UNIVERSIDADE DA BEIRA INTERIOR

Faculdade de Ciências

Functionalization and characterization of carbohydrates for organotriethoxysilane precursors' synthesis

(Versão final após defesa)

Rodrigo Gabriel Rodrigues Pacheco

Dissertação para obtenção do Grau de Mestre em

Química Medicinal

(2º ciclo de estudos)

Orientador: Professora Doutora Maria Isabel Guerreiro da Costa Ismael

Coorientador: Professora Doutora Sílvia Cristina Cláudio Nunes

Covilhã, agosto de 2019

To my father and mother

Acknowledgements

This presented work has been performed at the Department of Chemistry, University of Beira Interior, in the synthesis and structural characterization laboratory, between September 2016 and January 2019. During this time, many contributed for this achievement, physically and psychologically.

Before all else, would like to thank my parents, without them, would be impossible to walk this long course. Never giving up on me, they encouraged me to continue this arduous path, making me believe in myself.

I would like to thank my thesis advisor Ph.D. Maria Isabel Guerreiro da Costa Ismael and co-advisor Ph.D. Silvia Cristina Cláudio Nunes for all the support and patience in all this way. Also, I would like to thank Ph.D. José Albertino Almeida de Figueiredo for all support and availability throughout this work. Especially thankful for all the knowledge shared, and all the never-ending support from all my family and friends.

Could never rightfully thank to all people who helped me and gave me motivation to surpass this task in the most arduous moments. To all, the biggest appreciation for all the support.

Resumo alargado

Os hidratos de carbono estão presentes em todos os organismos vivos e plantas, desempenhando um papel fundamental em vários processos biológicos necessários à sua sobrevivência. Posto isto, é de extrema importância o seu estudo e o desenvolvimento de novas aplicações biomédicas baseadas neles. Devido as suas fantásticas características e versatilidade, estes têm sido utilizados no desenvolvimento de sistemas de entrega de fármacos, especialmente no tratamento do cancro, que apesar do estudo intensivo, continua a ser uma das maiores causas de mortes no mundo.

Com os avanços no estudo dos hidratos de carbono, cada vez mais derivados têm sido desenvolvidos, possibilitando a sua combinação com nano-estruturas, formando sistemas com aplicabilidades em inúmeras áreas como a química, engenharia, biologia, medicina, e muitas outras. Através desta sinergia é possível ultrapassar muitos problemas, ambientais e médicos, atualmente existentes.

Apesar das inúmeras possibilidades de nano estruturas, algumas têm sofrido principal atenção. Como exemplo temos as estruturas mesoporosas, com aplicações em áreas como cromatografia e de sensores, que nos últimos anos têm sido extensivamente estudadas e aplicadas em diversas áreas. Concomitantemente com este trabalho, temos os materiais mesoporosos de sílica. Tendo sido descobertos há relativamente pouco tempo, estes materiais têm sido intensivamente estudados de forma a desenvolver materiais cada vez mais organizados, com porosidades e estruturas cada vez mais definidas. Ao longo do seu desenvolvimento, estes materiais possibilitaram o encapsulamento de moléculas orgânicas à matriz inorgânica. Com esta combinação de compostos orgânicos e inorgânicos, surgiram os materiais ordenados mesoporosos de organosilica, e posteriormente os materiais periódicos mesoporosos de organosilica. Esta combinação, resulta numa sinergia entre as componentes orgânicas e inorgânicas, melhorando as características de ambas.

Juntando todo este conhecimento recentemente desenvolvido, sobre estruturas mesoporosas, com a quase infinita versatilidade dos hidratos de carbono, temos o principal objetivo deste trabalho: o desenvolvimento de precursores organossilanos, para posterior utilização no desenvolvimento de estruturas mesoporosas organizadas baseados em hidratos de carbono.

Neste trabalho, algumas funcionalizações de açucares irão ser abordadas, com o principal objetivo de proteger os grupos hidroxilo presentes nos açucares, melhorando a sua solubilidade nos solventes orgânicos e permitindo uma ligação regiosseletiva ao material silicioso (isocianato de propil-trietoxisilano (ICPTES)), através de uma ligação uretano.

Este trabalho divide-se em duas fases. Na primeira foram preparados derivados de glúcidos, através da modificação dos grupos funcionais. Na segunda foram sintetizados precursores organossilanos, com base nos derivados e no composto silicioso isocianato de propil-trietoxisilano.

A primeira fase começa pela funcionalização do composto comercialmente disponível 1,2:5,6-di-O-isopropilideno-α-glucofuranose. Esta funcionalização consiste numa benzilação do hidroxilo na posição 3, na desproteção seletiva do grupo isopropilideno, seguida de uma oxidação dos dióis vicinais, e uma posterior redução do aldeído. Seguidamente realizou-se a funcionalização da D-ribose através de uma síntese de um só passo, onde ocorre a metilação da posição 1 e a formação de um grupo isopropilideno na posição 2 e 3. Seguidamente foi funcionalizada a N-acetilglucosamina através da metilação da posição 1 e da adição de um grupo benzilideno na posição 3 e 4. A síntese de derivados de glúcidos dá-se por terminada com a funcionalização da D-glucose, que foi feita através da benzilação dos grupos hidroxilos, seguida da acetilação seletiva da posição 6, e respetiva desacetilação da mesma posição, resultando num grupo hidroxilo desprotegido.

Seguidamente foi realizada a síntese dos precursores organossilanos, para os quais foram utilizados os anteriormente referidos derivados de glúcidos, bem como os comercialmente disponíveis 1,2:5,6-di-O-isopropilideno-α-D-glucofuranose, 1,2-O-Isopropilideno-α-D-xilofuranose, e 2,3,4,6-tetra-O-benzil-α-D-glucopiranose. Esta síntese baseou-se na formação de uma ligação uretano entre os derivados de glúcidos e o isocianato de propil-trietoxisilano.

A síntese e caracterização dos compostos e precursores foi acompanhada pela análise através de ressonância magnética nuclear de carbono e protão, comprovando a sua estrutura, e a reação de formação dos precursores foi controlada por espetroscopia de infravermelho.

Com este trabalho, realizou-se a combinação entre materiais siliciosos e hidratos de carbono, uma combinação inovadora com muito potencial de desenvolvimento e inúmeras aplicabilidades.

Palavras-chave

Derivados de glúcidos, materiais mesoporosos, precursores organossilanos, materiais híbridos, sistemas de entrega de fármacos.

Abstract

Carbohydrates are ubiquitous in all living beings, from the most complex – the humans – to the unicellular organisms. Fundamental in all kinds of biological processes, carbohydrates represent expedient candidates for biomedical applications. Through their use, countless barriers could be overcome, especially the lack of selectivity on cancer's treatment. Although their advantages, carbohydrate synthesis is still far from completely unearthed and understood. However, the growing necessities thrust the field to more complex subjects, leading to the discovery of new potent devices capable of overwhelming the field of medicine.

The same driving force pushed the field of nanotechnology to the development of new materials, with applicabilities in uncountable fields. One of these materials was the mesoporous materials, which were recently discovered, and gain major focus of research in past years. This research flows towards the creation of materials progressively more complex and organized, ultimately leading to periodic mesoporous materials. These materials can be packed with organic moieties, leading to a synergetic combination between the organic and the inorganic features.

This combination conducted to the objective of this work, which can be divided in two phases. The first is synthesis of glycoside derivatives, through their functionalization, for posterior linkage to a siliceous material - in phase two - resulting in mono/di-organosilane precursors, which can be used to prepared mesoporous materials – ordered or periodic. The use of carbohydrate derivatives in combination with these materials is an innovative field, with scarce research carried, and since the synergetic combination of the organic/inorganic features, is a promising field for the development of more efficient biomedical devices, for example, drug delivery systems.

Keywords

Glycoside derivatives, organosilane precursor, mesoporous organosilica, drug delivery system.

Index

Figure Index

Scheme Index

Graphic Index

Table Index

Acronym list

µm	Micrometre
Å	Angström
λ	Lambda
Ac_2O	Anhydride acetic
AcCh	Acetyl chloride
AcOH	Acetic acid
AM1	Austin model 1
ATR	Attenuated total reflectance
BnBr	Benzyl bromide
cm	Centimetre
DAG	Di-acetone-D-Glucose
DCM	Dichloromethane
DDS	Drug delivery system
DMAP	4-(dimethylamino) pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRIFTS	Diffuse reflectance infrared Fourier transform spectroscopy
EA	Element analysis
EISA	Evaporation induced self-assembly
EtOH	Ethanol
FT-IR	Fourier-transform infrared
g	Grams
GNP	Glyconanoparticle
HMF	5-hydroxymethylfurfural
ICPTES	3-(Triethoxysilyl)propyl isocyanate
IUPAC	International union of pure applied chemistry
LCT	Liquid-crystal templating
mbar	Millibar
MeOH	Methanol
MCM	Mobile crystalline material

MHz	Mega hertz
mm	millimeter
mmol	Millimole
MS	Mesoporous silica
n.a.	Not applicable
NaOMe	Sodium methoxide
n.d.	Not defined
nm	Nanometer
NMR	Nuclear magnetic resonance spectroscopy
OMO	Ordered mesoporous organosilica
OMS	Ordered mesoporous silica
O.N.	Over night
overl.	overlapping
PEO	Poly(ethylene oxide)
PMO	Periodic mesoporous organosilica
PMS	Periodic mesoporous silica
PSD	Pore size distribution
R.f.	Retention factor
r.t.	Room temperature
SDA	Structure directing agent
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
TEOS	Tetraethyl orthosilicate
TGA	Thermo gravimetric analysis
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
XRD	X-ray powder diffraction

1. Introduction

Carbohydrates are ubiquitous in all living beings[1], although the importance of their existence, such as in reproduction, inflammation, signal transmission and infection[2], the development of medical tools based on these biomolecules[3] is of increasing importance. The biocompatibility of the carbohydrates, and their ability to be recognized by cell-surface receptors denote their potential for therapeutic applications.[2,4,5,6]

This major class of naturally occurring organic compounds, gained their designation due to their general formula $C_n(H_2O)_m$ with n equal to or greater than three, which means that carbon is bonded to water molecules forming "hydrates of carbon". Nevertheless, many derivatives of carbohydrates exist with other components in their structure. Therefore the formula should not be used as a carbohydrate general formula. Among them are various sugars, starches, and cellulose, all of which are important for the maintenance of life in both plants and animals.[7]

Due to the increased attention on the subject, and the advances inherent to it, is now possible to overcome the problems on the synthesis of carbohydrates that existed a few decades ago.[2] These group of biomolecules exhibits innumerous biomedical applications, and have recently being used and researched - as glyconanosystems - for the development of carbohydrate-mimetic diagnostics and drug candidates.[2,8]

Attributable to their versatility, the development and research in the area is of extreme importance. Carbohydrate can be used in uncountable medical applications–such as vaccines, drug delivery systems (DDS), and some more that will be briefly summarized in this work.

With this increased research in the field, more commonly the term glycoscience - *i.e.*, the group of disciplines that study carbohydrates and their interactions with biomacromolecules and intrinsic biological processes - has been applied.[2] The advances in glycoscience enabled a new specter of applications thrusted by all information acquired with the past research years. One of the focus is the development of anti-cancer DDS.

Hence its complexity, cancer has more than one hundred different types, and besides all the effort and research in the area, still has high rates of mortality and occurrence[9]. It is characterized by uncontrollable cell growth and dissemination of malignant cells.[9,10] The common treatments are the conventional therapies - using chemotherapy as main resource, bringing many undesirable effects attached. These side effects are mainly caused by the lack of selectivity of the chemotherapeutic agents, causing damage to the normal cells.[11]

The use of carbohydrates enables a wide number of possibilities to overcome the selectivity problems, using the glycosidic receptors, and their interactions to selectively attack the

malign cells. Adding all this know-how with the advances in the development of more complex and precise DDS, is nowadays possible to do a more accurate drug delivery, enhancing the selectivity and efficiency of the treatments. Furthermore, there always have been difficulty in trespassing biological barriers.[12]

In the last years, the ever-growing necessities of engineering, chemistry, materials science, and biology strongly encouraged the development of novel porous materials with more tunable features,[13-15] ranging from nanoparticles, polymers, hydrogels, and hybrid materials. In this latter mentioned class, also known as nanocomposites, the combination of organic and inorganic moieties is achieved in a synergetic way. One of the most attractive materials in this class is the silica-based mesostructures. These materials, with applicabilities in many areas, leaded to the development of increasingly more organized materials, starting with ordered mesoporous organosilicas (OMOs) and ultimately leading to the discovery of the periodic mesoporous organosilicas (PMOs).

Through these materials is possible to overcome many existing barriers and is possible to synergistically combine them with the excellent features of carbohydrates, permitting their disposal in a multivalent fashion-way, creating synthetic "scaffolds" with varying valency and spatial organization. However for the production of these materials, first in necessary the preparation of organosilane precursors, where the organic part is covalently linked to the siliceous materials, which are posteriorly introduced in the inorganic matrices. The development of these precursors is of extreme importance and that was the thrusting force for the realization of the work herein presented.

1.1. A brief introduction to carbohydrates

Due to the long and awkward names, given by the IUPAC system, to the saccharides, a highly specialized nomenclature system has been developed exclusively for carbohydrates.[7]

Some of the most abundant five-carbon sugars are D-ribose, 2-deoxy-D-ribose, and D-xylose, which are aldopentoses. Some of the most common six-carbon sugars (hexoses) were studied on this work, such as D-glucose and n-acetylglucosamine, belonging to the aldohexose group.[7]

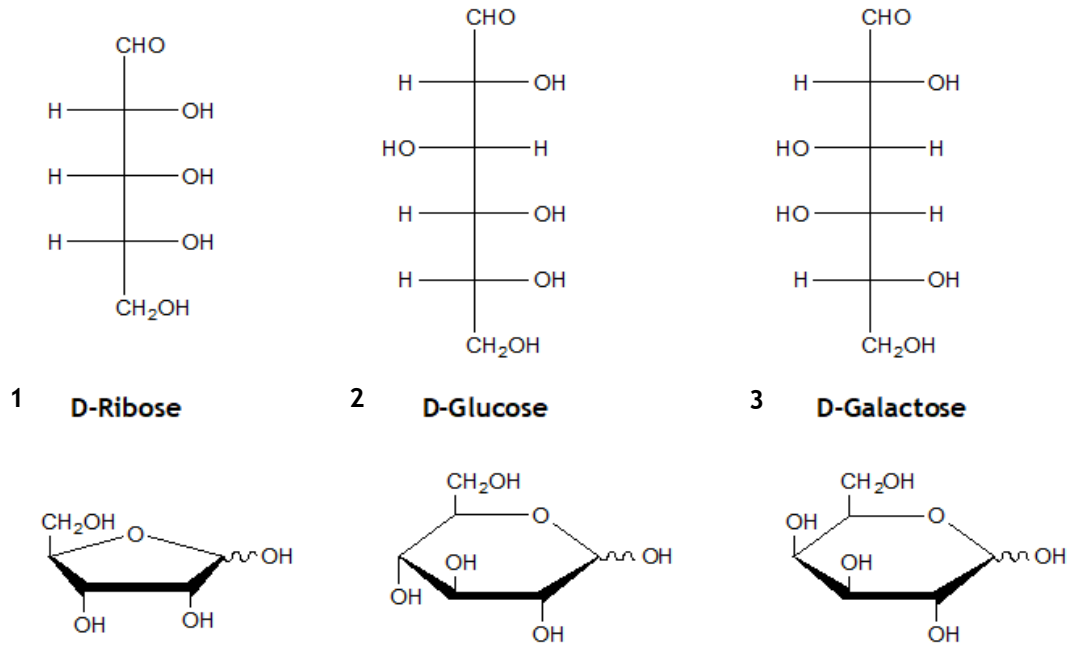


Figure 1 - Demonstration of the aldopentoses and aldohexoses (top), and respective hemiacetal (bottom). On the left we have D-ribose **1** with the aldopentose on top, and directly under the respective hemiacetal (furanose). On the center and right, is D-glucose **2** and D-galactose **3**, with the aldohexose on top, and right under is the corresponding hemiacetal (pyranose).

The name 'monosaccharide' denotes a single unit without any glycosidic connection. In chemical terms, they are either aldoses or ketoses, the ending 'ose' is the indicative suffix of a sugar.[16] In the solid state or in solution monosaccharides exist in cyclic hemiacetal/hemiketal form, ring closure correspondent to the reaction between the aldehyde or ketone group and either the C_4-OH or C_5-OH.[7,16] Cyclization involving C_4-OH results in a five-carbon ring structurally related to furan and therefore designated as a *furanose*. The second cyclization, of O-5, gives rise to a six-membered ring - a strain-free hemiacetal - hence a sterically more favored derivate of pyran, henceforth termed as *pyranose*.[16]

Both ring formations generate a new asymmetric carbon atom at C_1, anomeric center, thereby giving rise to diastereomeric hemiacetals which are labeled α and β (figure 2).[16]

The understanding of the conformational concepts is essential to a proper understanding of the structure-property relationships of carbohydrates, especially for the regio-stereoselectivities of their reactions.[7,16]

Hence, the rhombus-shaped Haworth formulas which imply a planar ring, and the equally flat dashed-wedged line configurational depictions by Mills are inadequate to represent the actual three-dimensional shape of the rings and the steric orientation of the ring substituents (OH and CH_2OH groups), thus they still are the preferred way of drawing furanose forms. For the

six-membered pyranose ring several recognized conformers exist: two chairs, six boats, six skews and twelve half-chairs (figure 2).[16,17]

Although the exceptions, most aldohexoses adopt the chair conformation that places the bulky hydroxymethyl group at the C-5 terminus in the equatorial position, especially the $^{4}C_{1}$ chair conformation that is energetically more favored than the $^{1}C_{4}$ conformation.[16]

Through the glycosidic linkages between monosaccharide unites, the oligosaccharides are formed - i.e., simple polymers containing between two or ten monosaccharide residues. The oligosaccharides can be either homo- (consisting of only one type of monosaccharide) or hetero-oligosaccharide.[16]

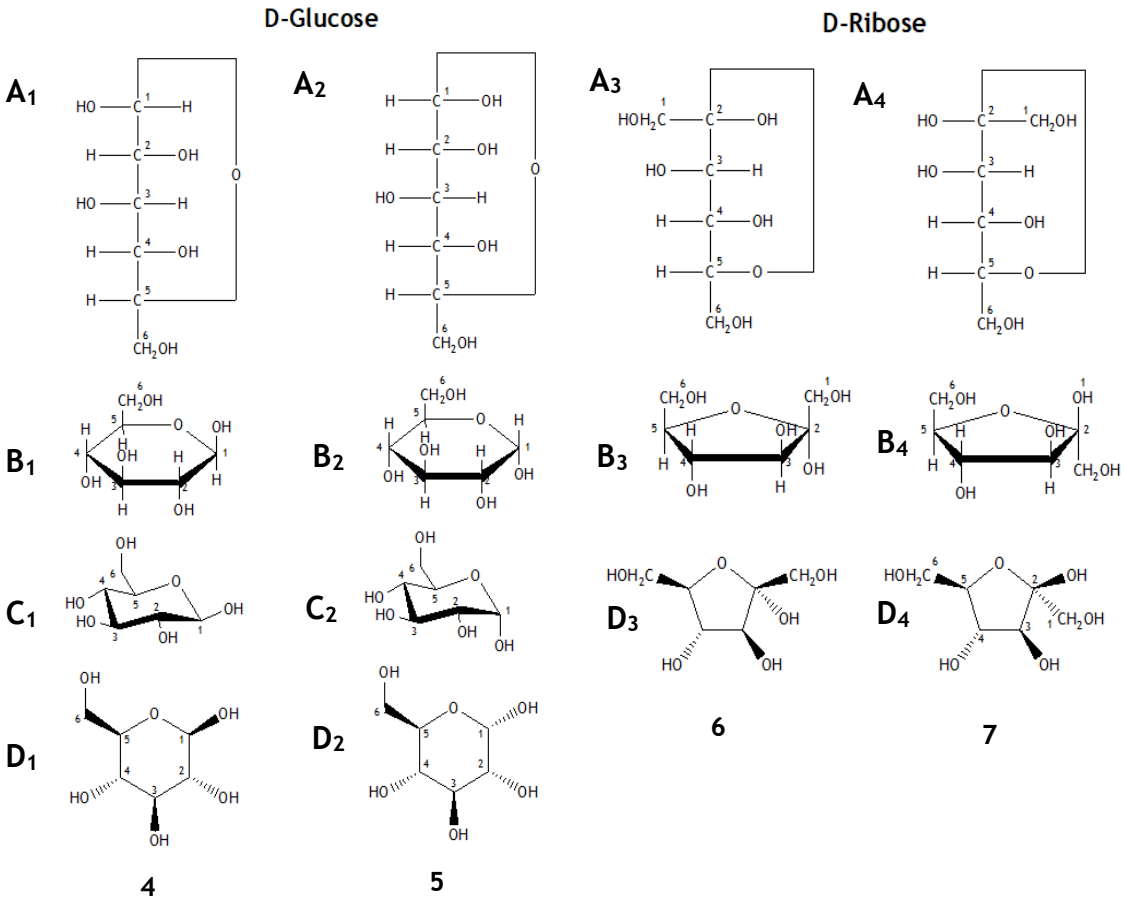


Figure 2 - Demonstration of Fisher's, Haworth's, and the "chair's" projections. (A) represents the Fisher's projection. (B) the Haworth's projection. (C) is the "chair" conformation. In addition (D), represents the planar projection of all the represented carbohydrates. The sugars represented correspond to α-D-glucose (**4**), β-D-glucose (**5**), α-D-fructose (**6**), and β-D-fructose (**7**).

Due to all the complexity of the subject in study, I though a brief introduction was needed to a further understanding of the thesis content. Hence done, I will now demonstrate some of the most used synthesis paths and reaction methods on glycoscience.

1.2. Synthesis of glycosides

Has previously said, the synthesis of carbohydrates weren´t always possible, neither their interaction mechanisms were known to permit their efficient application. However, through the past decades, advances in technology and knowledge opened new doors, allowing innumerous opportunities. A withstanding challenge in glycoscience is the regioselective monofunctionalization in addition to stereoselectivity (specifically, how to control whether α or ß anomers form).

Selective protection of secondary hydroxyl groups of carbohydrate building blocks is significantly challenging. Chemists commonly use a series of protection and deprotection steps in processes that are wasteful, costly, time consuming and that, in the end, have low yields. One solution to the problem is to use enzymes - i.e., glycosyltransferases - to perform selective glycosylation reactions, but enzymes are very substrate specific and their application to large industrial scale is often difficult.[18] With so, further investigation on the field is of major importance, to a better understanding of the interactions between carbohydrates and biomolecules, and themselves.

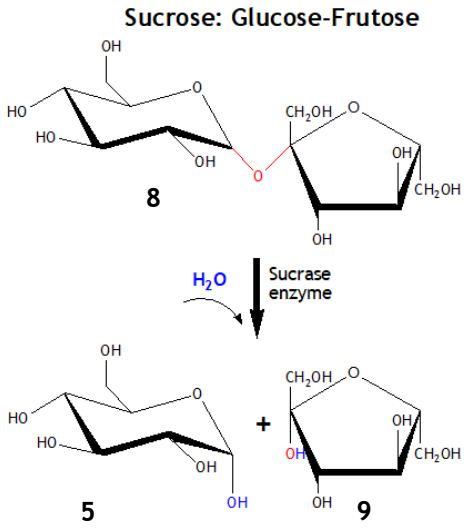
1.2.1. General reactions

Only the relative reactions and mechanisms will be discussed in this chapter, since the reaction possibilities with carbohydrates are enormous.

Carbohydrates are polyfunctionalized compounds that contain primary and secondary hydroxyl groups differing in terms of reactivity. Some chemical transformations of these functions have been exhaustively studied in the last years to permit the stereoselective functionalization of the hydroxyl groups.[19] Some of those transformations are thereby shown and explained in this part.

Since the enormous reaction possibilities involving carbohydrates, only the reactions and mechanisms of interest will be discussed. However, some of the general carbohydrate-involving processes will be briefly attended for a clear and further understanding on the subject.

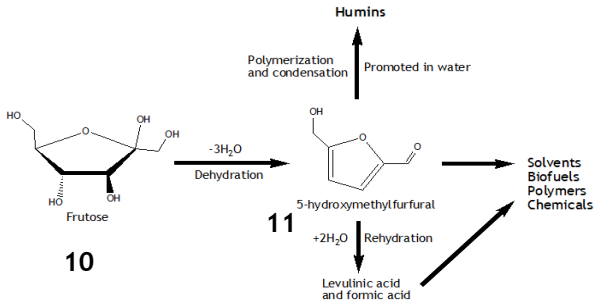
As referred, polysaccharides are formed by "chains" of many sugar units. For the separations of these "chains", hydrolysis can be achieved through enzymes – *i.e.* glycosidases – or chemically – through acid treatments – for the release of the monosaccharide units.[16]



Scheme 1 - Hydrolysis reaction of disaccharide α-D-glucopyranosyl-ß-D-frutofuranoside (8) (sucrose), by means of sucrase enzyme, resulting in two isolated monosaccharides, α-D-glucose (5) and ß-D-fructose (9).[16]

The enzymatic way proceeds with higher specificity towards both the sugar and the configuration at the anomeric center. The chemical way includes much more harsh conditions, like very acidic conditions and high temperatures.[16]

Using the chemical hydrolysis path is impossible to avoid the degradation of the sugar constituent – due to the harsh hydrolysis conditions. However, if this degradation is manipulated properly, it can be used to produce important chemicals. For example, when harsh acidic conditions are used, strong acids induce water elimination – *i.e.* dehydration - through this, the furfural's production process can be achieved, as demonstrated in the scheme 2 with some other chemical's process.[16,20]



Scheme 2 - Example of dehydration reaction on fructose. This is an important reaction to synthesize 5-hydroxymethylfurfural (HMF), used in the production of many other substances, such as levulinic acid and humins.

