43, 29.08, 28.99 (bulk- CH_2), 27.48/ 27.43, 27.34 / 27.29 (C-2, C-2), 22.30x2 (C-1, C-1), 20.36, 20.32x2 (Ac), 13.71, 13.68 (C-1, C-1). Elemental anal. For $C_{27}H_{47}NO_9$: C, 62.21; H, 11.26; N, 2.64. Found: C, 61.94; H, 9.90; N, 2.44.

Methyl-6-deoxy-6-(2-hexyl-decanoyl)- α -D-glucopyranoside [7c]



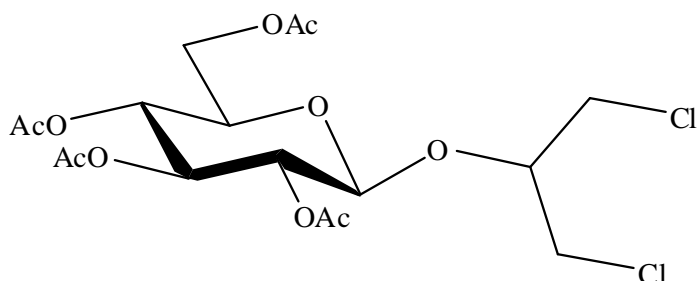
Compound [7c] (1.08g, 1.93mmol) was deacetylated according to general procedure 6.4.8.1 to produce compound [8c] (0.81g, 96 %) as white crystals. mp 154 °C (25 KJ mol⁻¹). $[\alpha]_D^{25} = +128$ (c 0.2, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = 4.65 (d, H-1), 3.67-3.59 (m, H-6A), 3.61 (dd~t, H-3), 3.54 (ddd, H-5), 3.43-3.33 (m, 2H, H-2 & H-6B), 3.39 (s, 3H, Me), 3.11 (dd~t, H-4), 2.23 (mc, -CH), 1.55, 1.38 (2mc, 2x2H, -CH₂), 1.28 (mc, 20H, bulk-CH₂), 0.89, (t, 6H, CH₃); ³J_{1,2}=3.5, ³J_{2,3}=9.5, ³J_{3,4}=9.5, ³J_{4,5}=10.0, ³J_{5,6A}=2.0, ³J_{5,6B}=7.5, ²J₆=14.0, ³J_{6A,NH}=6.0, ³J_{6B,NH}=6.0 Hz. ¹³C NMR (100 MHz, CD₃OD) = 180.27 (CONH), 100.62 (C-1), 74.76, 73.83, 73.56, 72.22 (C-2, C-3, C4 & C-5), 55.82 (CH₃), 48.37 (-CH), 41.33 (C-6), 33.24 (-2), 33.00, 32.90, 30.60x2, 30.42x2, 30.39, 30.37, 28.69x2 (bulk-CH₂) (-2), 23.64 (-1), 14.27 (). HRMS [M+H]⁺ calcd. For C₂₃H₄₆NO₆: 432.3325, 433.3359 (26 %) found, 432.3299 (100%), 433.3340 (28 %); [M+Na]⁺: calcd. For C₂₃H₄₅NO₆Na: 454.3450, 455.3145 (26%) found 454.3117 (100%), 455.3131 (26%); [2M+H]⁺ calcd. For C₄₆H₉₁N₂O₁₂: 863.6572, 864.6606 (51 %), found, 863.6559 (100 %), 864.6601 (54 %); [2M+Na]⁺: calcd. for C₄₆H₉₀N₂O₁₂Na: 885.6391, 886.6425 (51 %), found 885.6384 (100 %), 886.6412 (58 %).

1,2,3,4,6 Penta-O-acetyl- -D-glucopyranoside [10]



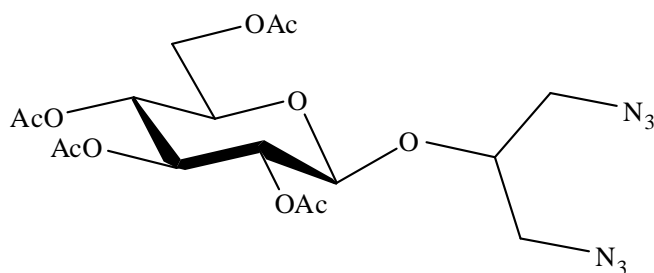
A mixture of glucose [9] (20 g, 110 mmol), acetic anhydride (100 mL) and sodium acetate (10 g, 150 mmol) was reacted according to the general procedure 6.4.1 to yield (33 g, 76%) of compound [10] as NMR pure white crystals, (Fischer, 1916).

1,3-Dichloro-2-propyl 2,3,4,6-tetra-O-acetyl- -D-glucopyranoside [11]



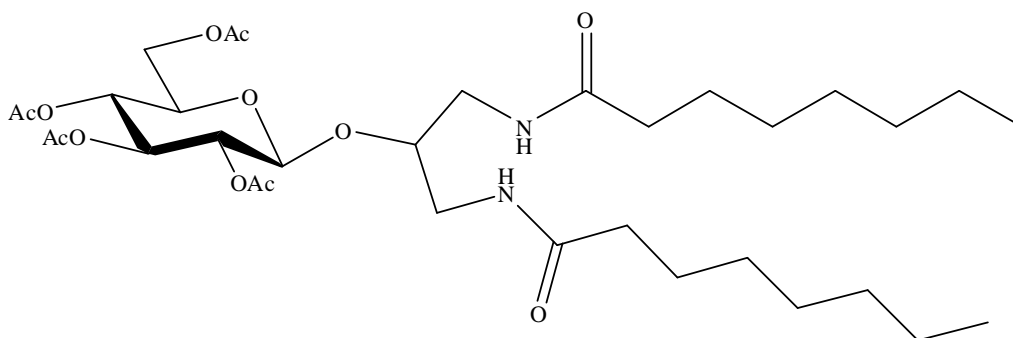
Compound [10] (5.0 g, 12.81 mmol) was glycosylated with 1,3-dichloro-2-propanol according to the general procedure 6.4.4 to furnish 1,3-dichloro-2-propyl 2,3,4,6-tetra-O-acetyl- -D-glucopyranoside [11] (2.8 g, 6.0 mmol, 47%) as white crystal, (Dahmén et al., 1983).

1,3-diazido-2-propyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside [12]



Compound [11] (2.5 g, 5.4 mmol) was reacted with sodium azide according to general procedure 6.4.5 to produce white crystal of compound [12] (2.0 g, 77.82%), (Carvalho et al., 2010).

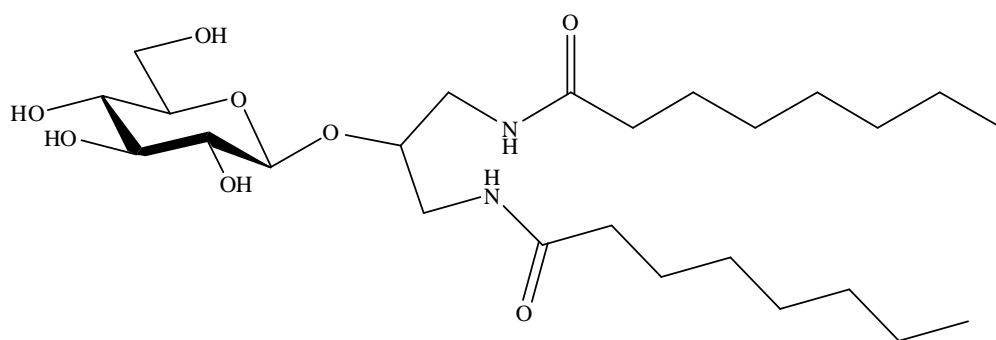
1,3-Dioctanamido-2-propyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranoside [13a]



Compound [12] (1.5 g, 3.17 mmol) was coupled with octonyl chloride $C_7H_{15}COCl$ and triphenylphosphine PPh_3 in dichloromethane (DCM) according to the general procedure 6.4.7.A to yield compound [13a] (1.4 g, 63%) as white crystals. mp $76\text{ }^\circ\text{C}$. $[\alpha]_D^{25} = -45$ (c 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 6.58, 6.19 (2t, 2H, NH), 5.18 (dd~t, H-3), 5.04 (dd~t, H-4), 4.95 (dd, H-2), 4.60 (d, H-1), 4.23 (dd, H-6A), 4.20 (dd, H-6B), 3.81-3.66 (m, 4H, H-5, OCH, 2 NCH_2 -A), 3.05 (ddd~t, NCH_2 -B), 2.67 (ddd, NCH_2 -B), 2.21, 2.18 (2t, 2x2 H, $-CH_2$), 2.07, 2.04, 2.03, 1.99 (4s, 4x3 H, Ac), 1.61 (mc, 4H, $-CH_2$), 1.27 (mc, 16 H, bulk- CH_2), 0.86 (2t, 2x3 H, CH_3); $^3J_{1,2} = 8.0$, $^3J_{2,3} = 9.5$, $^3J_{3,4} = 9.5$, $^3J_{4,5} =$

10.0, $^3J_{5,6A}=2.5$, $^3J_{5,6B}=4.5$, $^2J_6=12.0$, $^3J_{CH_2,CH}=5.0$, $^3J_{CH_2,NH}=5.0$, $^2J_{CH_2}=15.0$, $^3J_{CH_2,CH}=8.0$, $^3J_{CH_2,NH}=5.0$, $^2J_{CH_2}=15.0$ Hz. ^{13}C NMR (100 MHz, $CDCl_3$) = 175.34, 174.52 (CONH), 171.17, 170.57, 170.05, 169.97 (COAc), 100.90 (C-1), 77.76 (CH), 72.45 (C-3), 72.01 (C-5), 71.15 (C-2), 68.13 (C-4), 61.52 (C-6), 39.62, 38.62 (CH_2N), 36.49, 36.34 ($-CH_2$), 31.40 (2 -2), 28.97x2, 28.69x2 (bulk- CH_2), 25.48, 25.37 ($-CH_2$), 22.37 (-1), 20.44, 20.39, 20.26x2 (Ac), 13.69 (). Elemental analysis for $C_{33}H_{56}N_2O_{12}$: C 58.91, H 8.39, N 4.16; found C57.54, H 8.85, N 3.87; matching monohydrate $C_{33}H_{56}N_2O_{12} \times H_2O$, calcd.: C57.37, H8.46, N4.06.

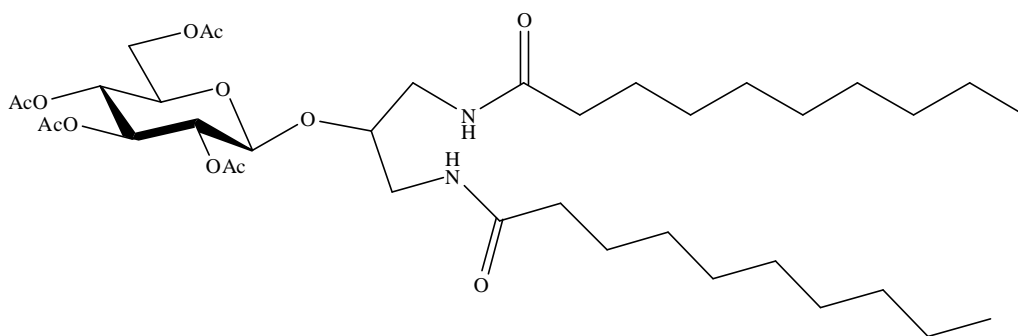
1,3-Dioctanamido-2-propyl- β -D-glucopyranoside [14a]



Compound [13a] (1.25 g, 1.82 mmol) was deacetylated according to the general procedure 6.4.8.1 to yield compound [14a] (0.87g, 95 %). mp 119 °C. $[\alpha]_D^{25} = -3.0$ (c 0.15, CH_3OH). 1H NMR (400 MHz, CD_3OD) = 7.95, 7.81 (2t, NH), 4.36 (d, H-1), 3.89 (dd, H-6A), 3.80 (mc, OCH), 3.70 (dd, H-6B), 3.49-3.22 (m, 7H, H-3, H-4, H-5, 2 CH_2N), 3.21 (dd, H-2), 2.22, 2.21 (2t, 4H, $-CH_2$), 1.60 (mc, 4H, $-CH_2$), 1.31 (mc, 16H, bulk- CH_2), 0.90 (t, 6H, CH_3); $^3J_{1,3}=8.0$, $^3J_{2,3}=9.0$, $^3J_{5,6A}=2.0$, $^3J_{5,6B}=5.5$, $^2J_6=12.0$ Hz. ^{13}C NMR (100 MHz), CD_3OD) = 175.35 x 2 (2 CONH), 104.84 (C-1), 79.80 (CH), 78.24, 78.10 (C-3 & C-5), 75.34 (C-2), 71.69 (C-4), 62.81 (C-6), 42.68, 41.99 (2 CH_2N), 37.21, 37.09 (2 $-CH_2$), 32.87x2 (2 -2), 30.27 x2, 30.12, 30.10 (bulk- CH_2), 26.96, 26.91 (2 $-CH_2$), 23.60 x 2 (2 -1), 14.29 x 2 (2).

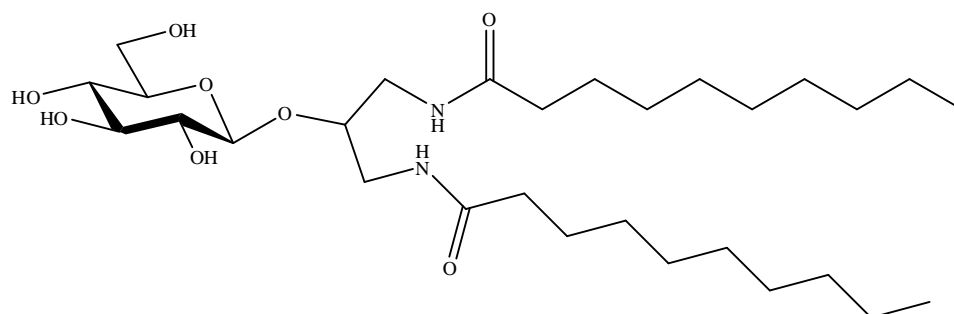
HRMS : $[M+H]^+$: calcd for $C_{25}H_{49}N_2O_8$: 505.3489 , 506.3522 (28 %); found : 505.3480 (100 %) , 506.3505 (31 %) ; $[M+Na]^+$ calcd. for $C_{25}H_{48}N_2O_8$: 527.3313, 528.3339 (28 %), found: 527.3313 (100 %) , 528.3339 (29 %).

1,3-Didecanaamido-2-propyl 2,3,4,6-tetra-O-acetyl- -D-glucopyranoside [13b]



Compound [12] (1.5g, 3.17 mmol) was coupled with decanoyl chloride $C_9H_{19}COCl$ and triphenylphosphine PPh_3 according to general procedure 6.4.7.A to provide compound [13b] (1.5 g, 62%) as whit crystals. Mp $80^\circ C$. $[\alpha]_D^{25} = -39$ (c 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 6.25 , 6.17 (2t, 2H, NH), 5.19 (dd~t, H-3), 5.05 (dd~t, H-4), 4.95 (dd, H-2), 4.61 (d, H-1), 4.23 (dd, H-6A), 4.18 (dd, H-6B), 3.82-3.66 (m, 4H, H-5, CH, 2 NCH₂-A), 3.05 (mc, NCH₂-B), 2.67 (mc, NCH₂-B), 2.21, 2.18 (2t, 2x2 H, -CH₂), 2.08, 2.05, 2.03, 2.00 (4s, 4x3 H, Ac), 1.61 (mc, 4H, -CH₂), 1.32-1.20 (m, 24 H, bulk-CH₂), 0.86 (2t, 2x3 H, CH₃); $^3J_{1,2} = 8.0$, $^3J_{2,3} = 9.5$, $^3J_{3,4} = 9.5$, $^3J_{4,5} = 10.0$, $^3J_{5,6A} = 2.5$, $^3J_{5,6B} = 4.5$, $^2J_6 = 12.0$ Hz. ^{13}C NMR (100 MHz, $CDCl_3$) = 175.34 x2 (CONH), 171.17, 170.58, 170.05, 169.98 (COAc), 100.92(C-1), 77.80 (CH), 72.46 (C-3), 72.04 (C-5), 71.117 (C-2), 68.15 (C-4), 61.53 (C-6), 39.61, 38.61 (CH₂N), 36.52, 36.38 (-CH₂), 31.59 (2 -2), 29.17 x2, 29.05 x4, 28.99 (bulk-CH₂), 25.49, 25.39 (2 -CH₂), 22.35 (2 -1), 20.45, 20.40, 20.27 x2 (Ac), 13.75 (2CH₃). Elemental analysis for $C_{37}H_{64}N_2O_{12}$: C 60.97 , H 8.85, N, 3.84 ; found C60.18, H 9.27 , N 3.69 ; matching hemihydrate $C_{37}H_{64}N_2O_{12} \times \frac{1}{2}H_2O$, calcd.: C60.22 , H8.88, N3.80.

