Synthetic Polymers from Sugar-Based Monomers

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Contents

1. Introduction

The low biodegradability of petroleum-based polymers and the exhaustible nature of the oil reserves have intensified interest in natural renewing resources for the chemical synthesis of polymers. Polymers based on naturally occurring products are promising new materials, with novel technical potential and enhanced properties with regard to biocompatibility and biodegradability. Consequently, the production of environmentally friendly and sustainable materials and the development of biomass-based polymers constitute a steadily growing field of attention.[1] Of the various renewable resources, carbohydrates are particularly convenient raw materials as they are inexpensive, readily available, and present considerable stereochemical diversity.

Therefore, an interesting approach to the synthesis of macromolecular materials is the development of novel polymers having characteristics comparable to those of the industrial polymers, but synthesized from sugar-based monomers derived from renewable raw materials. Furthermore, the synthetic polymers obtained would be able to mimic the structure and function of biological polymers.[2]

The incorporation of sugar-derived units into traditional step-growth polymers such as polyamides, polyesters, and polyurethanes is potentially a method of interest for preparing novel biodegradable and biocompatible materials for application in biomedical products and other sectors of greater consumption, such as foodstuff packaging.[3,4] The main reasons for this interest are the great abundance of natural sugars, their structural diversity, their multiple functionalities, their innocuousness for human health, and the hydrophilic nature of the resulting materials, resulting in enhanced hydrolytic degradability.[5] Moreover, their environmental impact is less than that of the classic polymers.[2] However, although polymers have been synthesized using sugar-derived monomers with free hydroxyl groups,[6-8] most syntheses of high-molecular-weight linear polymers involve derivatives having the hydroxyl groups appropriately protected.[9]

Published reviews on synthetic carbohydrate-based polymers and glycopolymers[10-15] refer mainly to poly(vinylsaccharide)s and other conventional functionalized polymers having sugars pendant from the main chain of the polymer. The present review concerns polymers having the sugar units incorporated into the main chain. This topic has been reviewed before,[9,16-22] but with the interest in this kind of carbohydrate-based polymer steadily rising, recent years have seen numerous papers on the subject. Thus, the following sections report on the syntheses of this type of sugar-based polymer that have been published mainly during the past decade. Patents have not been included so as to make the reference list more concise.

2. Carbohydrate-based monomers

Because of the sugar multifunctionalities, and in order to avoid having to control the reactivity of various different functional groups, selective protection-deprotection chemistry is usually required in the preparation of accurate sugar-based-monomers. In this section we include the monosaccharide-based monomers more frequently used in the preparation of polymers having the sugar units incorporated into the main chain.

2.1. Alditols

Alditols and anhydroalditols have been used as monomers to synthesize or modify polymers (Figure 1). The three stereoisomeric 1,4:3,6-dianhydroalditol monomers having D-*gluco*, D-*manno*, and L-*ido* configurations are designated isosorbide (**1**), isomannide (**2**), and isoidide (**3**), respectively. The bicyclic monomer **4**, having L-*ido* configuration was prepared from isomannide (**2**). All of them have been used to synthesize various kinds of step-growth polymer. The *O*-alkyl anhydro erythritol derivatives of **5** were used as monomers in ring-opening polymerizations (ROP). The *O*-protected alditol derivatives **6**-**29** have been used to prepare novel polymers, and also to carry out chemical modifications of other well-known materials.

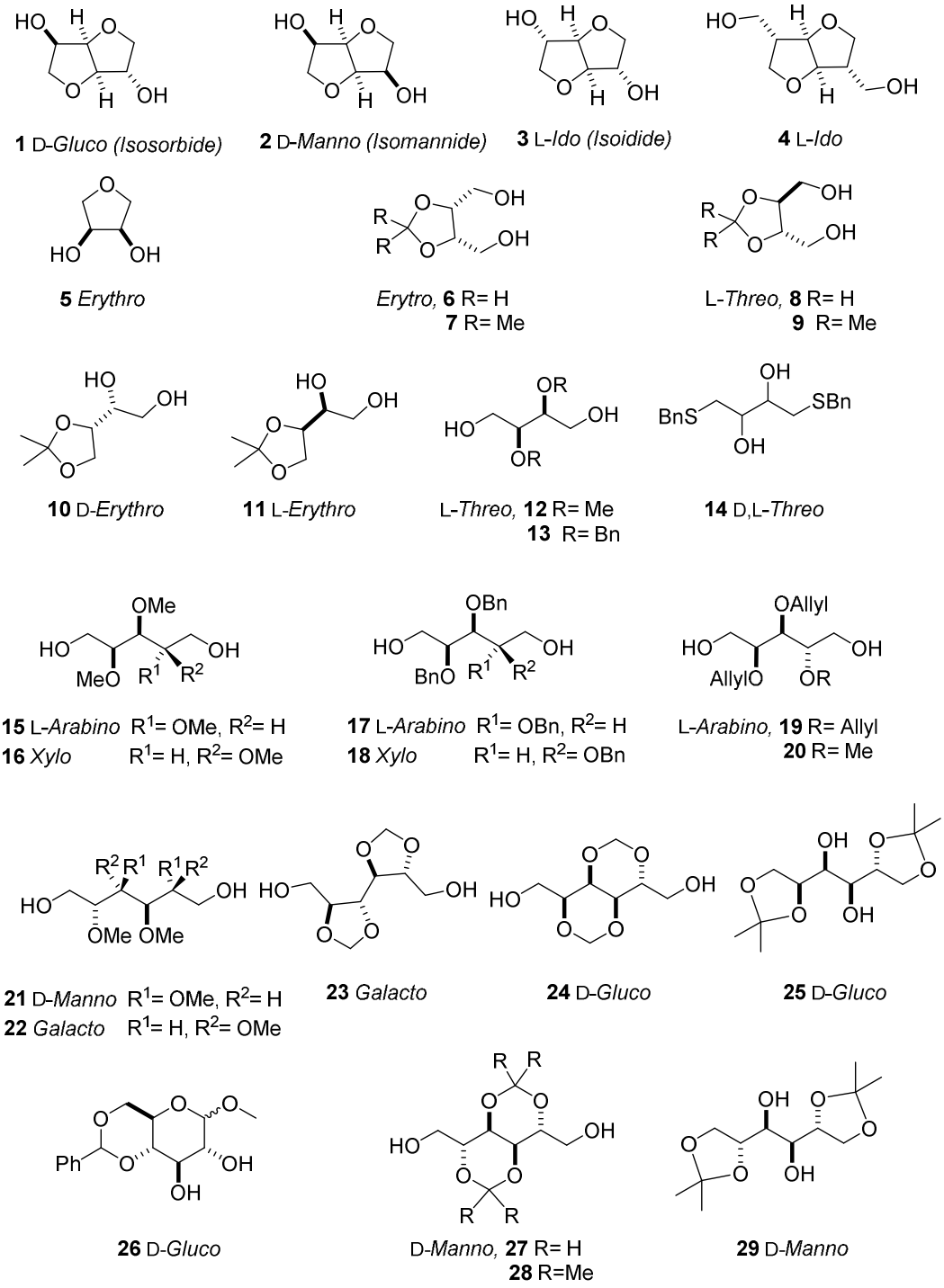


Figure 1. Alditol monomers

2.2. Aldonic acids and lactones

Various aldonic acids, aldonolactones, and alduronolactones (**30**-**41**) are useful monomers used in polycondensation and ring-opening polymerization (ROP) reactions (Figure 2).

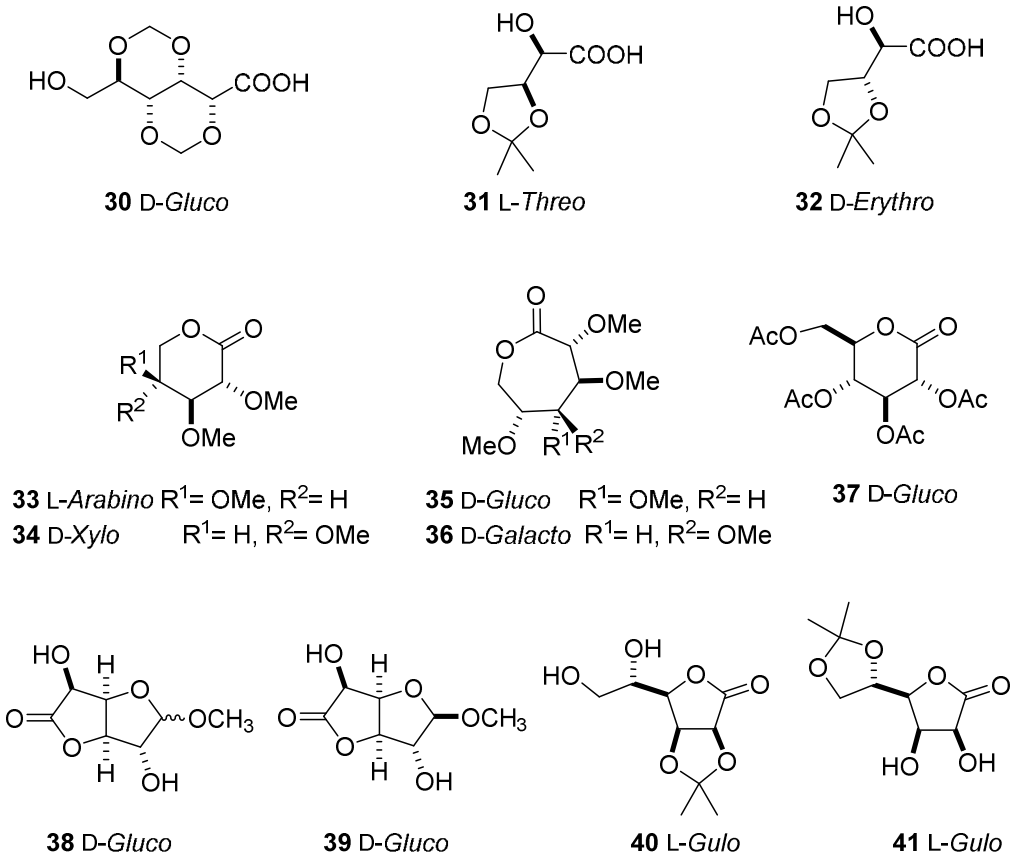


Figure 2. Aldonic and alduronic acids and lactone monomers

2.3. Aldaric acids

Aldaric acids **42**-**61** (Figure 3) have been extensively used in polycondensation reactions, mainly in the preparation of polyamides and polyesters.

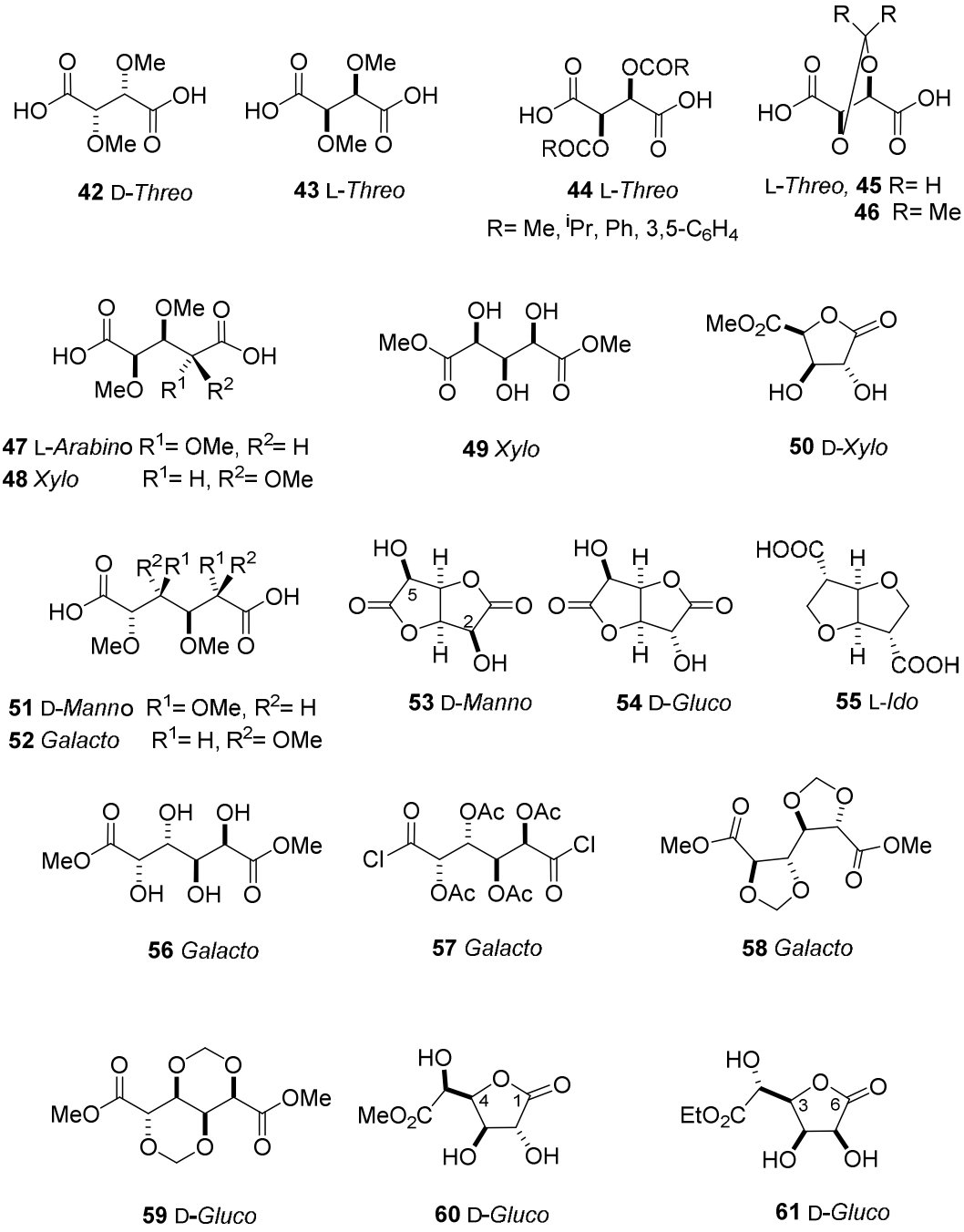


Figure 3. Aldaric acid monomers

2.4. Aminosugars

Amino- and diaminoalditols, aminoaldonic acids, diaminoanhydroalditols, and several other amino-sugar derivatives (**62**-**87**) have been widely used to prepare polyamides, polyurethanes and polyureas (Figure 4).

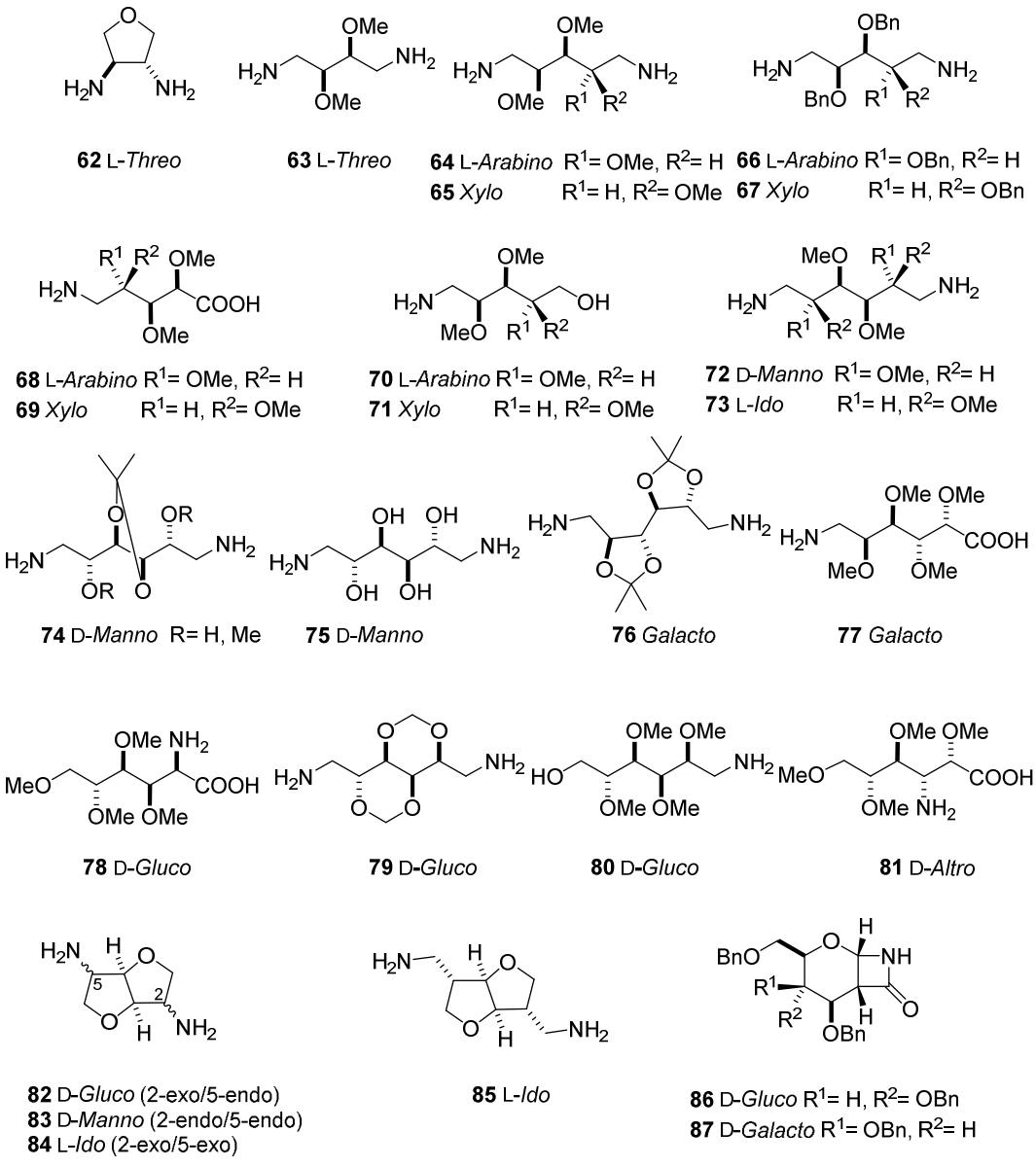


Figure 4. Aminosugar monomers

3. Polyesters

Carbohydrate-based polyesters are usually obtained by the polycondensation reaction of alditols and aldaric acid esters. Minor scope has been achieved by ring-opening polymerization (ROP) of carbohydrate lactones. Most aliphatic polyesters have been shown to be biodegradable, but they often lack good thermal and mechanical properties. Nevertheless, the use of certain carbohydrate-based monomers is leading to new materials with improved properties, which in addition are more hydrophilic and present enhanced biodegradability.

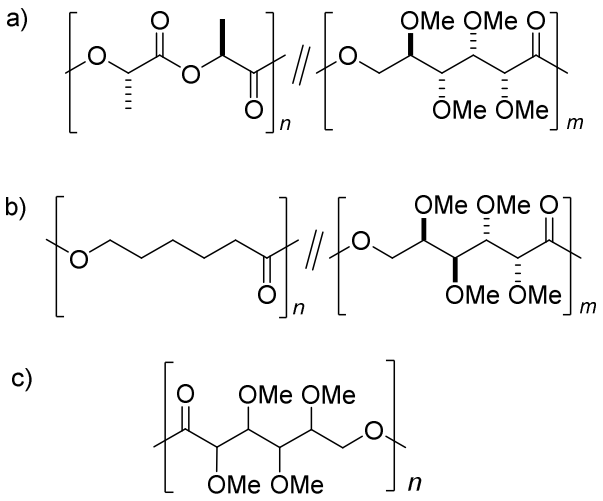
3.1. Aliphatic polyesters

Depending on the structural composition, there are two types of polyester: poly(hydroxy acid)s, which are obtained by ROP of lactones or by polycondensation reactions of hydroxy acids, and poly(alkylene dicarboxylate)s, synthesized by polycondensation reactions of diols with dicarboxylic acids. Monomers of this nature can be found within the carbohydrate framework; thus monosaccharides such as alditols, dianhydroalditols, lactones, aldonic acids, and aldaric acids (Figures 1-3) have been shown to be excellent candidates for the preparation of aliphatic polyesters.

3.1.1. From aldonic acids and lactones. Polyesterification reactions from aldonic acids have scarcely been explored. Early work by Drew and Haworth[23] mentioned the formation of oligomeric material from the trimethyl-L-arabinono-1,5-lactone (**33**), and Mehltretter and Mellies[24] described low-molecular-weight polyesters from 2,4;3,5-di-*O*-methylene-D-gluconic acid (**30**).