Since their low resistance to high temperatures, when exposed to them, carbohydrates also decompose/dehydrate, occurring the darkening – *i.e.* caramelization.[16] When submitted to basic condition, aldoses isomerize to their C-2 epimers and the respective ketoses. Through this, particular products can be prepared. For example, any of the three sugars, D-glucose, D-fructose, or D-mannose is converted into an equilibrium mixture containing D-glucose (57 %), D-fructose (28 %), and D-mannose (3 %), through mild basic conditions (figure 3).[16]

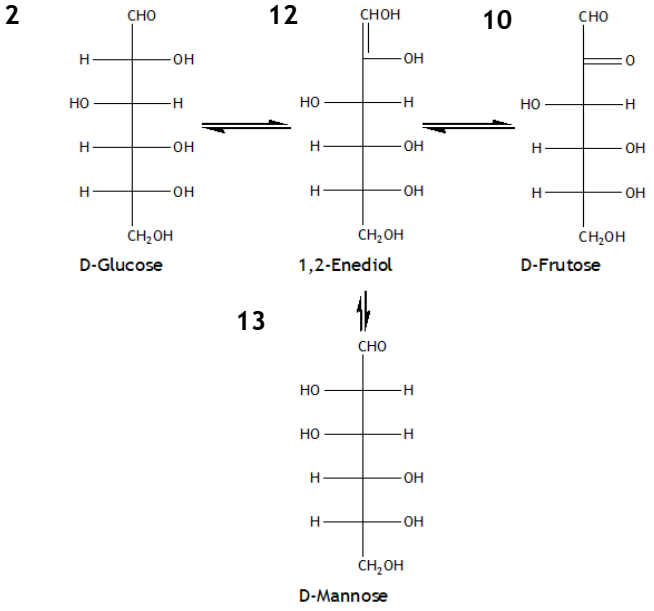
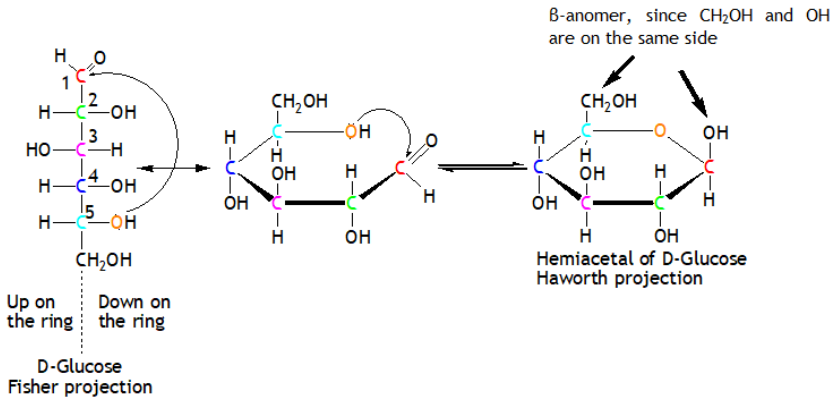


Figure 3 - Example of isomerization reaction, also known as Lobry de Bruyn-van Ekenstein rearrangement.[16]

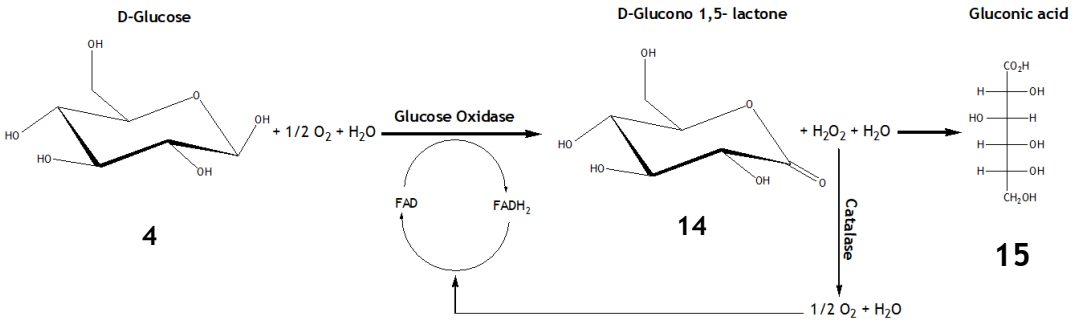
When in solution, sugars stablish an equilibrium between their pyranoid or furanoid hemiacetal forms through open-chain carbonyl species (scheme 3).[16]



Scheme 3 - Example of a carbonyl group reaction on glucose. Groups on the left side of Fisher projection are facing upwards, while groups on rigth side are facing downwards in Haworth's projection.The species are in equilibrium between the two forms.[16]

One important process in the history of glycoscience is glycosidation. When mixed with alcohols in the presence of acid catalysts, reducing sugars give the respective full acetals, named glycosides – *i.e.*, Fisher glycosidation.[16,21] Forwardly, depending on the distribution of the furanoid and pyranoid tautomeric form in the reaction mixture, not only glycosides with different ring sizes - i.e., glycopyranosides and glycofuranosides - can result, but also the corresponding α- and ß-anomer. For example, when D-glucose is heated with methanol in the presence of anhydrous hydrogen chloride, pure crystalline methyl α-D-glucopyranoside can be isolated in 90% yield, whilst the same reaction with D-galactose yields a mixture of the two furanoid and pyranoid methyl galactosides, from which the methyl α-D-galactopyranoside can be obtained in crystalline form but in a much lower yield.[16]

Another important process is the oxidation. Like in hydrolysis, oxidation can be achieved enzymatically – in a controlled stoichiometric fashion through dehydrogenases or oxidases – or chemically – with bromine or iodine in buffered solutions. [16,22]



Scheme 4 - Biochemical oxidation of ß-D-glucose to D-glucono-1,5-lactone by glucose oxidase and subsequent hydration to gluconic acid. Catalase enzyme degrades the hydrogen peroxide formed during glucose oxidation.

Forwardly, reactions of hydroxyl group's protection will be analyzed, with a more intense focus on the reactions used in the experimental section of this thesis.

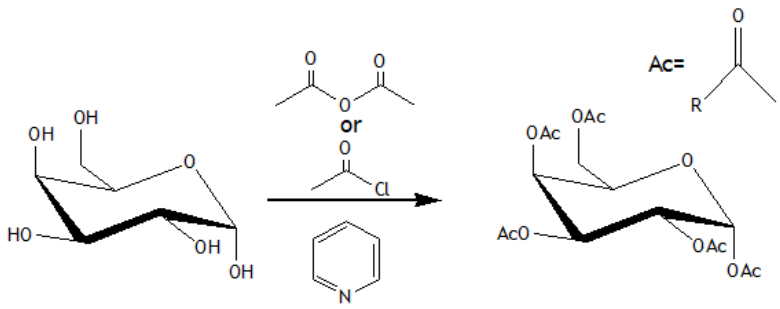
1.2.1.1. Hydroxyl group's protection

The alcohol and phenol protection are one of the most frequently employed reactions in organic synthesis, and so in glycoscience.[23] They are of extreme importance to the construction of oligosaccharides and to the functionalization of the carbohydrates, and to the synthesis of glyconanoparticles and sugar-based materials.

- **Acylation**

The acylation of functional groups, especially hydroxyl and amino groups is one of the most basic and frequently used transformations in glycoscience, as it provides a useful and efficient protection protocol in a multistep synthetic process.[24] Moreover, this reaction has a biomimetic importance, as acylation of xenobiotics is a metabolic pathway that increases lipophilicity.[24]

This protection method is normally achieved through anhydrides or acyl chlorides in the presence of tertiary amine bases such as either triethylamine or pyridine, Lewis or protonic acids, or sometimes solid acid catalysts, in suitable, when necessary, organic solvent, although acetic anhydride is the most commonly used - being less toxic.[23,24]



Galactose **16** **Galactose pentaacetate** **17**

Figure 4 - Acylation reaction of Galactose (α-anomer on the example) using acetic anhydride or acetyl chloride, in anhydrous pyridine.

The rate of acylation in the basic conditions is known to be raised multifold if 4-(dimethylamino)pyridine (DMAP) is used as a cocatalyst.[23,24] The most commonly used solvents, for this functionalization, are methylene chloride, acetonitrile and tetrahydrofuran.

The use of DMAP as catalyst exhibit a stereoselective effect on the reaction. DMAP and chiral DMAP derivatives are now commonly used as catalysts (catalytically or stoichiometrically) in many reactions, including peptide bond formation[25], the Baylis-Hillman reaction[26], and

Michael addition[27]. For carbohydrate chemists, DMAP-catalyzed acylation of alcohols represents an essential tool to functionalize sugars. Through various studies, was clear that the stereochemistry at the anomeric position affected the reactivity of the hydroxyls and the outcome of acylation. Researchers also found position C_4 to be nearly unreactive in the absence of DMAP, proving that reactivity may also depend on the acylating agent used.

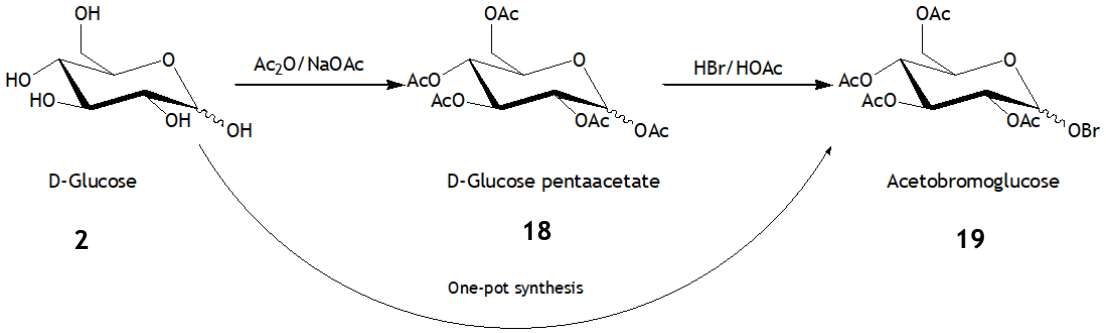
The most commonly used solvents, for this functionalization, are methylene chloride, acetonitrile and tetrahydrofuran (THF). The use of toxic metal derivatives and chlorinated hydrocarbons as solvents, apart from operational disadvantages, do not satisfy the requirements of green synthesis. Thus, a practical, efficient and greener alternative is needed. For that, B. Ranu *et al.* explored a greener method, with no solvent or catalyst needed.[24]

- **Acylated Glycosyl Halides**

Glycosyl halides can be formed smoothly, dissolving per-O-acetylated monosaccharides in cold solutions of the hydrogen halide in glacial acetic acid. However, acetates from acid-sensitive oligosaccharides may undergo cleavage of glycosidic bonds.[16,28,29]

Because of the dominance of the anomeric effect in the pyranosyl cases, the anomer with axial halide is substantially preferred.[16,21,30]

Accordingly, on acylation and subsequent HBr-treatment, usually performed as a one-pot operation, D-glucose yields the 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl or its benzoylated, pivaloylated analogues (scheme 5).[16]



Scheme 5 - Example of the per-O-acetylated glucose synthesis and subsequent anomeric bromination. As referred the one-pot synthesis leads to the synthesis of both 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl and the benzoylated analogues. [16]

- **Acetals**

Normally produced from the reaction of an aldehyde or ketone — benzaldehyde and acetone being the most common — with a geometrically suitable diol grouping, of which there is a large variety in free sugars, glycosides, and alditols.[16]

These reactions are carried out in aldehyde or ketone as solvent with an electrophilic catalyst (H_2SO_4 or $ZnCl_2$). The synthesis can be thermodynamically controlled and usually very specific, under these conditions. Ketones such as acetone or cyclohexanone predominantly bridge vicinal diols to form five-membered cyclic products (1,3-dioxolanes) as exemplified by the O-isopropylidene derivative of D-Ribose (figure 5).

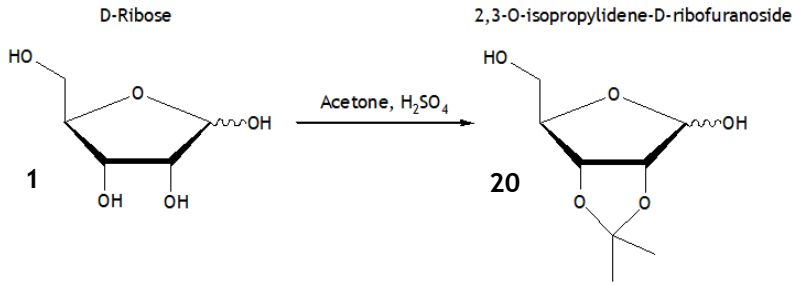


Figure 5 - Hydroxyl protection with an acetal group in D-ribose, resulting in a 1,3-dioxolane type group or an isopropylidene group.

Aldehydes, however, show a distinct preference for 1,3-diols, as illustrated by the six-membered 4,6-O-benzylidene and 3,4-O-benzylidene acetals of n-acetylglucosamine (figure 6). [16]

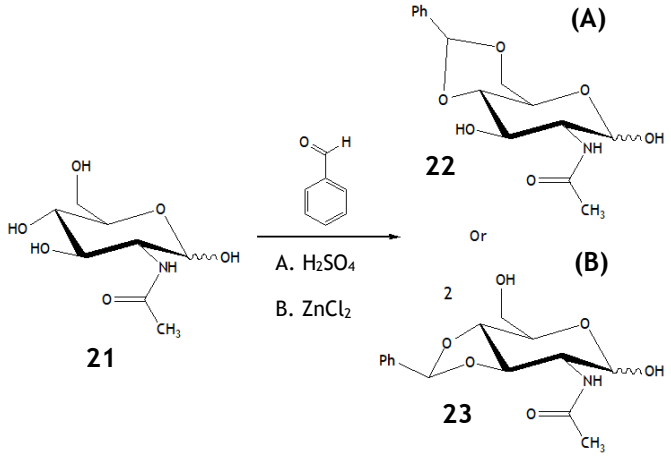


Figure 6 - Example of hydroxyl group protection with a benzylidene group. In this example, two synthetic routes are approached, both using benzaldehyde as solvent. In the first (A) the H_2SO_4 is used as catalyst, stereoselectivily attacking the hydroxyls in the C_4 and C_6 positions. In the second route (B), the $ZnCl_2$ is used as catalyst resulting in the benzylation of the C_3 and C_4 positions, respectively leading to 4,6-O-benzylidene-n-acetylglucosamine and 3,4-O-benzylidene-n-acetylglucosamine.

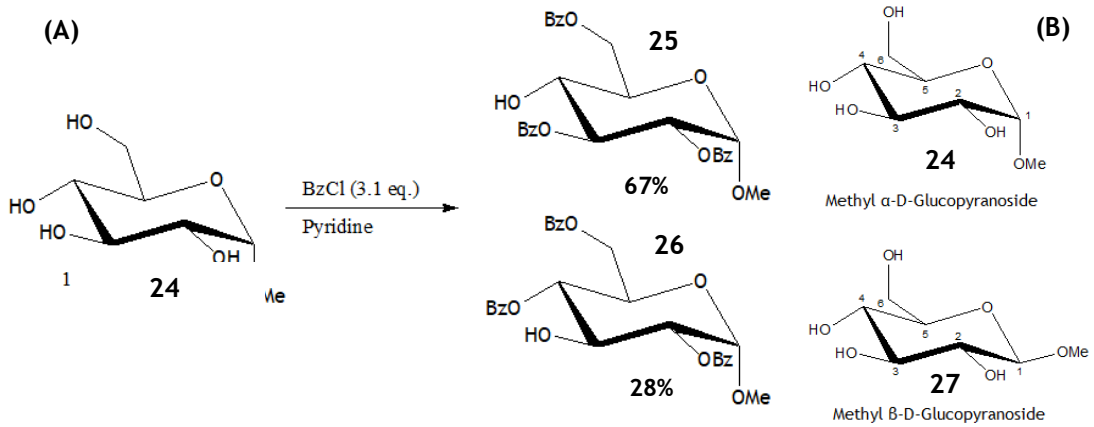
The introduction of cyclic acetal groups into sugars is quite satisfactory in terms of yields. As cyclic acetals are stable towards alkali, the entire repository of organic reactions requiring basic conditions can be applied.[16]

- **Thioacetals**

Sugars react rapidly with alkanethiols in the presence of acid catalysts at room temperature to give acyclic dialkyl dithioacetals as the main products[31], and therefore the reaction is markedly different from the Fischer glycosidation. These open-chain compounds can be used to prepare monosaccharide derivatives with a free carbonyl group and protected with acetyl groups in the other hydroxyl groups.[16]

1.2.2. Carbohydrates' stereoselectivity

For a better understand of the reaction selectivity on a sugar, Williams and Richardson in 1967 first ranked the secondary hydroxyls of three sugars - methyl α-D-glucopyranoside, methyl α-D-mannopyranoside and methyl α-D-galactopyranoside - according to how reactive each hydroxyl was under benzoylation conditions (Scheme 6, image (B))[18]

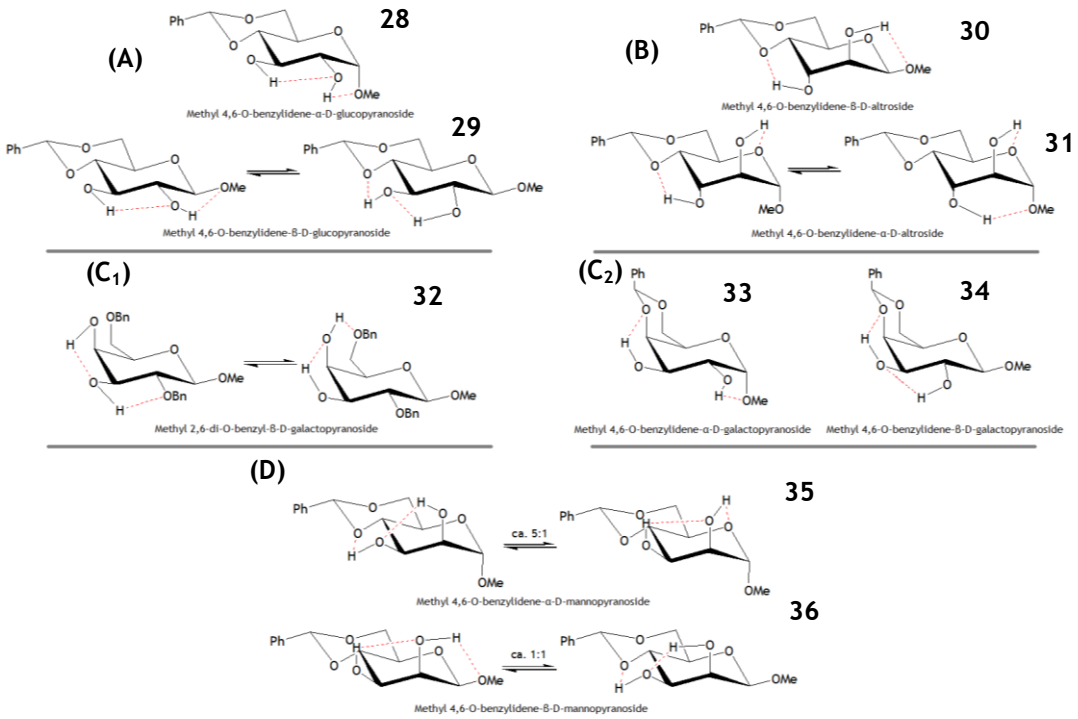


Scheme 6 - (A) Benzoylation of methyl-α-D-glucopyranoside, yielding two different products in two different ratios. (B) Carbon numbering according to how reactive each hydroxyl was under benzoylation conditions.[18,32]

Conclusively, the study revealed that the primary hydroxyl at position 6 of each sugar reacted first, demonstrating to be the most accessible of them all. The rest of the reactivity trends for secondary hydroxyls are the following: C_2-OH>C_3-OH>C_4-OH for the glucopyranoside, C_3-OH>C_2-OH>C_4-OH for the mannopyranoside, and finally C_2-OH, C_3-OH>C_4-OH for the galactopyranoside.[18] The theoretic proposition was that intramolecular hydrogen-bonding possibly influenced the reactivity of each hydroxyl. While the adjacent anomeric position may contribute an extra hydrogen bond to the C_2-OH, thereby increasing the reactivity of the C_2-

OH of the glucopyranoside, the C_2-OH is axial in the mannopyranoside, rendering it less reactive than the C_3-OH.[18]

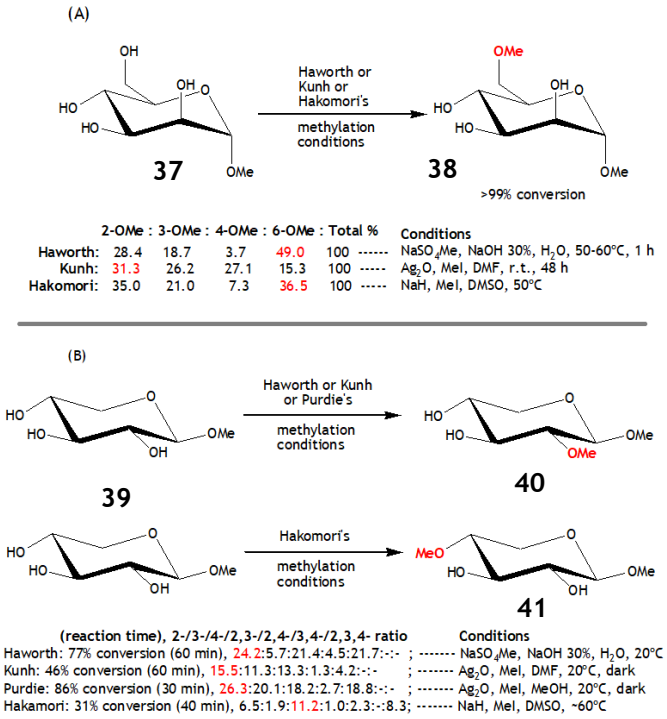
A few years later, Kondo et al. also demonstrated that the order of reactivity of the secondary hydroxyls of methyl 6-deoxy- α- and ß-D-glucopyranosides was the same as the order that Williams and Richardson previously observed for methyl α- and ß-D-glucopyranosides.[33] Researchers demonstrated that hydroxyls of different sugars have different intrinsic reactivity patterns that vary depending on the sugar explored (scheme 7).[18]



Scheme 7 - Representation of the intramolecular hydrogen bond network of four different monosaccharide derivates. (A) glucose; (B) altrose; ($C_{1,2}$) galactose; (D) mannose; The intramolecular network was determined by Vasella *et al.* and helped understand the stereoselectivity in the studied monosaccharides.[18]

These studies revealed that the selectivity is highly dependent on the conditions (methylating agent and base) and substrate. The substrate used with Haworth and Hakamori's conditions leads either to similar selectivities with methyl α-D-mannopyranoside or very different selectivities with methyl ß-D-xylopyranoside (Scheme 7, A and B).[18] One of the theoretic propositions was that the relative acidities of the hydroxyl groups in methyl ß-D-xylopyranoside is a major factor controlling the selectivity (Scheme 7, B).

All this research settles the stage for future work that could reveal whether extrinsic factors, such as the sterics of the reagent, also influence the products formed. Furthermore, the need for a method that selectively react at one hydroxyl over all the other hydroxyls urges. This method would greatly simplify the number of steps a chemist is required to perform when attempting to react at a specific position of a sugar, thereby reducing the amount of waste generated, the amount of time necessary, and the financial resources required to perform such reactions.



Scheme 8 - (A) Methods for regioselective methylation of methyl α-D-mannopyranoside under conditions reported by Haworth *et al.*, Kuhn *et al.*, and Hakamori, and simultaneous comparison of the synthetic route's' product ratio. (B) Methods for regioselective methylation of methyl ß-D-xylopyranose using conditions reported by Haworth *et al.*, Kuhn *et al.*, Purdie *et al.*, and Hakamori, and simultaneous comparison of the respective regioselectivity.[18]

Several groups investigated the intramolecular hydrogen bond network experimentally and computationally to better understand the sugar's hydroxyl order of reactivity. Surprisingly, with the pyridine-based experiments, a solvent that exchange hydrogen bond with the sugar, Williams and Richardson, obtained a fact that rendered this inference of the intramolecular hydrogen bond network less plausible.

However, a few groups have discovered that even in hydrogen bonding solvents, although it may be weakened, the intramolecular hydrogen bond network still exists, supporting Williams and Richardson's theory that the internal hydrogen bond network influences the reactions of sugars, even when performed in pyridine.

Through ^{1}H NMR studies, Davies *et al.* found differences in the number of hydrogen bonds - between hydroxyls - among anomers, concomitant, the methyl α-D-glucopyranoside only have one hydrogen bond between hydroxyls at C_4 and C_6, however, the α-anomer of glucose has an extensive hydrogen bond network, as shown in the figure 7.