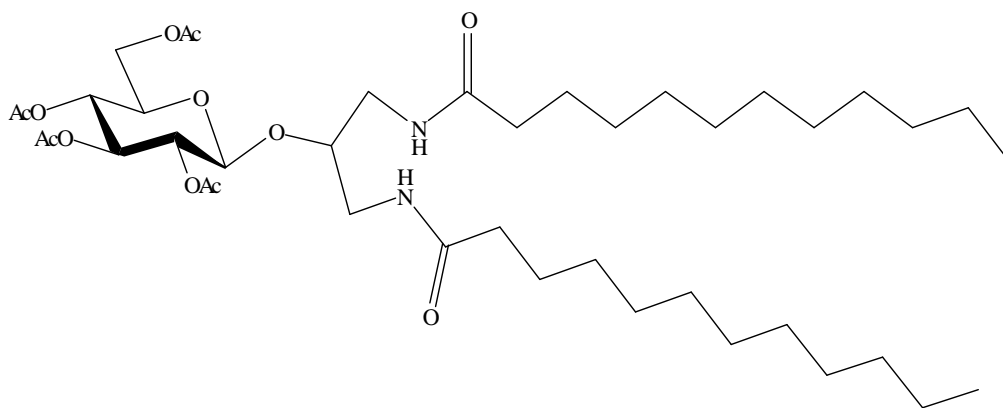
1,3-Didecanaamido-2-propyl- -D-glucopyranoside [14b]



Compound [13b] (1.25 g, 1.71 mmol) was deacetylated according to the procedure 6.4.8.1 to yield compound [14b] (0.93g, 96 %). mp 120 °C. $[\alpha]_D^{25} = -4.0$ (c 0.15, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = 7.94, 7.81 (2t, NH), 4.37, (d, H-1), 3.89 (dd, H-6A), 3.80 (mc, OCH), 3.67 (dd, H-6B), 3.49-3.24 (m, 7H, H-3, H-4, H-5, 2CH₂N), 3.21 (dd, H-2), 2.23, 2.21 (2t, 4H, -CH₂), 1.60 (mc~bs, 4H, -CH₂), 1.30 (mc~bs, 24H, bulk-CH₂), 0.90 (t, 6H, CH₃); ³J_{1,3}=8.0, ³J_{2,3} = 9.0, ³J_{5,6B} = 5.0, ²J₆ = 11.5 Hz. ¹³C NMR (100 MHz, CD₃OD) = 175.35 x 2 (2 CONH), 104.87 (C-1), 79.80 (CH), 78.24, 78.11, (C-3 & C-5), 75.35 (C-2), 71.69 (C-4), 62.82 (C-6), 42.67, 41.98 (2CH₂N), 37.10 x2 (2 -CH₂), 33.01x2 (2 -1), 30.58 x2, 30.46, 30.43, 30.38 x2, 30.31 x2 (bulk-CH₂), 26.96, 26.91 (2 -CH₂), 23.65x 2 (2 -1), 14.32 x 2 (2).

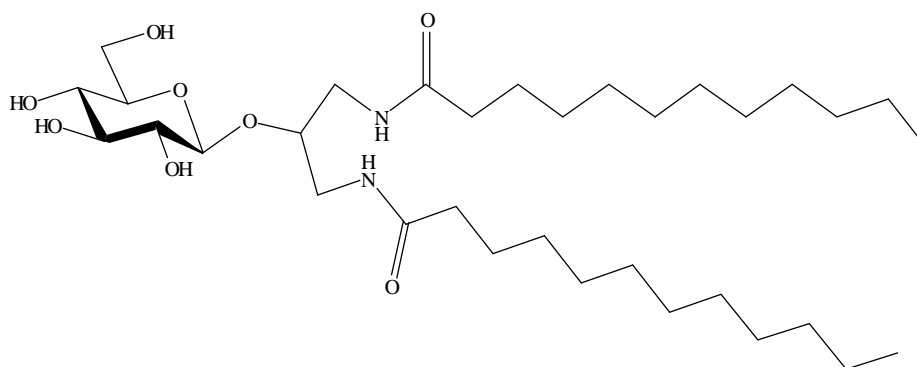
HRMS : [M+H]⁺: calcd for C₂₉ H₅₇ N₂ O₈ : 561.4115, 562.4148 (32 %); found : 561.4107 (100 %), 562.4138 (31 %); [M+Na]⁺ calcd. for C₂₉H₅₆N₂O₈Na: 583.3934, 528.3339, found: 583.3909 (100 %).

1,3-Didodecanaamido-2-propyl 2,3,4,6-tetra-O- -D-acetyl-glucopyranoside [13c]



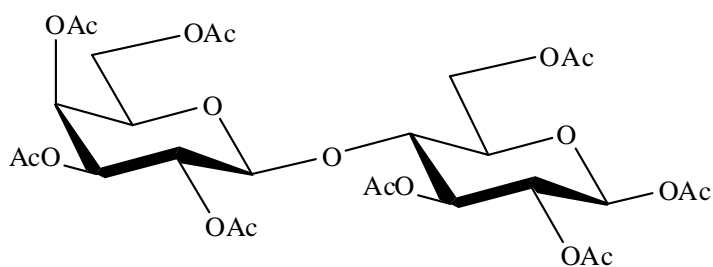
Compound [12] (1.5g, 3.17 mmol) was coupled with dodecanoyl chloride $C_{11}H_{23}COCl$ and triphenylphosphine PPh_3 according to the general procedure 6.4.7.A to yield compound [13c] (1.6 g, 60%) as white crystals. mp 86 °C. $[\alpha]_D^{25} = -35$ (c 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) δ = 6.57, 6.18 (2t, 2H, NH), 5.18 (dd~t, H-3), 5.04 (dd~t, H-4), 4.95 (dd, H-2), 4.60 (d, H-1), 4.23 (dd, H-6A), 4.18 (dd, H-6B), 3.81-3.60 (m, 4H, H-5, OCH, 2 NCH_2 -A), 3.05 (ddd~t, NCH_2 -B), 2.67 (ddd, NCH_2 -B), 2.21, 2.18 (2t, 2x2 H, $-CH_2$), 2.07, 2.04, 2.02, 1.99 (4s, 4x3 H, Ac), 1.60 (mc, 4H, $-CH_2$), 1.31-1.21 (mc, 32 H, bulk- CH_2), 0.86 (2t, 2x3 H, CH_3); $^3J_{1,2} = 8.0$, $^3J_{2,3} = 9.5$, $^3J_{3,4} = 9.5$, $^3J_{4,5} = 10.0$, $^3J_{5,6A} = 2.5$, $^3J_{5,6B} = 5.0$, $^2J_{6=} = 12.5$, $^3J_{CH_2,CH} = 5.0$, $^3J_{CH_2,NH} = 5.0$, $^2J_{CH_2} = 15.0$, $^3J_{CH_2,CH} = 8.0$, $^3J_{CH_2,NH} = 5.0$, $^2J_{CH_2} = 15.0$ Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.33, 174.50 (2CONH), 171.15, 170.56, 170.03, 169.96 (4COAc), 100.89 (C-1), 77.76 (CH), 72.44 (C-3), 72.01 (C-5), 71.14 (C-2), 68.13 (C-4), 61.51 (C-6), 39.60, 38.61 (CH_2N), 36.49, 36.34 ($-CH_2$), 31.40 (2 -2), 29.32 x4, 29.21 x2, 29.04 x6 (bulk- CH_2), 25.48, 25.37 ($-CH_2$), 22.35 (-1), 20.43, 20.38, 20.25 x2 (Ac), 13.74 (2 CH_3). Elemental analysis for $C_{41}H_{72}N_2O_{12}$: C 62.73, H 9.24, N 3.57; found C 62.47, H 9.68, N 3.39

1,3-Didodecanaamido-2-propyl- -D-glucopyranoside [14c]



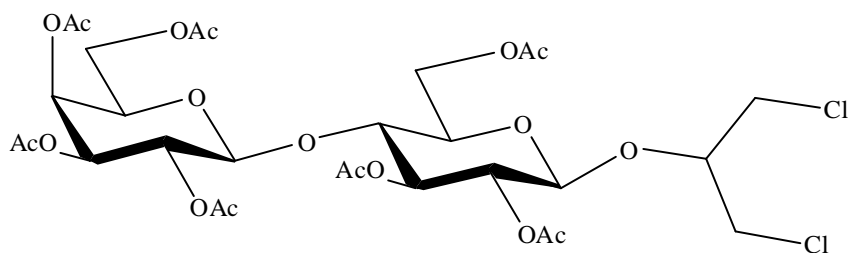
Compound [13c] (1.5 g, 1.91 mmol) was deacetylated according to the general procedure 6.4.8.1 to furnish compound [14c] (1.1 g, 93 %). mp 119 °C. $[\alpha]_D^{25} = -6.0$ (c 0.15, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = 7.95, 7.81 (2t, NH), 4.37, (d, H-1), 3.89 (dd, H-6A), 3.80 (mc, OCH), 3.76 (dd, H-6B), 3.49-3.24 (m, 7H, H-3, H-4, H-5, 2CH₂N), 3.21 (dd, H-2), 2.23, 2.21 (2t, 4H, -CH₂), 1.62 (mc, 4H, -CH₂), 1.36- 1.26 (mc, 32H, bulk-CH₂), 0.90 (t, 6H, CH₃); ³J_{1,3} = 8.0, ³J_{2,3} = 9.0, ³J_{5,6A} = 1.5, ³J_{5,6B} = 5.0, ²J₆ = 11.5 Hz. ¹³C NMR (100 MHz), CD₃OD) = 177.32 x 2 (2 CONH), 104.85 (C-1), 79.78 (CH), 78.25, 78.11, (C-3 & C-5), 75.35 (C-2), 71.70 (C-4), 62.82 (C-6), 42.68, 41.97 (2CH₂N), 37.22, 37.11 (2 -CH₂), 33.05 x 2 (2 -), 30.72 x 4, 30.63 x 2, 30.44 x 4, 30.32 x 2 (bulk-CH₂), 26.97, 26.92 (2 -CH₂), 23.66 x 2 (2 -), 14.32 x 2 (2). HRMS : [M+H]⁺: calcd for C₃₃ H₆₅ N₂O₈ : 617.4741, 618.4774 (37 %); found : 617.4739 (100 %), 618.4763 (36 %).

1,2,3,6,2',3',4',6'-Octa-O-acetyl- -D-lactopyranoside [16]



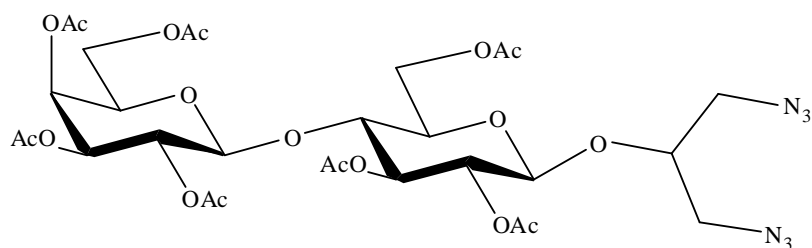
D-lactose [15] (20 g, 59.0mmol) was treated with 100 mL of acetic anhydride and (10 g, 150 mmol) of sodium acetate according to the general procedure 6.4.1 to yield 1,2,3,6,2',3',4',6'-octa-O-acetyl- -D-lactopyranoside[16] (30.5g,77%) as white crystals containing 10% β -anomer, (Fischer, 1916).

1, 3-Dichloro-2-propyl 2,3,6,2',3',4',6'-hepta-O-acetyl- -D-lactopyranoside [17]



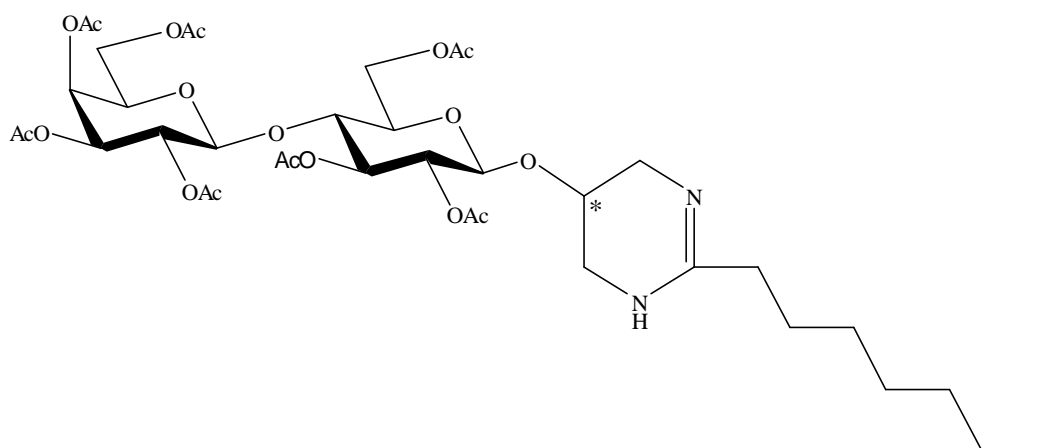
Compound [16] (5.0g, 7.4 mmol) was glycosylated with 1,3-dichloro-2-propanol according to the general procedure 6.4.4 to furnish compound [17] (2.75 g, 50%) as a white crystals, (Dahmén et al., 1983).

1,3-Diazido-2-propyl 2,3,4,2',3',4',6'-hepta-O-acetyl- -D-lactopyranoside [18]



Compound [17] (2.5 g, 3.4 mmol) was reacted with sodium azide NaN_3 according to the general procedure 6.4.5 to produce white crystal of compound [18] (1.9g, 95%), (Carvalho et al., 2010).

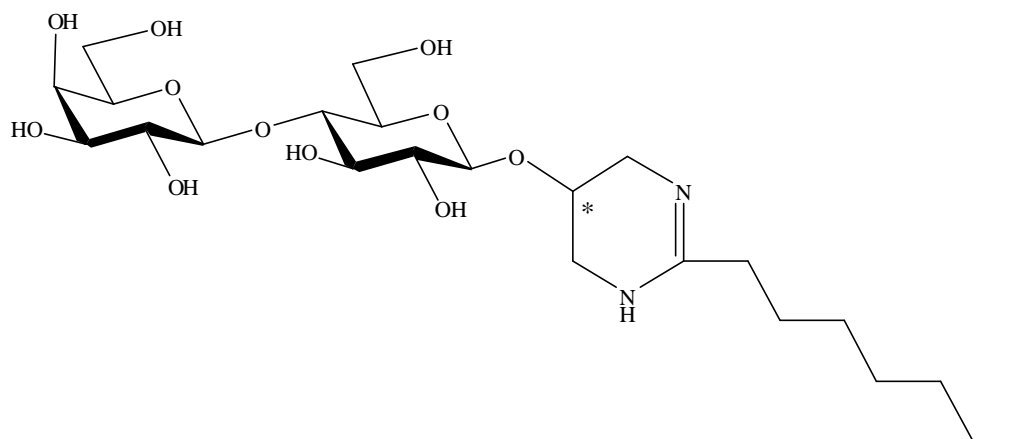
2-Heptyl-5-(2,3,6,2',3',4',6'-hepta-O-acetyl- -lactosyl)-1,4,5,6-tetrahydropyrimidine [20a]



Compound [18] (1 g, 1.31 mmol) was coupled with octanoyl chloride according to the general procedure 6.4.7 to yield compound [20a] (0.75g, 70%) as white crystals. mp. $188\text{ }^\circ\text{C}$. $[\text{D}]_{\text{D}}^{25} = +21.0$ (c 0.15, CHCl_3). $^1\text{H NMR}$ (400 MHz, CDCl_3) = 6.11, 5.72 (2dd~t, 1H, 1:4, NH), 5.32 (dd~d, H-4'), 5.17 (dd~t, H-3), 5.08 (dd, H-2'), 4.92 (dd, H-

3'), 4.87 (dd, H-2), 4.61, 4.46 (2d, 2x1H, H-1, H-1'), 4.49 (dd~d, H-6/6'), 4.15-4.01 (m, 3H, H-6/6'), 3.91 (mc, OCH), 3.85 (mc, H5/5'), 3.74 (dd~t, H-4), 3.67-3.25 (m, 5H, H-5, 2CH₂), 2.13, 2.09, 2.04 x2, 2.03 x2, 1.94 (7s, 21H, Ac), 1.86 (mc, 2H, -CH₂), 1.59 (mc, 2H, -CH₂), , 1.26 (mc, 8H, bulk-CH₂), 0.85 (t, 3H, CH₃). ³J_{1,2}=8.0 , ³J_{2,3} = 9.0 , ³J_{3,4} = 9.0 , ³J_{4,5} = 9.0, ³J_{1',2'}= 8.0, ³J_{2',3'} = 10.0, ³J_{3',4'} = 3.0, ³J_{4',5'} = 1 Hz. ¹³C NMR (100 MHz, CDCl₃) = 174.03 (C=N), 170.92, 170.90, 170.68, 170.63, 170.26, 170.22, 169.60 (C=O), 101.22, (101.10), 100.68 (C-1 , C-1'), 79.00 (CH), 76.13 (C-4), 72.83 (C-5), 72.60 (C-3), 71.91 (C-2), 70.86 (C-3'), 70.68 (C-5'), 69.02 (C-2'), 66.51 (C-4'), 61.57, 60.68 (C-6 , C-6'), (44.68), 43.82 (CH₂N), (41.29), 40.54 (CH₂NH), 36.37 (-CH₂), 31.38 (-2), 28.97. 28.67 (bulk-CH₂), 25.31 (-CH₂), 22.24 (-1), 20.45, 20.41, 20.27 x4, 20.14 (Ac), 13.65 (). Elemental analysis for C₃₇H₅₆N₂O₁₈: C 45.40 , H 6.91, N 3.43; found C 53.54 , H 7.17 ,N 3.47.