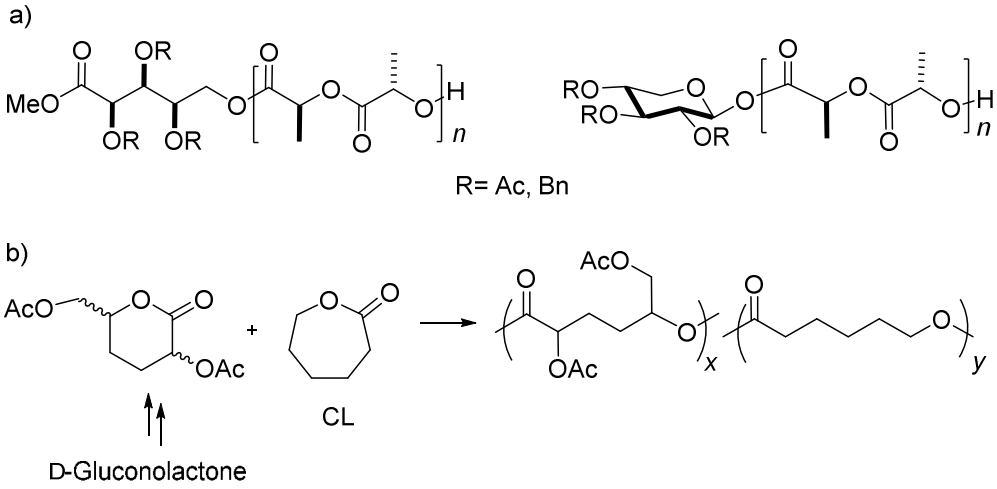
Galbis *et al.* reported a facile preparation of 1,5-lactones **33** and **34**, and 1,6-lactone **35**, susceptible to ROP.[25,26] Homopolymerization of these lactones was unsuccessful, while copolymerization of 2,3,4,5-tetra-*O*-methyl-D-glucono-1,6-lactone (**35**) with L-lactide, by bulk ROP (Scheme 1a), incorporated a maximum of 2.2% of the carbohydrate

monomer.[26] Similar results were obtained[27] from the tetramethyl-D-galactono-1,6-lactone (**36**) with ε-caprolactone (Scheme 1b). Guan *et al.* were successful in living ROP of racemic **36**, catalyzed by yttrium(III) isopropoxide, to develop degradable protein-resistant polyesters (Scheme 1c).[28]



Scheme 1. ROP of lactones: a) 35; b) 36; c) racemic 36

Williams *et al*. reported the synthesis of functionalized oligo- and copolyesters from carbohydrate lactones,[29] and lactide polymerization co-initiated by carbohydrate esters and pyranoses;[30-32] some copolymers of ε-caprolactone were scaffolds for tissue engineering (Scheme 2).[33]

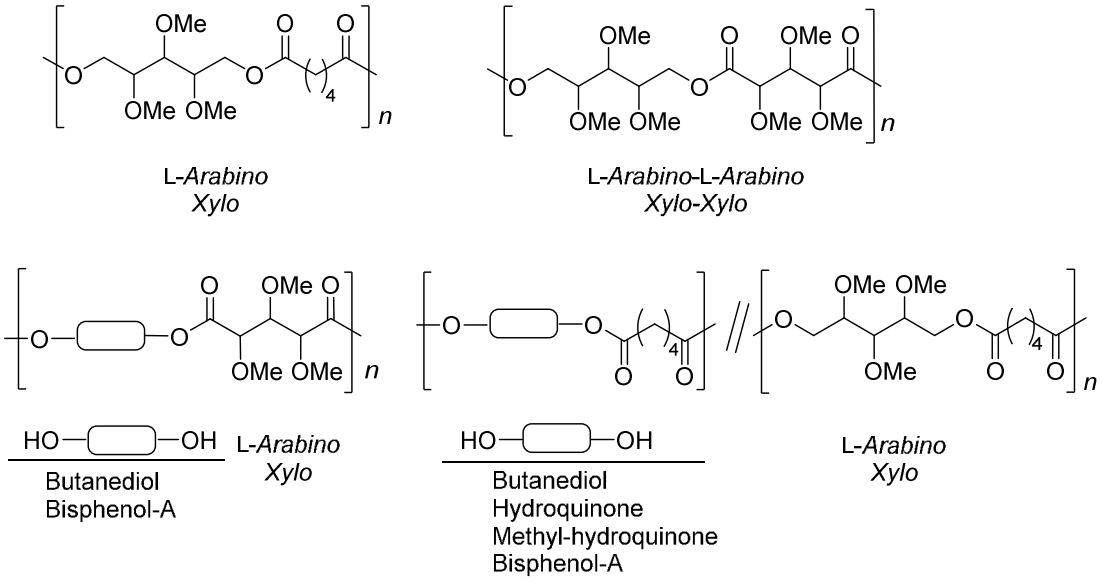


Scheme 2. a) Lactide polymerization co-initiated by carbohydrates. b) Copolymerization of lactone derived from D-gluconolactone and ε-caprolactone (CL)

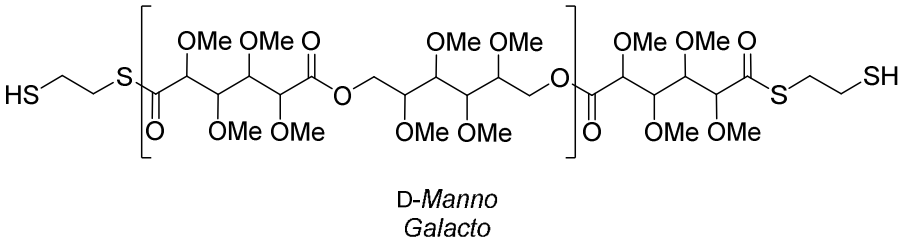
Polymerization biocatalyzed by *Candida antarctica* lipase B (Novozyme® 435, CALB) allowed the synthesis of new oligomeric compounds with ring-opened gluconolactone units included in the oligomeric chains, without previous derivatization of the sugar or activation of the acid monomer.[34]

3.1.2. From alditols and aldaric acids. Alditols are polyols extensively present in nature and which can also be obtained by reduction of aldoses and ketoses. Threitols, pentitols, and hexitols have been used to prepare polyesters, the secondary hydroxyl groups being mainly protected as methyl, benzyl, or acetal ethers. Galbis *et al.* described a variety of carbohydrate-based linear polyesters of the poly(alkylene dicarboxylate) type (Scheme 3) by the polycondensation reactions of pentitols 2,3,4-tri-*O*-methyl-L-arabinitol (**15**) and 2,3,4-tri-*O*-methyl-xylitol (**16**), and pentaric acids 2,3,4-tri-*O*-methyl-L-arabinaric acid (**47**) and 2,3,4-tri-*O*-methyl-xylaric acid (**48**); 1,4-butanediol and adipic acid were also used as comonomers.[35,36] These polymerizations were conducted in bulk or in solution, and copolyesters of the poly(alkylene-co-arylene dicarboxylate) type were also obtained using bisphenols as comonomers. Guan prepared

similar polyesters based in galactitol and D-mannitol but functionalized at their chain ends with ethane dithiol, [37] for use as protein-resistant biomaterials (Scheme 4).



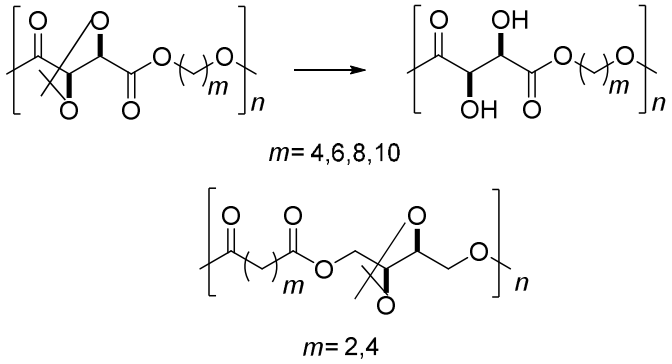
Scheme 3. Polyesters based on pentitols and pentaric acids



Scheme 4. Protein-resistant polyesters based on galactitol and D-mannitol

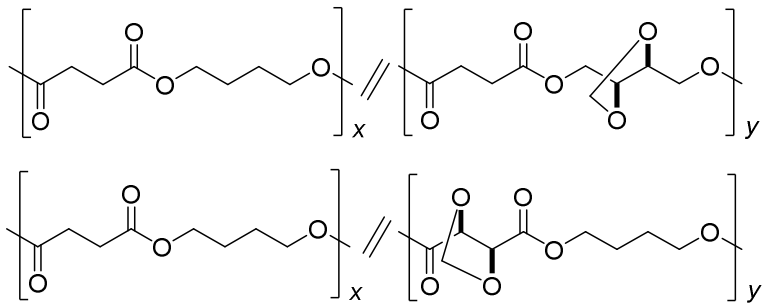
Tartaric acid has also attracted a great deal of interest as a substrate for the synthesis of functional polymers based on carbohydrates; for example, L-tartaric acid is a natural product mainly obtained from a large variety of fruits. Lately aliphatic copolyesters based on L-tartaric acid and easily modified post-polymerization have been synthesized and characterized. Jacob *et al.* prepared two different polyesters— the first[38] by polycondensation of dimethyl ester of 2,3-*O*-isopropylidene-L-tartaric acid (**46**) with

alkanediols, and the second[39] by reaction of 2,3-*O*-isopropylidene-L-threitol (**9**) with diacid chlorides (Scheme 5). Acid-catalyzed deprotection of the isopropylidene groups gave well-defined polyesters having pendant hydroxyl functional groups regularly distributed along the polymer chain.



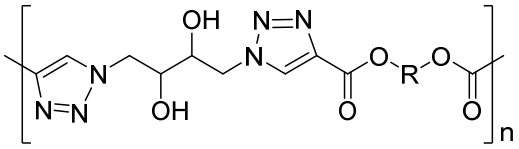
Scheme 5. Polyesters based on L-tartaric acid derivatives

The physical properties of poly(butylene succinate) (PBS) were modified by the insertion of monocyclic acetals 2,3-di-*O*-methylene-L-threitol (**8**) and dimethyl ester of 2,3-di-*O*-methylene-L-tartaric acid (**45**) over the whole range of compositions,[40] and the corresponding copolymers had a random chemical microstructure (Scheme 6). Some of them showed higher glass transition temperature (Tg) values, lower melting temperatures, and lower crystallinity compared with the parent PBS homopolyester. The presence of the stiff cyclic acetal units in the PBS chain caused an increase in the elongation at break and also a reduction in both elastic modulus and tensile strength of the polyester. Upon copolymerization the PBS notably increased its hydrolytic degradability and more slightly its susceptibility to degradation by lipases.



Scheme 6. PBS copolyesters based on L-tartaric acid derivatives

Click Cu(I)-catalyzed polymerization and thermal polyaddition of diynes having ester linkages and 1,4-diazido-1,4-dideoxyerythritol were carried out, affording polyesters having 1,2,3-triazole rings along the polymer chain (Scheme 7). These were hydrolytically degradable under physiological conditions.[41]

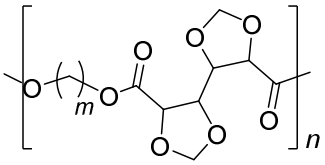


R= PEG, $(CH_2)_m$, isosorbide

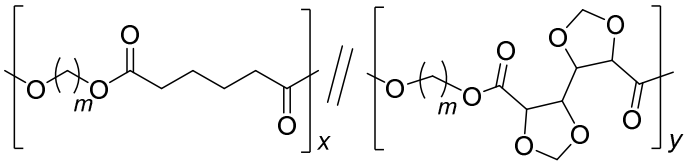
Scheme 7. Erythritol-based polyesters containing triazol rings

During the last five years, Muñoz-Guerra, Galbis, and co-workers have been reporting on a new series of biodegradable linear polyesters and copolyesters from bicyclic acetalized monosaccharide monomers derived from galactaric acid (**58**) (Scheme 8),[42,43] D-mannitol (**27**),[44] D-glucitol (**24**), and D-glucaric acid (**59**) (Scheme 9).[45] Homopolyesters and random copolyesters covering a broad range of compositions were obtained. The thermal properties, especially those of the copolyesters, were largely dependent on compositions, and also on the functionality of the replacing sugar unit. In general, the thermal stability of most of these fully biobased polyesters was greater than those of poly(alkylene dicarboxylate)s of reference. The replacement by bicyclic

carbohydrate-based monomers increased the rigidity of the polymer chains; in some cases Tg values increased by up to 68-70 ºC. Additionally these polymers hydrolyzed faster and exhibited degradation by the action of lipases.

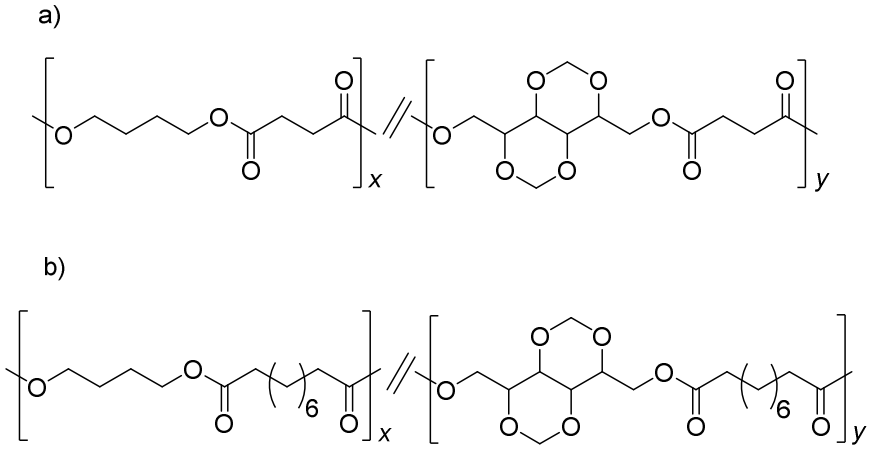


m= 6,8,10,12



m= 6,12

Scheme 8. Aliphatic copolyesters based on bicyclic acetalized galactaric acid



Scheme 9. Aliphatic copolyesters: a) based on bicyclic D-mannitol; b) based on bicyclic D-glucitol

The use of enzymes in polymer synthesis is important from the perspective of "green chemistry". Enzyme-catalysis toward polyesterification reactions avoids the high

temperatures required for polycondensations and toxic metal catalysts, leading to lack of selectivity and limiting the access to complex and well-defined structures. Additionally, prior protection or activation of certain functional groups can be avoided. Lipases and proteases are well-known as providing regioselectivity during esterification reactions at mild temperatures. An interesting review by Gross *et al.* describes the progress made, together with current limitations and future prospects for developing more-efficient enzyme-catalysts for industrial processes.[46]

The use of unprotected alditols to prepare polyesters was first accomplished by Kobayashi in 2000, from D-glucitol and divinyl sebacate, via enzymatic polymerization with a lipase derived from *Candida antarctica*.[47] In general, enzymatic polymerizations require the use of a highly active and selective lipase and a monophasic reaction mixture. Thus, Gross *et al*. described the enzymatic polymerization of adipic acid, glycerol, octanediol, and sorbitol in the presence of CALB.[48] Furthermore, unprotected alditols, such as erythritol, xylitol, ribitol, D-mannitol, D-glucitol, and galactitol, along with 1,8-octanediol and adipic acid, were used as monomers for lipase-catalyzed polycondensations.[49] Copolymers from D-mannitol had the highest degree of branching and, therefore, the greatest tendency for combined reactivity at both primary and secondary hydroxyl groups. Explanations for this difference in reactivity between sugars were put forward, concluding that a larger set of alditol substrates would be required to clarify this lack of correlation.

Kobayashi *et al.* carried out an extensive study of enzymatic polymerization for the synthesis of both novel and natural oligo- and polysaccharides, and polyesters.[50] These authors achieved enzymatic syntheses of a new class of cross-linkable polyester by the polymerization of divinyl sebacate and glycerol, using CALB in the presence of unsaturated higher fatty acids, and a similar route also afforded biodegradable epoxide-

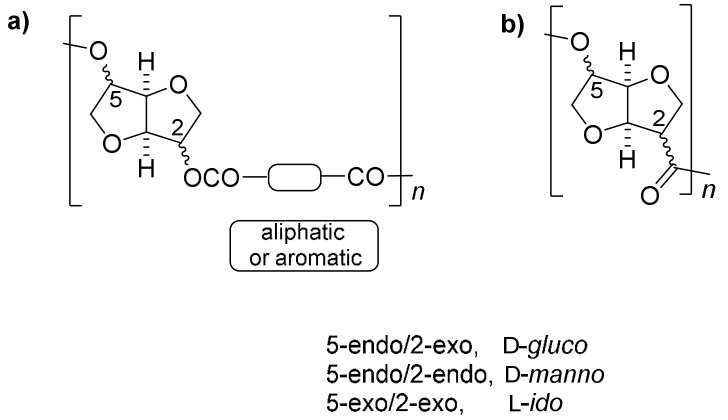
containing polyesters derived from glycerol and unsaturated fatty acids. Biocatalytic synthesis of polyesters from dianhydroalditols **1-3** and succinic acid with CALB demonstrated that the conversion decreased[51,52] in the order **2> 1>> 3**.

Enzymatic polycondensation reactions of alditols **15** and **16** with adipic acid were carried out successfully using CALB.[36] Catalani *et al.* have achieved the enzymatic polyesterification of dianhydrohexitols **1** and **2** and unsaturated diesters (*i.e.* diethyl itaconate, diethyl glutaconate, and others) by CALB.[53,54] Recent enzymatic copolymerization of D-glucose derivatives **24** and **59** with butanediol and diethyl sebacate in diphenyl ether, in the presence of CALB, gave satisfactory results.[45]

3.1.3. From 1,4:3,6-dianhydrohexitols. The 1,4:3,6-dianhydrohexitols isosorbide (**1**), isomannide (**2**), and isoidide (**3**) constitute the main building blocks for the preparation of chiral polycondensates. They are thermally stable, easily available from cereal-based polysaccharides, and provide stereochemical diversity. Monomers **1** and **2** are currently commercially available, and **3** is obtained from **1**.[55] The isosorbide-based polymers are non-stereoregular, in contrast to those based on isomannide and isoidide, which are stereoregular. The most important features of these monomers are linked to their rigidity, chirality, and non-toxicity. However, their relatively low reactivity has thus far prevented large-scale industrial applications in the polymer field. In general, the 1,4:3,6-dianhydrohexitol-based polymers present high Tg and good thermo-mechanical resistance, they have specific optical properties, and can be biodegradable.[19] The most-representative polymers that have been synthesized from monomers **1**-**3** are polyesters, polycarbonates, polyethers, poly(ester carbonate)s, poly(ester anhydride)s, polyurethanes, polyureas, and poly(ester amide)s.

Isosorbide (**1**) is classified by the Food and Drug Administration as a "generally recognized as safe" material; it can be incorporated into thermosets and thermoplastics.[19,20,56] For example, isosorbide epoxy resins are thermosets with mechanical properties comparable to those of bisphenol A epoxide. A variety of isosorbide-derived monomers have been synthesized for homo- and copolymerizations with commercially available polymers such as poly(ethylene terephthalate) and poly-L-lactide. The increasing Tg values and semicrystalline morphology of isosorbide copolyesters demonstrate a way to improve the performance of polyester thermoplastics in many applications. Isosorbide-based polymers could have a practical industrial role in the near future.

As we have reviewed,[17] Thiem, Bergmann, and Storbeck reported in the 80s that dianhydroalditol-based polymers had thermal and mechanical properties similar to those of the corresponding polymers obtained from the habitual petrochemical raw materials (Scheme 10a). Okada *et al.* have made an extensive study of biodegradable polymers based on the dianhydroalditols **1-3**.[57] Polyesters synthesized by polycondensation of the monomers **1-3** with aliphatic dicarboxylic acid dichlorides displayed biodegradability, which depended significantly on their molecular structures. Copolyesters were also obtained from monomers **1** and **2** with dimethyl dialkanoates and comonomers containing furan rings, in bulk, in the presence of titanium isopropoxide or tetrabutyl-1,3-dichloro-distannoxane. In general, the biodegradability of the **1**-based copolyesters decreased with increasing difuran dicarboxylate content, and copolymers containing sebacic acid units presented the highest biodegradability. The enzymatic degradability of the polyesters based on isomeric 1,4:3,6-dianhydrohexitols and sebacic acid decreased in the order **1>2>3**.



Scheme 10. **a)** AABB-Polyesters and **b)** AB-Polyesters, based on 1,4:3,6-dianhydroalditols (**1-3**)

The isohexides and other saccharide derivatives were found to be chiral components of cholesteric materials with interesting optical properties.[58] Chirality is very important in combination with the liquid crystalline character of low- or high-molecular-weight materials. Thiem reported a systematic study on the twisting power of **1-3** derivatives that drew attention to these monomers as building blocks of cholesteric polymers.[59] The finding of suitable combinations of monomers would allow incorporation of the sugar component without loss of the liquid crystalline character. Kricheldorf extensively studied cholesteric polyesters prepared from isohexides (**1**-**3**).[60]

More recently, Koning *et al.* prepared semicrystalline polyesters via melt polymerization[61] based on the L-*ido*-configured dicarboxylic acid **55**, which was obtained from isomannide **2**. Polymers with shape memory effect were obtained by cross-linking of polyesters based on isosorbide, itaconic acid, and succinic acid[62] presenting Tg values up to 74 ºC. Furthermore, dimethyl itaconate cross-linked copolyesters showed a one-way shape memory effect upon heating after deformation at their respective Tg values. Isosorbide-containing polymers have lately shown very attractive applications, such as high-strength non-cytotoxic bioelastomers,[63]

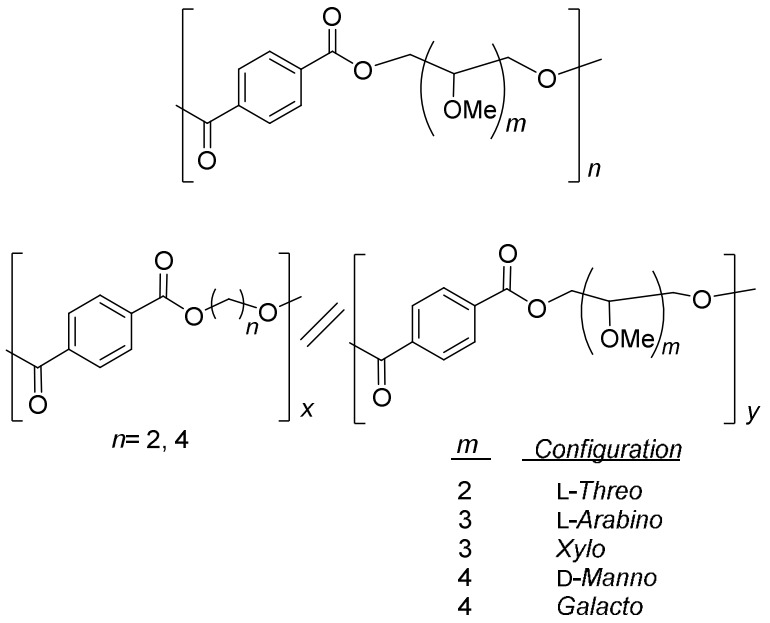
copolyesters having very high Tg,[64] bioactive polyester scaffolds,[65] or photoinduced antibacterial materials.[66]

The synthesis of a new kind of 1,4:3,6-dianhydrohexitol-based monomers, containing one methoxycarbonyl group and a secondary hydroxyl group in all four possible stereo isomers (*RR*, *RS*, *SR*, *SS*), has recently been described.[67] Step-growth polymerization from these monomers afforded fully sugar-based stereo-regular AB-type polyesters (Scheme 10b). Homo-polyesters based on the *RR* and *RS* monomers were obtained with intermediate molecular weights by melt polymerization (Mn 2400 and 2500), showing unexpectedly low glass-transition temperatures (20 ºC and 15 ºC). The stereoisomeric monomers having *SR* and *SS* configuration yielded only low-molecular-weight oligomers. Copolymerization of the *RR* and *SR* monomers gave a polyester with higher molecular weight (Mn 4100) and a higher Tg (80 ºC).