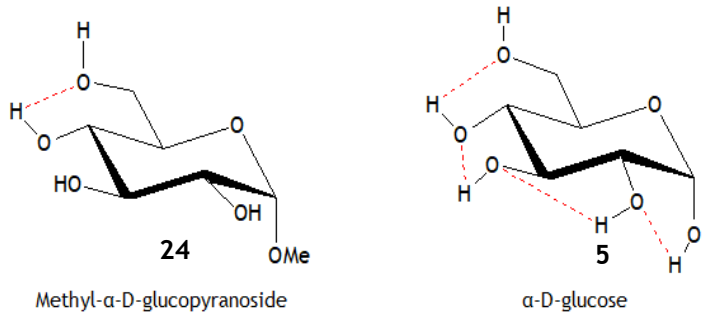


Figure 7 - Hydrogen bond network of methyl α-D-glucopyranose and the α-anomer of glucose, proposed by Davies.[18]

Using a semi empiric method - *i.e.*, the Austin Model 1 (AM1) - Brewster *et al.* rationalized the reactivity of the hydroxyls of glucose by determining the acidities of the hydroxyls of α-D-glucopyranose and determined that the C_6-OH is the least acidic along with the following order of acidity: C_1-OH>C_4- OH>C_3-OH>C_2-OH>C_6-OH.

This could explain the lack of reactivity on the acylation at C_6, shown by Kurahashi, Mizutani and Yoshida, even though the availability of primary hydroxyl.[18] However, if more than an equivalent of acylating agent is used on an unprotected pyranoside, position C_6-OH shows to be one of the most reactive towards alkylation and acylation, as it is the least hindered position - *i.e.*, the most accessible to electrophiles.[18]

Due to the importance of all moieties of the reaction, many research groups focus their efforts on the role of the acylating agent when selectively protecting sugars. The acylating agent influences the selectivity, and therefore the products formed on the reaction. Kattnig *et al.* concluded that homogeneous acylation with acetyl chloride, pyridine (as base) and DMAP (as catalyst) are faster than those with acetic anhydride under the same conditions.

Hung and co-workers, shown that using triethylamine and either acetic or benzoic anhydride, the position C_2 could be selectively functionalized, when an excess of triethylamine was used. On the other hand, when pyridine was used, instead of triethylamine, an almost random functionalization occurred.[18]

All these studies highlight the complex nature of the hydrogen bond network and its impact on the regioselectivity of various transformations. For example, hydrogen bond network modulates the acidity of the different hydroxyl groups involved, the more hydrogen bonded is an oxygen of a hydroxyl group, more acidic it is. Conclusively, in presence of a base, the most

acidic group is the most reactive as it is the first to be converted into a more reactive alkoxide. However, under neutral conditions, it is the least reactive as its lone pairs are interacting with surrounding hydrogen bond donor groups and is consequently less nucleophilic.[18]

Nevertheless, the most accessible group - i.e., position C_6 - is not the necessarily the first to react, the hydrogen bond network can be modulated by the presence of acids. As result, glycopyranosides can be differently functionalized under different conditions - e.g., with or without a base - knowing its intrinsic hydrogen bond network, showing again, the importance of understanding the hydrogen bond network.

Previous investigators have shown that the beta methyl D-glucosides, D-mannosides, D-galactosides, D-xylosides, and L-arabinosides are hydrolyzed slightly more rapidly than the corresponding alpha isomers.[34]

Conclusively, paraphrasing Levy and Fügedi in 2006, "The holy grail of glycosylations - the generally applicable, stereoselective and technically simple glycosylation method - is yet to be found."[18], and to do so, more research is needed in the field.

1.3. A brief introduction to glyconanotechnology

In the last decades, glycoscience have been fundamental to nanobiotechnology. Throughout these years, several nanoparticle-based products for diagnostics and therapeutic have been approved for clinical applications, and more are currently under clinical trials.

Besides the clinical and therapeutic applications, the advent of more complex nanomaterials stems from advances in nanofabrication techniques, turning classic nanosystems synthesis supererogatory, and pushing material scientists through more complex engineering perspectives.

Moreover, the growing medical needs thrust the nanotechnology field into more specialized and intricate processes. For example, the heterogeneity of cancers necessitates image-guided therapies, in which personalized disease treatments are planned based on the individual patients' pathological conditions and responses to the treatment. Additionally, after administration into the body, drugs must pass different barriers - *e.g.*, several layers of cells, cell membrane itself, or the blood-brain barrier.[31] Thus, there always have been the difficulty in the permeation through biological barriers. For this reason, is of extreme importance to understand the mechanism of drug transportation, to a precise, therefore more efficient drug delivery.[12]

The membrane permeability differs in large limits but there are several main mechanisms for the drug passing through the cell membrane: [12]

- Passive diffusion – consisting in the main mechanism, depends on the gradient of concentration from outside of the cell where there is a region of higher concentration to inside the cell, with a lower concentration, and has no energetic cost;

- Carrier mediated-transport – can occur without an energy consume (facilitated diffusion) or with an energy request (active transport), both types of processes involve a carrier molecule;

- Vesicular transport – is when the cell membrane forms a small cavity that gradually covers the drug molecules, internalizing them into the cell in the form of a vesicle or vacuole. The process is called endocytosis (when the molecule is going inside the cell), exocytosis (when the molecule exits the cell) and transcytosis (when the molecule is moving across the cell).

These biological barriers, in some cases, represent the last resistance to defeat some diseases, being the main challenge the increase of the transport of the drugs across these barriers while preserving the defense capacity. For that the development of new targeted drug delivery systems is required, allowing the controlled drug delivery kinetics and the most important, to target specific sites thus reducing side effects and unwanted high doses. This targeting is achieved through two methods: [12]

- Drug functionalization (prodrugs) with aim to increase the pharmacologic activity of the biomolecule, after the metabolization.

- Use of nanocarriers or nanotransporters, which are capable of delivering the therapeutic agent *in situ*.

Nanostructured matrices can be produced presenting the molecules in a multivalent fashion-way, forming synthetic "scaffolds" with varying valency and spatial organization. This allows the multimerization of carbohydrates, enhancing the affinity of monomers towards their counter-receptors.[6] These features turns carbohydrates in excellent organic moieties to introduce in nanomaterials for DDS. This organo-inorganic blending leads to the construction of hybrid materials. [35,36]

1.3.1. Synthesis of Glyconanosystems

In this brief introductory chapter on the synthetic pathways of the glyconanosystems, some synthetic methods will be approached, with major attention on the ones of interest in this work's objective.

Overall, the synthesis of glyconanostructures can be proceeded in two ways:[6]

- Direct method - one-step method;
- Indirect method – multistep method.

However these methods can be sub-categorized in distinct processes for each material. Additionally, the crosslinking between the three-dimensional networks can be divided in chemical and physical. The physical approach avoids the use of crosslinking agents, which can be advantageous for many pharmaceutical and biomedical applications. Contrarily, chemically-crosslinking result in a high mechanical strength and - depending on the nature of the chemical bonds in the building blocks and crosslinks - in relatively long degradation times.[37]

Furthermore, the functionalization of the inorganic matrices can be sub-divided in two approaches: The "grafting to" method, and the "grafting from" method. In the first, the matrices are usually synthesized separately, and the glyco-moiety is then immobilized on the nanostructure in a covalent or non-covalent fashion. On the later mentioned method, the synthesized matrices are normally functionalized with vinyl or bromine groups and glycomonomers are grown from the structure's surface, either by conventional or living free radical polymerization.[38]

Covalent bond with silica has been largely suggested for various glycosides. However, much more studies with sophisticated analysis are still needed to prove it. An extended investigation of surfaces and internal composition of organic/inorganic hybrids will enable a much better understanding about how silica precursors, crosslinkers, and glycosides interact and associate with each other.[39]

Through the hybrid materials' synthetic proposition, the idea of functionalization of inorganic matrices with carbohydrates has appeared. The innovative proposal of the integration of glyco-moieties into mesoporous materials is presented in this thesis. However, first a brief introduction to the mesoporous concept must be made.

1.3.2. Hybrid materials

The linkage between the organic and inorganic moiety leads to the formation of hybrid materials, also known as nanocomposites, where the organic phase renders the optical, electrical, and reactive physical-chemical properties, and the inorganic moiety increases the mechanical strength, thermal stability, permits the modulation of the refractive index, and favors the rheological properties, *i.e.*, varying the shape and size of the final material.[35]

These hybrid materials are divided in three major classes, concerning the connection strength between the two phases that are inherent from the way they are synthesized: Class I (weak bonds - Van der Waals bonds, hydrogen bonds or electrostatic bonds) (figure 8, A), Class II (strong bonds – covalent or ionic bonds) (figure 8, B) and Class III (combination of both weak and strong bonds).[35,36]

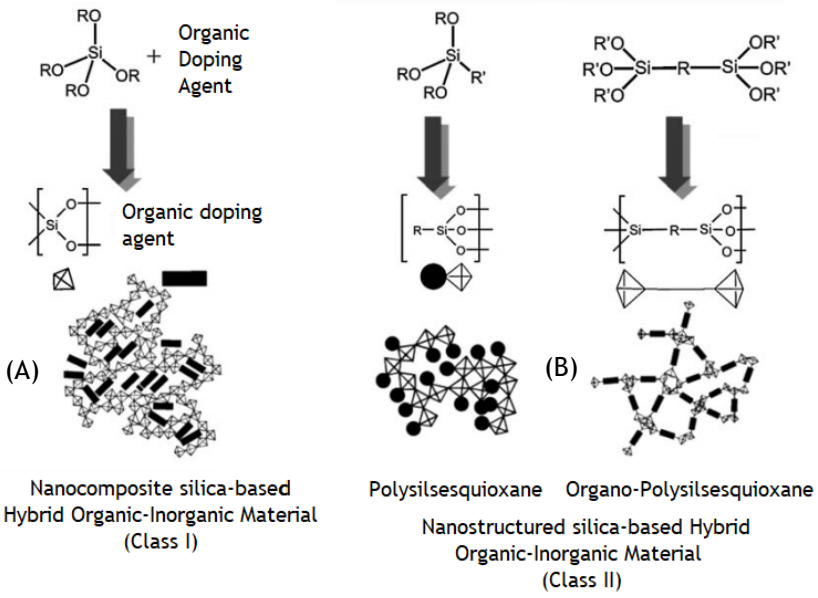


Figure 8 - Sol-gel mechanisms to organic–inorganic hybrids based on polysilsesquioxanes matrices of class I or II. Figure adapted from bibliography.[36]

Additionally these materials can be characterized by several techniques like X-ray powder diffraction (XRD), diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), element analyses (EA), thermo gravimetric analysis (TGA), solid state ^{29}Si and ^{13}C NMR, and surface analysis like pore size, volume and distribution (PSD) measurements.

1.4. Mesoporous materials

In the last years, the ever-growing necessities of engineering, chemistry, materials science, and biology strongly encouraged the development of novel porous materials, with more tunable features.[13-15]

These materials, having a wide spectrum of applications - e.g., adsorption, separation, catalysis, and sensors - and the ability to interact with atoms, ions, molecules and nanoparticles not only at their surfaces, but throughout the bulk materials, attracted great interest and attention from researchers from various fields for advancements in electronic, optical, magnetic and mechanical devices.[13-15]

Derived from the pore-caused interaction, the pore presence in the nanostructured materials inherently promotes their physical and chemical properties. Recently, the better understanding, design, and manipulation of pores have significantly advanced science and technology, been increasingly important in modern society.[14,15] According to the definition of the International Union of Pure and Applied Chemistry (IUPAC), porous materials can be classified in:[14,15,40]

- Microporous - pore diameter <2nm;
- Mesoporous – pore diameter 2-50nm;
- Macroporous – pore diameter >50nm.

Concomitantly, the mesoscaled structure of pores formed by surfactants and amphiphilic block copolymer templating can be summarily grouped in four high symmetry structures, as represented in the figure 9.[40]

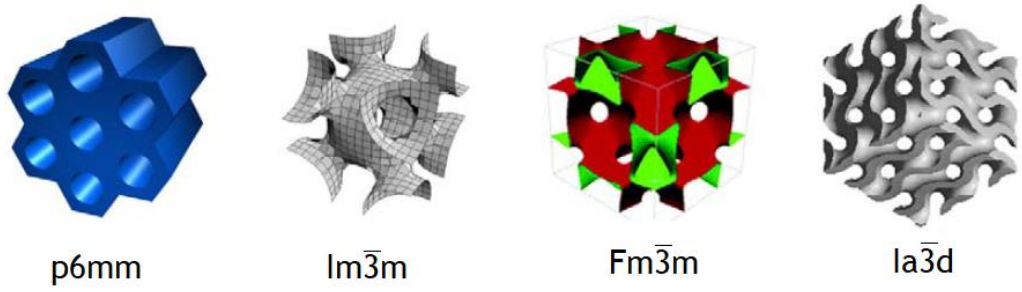


Figure 9 - From left to right they are categorized in 2D hexagonal, body-centered cubic, face-centered cubic, and gyroid structures.[40]

Through the variation of the synthetic conditions and the nature of the reagents, it's possible to modify the structure, composition, and pore size, making them tunable for the specific requirements of different application.[41]

Silica matrices can be prepared using room-temperature sol-gel process, which allow the hybridization of silica with biological solvents and drugs.[39] Silica matrices can be metabolized to silicic acid, which can be excreted through the kidney, and have good bioactivity, since their atomic composition is similar to that of bioactive glasses.[39]

However, these mesoporous materials have disordered pores, that can lead to the pore coking, and with the ever-growing necessities and technical advances in chemistry, materials science, biology, and engineering, the lack of organization had to be surpassed.[14] In 1992, the Mobil Corporation introduced the first ordered mesoporous silica (OMS), obtained through hydrothermal sol-gel process and liquid template mechanism, with porous ranging between the 2-10 nm.[15,40,42,43] Through the use of surfactants, the templating-imposed barrier of crystalline microporous zeolites (1-2 nm) was overcome. Exhibiting remarkable features, *e.g.*, well-defined sized pores and uniform shapes, the MCM-41 (Mobil crystalline material 41) based materials also denote excellent thermal, hydrothermal, and hydrolytic stabilities. Additionally they can be synthesized through anionic, cationic, or neutral surfactants or non-surfactant template pathways.[13]

Throughout the innumerous studies, three different mesophases have been identified in this family:[13,44]

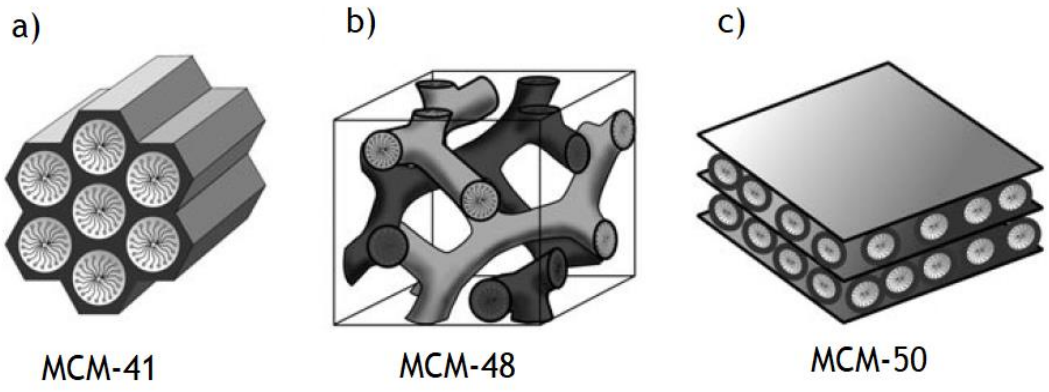


Figure 10 - schematic representation of three different mesophases, MCM-41, MCM-48, and MCM-50. The hexagonal phase possesses highly regular arrays of uniform-sized cylindrical mesopores, being the most stable and uniform.[42,45]

A few years later, in 1999, the first periodic mesoporous organosilicas (PMO) was reported. With this breakthrough, silsesquioxane species $(RO)_3Si\text{-}R'\text{-}Si(OR)_3$ could now be integrated into the walls of a mesoporous silica matrix through Si-C bonds.[14,15]

Combining both, organic chemistry and solid-state silica materials' synthesis enabled the synthesis of nanomaterials with uniform distribution of organic spacer and pore size, with both organic and inorganic enhanced inherent features.[15] Introducing organic moieties in inorganic matrixes, rapidly remembered researchers of the almost inexhaustible source of raw materials, and previously-mentioned, that carbohydrates represent. With the glycoscience advances, carbohydrates became more easily modified, founding applicabilities in many research areas. Albeit the incredible advantages of carbohydrates - *e.g.*, flexibility, low density, toughness, and formability - they also present drawbacks - *e.g.*, low functionality and low aqueous solubility. However, combining them with silica matrixes can help overcome these drawbacks and even synergize the features of both, organic and inorganic moieties.[39]

Nevertheless, this synergetic combination is still maturing through recent trials, encountering many difficulties, especially in the compatibility of the carbohydrates with the sol system.[39]

The combination of organic and inorganic moieties unleashed the creation of innumerous new materials with such mechanical, thermal, electrical and magnetic properties, that the new hybrid material trend appeared all over the research groups of chemistry, material science, and engineering.[39] With the acquired knowledge from over the years of research in the field, researchers sculpted the resulting hybrid properties in materials increasingly more organized.[45]

The mesoporous materials can be summarily resumed in porous/non-porous, non-organized, ordered or periodic mesoporous silica or organosilica materials (figure 11), being the two latter-mentioned the more important, since, like their name denote, they have a more organized matrix structure and defined pore size and structure.

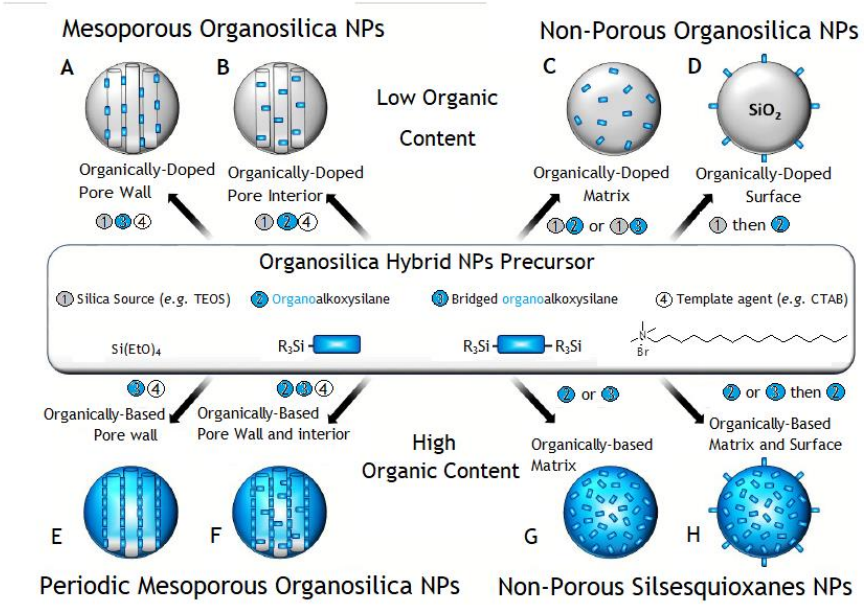


Figure 11– General mechanisms of mesoporous silicas. On this scheme is represented the mechanisms of synthesis of porous (A, B, E, F)/non-porous (C, D, G, H) non-organized (C, D, G, H), ordered (A, B) or periodic (E, F) mesoporous organosilica materials.[46]

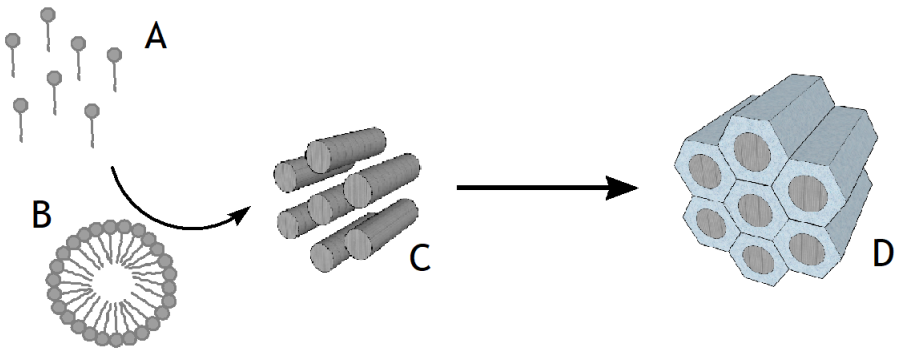
1.4.1. Mechanisms of Ordered Mesoporous Materials

Nowadays, ordered mesoporous materials can be synthesized combining two synthetic strategies:[14]

- Cooperative self-assembly;
- "true" liquid-crystal templating (LCT) process.

In the former approach, inorganic species interact with surfactants driven by Coulomb force, covalent bond or hydrogen bonding. The inorganic species at the interface polymerize and crosslink, thus cooperatively assembling with surfactants. Upon reaction, the cooperative arrangements of surfactants and the charge density between inorganic and organic species influence each other. Hence the compositions of inorganic-organic hybrids differ to some extent. Matching the charge density in the inorganic/organic interface govern the assembly process, therefore resulting in phase separation and reorganization, leading to the formation of ordered 3D arrangement with the lowest energy. The "true" LCT process is based on true or semi-liquid-crystal mesophase micelles produced by high-concentration surfactants as templates.[14] Due to the confined growth around surfactants, the condensation of the inorganic precursors is enhanced, resulting in ceramic-like frameworks. After condensation,

the organic templates can be removed. The inorganic moiety "nanocast" the mesostructure, pore size, and symmetries from the liquid-crystal scaffolds.[14,40]



Scheme 9 – Schematic representation of template-directed synthesis. In the image we can observe: (A) surfactant molecules in solution, starting aggregation form (B) surfactant micelles, and subsequently (C) the nanorods that will serve as template for the nanocasting of (D) the mesoporous material.

Through this soft-templating method, numerous new ordered mesoporous materials composed of inorganic, organic, and inorganic-organic composite frameworks have been prepared *via* various synthetic methods - *e.g.*, aqueous process, nonaqueous approach or evaporation induced self-assembly (EISA) process, and hydrothermal method. Additionally, plenty of soft templates like cationic, anionic and non-ionic surfactants, and mixtures of surfactants, have been used to synthesize ordered mesoporous materials with tunable structures and pore architecture.[14]

Despite the soft-templating approach's great success, soon was realized that was not enough to prepare many non-siliceous mesostructured materials, because the non-siliceous precursors are more susceptible to hydrolysis, lack of condensation, redox reactions, weak connection with surfactants or phase transitions and inherent thermal breakdown of the structure integrity, which turns difficult the ordered mesostructure construction and the aftermost template removal.[14] Meaningfully in this context, Ryoo *et al.* employed KIT-6 (molecular sieves) as a hard template for the synthesis of ordered mesoporous materials *via* three steps (figure 12).[14]

Through this approach, a number of mesoporous materials, previously unavailable *via* soft-templating route, could now be synthesized in this so-called nanocasting approach, where the regular arrangement builds-up from the preformed ordered mesoporous template.[14]

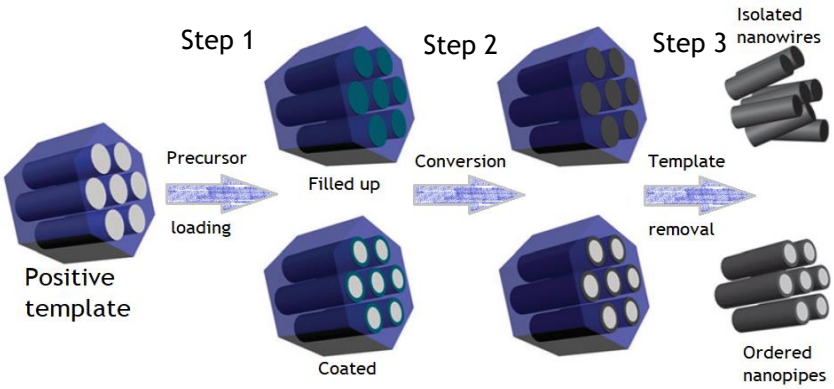


Figure 12 - Representation of the hard-templating method for the synthesis of ordered mesoporous materials or isolated nanowires. This method is divided in three steps: Step 1 - Infiltration of the precursor inside the mesochannels of the silica template; Step 2 - Conversion of the precursor in the mesochannels; Step 3 - Removal of the mesoporous silica templates or nanocasting.[14]

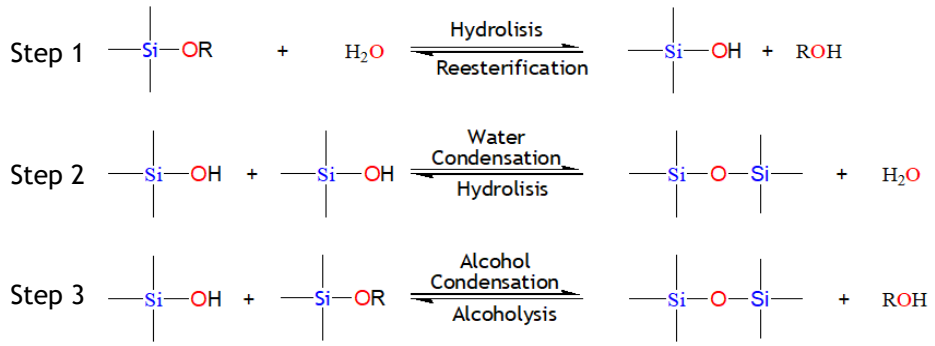
1.4.1.1. Sol-gel process

Inherent of some hybrid materials, this process consists in the polymerization of an organosilane precursor in a polymeric matrix. The sol term defines a dispersion of colloidal particles stabilized in a fluid, while the gel term refers to a system formed by the rigid structure of colloidal particles (colloidal gel) or polymer chains (polymer gel), immobilizing the liquid phase in the interstices.