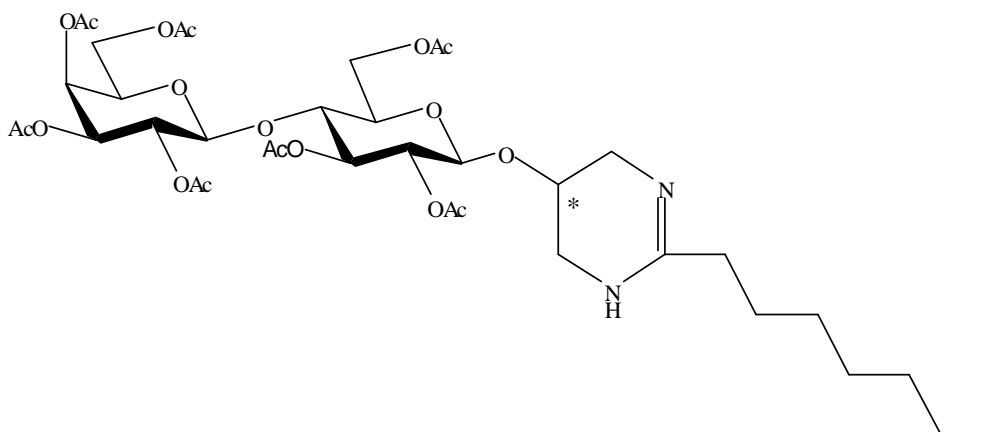
**2-Heptyl-5-(4-O- -D-galactopyranosyl- -D-gluco-
pyrimidine [21a]**



Compound [20a] (0.5 g, 0.61 mmol) was deacetylated according to procedure to the general procedure 6.4.8.1 to furnish a diastereomeric mixture of compound [20b] (0.3 g, 94%) as white crystals. mp 183-185 °C. [_D²⁵ = + 5.0 (c 0.15, CH₃OH). ¹H NMR (400

MHz, CD₃OD) = (4.48)/4.45 , 4.36/(4.35) (2x2 d , 2H, H-1, H-1'), 4.02-3.25 (m, 17H), (2.38)/2.21 (mc, 2H, -CH₂), 1.61 (mc , 2H, -CH₂), 1.32 (mc, 8H, bulk-CH₂), 0.90 (t, 3H, CH₃) ; ³J_{1,2} = 8.0/ 7.5 , ³J_{1',2'} = 7.5/8.0 Hz. ¹³C NMR, CD₃OD) = 177.50 (C=N) , 105.51 ,105.33 (C-1, C-1'), 80.71, 80.28, 77.30, 76.81, 76.46, 75.02 x2, 72.73, 70.48, 62.63, 61.96 (C-6, C6'), 45.50 (CH₂N). 41.59 (CH₂NH), 37.14 (-CH₂), 32.84 (-), 30.23, 30.05 (bulk-CH₂), 26.86 (-CH₂), 23.55 (-), 14.24 ().

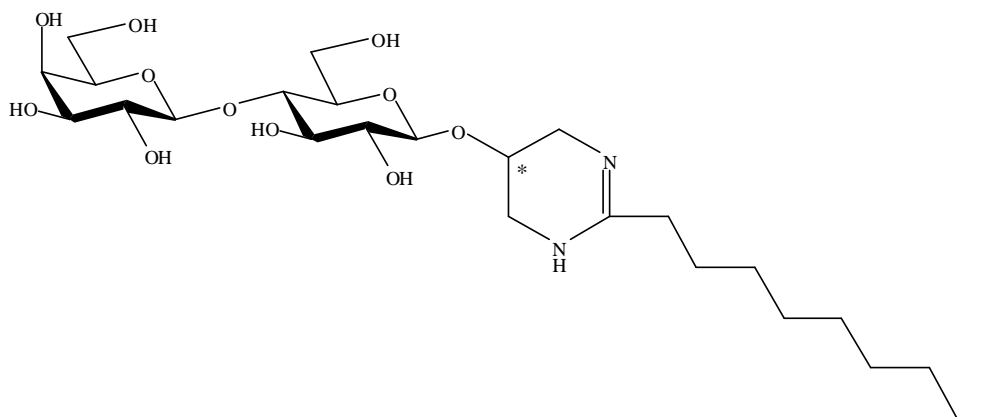
2-Nonyl-5-(2,3,6,2',3',4',6'-hepta-O-acetyl- -lactosyl)-1,4,5,6-tetrahydro-pyrimidine [20b]



Compound [18] (1 g, 1.31 mmol) was coupled with decanoyl chloride C₉H₁₉COCl and triphenylphosphine PPh₃ according to general procedure 6.4.7.A to produce compound [20b] (0.78g, 70%) as white crystals. mp 195 °C. [α]_D²⁵ = + 8.0 (c 0.15, CHCl₃). ¹H NMR (400 MHz , CDCl₃) = 5.98, 5.59 (2dd~t, 1H, 2:3, NH), 5.20 (dd~d, H-4'), (5.08) / 5.05 (dd~t, H-3), (4.98) /4.96 (dd, H-2'), (4.83)/ 4.82 (dd, H-3'), (4.78) / 4.75 (dd, H-2), 4.49/ (4.44). (4.37) / 4.34 (2d, 2x1H, H-1, H-1'), 4.38 (dd~d, H-6/6'A), 3.99 (dd, H-6'/6A), 3.95 (dd, 6/6'B), 3.92 (dd, H6'/6B), 3.82-3.66 (m, 2H, CH, H-5), 3.62 (dd~t, H-4), 3.54-3.14 (m, 5H, H-5, CH₂N) 2.01 x2, 1.98 x2, 1.92, 1.91 x2, 1.90. 1.82, 1.81 (Ac), 1.55 (mc, 2H, -CH₂), 1.46 (mc, 2H, -CH₂), , 1.18-1.09 (mc, 12H, bulk-CH₂), 0.73 (t, 3H,

CH₃). ³J_{1,2}=8.0 , ³J_{2,3}= 10.0 , ³J_{3,4}= 9.5 , ³J_{4,5}= 9.5, ³J_{1',2'}= 8.0, ³J_{2',3'}=10.0, ³J_{3',4'}=3.0, ³J_{4',5'} 1 Hz. ¹³C NMR (100 MHz, CDCl₃) = 174.21,173.99 (C=N), 170.92, 170.89, 170.68, 170.63, 170.38, 170.26, 170.22, 170.17, 169.60, 169.55 (C=O), 101.25, 101.23, 101.01, 100.66 (C-1 , C-1'), 80.89, 78.99 (CH), 76.13 , 75.81 (C-4), 73.02, 72.81 (C-3), 72.59 (C-3'), 72.27, 71.90 (C-2), 71.21, 70.85 (C-2'), 70.67 (C-5'), 69.06 , 69.01(C-5), 66.50 (C-4'), 61.56, 60.33, 60.67, 60.64 (C-6 , C-6'), 44.65, 43.80 (CH₂N), 41.24, 40.50 (CH₂NH), 36.35,36.13 (-CH₂), 31.55 (-), 29.15. 29.13. 29.07, 29.03, 28.97, 28.94 (bulk-CH₂), 25.33, 25.31 (-CH₂), 22.30 (-), 20.51, 20.44, 20.41. 30.38, 20.28, 20.15 (Ac), 13, 70 (). Elemental analysis for C₃₉H₆₀N₂O₁₈: C55.44 , H 7.16, N 3.32; found C 55.72 , H 7.26 ,N 3.72.

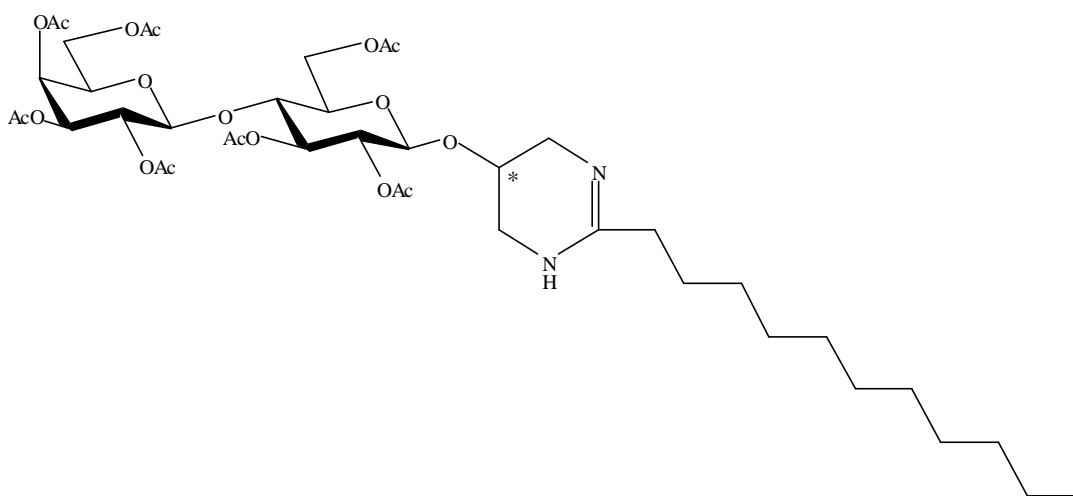
2-Nonyl-5-(4-O- -D-galactopyranosyl- -D-glucopyranosyl)-1,4,5,6-tetrahydro-pyrimidine [21b]



Compound **[21a]** (0.5 g, 0.58 mmol) was deacetylated according to procedure to the general procedure 6.4.8.1 3.6 to furnish compound **[21b]** (0.3 g, 94%) as a white crystals. mp 190°C (dec.). [α]_D²⁵ = + 15.0 (c 0.15, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = (4.47)/4.45 , 4.36/ (4.35) (2x2 d , 2H, H-1 & H-1'), 4.04-3.25 (m, 17H), 2.21 (t, 2H, -CH₂), 1.61 (mc , 2H, -CH₂), 1.31 (mc, 12H, bulk-CH₂), 0,90 (t, 3H, CH₃) ; ³J_{1,2}=

8.0/ 7.5 . Hz. ^{13}C NMR, CD_3OD) = 177.49(C=N) , 105.52 ,105.35/ (104.20) (C-1, C-1'), (80.80)/ 80.75/ (79.49), 77.32, 76.82, 76.52 x2, (76.47), 75.06 x2/ (74.88), 72.75 ,70.49, 62.63, (62.06)/ 62.01 (C-6, C6'), 45.50/(45.04) (CH_2N). (42.65)/41.62 (CH_2NH), 37.15/ (73.03) ($-\text{CH}_2$), 32.97 ($-\text{O}$), 30.54, 30.38, (30.40) , 30.32, 30.28 (bulk- CH_2), (26.89)/26.86 ($-\text{CH}_2$), 23.60 ($-\text{O}$), 14.2 ($-\text{CH}_3$).

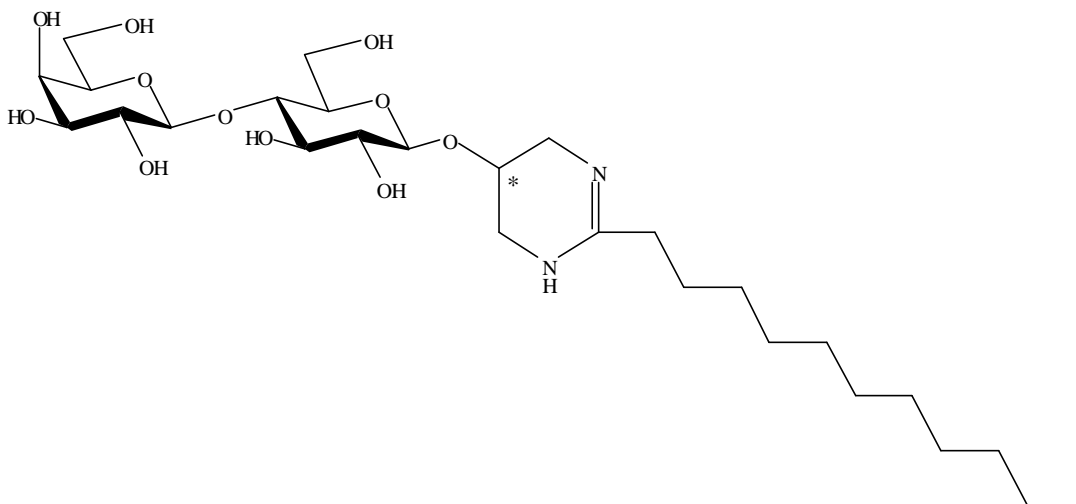
2-Undecyl-5-(2,3,6,2',3',4',6'-hepta-O-acetyl- β -lactosyl)-1,4,5,6-tetrahydro-pyrimidine [20c]



Compound [18] (1 g, 1.31 mmol) was coupled coupled with dodecanoyl chloride $\text{C}_{11}\text{H}_{23}\text{COCl}$ and triphenylphosphine PPh_3 according to the general procedure 6.4.7.A to produce compound [20c] (0.82g, 70%) as white crystals. mp 199°C . $[\text{D}]_{\text{D}}^{25} = +8.0$ (c 0.15, CHCl_3). ^1H NMR (400 MHz, CDCl_3) = 5.99, 5.61 (2dd~t, 1H, 1:3, NH), 5.21 (dd~d, H-4'), (5.08) / 5.05 (dd~t, H-3), (4.98)/ 4.97 (dd, H-2'), (4.83)/ 4.82 (dd, H-3'), 4.76 (dd, H-2), 4.49 / (4.45) , (4.38) 4.35/ (2d, 2x1H, H-1, H-1'), 4.39 (dd~d, H-6/6'A), 4.00 (dd, H-6'/6A), 3.96 (dd, H-6-6'B), 3.93 (dd, H6'/6B), 3.80 (mc, CH), 3.74 (ddd, H-5), 3.63 (dd~t, H-4), 3.51(dd, $\text{CH}_2\text{N-A}$) 3.41 (dd, $\text{CH}_2\text{N-B}$) 3.51-3.27 (m, 2H, H-5, $\text{CH}_2\text{NH-A}$) 3.20 (ddd~t, $\text{CH}_2\text{NH-B}$), 2.02,1.98,1.93, 1.92 x2,1.91, 1.83 (7s, 21H, Ac), 1.64 (mc, 2H, $-\text{CH}_2$), 1.47 (mc, 2H, $-\text{CH}_2$), , 1.18-1.08 (mc, 16H, bulk- CH_2), 0.74 (t, 3H, CH_3). $^3\text{J}_{1,2}$

$=8.0$, ${}^3J_{2,3} = 9.5$, ${}^3J_{3,4} = 10.0$, ${}^3J_{4,5} = 9.5$, ${}^3J_{1',2'} = 8.0$, ${}^3J_{2',3'} = 10.0$, ${}^3J_{3',4'} = 3.0$, ${}^3J_{4',5'}$ 1, ${}^3J_{5.5',6/6'A} = 1.0$, ${}^3J_{5/5',6/6'B} = 7.0$, ${}^2J_{6/6'} = 11.5$, ${}^3J_{5'/5.6'/6A} = 6.0$, ${}^3J_{5'/5.6'/6B} = 7.5$, ${}^2J_{6/6'} = 11.0$, ${}^3J_{CH,CH2N-A} = 4.0$, ${}^3J_{CH,CH2N-B} = 6.0$, ${}^2J_{CH2N} = 12.0$, ${}^3J_{CH,CH2NH-B} = 7.5$, ${}^3J_{NH,CH2NH-B} = 6.0$, ${}^2J_{CH2,NH} = 14.0$, Hz. ${}^{13}C$ NMR (100 MHz, $CDCl_3$) = (174.23), 174.00 (C=N), 170.91, 170.89, 170.67, 170.62 (170.38), 170.26, 170.22 (170.18), 169.60 (169.55) (C=O), 101.21, (101.09), 100.65 (C-1 , C-1'), (80.870/ 78.97 (CH), 76.12/ (75.80) (C-4), (73.01)/ 72.81 (C-5), 72.58/(72.26) (C-3), 71.89 (C-2), (71.20)/ 70.85 (C-3'), 70.67 (C-5'), (69.05)/ (69.00) (C-2'), 66.50 (C-4'), 61.55/ (61.33), 60.67/ (60.63) (C-6 , C-6'), (44.65), 43.80 (CH_2N), (41.23), 40.49 (CH_2NH), 36.35/(36.13) ($-CH_2$), 31.60 (-2), 28.28 x2, (29.20) , 29.17 , (29.07), 29.03 x2 , 29.00 (bulk- CH_2), (25.33)/ 25.30 ($-CH_2$), 22.32 (-1), 20.50, 20.44 x2, 20.41, (20.37), 20.27 x3, 20.14 (Ac), 13,71 (). Elemental analysis for $C_{41}H_{564}N_2O_{18}$: C56.41 , H 7.39, N 3.21; found C 57.54 , H 7.91 ,N 3.74.