3.2. Aromatic polyesters

3.2.1. From alditols and aldaric acids. Poly(alkylene terephthalate)s, especially PET [(poly(ethylene terephthalate)] and PBT [(poly(butylene terephthalate)], are currently the most used thermoplastic polyesters, but they are produced entirely from fossil resources. Their production from renewable raw materials is currently an outstanding challenge, and carbohydrates are the most-promising easily available starting materials. With this in mind, Muñoz-Guerra, Galbis and co-workers began with the structural modification of PET and PEI [(poly(ethylene isophthalate)] by total replacement of the ethylene glycol units with *O*-protected alditols (Scheme 11), such as 2,3-di-*O*-methyl-L-threitol (**12**)[68] and *O*-methyl-alditols having D-*manno* (**21**), *galacto* (**22**),[69] L-*arabino* (**15**) and *xylo* (**16**) configurations.[70,71]The 2,3,4-tri-*O*-benzyl ethers of

L-arabinitol (**17**) and xylitol (**18**) were also used to prepare PET- and PBT-analogous polyesters.[72] Butylene copolyesters based on per-*O*-methyl aldaric acids and terephthalic acid, were also prepared and characterized.[73] The hydrolytic degradation of a series of homo- and copolyesters analogous to PET and PEI based on **15, 16, 21,** and **22** was fairly rapid at temperatures 10 ºC above their respective Tg.[74]

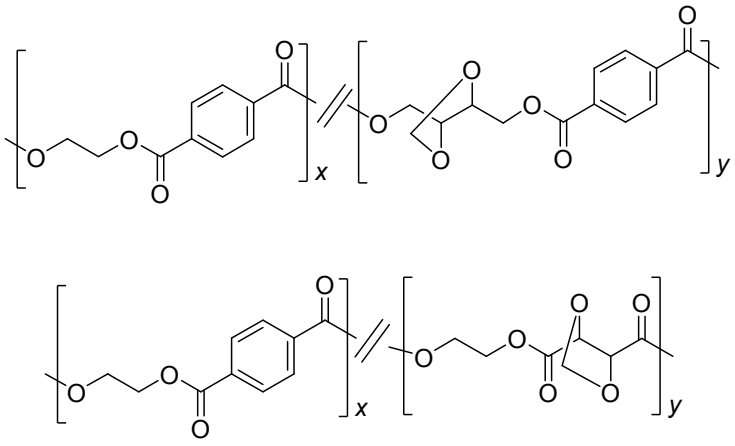


Scheme 11. Aromatic copolyesters of the PET type based on per-*O*-methylated alditols

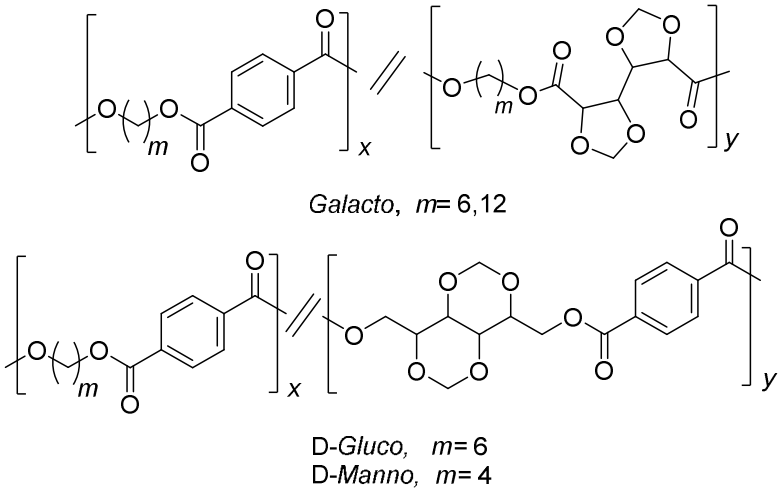
Muñoz-Guerra *et al*. have demonstrated that bicyclic carbohydrate-derived difunctional compounds are building blocks able to modify the original aromatic polyester structures leading to materials with high Tg values and more easily degradable or biodegradable.[22,75] A comparative study regarding isosorbide **1** and diacetalized alditols **23** and **27** as sustainable comonomers for the preparation of sugar-based aromatic copolyesters revealed that diacetalized diols had a greater facility than isosorbide to react under similar conditions.[76] The three bicyclic diols contributed to increase the thermal stability and also the Tg values of PBT, *i.e*. the replacement of 40% of 1,4-

butanediol by sugar-based diols increased the Tg values of PBT by 30 °C using **23** and up to 90 °C using **27**.

PBT, PET, and PHT (polyhexamethylene terephthalate) copolyesters made from cyclic monomers derived from tartaric acid (**8** and **45**) (Scheme 12) also displayed physical properties consistent with the presence of the sugar moiety, such as enhanced hydrolytic degradation and a certain biodegradability by lipases.[77-79]



Scheme 12. Aromatic copolyesters of the PET type based on cyclic L-tartaric acid



Scheme 13. Aromatic copolyesters of the PET type based on bicyclic alditols and aldaric acids

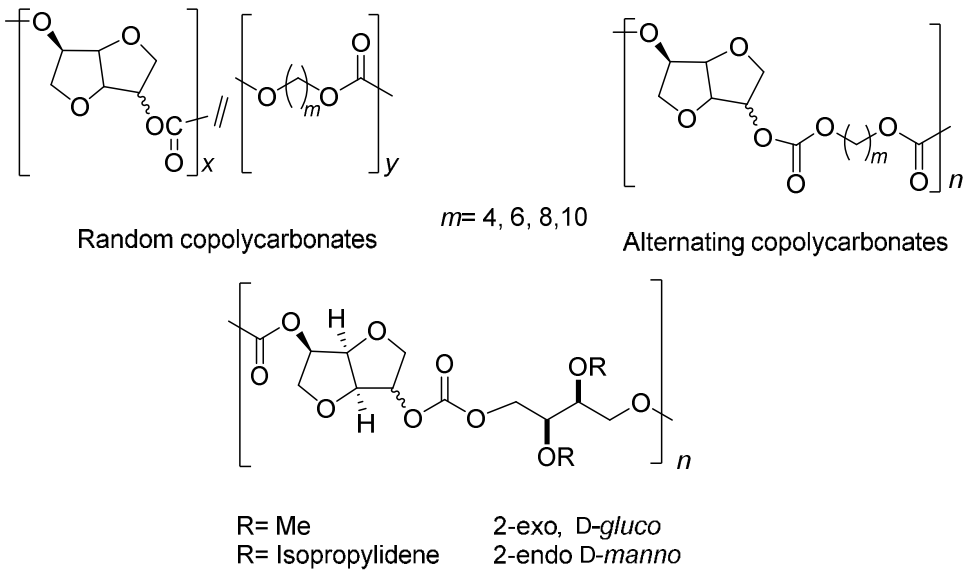
Muñoz-Guerra, Galbis, and co-workers[80-87] prepared a series of aromatic polyesters and copolyesters based on bicyclic acetalized alditols having *galacto* (**23**), D-*gluco* (**24**), and D-*manno* (**27**) configurations, as well as dimethyl galactaric (**58**) and D-glucaric (**59**) esters (Scheme 13). Of the new materials, those based on D-glucose presented the best thermal properties, probably due to the inherently rigid structure, and were biodegradable. Thus, PET copolyesters based on **24** and **59** showed a good thermal stability and the Tg values increased dramatically with the incorporation of the sugar moieties, especially[86] with **24**. Compared with PET, the copolyesters based on **24** exhibited a higher hydrolysis rate and an appreciable susceptibility towards biodegradation. Likewise, the corresponding PBT and PHT copolyesters displayed Tg values that steadily increased with the incorporation of glucitol units in the polyester chain, and were degraded by lipases.[87,88] Solid-state modification of PBT with glucitol **24** gave block-like copolyesters which were semicrystalline and displayed extraordinary thermal properties.[89]

3.2.2. From 1,4:3,6-dianhydrohexitols. Since the earlier work of Thiem and others, increasing interest is being focused on the use of renewable 1,4:3,6-dianhydrohexitols to synthesize polyterephthalates, especially during the last decade.[16,19,20] A new monomer having isoidide configuration (**4**) has afforded PET and PBT copolyesters through melt polymerization with dimethyl esters of terephthalic acid and furan-2,5-dicarboxylic acid.[90] Subsequent solid-state post-condensation of the prepolymers rendered materials with high values of Mw, Tg, and Tm—the first examples of semi-aromatic homopolyesters containing isohexide derivatives obtained via industrially relevant procedures.

4. Polycarbonates

Aliphatic polycarbonates are an important kind of biodegradable polymer and have commonly been used as integral components of engineered tissues, medical appliances, and drug and gene delivery systems. Furthermore, aliphatic carbonates bearing functional/reactive groups currently attract great interest, and they can be accessible starting from carbohydrates.[91,92]

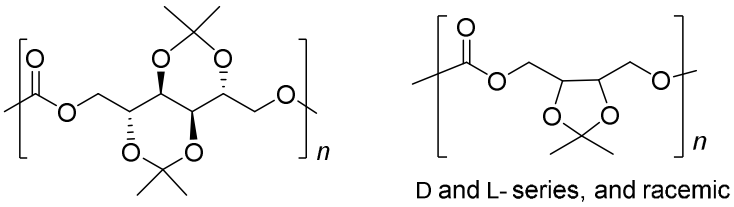
Okada *et al.* prepared copolycarbonates from the isohexides **1-3** and aliphatic diols in both bulk and solution polycondensations.[93] The environmental and enzymatic degradability of copolycarbonates based on isosorbide (**1**), isomannide (**2**), and alkylene diols or oligo(ethylene glycols) (Scheme 14) was also studied.[94] The same authors studied polycarbonates based on 1,4:3,6-dianhydrohexitols and L-tartaric acid derivatives[3] having pendant methoxy or isopropylidene groups. Deprotection of the isopropylidene groups afforded polyhydroxy polycarbonates which degraded remarkably quickly.



Scheme 14. Aliphatic polycarbonates from anhydroalditols 1 and 2

Homopolycarbonates based on isosorbide (**1**) and isomannide (**2**) have been also prepared by various groups. The interfacial polycondensation is impractical with alditols, including **1**, because they are water-soluble and less acidic than diphenols. The **1**-based homopolycarbonate was prepared by reaction of the sugar diol, with phosgene or diphosgene in pyridine-containing solvent mixtures at low temperatures. An alternative approach is polycondensation of the isosorbide bis(chloroformate) in pyridine, used by Kricheldorf *et al.* to prepare cholesteric polycarbonates derived from isosorbide (**1**) bis(phenyl carbonate), methyl hydroquinone, and 4,4'-dihydrobiphenyl.[95] More conveniently, trichloromethyl chloroformate was successfully used as a substitute of phosgene for all these polycondensations.

The same authors synthesized a series of polycarbonates derived from isosorbide bis(chloroformate), hydroquinone 4-hydroxybenzoate (HQHB) as mesogenic diphenol, and 4,4'-dihydroxychalcone in pyridine.[96,97] Isosorbide and equimolar amounts of various diols were polycondensed with diphosgene in pyridine and different bisphenols, using 1,3-bis(4-hydroxybenzyloxy)propane, and 1,4-cyclohexanediol as comonomers.[98] The formation of large amounts of cyclic oligo- and polycarbonates was sometimes detected.

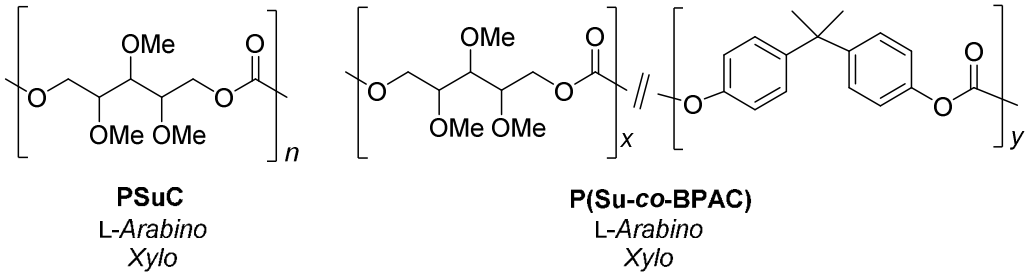


Scheme 15. Polycarbonates based on isopropylidene D-mannitol and tartaric acid derivatives

Bioerodible polymers having pendant functional groups are particularly interesting, being capable of covalent pro-drug formation. Thus, biodegradable

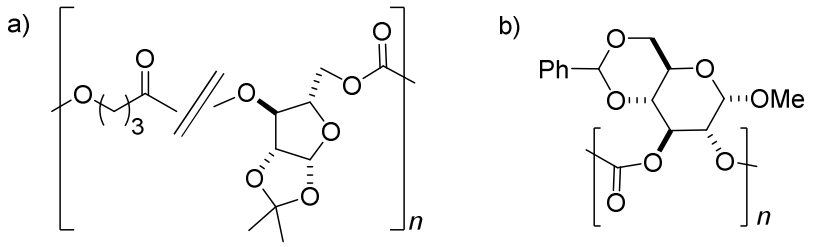
poly(hydroxyalkylene carbonate)s from the optically active and racemic 2,3-*O*-isopropylidene-threitol (**9**) and 2,4:3,5-di-*O*-isopropylidene-D-mannitol (**28**) with diethyl carbonate have been prepared[99] in the presence of dibutyl tin oxide (Scheme 15). Isopropylidene groups of the polycarbonates were hydrolyzed, and the free hydroxyl groups were derivatized to obtain esters, orthoesters, and carbamates. Functionalized polycarbonates derived from L-tartaric acid were also prepared by enzymatic ring-opening polymerization (ROP) of a cyclic carbonate derivative.[100]

Galbis *et al*. also used L-arabinitol **15** and xylitol **16** in the synthesis of polycarbonates with a commercial solution of phosgene in toluene (Scheme 16). Sugar-based homopolycarbonates (PSuC) and copolycarbonates with bisphenol A (BPA), P(Su-co-BPAC), showed high resistance to chemical hydrolysis; however, they were enzymatically degraded to different degrees.[4] The fastest degradation promoted by CALB was observed for the xylitol-based homo-polycarbonate, followed by copolycarbonates also based on xylitol, revealing the high stereospecificity of the enzyme toward this sugar.



Scheme 16. Polycarbonates from alditols 15 and 16

Gross *et al.* synthesized high-molecular-weight copolycarbonates derived from 1,2-*O*-isopropylidene-D-xylofuranose[101-104] (Scheme 17a), whose isopropylidene groups were successfully removed. Anionic ROP of a 2,3-*O*-carbonyl-D-glucopyranosyl derivative (Scheme 17b), afforded polycarbonates of medium molecular weights.[105]



Scheme 17. Polycarbonates based on D-xylose and D-glucose

ROP of cyclic carbonate monomers yielded hydrophilic polycarbonates, which are a promising alternative to PEG-based stealth materials.[106] Among successful applications of sugar-based polycarbonates,[92] the following are of special interest: self-assembled glycopolymer micelles with a high density of D-galactose in the shell displayed strong interaction with a specific type of liver cancer cells; polyethyleneimine (PEI) grafted with D-mannose had similar gene binding ability to the parent PEI; D-galactose-functionalized cationic polycarbonate diblock copolymer has been used for targeted gene delivery to hepatocytes.

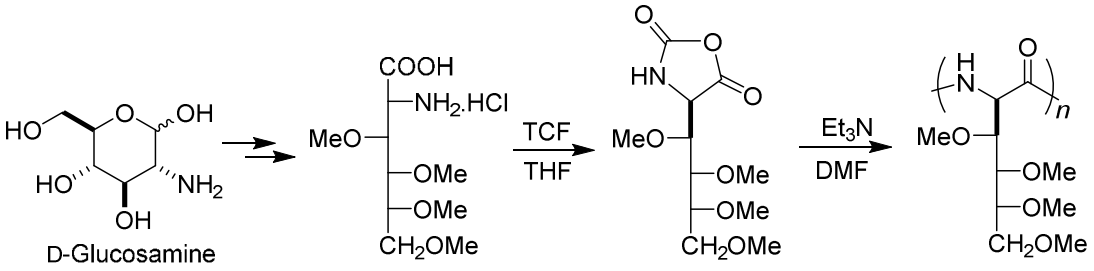
5. Polyamides

Owing to their good thermal and mechanical properties, Nylon-type polyamides constitute one of the most important groups of condensation polymers, and are extensively used in industry for injection molding, and film or fiber applications. So, the preparation of more-hydrophilic and degradable Nylon-type polyamides from sugar-based monomers represents a great challenge. The first syntheses of sugar-based polyamides yielded only brittle, low-molecular-weight fibers. The sugar monomers required for the synthesis of polyamides are diamino-sugars, aldaric acids, or aminoaldonic acids. The introduction of amino groups is usually accomplished

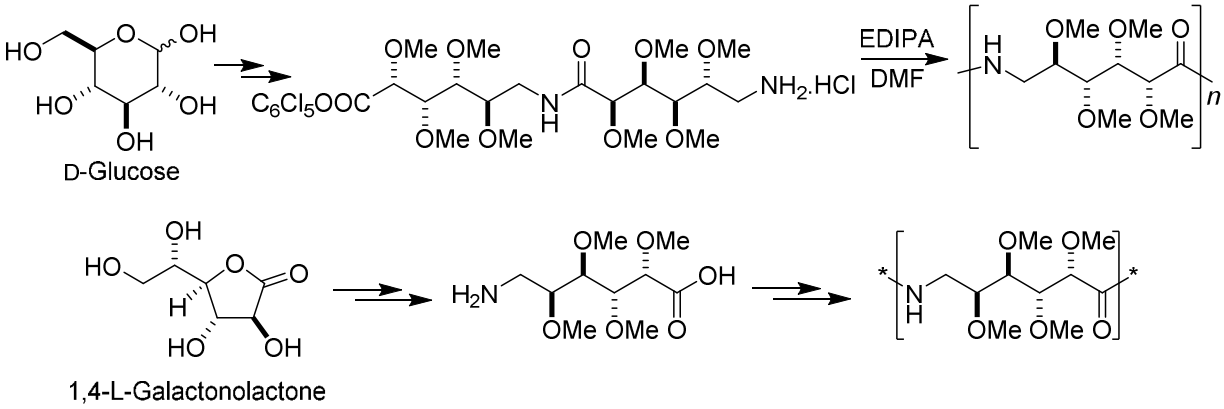
throughout a sulfonyl ester, S_N2 displacement by azide, and following hydrogenation reaction.[35] An alternative method based on the Mitsunobu reaction has been described for the preparation of the diaminopentitols **66** and **67**.[107]

5.1. AB-Type polyamides

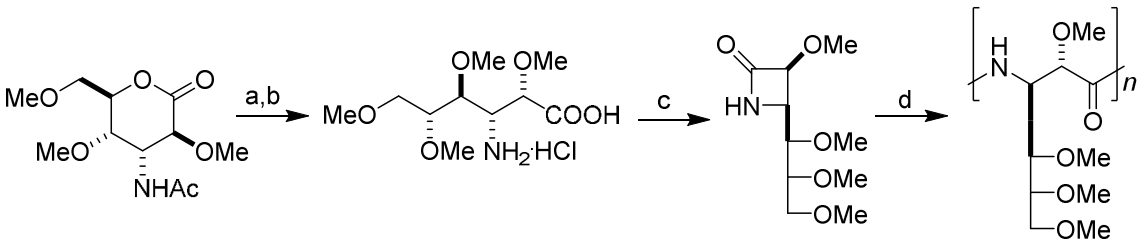
In an early paper from our laboratory[108] two stereoregular polygluconamides were described starting from D-glucosamine and D-glucose. A polyamide of the polypeptide type[108,109] was obtained by ROP of the 2-amino-2-deoxy-3,4,5,6-tetra-*O*-methyl-D-gluconic acid *N*-carboxyanhydride (Scheme 18). At the same time, a Nylon 6 analog was obtained from D-glucose[108,110] through a dimeric active ester of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-gluconic acid (Scheme 19). This polyamide was highly crystalline, and afforded resistant films with a spherulitic texture. Varela *et al.* subsequently prepared, from the D- and L-galactono-1,4-lactones,[111] the 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-(and L-)galactonic acids, which were polymerized by the same method[108] to give stereoregular sugar-based polyamides[112] having D- or L-*galacto* configuration (Scheme 19). Oligomers of *O*-protected-6-amino-6-deoxy-D-allonate[113] and D-galactonate has been described,[114] as intermediates in the synthesis of polyhydroxylated Nylon 6 analogs. Chiral polyamides 3 were also prepared by ROP of the β-lactam of 3-amino-3-deoxy-2,4,5,6-tetra-*O*-methyl-D-altronic acid[115,116] and from isopropylidene-D-glyceraldehyde (Scheme 20).[117,118]



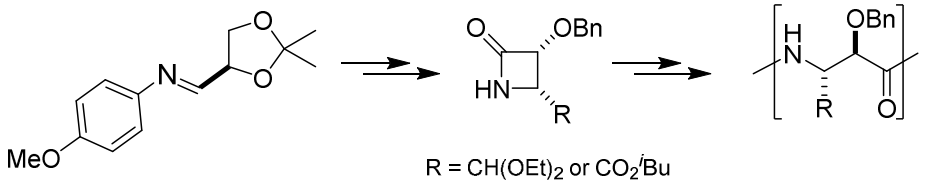
Scheme 18. Polygluconamides from D-glucosamine



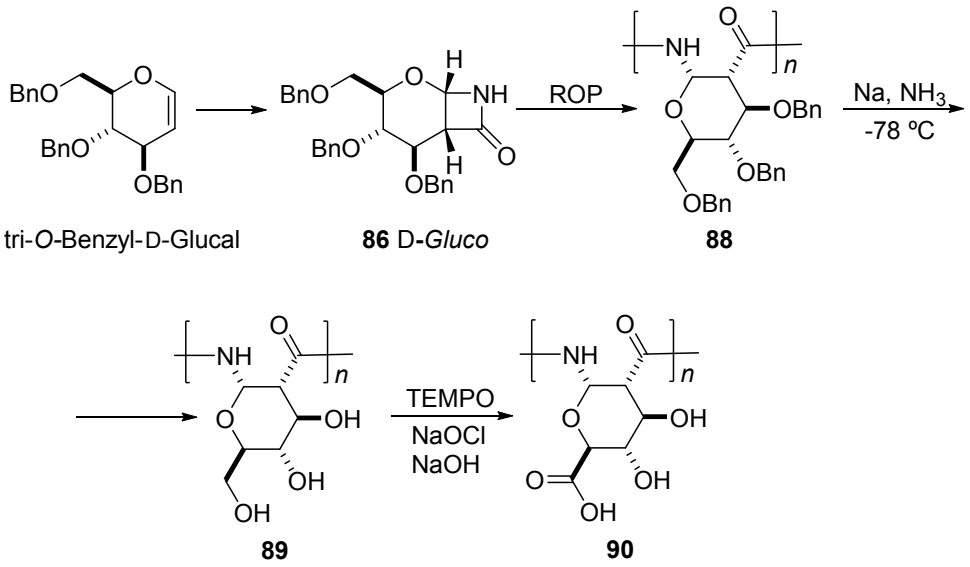
Scheme 19. Stereoregular polyamides 6



(a) MeI, KOH, THF; (b) 4M HCl; (c) 1. DIPEA, MeCN; 2. MsCl, $NaHCO_3$, MeCN; (d) ^tBuOK, CH_2Cl_2.