This process involves three steps:[35]

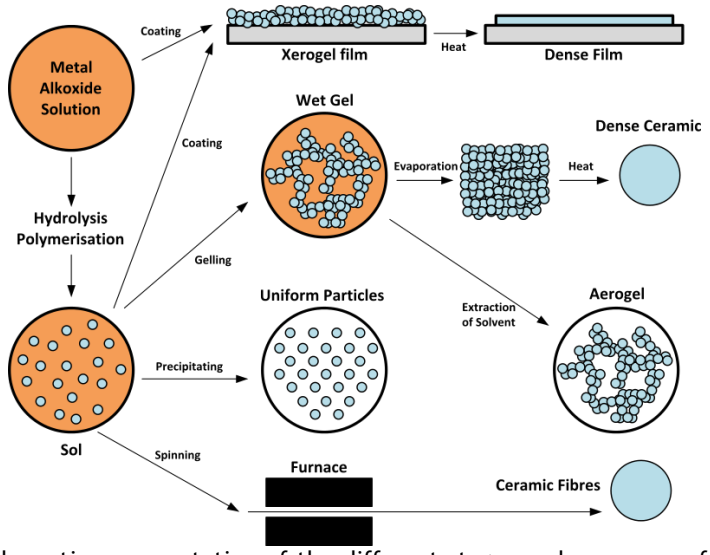
- the copolymerization of functional organosilanes, metal alkoxides and macromonomers
- the encapsulation of organic compounds based in silica or metal alkoxides
- and the functionalization of nanoparticles, nanoclays or other compounds with lamellar structures, etc.

The synthetic pathway is divided in three steps (scheme 11): hydrolysis (step 1), where the OR groups are replaced by silanol groups (Si–OH), subsequently, these silanol groups can react with each other (step 2), or with other groups OR (step 3) via condensation reactions by forming siloxane bonds, rendering a three-dimensional silica network.[35]



Scheme 10 – Representation of the chemical reactions on the classical sol-gel polymerization.

It is already known that cationic charge and the efficient hydrogen-bonding site is indispensable to the sol-gel transcription in order to absorb 'anionic' silica particles onto the organic molecular assemblies.[48,49] The gelators in the sol-gel process can be categorized into two classes, according to the driving force for molecular aggregation, the nonhydrogen-bond-based and the hydrogen-bond-based.[48] The gelation rate in this process can be decreased by means of a silicon precursor, thus a great control of the gelling process can be achieved, modulating the final characteristics of the resulting material - *e.g.* size and shape of particles, volume and pore size distribution.[35]



Scheme 11 – Schematic representation of the different stages and processes of the sol-gel technique. Image adapted from bibliography.[46,47]

The products of this process exhibit remarkable features, such as mechanical, thermal, electrical, and magnetic, and good biocompatibility, biodegradability and low bio-toxicity. Which turns them in expedient materials for many applications.[50]

1.4.2. Organo-functionalization of mesoporous materials

The introduction of organic groups in the mesoporous materials permitted the tuning of surface properties, the alteration of the surface reactivity and its protection or hydrophobization, and the modification of the bulk properties of the materials while at the same time stabilizing them towards hydrolysis.[13,45] Additionally, enabled the pore's polarity adjustment, that is crucial and opens innumerous doors in the field of chromatography. The modification of inorganic matrixes with organic functionalities - e.g., C-C multiple bonds, alcohols, thiols, sulfonic and carboxylic acids, amines, carbohydrates, etc. - allows localized organic or biochemical reactions to be carried on a stable and solid inorganic matrix.[13,51,52]

For the functionalization of mesoporous materials there are two major strategies:

- Post-synthetic grafting - indirect synthesis (Figure 13, A);

Post-synthesis grafting refers to the ornamentation of the siliceous pore walls with organic groups, which can be performed by reacting the calcined/extracted (template free) mesoporous silicas or as prepared (template containing) siliceous mesostructures with reactive organosilanes.[13,51] If the organosilanes react preferentially at the pore openings, in the initial stage of the synthetic process, the diffusion of further molecules can be impaired, leading to nonhomogeneous distribution of the organic moiety within the pores, and ultimately to complete pore closure. To overcome this limitation, the majority of OMOs have been prepared by direct/one-pot synthesis, which involves the co-condensation of alkoxyorganosilanes with or without TEOS through a sol-gel process.[13,51] Through this method, a variety of organic groups can be internalized by the variation of the organic residue R, with the advantage of retaining the mesostructured of the starting silica phase, whereas the lining of the walls is accompanied by a reduction in the porosity of the hybrid material, albeit depending upon the size of the organic residue and the degree of occupation.

- Co-condensation - direct/one-pot synthesis (Figure 13, B).

The direct route is well suited for the preparation of OMOs with bulky organic groups, high loadings of organic moieties, and large and ultra-large pore diameters.[13,51] These features are caused by the formation of the functionalized mesostructure in the presence of micelles and the lack of the calcination step which leads to a substantial structure shrinkage.[51]

Moreover, this route is simpler and faster, and led to the discovery of the periodic mesoporous organosilicas (Figure 13, C) which will be discussed in the next chapter.

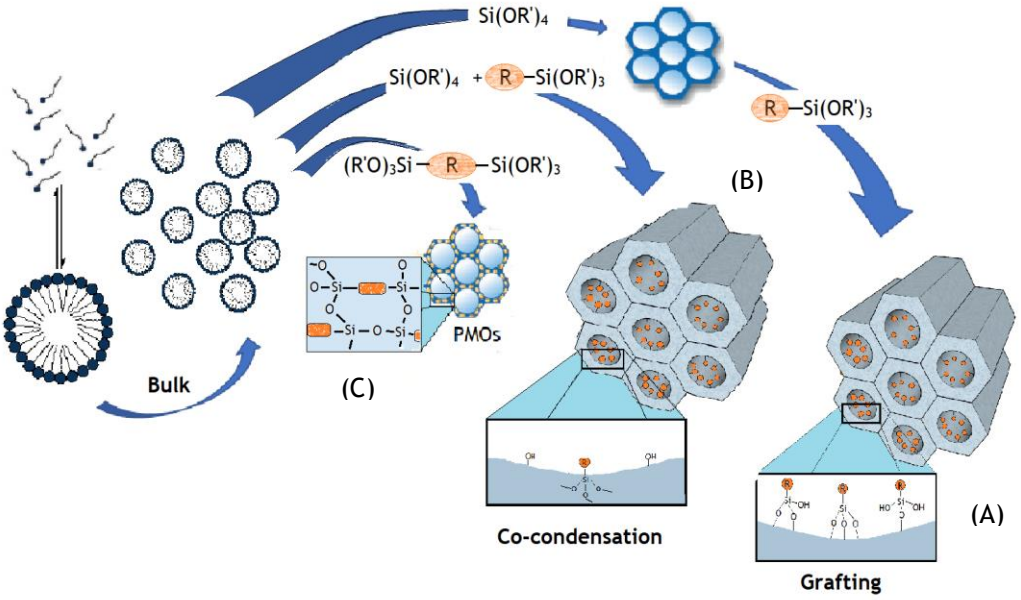


Figure 13 – Functionalization of siliceous mesoporous through three different approaches resulting in three different hybrid materials. (A) Post-synthetic grafting, or indirect synthesis, consists in a two-step procedure, where initially the siliceous matrix is produced to be posteriorly grafted with the organosilane precursors. (B) Direct/one-pot synthesis, consists in the co-condensation of tetraalkoxysilanes [$(RO)_4Si$ (TEOS)] with terminal trialkoxyorganosilanes of the type $(R'O)_3SiR$ in the presence of structure-directing agents (SDA) conducting to materials with organic residues anchored covalently to the pore walls. (C) Through the use of bridged organosilane precursors, periodic mesoporous materials are obtained, in which the organic moiety is internalized in the pore's walls. Image adapted from the bibliography.[45]

1.4.3. Periodic mesoporous organosilica

Forming a new class of materials, characterized by large specific surface areas and pore sizes between 2 and 15 nm, the periodic mesoporous hybrid materials are obtained through hydrolysis and condensation of bridged organosilica precursors of the type $(R'O)_3Si\text{-}R\text{-}Si(OR')_3$. In this case, the organic units are incorporated in the three-dimensional network structure of the silica matrix through two covalent bonds, thus homogeneously distributed in the pore walls.[45] PMOs have several unique features built into their structure due to the matrix's organization. The transfer of the concept of the structure-directed synthesis of pure silica mesophases by surfactants to the bissilylated organosilica precursors allows the construction of this new class of mesostructured organic-inorganic hybrid materials – PMOs.

The difference between PMO and PMS (periodic mesoporous silica) is the composition, being the later entirely composed by silica, which limits its use in areas when hydrophobicity is required or when the interaction between porous host and guest species needs to be tuned and designed. To overpass this drawback, researchers added organosilanes firstly through: grafting of monofunctional organosilanes on the pore surface of PMS, and co-condensation of

organosilanes with pristine silica precursors - *e.g.*, TEOS (tetraethyl orthosilicate) - through a sol-gel process.[15,40,45]

The former route usually suffers from incomplete surface coverage and pore blockage, while the latter, also known as direct synthesis, suffers from inhomogeneous distribution of organic moieties and a limiting 25% loading of organosilanes.[40,45]

On the other hand, PMO is composed entirely of organosilica and has a uniform distribution of organic groups in the pore wall at the molecular level, additionally have high loading capacity of organic groups.[15,40]

PMOs distinguishes itself from the ordered materials by the chemical composition of its pore wall, which is made of organosilica, *i.e.*, each individual organic group is covalently bonded to two or more silicon atom, forming the bridged organosilanes.[15] After their first synthesis in 1999, PMOs with a large number of organic bridging groups, pore sizes, and pore geometries have been rapidly synthesized and characterized.[40]

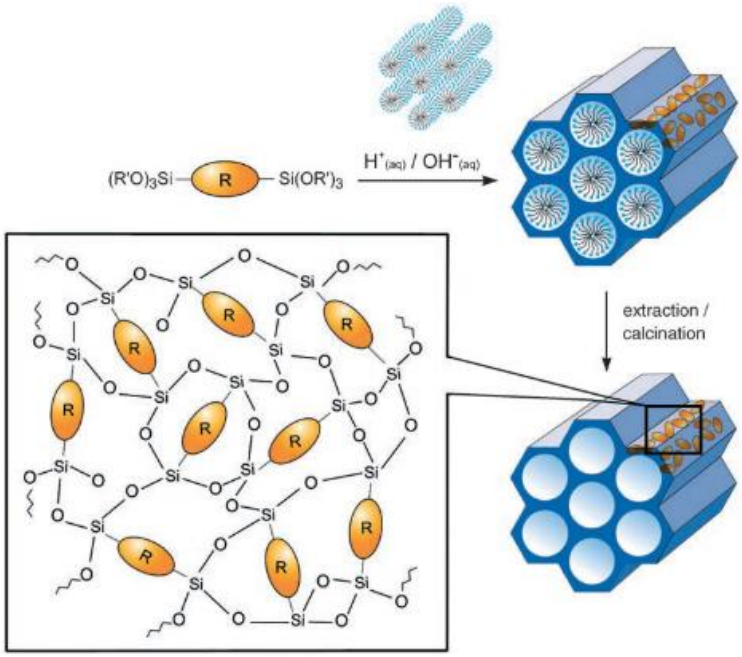


Figure 14 - General synthetic pathway to PMOs using bissilylated organic bridging units. R= organic bridge. Figure adapted from bibliography.[45]

In the late endeavors of maturing PMOs synthetic techniques, researchers came up with two major features, of these materials, that emphasizes and distinguish them from the rest, and ultimately gave its name: The inorganic-organic hybrid composition and the ordered porous structure.

The former feature of PMO, its chemical composition, involves the condensation of the three silanol groups in a silicon atom (-$Si(OH)_3$) to form Si-O-Si bonds, so that every oxygen is shared between two silicon atoms, resulting in the so-called silsesquioxanes.[40]

When prepared in xero- and aerogels form, bridged polysilsesquioxanes are highly porous, often transparent and lightweight.[40] The later said feature is its ordered porous structure.

Many presented studies confirm the feasibility of using the synergistic interface chemistry of inorganic and organic species to create periodic mesostructures with cationic or anionic inorganic species including transition metal oxides and cationic or anionic surfactants. Through these studies, a wide variety of surfactants can be presented including lipid and zwitterionic-type surfactants to directly introduce this chemistry in biomimetics.[14]

With the tools to tailor PMO morphology, pore size and wall composition, is now required the engineering of new applications. Clearly, there is a vast advantage in adding organic function into the backbone of mesoporous silicas, ordered mesoporous organosilicas (OMOs) always lacked internal loadings of silsesquioxanes before structural collapse of the porous framework, and pendant organic groups have the tendency to block pore openings.

These problems are avoided in PMOs that incorporate bridge-bonded organic groups directly into the skeletal structure of the mesoporous organosilica, which modifies the chemical function and mechanical properties of the resulting hybrid material.[15]

The growing accessibility of precursors available to tune properties and to develop novel templating methods are likely to increase the compositional breadth of PMOs. The ability to incorporate organic groups into the walls provides a direct method to engineer chemical and material properties making PMOs advantageous over conventional organic modified mesoporous silicas.

Bridged silsesquioxanes can be used for their ability to promote the self-assembly of organic units for applications that require molecular periodicity. These bridged silsesquioxanes can host organic fragments of varied sizes from phenyl to polyaromatic and porphyrin bridges.[52] The main challenge for the synthesis of bridged silsesquioxanes is the limited number of silane precursors which are commercially available.

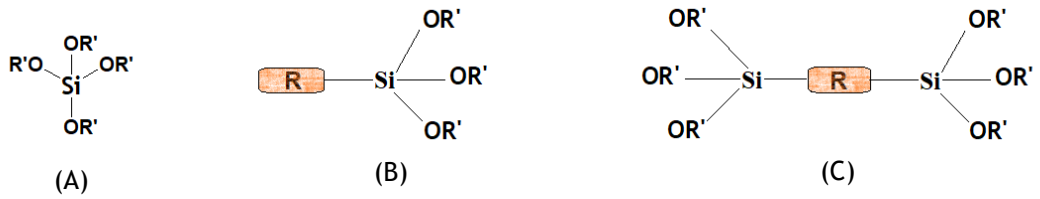
PMO materials are considered highly promising candidates for a series of technical applications, *e.g.*, catalysis, adsorption, chromatography, nanoelectronics, or the preparation of DDSs.[45] Additionally, the remarkable control of the synthesis and composition of such materials thus offer a vast field of research for the years to come.

1.4.4. Organosilane precursors

As above referred, the discovery of new siliceous precursors is of extreme importance. Initially the production of inorganic precursors permitted the synthesis of inorganic matrices though LCT process. With the advent of the hybrid materials, the need of new hybrid organo-inorganic precursors is constantly growing. The research of new precursors enables the formation of nanomaterials with groundbreaking features.

In the mesoporous organosilica materials' case, the discovery of organosilane precursors is vital. Through these precursors, the features of such matrices can be tuned through the introduction of the correct organosilane precursor.[53] However, this is not a simple task. Due to the organic group's (R) size and complexity limitation (such as ethylene, phenylene bridging groups)[43], the production of functional organosilane precursors need to be furtherly studied. Although, with the recent advances in the area, the number of available organosilane precursors is in a fast and undergoing expansion.[54-56] The development of efficient and functional hybrid materials is extremely dependent of the discovery of new organosilane precursors.

Throughout this theoretic introduction, the precursor designation had appeared various times, being the most focused the silsesquioxane precursors (figure 15, A), and organosilane (figure 15, B) and bissilylated (figure 15, C) organosilica precursors.



(A) (B) (C)

Figure 15 – General representation of silsesquioxane (A), mono-organosilane (B), bissilylated (C) precursors, for the synthesis of mesoporous silicas (MSs), OMOs, and PMOs, respectively.[54,57,58]

The theoretic introduction is herein concluded with the highlighting of the discovery of new and innovative (with unused organic moieties, like carbohydrates) precursors, which is the main aim of this work. Furtherly, some applications of the glycosylated nanostructures will be presented, as also some of the siliceous mesoporous materials' applicabilities.

1.4.5. Glyconanotechnology applications

With the advent of nanotechnology, glycosylated nanostructures received a lot of attention. With applications ranging from studies of carbohydrate/protein interactions, carbohydrate/carbohydrate interactions, *in vivo* cell imaging, vaccine development, targeted drug delivery, and bioassays.[59] All the above-mentioned leads to the importance of the

availability of specifically designed, synthetic, multimeric carbohydrates, that are highly desirable to perform carbohydrate-based molecular recognition studies.[6] Through the introduction of carbohydrate moieties on inorganic matrices, and the inherent features of this synergy, the glyconanosystems consist in expedient candidates for uncountable applications in innumerous fields – such as electronics, optics, mechanics, energy, environment, biology and medicine.[35] Through their use, innumerous drawbacks can be overcome – such as low selectivity, biocompatibility, and toxicity – in the development of new therapeutics.[35]

Hybrid materials, for instance, have been extensively studied for the development of DDS, since their high loading capacity and physicochemical properties, and their ability to incorporate lipophilic and hydrophilic substances in suitable dosage and deliver them *in situ*, merging the "bio-friendly" features of both organic and inorganic moieties.[35] They can be used to develop multifunctional systems - *e.g.*, "smart" stimuli-responsive (physical and chemical stimulus) hydrogels, microspheres, film forming materials, microarrays, biosensors, and many more, that can be useful in the development of drug delivery systems, biosensing/imaging and protein-interaction tools, absorbents, and other applications in electronics, and optics.[35,60–63]

Likewise, glycopolymers can be used to produce: cationic glycopolymers – for gene delivery systems[59,37], glycan microarrays – for glycan binding protein interactions[3], "smart" stimuli-responsive systems – for temperature[2,35,64] and pH[2,37] sensitive polymers in DDS, nonviral gene delivery agents - for DNA delivery[2,65], and polymers - for carbohydrate-mediated signal transduction and protein stabilization[2,59]. Since their biocompatibility, they can be used to present carbohydrate in a controlled multivalent fashion, permitting bioactivity and multivalency in crucial biological recognition processes – such as cell-cell adhesion, development of new tissues, and infectious pathogenesis of virus and bacteria.[59,66]

When functionalizated with the glyco-moiety, nanoparticles form glyconanoparticles (GNPs), that can be sub-categorized in four types: Gold GNP, Silver GNP, Semiconductor quantum dots GNP[37,38], and magnetic (iron oxide) GNP.[1] Presenting well-known living synthesis and with a "friendly" biocompatibility and toxicity, this material's class is an expedient candidate for vaccine development and pathogen inhibition, DDS and gene delivery, contrast agents, bioadhesive materials, and for specific cell surface receptor and protein interaction.[1,2,37,38]

Cancer's treatment requires a personalized aim, which is planned based on the individual response of the patient to treatments. Treatment regimens like this, fosters the development of theranostic nanoparticles - i.e., combining diagnosis, drug monitoring, targeted delivery, and controlled drug release into the same platform. Furthermore, multimodal imaging nanoparticles offer better images at multiple light scales or treatment stages, enhancing the disease diagnosis and prognosis.[67] This treatments' efficiency can be enhanced through the use of nanosystems functionalized with carbohydrates. Concomitantly, PMO and PMS have

received growing attention in this field, and many others, since their multifunctional features and biocompatibility. These materials can also be used in various areas, such as catalysis, adsorption, chromatography, nanotechnology, metal ion extraction, and imprinting for molecular recognition.[13,52] Additionally, their tunable features turns them into magnificent candidates for the development and designing of controlled release systems, biosensors, enzyme immobilization, and separation biotechnology.

2. Aims

As indicated by the dissertation's title the aim of this work is the synthesis and characterization of mono-organosilane precursors, from type Z_3Si-R, being Z and hydrolysable group (usually ethoxy groups) and R is an organic group. Passing through the functionalization and protection of the hydroxyl groups on the carbohydrate molecules for the posterior linkage to the silica moiety, forming carbohydrate-based precursors for the synthesis of mesoporous organosilicas. Using the synergetic combination of the almost inexhaustible resource of sugars with the ever-growing field of the mesoporous materials, the answer for many present-day problems could be revealed. The expedient features of both, makes their study indispensable and a very promising field for all kind of applications.

The preliminary chapter focused, firstly, in a brief analysis on carbohydrate subject. After a small introduction, their synthesis was shortly considered and so their functionalization and inherent stereoselectivity, deepening the glycoscience term. Subsequently, the glyconanotechnology denomination was introduced through the demonstration of some of the general glyconanostructures and respective synthesis applications. Due to the dissertation's main objective, the category of the hybrid mesoporous materials was furtherly deepened, with a major focus on the periodic and ordered mesoporous organosilicas.

Although the final objective of this work was the synthesis of the so-called hybrid mesoporous materials, it didn't come to that end. The lack of time caused by logistic and experimental problems resulted in the production of only the mono-organosilane precursors, serving as an indicator of some possible, facile, and green functionalization for carbohydrate and feasible precursors for mesoporous materials with the use of carbohydrates. Throughout this dissertation, always looked for the eco-friendly and least costly/time-consuming methods, always attempting for the reutilization and proper elimination of the reactions' by-products and respective solvents.

3. Discussion and results

Starting with the carbohydrate functionalization, the obtained and even some of the failed synthesis will be presented, sometimes for reference of the stereoselectivity on carbohydrates. Forwardly, the mono-organosilane precursors' results will be presented in a chronological order in which the respective reactions were carried-out.

3.1. Synthesis of glycoside derivates

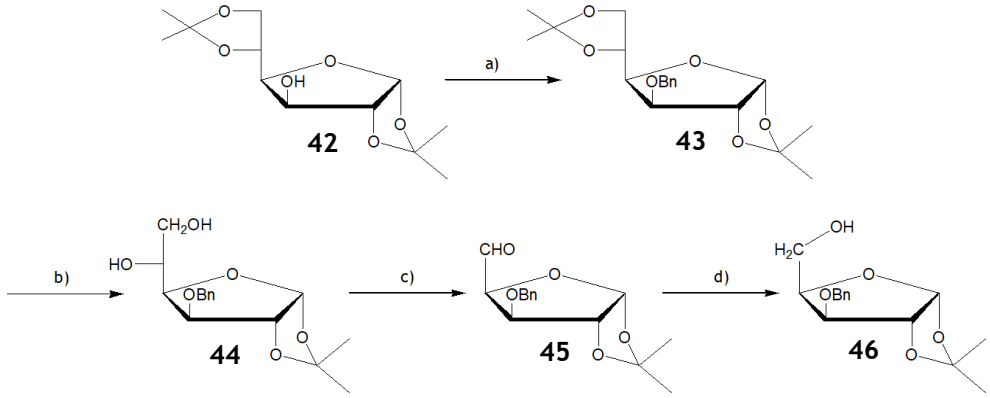
As aimed in the objective section, all the synthetic routes were the maximum eco-friendly possible, always trying to use non/least-toxic reagents as possible.

The objective of the synthesis focusses on the functionalization of the carbohydrate molecules, for the protection of all hydroxyl groups less one (and in one case two). Through this hydroxyl group a covalent urethane cross-link was generated, connecting the sugar to the siliceous moiety – 3-trietoxysilyl)propyl isocyanate (ICPTES). Additionally, due to the lack of solubility of the carbohydrates in THF, which is the solvent used in the synthesis of the mono-organosilane precursors, a series of selective and non-selective protections and deprotections, of the hydroxyl groups, is needed to improve the solubility of the derivates in the polar aprotic solvent.

3.1.1. Synthesis of the 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*gluco*-pentodialdo-1,4-furanose (46)

The carbohydrate derivate **46** was synthesized by a sequential reaction, initialized with the benzylation of the hydroxyl in position 3 of diacetone-D-glucose **42** (DAG)[68], proceeded by a selective hydrolysis of isopropylidene group in $C_{5,6}$.[69] In the next step, an aldehyde is produced through an oxidative cleavage[69] followed by the formation of an alcohol on C_5, through the reduction of the aldehyde group[22] in C_5. The reaction steps are explained in detail on scheme 15.

The compound **46** was synthesized and stored, however it degraded over time, thus the respective characterization could not be achieved, and wasn't used in phase's two precursor synthesis.



Scheme 12 - Synthetic pathway to obtain compound **46**. Conditions and yield: a) BnBr, NaH/DMF, r.t., 20 min, 93%; b) AcOH 80%, 1h, 60ºC, 89%; c) 1.EtOH 2.$NaIO_4/H_2O$, 20 min, 96%; d) $NaBH_4$/EtOH 70%, 1h, 0ºC, 89%.