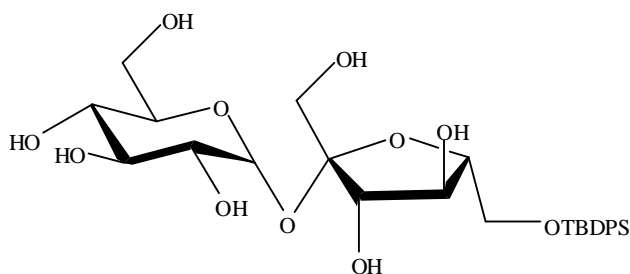
2-Undecyl-5-(4-O- -D-galactopyranosyl)- -D-glucopyranosyl)-1,4,5,6-tetrahydro-pyrimidine [21c]



Compound **[20c]** (0.5 g, 0.58 mmol) was deacetylated according to procedure 6.4.8.1 to furnish compound **[21c]**(0.3 g, 93%) as white crystals. mp 190°C (dec.). $[\alpha]_D^{25} = +10.0$ (c 0.15, CH_3OH). 1H NMR (400 MHz, CD_3OD) = (4.47)/4.45 , 4.36/ (4.35) (2x2 d , 2H,

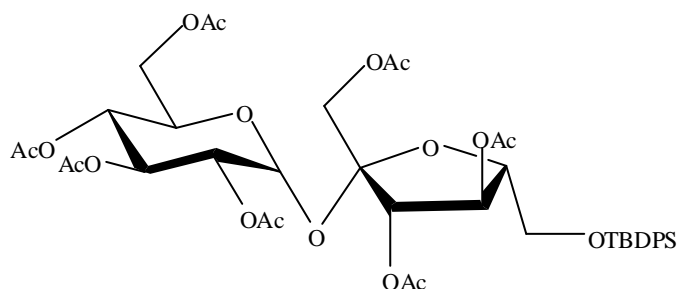
H-1 & H-1'), 4.04-3.25 (m, 17H), 2.21 (t, 2H, -CH₂), 1.61 (mc , 2H, -CH₂), 1.29 (mc, 16H, bulk-CH₂), 0,90 (t, 3H, CH₃) ; ³J_{1,2} = 8.0/ 7.5 . Hz. ¹³C NMR, CD₃OD) = 177.48(C=N), 105.50, 105.35(C-1, C-1'), (80.74)/ 80.27/ (79.48), 76.81, 77.32, 76.81 x2, 76.50/ (70.45), 75.04 x2/ 74.86, 72.74, 62.63 (62.03)/ 61.97 (C-6, C6'), 45.49/(45.03) (CH₂N). (42.65)/41.60 (CH₂NH), 37.15/ (73.02) (-CH₂), 33.01 (-2), 30.66 x2, 20.58, 30.39 x2, 30.28 (bulk-CH₂), (26.90)/26.87 (-CH₂), 23.62 (-1), 14.27 ().

6'-O-tert-butyldiphenylsilyl-sucrose [25]



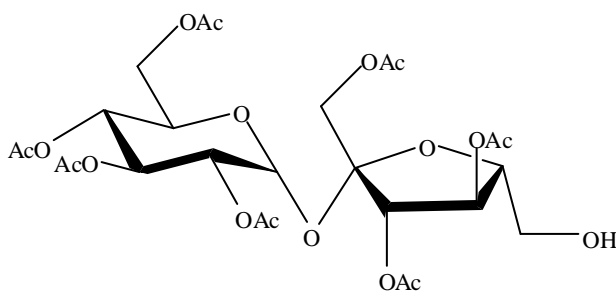
Sucrose [24] (5g,14.61 mmol) was reacted with tertbutyldiphenylsilyl chloride and catalytic amount of 4-(dimethylamino) pyridine in pyridine according to general procedure 6.4.3.2 to give compound [25] (6.0g, 73%), which was used without any further purification, (Karl et al., 1982, Jarosz et al., 2000).

2,3,4,6,1',3',4' -hepta-O-acetyl -6'-O-tert-butylidiphenylsilyl-sucrose [26]



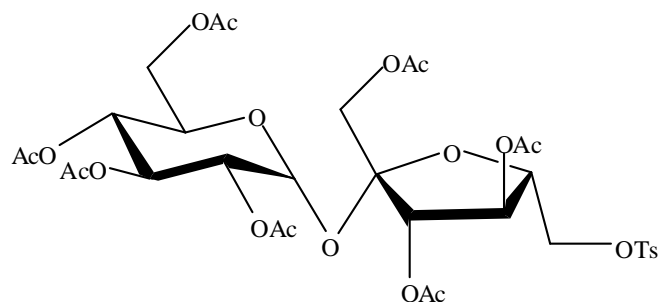
Compound [25] (5g,0.000089 mmol) was acetylated with (15 ml) of acetic anhydride in pyridine according to general procedure 3.4.3.1 to give compound [26] (5.5.0g, 72%)which was used without any further purification,(Khan et al., 1978).

2,3,4,6,1',3',4', -hepta-O-acetyl-sucrose [27]



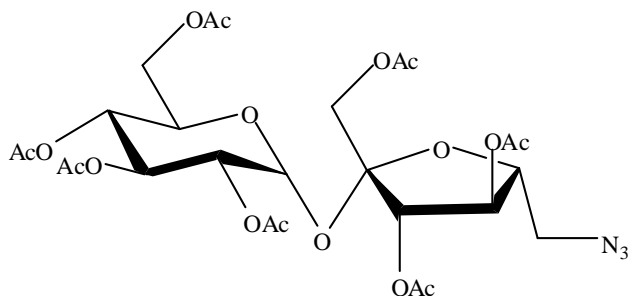
Compound [26] (5g, 8.61mmol) was treated with tert-butylammonium fluoride in tetrahydrofuran THF according to the general procedure 6.4.8.2 to yield compound [27] (3.2 g, 80%), which was used without further purification.

2,3,4,6,1',3',4'-Hepta-O-acetyl-6'-O-tosyl-sucrose [28]



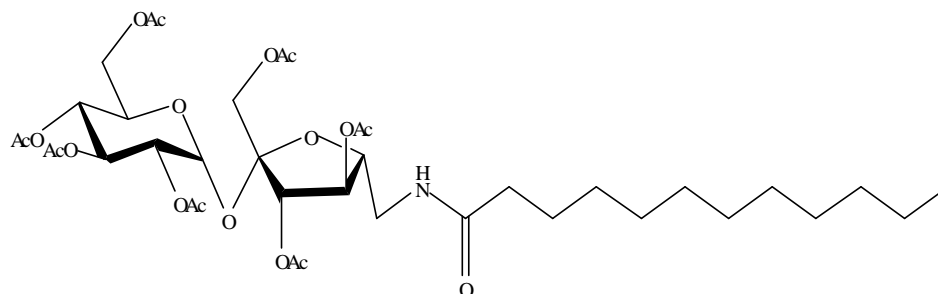
Compound [27] (3 g, 4.71 mmol) was treated with tosyl chloride in pyridine according to the general procedure 6.4.2.2 to yield [28] (2.78g 75%) as NMR pure crystals after crystallized from ethanol.

2,3,4,6,1',3',4'-Hepta-O-acetyl-6'-O-azido-sucrose [29]



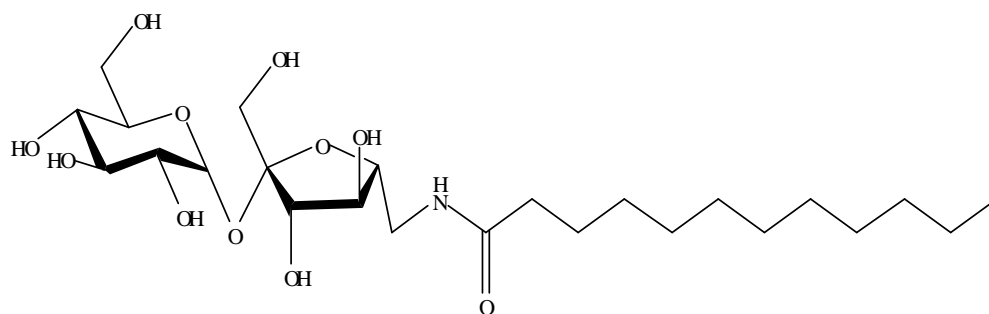
Compound [28] (2.75 g 3.48 mmol) was reacted with sodium azide in DMF according to the general procedure 6.4.5 to yield [29] (1.77g 71%) as NMR pure white crystals after crystallized from ethanol.

2,3,4,6,1',3',4'-Hepta-O-acetyl-6'-O-dodecanamido-sucrose [30]



Compound **[29]** (1.5g, 2.27 mmol) was coupled with dodecanoyl chloride $C_{11}H_{23}COCl$ and triphenylphosphine PPh_3 according to the general procedure 6.4.7.A to produce compound **[230]** (1.25 g, 68%) as NMR pure white crystals. $[\alpha]_D^{25} = +33.0$ (c 0.15, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) = 5.62 (d, 1H, H-1), 5.42 (dd~t, 1H, H-3), 5.39 (dd~t, 1H, H-3'), 5.19 (dd~t, 1H, H-4), 5.02 (dd~t, 1H, 4'-H), 4.82 (dd, 1H, 2-H), 4.05 – 4.44 (m, 6H, H-1'A, H-1'B, H-5, H-5', H-6B, H-6'A), 3.70 (ddd, 1H, H-6A), 3.32 (ddd, 1H, H-6'B), 2.17 (m, 2H, $-CH_2$), 2.14, 2.09, 2.08, 2.07, 2.06, 2.02, 1.99 (7s, 21H, Ac), 1.61 (m, 2H, $-CH_2$), 1.22 (s, 16H, bulk- CH_2), 0.85 (t, 3H, CH_3). $^3J_{1,2}=3.5$, $^3J_{2,3}=10.0$, $^3J_{3',4'}=9.5$, $^2J_6=14$, $^2J_{6'}=13.0$, $^3J_{6',NH}=5.5$ Hz. ^{13}C NMR (100 MHz, $CDCl_3$) = 173.54 (CONH), 170.66 x2, 170.11 x2, 196.98, 196.63, 196.56 ((C=O), 103.86 (C-2'), 89.80 (C-1), 79.90 (C-5'), 75.85 (C-3'), 75.83 (C-4'), 70.41 (C-2), 69.37 (C-3), 68.67 (C-5), 68.29 (C-4), 63.40 (C-6), 61.76 (C-1'), 41.37 (C-6'), 36.50 ($-CH_2$), 31.88 (C-2), 29.61, 29.59, 29.48, 29.36, 29.31 x2 (bulk- CH_2), 25.54 ($-CH_2$), 22.66 (C-1), 20.75, 20.73, 20.66 x2, 20.63, 20.60, 20.57 (Ac), 14.09 (CH_3). Elemental analysis for $C_{38}H_{59}NO_{18}$: C 55.81, H 7.27, N 1.71; found C 55.84, H 7.33, N 1.75.

6'-Dodecanamido-sucrose [31]

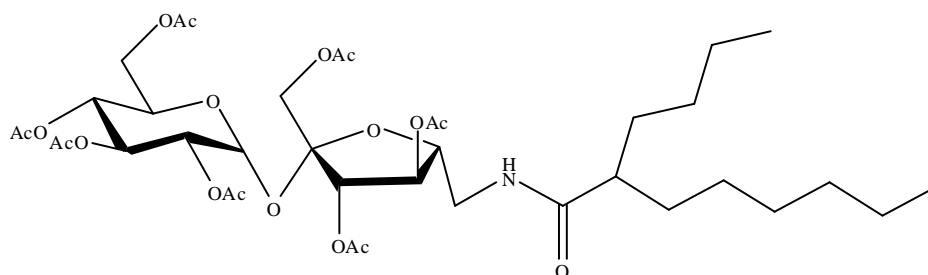


Compound [30] (1g) was deacetylated with sodium methoxide in methanol according to the general procedure 6.4.8.1 to yield compound [31] (0.6g , 94%) as NMR pure white crystals. mp 204 °C (dec.). $[\alpha]_D^{25} = +43.0$ (c 0.15, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = 3.5 (d , 1H , H-1) , 4.07 (d, C-5'), 3.89- 3.59 (m, 7H, H-2', H-3' ,H-3 , H-6 , H-4, 2H-6'), 2.42 (dd~t, 1H, H-2), 3.48 (dd~t , 1H, H-1'A), 3.28 (m , 1H, H-1'B), 2.21 (m, 2H, -CH₂), 1.61 (m, 2H, -CH₂), 1.31 (s, 16H, bulk-CH₂), 0.91 (t, 3H, CH₃) Hz, ³J_{1,3} = 3.5 , ³J_{2,3} = 10.0 , ²J₆ = 13.5).

¹H NMR (400 MHz, CD₃OD) = 175.58 (CONH), 104.67 (C-2'), 92.16 (C-1), 80.19 (C-3'), 78.10 (C-5') , 77.00 (C-5) , 73.37 (C-3) , 73.08 (C-4'), 72.08 (C-2), 70.64 (C4), 63.23 (C-6), 61.42 (C-1'), 42.29 (C-6') , 35.75 (-CH₂), 31.73 (-2), 29.40 x3, 29.12 x2, 28.99 x3, 28.94 x2 (bulk-CH₂), 25.64 (-CH₂), 22.38 (-1), 13.08 ()

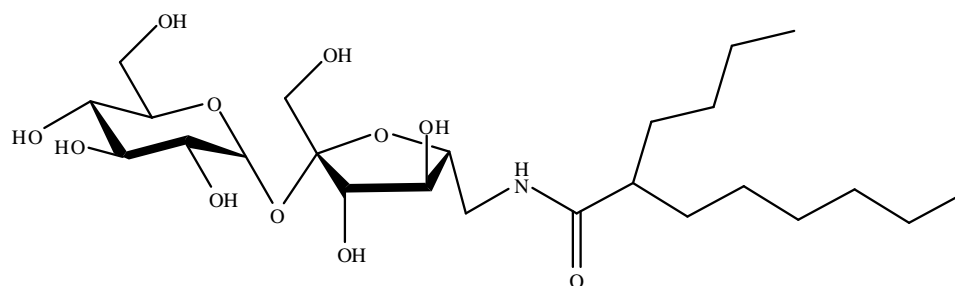
HRMS : [M+H]⁺: calcd for C₂₄H₄₅NO₁₁: 524.3065 (100%) , 525.3098 (28 %); found : 524.3039 (100 %) , 525.3064 (25 %) ;[M+Na]⁺: calcd for C₂₄H₄₅NO₁₁Na: 546.2884 (100%) , 547.2917 (28%) ; found : 546. 2878 (100%), 547.2905 (28%).

2,3,4,6,1',3',4'-Hepta-O-acetyl-6'-O-(2-butyl-octanamido)-sucrose [32]



Compound [29] (1.5g, 2.27 mmol) was coupled with 2-butyl-octanoyl chloride $C_6H_{13}(COCl)C_4H_9$ and triphenylphosphine PPh_3 according to the general procedure 6.4.7.A to produce compound [31] (1.2g, 65%) as NMR pure white crystals. $[\alpha]_D^{25} = +27.0$ (c 0.15, $CHCl_3$). 1H NMR (400 MHz, CD_3OD) = 5.17 (d, 1H, H-1), 5.48 (dd~t, 1H, H-3), 5.46 (dd~t, 1H, H-3'), 5.06 (dd~t, 1H, H-4), 5.32 (dd~t, 1H, 4'-H), 4.94 (dd, 1H, 2-H), 4.23-4.14 (m, 4H, H-1'B, H-5, H-5', H-6B, H-6'A), 3.71 (ddd, 1H, H-6A), 2.22 (m, 2H, -CH₂), 3.32 (m, 1H, -CH), 2.19, 2.12, 2.11, 2.09, 2.08, 2.06, 2.02 (7s, 21H, Ac), 1.58 (m, 2H, -CH₂), 1.29 (m, 16H, bulk-CH₂), 0.91 (t, 3H, CH₃). $^3J_{1,2} = 3.5$, $^3J_{2,3} = 10.0$, $^3J_{3',4'} = 9.5$, $^2J_6 = 14$ Hz. ^{13}C NMR (100 MHz, CD_3OD) = 177.39 (CONH), 170.41, 170.34 x2, 170.30, 196.92, 196.90 ((C=O), 88.96 (C-2'), 79.92 (C-1), 76.27 (C-5'), 76.07 (C-3'), 70.25 (C-4'), 69.58 (C-2), 68.69 (C-3), 68.48 (C-5), 68.29 (C-4), 62.95 (C-6), 62.07 (C-1'), 41.71 (C-6), 32.84, 32.74 (-CH₂), 29.61, 29.59, 32.50, 32.37, 31.98 (bulk-CH₂), 31.48, 31.31 (-CH₂), 22.66 (-), 29.47, 29.00, 28.95 (Ac), 19.30, 19.15 (). Elemental analysis for $C_{38}H_{59}NO_{18}$: C 55.81, H 7.27, N 1.71; found C 55.85, H 7.38, N 1.74.