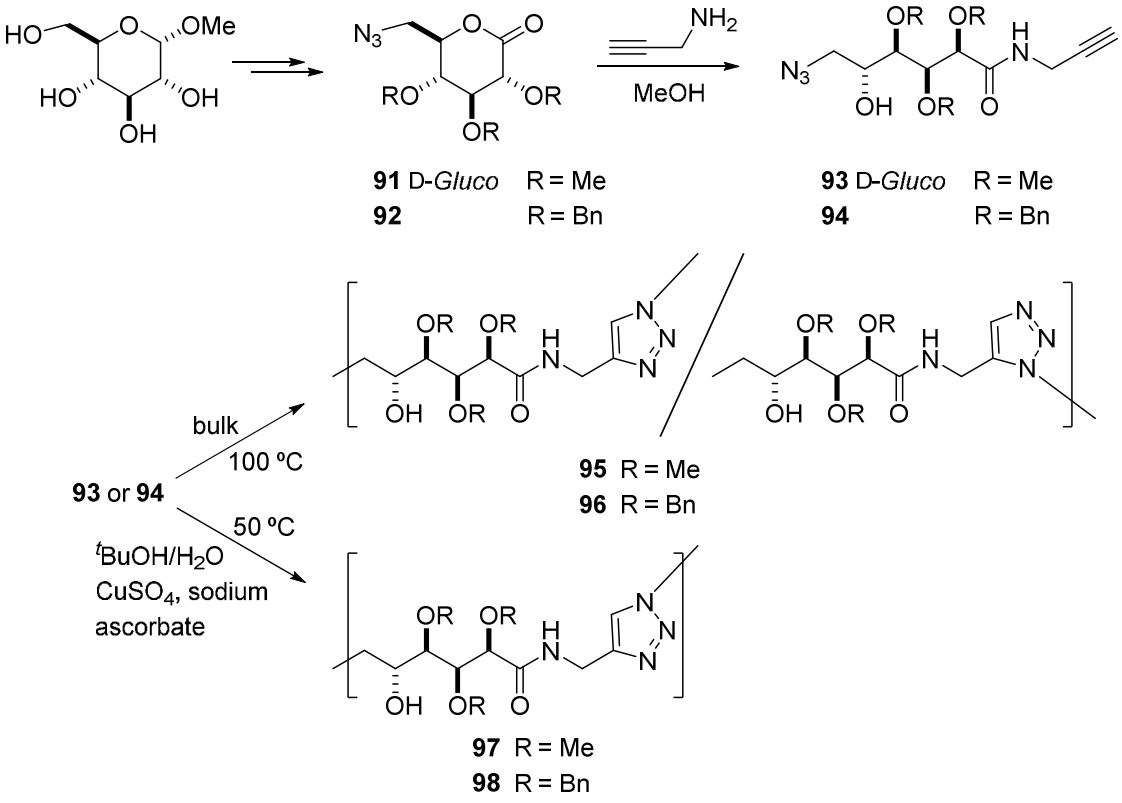
Scheme 20. Stereoregular polyamides 3



Scheme 21. Stereorgular β-polyamido-saccharides

An enantiopure chiral β-polyamido-saccharide (**88**) was synthesized by Grinstaff *et al.*[119] by an anionic ROP of the bicyclic β-lactam monomer **86** synthesized in one step from benzyl-protected D-glucal (Scheme 21).[120] Circular dichroism experiments suggest that the deprotected polymer (**89**) possesses a regular secondary structure in aqueous solution, which agrees favorably with the prediction of a helical structure using molecular modeling. The polymers bind the lectin concanavalin A at the same site as natural carbohydrates, showing the potential of these polyamides to mimic natural polysaccharides. Other chiral β-polyamido-saccharides having D-*galacto* configuration have also been prepared by the same authors by ROP of the chiral β-lactam monomer **87** derived from D-galactal.[121] A hydrophobic glucose octyl ether polyamido-saccharide analogous to **88** has been prepared by using a controlled anionic ROP of a glucose-derived β-lactam sugar monomer derived from tri-*O*-octyl-D-glucal.[122] TEMPO-mediated oxidation of the primary alcohol at the C6-position of the repeat unit of **89** gave a carboxylated β-polyamide (**90**) comparable to the glucuronic acid.[123]

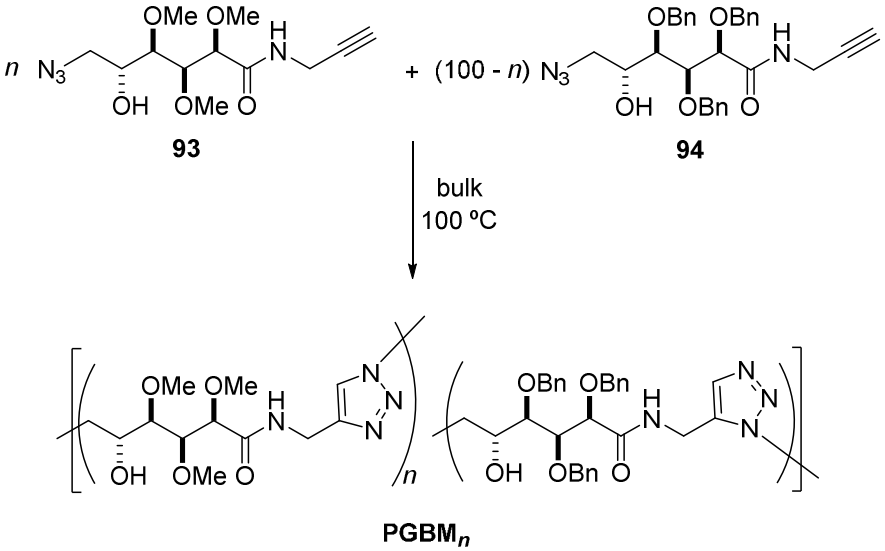
The synthesis and click polyaddition reaction of a new A-B-type amide monomer containing the alkyne and azide functions have been described.[124] From methyl-α-D-glucopyranoside the lactones **91** and **92** were obtained by previously described methods.[110,125] The lactone ring was opened with propargylamine in dry methanol under reflux, to obtain the monomers 6-azido-6-deoxy-2,3,4-tri-*O*-methyl-*N*-(prop-2-yn-1-yl)-D-gluconamide (**93**) and 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-*N*-(prop-2-yn-1-yl)-D-gluconamide (**94**) in good yield (Scheme 22).[124]



Scheme 22. Synthesis of linear poly(amide triazole)s

These monomers could be handled at room temperature for hours or stored at low temperature (−20 ºC) for several months without traces of coupling reactions as determined by ^{1}H NMR. The synthesis of the poly(amide triazole)s was carried out by copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) in solution[126] or by catalyst-

and solvent-free 1,3-dipolar thermal Huisgen cycloaddition reaction[127] (Scheme 22). Monomers **93** and **94** were first polymerized by CuAAC following the Sharpless classical conditions,[124] in ^{t}BuOH/H_2O mixtures, and catalyzed by copper sulfate in the presence of sodium ascorbate. The reaction was regiospecific, and polymers **97** and **98** were obtained, after purification, in high yield. Metal- and solvent-free click polymerization was also performed to rule out the presence of copper ions in the resulting polymers. Monomers **93** and **94** were heated at 100 ºC for 24 h to synthesize poly(amide triazole)s **95** and **96**, respectively. The polymers were obtained as colorless glassy materials in quantitative yield. Under these conditions, the polyaddition was non-regioselective, as could be observed by NMR spectroscopies. Compared with previous studies on thermal Huisgen polyaddition, the particularly high reactivity of these monomers afforded the completion of the reaction after short reaction times at moderate temperature. The polymers exhibit similar features, but the thermal polymerization process has the advantage of being less toxic and more environmentally friendly.



Scheme 23. Synthesis of linear co-poly(amide triazole)s

Mixtures of the monomers **93** and **94** could also be copolymerized by catalyst- and solvent-free 1,3-dipolar Huisgen cycloaddition reaction, leading to random and diblock copolymers (Scheme 23).[128] They were abbreviated as $PGBM_n$, where *n* indicates the percentage of methylated monomer (**93**) incorporated in the copolymer chain. Thus, $PGBM_{93}$, $PGBM_{63}$, and $PGBM_{38}$ were obtained. All the copolymers were easily soluble in highly polar aprotic solvents, such as NMP, DMSO, or DMF. The copolymer $PGBM_{93}$ contained the highest ratio of hydrophilic methoxy groups, making this copolymer easily soluble in water and it was quickly hydrolyzed in buffer solution (pH 10) at 80 ºC. Copolymers $PGBM_{63}$ and $PGBM_{38}$ were insoluble in water, but soluble in dichloromethane or chloroform. The free secondary alcohol function present in the polymer chain can also be used to produce new materials with tunable properties, such as —for instance— hydrogel polymeric networks.

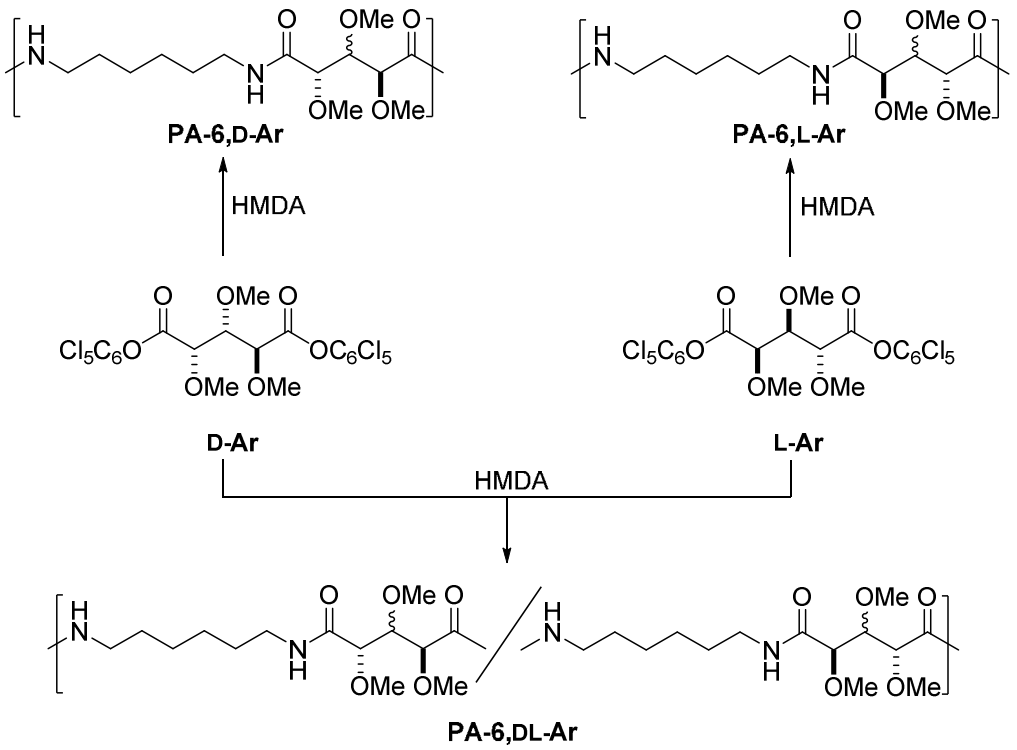
5.2. AABB-Type polyamides

Muñoz-Guerra, Galbis, and co-workers initiated a systematic study of a series of sugar-based AABB linear polyamides. These polyamides are derived from appropriately *O*-protected aldaric acids and/or α,ω-diamino-dideoxyalditols (Figures 3 and 4). The advances achieved in the study of polyamides made from carbohydrate-based monomers have been reviewed.[9,17,129,130]

A characteristic of particular interest regarding the behavior of carbohydrate-derived polyamides is crystallinity, a property usually thought to be closely associated to chain stereoregularity. AABB-type polyamides obtained by conventional polycondensation will be stereoregular when their monomers have a 2-fold axis of symmetry; if not they may enter the polymer chain in two opposite orientations, giving rise to aregic and non-stereoregular polyamides. Such symmetry restriction is met only by the aldaric or alditol

based monomers having *threo*, *manno* and *ido* configurations.[131] Nonetheless, stereoregular AABB-type polyamides derived from non-centrosymmetric D-glucaric acid have been prepared by Kiely *et al.* using synthetic methods able to differentiate the reactivity toward the aliphatic diamine of the aldaric acid's two carboxyl groups.[7,8]

In our investigation of the sugar-based polyamide family, both stereoregular and non-stereoregular AABB-type polyamides have been synthesized and fully characterized. From these studies, the fact that stereoregularity and crystallinity of these systems do not correlate with each other was evidenced. Whereas stereoregular polyamides derived from D- or L-tartaric acid, having *threo* configuration, were found to be semicrystalline polymers,[132-134] polyamides derived from 1,6-diamino-mannitol did not show crystallinity, although they also being stereoregular.[135-137] Conversely, non-stereoregular polyamides made from non-centrosymmetric arabinaric or xylaric acids displayed an intense crystallinity.[35,131,138,139] These results led to the conclusion that monomer configuration cannot be the only factor determining the ability of the sugar-containing polyamides to crystallize.

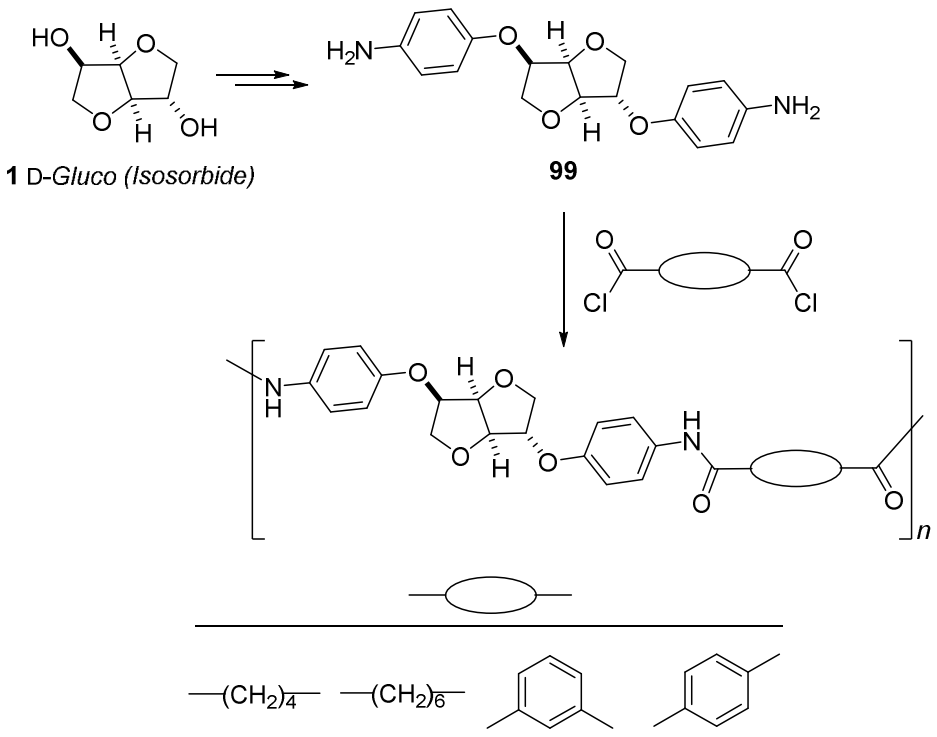


Scheme 24. Synthesis of polyamides 6,5 (PA-6,Ar)

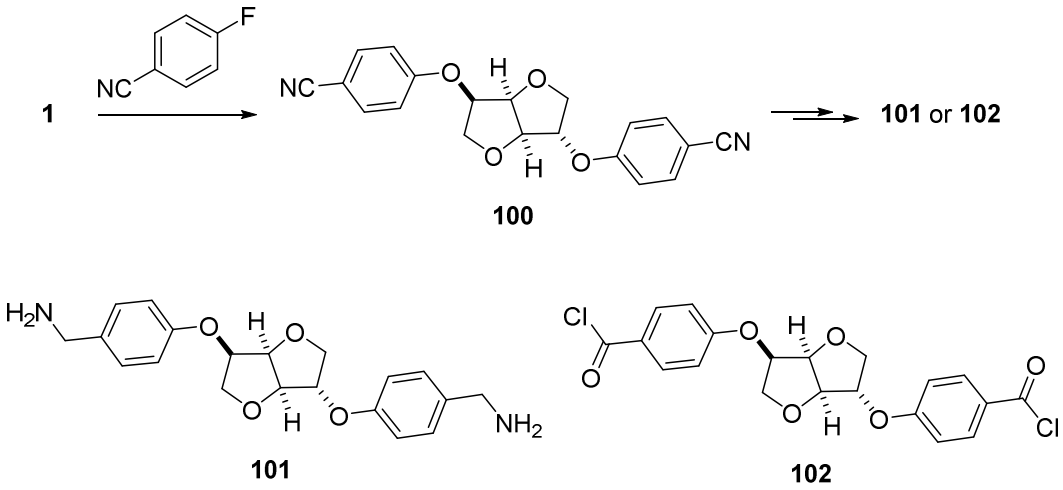
A comparative experimental study of crystal structure and crystallization kinetics has been carried out on stereoisomeric polyamides made from 1,6-hexamethylenediamine (HMDA) and either tri-*O*-methyl-D- or -L-arabinaric acid (D-Ar or L-Ar), and from HMDA and the racemic tri-*O*-methyl-D,L-arabinaric acid (DL-Ar) (Scheme 24). The obtained polyamides were aregic and non-stereoregular, as demonstrated by ^{13}C NMR spectroscopy.[140] However, the DSC of the polyamides displayed well-defined endothermic peaks characteristic of melting transitions. Their crystal structure was examined by X-ray and electron diffraction in powders, films, fibers, and lamellar crystals. The main conclusion drawn from this study was that all these polyamides were semicrystalline despite their aregic and non-stereoregular structure. It could also be concluded that heterogeneity in configuration does not significantly affect either their thermal properties or their crystal structure. The thermal properties and crystal structure

of the racemic mixture of the two enantiomerically pure polyamides shown that no stereo-complex is formed in this system, in contrast with the behavior of other sugar-containing polyamides.[141]

The synthesis and degradability of segmented silicone polyamides obtained from activated D-glucaric and galactaric acid derivatives and various α,ω-diaminoalkyl polydimethylsiloxanes have been described.[142] The galactaric acid based polymers present a higher Tg than their glucaric acid analogs. These materials can be enzymatically degraded, with the amide function as breaking point. The same group[143] described a series of polyamides synthesized by interfacial polycondensation of aromatic or aliphatic diacyl chlorides with diamines (**82**-**84**) derived from isosorbide (**1**), isomannide (**2**), and isoidide (**3**). They found that by using the diamines **82** and **84**, with the amino groups in the disposition *exo/endo* and *exo/exo*, respectively, polyamides with high degrees of polymerization could be obtained. Later, Caouthar *et al*.[144] reported the synthesis of chiral polyamides (Scheme 25) by the microwave-assisted polycondensation of an optically active isosorbide-derived diamine (**99**) with different diacyl chlorides in the presence of a small amount of *N*-methylpyrrolidinone. Other chiral isosorbide-derived monomers were prepared (Scheme 26) and polycondensated by the same method.[145]



Scheme 25. Synthesis of isosorbide-based polyamides



Scheme 26. Isosorbide-based monomers

Koning *et al.*[146] described fully biobased homo- and copolyamides from sebacic acid, 2,5-diamino-2,5-dideoxy-1,4;3,6-dianhydroiditol (diaminoisoidide, **84**) and 1,4-diaminobutane. Low-molecular-weight polyamides were obtained by melt

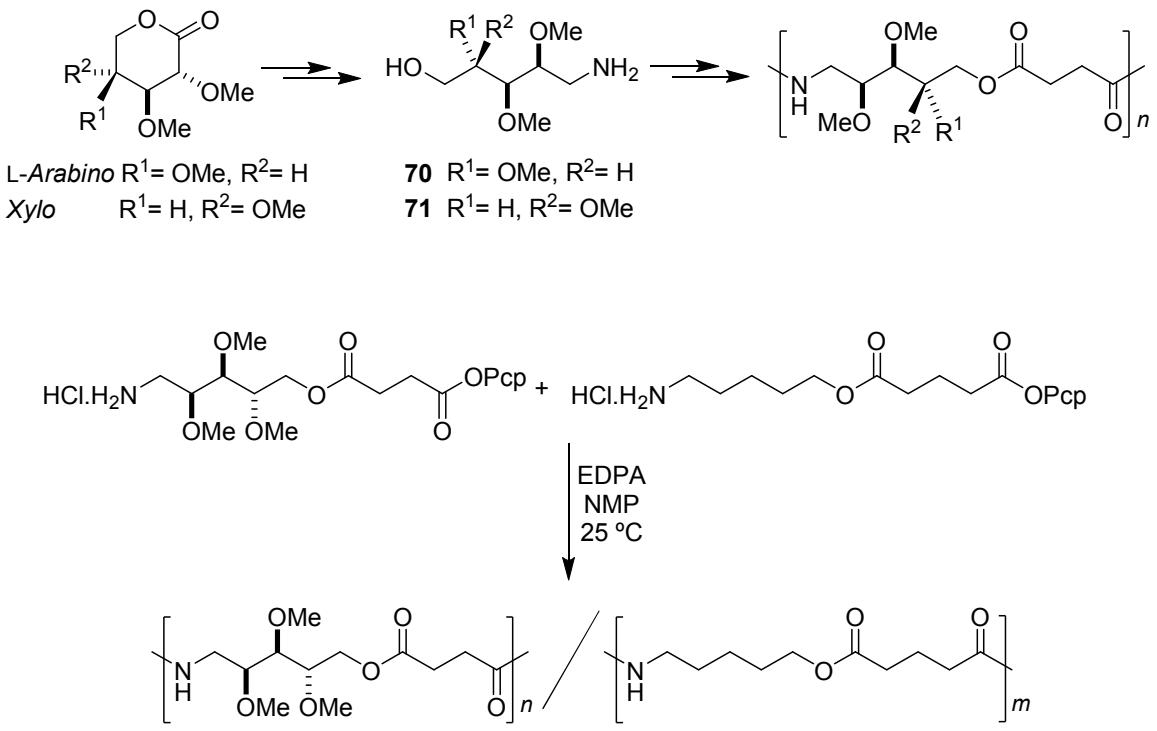
polycondensation of the salts based on these monomers or by interfacial polycondensation. Higher-molecular-weight polyamides were obtained by solid-state polymerization (SSP) of the prepolymers. FT-IR and X-ray techniques were used for the investigation of the crystal structure of the polymers after SSP. Local conformation and co-crystallization of these diaminoisoidide-based polyamides were studied by FT-IR, solid-state NMR, and WAXD.[147] The chemical structure, the conformation, and the flexibility of the polymer chain fragments present in the polyamides synthesized from diaminoisosorbide (**82**), 1,4-diaminobutane, and sebacic or brassylic acid have also been studied.[148] New semicrystalline polyamides and copolyamides were synthesized by the same group[149] from the new carbohydrate-based diamine, isoidide-2,5-dimethyleneamine (**85**). In combination with 1,6-hexamethylene diamine and the biobased sebacic acid or brassylic acid, the desired copolyamides were obtained via melt polymerization of the salts followed by SSP. The incorporation of methylene segments between the isohexide group and the amide groups enables hydrogen bond formation and the organization of the polymer chain fragments of these new polyamides.