3.1.1.1. Benzylation

The first step of the reaction sequence was the protection of hydroxyl group in C_3 through the addition of a benzyl group[68]. The benzylation was driven in N,N-dimethylformamide (DMF) with benzyl bromide (BnBr) as Lewis base, and sodium hydride (NaH) as catalyst to obtain 3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **43** in a 93% yield.

3.1.1.2. Selective deprotection of $C_{5,6}$ hydroxyl groups

Next, a selective deprotection of isopropylidene group[69] on C_5 and C_6 was performed in order to obtain 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose **44**. Using a solution of acetic acid (HOAc) (80%), compound **44** was obtained with a yield of 88%.

3.1.1.3. Oxidative cleavage

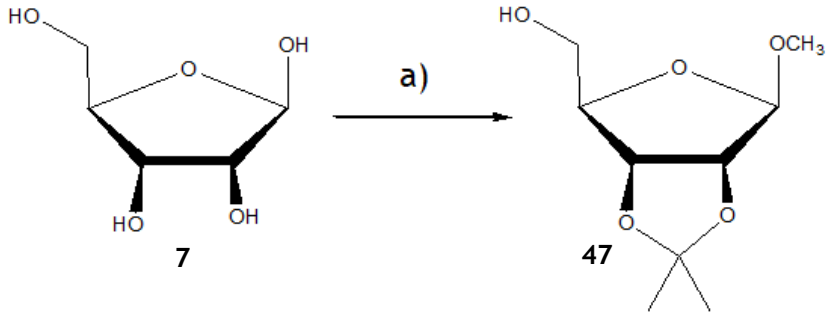
On this reaction, the cleavage of the vicinal diols of compound **44** was performed, in order to obtain an aldehyde group on C_5. Through an oxidative cleavage using sodium periodate in ethanol in a dark medium the 3-*O*-benzil-1,2-*O*-isopropilideno-α-D-xylo-pentodialdo-1,4-furanose **45** was obtained with a 96% yield.

3.1.1.4. Aldehyde reduction

In order to obtain an alcohol group on position C_5, the aldehyde reduction was performed using $NaBH_4$ dissolved on an ethanol solution at 70%, at a temperature of 0ºC. The inorganic moiety was then extracted with a mixture of chloroform and dichloromethane, in order to obtain 3-*O*-benzyl-5-hydroxyl-1,2-*O*-isopropylidene-α-D-*gluco*furanose **46** with a 89% yield.

3.1.2. Synthesis of the 1-O-Methoxy-2,3-O-isopropylidene-ß-D-ribofuranose (47)

Through the synthetic procedure (scheme 13), the protection of the anomeric hydroxyl group in C_1, with a methyl group, and the protection of the hydroxyls on C_2 and C_3, with an isopropylidene group, was carried-out in a one-pot reaction[70].



Scheme 13 - One-pot synthesis of the D-Ribose derivate **47**. Conditions and yield: a) Acetone, methanol, $CuSO_4$, r.t., 48h, 90%.[71,72]

Although the reaction conditions worked, the yield was low, and the resulting product had too many side products. Therefore, through the heating of copper (II) sulfate pentahydrate, it was possible to obtain copper (II) sulfate. Using copper (II) sulfate in a catalytic amount[72] was possible to considerably enhance the reaction yield to approximately 90%.

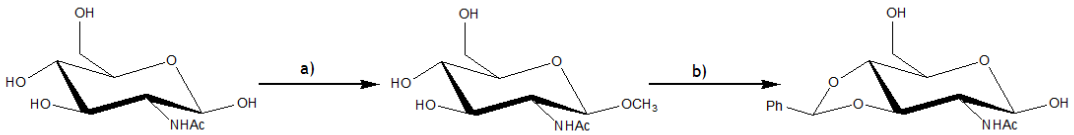
Table 1 - ^{13}C-NMR and ^{1}H-NMR spectrum data of compound 1-O-methyl-2,3-O-isopropylidene-ß-D-ribofuranoside **47** in comparison to α-D-ribose **7**.

		O-CH_3 (Hz)	CH-1 (Hz)	CH-2 (Hz)	CH-3 (Hz)	CH_2-5 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	47	b)	b)	b)	b)	b)	b)	b)
^{1}H-NMR		3.30	4.89	n.a.	4.56	3.56-3.67	1.25, 1.37	a)
^{13}C-NMR[73]	α-D-ribose	a)	97.8	72.4	71.50	62.9	a)	a)
^{1}H-NMR[73]		a)	5-6	2.1-3.1	4.81	3.8-4.3	a)	a)

a) Not applicable (n.a.); b) Not defined

3.1.3. Synthesis of the 1-O-methyl-2-N-acetylamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside (50)

Through a two-step procedure, the glucopyranoside **50** was synthesized[74]. First through the protection of the anomeric C_1, of the commercially available ß-N-acetylglucosamine **48** with a methyl group, and afterwards with a benzylidene on the hydroxyl groups at C_4 and C_6. This was a difficult synthesis since the low solubility of N-acetylglucosamine and the derivatives on organic solvents. Due to this, the reactions couldn't be accompanied through TLC (thin layer chromatography), and NMR samples caused some solubility issues on preparation, hence influencing the final spectra.



48 **49** **50**

Scheme 14 - Synthetic path of compound **50**. Conditions and yield: a) Acetyl chloride, anhydrous methanol, r.t., 5h, 62%; b) Benzaldehyde, zinc chloride, r.t., 4h, 58%.

3.1.3.1. Methylation

Through a mixture of acetyl chloride and anhydrous methanol, the methylation of the anomeric hydroxyl was achieved, leading to the synthesis of methyl 2-N-actemido-2-deoxy-α-D-glucopyranoside **49** in a 62% yield. The mixture was reacted 2 additional hours in comparison to the bibliography[72], resulting in 5 hours of reaction time.

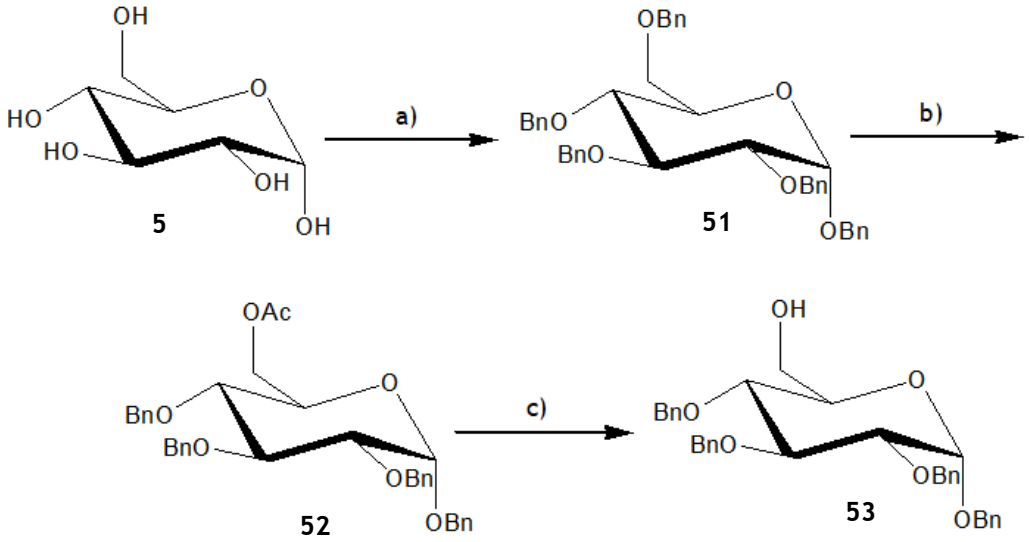
3.1.3.2. Benzylidene addition

With benzaldehyde, previously dried with sodium sulfate, and zinc chloride as catalyst, the addition of a benzylidene group between C_4 and C_6 was carried. The mixture of the benzaldehyde and the zinc chloride had to be strongly agitated for 30 minutes before the addition of the methyl glucopyranoside **49.** Through this approach the methyl 2-N-acetylamido-3,4-O-benzylidene-2-deoxy-α-D-glucopyranoside **50** was synthesized with a yield of 58%.

The ^{13}C-NMR and ^{1}H-NMR spectrum were too noisy, consequently the respective peak attribution could not be carried-out.

3.1.4. Synthesis of the 1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside (53)

Through the used synthetic paths, an expedient synthesis of the glucopyranoside **53** was carried out[68]. This reactional sequence passes, firstly, through the benzylation of all α-D-glucose's hydroxyls ($C_{1\text{-}4,6}$). Afterwards the selective substitution of the benzyl group on C_6 for an acetyl group and then followed by a selective deprotection of the added acetyl group on C_6. Through this method is possible to synthesize this widely-used building block in excellent yields, with a fast and facile synthesis.



Scheme 15 – Synthetic path for the synthesis of compound **53**. Conditions and yield: a) 1.DMF/NaH 2.BnBr, r.t., O.N., 61%; b) $ZnCl_2$/1:5 HOAc-Ac_2O, r.t., 1.5h, 95%; c) MeOH/NaOMe, r.t., 5h, 79%.

3.1.4.1. Benzylation

Through the use of benzyl bromide in a mixture of α-D-glucose **5** dissolved in DMF with NaH, the benzylation of all hydroxyl groups were expediently achieved. After chromatography and recrystallization the obtained 1,2,3,4,6-penta-O-benzyl-α-D-glucopyranoside **51** resulted in a crystal-clear needlelike structure, and a yield of 61%.

3.1.4.2. Acetylation

The acetylation of the O-benzyl group on C_6 was achieved using freshly fused zinc chloride (through high temperature and vacuum) and a mixture of acetic anhydride (Ac_2O) and HOAc under low temperature, for a more selective acetylation. Purification by chromatography gave 6-O-acetyl-1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside **52** as a white solid with a yield of 95%.

3.1.4.3. Selective deacetylation

This selective deprotection on C_6 was carried-out in methanol with sodium methoxy in mild conditions. Through column chromatography and recrystallization in ethanol, the 1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside **53** was obtained as white needles in a yield of 79%.

NMR ^{13}C and ^{1}H, and FT-IR spectra of compound **53** were in accordance with the bibliography.[75]

Table 2 – ^{13}C NMR data of compound **53**, in comparison with the bibliography data of compound **52**.

		Ar-C	C-Ar-C	C-1	C-2	C-3	C-4	C-5	C-6	CH_2-Ar	CH_2-6a	CH_2-6b
^{13}C-NMR	**52**[68]	128.4, 128.3, 128.2, 128.0	138.1	102.2	77.2	84.5	72.7	82	63.0	71.0, 74.7, 74.8, 75.6	84.07	
	53	128.60, 128.29 (2C), 128.13, 128.02	138	102.18	77.75	84.14	72.47	82.12	63.18	74.99, 74.38, 74.23,	84.16	

Table 3 – ^{1}H NMR data of compound **53**, in comparison with the bibliography data of compound **52**.

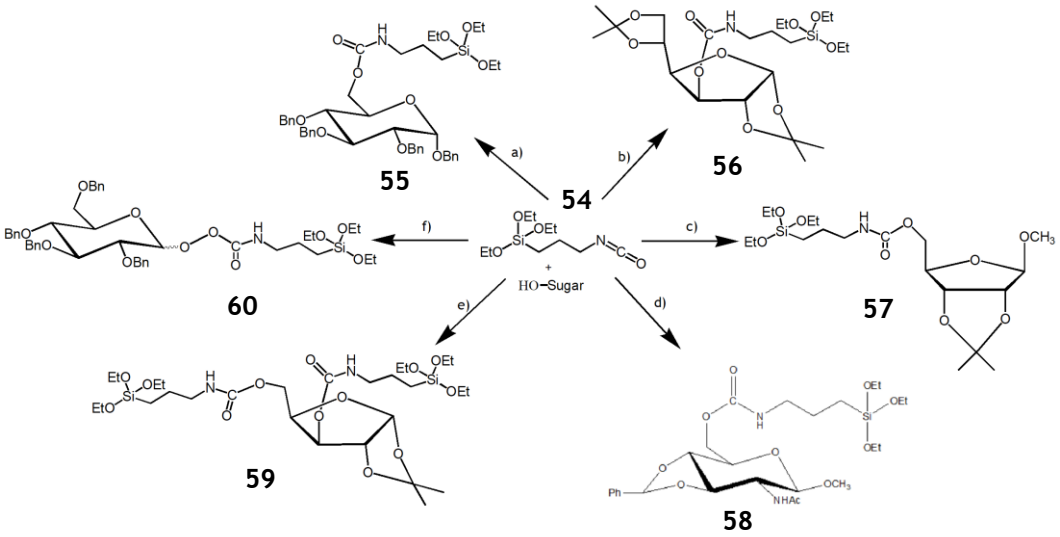
	(Hz)	H-1	H-2, H-4, H-5	H-3	H6a	H-6b	Phenyl
^{1}H NMR	**52**[68]	4.49–4.84 (m, 6H)	3.48–3.61 (m, 3H)	3.67 (overl. dd, H3)	4.24 (dd, 1H)	4.35 (d, 1H)	7.21-7.40 (m, 20H)
	53	4.52-4.86 (m, 6H)	3.45-3.63 (m, 3H)	3.68 (m, 1H)	a)	a)	7.28 (m, 20H)

a) Not defined (n.d.)

3.2. Synthesis of mono-organosilane precursors

In this stage of the present work, the mono-organosilane precursors were prepared using the referred synthetic path[76] (scheme 16), through a urethane cross-link between the carbohydrate derivates and the inorganic moiety 3-(Triethoxysilyl)propyl isocyanate (ICPTES) **54**. Since this technique was based on a SN1 reaction, the use of a polar aprotic solvent (*e.g.*, THF) promote the deceleration of the reaction. The reaction was initiated by a nucleophilic

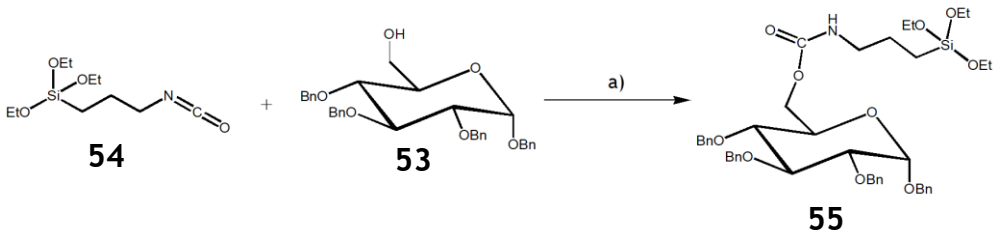
attack of the unprotected hydroxyl group (on the carbohydrate-derivate) to the carbonyl group of isocyanate - on the siliceous moiety, **54** ICPTES).



Scheme 16 - Synthesis of carbohydrate-based organosilane precursors. The conditions were the same[76] for all precursors (THF, 55ºC–60ºC), only differing on the reaction time which was controlled by FTIR. Glycoside, reaction time and yields: a) **53**, 8 days, 92%; b) **42**, 12 days, 93%; c) **47**, 6 days, 68%; d) **50**, 12 days, 89%; e) **61**, 7 days, 71%; f) **62,** 12 days, 88%.

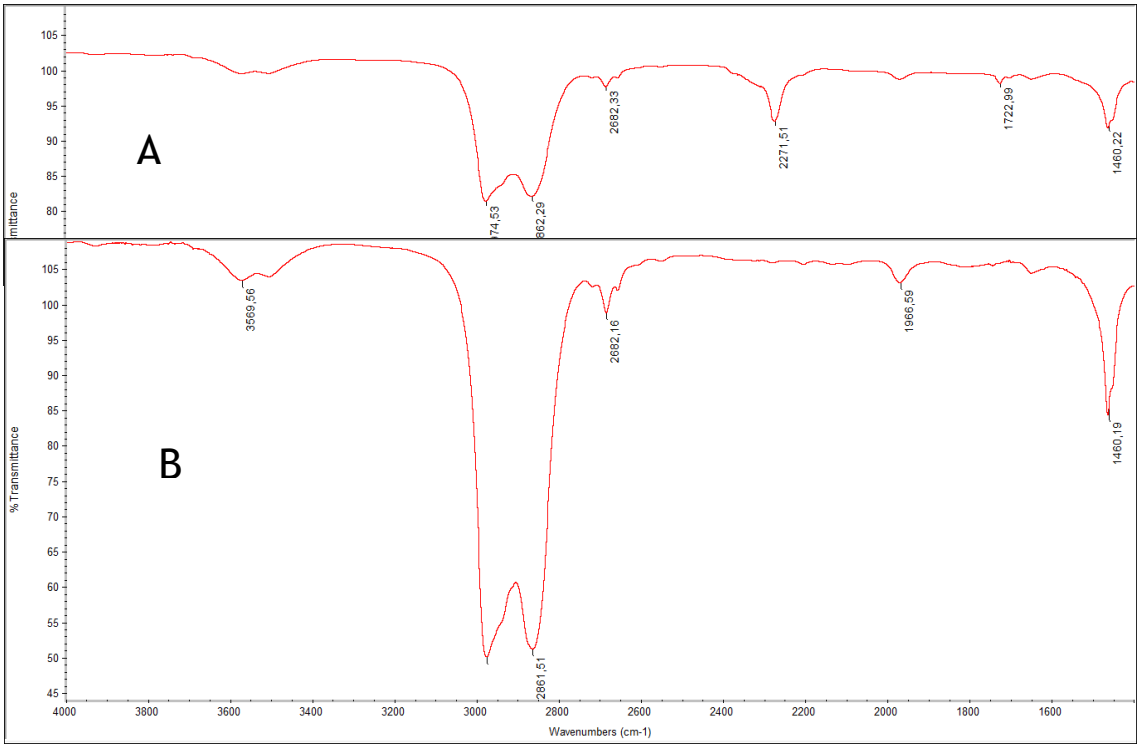
3.2.1. 6-O-methyl(3-(triethoxysilyl)propyl)carbamate-1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside (55)

The synthesis of the precursor **55** was carried-out through the referred procedure[76], through the mixture of the glycoside **53** with the siliceous compound **54** in THF at 60ºC. (scheme 17)



Scheme 17– Synthetic route[76] to prepare de precursor **55**. Conditions and yield: THF, 60ºC, 8 days, 92%.

The control of the reaction was performed by FTIR specters, in which is possible to recognize the terminus of the reaction with the disappearance of the sharp adsorption band at 2271 cm^{-1}. This band is characteristic of the isocyanate group, and the respective fading of this band indicates the formation of the urethane cross-link. It is also possible to notice the appearance of a band at 1966 cm^{-1}. However, the spectra seem to be too diluted and it's not possible to notice the increase of the amide band.



Graphic 1 - Contrast between the reaction FTIR spectrum at day 0 (A) and day 8 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2271 cm^{-1}.

Table 4 - ^{1}H-NMR spectra data of glycoside **55**.

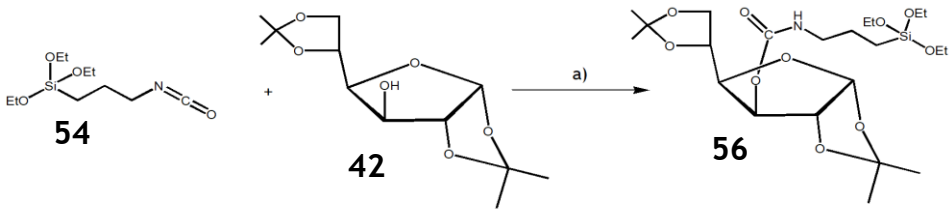
		H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	H-4 (Hz)	H-5 (Hz)	CH_2-6a (Hz)	CH_2-6b (Hz)	C-CH_3
^{1}H-NMR	55	5.16 (d,1H)	5.33 (d,1H)	4.14 (d,1H)	4.86 (t, 1H)	4.73 (dd, 1H)	4.11-3.91 (m, 2H)		1.73, 1.62 (2m)

Table 5 – ^{13}C-NMR spectra data of glycoside **55**.

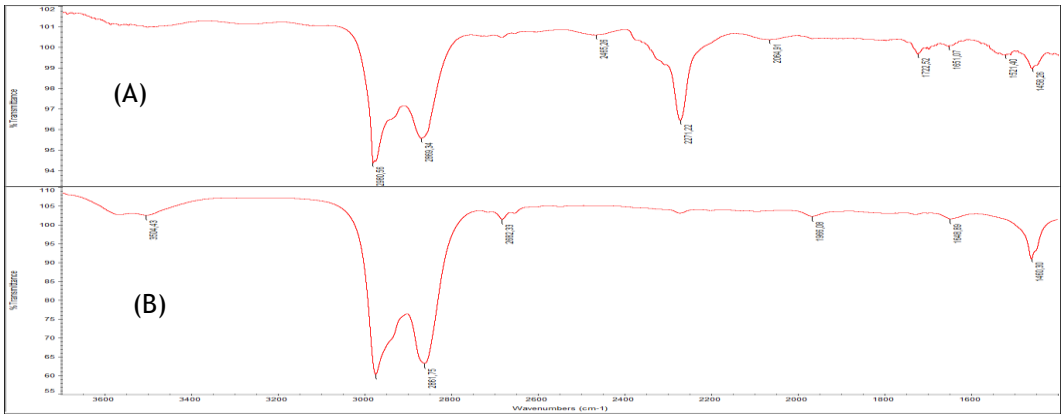
		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	**55**	109.27	81.27	83.43	85.16	67.40	25.11, 26.68	111.62

3.2.2. 3-O-Methyl(3-(triethoxysilyl)propyl) carbamate-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (56)

The precursor **56** was synthesized through the same method[76], and urethane cross-link was achieved between ICPTES **54** and compound **42** (scheme 18), and proved in the FTIR spectrum (graphic 2) with the disappearance of the isocyanate group's inherent sharp band at 2271 cm^{-1}.



Scheme 18 - Synthetic route[76] to prepare de precursor **56**. Conditions and yield: THF, 60ºC, 12 days, 93%.



Graphic 2 - Contrast between the reaction FTIR spectrum at day 0 (A) and day 12 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2271 cm^{-1}.

Table 6 - ^{13}C-NMR spectra data from compound **56.**

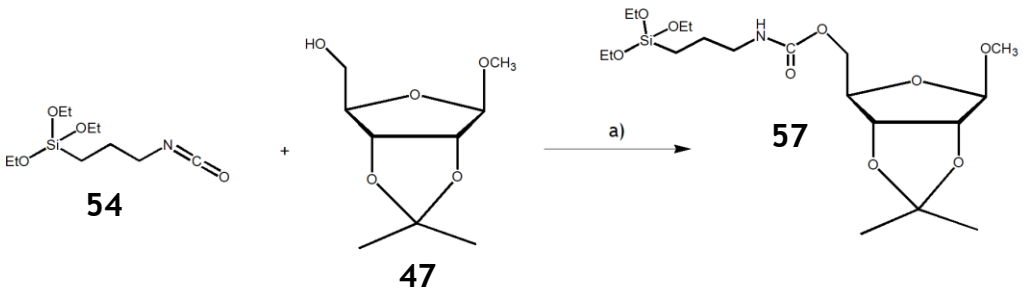
		C-1 (HZ)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	C-6 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	**56**	102.3	84.34	74.94	82.35	74.22	67.48	25.60, 24.07, 23.49	102.30, 7.73

Table 7 - ^{1}H-NMR spectra data from compound **56.**

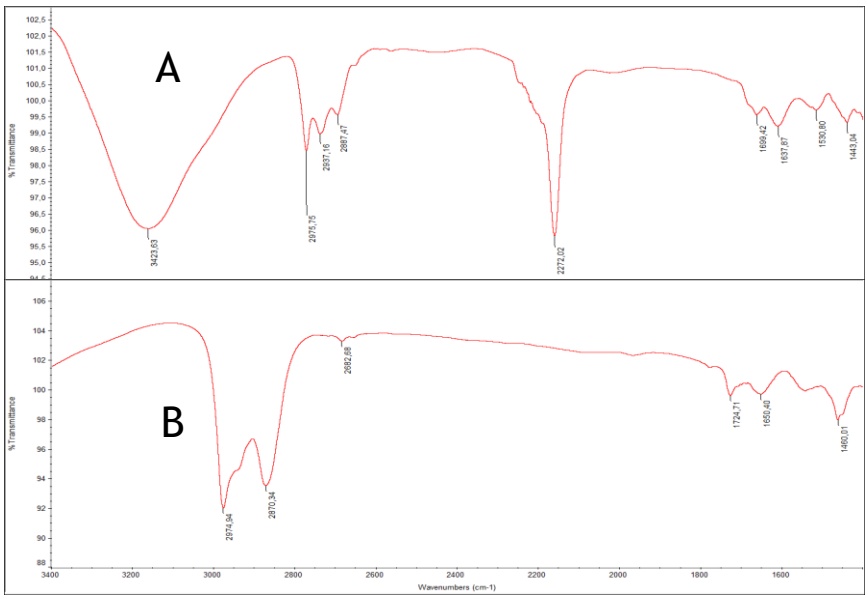
		H-1 (HZ)	H-2 (HZ)	H-3 (HZ)	H-4 (HZ)	H-5 (HZ)	CH_2-6a (HZ)	CH_2-b (HZ)	CH_3 (HZ)
^{1}H-NMR	**56**	5.83 (t,1H)	4.53 (d, 1H)	4.28-4.24 (m, 1H)	4.05 (d, 1H)	n.a.	4.17 (s, 1H)	3.95 (dd, 1H)	1.46, 1.41, 1.36, 1.28 (4s,12H)

3.2.3. 5-O-Methyl(3-(triethoxysilyl)propyl)carbamate-1-O-methoxy-2,3-isopropylidene ß-D-ribofuranose (57)

The precursor **57** resulted from the previously applicated methodology[76], and the urethane cross-linking between the ribofuranoside 47 and the ICPTES **54** is again accompanied with the disappearing of the isocyanate's sharp band at 2272 cm^{-1}. However, in this example is possible to notice the increase of the amide corresponding band at 1724 cm^{-1}.