6'-(2-Butyl-octanamido)-sucrose [33]

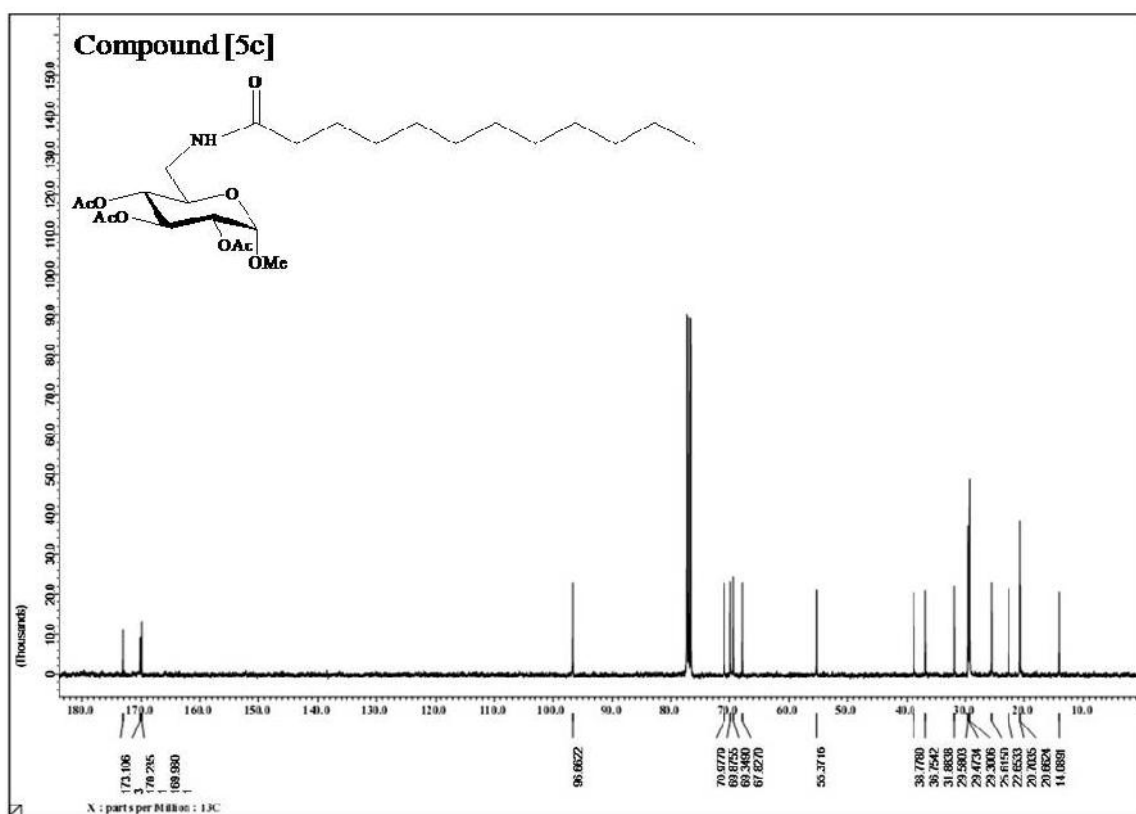
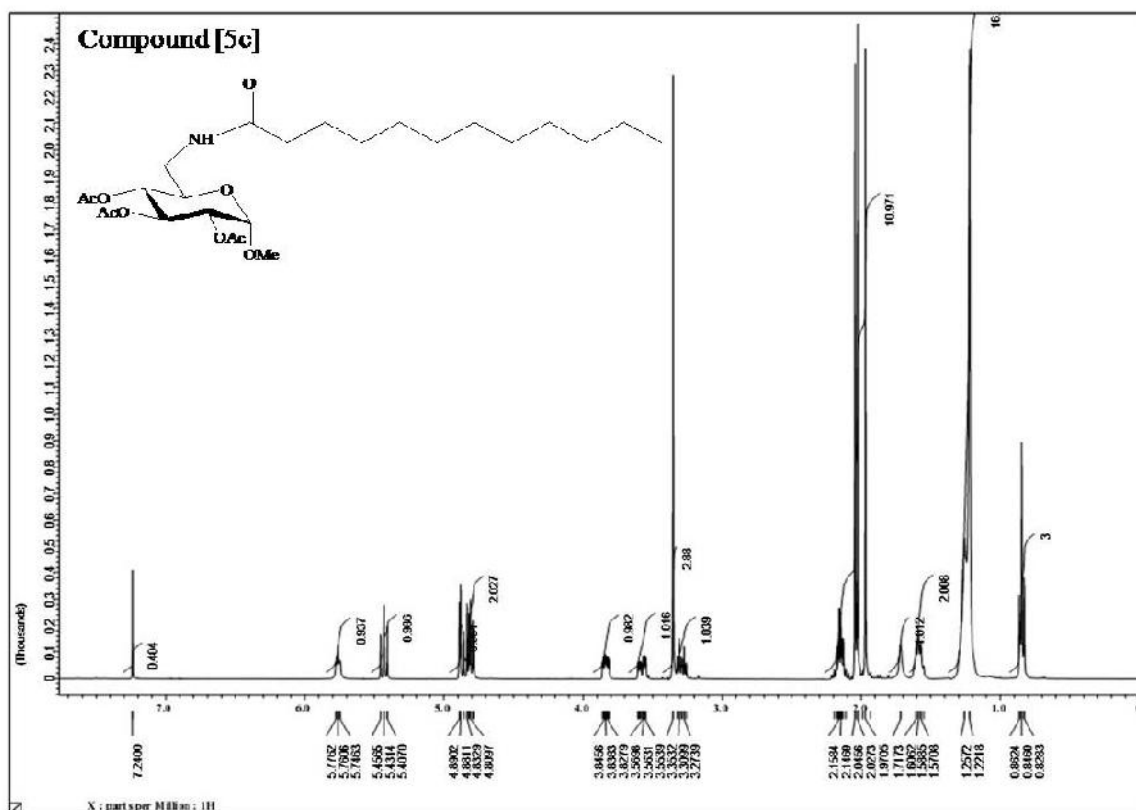


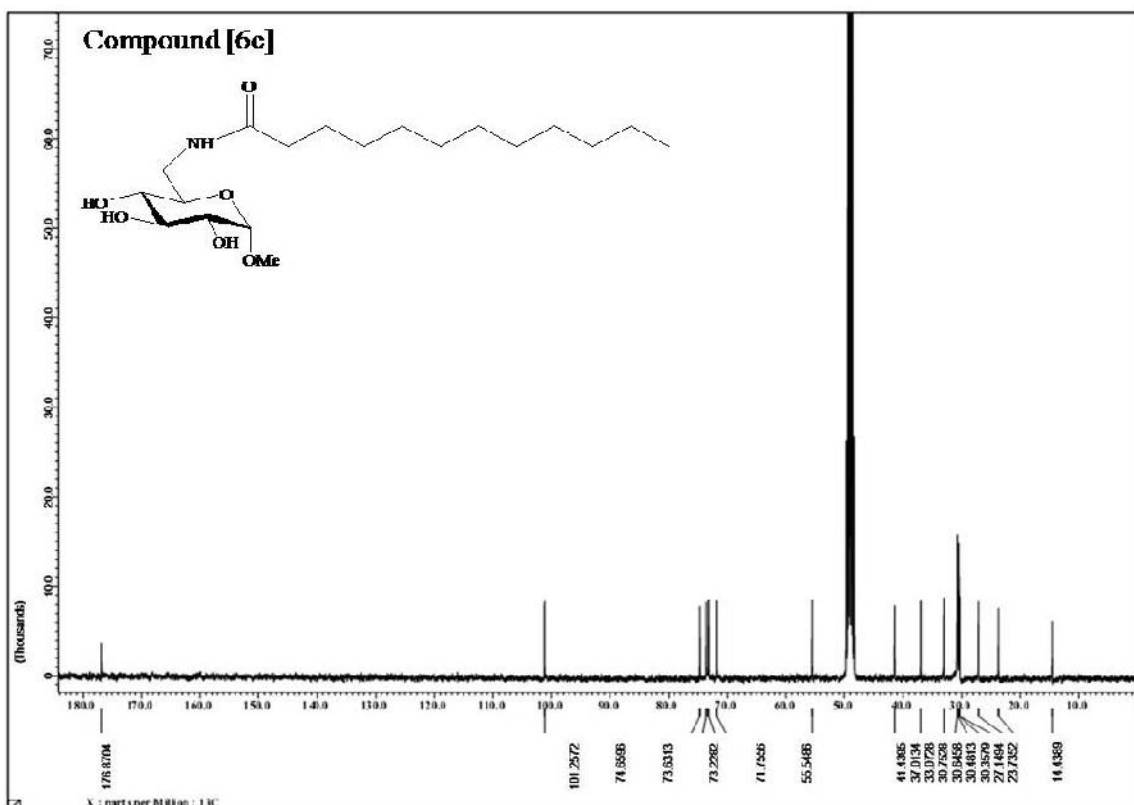
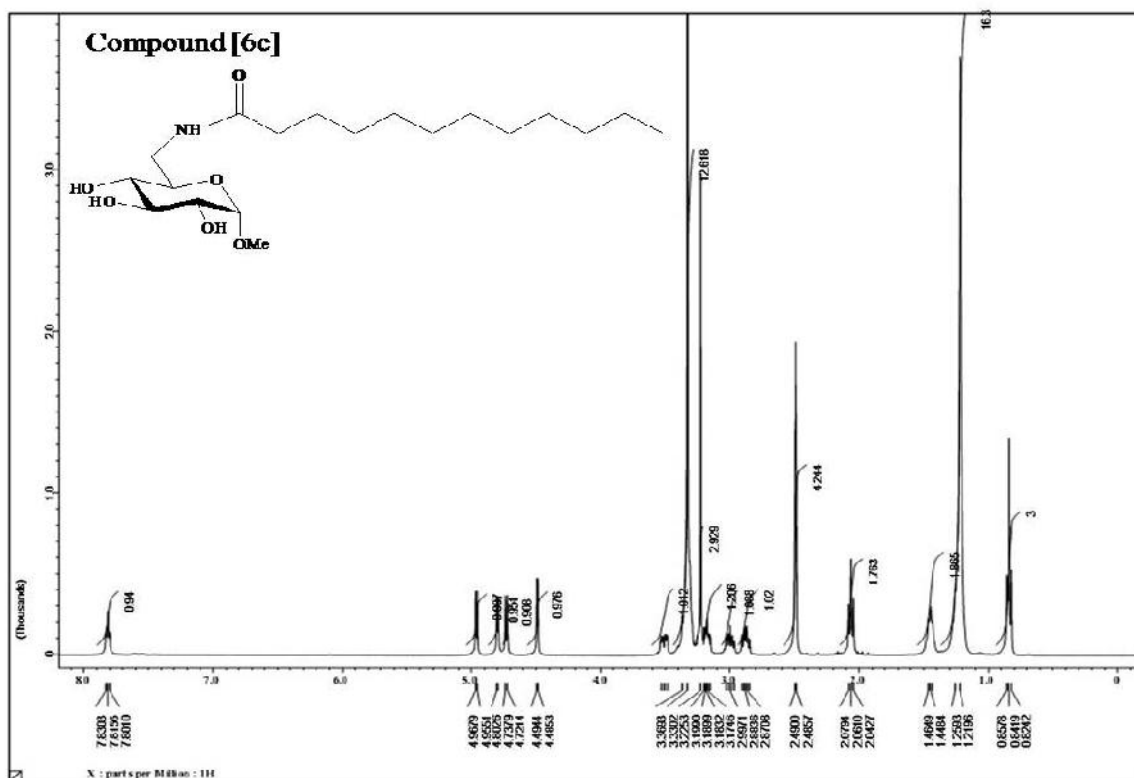
Compound [32] (1g) was deacetylated with sodium methoxide in methanol according to the general procedure 6.4.8.1 to yield compound [32] (0.59 g, 92%) as NMR pure white crystals. $[\alpha]_D^{25} = +43.0$ (c 0.15, CH₃OH). ¹H NMR (400 MHz, CD₃OD) = 5.38 (d, 1H, H-1), 4.07 (d, C-5'), 3.89- 3.49 (m, 7H, H-2', H-3', H-3, H-6, H-4, 2H-6'), 3.44 (m, 1H, H-2), 3.29 (m, 2H, H-1'A, 1'B), 2.20 (m, 2H, -CH₂), 1.56 (m, 2H, -CH₂), 1.35 (s, 16H, bulk-CH₂), 0.91 (t, 3H, CH₃) Hz, ³J_{1,3}=3.5, ³J_{2,3}=10.0, ²J₆=13.5).

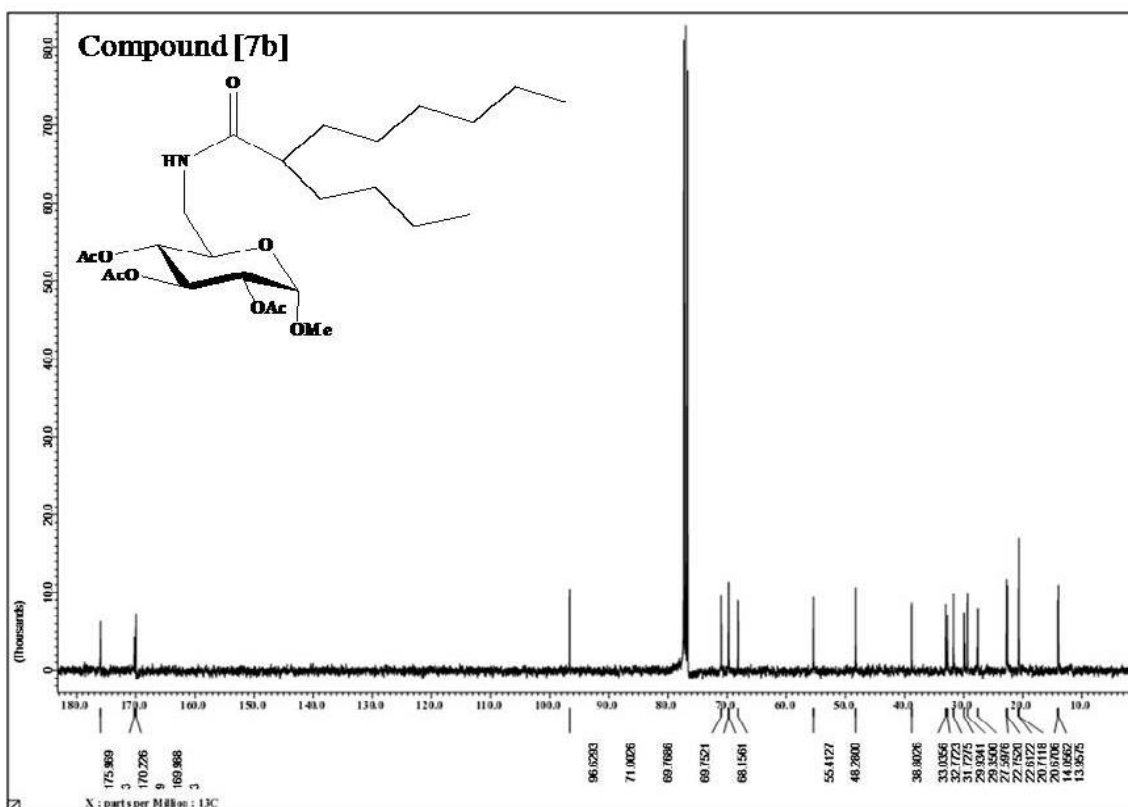
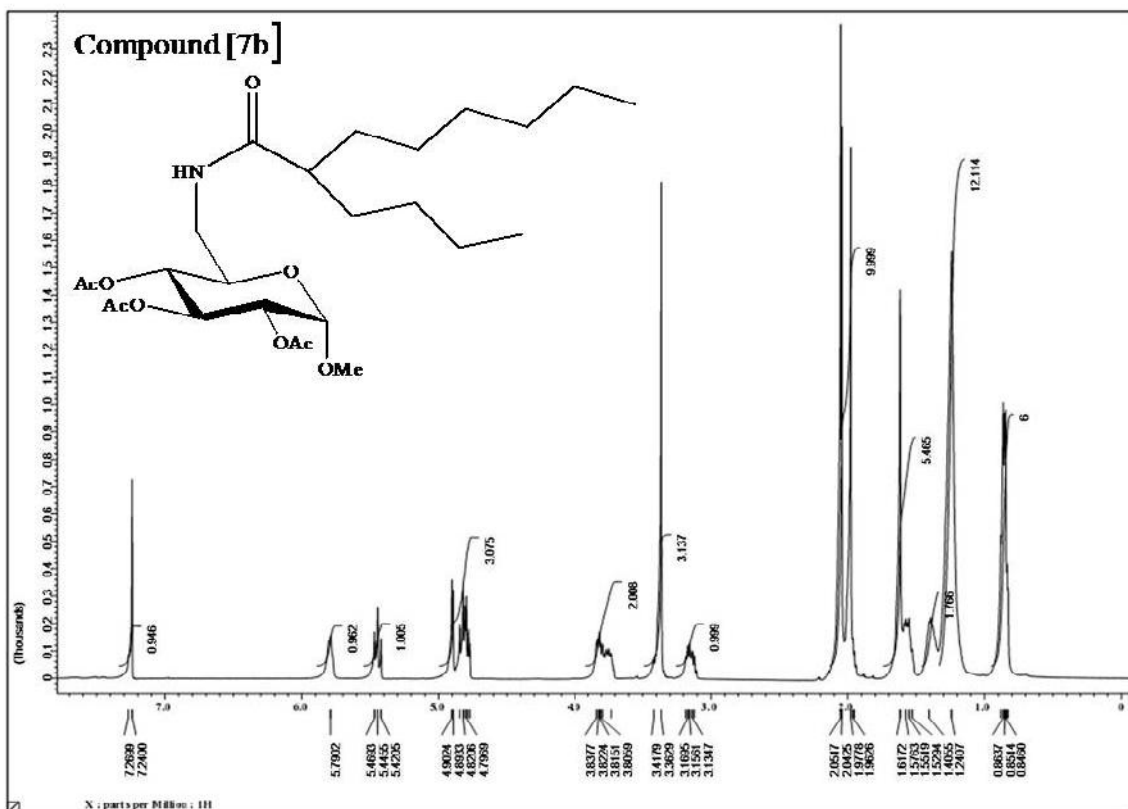
¹H NMR (400 MHz, CD₃OD) = 177.88 (CONH), 104.11 (C-2'), 92.08(C-1), 80.28 (C-3'), 78.52 (C-5'), 77.26 (C-5), 73.34 (C-3), 73.16 (C-4'), 71.97(C-2), 70.46 (C4), 62.97 (C-6), 61.50 (C-1'), 42.50 (C-6'), 32.86, 32.76, 32.53, 32.44 (-CH₂), 31.53 x2 (-2), 29.49 x3, 29.42, 29.11, 29.05 (bulk-CH₂), 27.21, 27.14 (-CH₂), 22.39, 22.35, 22.72 (-1), 13.01, 12.94 ().