6. Polyesteramides

The degradability of the aliphatic polyamides may be enhanced by inserting hydrolytically cleavable ester bonds into the chain, resulting in poly(ester amide)s. This type of polymer combines the good mechanical and processing properties of polyamides and the biodegradability of polyesters. The hydrolytically cleavable ester bonds and the lowering of the crystallinity make them promising materials for biomedical applications.[150-153] However, though abundant papers have been published on the

synthesis of biodegradable and biobased poly(ester amide)s,[154-160] those on carbohydrate-based poly(ester amide)s are scarce.

Chiral poly(ester amide)s based on isosorbide (**1**) have been reported. They were prepared by reaction of diacid chlorides with biphenolic azo chromophores and isosorbide in dimethyl acetamide at 100 °C.[161] Biodegradable poly(ester amide)s were also prepared by a two-step method.[162] First, isosorbide (**1**) or isomannide (**2**) were esterified with α-amino acids in the presence of *p*-toluenesulfonic acid, and the resulting bis(ammonium tosylates) esters were isolated. Next, the amino groups were liberated and polycondensed with *p*-nitrophenyl esters of aliphatic dicarboxylic acids. The resulting poly(ester amide)s were characterized and their enzymatic degradation was studied using chymotrypsin or lipase. These studies revealed that the tendency of the poly(ester amide)s to undergo α-chymotrypsin-catalyzed hydrolysis decreases with increasing hydrophobicity of the diacid residue in the polymer backbone. A similar procedure was followed in the preparation of a series of biodegradable poly(ester amide)s from isosorbide (**1**).[163] The *p*-toluenesulfonic acid salts were obtained by the reactions of isosorbide with alanine, glycine, and glycylglycine, respectively, in the presence of *p*-toluenesulfonic acid. Next, the polycondensations were carried out in *N*-methylpyrrolidone at 40 °C in the presence of triethylamine. Soil burial degradation tests, Biochemical Oxygen Demand tests in an activated sludge, and enzymatic degradation tests using *Porcine pancreas* lipase and papain indicated that these poly(ester amide)s were biodegradable, and that their biodegradability markedly depends on the molecular structure.[163]

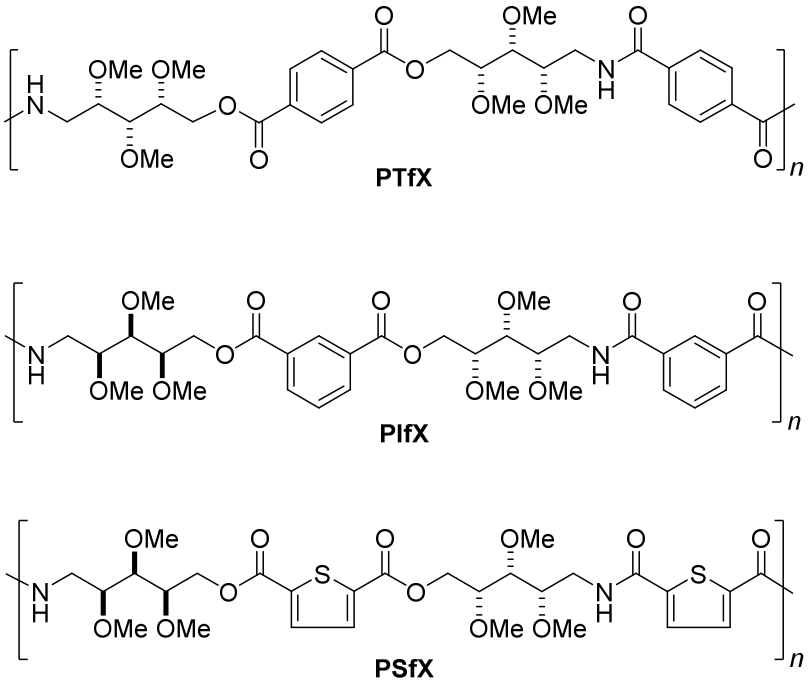


Scheme 27. Poly(ester amide)s and co-poly(ester amide)s

Our group has used naturally occurring L-arabinose and D-xylose as starting materials (Scheme 27) to obtain stereoregular *O*-methyl-poly(ester amide)s. We prepared 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol (**70**) and -xylitol (**71**), which were then transformed into a series of poly(ester amide)s.[164,165] The polymers obtained by the active ester polycondensation method were characterized. Copoly(ester amide)s were also prepared[166] by random copolymerization of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy) succinyl]-L-arabinitol hydrochloride and 5-amino-1-*O*-[(pentachlorophenoxy) glutaryl]pentanol hydrochloride by the active ester polycondensation method (Scheme 27). The molar ratios of the two comonomers in the feed varied from 1/99 to 50/50. The two monomeric units were randomly distributed within the copolymers, as demonstrated by NMR analysis, and the degree of randomness and average sequence lengths of the different copoly(ester amide)s were

experimentally determined. Thermal properties depend on the copoly(ester amide) composition, since it was found that the melting and the decomposition temperatures decreased as the molar fraction of carbohydrate-based monomer unit increased, whereas the glass-transition temperature increased in parallel. Their hydrolytic degradation was carried out in phosphate buffer at room temperature and determined by weight loss and intrinsic viscosity measures. The degradation of the copoly(ester amide)s was greatly enhanced with increasing amount of arabinose-succinyl monomer incorporated in the polymer chain. The presence of small amounts of this monomer was enough to produce a noticeable increase in polymer degradability. Spectroscopic investigations of the hydrolysis products provided evidence for succinimide ring formation, supporting the general mechanism proposed for the hydrolysis of poly(ester amide)s containing four-carbon diacid units in their structure.[167-169]

We have also prepared[170] a series of stereoregular aromatic poly(ester amide)s by the polycondensation method using the amino-tri-*O*-methyl-xylitol (**71**) and the aromatic diacids terephthalic, isophthalic, and thiophene-2,5-dicarboxylic acids as starting materials. Thus, three novel carbohydrate-derived poly(ester amide)s, PTfX, PIfX, and PSfX, were prepared (Scheme 28). The obtained polymers were hydrophilic and mainly amorphous. Their hydrolytic degradation can be described by a simple hydrolysis of the ester bonds, being characterized by rapid rates of hydrolysis to yield final compounds with the amide functions preserved.



Scheme 28. Stereoregular aromatic poly(ester amide)s

7. Polyurethanes

Polyurethanes have been extensively studied for the last few decades, and they have been the subject of numerous patents, papers, and books. They are mostly used as commodity materials and in industrial applications. However, because some of them are biodegradable and biocompatible, their use in medical applications is being widely investigated due to their low toxicity, potential biodegradability, biocompatibility, and versatile structures, which make them suitable as part of drug administration systems, as dermatological dressings, as hemocompatible materials for catheters, and as filters in biomedical instrumentation and devices.

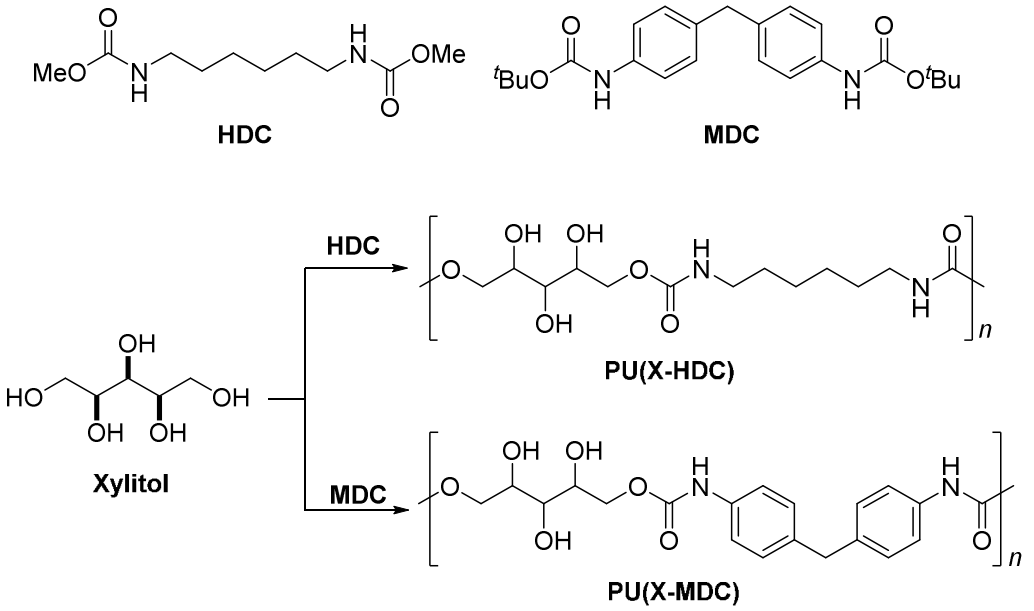
The synthesis of linear sugar-based polyurethanes (PU) is generally accomplished by reaction of sugar-based diols and diisocyanates in a varied range of conditions, either in solution or in bulk, leading to [AABB]-type polyurethanes.

The solvents most commonly used are *N,N*-dimethylacetamide (DMAc),[171] *N,N*-dimethylformamide (DMF),[172] and tetrahydrofuran (THF),[173] and, to a lesser extent, butanone,[174] dimethylsulfoxide (DMSO), and hexamethylphosphoramide (HMPA).[175] The polymerization can be catalyzed by a metal catalyst, the most widely used being dibutyltin dilaurate (DBTDL),[176] tetrabutyl titanate (TBT),[177] and a family of commercial tin mercaptide esters registered as Metatin™.[178] Tertiary amines can also speed up this process; among them, the most extensively selected catalysts are 1,4-diazabicyclo[2.2.2]octane (DABCO)[179] and *N,N*-dimethylcyclohexylamine (DMCHA).[180] Triethylamine (TEA) was chosen as co-catalyst in the preparation of segmented PU.[181] These reactions are carried out under inert atmosphere and in the absence of moisture, at moderate temperatures, ranging from room temperature to 80 ºC, with high conversions within 3-24 hours.

When the polymerization is performed in bulk, high temperatures are required as well as the incorporation of a liquid diol or polyol in the formulation, namely polyethylene glycol (PEG),[182-184] polyglycerol (PGL),[185] polypropylene glycol (PPG),[185,186] and polycaprolactone (PCL).[187]

To avoid the use of diisocyanates, a variety of new materials can be obtained by polycondensation of diamines or diols with freshly prepared bis(chloroformate)s[188] and dicarbamates,[177] respectively. For example, linear homogeneous polyurethanes with enhanced hydrophilic character have been successfully prepared[177] from sugar-based monomers having their hydroxyl groups free (Scheme 29). By reaction of the primary

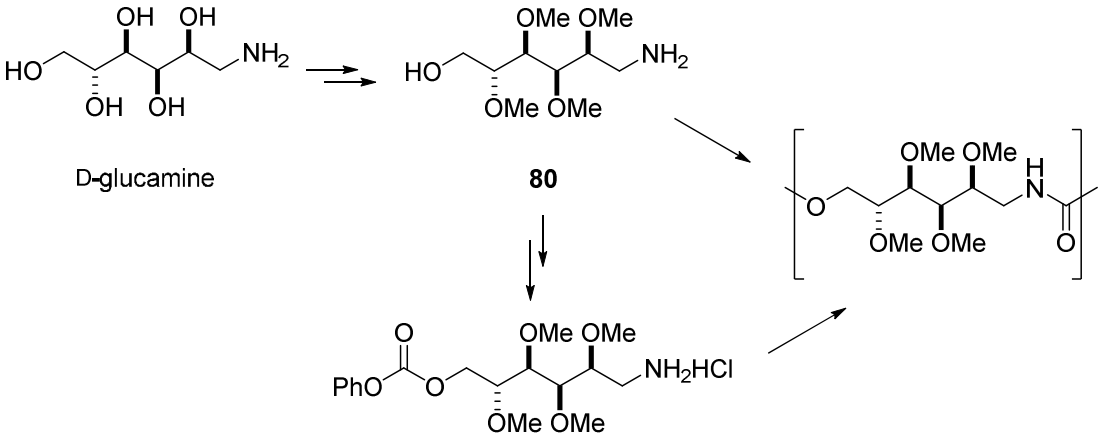
hydroxyl groups of xylitol with dimethyl hexamethylene dicarbamate (HDC) or di-*tert*-butyl-4,4'-diphenyl methyl dicarbamate (MDC), two new linear semicrystalline polyurethanes [PU(X-HDC) and PU(X-MDC)] have been prepared.



Scheme 29. Linear polyurethanes prepared from diols and dicarbamates

To attempt the synthesis of linear [AB]-type homopolyurethanes, both the nucleophilic and the electrophilic groups need to be present in one sole monomer: for example, hydroxyl and isocyanate groups[176,189,190] or amine and activated carbonate groups (*O*-phenyl carbonate).[190] The synthesis of 12-polyurethane, an aliphatic [AB]-polyurethane, as well as an overview of its thermal properties, crystal structure, and crystallization was described in a recent review.[189] The article reported the synthesis of that polymer from 12-amino-1-dodecanol by applying a two-step method without isolation of the isocyanate alcohol precursor. In another study, both methods mentioned above were tested in the synthesis of a sugar-based [AB]-polyurethane (Scheme 30). The aminoalcohol 1-amino-1-deoxy 2,3,4,5-tri-*O*-methyl-D-glucitol (**80**) was the precursor for the synthesis of α,ω-hydroxyl isocyanate monomer, which polymerized in the

presence of a catalyst [$Zr(acac)_4$, $Sn(oct)_2$ or TEA]. An alternative method was proposed: the free hydroxyl group of **80** was activated preparing the α-amino-ω-phenylcarbonate monomer, and further self-polycondensation was conducted in THF and in the presence of diisopropylethylamine (DIPEA). Both methods yielded polymers of low molecular weights.[190]



Scheme 30. Synthesis of [AB]-polyurethane from 1-amino-1-deoxy-D-glucitol

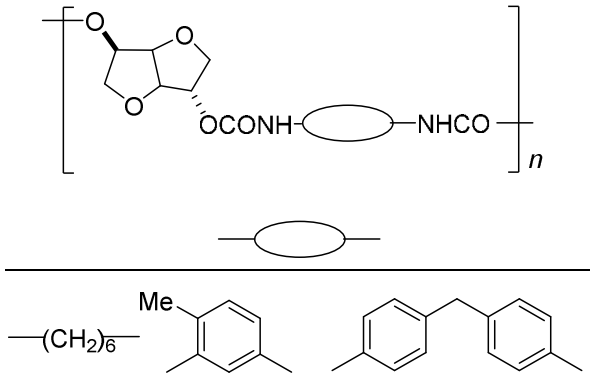
The preparation of cross-linked sugar-based PU is generally accomplished by the use of one monomer with functionality above two. In general, this is achieved by choosing a mono- or disaccharide with all its hydroxyl groups unprotected. The main cross-linkers in carbohydrate-based networks are glucose and sucrose[185-187,191,192] and, to a lesser extent, other monosaccharide and disaccharide derivatives such as glucosides,[192] maltose,[183] and xylaric acid.[184] Just one work was found in which the polyfunctionalized monomer was a polyisocyanate: a L-lysine triisocyanate derivative.[182] For example, Ates *et al.*[183] prepared some cross-linked non-aromatic polyurethanes with potential use as surgical tissue adhesives. PEG diol and 4,4'-methylenebis(cyclohexyl isocyanate) (MCI) were polymerized with a chosen amount of a disaccharide (maltose or sucrose) as cross-linker. The reaction was carried out in THF, at high temperatures in the absence

of catalyst. The prepared polyurethane films exhibited suitable properties for use as adhesive material in medical applications.

When the aim of the work is the study of segmented PU and carbohydrate-based cross-linked materials with differentiated regions, the preparation can be attempted in a single stage in which the soft segments, namely aliphatic polyether or polyester such as PCL,[178] PEG,[182-184] PPG,[185,186] PGL,[180] or oleic acid ester derivatives,[192] are incorporated into the polymer feed together with the sugar-based monomers and the other components. So, for example,[180] Ionescu *et al.* described the synthesis of highly functionalized low-molecular-weight polyether-polyols initiated by polyglycerol (PGL) and mixtures of PGL and sucrose. The polyether-polyols constituted the soft segment in the formulation for the "one pot" preparation of rigid polyurethane foams. They were prepared from the synthesized PGL-based polyether polyols and 4,4'-methylene-bis(phenyl isocyanate) (MDI), in bulk, and using *N,N*-dimethylcyclohexylamine as catalyst. Those materials displayed good physical and mechanical properties, excellent dimensional stability, and low friability. However, enhanced microphase separation can be achieved if the polymerization is performed in two stages: first, the soft segment is incorporated by either a reaction of a flexible aliphatic diol or polyol [for example, PCL[187] or polytetramethylene glycol (PTMG)[193]] with a small excess of a rigid diisocyanate, or by the insertion of a flexible aliphatic diisocyanate[174,181] during this step. Then, a chain extender is added and the polymerization proceeds to give the final material. This last step promotes the formation of urethane or urea linkages in the so-called hard region with a high density of hydrogen bonds, which provides stiffness to that section and elastomeric properties to the final product.

The rigid 1:4,3:6-dianhydrohexitols (**1-3**) have also been used in the synthesis of PUs. Polyurethanes containing isosorbide (**1**) have been prepared by various research groups,

and complex polyurethanes with an elastomeric character and good mechanical properties were in the subject of a number of patents. They were obtained from isosorbide (**1**) and diisocyanates with the use of suitable catalysts (Scheme 31).



Scheme 31. Polyurethanes derived from Isosorbide (1)

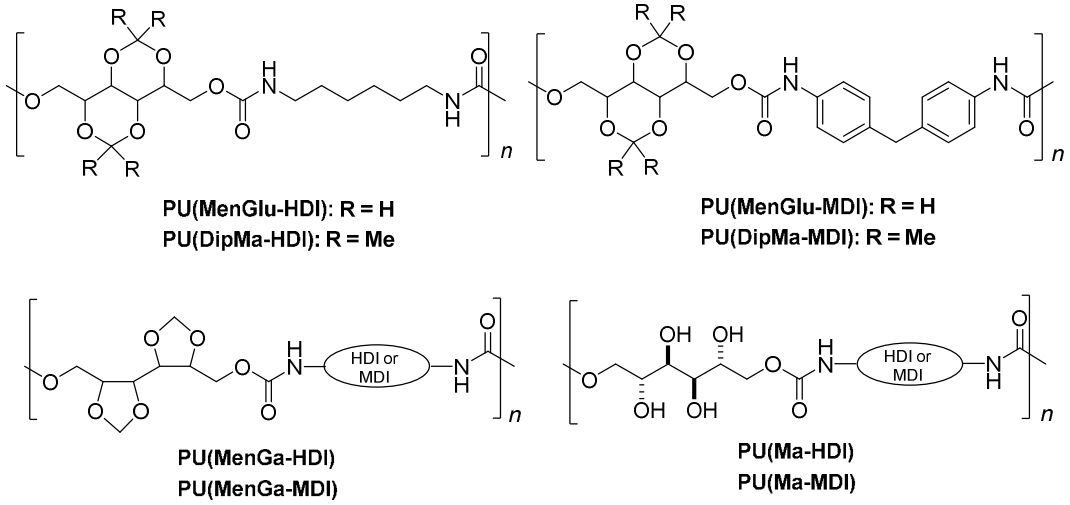
Catalytic polymerization of 2-deoxy-1,4:3,6-dianhydro-2-isocyanato-L-iditol afforded corresponding new AB-type polyurethane. An alternative synthesis has been described throug the 2-azido-5-*O*-chloroformyl-1,2-dideoxy-1,4:3,6-dianhydro-L-iditol which underwent spontaneous polycondensation by catalytic hydrogenation via the 2-amino-5-*O*-chloroformyl isoidide.[176] Transformation of the 2,5-diamino-dianhydrohexitols **82-84** into the corresponding diisocyanates was achieved by reaction with phosgene.[194] Likewise, the dithiodiisocyanate derivative was prepared from the 2,5-diamino-2,5-dideoxy-L-idide (**84**) and thiophosgene. Thus, poly(thio)urethanes and poly(thio)ureas were synthesized from the three monomers (**82-84**).[194]

Beldi *et al.*[171] studied the polymerization of 1,6-hexamethylene diisocyanate (HDI) and MDI with (**1**-**3**) as well as another novel isosorbide-based ether-diol in DMAc. They established the nature of the end groups and the fraction of cyclic and noncyclic polyurethanes by NMR and MALDI-TOF MS and demonstrated that the two combined

techniques provide a robust method for the identification of structures, chain terminations, and by-products derived from side reactions.

Muñoz-Guerra *et al.*[178] prepared segmented PU from hydroxyl-end-capped polycaprolactone (3000 g/mol) as soft segment, diisocyanates HDI or MDI, and 1,4-butanediol, isosorbide (**1**), and/or 2,4:3,5-di-*O*-methylene-D-glucitol (**24**) as extenders. The comparative effect of the preparation method (in solution or in bulk) and the influence of the selected extender, (**1** or **24**), on the properties of the resulting segmented PUs were evaluated. Hydrolytic degradability increased significantly with the presence of sugar units, although polymer degradation took place fundamentally by hydrolysis of the polyester soft segment. The same authors also carried out a comparative study of non-segmented polyurethanes with the purpose of evaluating the effect of the replacement of 1,4-butanediol by the bicyclic diol isosorbide (**1**). The polymerizations were accomplished by standard methods using HDI and MDI as isocyanates.[195] It was observed that Tg values of PU increased with the content in **1**.