Scheme 19 - Synthetic route[76] to prepare de precursor **57**. Conditions and yield: THF, 60ºC, 6 days, 68%.



Graphic 3 - Contrast between the reaction FT-IR spectrum at day 0 (A) and day 6 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2272 cm^{-1}.

Table 8 - ^{1}H-NMR data of precursor **57** in comparison with the data of compound **47**.

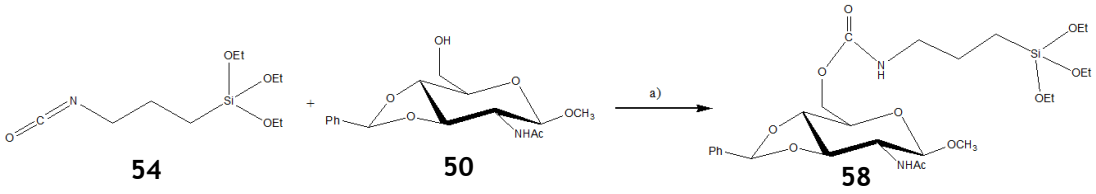
		H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	H-4 (Hz)	CH_2-5 (Hz)	CH_3 (Hz)
^{1}H-NMR	**47**[71]	4.93 (s, 1H)	4.79 (dd, J=6.5, 5.3, 1H)	4.55 (dd, J=6.0, 2.3, 1H)	4.37 (dd, J=7.2, 2.7, 1H)	3.54-3.63 (m, 2H)	1.28, 1.44 (2s, 6H)
	57	5.09 (s, 1H)	4.68 (dd,, 1H)	4.50 (dd, 1H)	4.32 (m, 1H)	4.15-4.08 (m, 2H)	1.31, 1.47 (2s, 6H)

Table 9 - ^{13}C-NMR data of precursor **57** in comparison with the data of compound **47**.

		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	**47**[71]	110.10	81.60	85.90	88.40	64.10	24.80, 26.50	112.20
	57	107.69	81.27	81.75	67.82	68.43	23.23, 23.13	112.78

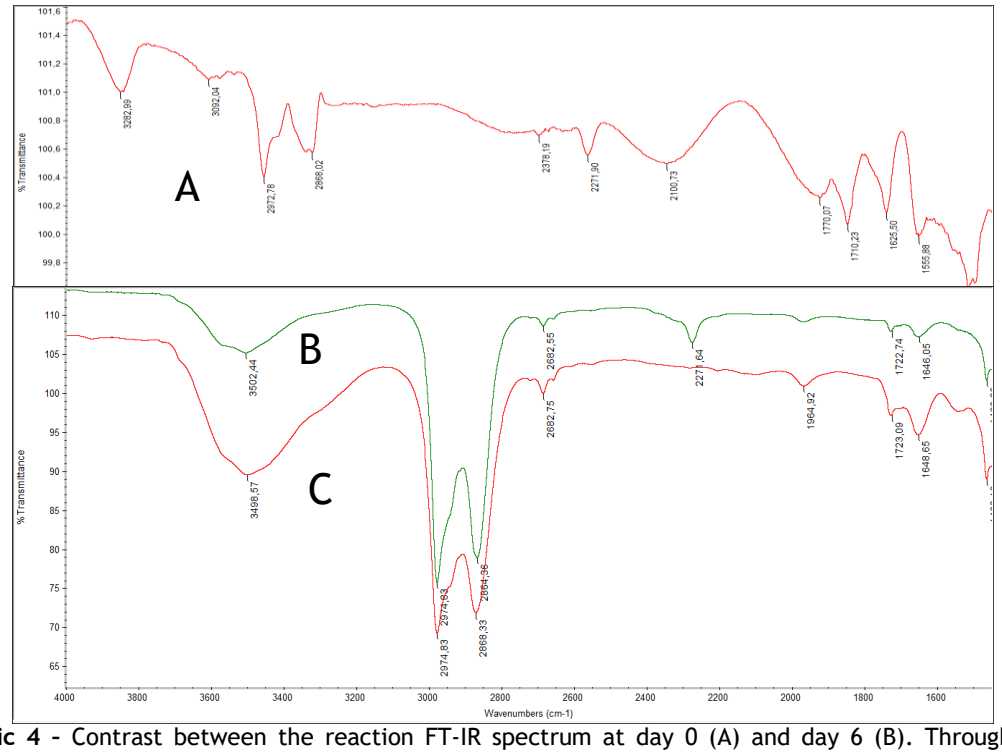
3.2.4. 3-O-Methyl(3-(triethoxysilyl)propyl)carbamate-1-O-methoxy-2-N-acetamido-4,6-O-benzilidene-2-deoxy-D-glucopyranoside (58)

The synthetic path[76] used resulted in the urethane cross-linking between the glycofuranoside **50** and the ICPTES **54**.



Scheme 20 - Synthetic route[76] to prepare de precursor **58**. Conditions and yield: THF, 60ºC, 12 days, 89%.

Due to the low solubility of compounds **42** and **50** on organic solvents, their involving synthetic paths were always a challenge. Nonetheless the lack of polished peaks on spectrum (graphic 4, A), it is possible to notice the disappearance of the isocyanate's inherent sharp band at 2271 cm^{-1} after 12 days.



Graphic 4 - Contrast between the reaction FT-IR spectrum at day 0 (A) and day 6 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2271 cm^{-1}.

Since the lack of corrected base line on the spectra of reaction's day 0, the data from day 7 is presented (C) where is possible to notice the disappearing of the respective isocyanate band and the strengthen of the amide respective band at 1723 cm^{-1}.

Table 10 - ^{1}H-NMR data of precursor 58.

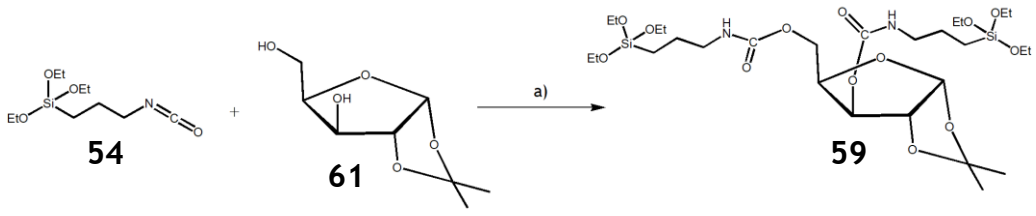
		H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	H-4 (Hz)	H-5 (Hz)	CH_2-6a (Hz)	CH_2-6b (Hz)	C-CH_3
^{1}H-NMR	**58**	4.81 (d, 1H)	5.51 (m, 1H)	4.07 (m, 1H)	4.96 (t, 1H)	4.72, 4.67 (dd, 1H)	3.81 (m, 2H)		2.02 (dddd)

Table 11 - ^{13}C-NMR data of precursor 58.

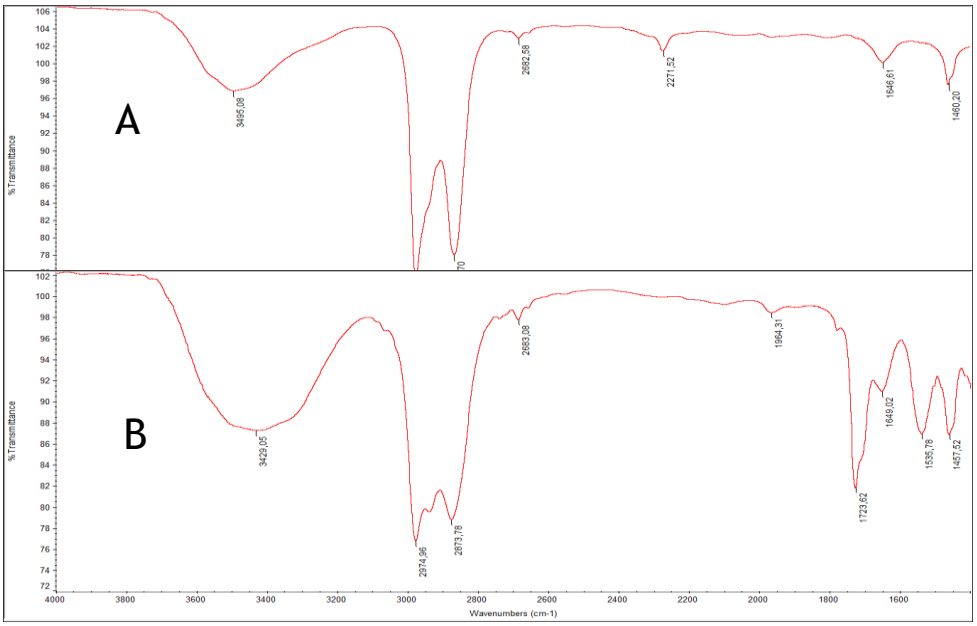
		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	C-6 (Hz)	CH_3 (Hz)	C=O (Hz)
^{13}C-NMR	**58**	98.1	77.15	67.34	68.40	66.96	60.39	23.53, 23.37, 23.13	156.21, 155.97

3.2.5. Bis(3,5-O-Methyl(3-(triethoxysilyl)propyl)carbamate-1,2-O-isopropylidene-α-D-glucofuranose (59)

This synthetic strategy[76] was proven to be effective on the formation of the urethane cross-link between 1,2-*O*-Isopropylidene-α-D-xylofuranose **61** and ICPTES **54**. Since the disappearance of the isocyanate band at 2271 cm^{-1}.



Scheme 21 - Synthetic route[76] to prepare de precursor 59. Conditions and yield: THF, 60ºC, 7 days, 71%.



Graphic 5 - Contrast between the reaction's FT-IR spectrum at day 0 (A) and day 7 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2271 cm^{-1}. In this example is clearly visible the increase of the sharp band at 1723 cm^{-1}, corresponding to the amide group. In this case this is more noticeable, probably because of the formation of two amides in the urethane linkage, instead of one like in the other examples.

Table 12 - ^{1}H-NMR data from precursor 59.

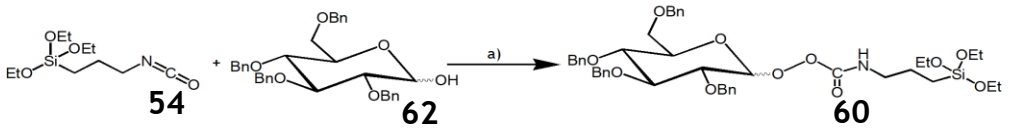
		H-1 (HZ)	H-2 (HZ)	H-3 (HZ)	H-4 (HZ)	C-CH_3 (HZ)	CH_2-5a (HZ)	CH_2-5b (HZ)
^{1}H-NMR	59	5.55 (d,1H)	4.96 (d,1H)	5.24-5.22 (m, 1H)	4.57-4.46 (m, 1H)	n.a.	4.43 (dd,1H)	4.26 (dd,1H)

Table 13 - ^{13}C-NMR data from precursor **59**.

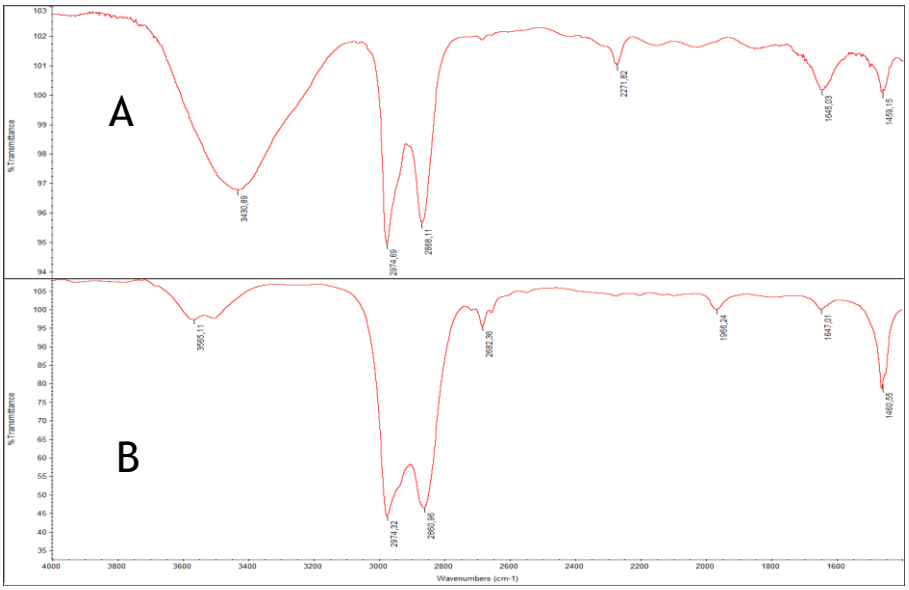
		C-1 (HZ)	C-2 (HZ)	C-3 (HZ)	C-4 (HZ)	C-5 (HZ)	C-CH_3 (HZ)	CH_3 (HZ)
^{13}C-NMR	59	107.86	80.11	84.96	76.68	69.4	n.a.	25.63, 25.15

3.2.6. 1-O-Methyl(3-(triethoxysilyl)propyl)carbamate-2,3,4,6-O-benzyl-D-glucopyranoside (60)

The precursor **60** was obtained through the same synthetic via[76] than the previous precursors, and the hybrid linkage between the organic and inorganic moieties was proven by the disappearance of the isocyanate band at 2271 cm^{-1}.



Scheme 22 - Synthetic route[76] to prepare de precursor **60**. Conditions and yield: THF, 60ºC, 12 days, 88%.



Graphic 6 – Contrast between the reaction's FT-IR spectrum at day 0 (A) and day 12 (B). Through this comparison is possible to notice the disappearing of the band associated to isocyanate group at 2271 cm^{-1}.

In this FT-IR spectrum is possible to notice the increase of two peaks at 1966 cm^{-1} and 1647 cm^{-1}, probably caused by the formation of the urethane linkage. The peak at 1460 cm^{-1} is caused by the presence of THF. Although is not completely noticeable, the increase of the amide corresponding peaks can be perceptible by the comparison of the surrounding peak's intensity.

Table 14 - ^{1}H-NMR data from precursor **60**.

		H-1 (HZ)	H-2 (HZ)	H-3 (HZ)	H-4 (HZ)	H-5 (HZ)	CH_2-6a (HZ)	CH_2-b (HZ)	CH_3 (HZ)
^{1}H-NMR	60	5.78 (t,1H)	4.51 (d, 1H)	4.24 (m, 1H)	4.04 (m, 1H)	4.35 (t, 1H)	4.17 (d, 1H)	3.96 (d, 1H)	1.36, 1.16, 1.14, 1.13 (4s)

Table 15 - ^{13}C-NMR data from precursor **60**.

		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	60	n.d.	82.96	79.63	67.67	n.d.	23.22, 23.11	n.d.

4. Conclusions and future work

This work can be divided in two objectives. The first is the functionalization of carbohydrates to produce glycoside derivates with only one unprotected hydroxyl group. Subsequently, the covalent urethane linking was performed between the glyco-derivates and the siliceous compound ICPTES **54**, thus summarizing the second objective.

Although some failed synthesis, the major and more interesting were accomplished, respectively the synthesis of precursor **55**, **56**, **57**, **58**, **59,** and **60**.

Some reactions were found to take more time than the referred in the bibliography, respectively both steps in the synthesis of **50**.

Through this work, DMF (N,N-dimethylformamide) was used as solvent in the synthesis of the compound **43** and **53**. DMF was found to evaporate smoothly in rotavapor, with the bath's temperature at ~55ºC and pressure at 15~20 mbar. However when the final product was needed dry, a co-evaporation with toluene was implemented.

The use of Cu(II) sulfate, instead of H_2SO_4, showed to be effective in enhancing the compound' **47** synthesis, resulting in the production of less side products, thus in a higher yield.

Commercially carbohydrate **48** showed low yield on the used synthetic strategy[61]. The major struggle was the low solubility on organic solvents, thus the hard reaction's monitorization through TLC. Additionally, the first step of the synthesis of **50** could not be revealed through the revealing method, as the second, but in this case could be revealed through UV light (254 nm) due to the addition of the benzylidene group to $C_{5,6}$.

The synthesis of the compound **53**, showed to be expedient, in both yields and reaction techniques. The resultant product**,** after chromatography and recrystallization, yielded cotton-like crystal needles. The benzylation step was carried in a three phase BnBr/NaH addition, resulting in a more efficient benzylation, when compared to compound's **43** synthesis. The chromatographic column used on compound's **51**, **52** and **53** purification were carried on a mixture of EA/nH as eluent (1:5, 1:2, and 1:2, respectively), showing to be more efficient than those presented on bibliography.[69]

The precursor synthesis showed that, like referred on the introductory chapter, the position 6 of the glycosides is less hindered to reaction than the position 3, since the reaction times of the precursors **55**, **57** and **59** were more rapid then precursors **58** and **56**. Position 1 of glycoside **62** shown to take a little longer, probably because of the large benzyl group on position 2.

5. Experimental section

5.1. General methods

Reagents and solvents were bought from Fluka, Merck, Aldrich or Acros Organics, being analytically pure. When necessary, the solvents were dried with molecular sieves 4 Å, except for methanol, that have to be dried in molecular sieves of 3 Å due to the molecular size. The chromatographic columns were performed in distilled eluents.[78]

For the evaporation of solvents and the drying of compounds a rotational evaporator was used, using the bath temperature between 30~60ºC and the cooling system between 7~12ºC, depending on the volatility of the solvent or the lability of the product.

All reactions, except the all precursors' and compound's **9** reactions, were controlled through TLC, as the column chromatography technique used in some purification steps. The used TLC plates (aluminum plates of 2mm, coated with Silica-gel (Macherey-Nagel 60 G/UV_{254}) were analyzed through a revealing solution and with UV light (λ=254) (Vilber Lourmat CN-6, model VL-6). The revealing solution was a mixture of sulfuric acid (1,5 mL) and vanillin (2,5~3g) in ethanol (100mL). Each reaction needed a different eluent and volumetric proportion, which are described for each situation with the respective Rfs (retention factors), calculated by the ratio between the distance eluted by the compound and the eluent.

The final compounds, and some required intermediates, were purified through chromatographic columns using silica gel 60G (40-63 μm and 230-400 mesh), with atmospheric pressure or pump-assisted chromatography.

Characterization and reaction control, performed through FTIR spectra, were achieved using attenuated total reflectance mode (ATR) in a Thermoscientific Nicolet IS10: smart iTR (Smart Omni Transmission Accessory; SmartrankBR) and processed on Omnic 9.2 software. Precursors were analysed in solution with the aprotic solvent of the reaction (THF). The sample was applied in solution, on the surface of a highly polished KBr pellet, and the data was collected at room temperature, with an average of 32 scans between 4000-600 cm^{-1} with a resolution of 4 cm^{-1} and a sensibility of 60%.

NMR characterization was conducted with ^{1}H NMR and ^{13}C NMR spectra, obtained on a Bruker spectrometer, model Brüker Avance III (400,13 MHz and e 100,62 MHz, respectively), at Universidade da Beira Interior (Faculdade de Ciências da Saúde). Tetramethylsilane (TMS) was used as internal standard, and DMSO-d_6 or $CDCl_3$ as solvents and internal standards (DMSO-d_6, δ = 2,50 ppm and 39,52 ppm; $CDCl_3$, δ = 7,26 ppm and 77,16 ppm in ^{1}H and ^{13}C NMR, respectively). Data was analyzed on MestReNova 9.0 software.

Correlated spectrometry, for assignment of certain signals, was conducted through homonuclear 2-dimensional COSY type. Chemical shifts (δ) of the various signals are expressed in parts per million (ppm). The coupling constants (J) are given in Hertz (Hz) and the multiplicity of signals is indicated on the spectra, using the abbreviations: bs (broad singlet), s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), td (triple doublet), ddd (double double doublet), m (multiplet) and t (triplet).

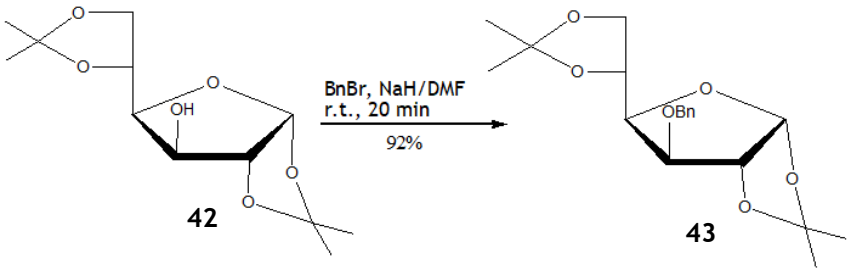
Reactional schemes and molecular draws were obtained with ChemDraw 8.0 Pro software. The images were adjusted using Microsoft Paint, and some were edited on Adobe Illustrator CC 22.1 software. Mesoporous structures were produced with SketchUp Pro 2019 v.19.1.174.

5.2. Synthesis of glycoside derivates

For the posterior preparation of the organosilane precursors, the glycoside derivatives **46**[22,68,69], **47**[70,71], **50**[31], and **53**[68] were produced following the referred literature.

5.2.1. Preparation of 3-*O*-benzyl-5-hydroxyl-1,2-*O*-isopropylidene-α-D-*gluco*furanose (46)

5.2.1.1. 3-O-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (43)



Scheme 23 – Reaction of 42 to obtain 43. Yield: 92%.

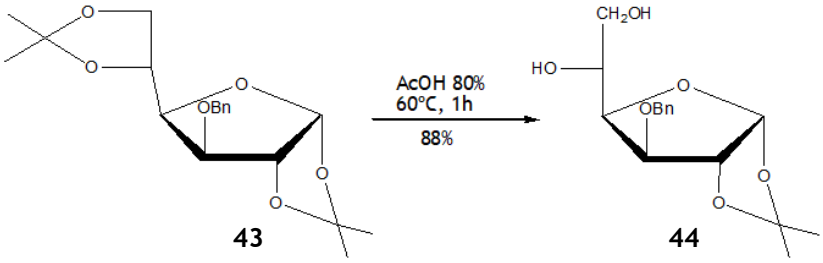
Chemical formula: $C_{19}H_{26}O_6$

M.W.= 348.38 g/mol

To a solution of D-glucose diacetone (2,5 g, 9.605 mmol) in anhydrous DMF (4 mL) was added benzyl bromide (BnBr) (2.275 mL, 13.3 mmol) dropwise for 5-min period. Afterward, the solution was cooled in an ice bath and the sodium hydride (NaH) (1.29 g of 60% dispersion in mineral oil, 32 mmol) was added slowly and carefully, due to the high exothermicity of the reaction and the high reactivity in contact with the ice bath's water. After 10 min the ice bath is removed, because the solution can freeze, then the round bottom flask was closed

with a calcium chloride drying tube, to prevent the entry of water. The reaction was completed after 20 min (verified through TLC) at room temperature. When the reaction was completed, 2 mL of MeOH was added dropwise to neutralize de excess NaH, and the DMF was removed under reduced pressure (20 mbar, 55ºC). To a complete dry effect, the mixture was co-evaporated with toluene. The residue was dissolved in dichloromethane (DCM) (25 mL) and washed with water and brine solution, dried with magnesium sulphate ($MgSO_4$), filtered, and evaporated to give a yellow oil **43**. (Scheme 26)[57] Yield: 92%. Rf: 0.57 (Ethyl Acetate/n-Hexane (EA/nH): 1:1)

5.2.1.2. 3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (44)



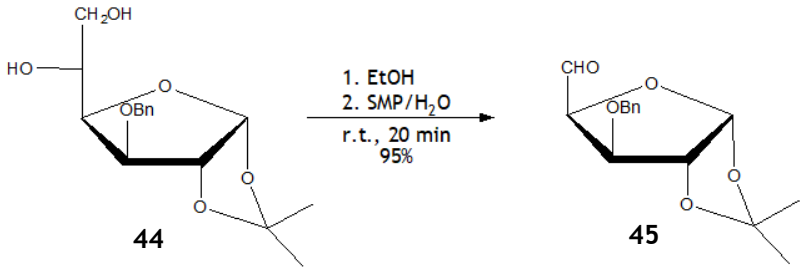
Scheme 24 - Schematic representation of the synthesis of compound **44**. Yield: 88%

Chemical formula: $C_{16}H_{22}O_6$

M.W.= 310.33 g/mol

The oil **43** (0.92 g, 2.86 mmol) was dissolved in acetic acid 80% (20 mL) and stirred for 1 h at 60ºC. Afterward, the mixture was concentrated in the rotavapor with toluene (3x15 mL). The residue was purified through column chromatography using a pump, with a mixture of EA/nH (1:1) as eluent, resulting in a yellow oil **44**. Yield: 88%. Rf: 0.85 (EA/nH 1:1).