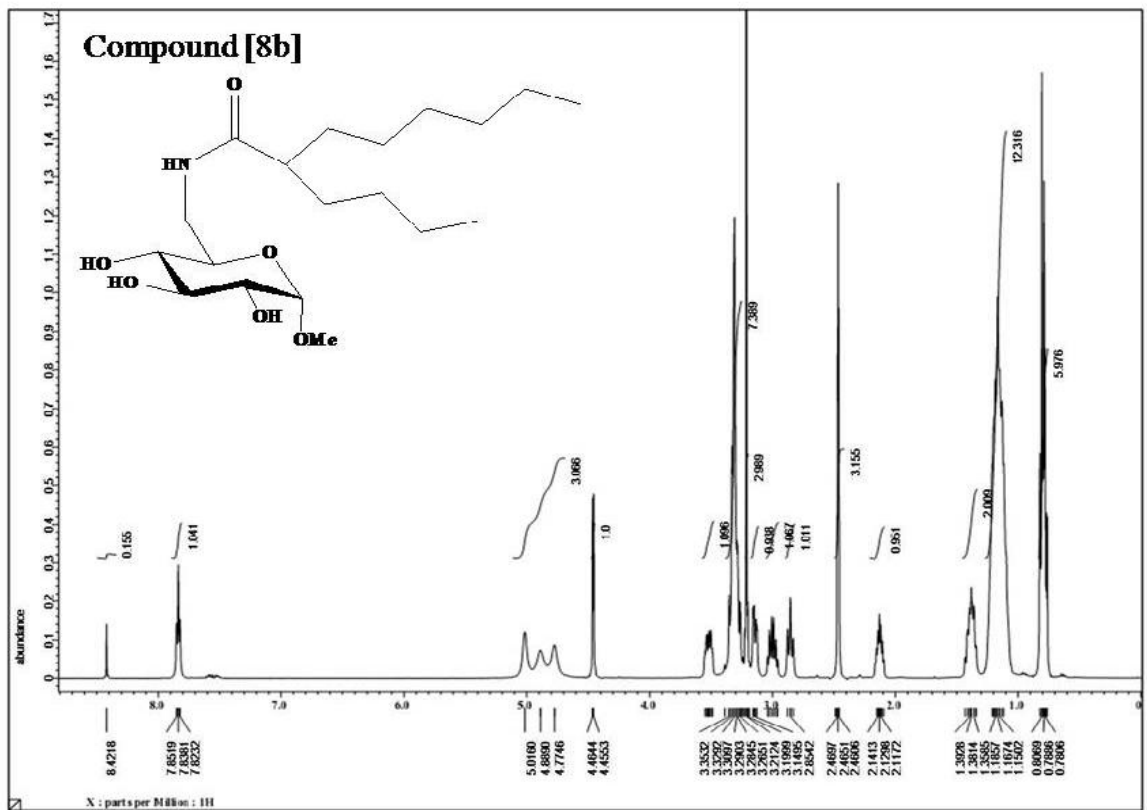
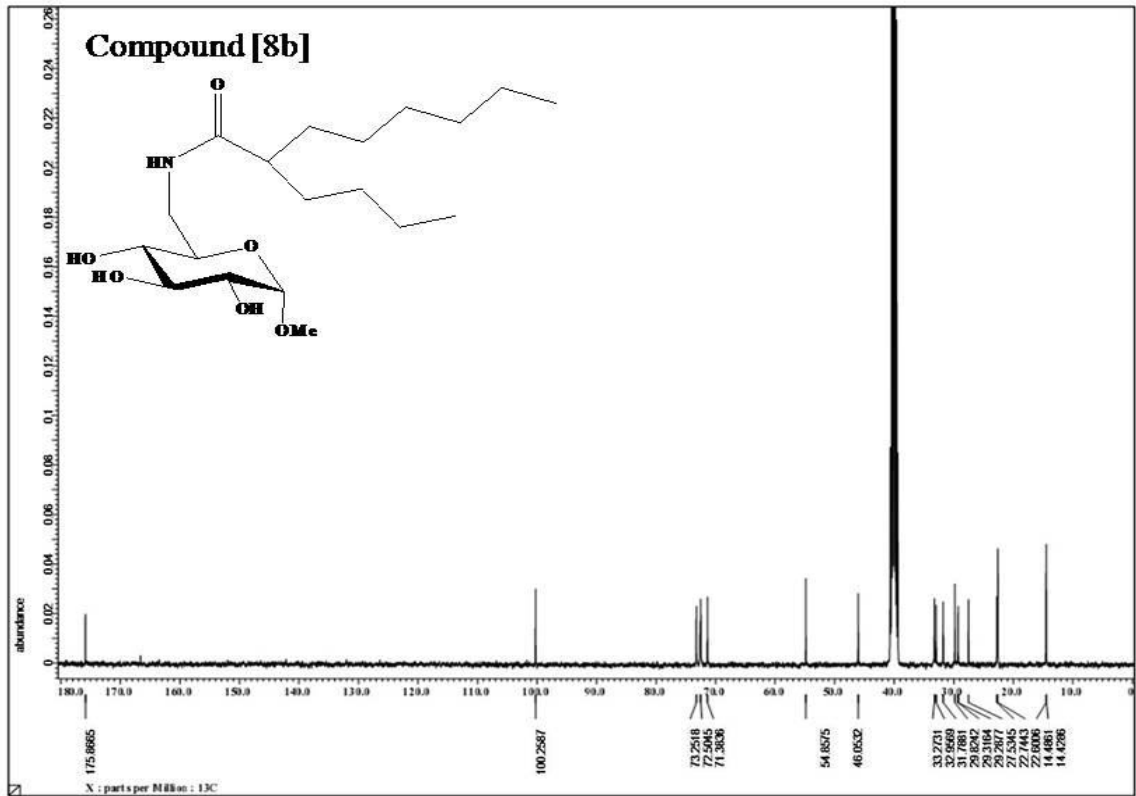
HRMS : [M+H]⁺: calcd for C₂₄H₄₅NO₁₁: 524.3065 (100%), 525.3098 (28%); found : 524.3163 (very weak) ;[M+Na]⁺: calcd for C₂₄H₄₅NO₁₁Na: 546.2884 (100%), 547.2917 (28%); found : 546. 2988 (100%), 547.3017 (24%).

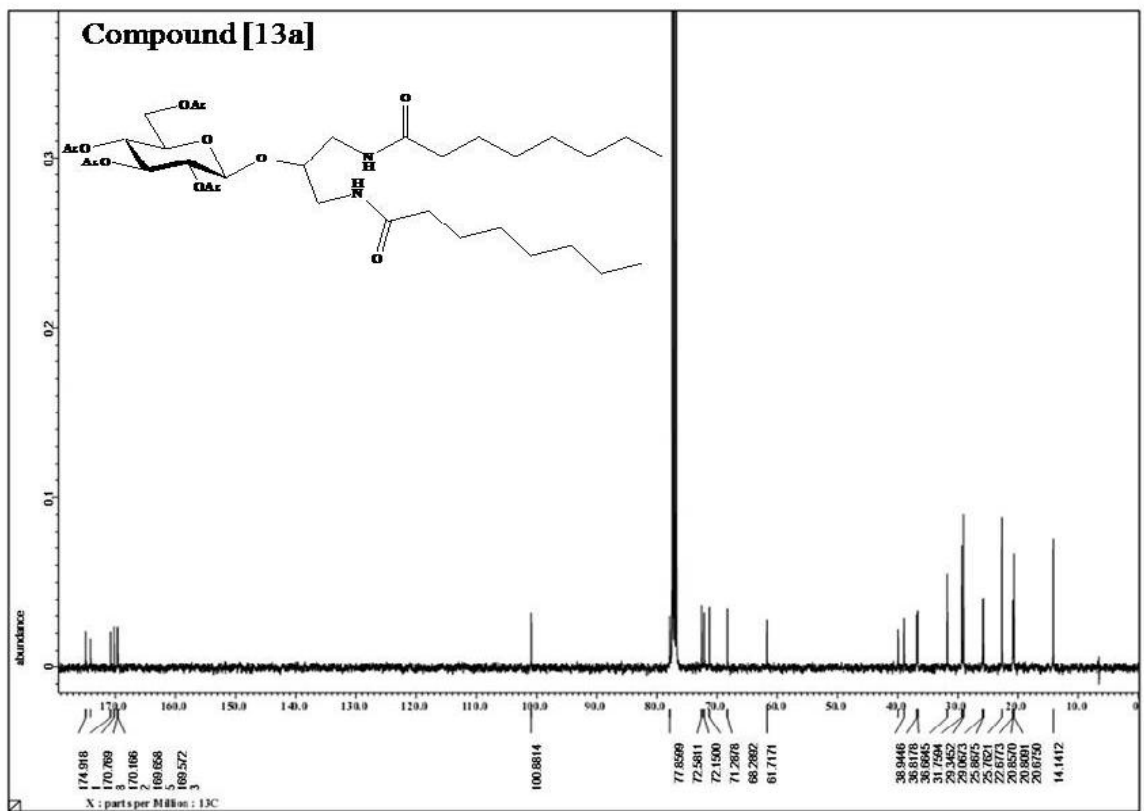
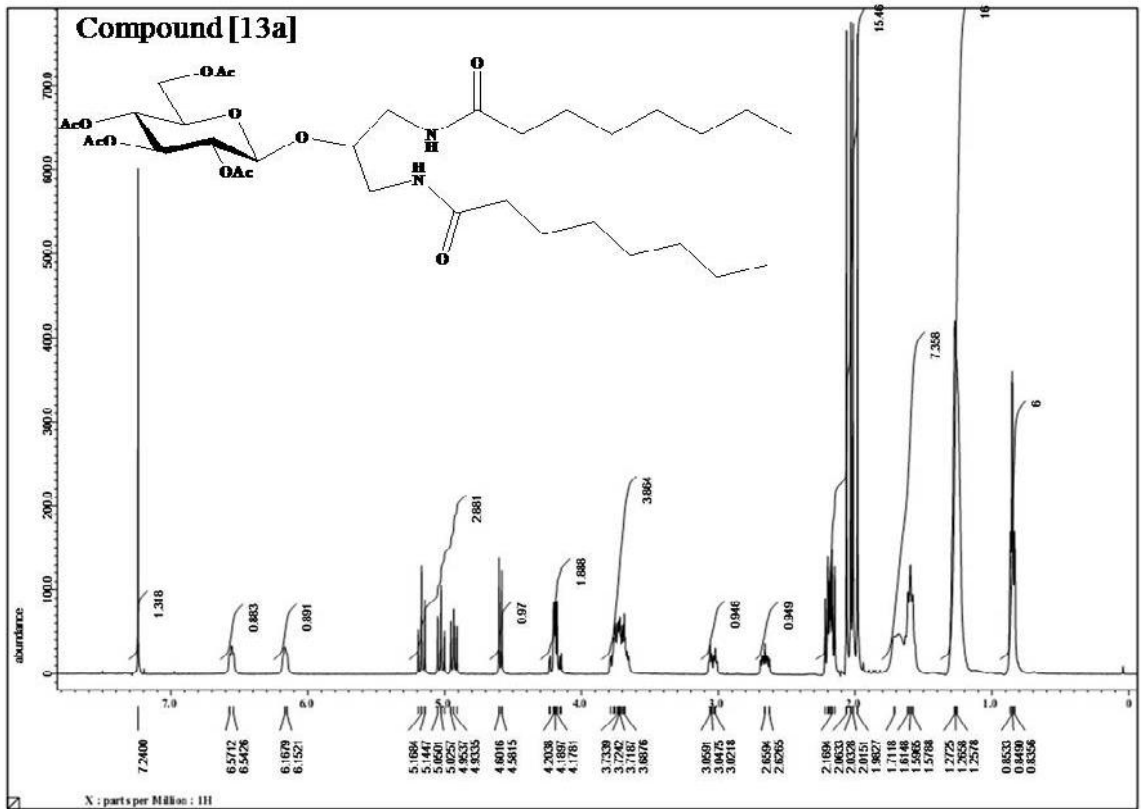
Appendix 1: NMR spectra

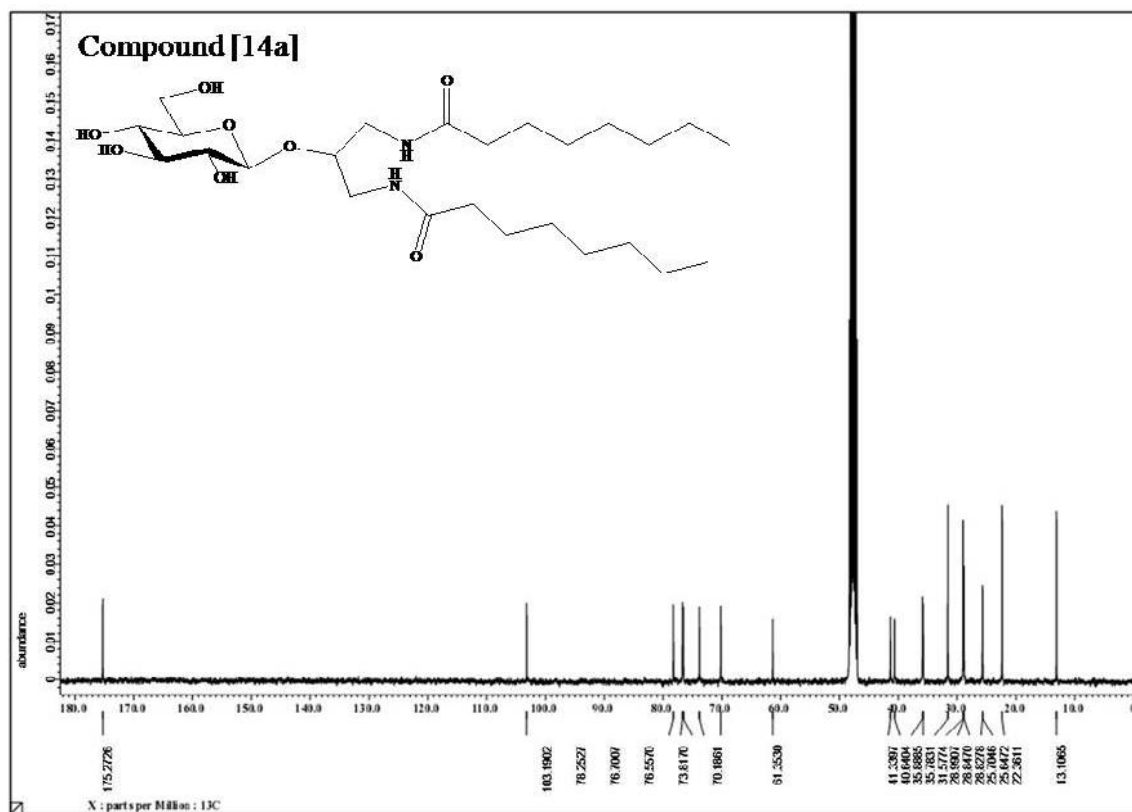
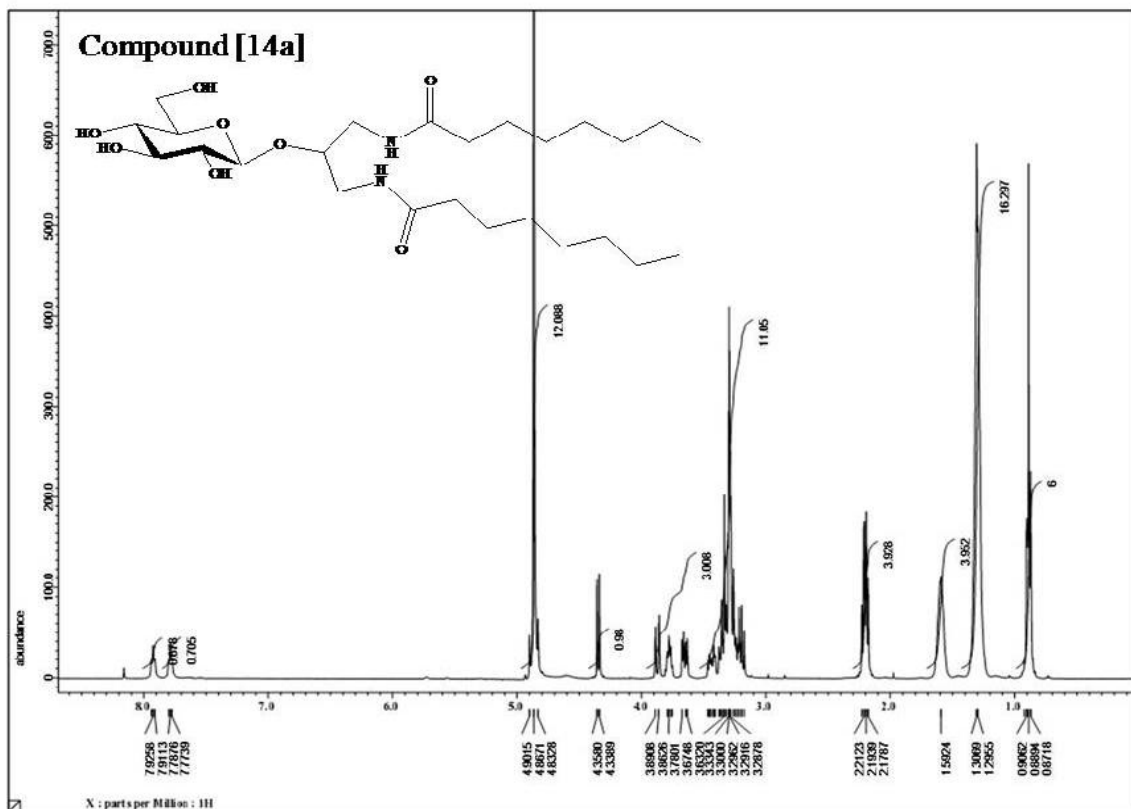