The bicyclic structures of the dianhydrohexitols mentioned above are of interest due to their capacity for adding conformational restriction and stiffness to the polymer chain, with a significant increase in the Tg. Galbis *et al.*[196] reported new conformationally restricted linear polyurethanes constructed from bicyclic carbohydrate-based monomers having D-*gluco*, *galacto*, and D-*manno* configurations and their secondary hydroxyl groups protected as cyclic acetals (**23, 24, 28**) (Scheme 32). The Tg values of these conformationally restricted polymers were similar to those observed for the polyurethanes [PU(Is-HDI) and PU(Is-MDI)] based on the isosorbide (**1**)[195] and higher than their acyclic analogs. The authors also proved that the diacetalization of the sugar unit of the polyurethane chain improved the thermal stability, which was comparable to that of PUs based on isosorbide.



Scheme 32. Linear polyurethanes based on hexitols

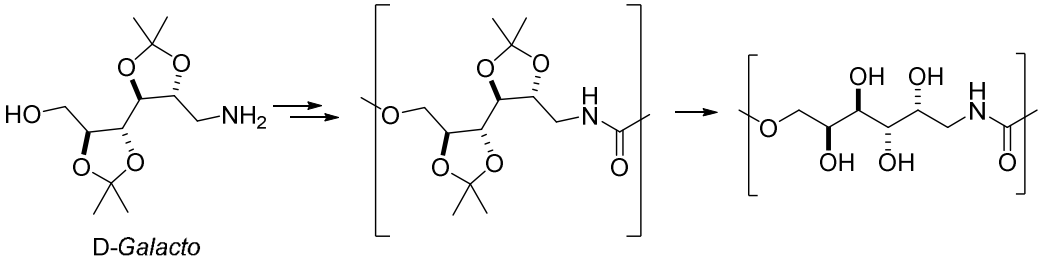
The preparation of novel PUs with free hydroxyl groups has been the target of numerous research groups. Thus, deacetalization of those polyurethanes containing di-*O*-isopropylidene-D-mannitol units (**28**) yielded multihydroxy polymers in good yields without apparent degradation of the polymer chain.[196] The latter polymers showed enhanced hydrophilicity and hydrolytic degradability as well as lower Tg values and thermal stability than their acetalized counterparts. The deprotected polyurethanes PU(Ma-HDI) and PU(Ma-MDI), were incubated in aqueous buffer at pH 7 and 70 ºC and the degradation was total for PU(Ma-HDI) after 40 days of incubation.

The synthesis of two new polyurethanes achieved by reaction of HDI with methyl 2,6-di-*O*-pivaloyl-α-D-glucopyranoside or methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**26**), catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) has been reported by Garcon *et al*.[179] Similarly, the diol methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**26)** was also polymerized with HDI and the methyl ester of L-lysine diisocyanate (MELDI)[182] as well as the diol 1,2:5,6-di-*O*-isopropylidene-D-glucitol (**25**). Both of them present hydrolyzable acetal groups (benzylidene and isopropylidene groups,

respectively) and novel hydroxy-bearing polyurethanes were synthesized by the subsequent deprotection in aqueous trifluoroacetic acid solution.

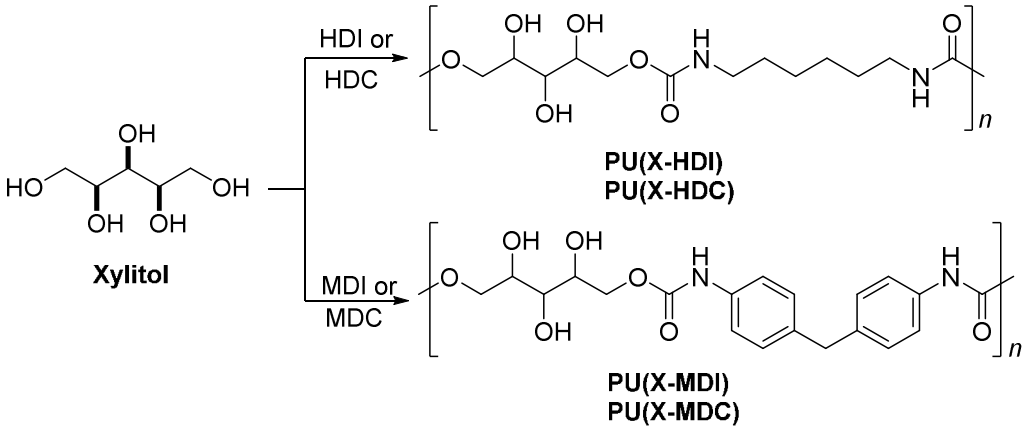
Galbis *et al.*[175] obtained linear polyhydroxylated polyurethanes having D-*manno* configuration, with enhanced hydrophilicity and degradability, by removal of the protecting isopropylidene groups from the sugar moiety. Marin and Muñoz-Guerra[178] reported the synthesis and degradation studies of new linear PUs based on acetal derivatives of D- and L-threitol. PUs with free hydroxyl groups were obtained by cleaving the isopropylidene acetal moiety in acid media. However, methylidene acetal groups were stable under the hydrolytic trial conditions. The *O*-deprotected polyurethanes were semicrystalline and hydrolytically degradable polymers, being the most-degradable material the aliphatic HDI-based hydroxylated polyurethane.

Gómez and Varela[199] described the synthesis of a stereoregular [AB]-polyurethane from 1-deoxy-1-isocyanate-2,3:4,5-di-*O*-isopropylidene-D-galactitol (obtained from 1-amino-1-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactitol) and the later hydrolysis of the isopropylidene groups (Scheme 33); however, hydrolytic degradation studies were not accomplished. They tested the solubility of both PUs, confirming that the former, substituted by acetonide groups, was highly soluble in organic solvents whereas the unprotected polyhydroxy [AB]-polyurethane displayed poor solubility even in polar solvents such as water, DMF, and DMSO.

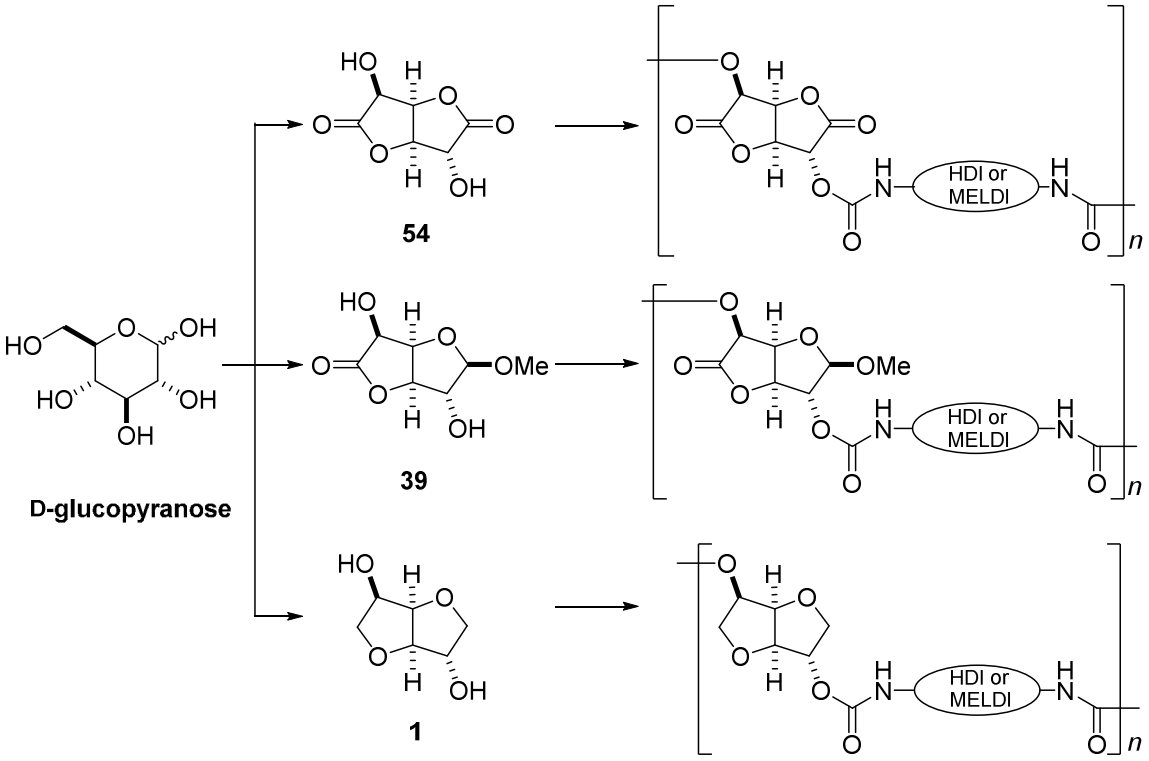


Scheme 33. [AB]-Polyurethanes from 1-deoxy-1-isocyanate-2,3:4,5-di-*O*-isopropylidene-D-galactitol

As mentioned above, hydrophilic PUs based on xylitol with their hydroxyl groups free were prepared by two different methods (Scheme 34).[177] The selective reaction of primary hydroxyl groups of xylitol with dimethyl hexamethylene dicarbamate (HDC) or di-*tert*-butyl-4,4'-diphenyl methyl dicarbamate (MDC) led to two new linear polyurethanes [PU(X-HDC) and PU(X-MDC)]. The reaction proceeded in bulk, at high temperature. Likewise, by reaction of xylitol with the analogous diisocyanates HDI or MDI, similar polyurethanes [PU(X-HDI) and PU(X-MDI)] were obtained. However, the reaction conditions needed to be adjusted, with low temperatures being required. Even so, a certain degree of cross-linking was encountered because of the higher reactivity of the diisocyanate comonomers. Polyurethanes PU(X-HMDC) and PU(X-MDC) were semicrystalline materials showing well-defined melting transitions with high melting enthalpies. They were hydrolytically degradable under physiological conditions, in contrast with less-hydrophilic linear polyurethanes previously described.[200]



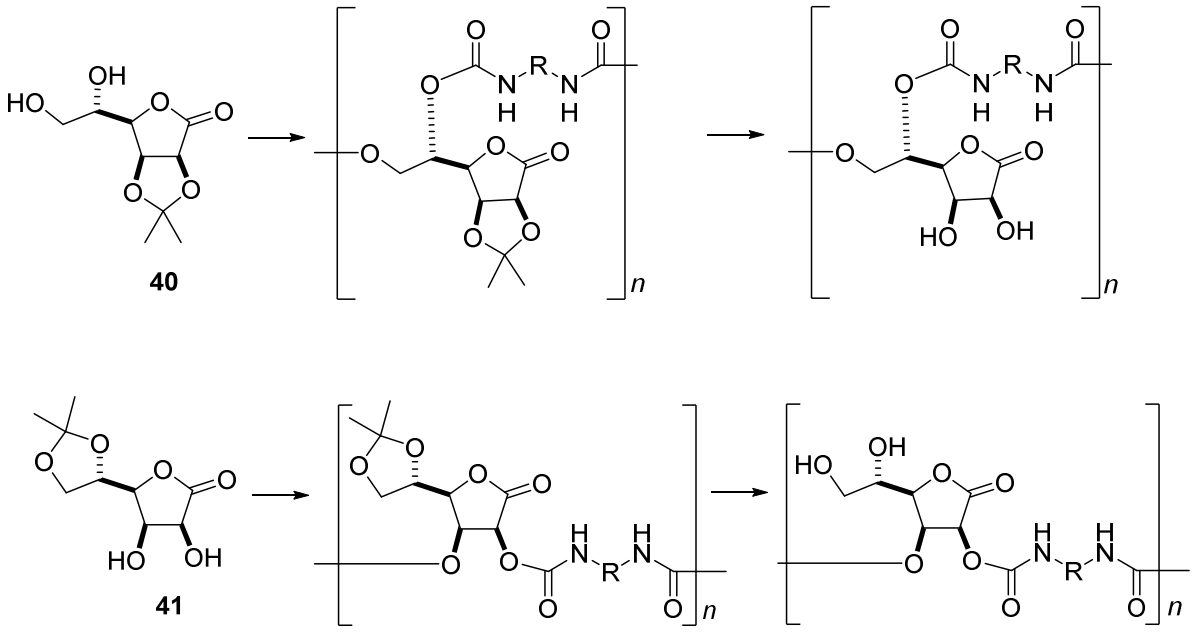
Scheme 34. Linear polyurethanes with enhanced hydrophilic character



Scheme 35. Bio-based polyurethanes from D-glucose-derived diols

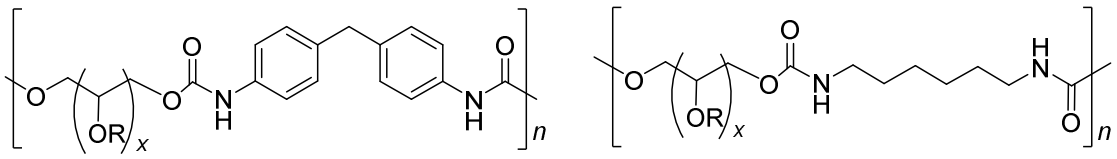
The alditols 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**29**) and 1,2-*O*-isopropylidene-D,L-erythritol were the starting material for the preparation of new linear multihydroxy polyurethanes by polyaddition with HDI and MELDI and subsequent deprotection in acid media.[193] Similarly, copolyurethanes from **29** and poly(oxytetramethylene) glycol were also prepared to estimate the effects of the D-mannitol unit on their degradability. The same authors had previously reported the synthesis of biobased polyurethanes from D-glucose-derived diols such as D-glucaro-1,4:6,3-dilactone, (**54**) methyl D-glucofuranosidurono-6,3-lactone (**39**) and **1** (Scheme 35). They found that polyurethanes containing lactone or dilactone rings (prepared from **39** and **54**, respectively), were hydrolyzed in a neutral phosphate buffer solution at 27 ºC, whereas the polyurethanes prepared from **1** –and hence, without lactone rings in their structure–

were less degradable under similar conditions.[197,201] Thus, the ring-opening hydrolysis of lactone rings is inferred to enhance the hydrophilicity and degradability of the synthesized polyurethanes.



Scheme 36. Polyaddition of L-gulonic acid-based diols to diisocyanates

Other polyurethanes bearing not only lactone rings but also free hydroxy groups in the repeating units were prepared[202] by the polyaddition reaction of L-gulonic-acid-based diols (**40** and **41**) with diisocyanates and the subsequent hydrolysis of the isopropylidene groups (Scheme 36). They found that those free-hydroxyl groups also enhanced the hydrolysis of lactone rings and, hence, of carbamate groups in the polyurethanes. The multihydroxy polyurethane prepared from L-gulonolactone **40** and HDI was degradable at pH 7.0 under mild temperatures.



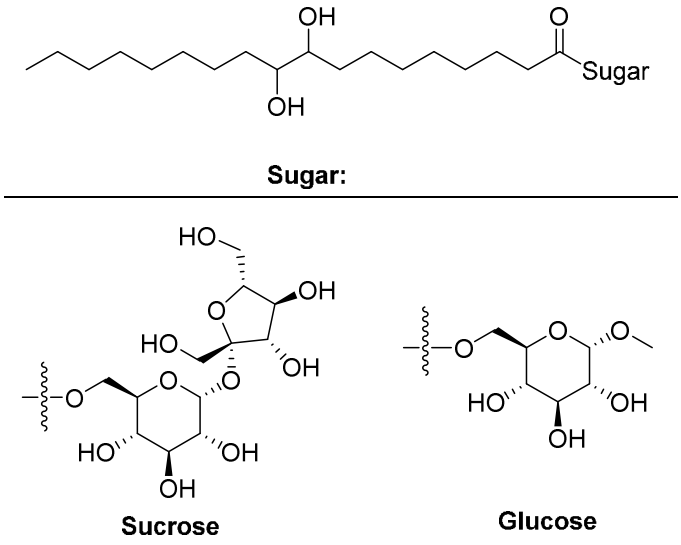
R= Me, Bn
***x*= 2, 3 (L-*Threo*, L-*Arabino*, *Xylo*)**

Scheme 37. Polyurethanes derived from alditols

Galbis, Muñoz-Guerra *et al.* also explored sugar-based diol monomers for the preparation of novel PUs.[200] They used *O*-protected L-threitol, L-arabinitol and xylitol diols (**12-13, 15-18**) to prepare a series of linear [AABB]-type polyurethanes (Scheme 37) by polyaddition reaction to HDI and MDI. The *O*-methyl protected polyurethanes derived from **5**, **10**, and **11** were amorphous; their Tg was highly dependent on the aliphatic or aromatic nature of the diisocyanate used, but barely dependent on the chemical structure of the alditol moiety. Hydrolytic studies led to the conclusion that the alditol size—that is, the number of methoxy side groups present in the repeating unit—seems to be key in determining the hydrodegradability of these polyurethanes. The polyurethanes derived from **13**, **17**, and **18** were prepared and the effect of pendant bulky benzyl groups in the polymer chain was investigated.[107,202] When hydrogenolysis of benzyl groups was carried out to render multihydroxyl compounds, severe reaction conditions were required, and the degree of deprotection was followed by ^{1}H NMR. Best results were obtained for the PU derived from L-threitol [PU-(LThBn-HDI)], which became debenzylated up to 70%. The completely *O*-benzylated PUs were highly resistant to hydrolytic degradation, whereas polyurethanes with free hydroxyl groups degraded considerably under physiological conditions.

To achieve a facile preparation of sugar-based multihydroxy PUs, the use of unprotected saccharides has also been investigated. Thiem *et al.* reported the synthesis

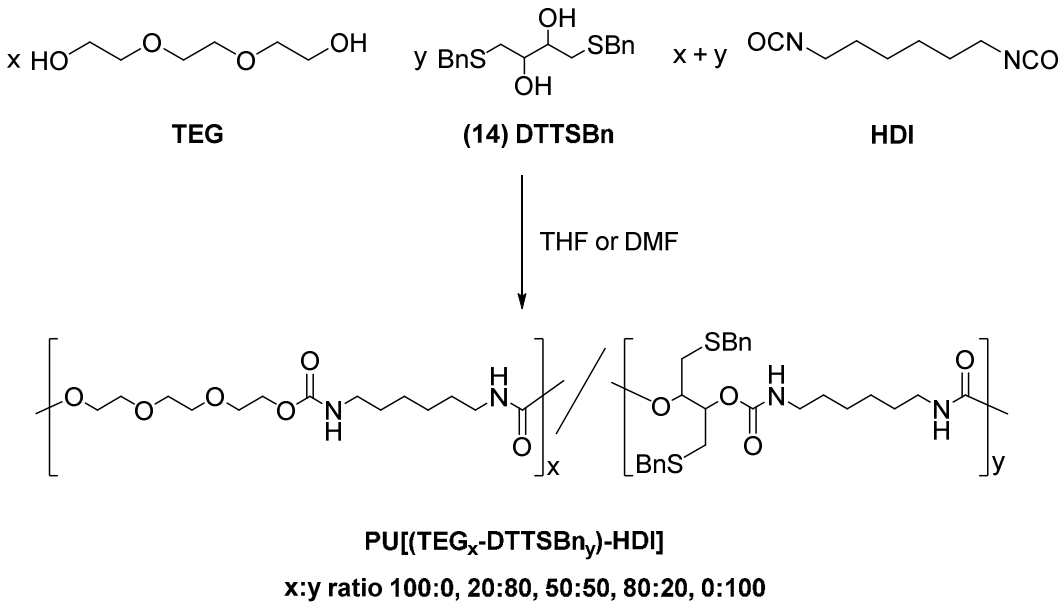
of linear poly(thio)urethanes and poly(thio)ureas based on modified glycosylamines or glucosamines (with functionality ≥ 2) and HDI or L-idide-derived diisocyanate and dithioisocyanate, at room temperature or above, using dibutyltin dilaurate (DBTDL) and triethylamine (TEA) as catalysts.[175] It was found that the anomeric hydroxyl groups were more reactive than the amino groups.



Scheme 38. Diol monomers synthesized from methyl α-D-glucopyranoside or sucrose and epoxidized methyl oleate

Two novel sugar-based polyol monomers from methyl α-D-glucopyranoside and sucrose and epoxidized methyl oleate were synthesized (Scheme 38).[192] Linear and cross-linked PUs were obtained by polyaddition with isophorone diisocyanate as comonomer. The polymerization reactions were carried out at 60 ºC using DBTDL as catalyst. The amphiphilic nature of the sugar-based monomers had a marked impact on the final product isolated. Thus, linear or cross-linked PUs were obtained depending on the solvent used, *i.e.* THF or DMF. It was found that the polyol monomers were fully soluble in DMF and, therefore, cross-linked PU's were obtained. In contrast, the formation of linear PUs with one pendant sugar moiety per monomer unit was attained in THF. The hydroxyl functions from the sugar moiety were quasi non-reactive under

those conditions due to the self-assembly of the sugar-based polyols into nanoparticle structures.