5.2.1.3. 3-O-benzil-1,2-O-isopropilideno-α-D-xylo-pentodialdo-1,4-furanose



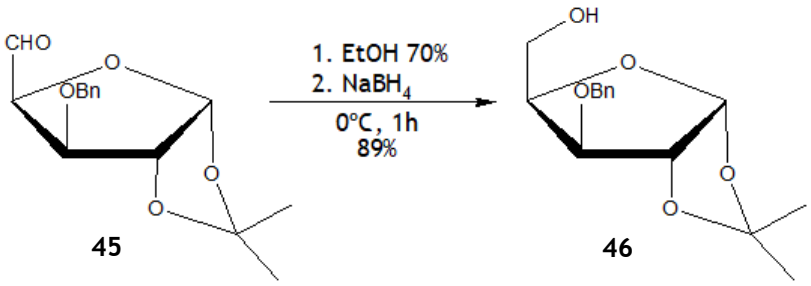
Scheme 25 – Schematic representation of compound 44 reaction to form compound 45. Yield: 96%

Chemical formula: $C_{15}H_{18}O_5$

M.W.= 278.30 g/mol

The oil **44** (1 g, 3.14 mmol) was dissolved in ethanol (3 mL), and a solution of sodium (meta)periodate (SMP) (1.67 g, 7.8 mmol) in water (35 mL) was added. The flask was sealed and covered with aluminum foil, and the mixture was stirred at room temperature for approximately 20 min. After, ethanol (330 mL) was added for the precipitation of organic salts, the mixture was filtered and concentrated at low pressure and low water bath's temperature. The residue was extracted with DCM (3x40 mL), dried (anhydrous sodium sulphate, Na_2SO_4), filtered and concentrated in the rotavapor. (Scheme 28) Yield: 96%. Rf: 0.84 (EA/nH 2:1)

5.2.1.4. 3-*O*-benzyl-5-hydroxyl-1,2-*O*-isopropylidene-α-D-*gluco*furanose (46)



Scheme 26 – Schematic representation of the reactional formation of compound **46**. Yield: 89%

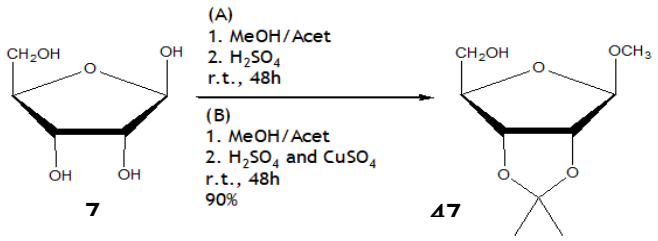
Chemical formula: $C_{15}H_{20}O_5$

M.W.= 280.31 g/mol

The aldehyde derivate **45** (1 g, 3.9 mmol) was dissolved in ethanol 70% (28,7 mL) at 0ºC, and sodium borohydride (0.326 g, 8.6 mmol) was added. The mixture was stirred for 1 h at 0ºC,

extracted with a mixture of chloroform/dichloromethane (1:1), and evaporated under high vacuum. (Scheme 26) Yield: 89%. Rf: 0.63 (EA/nH 1:1).

5.2.2. Preparation of Methyl-2,3-O-isopropylidene-α-D-ribofuranoside (47)



Scheme 27 – Schematic representation of two synthetic approaches (A and B) for the production of compound **47**. (A) Yield: n.a. (B) Yield: 90%

Chemical formula: $C_9H_{16}O_5$

M.W.= 204.21 g/mol

5.2.2.1. Methanol/Acetone/H_2SO_4 method (A)[70]

The commercially available D-ribose **7** (1 g, 6.66 mmol) was dissolved in a solution of dried acetone/methanol 1:1 (10 mL). A catalytic amount of sulfuric acid (0.5 mL) was added and the mixture was stirred at room temperature for 48 h. Afterwards, the mixture was neutralized with sodium carbonate (Na_2CO_3), filtered, and concentrated under high vacuum. The resulting residue was dissolved in water (20 mL), extracted with ethyl acetate (3x20 mL), dried (magnesium sulfate, $MgSO_4$), filtered and evaporated under high vacuum. (Scheme 27, A) Yield: not applicable. Rf: 0.58 (EA/nH 1:4)

5.2.2.2. Methanol/Acetone/H_2SO_4/ $CuSO_4$ method (B)[71]

The commercially available D-ribose **7** (1 g, 6.66 mmol) was dissolved in a solution of dried acetone/methanol 1:1 (10 mL). A catalytic amount of sulfuric acid (0.5 mL) and copper (II) sulfate (2,12 g, 13 mmol) was added and the mixture was stirred at room temperature for 48 h. Afterwards, the mixture was neutralized with sodium carbonate (Na_2CO_3), filtered, and concentrated under high vacuum. The resulting residue was dissolved in water (20 mL), extracted with ethyl acetate (3x20 mL), dried (magnesium sulfate, $MgSO_4$), filtered and evaporated under high vacuum. Column chromatography (1:4 EA/nH) provided **47** as an oil. (Scheme 30, B) Yield: 90%. Rf: 0.58 (EA/nH 1:4)

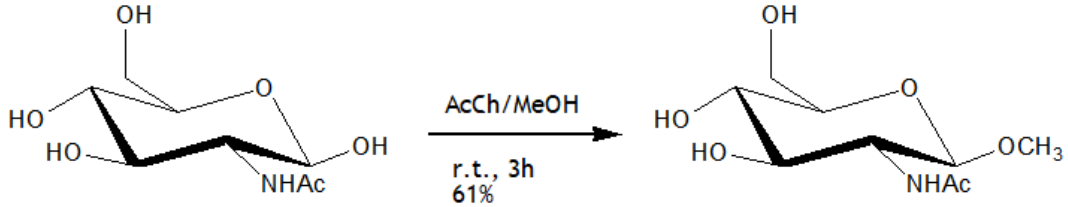
FT-IR (cm^{-1}): 3454.60 (OH), 2988, 2940, 1381, 1210, 1092, 870 cm^{-1}. According with the literature.[71]

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.25 (C-CH_3), 1.37 (C-CH_3), 3.56-3.67 (CH_2-5), 4.56 (CH-3), 4.89 (CH-1), 3.30 (O-CH3). In accordance to bibliography.[71]

^{13}C NMR (101 MHz, DMSO-d_6) n.d.

5.2.3. Preparation of 1-O-methyl 2-N-acetylamido-4,6-O-benzylidene-2-deoxy-β-D-glucopyranoside (50)

5.2.3.1. Methyl 2-N-actemido-2-deoxy-β-D-glucopyranoside (49)



48 **49**

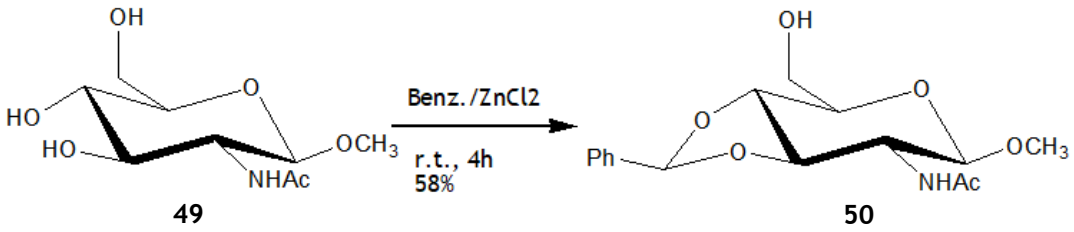
Scheme 28 – Schematic representation of the first reaction to synthesize compound **49** from commercially available compound **48**. Yield: 61%

Chemical formula: $C_9H_{15}NO_6$

M.W.= 233.22 g/mol

Firstly, a solution of acetyl chloride (CH_3COCl, AcCh) (0.2 mL) in anhydrous methanol (20 mL) was prepared, stirring the mixture at room temperature. Successively, the commercially available compound **48** (1 g, 4.5 mmol) was added to the mixture and stirred at room temperature. After 5 h, the solution was neutralized with potassium carbonate (K_2CO_3), filtered over celite and concentrated under high vacuum. Yield: 61%. Rf: n.a.

5.2.3.2. 1-O-Methyl 2-N-acetylamido-4,6-O-benzylidene-2-deoxy-ß-D-glucopyranoside



49 **50**

Scheme 29 – Schematic representation of the second reaction of compound's **50** synthesis. Yield: 58%

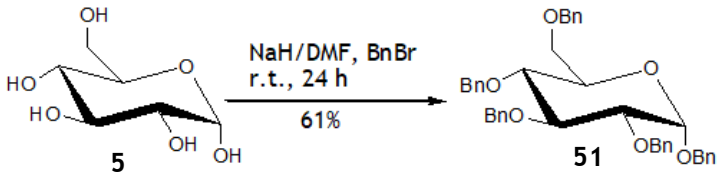
Chemical formula: $C_{16}H_{19}NO_6$

M.W.= 321.32 g/mol

To previously dried (with Na_2SO_4) benzaldehyde (13 mL), zinc chloride ($ZnCl_2$) (4 g, 29 mmol) was added, and the mixture was strongly stirred for 30 min (until the mixture turns compact-looking). Afterwards, compound 4**9** (4 g, 18 mmol) was added and the solution was stirred at room temperature for 4 h. Sequentially, a mixture of water/petroleum ether (W/PE, 1:1) (20 mL) was added and the precipitation of a white solid occurred. The precipitated solid was filtered, washed with a mixture of W/PE (1:1) (4x60 mL), and dried in an exicator overnight. Yield: 58%. Rf: n.a.

5.2.4. Preparation of 2,3,4-tri-O-benzyl-α-D-glucopyranoside (53)

5.2.4.1. 1,2,3,4,6-penta-O-benzyl-α-D-glucopyranoside (51)



5 **51**

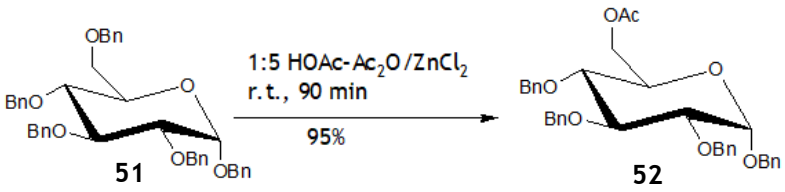
Scheme 30 – Schematic representation of the synthetic approach used to produce compound **51** from commercially available **5**. Yield: 61%

Chemical formula: $C_{41}H_{42}O_6$

M.W.= 630.77 g/mol

To a suspension of α-D-glucose **5** (1.1 g, 6.1 mmol) in DMF (30 mL), NaH (0.73 g of 60% dispersion in mineral oil, 18.3 mmol) was added at room temperature. The suspension was stirred for 30 min, then cooled in an ice bath. Then BnBr (2.5 mL, 21.35 mmol) was added dropwise over a 5-min period, and after 10 min the ice bath was removed. The suspension was stirred for 2.5 h, and then the last procedure was repeated with the addition of the same amount of NaH and BnBr. After another 2.5 h, NaH (0.48 g, 20.33 mmol) and BnBr (1.5 mL, 12.6 mmol) were consecutively added, and the mixture was let to react overnight. Afterwards, MeOH (3 mL) was added slowly, to neutralize the NaH, and DMF was removed under high vacuum (with a bath temperature of 55ºC, and a pressure of 25 mbar). The resulting residue was dissolved in dichloromethane (30 mL), washed with water and brine solution, dried with $MgSO_4$, filtered and evaporated under high vacuum, yielding a yellow oil. Through column chromatography (1:5 EA/nH), a white solid was obtained, and recrystallization from MeOH gave **51**, also as a white solid. Yield: 61%. Rf: 0.58 (1:5 EA/nH)

5.2.4.2. 6-O-acetyl-1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside (52)



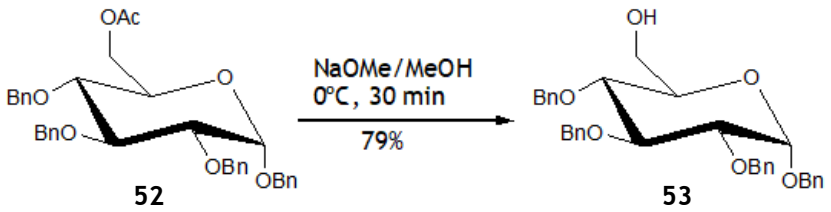
Scheme 31 – Schematic representation of the synthetic formation of compound **52**. Yield: 95%

Chemical formula: $C_{36}H_{38}O_7$

M.W.= 582.68 g/mol

To a mixture of glacial acetic acid and acetic anhydride (HOAc–Ac_2O, 1:5) (5 mL), freshly fused (under high vacuum and temperature) zinc chloride (0.495 g, 3.63 mmol) was added and the solution was cooled down to 0ºC. Then, a solution of **51** (0.5 g, 0.7 mmol) in 1:5 HOAc–Ac_2O (5 mL) was added dropwise. After stirring for 90 min at room temperature, 17 mL of ice water was added to the mixture, resulting in a light-brown precipitate. The suspension was filtered and washed with cold water. Through a chromatographic column (1:2 EA/nH) the compound **52** was obtained as a white solid. Yield: 95%. Rf: 0.62 (1:2 EA/nH)

5.2.4.3. 1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside (53)



Scheme 32 – Schematic representation of the synthetic path to produce compound **53**. Yield: 79%

Chemical formula: $C_{34}H_{36}O_6$

M.W.= 540.64 g/mol

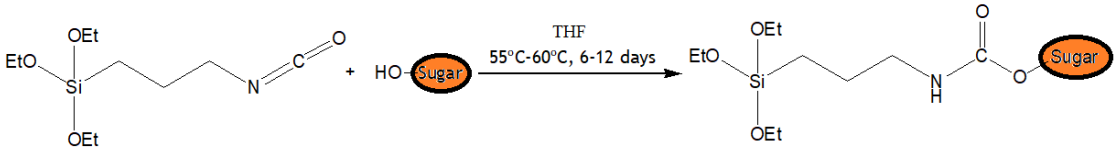
A solution of sodium methoxide (NaOMe) 0.025 M in methanol was prepared, and the compound **52** was added to the solution (50 mL). The suspension was stirred for 5 h and then poured into 200 mL of ice water and stirred for 30 min, maintaining the mixture at low temperature. The resulting precipitate was filtered and washed with a saturated solution of sodium carbonate ($NaHCO_3$) and water. The resulting solid was dried under high vacuum, and after recrystallization from ethanol, compound **53** resulted in cotton-like white needles. Yield: 79%. Rf: 0.8 (1:2 EA/nH)

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.28 (m, 20H), 4.86 (d, 1H), 4.82 (d, 1H), 4.77 (d, 1H), 4.68 (d, 1H), 4.65 (d, 1H), 4.62 (d, 1H), 4.52 (d, 1H), 3.68 (m, 1H), 3.63 (t, 1H), 3.51 (t, 1H), 3.45 (t, 1H), 3.35 (m, 1H);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 138.51, 138.00, 128.60, 128.29 (2C), 128.13, 128.02, 127.96, 127.93, 102.18, 84.16, 82.12, 74.99.

5.3. General procedure for synthesis of organosilane precursors

Via the previously functionalized glycosides, the organosilane precursors were synthesized through an urethane linkage between the carbohydrate moiety and the siliceous material, ICPTES **54**.

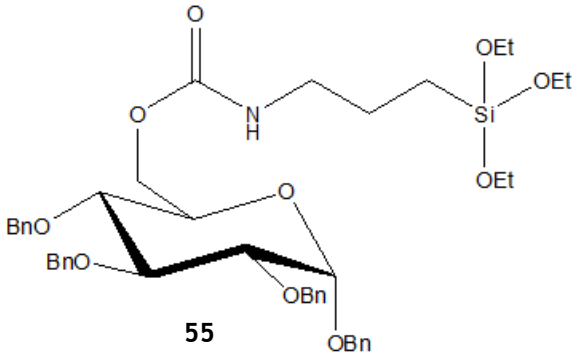


Scheme 33 – General procedure for the synthesis of organosilane precursors, through the functionalized carbohydrate-derivates **42**, **47**, **50**, **53**, **61**, and **62**, reaction with ICPTES **54**.

5.3.1. Mono-silylated precursors[76]

The glycoside (1 eq.) was dissolved in THF (minimum possible) in continuous stirring. Then, ICPTES **54** (1 eq.) was added to the solution. The flask was sealed and stirred for 6-12 days at 55ºC~60ºC. The reaction was controlled through FT-IR, and after the reaction terminus the solvent was removed under pression to give the corresponding monosilylated precursor (**55**-**58**, **60**). The final precursors were characterized through FT-IR, NMR (^{13}C and ^{1}H).

5.3.1.1. 6-O-methyl(3-(triethoxysilyl)propyl)carbamate-1,2,3,4-tetra-O-benzyl-α-D-glucopyranoside (55)



55

Figure 16 – Structure of precursor **55**. Yield: 92%

Chemical formula: $C_{44}H_{57}NO_{10}Si$

M.W.= 787.96 g/mol

The precursor **55** was prepared from glycoside **53** through an urethane linkage.

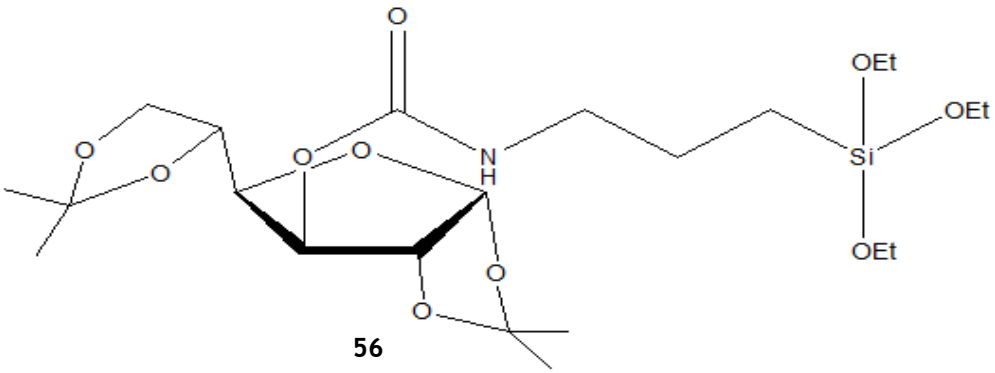
Reaction time: 8 days. **Yield:** 92%.

FT-IR (cm^{-1}): 2988 (C=C), 2940, 2836 (CH), 1757 (urethane), 1641 (urethane), 1043 (SiOEt), 961 (NCH_2), 774 (Si-O).

^{1}H NMR (400 MHz, $CDCl_3$) n.d.

^{13}C NMR (101 MHz, $CDCl_3$) δ 67.40 (C-5), 58.48 (CH_2CH_3), 43.41 (CH_2N), 23.11 (CH_2-CH_2), 18.16(CH_3-CH_2), 7.57 (CH_2-Si).

5.3.1.2. 3-O-Methyl(3-(triethoxysilyl) propyl) carbamate-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (56)



56

Figure 17 – Structure of precursor **56**. Yield: 93%

Chemical formula: $C_{22}H_{41}NO_{10}Si$

M.W.= 507.64 g/mol

The precursor **56** (figure 17) was prepared via commercially available compound **42**.

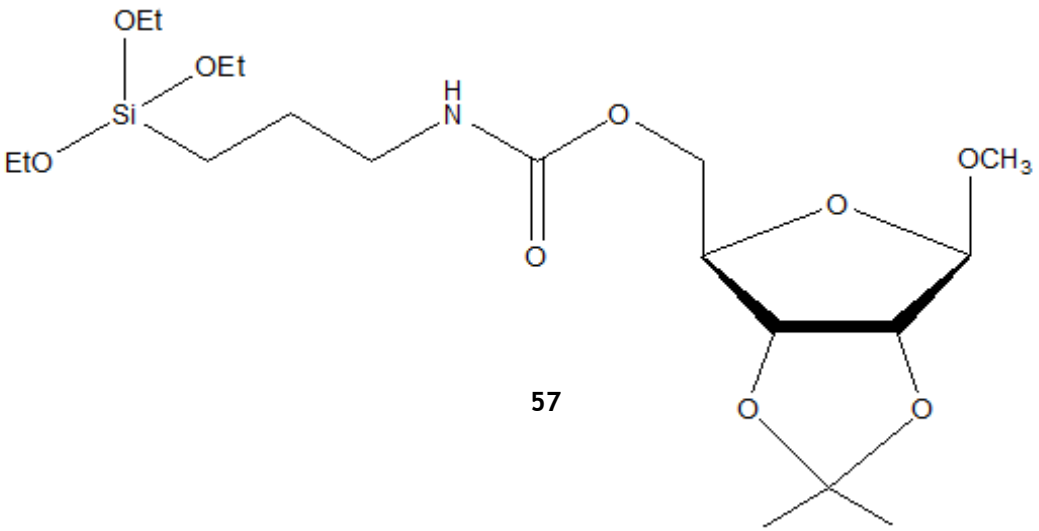
Reaction time: 12 days. **Yield:** 93%.

FT-IR (cm^{-1}): 3504 (NH), 1648 (urethane), 1069 (SiOEt).

^{1}H NMR (400 MHz, $CDCl_3$) n.d.

^{13}C NMR (101 MHz, $CDCl_3$) n.d.

5.3.1.3. 5-O-Methyl(3-(trietoxysilyl)propyl)carbamate-1-O-methoxy-2,3-isopropylidene ß-D-ribofuranose (57)



57

Figure 18 – Structure of precursor **57**. Yield: 68%

Chemical formula: $C_{19}H_{37}NO_9Si$

M.W.= 451.57 g/mol

The precursor **57** (figure 18) was prepared from glycoside **47**.

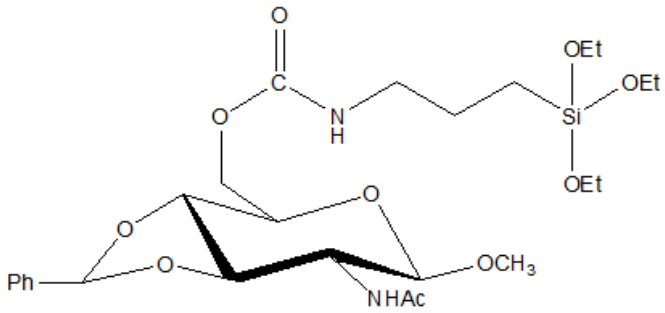
Reaction time: 6 days**. Yield**: 68%.

FT-IR (cm^{-1}): 3502 (NH), 1644 (urethane), 1069 (SiOEt), 956 (NCH_2).

^{1}H NMR (400 MHz, $CDCl_3$) n.d.

^{13}C NMR (101 MHz, $CDCl_3$) n.d.

5.3.1.4. 3-O-Methyl(3-(triethoxysilyl)propyl)carbamate-1-O-methoxy-2-N-acetamido-4,6-O-benzilidene-2-deoxy-D-glucopyranoside (58)



58

Figure 19 – Structure of precursor **58**. Yield: 89%

Chemical formula: $C_{26}H_{40}N_2O_{10}Si$

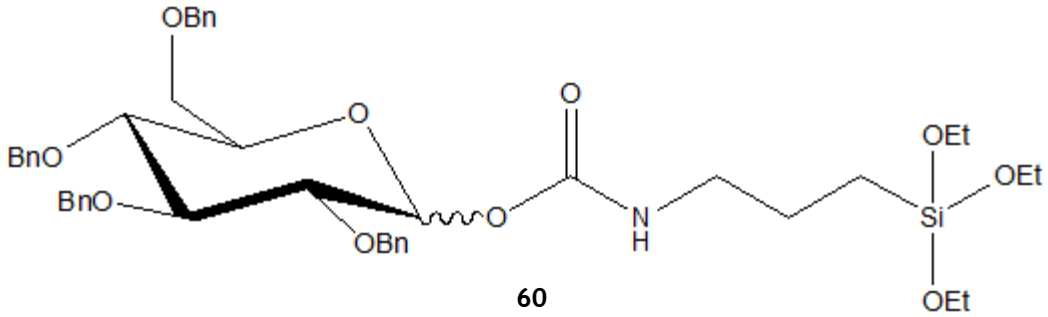
M.W.= 568.68 g/mol

The precursor **58** (figure 19) was prepared from glycoside **50**.

Reaction time: 12 days. **Yield:** 89%

FTIR (cm^{-1}): 1751 (urethane), 1658 (C=O), 1648 (urethane), 1243, 1068 (SiOEt), 925 (NCH_2) 777 (Si-O).

5.3.1.5. 1-O-Methyl(3-(triethoxysilyl)propyl)carbamate-2,3,4,6-O-benzyl-D-glucopyranoside (60)



60

Figure 20 – Structure of precursor **60**. Yield: 88%

Chemical formula: $C_{44}H_{57}NO_{10}Si$

M.W.= 787.96 g/mol

The precursor **60** was prepared from commercially available 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose **62**.

Reaction time: 12 days. **Yield:** 88%

FTIR (cm^{-1}): 3565 (NH), 1647 (urethane), 1289, 1069 (SiOEt), 910 (NCH_2), 772 (Si-O).