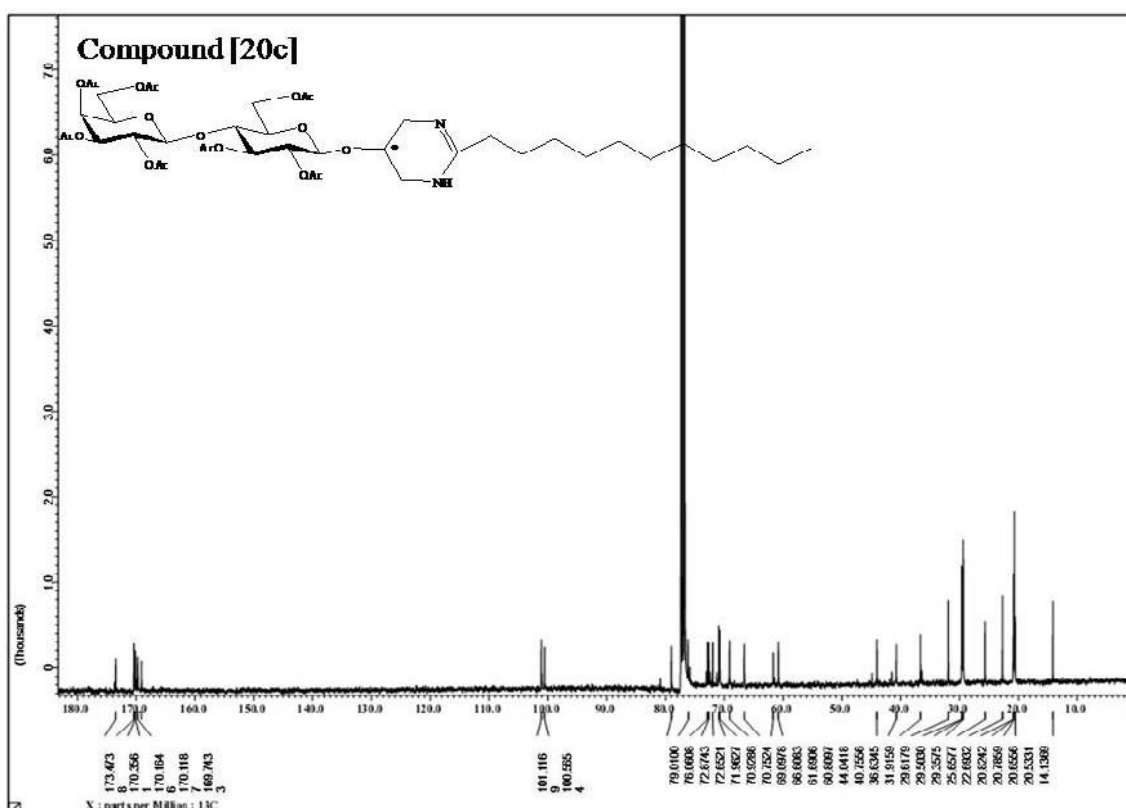
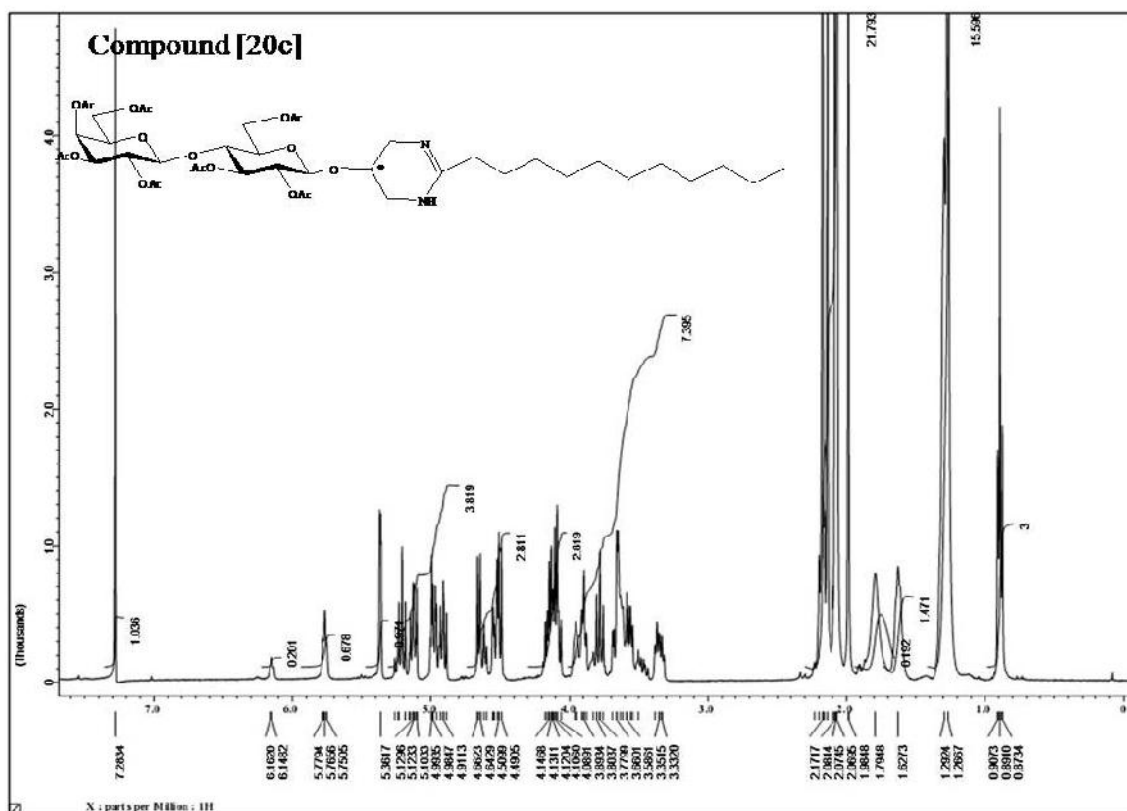


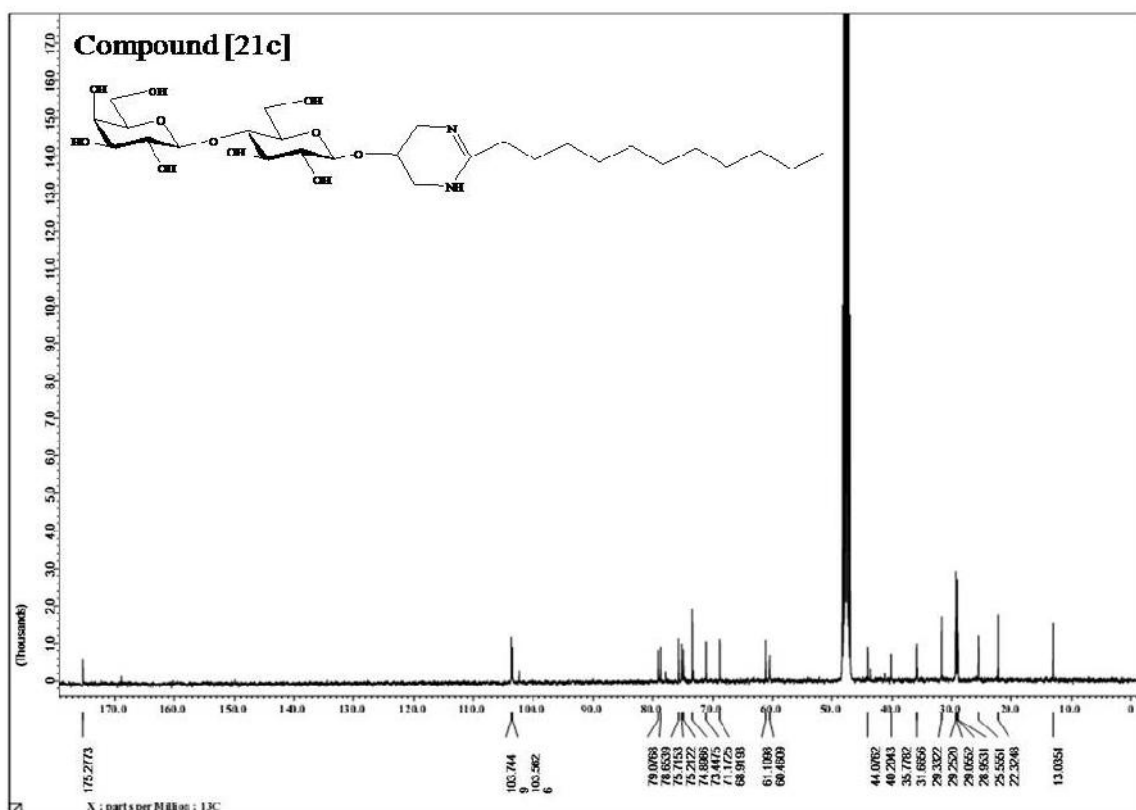
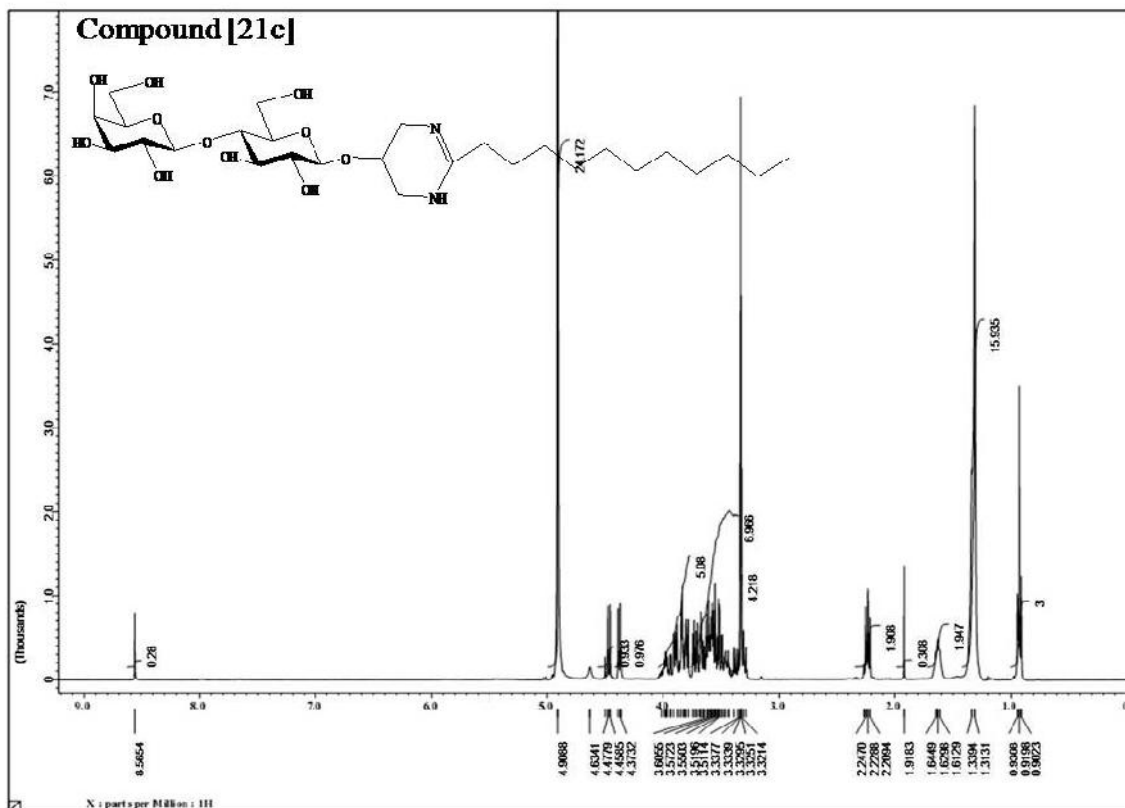


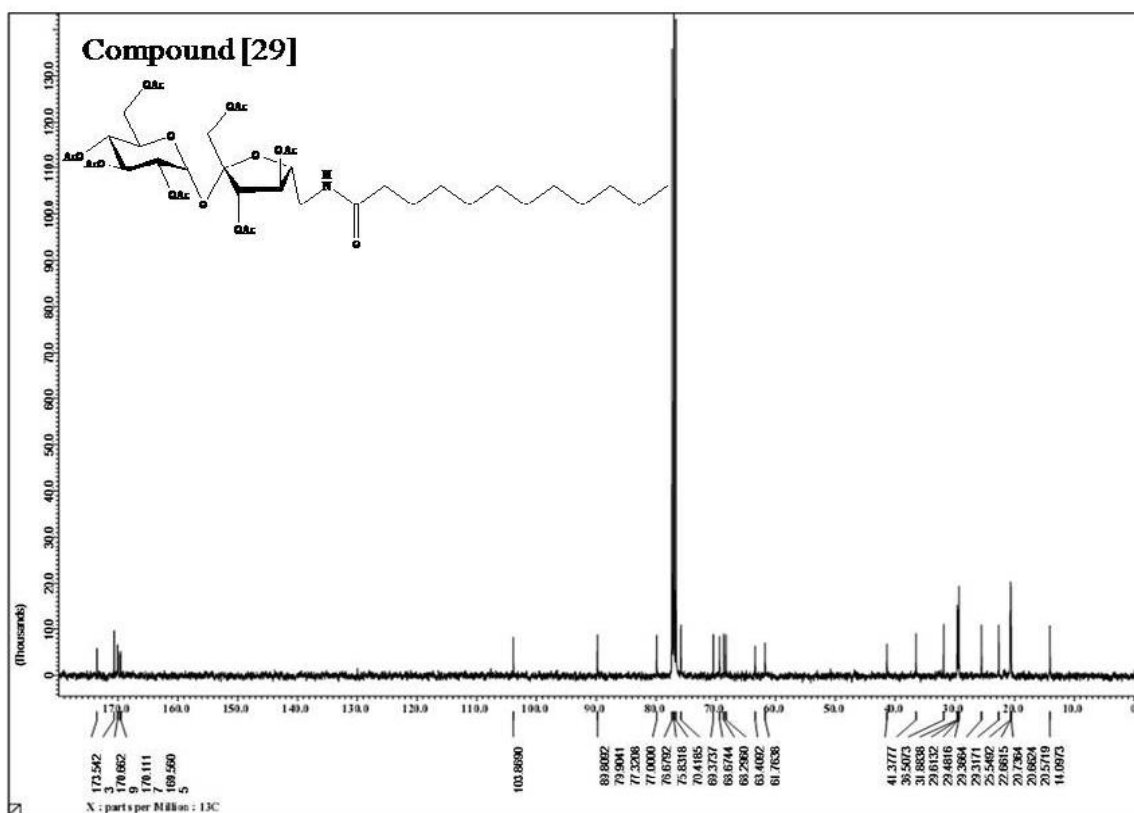
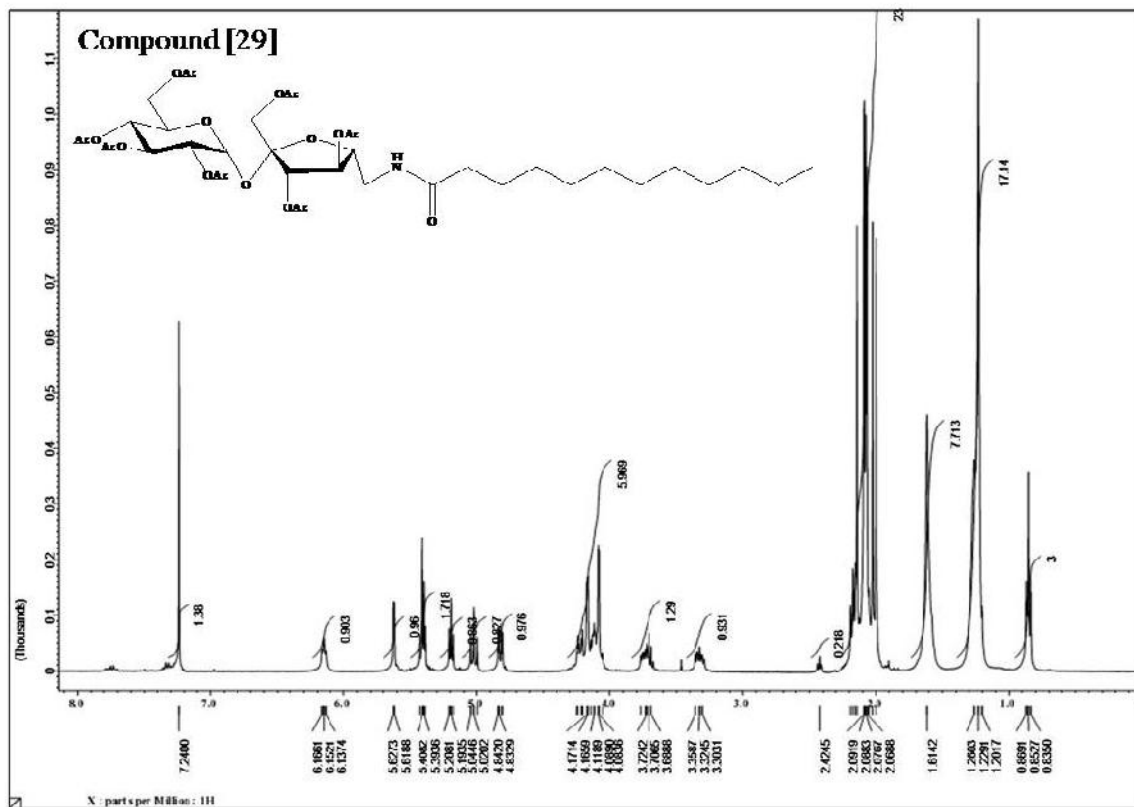