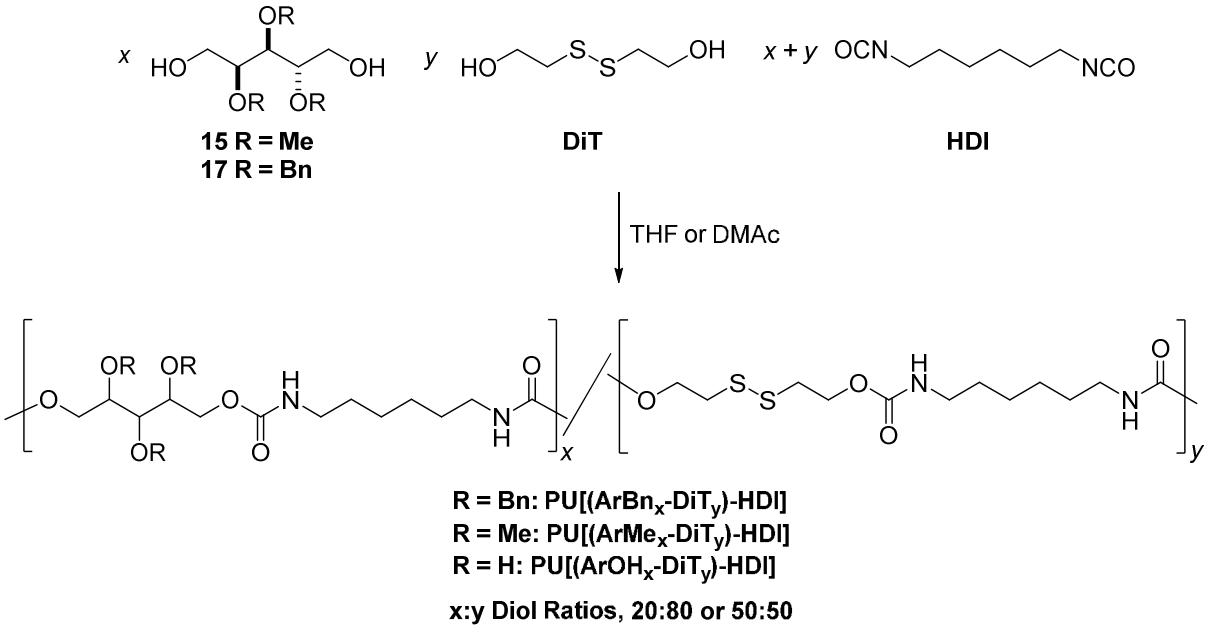
Scheme 39. Copolyurethanes based on D,L-dithiothreitol

To improve the hydrophilic character of polyurethanes and, hence, their degradability, the inclusion of a hydrophilic monomer (triethylene glycol, TEG) was explored. A batch of new homo- and copolymers (Scheme 39) was successfully synthesized by reaction of HDI and mixtures of TEG and 1,4-di-*S*-benzyl-D,L-dithiothreitol (DTTSBn) (**14**).[173] The copolymer compositions were in good agreement with that of their corresponding feed. The PU(TEG-HDI) homopolymer exhibited a high crystallinity, and reductions in TEG content of the copolymers led to loss of crystallinity and flexibility, with associated increases in their Tg values. The homo- and copolymers were thermally stable up to 250 ºC, with higher thermal resistance displayed by the polymers with higher TEG content. Chemical and enzymatically catalyzed hydrolytic degradations of the macromolecules were tested under physiological conditions. Two proteolytic enzymes (papain and α-chymotrypsin) and two esterase enzymes

(cholesterol esterase and lipase) were chosen to perform enzyme-mediated hydrolysis trials —the first reported use of pancreatic lipase for urethane-bond hydrolysis in polyurethanes. A study of the properties of the biodegradable homopolyurethane PU(TEG-HDI) as matrix-forming excipient for controlled drug delivery has been carried out.[203]

Several degradation mechanisms of polyurethanes—hydrolytic, enzymatic, and oxidative—have been reported.[204-207] Galbis *et al.* proposed disulfide bonds as an alternative approach to enhance the degradability of polyurethanes in biological systems.[208] Disulfide bonds are the bridging structure most commonly encountered in biological systems, and can be cleaved by the action of the natural tripeptide γ-glutamyl-cysteinyl-glycine (glutathione, GSH), which is the most abundant low-molecular-weight biological thiol, and one of nature's premier antioxidants and free-radical scavengers. The authors reported the introduction of disulfide linkage into the polymer backbone of novel reduction-sensitive biodegradable sugar-based polyurethanes. Although hydrolytic degradation of PUs has been extensively reported, a faster degradation method under milder degradation conditions was achieved.[208] Thus, polyaddition reaction of mixtures of 2,2'-dithiodiethanol (DiT) and 2,3,4-tri-*O*-methyl-L-arabinitol (**15**) or 2,3,4-tri-*O*-benzyl-L-arabinitol (**17**) to HDI were carried out (Scheme 40). PU(DiT-HDI) homopolymer exhibited high crystallinity but the introduction of the L-arabinitol-based diols led to a reduction in the crystallinity of the copolymers. In their TG curves, the copolymers displayed a mixed trend of the related homopolymers, and all of them were thermally stable, with degradation temperatures above 220 ºC. The degradation properties of the macromolecules under physiological conditions in the presence of glutathione were tested. All the copolyurethanes proved to be biodegradable under physiological conditions. The crystallinity played an important

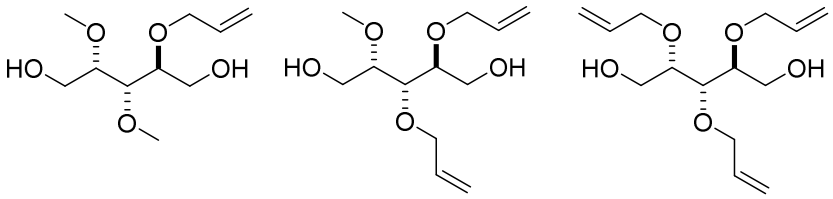
role in the degradation rate in the case of the copolymers. Thus, the amorphous copolymers with low DiT-HMDI repeating unit contents were more easily cleaved, despite the lower disulfide ratio. Their DiT-HMDI repeating units do not pack into semicrystalline segments and were, as a result, more accessible to the reducing agent. Therefore, the amorphous copolymers PU[(ArBn$_{80}$-DiT$_{20}$)-HMDI] and PU[(ArMe$_{80}$-DiT$_{20}$)-HMDI] were those with enhanced degradation trends.



Scheme 40. Copolyurethanes degradable by glutathione under physiological conditions

The modification of polymers after the successful achievement of a polymerization process is an important task in macromolecular science. Click chemistry (CC) may serve as a powerful strategy in its pursuit. CC has emerged as a widespread approach that uses only the most-practical and -reliable chemical transformations. The thiol-ene coupling reaction is a well-established click reaction that combines a thiol moiety and an alkene/alkyne group in a robust, efficient, and orthogonal method for the functionalization of different compounds. Allyl groups can be used in thiol-ene

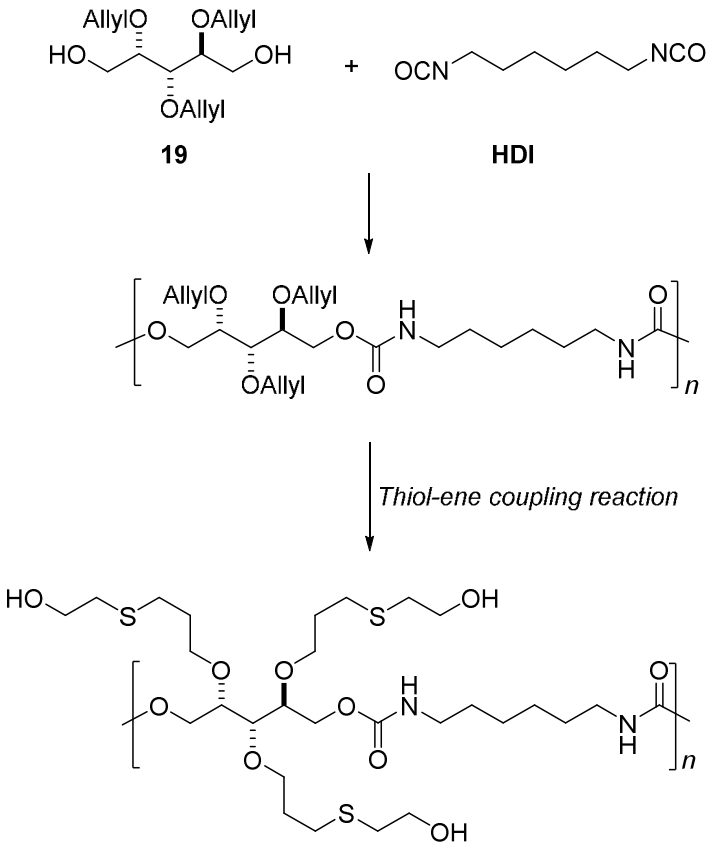
coupling reactions as the *ene* part with great success. Therefore, Galbis *et al.* tackled the preparation of new polymerizable diols — based on mono-, di-, and tri-*O*-allyl-L-arabinitol derivatives — prepared from L-arabinitol (Scheme 41) as versatile materials for the preparation of tailor-made polyurethanes with varied degrees of functionalization.[209] Their allyl functional groups can take part in thiol-ene reactions, to obtain greatly diverse materials.



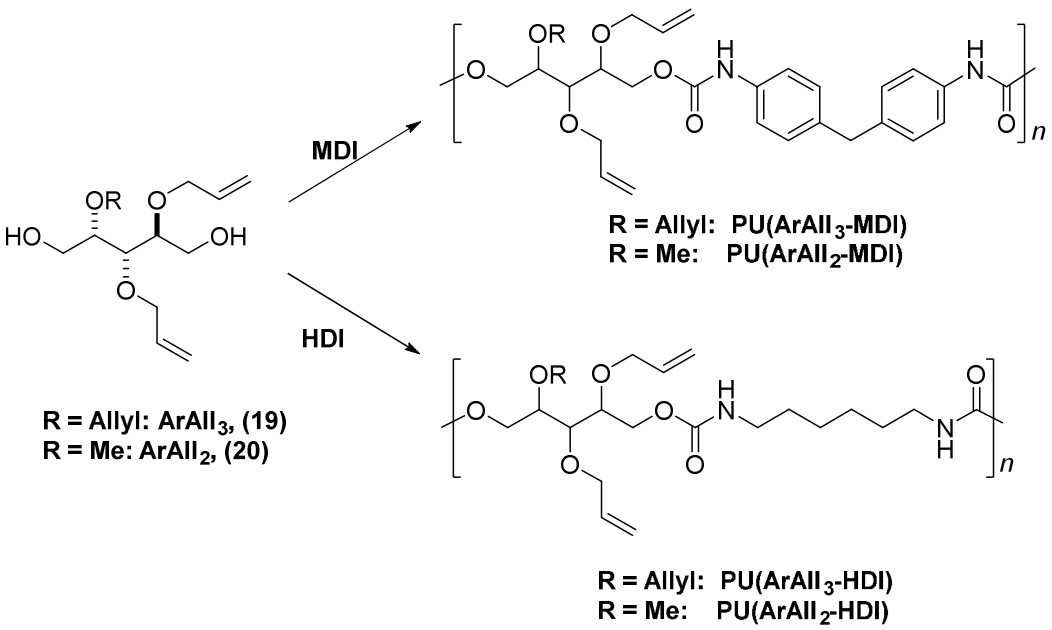
ArAll $ArAll_2$, **20** $ArAll_3$, **19**

Scheme 41. *O*-Allyl polymerizable diols prepared from L-arabinitol

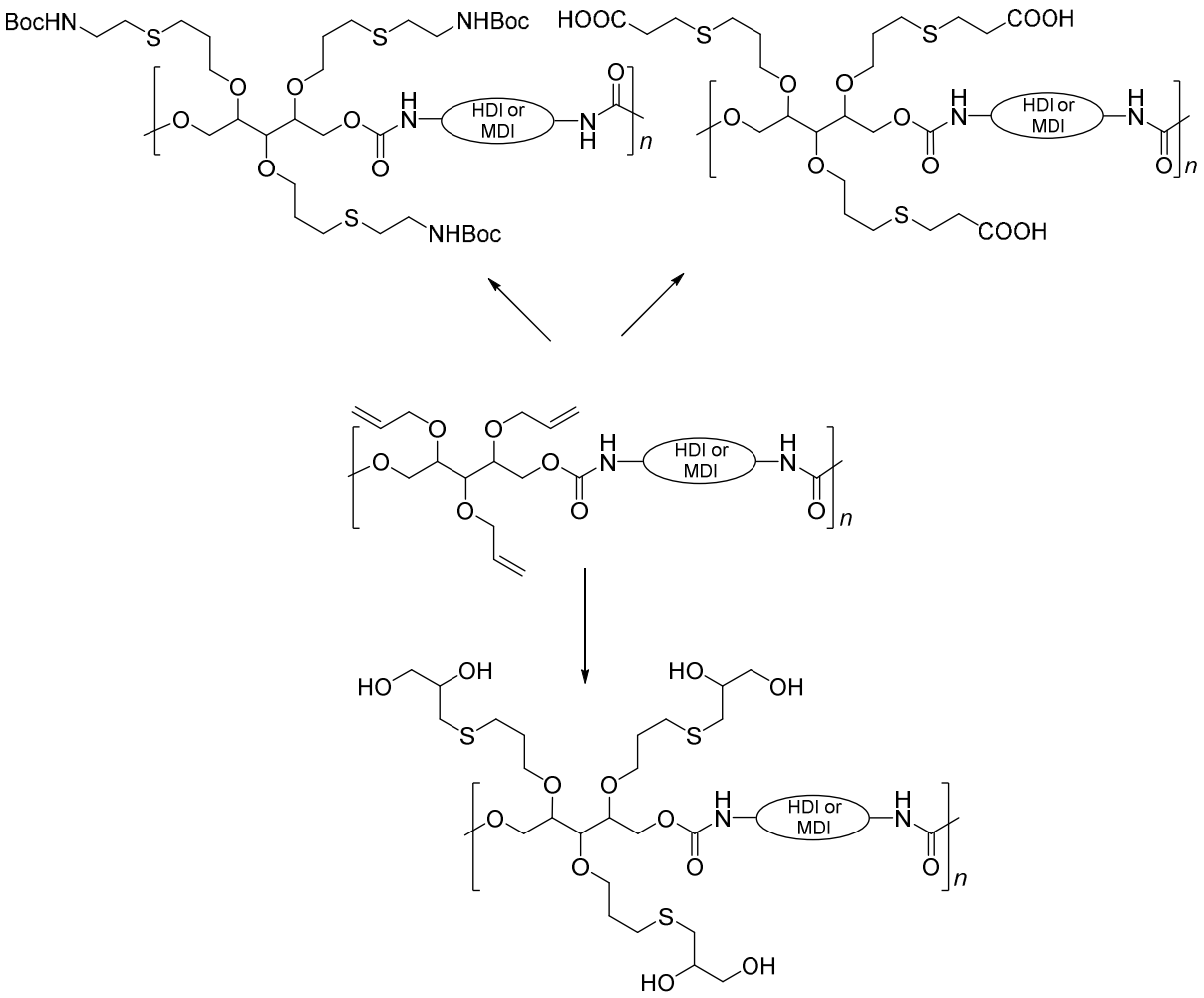
A polyurethane with multiple pendant allyl groups was synthesized (Scheme 42) by polyaddition reaction of 2,3,4-tri-*O*-allyl-L-arabinitol (**19**) with HDI, and then functionalized by thiol-ene reaction with 2-thioethanol. Novel polyurethanes with multiple pendant allyl groups were synthesized from L-arabinitol (Scheme 43) and proved to be versatile materials for the preparation of tailor-made polyurethanes with distinct degrees of functionalization.[210] Their *O*-allyl functional groups took part in thiol-ene reactions to obtain greatly diverse materials. Thus, new highly functional polyurethanes were prepared by CC from the PUs based on the diol **19** to give polymers with NHBoc, carboxylic, and 1,2-dihydroxyethyl side groups (Scheme 44). This strategy provides a simple and versatile platform for the design of new materials whose functionality can be easily modified to anchor diverse biologically active molecules.



Scheme 42. Functionalization of *O*-allyl polyurethanes by the click thiol-ene reaction



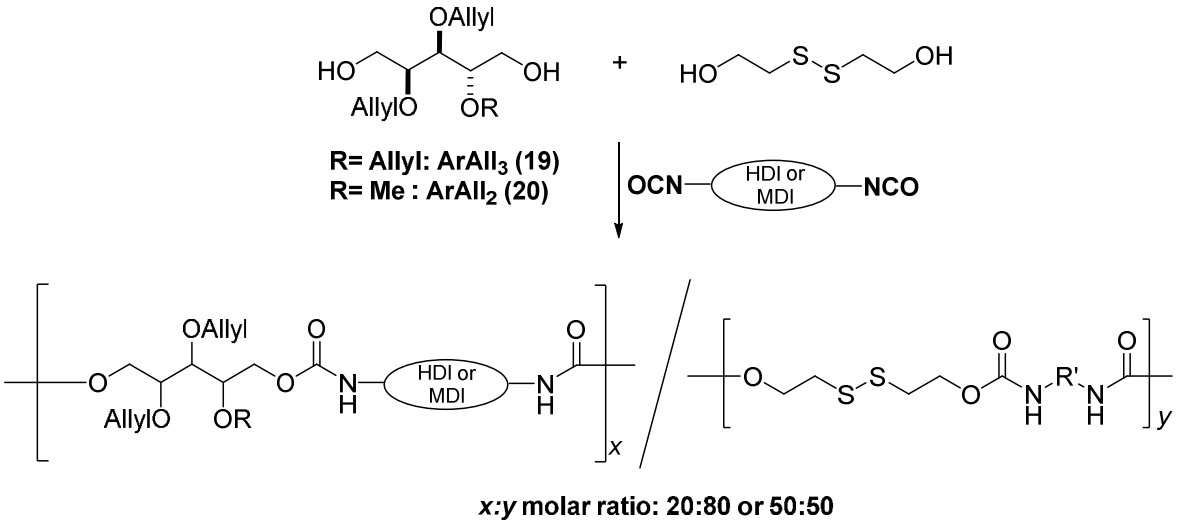
Scheme 43. Synthesis of allyl homopolyurethanes



Scheme 44. Functional polyurethanes prepared by click reactions on *O*-allyl polyurethanes

With the aim of attaining promising functional biomaterials, Galbis *et al.* united two features for the rational design of polymers tailored for use as drug delivery vehicles in the colon: functionality *via* CC, and enhanced degradability, in reductive environments, *via* the introduction of disulfide linkages. Thus, the preparation of novel reduction-sensitive biodegradable multiallyl- and multiamine-based copolyurethanes, useful as carriers of anionic drugs (at physiological pH) or gene materials, was successfully achieved.[211] The copolymerization procedure, as well as the degradability, was initially tested by preparing various multiallyl disulfide-containing copolyurethanes. The two

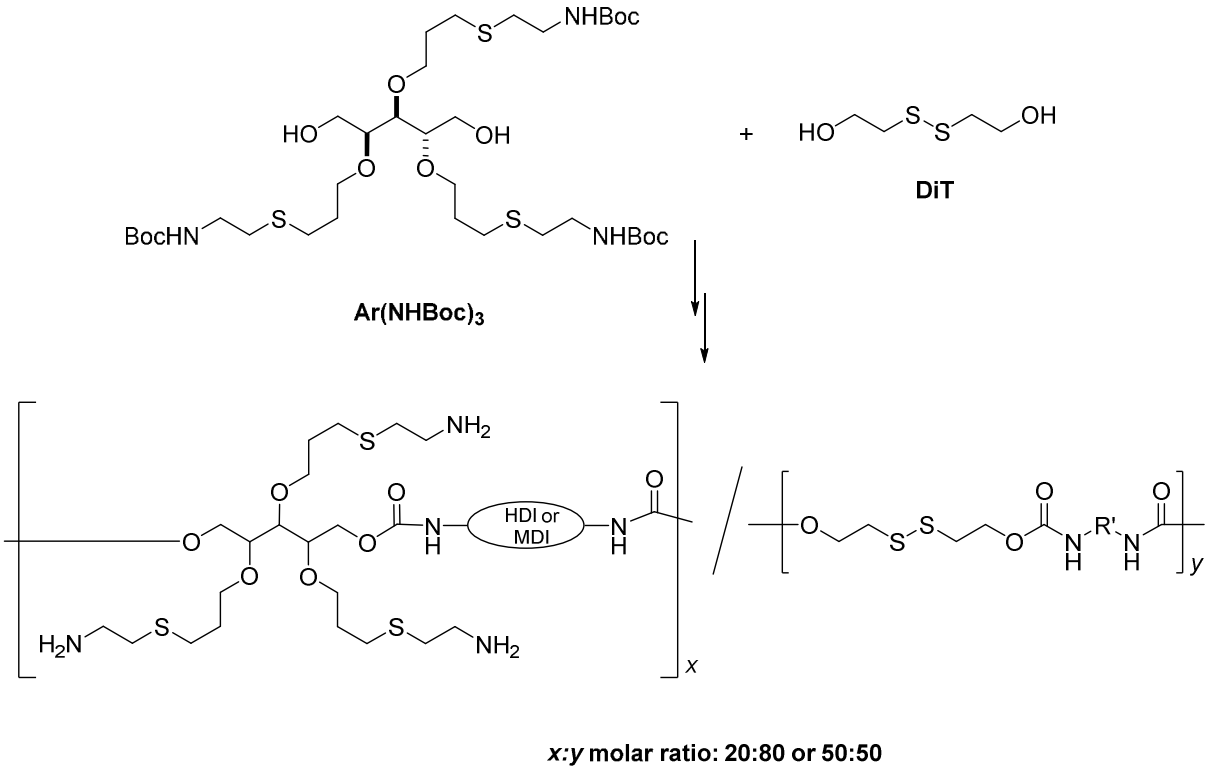
functional allyl diol monomers 2,3,4-tri-*O*-allyl-L-arabinitol ($ArAll_3$, **19**) and 3,4-di-*O*-allyl-2-*O*-methyl-L-arabinitol ($ArAll_2$, **20**), and the commercial 2,2'-dithiodiethanol (DiT), were the starting diol materials for the preparation of the novel linear multiallyl-based copolyurethanes (Scheme 45).



Scheme 45. Multiallyl disulfide-containing copolyurethanes

The procedure used to synthesize the reduction-sensitive multiamine copolymers was analogous to the method mentioned above for multiallyl-based copolyurethanes; the chosen sugar-based diol monomer was $Ar(NHBoc)_3$, with the amine groups conveniently protected to prevent undesirable side reactions (Scheme 46). Once the polymerization was accomplished, deprotection of the amine groups led to the target materials in high yields. The copolymers functionalized with amino groups (protected or free) exhibited lower thermal stability than those bearing allyloxy pendant groups. Functionalization of the sugar moieties greatly affected the Tg of the polymer precursors. At the same time, the DiT diol content controlled the Tm values of the random copolymers. The highest degradation rates in reductive environments were obtained for the aliphatic amino-based copolymer, with an associated weight loss close

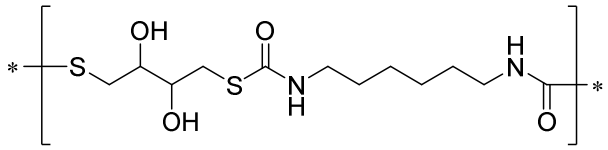
to 90% after ten days. This polymer was used in the preparation of colon-targeted drug delivery systems. An *in vitro* study of tablets containing the anticancer drug methotrexate demonstrated its impressive ability to control the drug's release, despite its low concentration in the tablet.[211]



Scheme 46. Synthesis of reduction sensitive multiamine copolyurethanes

Although polyurethanes are widely investigated, their sulfur analogs, polythiourethanes (PTU) are a relatively poorly investigated group of polymeric materials.[175,212] The synthesis and characterization of a new linear functional polythiourethane based on D,L-1,4-dithiothreitol [PTU(DTT-HDI) have been accomplished and its properties as excipient in drug-release formulations investigated.[213] This polythiourethane (Scheme 47), with free hydroxyl groups in its structure, showed a great ability to form matrix systems and promoted a significant decrease in the release rate of the model drug

theophylline; as a result, it proved to be an excellent controlled-release matrix-forming excipient.