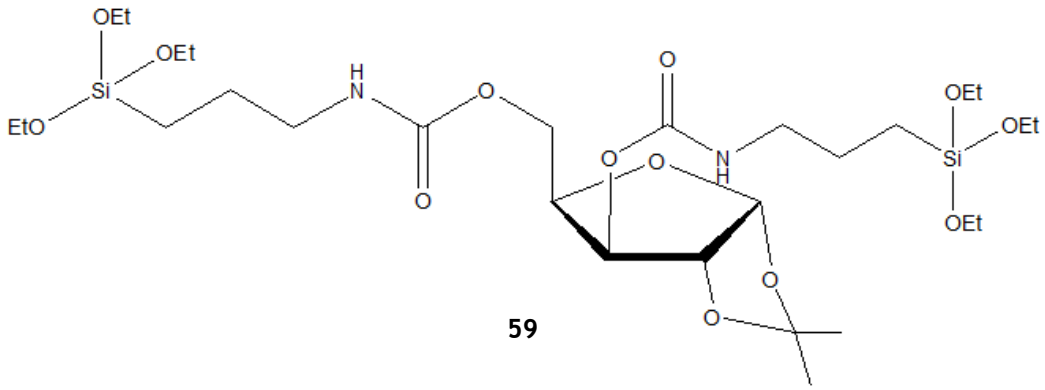
^{1}H NMR (400 MHz, DMSO) n.d.

^{13}C NMR (101 MHz, DMSO) δ 79.63 (C-6), 58.14 (CH_2CH_3), 40.62 (CH_2N), 23.11 (CH_2-CH_2), 18.65 (CH_2CH_3), 7.71 (CH_2-Si).

5.3.2. Bi-silylated precursors [76]

The glycoside (1 eq.) was dissolved in THF (minimum possible) in continuous stirring. Then, ICPTES **54** (2 eq.) was added to the solution. The flask was sealed and stirred for 7 days at 55ºC-60ºC. The reaction was controlled through FT-IR, and after the reaction terminus the solvent was removed under pression to give the corresponding monosilylated precursor (**59**). The final precursors were characterized through FT-IR, NMR (^{13}C and ^{1}H).

5.3.2.1. Bis(3,5-O-Methyl(3-(triethoxysilyl)propyl)carbamate-1,2-O-isopropylidene-α-D-glucofuranose (59)



59

Figure 21 – Structure of precursor **59**. Yield: 71%.

Chemical formula: $C_{27}H_{55}N_2O_{13}Si_2$

M.W.= 684.91 g/mol

Precursor **59** (figure 21) was prepared from commercially available 1,2-O-Isopropylidene-α-D-xylofuranose **61**.

Reaction time: 7 days. **Yield:** 71%

FTIR (cm^{-1}): 3392 (NH), 1723 (urethane), 1649 (urethane), 1245, 1070 (SiOEt), 957 (NCH_2) 777 (Si-O).

6. References

[1] A. K. Adak; B. Y. Li; C. C. Lin; “Advances in multifunctional glycosylated nanomaterials: Preparation and applications in glycoscience” *Carbohydr. 2015, 405, 2-12.*

[2] R. Sunasee; C. K. Adokoh; J. Darkwa; R. Narain; “Therapeutic potential of carbohydrate-based polymeric and nanoparticle systems” *Expert Opin. Drug Deliv.* 2014, 11 (6), 867-884.

[3] X. Han; Y. Zheng; C. J. Munro; Y. Ji; A. B. Braunschweig; “Carbohydrate nanotechnology: Hierarchical assembly using nature’s other information carrying biopolymers” *Curr. Opin. Biotechnol.* 2015, 34, 41-47.

[4] D. Sebasti; “Glyco-NanoParticles (GNPs) and their potential biomedical applications”, 2012.

[5] M. Ahmed; P. Wattanaarsakit; R. Narain; “Recent advances in the preparation of glycopolymer bioconjugates” *Eur. Polym. J.* 2013, 49 (10), 3010-3033.

[6] M. Marradi; F. Chiodo; I. García; S. Penadés; “Glyconanoparticles as multifunctional and multimodal carbohydrate systems” *Chem. Soc. Rev.* 2013, 42 (11), 4728-4745.

[7] John D. Robert; Marjorie; C. Caserio; "Basic Principles of Organic Chemistry" 1977.

[8] X. P. He; Y. L. Zeng; Y. Zang; J. Li; R. A. Field; G. R. Chen, “Carbohydrate CuAAC click chemistry for therapy and diagnosis” *Carbohydr. Res.* 2016, 429, 1-22.

[9] P. Lauren; “Molecular Biology of Cancer: Mechanisms, targets, and therapeutics” *Oxford Univ. Press*. 2012, 3, 1-342.

[10] J. Boultwood; C. Fidler; "*Molecular Analysis of Cancer" Humana Press,* 2001, 68.

[11] K. Cheung-Ong; G. Giaever; C. Nislow; “DNA-damaging agents in cancer chemotherapy: Serendipity and chemical biology” *Chem. Biol.* 2013, 20 (5), 648-659.

[12] C. A. Peptu; L. Ochiuz; L. Alupei; C. Peptu; M. Popa; “Carbohydrate based nanoparticles for drug delivery across biological barriers” *J. Biomed. Nanotechnol.* 2014, 10 (9), 2107-2148.

[13] Z. A. Alothman; “A Review: Fundamental Aspects of Silicate Mesoporous Materials” *Mater.* 2012, 5, 2874-2902.

[14] W. Li; D. Zhao; “An overview of the synthesis of ordered mesoporous materials” *Chem. Community*. 2013, 49, 943-946.

[15] W. J. Hunks; G. A. Ozin; G. Alan; “Challenges and advances in the chemistry of periodic mesoporous organosilicas (PMOs)” J. Mater. Chem., 2005, 15, 3716-3724.

[16] F. W. Lichtenthaler; “Carbohydrates : Occurrence , Structures and Chemistry,” Ullmann's Encycl. Ind. Chem. (Ed.), 2010.

[17] N. Sharon; “Conformational nomenclature of glycoproteins , glycopeptides and peptidoglycans” IUPAC-IUB (JCBN), 1988, 60 (9), 1389-1394.

[18] J. Lawandi; S. Rocheleau; N. Moitessier; “Regioselective acylation, alkylation, silylation and glycosylation of monosaccharides” *Tetrahedron*, 2016, 72 (41), 6283-6319.

[19] N. Thiebault; D. Lesur; P. Godé; V. Moreau; F. Djedaïni-Pilard; “Efficient regioselective chemical modifications of maltotriose: an easy access to oligosaccharidic scaffold” *Carbohydr. Res.*, 2008, 343 (16), 2719-2728.

[20] J. N. Chheda; Y. Román-Leshkov; J. A. Dumesic; “Production of 5-hydroxymethylfurfural and furfural by dehydration of biomass-derived mono- and poly-saccharides” *Green Chem.*, 2007, 9 (4), 342-350.

[21] A. V. Demchenko; “General Aspects of the Glycosidic Bond Formation” *Handb. Chem. Glycosylation Adv. Stereoselectivity Ther. Relev.*, 2008, 1–27.

[22] P. Shapley; “Oxidation Reactions of Sugars Oxidation States in Sugar Reactions” *Chem. (Easton)*, 2012.

[23] F. Lugemwa; K. Shaikh; E. Hochstedt; “Facile and Efficient Acetylation of Primary Alcohols and Phenols with Acetic Anhydride Catalyzed by Dried Sodium Bicarbonate” *Catalysts*, 2013, 3 (4), 954-965.

[24] B. C. Ranu; S. S. Dey; A. Hajra; “Highly efficient acylation of alcohols, amines and thiols under solvent-free and catalyst-free conditions” *Green Chem.*, 2003, 5 (1), 44-46.

[25] N. L. Benoiton; "*Chemistry of peptide Synthesis*" Taylor & Francis Group (CRC Press), 2005.

[26] A. Bugarin; B. T. Connell; “Acceleration of the Morita - Baylis - Hillman Reaction by a Simple Mixed Catalyst System” *J. Org. Chem.*, 2009, 3012 (10), 4638-4641.

[27] R. P. Wurz; “Chiral Dialkylaminopyridine Catalysts in Asymmetric Synthesis” Chem. Rev., 2007, 107 (12), 5570-5595.

[28] M. A. Brito-Arias; “Synthesis and Characterization of Glycosides: O-Glycoside Formation” *Springer, 2007, 68-137*.

[29] M. A. Brito-Arias; "*Synthesis and characterization of glycosides*" Spinger, 2007.

[30] J. Guo; X. S. Ye; “Protecting groups in carbohydrate chemistry: Influence on stereoselectivity of glycosylations” *Molecules*, 2010, 15 (10), 7235-7265.

[31] D. *Horton*; "*Advances in carbohydrate chemistry and biochemistry*" Academic press, 2001, 57.

[32] M. Miljkovic; "*Carbohydrates Synthesis, Mechanisms, and Stereoeletronic Effects" Springer, 2009*.

[33] Y. T. A. R. Kondo; "Selective Benzoylation of Methyl 6-Deoxy-α- and ß-D-glucopyranosides" Can. J. Chem., 1973, 51 (19), 6–8.

[34] H. S. Isbell; H. L. Frush; "Alpha and beta methyl lyxosides, mannosides, gulosides, and heptosides of like configuration" *J. Res. Natl. Bur. Stand. (U. S.)*, 1939, 24, 125.

[35] J. A. Oshiro; M. P. Abuçafy; E. B. Manaia; B. L. Da Silva; B. G. Chiari-Andréo; L. A. Chiavacci; "Drug delivery systems obtained from silica based organic-inorganic hybrids" *Polymers (Basel).*, 2016, 8 (4).

[36] L. Klein; M. Aparicio; A. Jitianu; "*Handbook of Sol-Gel Science and Technology*" Springer, 2018, (2).

[37] R. Narain; "Engineered *Carbohydrate-Based Materials for Biomedical Applications: Polymers, Surfaces, Dendrimers, Nanoparticles, and Hydrogels*" Willey, 2011, (1).

[38] Y. Wang; S. Quan; P. Kumar; R. Narain; "Glycopolymer Code: Synthesis of Glycopolymers and their Applications" The Royal Soc. Chem., 2015, 15, 196–220.

[39] A. Salama; "Polysaccharides/silica hybrid materials : New perspectives for sustainable raw materials" *J. Carbohydr. Chem.*, 2016, 35 (3), 131–149.

[40] W. Li; D. Zhao; "An overview of the synthesis of ordered mesoporous materials" Chem. Commun., 2013, 49, 943-946.

[41] W. Wang; "Periodic Mesoporous Organosilica and Silica" Dep. Chem (Toronto), 2011.

[42] M. Mart; Y. K. Gun; M. Vallet-Regi; "Mesoporous Silica Materials as Drug Delivery: "The Nightmare" of Bacterial Infection" *Pharmaceutics*, 2018, 10 (4), 279.

[43] A. Ra; R. P. Real; J. Pe; "A New Property of MCM-41 : Drug Delivery System" Chem. Mater., 2001, 13 (2), 308-311.

[44] N. Mizoshita; T. Tani; S. Inagaki; "Hybrid materials themed issue: Synthesis, properties and applications of periodic mesoporous organosilicas prepared from bridged organosilane precursors w" Chem. Soc. Rev, 2011, 40, 789-800.

[45] C. T. Kresge; W. J. Roth; "The discovery of mesoporous molecular sieves from the twenty year perspective" *Chem. Soc. Rev.*, 2013, 42, 3663–3670.

[46] F. Hoffmann; M. Cornelius; J. Morell; M. Fröba; "Silica-Based Mesoporous Organic – Inorganic Hybrid Materials" Angew. Chem., 2006, 45, 3216-3251.

[47] J. G. Croissant; M. Wong; C. Man; N. M. Khashab; "Organosilica Hybrid Nanomaterials with High Organic Content: Synthesis andapplications of Silsesquioxanes" Nanoscale., 2015, 00, 1-3.

[48] J. H. Jung; S. S. Lee; V. S. Shinkai; R. Iwaura; T. Shimizu; "Novel Silica Nanotubes

Using a Library of Carbohydrate Gel Assemblies as Templates for Sol-Gel Transcription in Binary Systems" Bull. Korean Chem. Soc., 2004, 25 (1), 4–9.

[49] S. Inagaki; S. Guan; Y. Fukushima; T. Ohsuna; "Novel Mesoporous Materials with a Uniform Distribution of Organic Groups and Inorganic Oxide in Their Frameworks" J.Am. Chem. Soc. 1999, 121, 9611-9614.

[50] M. A. Aegerter; M. Prassas; "*Advances in Sol-Gel Derived Materials and Technologies*" *Springer*, 2011.

[51] C. J. Brinker; G. W. Scherer "Sol-Gel Science: The physics and chemistry of sol-gel processing" Acad. press, 2013.

[52] A. Hou; Y. Shi; Y. Yu; "Preparation of the cellulose/silica hybrid containing cationic group by sol–gel crosslinking process and its dyeing properties" *Carbohydr. Polym.*, 2009, 77 (2), 201-205.

[53] J. M. Chem, "A new approach to synthesis of periodic mesoporous organosilicas: taking advantage of self-assembly and reactivity of organic precursors" J. Mater. Chem., 2011, 21, 6389-6394.

[54] Y. Chen; P. Xu; H. Chen; Y. Li; W. Bu; Z. Shu; Y. Li; J. Zhang, L. Zhang; L. Pan; X. Cui; Z. Hua; J. Wang; L. Zhang; J. Shi; "Colloidal HPMO Nanoparticles : Silica-Etching Chemistry Tailoring , Topological Transformation , and Nano- Biomedical Applications" Adv. Mat., 2013, 25, 3100–3105.

[55] J. L. Blin; M. Impéror-Clerc; "Mechanism of self-assembly in the synthesis of silica mesoporous materials: *in* situ studies by X-ray and neutron scattering" Chem. Soc. Rev., 2013, 42, 4071–4082.

[56] A. Paula, A. Carvalho, B. G. Soares, and S. Livi, "Organically modified silica (ORMOSIL) bearing imidazolium – Based ionic liquid prepared by hydrolysis / co-condensation of silane precursors : Synthesis , characterization and use in epoxy networks," *Eur. Polym. J.*, vol. 83, pp. 311–322, 2016.

[57] E. G. Barrera; P. R. Livotto; J. H. Z. Santos; "Hybrid silica bearing different organosilanes produced by the modified Stöber method" *Powder Technol.*, 2016, 301, 486–492.

[58] D. R. Dunphy; B. Smarsly; C. J. Brinker; "The Supramolecular Chemistry of Organic-Inorganic Hybrid materials: Control of Morphology in Mesoporous and Hybrid Materials" Wiley, 2010, 531–545.

[59] A. Chemtob; L. Ni; C. Croutxé-barghorn; B. Boury; "Ordered Hybrids from Template-Free Organosilane Self-Assembly" Chem. Eur. J., 2014, 20, 1790–1806.

[60] R. Sunasee; R. Narain; "Glycopolymers and Glyco-nanoparticles in Biomolecular Recognition Processes and Vaccine Development" *Macromol. Biosci.*, 2013, 13 (1), 9–27.

[61] F. Santoyo-Gonzalez; F. Hernandez-Mateo; “Silica-based clicked hybrid glycomaterials” *Chem. Soc. Rev.*, 2009, 38 (12), 3449–3462.

[62] R. Narain; Y. Wang; M. Ahmed; B. F. L. Lai; J. N. Kizhakkedathu; “Blood components interactions to ionic and nonionic glyconanogels” *Biomacromolecules*, 2015, 16 (9), 2990–2997.

[63] Y. Kotsuchibashi; “Spatiotemporal control of synergistic gel disintegration consisting of boroxole- and glyco-based polymers via photoinduced proton transfer” *J. Phys. Chem.*, 2015, 119 (6), 2323–2329.

[64] K. Van der Heyden; K. Babooram; M. Ahmed; R. Narain; “Protein encapsulation and release from degradable sugar based hydrogels” *Eur. Polym. J.*, 2009, 45 (6), 1689-1697.

[65] N. Idota; M. Ebara; Y. Kotsuchibashi; R. Narain; T. Aoyagi; “Novel temperature-responsive polymer brushes with carbohydrate residues facilitate selective adhesion and collection of hepatocytes” *Sci. Technol. Adv. Mater.*, 2012, 13 (6).

[66] M. Ahmed; R. Narain; “The effect of polymer architecture, composition, and molecular weight on the properties of glycopolymer-based non-viral gene delivery systems” *Biomaterials*, 2011, 32 (22), 5279–5290.

[67] I. Fokt; S. Skora; C. Conrad; T. Madden; M. Emmett; W. Priebe; “D-Glucose and d-mannose-based metabolic probes: Synthesis of specifically deuterated d-glucose, d-mannose, and 2-deoxy-d-glucose” *Carbohydr. Res.*, 2013, 368, 111–119.

[68] S. S. Syamchand; G. Sony; “Multifunctional hydroxyapatite nanoparticles for drug delivery and multimodal molecular imaging” *Microchim. Acta*, 2015, 182 (9–10), 1567–1589.

[69] W. Lu; L. Navidpour; S. D. Taylor; “An expedient synthesis of benzyl 2,3,4-tri-O-benzyl-ß-D- glucopyranoside and benzyl 2,3,4-tri-O-benzyl-ß-D-mannopyranoside” *Carbohydr. Res.*, 2005, 340 (6), 1213–1217.

[70] A. P. Rauter; J. A. Figueiredo; I. M. Ismael; “Synthesis of pseudo-c-nucleosides” Carb. Res., 1989, 188, 19–24.

[71] J. Schleiss; P. Rollin; A. Tatibou; “Palladium-Catalyzed Coupling Reactions of Thioimidate N-Oxides : Access to α-Alkenyl- and α-Aryl-Functionalized Cyclic Nitrones” Angew. Chem. Int. Ed., 2010, 49, 577–580.

[72] A. K. Ghosh; W. Liu; “Total Synthesis of (+)-Sinefungin” J. Org. Chem., 1996, 61, 6175-6182.

[73] C. S. Hudso; S. M. Canto; “Advances in Carbohydrate Chemistry” *Acad. Press INC., 1951, 6, 457.*

[74] “Omicron” 46617.

[75] D. P. G. Emmerson; P. Hems; B. G. Davis; “Carbohydrate-derived aminoalcohol ligands for asymmetric Reformatsky reactions” Tetrahedron: Asymmetry, 2005, 16, 213–221.

[76] D. B. Berkowitz; M. Bose; T. J. Pfannenstiel; T. Doukov; “α-Fluorinated Phosphonates as Substrate Mimics for Glucose 6-Phosphate Dehydrogenase : the CHF Stereochemistry Matters” J. Org. Chem., 2000, 65 (2), 4498–4508.

[77] V. D. Z. Bermudez; M. C. Gon; L. D. Carlos; “Coordination of in Mono-Urethane Cross-Linked Hybrid Xerogels” Ionics, 1999, 5, 251–252.

[78] W. L. F. Armarego; C. Chai; "*Purification of laboratory chemicals*" Butterworth-Heinemann (Elsevier), 2009, 6, 752.

7. Attachments

Part of the present work was presented in a scientific meeting as:

- "Hybrid mesoporous organossilicas functionalized with carbohydrates"-R. G. Pacheco, A. Marta, S. C. Nunes, P. Almeida, S. Silvestre, J. A. Figueiredo, M. I. Ismael, in: V Ciclo de Conferências da Faculdade de Ciências, in UBI, Covilhã, at 21st january of 2017, as a poster communication.

Funcionalização de híbridos mesoporosos de organossílica com hidratos de carbono

A. Marta[1,2], R. G. Pacheco[1,2], S. C. Nunes,[2,3,4], P. Almeida[2,3], S. Silvestre[3], J. A. Figueiredo[1,2], M. I. Ismael[1,2*]

[1]*FibEnTech, Universidade da Beira Interior, 6201-001 Covilhã, Portugal*

[2]*Departamento de Química, Universidade da Beira Interior, 6201-001 Covilhã, Portugal*

[3]*CICS-Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, 6201-001 Covilhã, Portugal*

[4]*Departamento de Química, Universidade de Trás-os-Montes e Alto Douro, 5000-001 Vila Real, Portugal*

**e-mail: iismael@ubi.pt*

Nas últimas décadas, os avanços da nanotecnologia permitiram o desenvolvimento de novos nanotransportadores na área da química medicinal [1]. Estes nanosistemas permitem superar alguns problemas dos sistemas atuais de entrega de fármacos, nomeadamente fraca estabilidade, elevada toxicidade, tempos de meia vida curtos, tendências de agregação reduzida travessia das barreiras biológicas, como a barreira hematoencefálica. Além disso, estes avanços permitiram a abertura de diversos campos na área de química medicinal, possibilitando o desenvolvimento de novas abordagens [2] para o tratamento de doenças, como o cancro, permitindo a libertação controlada dos fármacos, resultando uma melhor eficiência terapêutica [2-3]. De entre os nanomateriais, os híbridos mesoporosos de organossílica [4] apresentam-se como bons candidatos para aplicações nano-médicas, devido às suas características únicas, como a distribuição densa e uniforme de grupos orgânicos covalentemente ligados à matriz de sílica, área de superfície específica elevada, grande volume de poros e sua dimensão controlável, bem como uma morfologia de poro variável, permitindo, deste modo, ajustar a interação entre a estrutura alvo e a molécula desejada [5]. Adicionalmente, estes materiais têm uma baixa reatividade com compostos quelantes presentes no organismo, uma elevada estabilidade química e permitem a modificação da sua superfície [5], bem como a sua endocitose seletiva através do efeito de permeabilidade e retenção e biocompatibilidade [6,7]. A funcionalização dos híbridos mesoporosos com precursores mono-organossilanos, permite melhorar as suas propriedades mecânicas, bem como a sua permeação membranar e distribuição e, assim, aumentar a sua aplicabilidade. Têm sido realizados muitos estudos conducentes a uma maior variedade deste tipo de nanotransportadores [4], incluindo a sua funcionalização com hidratos de carbono, considerados atualmente os produtos naturais mais versáteis, principalmente na área farmacêutica [8]. De facto, a importância dos hidratos de carbono e seus derivados já foi reconhecida em muitos processos biológicos e, por este motivo, observou-se um elevado desenvolvimento na química medicinal dos hidratos de carbono ao longo dos anos [9].

Desta forma, o objetivo deste trabalho foi a síntese de precursores mono-organossilanos com derivados de hidratos de carbono. O uso dos hidratos de carbono na formação dos precursores é um trabalho inovador, esperando-se que muitas das propriedades desejáveis num nanotransportador, como a biodegradabilidade, boa solubilidade, e a possibilidade de formação de conjugados com um grande número de compostos, sejam atingidos e, como tal, aumentem a sua aplicabilidade na área da biomedicina. Após a devida funcionalização dos híbridos mesoporosos de organossílica com os precursores anteriores, espera-se conseguir uma posterior libertação mais controlada dos fármacos inseridos na sua matriz, através de estímulos físicos ou químicos [10]. A primeira parte do estudo consistiu na síntese dos componentes orgânicos, sendo que alguns derivados foram sintetizados a partir da D-glucose, D-ribose, D-xilose e metil-α-D-glucopiranosido. Posteriormente, foram preparados os precursores mono-organossilanos, através da ligação entre os derivados de hidratos de carbono e o (3-isocianatopropil) trietoxisilano (ICPTES). Por fim, os precursores anteriormente descritos serão utilizados na síntese dos híbridos mesoporosos de organossílica, permitindo o encapsulamento de potenciais novos fármacos, ou de fármacos já existentes no mercado, melhorando a sua eficiência e seletividade.

Referencias

[1] I. I. Slowing, J. L. Vivero-Escoto, C.-W. Wu, and V. S.-Y. Lin, Adv. Drug Deliv. Rev., vol. 60, pp. 1278–1288, (2008).
[2] L. Yan and X. Chen, Nanomaterials for Drug Delivery, Second Edi. Elsevier Ltd, (2013).
[3] Giret S, Théron C, Gallud A, et al. A designed 5-fluorouracil-based bridged silsesquioxane as an autonomous acid-triggered drug-delivery system. *Chem - A Eur J*. 2013;19(38):12806-12814. doi:10.1002/chem.201301081.
[4] M. Moritz and M. Geszke-Moritz, Mater. Sci. Eng. C, vol. 49, pp. 114–151, (2015).
[5] S. C. Nunes, et al, "Ordered Mesoporous Sol-Gel Materials", In The Sol-Gel Handbook, Vol. 1: Synthesis and Shaping, D. Levy and M. Zayat Eds., Wiley-VCH, Weinheim, 2015 ISBN 978-3-527-33486-5 (INVITED).
[6] S. C. Nunes, P. Almeida, V. de Zea Bermudez "Ordered Mesoporous Sol-Gel Materials" In The Sol-Gel Handbook, Volume 1: Synthesis and Shaping, D. Levy and M. Zayat Eds., Wiley-VCH, Weinheim, 2015 ISBN 978-3-527-33486-5
[7] Carbonaro CM, Anedda A, Grandi S, Magistris A. Hybrid materials for solid-state dye laser applications. *J Phys Chem B*. 2006;110(26):12932-12937. doi:10.1021/jp056448+.
[8] R. V Stick, Carbohydrates: The Sweet Molecules of Life, Academic, (2001).
[9] P. Newell, Polit. Geogr., vol. 17, no. 3, pp. 370–371, (1998).
[10] Ciriminna R, Fidalgo A, Pandarus V, Béland F, Ilharco LM, Pagliaro M. The sol-gel route to advanced silica-based materials and recent applications. *Chem Rev*. 2013;113(8):6592-6620. doi:10.1021/cr300399c.