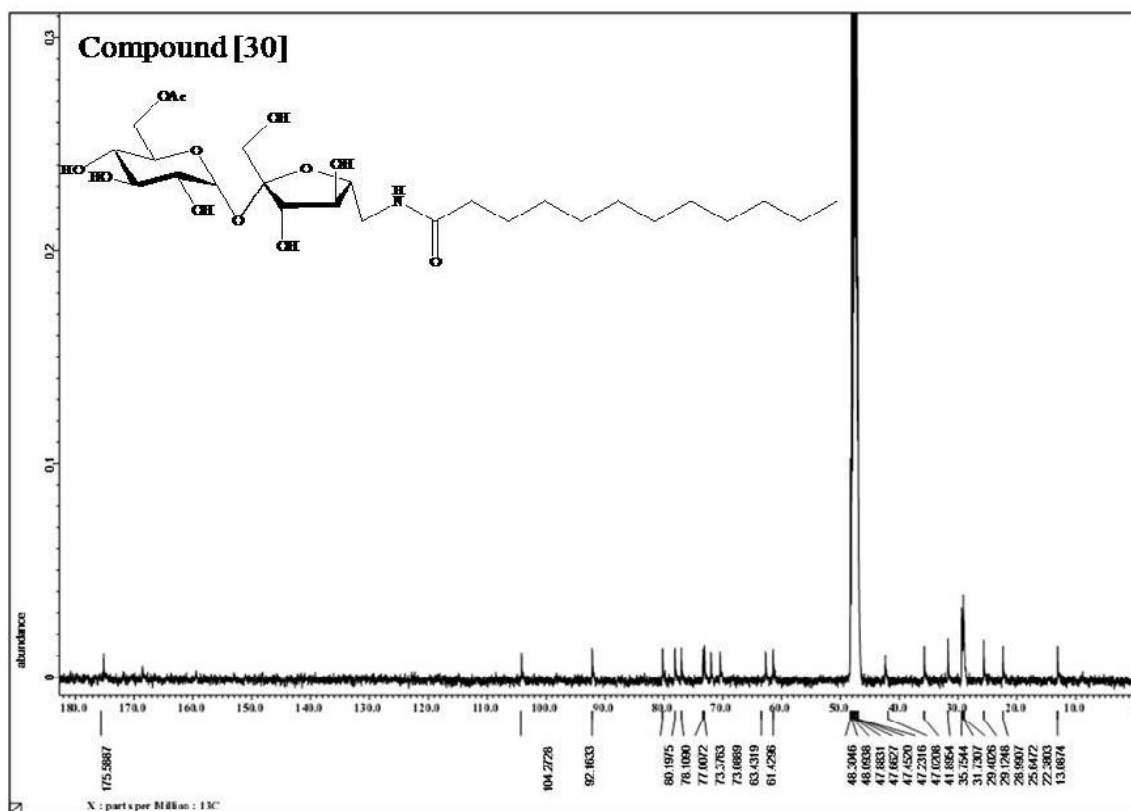
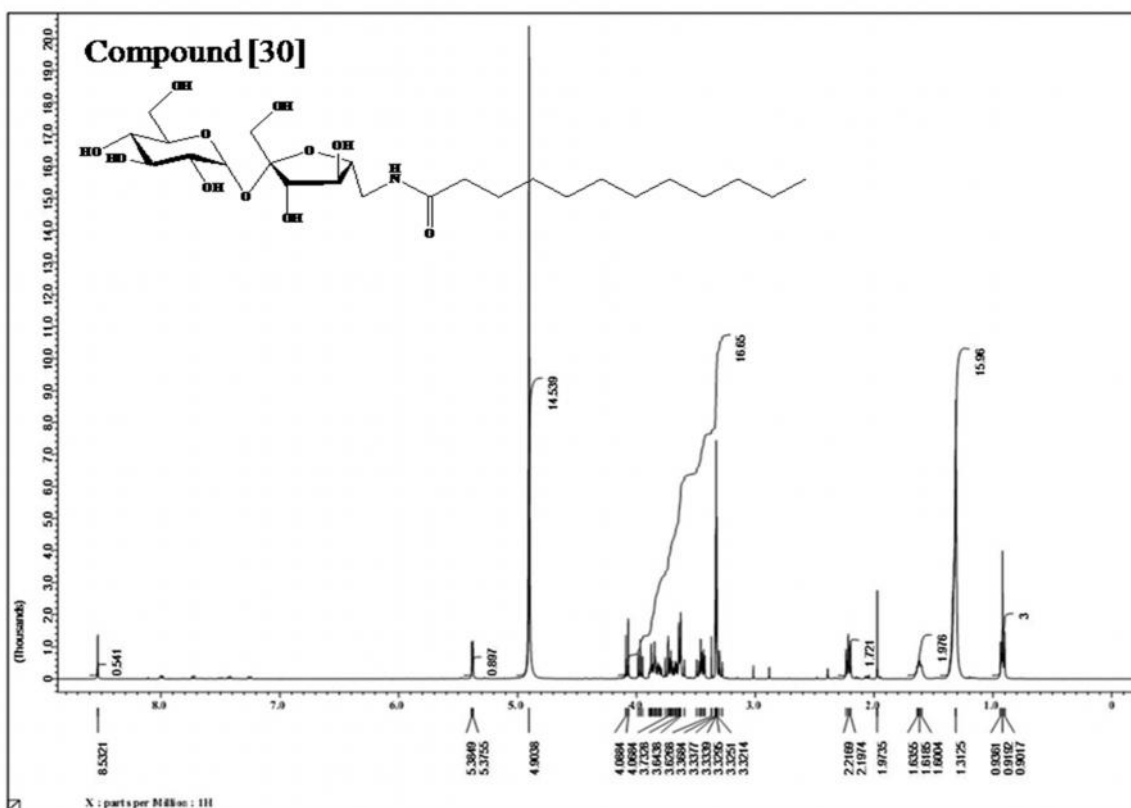


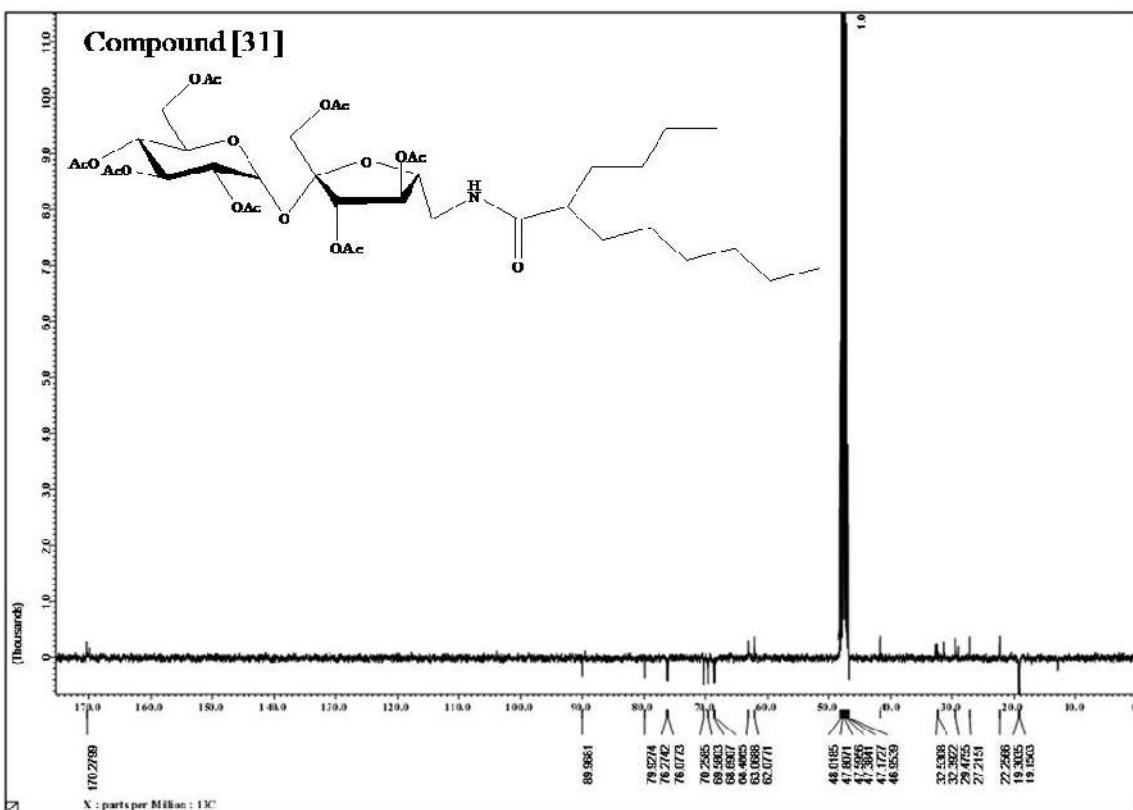
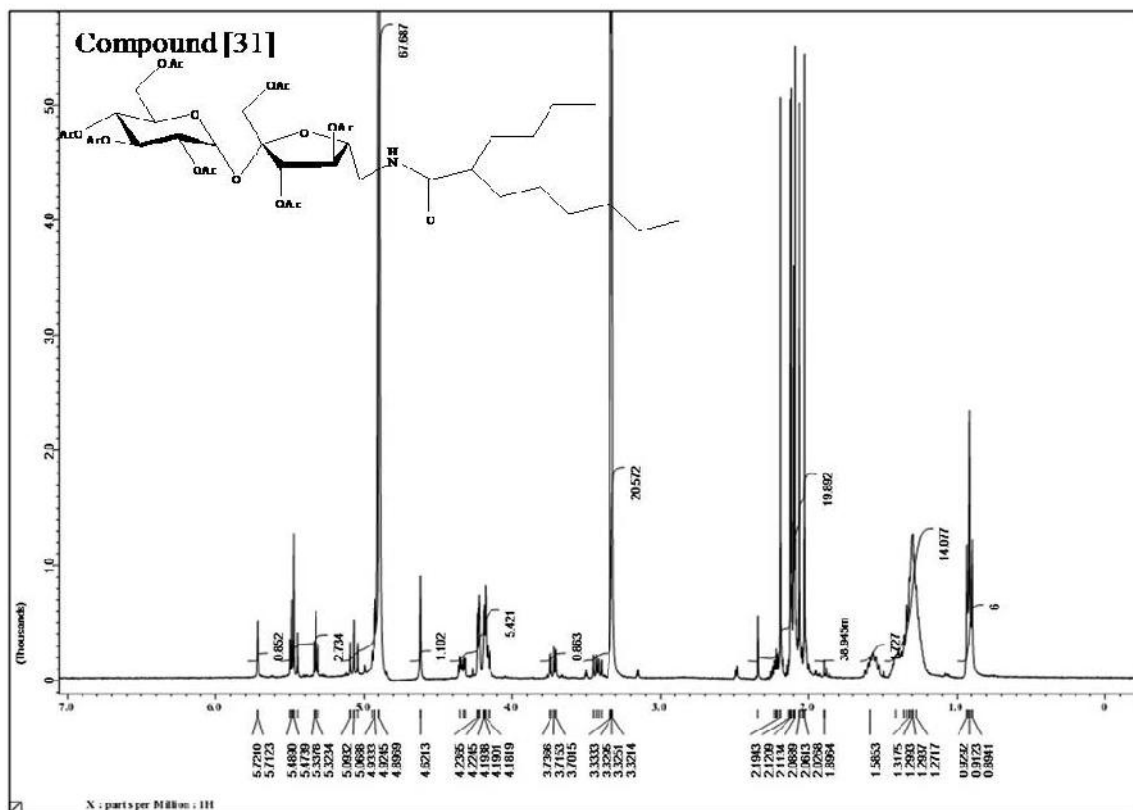


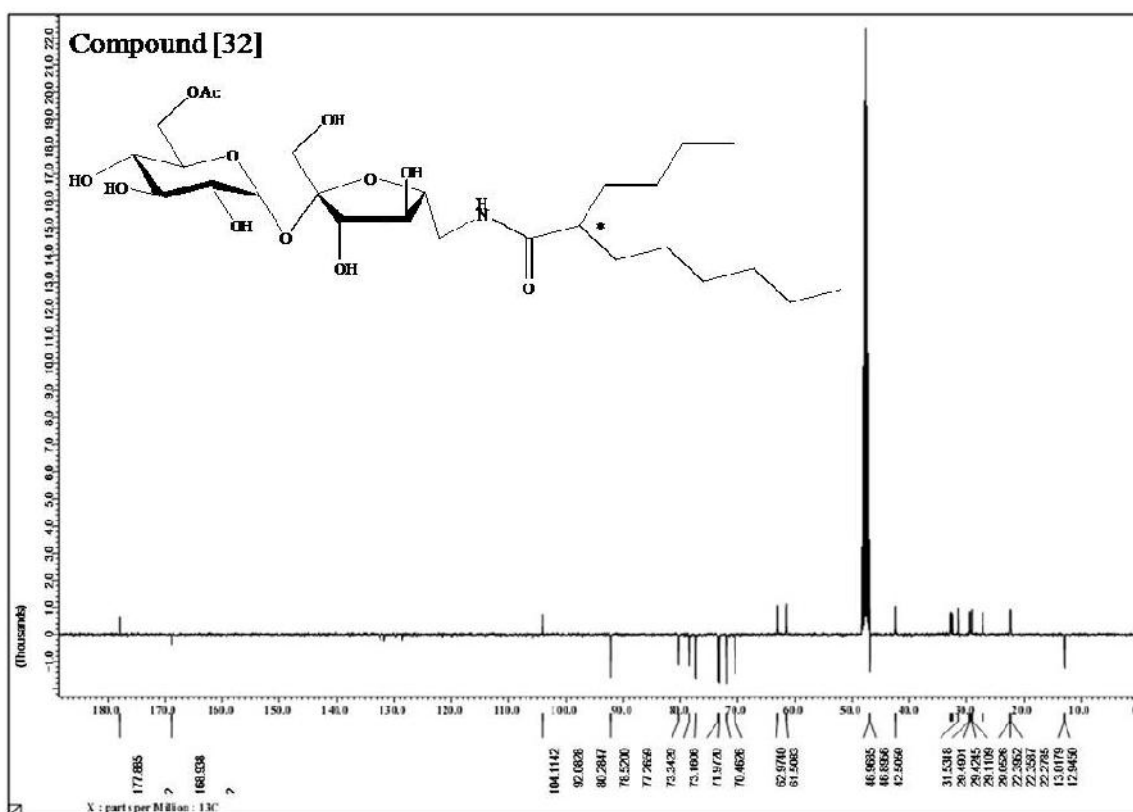
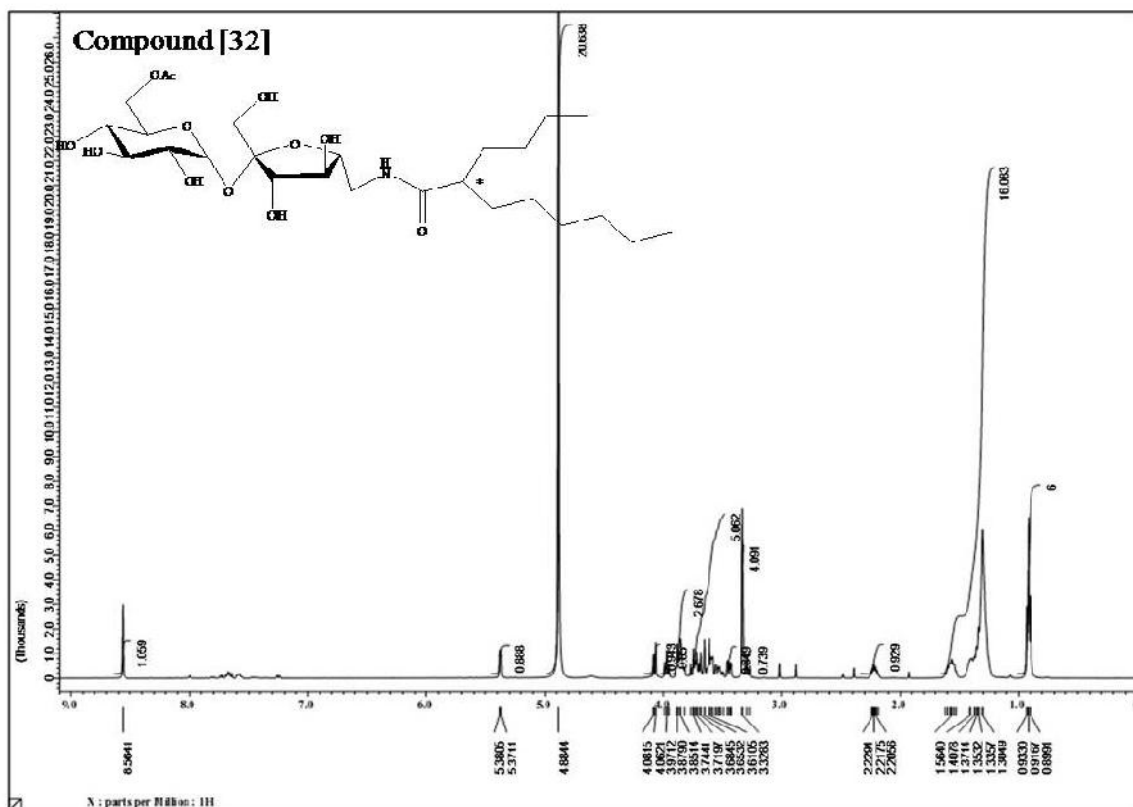












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