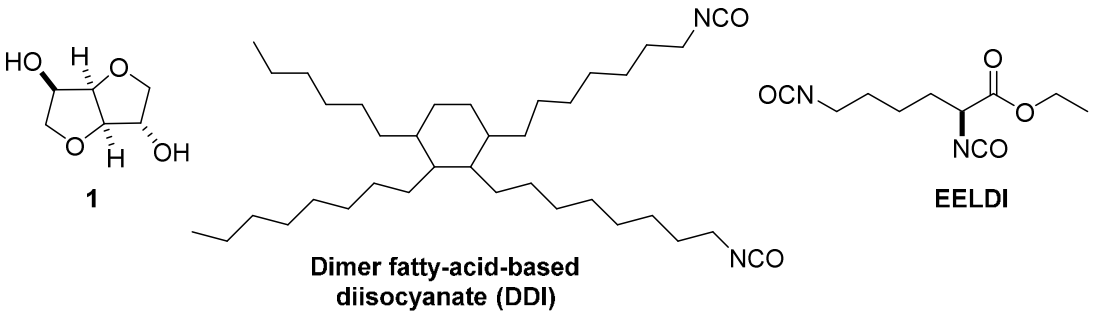


PTU(DTT-HDI)

Scheme 47. Structure of D,L-1,4-dithiothreitol-based polythiourethane

In recent times oil prices and environmental concerns have boosted the production of biomass-based poly(urea urethane) (PUU) building blocks, such as plant-oil-based polyols, sugar-based dianhydrohexitol isomers and their corresponding diamines, as well as some diisocyanates [ethyl ester L-lysine-based diisocyanate (EELDI) and a dimer fatty-acid-based diisocyanate (DDI), for example]. Koning *et al.*[174] have described the preparation of aqueous polyurethane prepolymer dispersions from a dimer fatty-acid-based diisocyanate (DDI), neutralized 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoic acid (DMPA) as the internal dispersing agent, and isosorbide, containing at least 92 wt% of renewable compounds (Scheme 48). The NCO-end-capped hydrophobic PU prepolymers were synthesized in butanone, at 70 ºC and with catalytic amounts of DBTDL. The resulting prepolymer dispersion was chain-extended with diamines, diols, or water to obtain high-molecular-weight PUU products. Finally, the ketone was removed from the dispersions, resulting in a solvent-free polyurethane dispersion (PUD) system. The extenders and other variables such as the chain-extension temperature and the utilization of a catalyst (triethylamine, TEA) were investigated as well. When water was used as chain extender, instantaneous water chain extension took place at 50-70 ºC. At 50 ºC, a stable dispersion with a relatively high molecular weight, a small particle size, and a narrow particle size distribution was reached. All PUDs showed good storage stability for several months and their Tg values, determined by

DSC measurements, were all around room temperature, which facilitates film formation at ambient temperature.

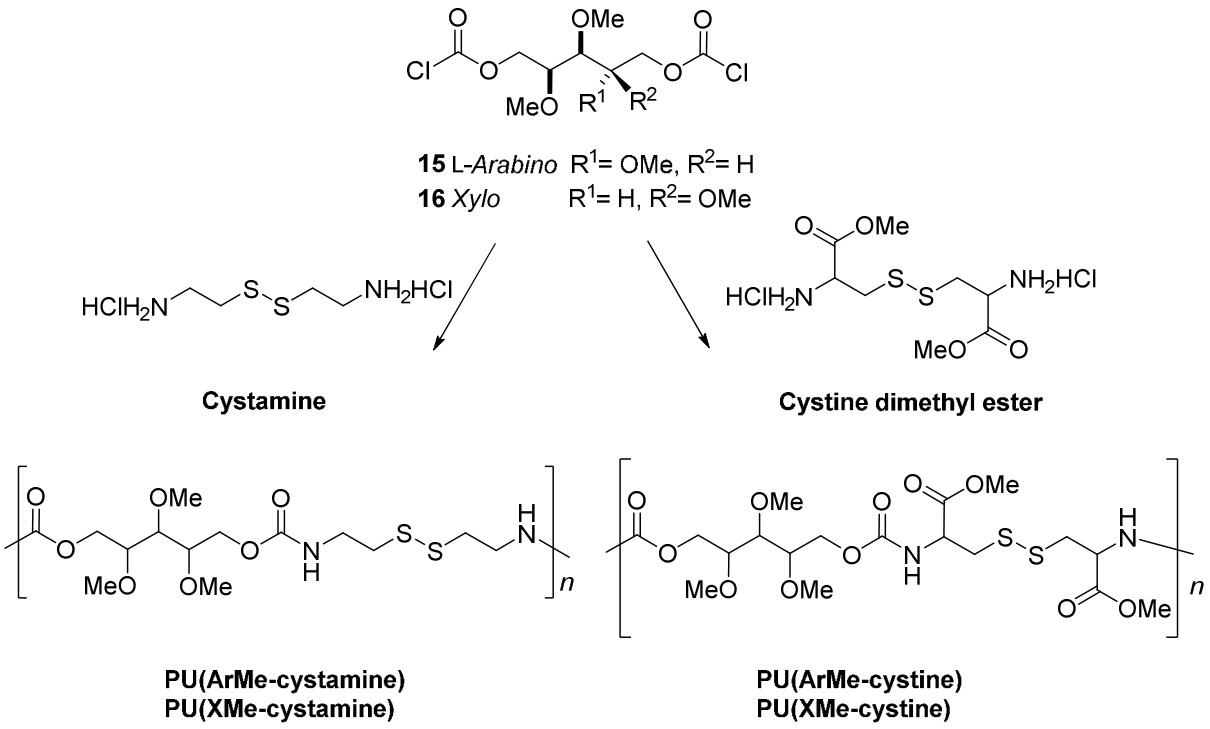


Scheme 48. Monomers for fully biobased polyurethanes

The thermal and mechanical properties, as well as the morphology, of some isosorbide (**1**) biobased poly(urethane urea) dispersion-cast films prepared were studied by the same authors.[181] A dimer fatty-acid-based diisocyanate (DDI) and ethyl ester L-lysine diisocyanate (EELDI) were the chosen diisocyanates. The films showed good electrostatic stability at pH values ranging from 4 to 12. An enhanced thermal stability was observed for films with reduced concentration of urethane and urea contents.

As described so far, polymerization reactions of diisocyanates with diols are the main method to synthesize linear PUs. However, and due to the toxicity of the stannous catalysts and common aromatic diisocyanates such as MDI and toluene diisocyanate (TDI), other methods have been explored. Thus, reactive bis(chloroformates) were formed from sugar-based diols, and polymerized by interfacial polycondensation with selected diamines.[188] In contrast with the diisocyanate method, a wide range of PUs can be prepared from a large set of commercial diamines, and hence the chemical versatility of the new materials may be highly improved. The diamines used were derivatives of the natural amino acid L-cysteine, and were chosen as bearing the labile disulfide bond

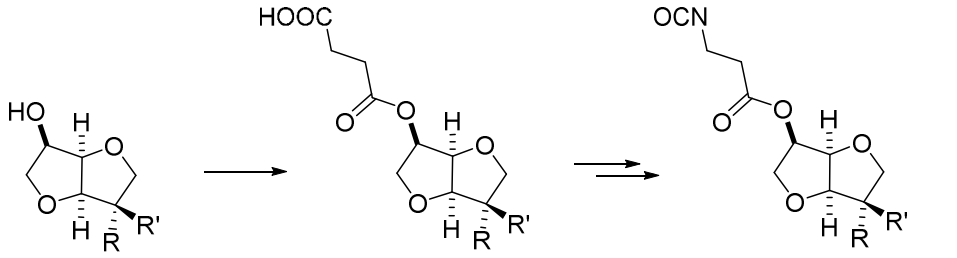
in their structure (Scheme 49). This method avoided the use of a second monomer to introduce the disulfide function into the polymer chains. The preparation of bis(chloroformate)s monomers derived from diols **15** and **16** by means of phosgene is safe since its excess can be completely removed prior to the polymerization process.[188] DSC studies showed that all the new materials are semicrystalline and the incorporation of a pendant methoxycarbonyl group into the diamine unit (L-cystine dimethyl ester-based homopolymers) results in a more rigid material. Moreover, the presence of methoxycarbonyl side groups makes the PUs more degradable, not only in the hydrolytic trials but also in the degradation under reductive environments, probably due to their lower crystallinity and a better water/glutathione penetration in their structure.



Scheme 49. Reduction-sensitive homopolyurethanes from diamines and bis(chloroformate)s

Of interest in the search for alternative methods of preparing bio-renewable polyurethanes is the synthesis of new diisocyanates without using stoichiometric

petroleum-based reagents. Thus, two non-hindered diisocyanates based on isosorbide (**1**) and isomannide (**2**) were successfully prepared with overall conversions ranging from 52% to 60%.[214] The general procedure (Scheme 50) started with a double esterification of the diols **1** or **2** with succinic anhydride in bulk at 120 ºC, and then the crude acids were transformed into the corresponding diacid chlorides at low temperatures. Diisocyanate formation was achieved *via* a two-step Curtius rearrangement of diacid chlorides through the diacyl azide intermediates. To assess the suitability of both diisocyanates for the synthesis of high-performance materials, the preparation of a stereoregular PU (with D-*manno* configuration in all the monomers) as well as a non-stereoregular PU (with D-*gluco* configuration) was attempted.



Scheme 50. Synthesis of isosorbide- and isomannide-based diisocyanates through Curtius rearrangement

Surprisingly, the diacid derived from isosorbide proved to be so tacky under ambient conditions that, in a parallel study by the same authors,[215] an interesting group of low-cost tackifiers with up to 100% biocontent was synthesized and characterized.

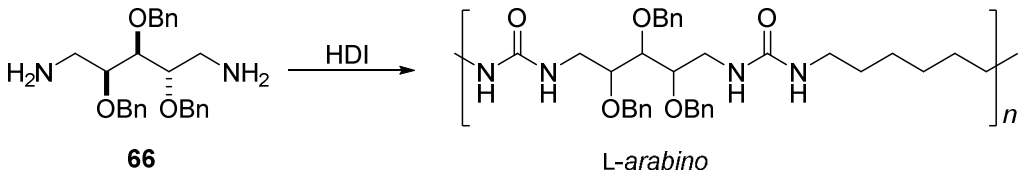
Besse *et al.* reported the preparation of linear and branched isosorbide-based polyhydroxyurethanes, with low Tg values (from -8 ºC to 59 ºC), through an isocyanate-free synthetic procedure. The step-growth polyaddition reactions of dicyclocarbonates derived from isosorbide and commercial diamines were achieved.[216] The isosorbide-

based cyclocarbonate monomers and oligomers involved in this work were produced from epoxides in accord with the method previously described by Brocas *et al.*[217] Unfortunately, the materials isolated were of low molecular weight and highly polydisperse..

8. Polyureas

Although some degradable poly(urethane urea)s based on renewable resources –such as L-cystine– have aroused a certain interest because they could potentially be applied as temporary biomaterials,[218] sugar-based polyureas has attracted less attention to date. Koning *et al.* have described some poly(urethane urea) dispersions containing renewable building blocks including isosorbide (**1**),[181] and thermoplastic poly(ester urethane urea)s from biobased monomers, such as L-lysine diisocyanate, isoidide diisocyanate, 1,4-diaminobutane, and diaminoisoidide (**84**).[219]

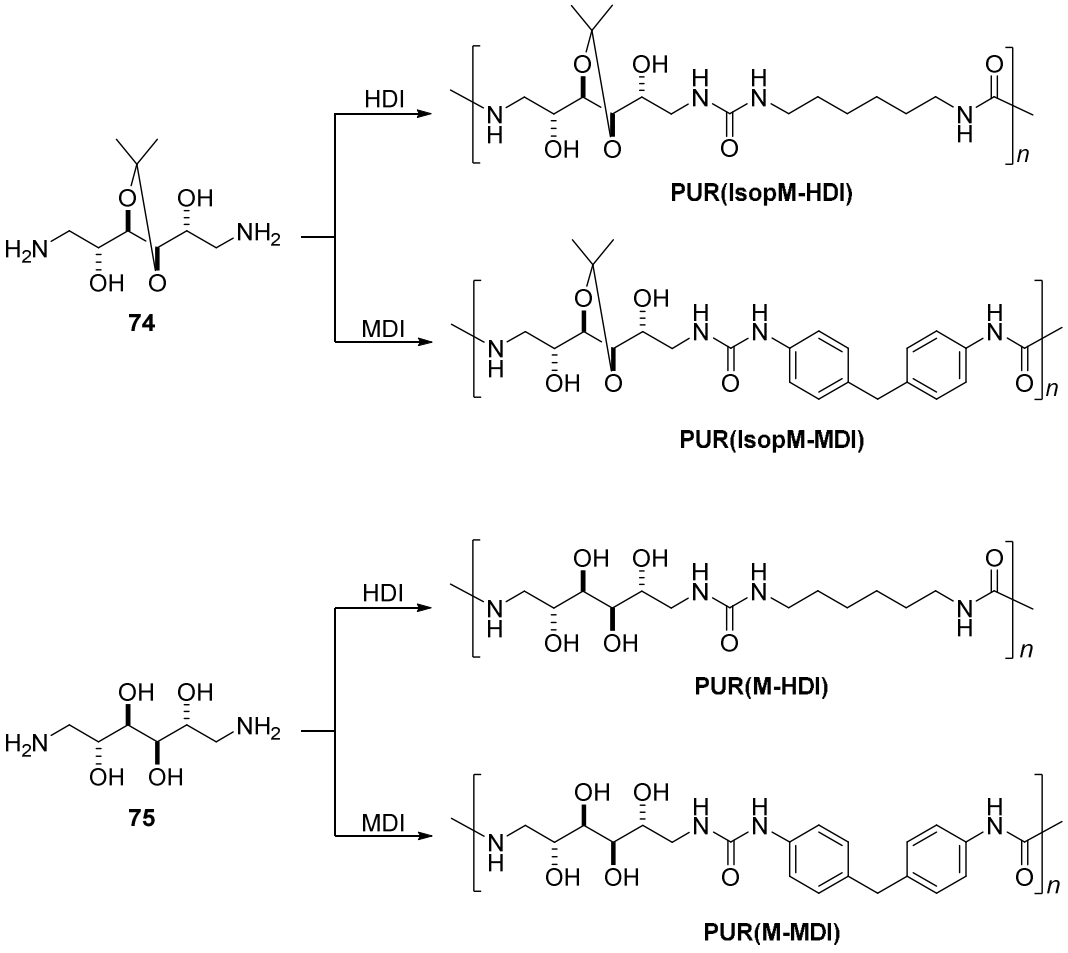
Thiem *et al.*[194] described the preparation of fully sugar-based polyureas by polyaddition reactions of the 1,6-diamino-1,6-dideoxy-dianhydrohexytols (**82**-**84**) to the isoidide diisocyanate. Galbis and co-workers[107] also described the synthesis of a semicrystalline polyurea (Scheme 51) by polyaddition reaction of the *O*-benzyl-1,6-diamino-L-arabinitol (**66**) to HDI.



66 L-*arabino*

Scheme 51. L-Arabinose-based polyurea

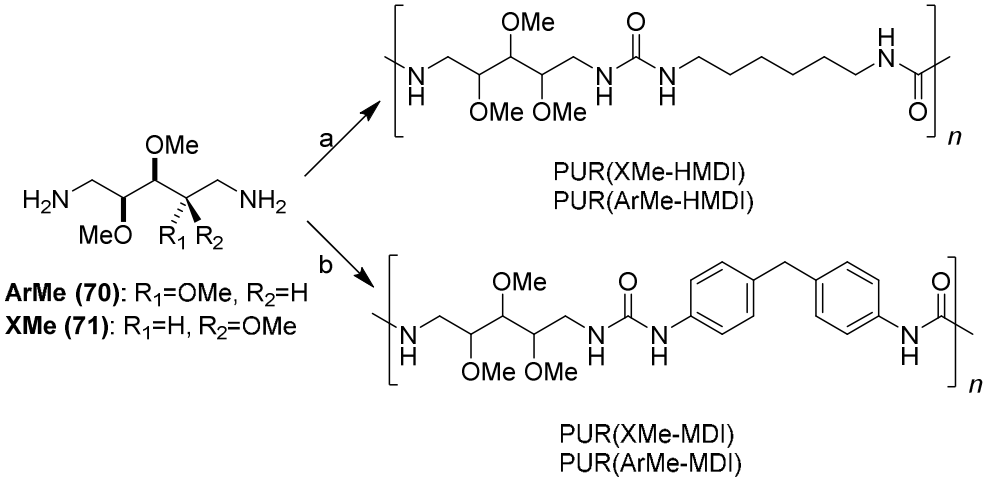
A novel series of linear hydrophilic polyureas having free hydroxyl groups joined to the main chain has also been prepared by the same group[177] by reaction of HDI and MDI with 1,6-diamino-1,6-dideoxy-D-mannitol and 1,6-diamino-1,6-dideoxy-3:4-*O*-isopropylidene-D-mannitol (Scheme 52). This type of polyhydroxylated polyurea had not been described previously in the literature. The DSC studies showed that the new polyureas presented a semicrystalline behavior and all of them were stable up to temperatures of about 220 ºC, markedly higher than their melting temperatures.



Scheme 52. Novel polyhydroxylated polyureas

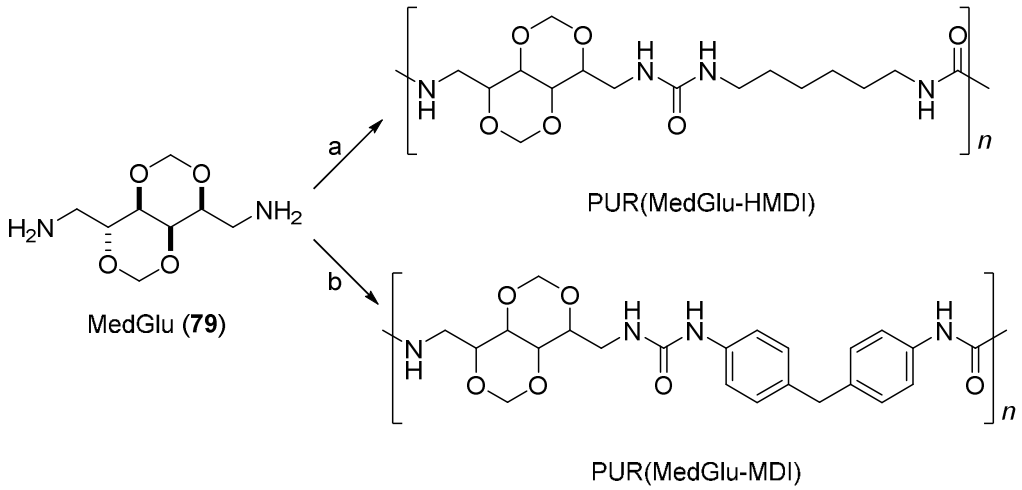
A batch of linear [AABB]-type sugar-based polyureas was synthesized by polyaddition reaction in solution from HDI or MDI with the acyclic diamino-alditols having L-

arabino (**70**) or *xylo* (**71**) configurations (Scheme 53), or the bicyclic 1,6-diamino-1,6-dideoxy-2,4:3,5-di-*O*-methylene-D-glucitol (**79**, Scheme 54).[220] The polymers were obtained in good yields and fair molecular weights. All these polyureas were semicrystalline materials showing well-defined melting transition, with Tg values being dependent on the aliphatic or aromatic nature of the diisocyanate used, and on the cyclic or acyclic chemical structure of the sugar moiety. They were found to be stable up to around 240°C, decomposing at higher temperatures through a one- or two-stage mechanism.



a) HMDI, DMAc, 25 ºC; b) MDI, DMAc, 25 ºC

Scheme 53. Acyclic-sugar-based polyureas



a) HMDI, DMAc, 40 ºC; b) MDI, DMAc, 40 ºC

Scheme 54. Polyureas from bicyclic sugar-based monomers

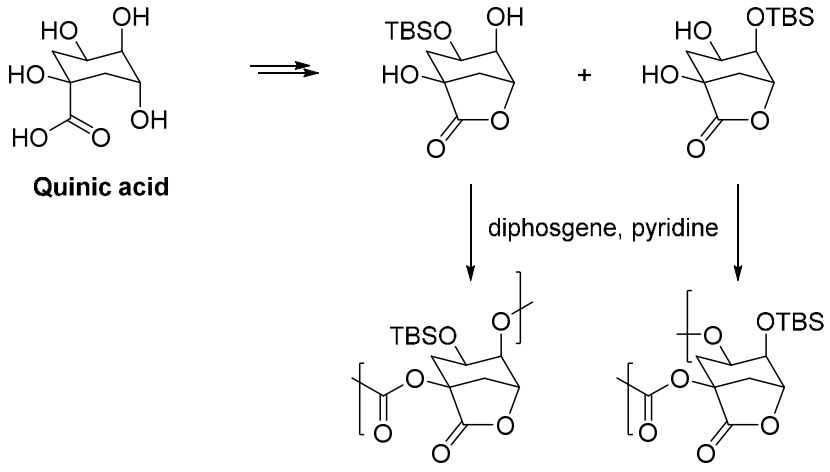
9. Other carbohydrate-based polymers

Biobased, renewable resources are considered potential substitutes for crude oil as feedstocks for polymer materials. Thus, Chatti *et al.*[221] studied the preparation of new poly(ether-ester)s from biomass derivatives and more especially from an ether-diol based on isosorbide (**1**) and two dicarboxylic acid dichlorides (adipoyl chloride and terephthaloyl chloride). The polymerizations were carried out in bulk, at high temperature, and the best results were achieved under microwave activation. The reaction proceeded roughly five times faster under microwave irradiation, and the new semicrystalline polymers were studied by MALDI-TOF MS and NMR.

Koning *et al.* [219] have reported the preparation and the characterization of a series of fully renewable thermoplastic poly(ester urethane urea)s based on a renewable polyester diol [poly(1,2-dimethylethylene adipate], two biobased diisocyanates [ethyl ester L-lysine diisocyanate (EELDI) and isoidide diisocyanate], and several renewable diamine

chain extenders. When incorporating the renewable L-lysine diisocyanate in the polymers, the use of di(4-aminobutyl)urea was necessary to attain good phase separation and, hence, good mechanical properties. As expected, the polymers based on isoidide diisocyanate exhibited a higher E-modulus than the corresponding L-lysine diisocyanate counterparts.

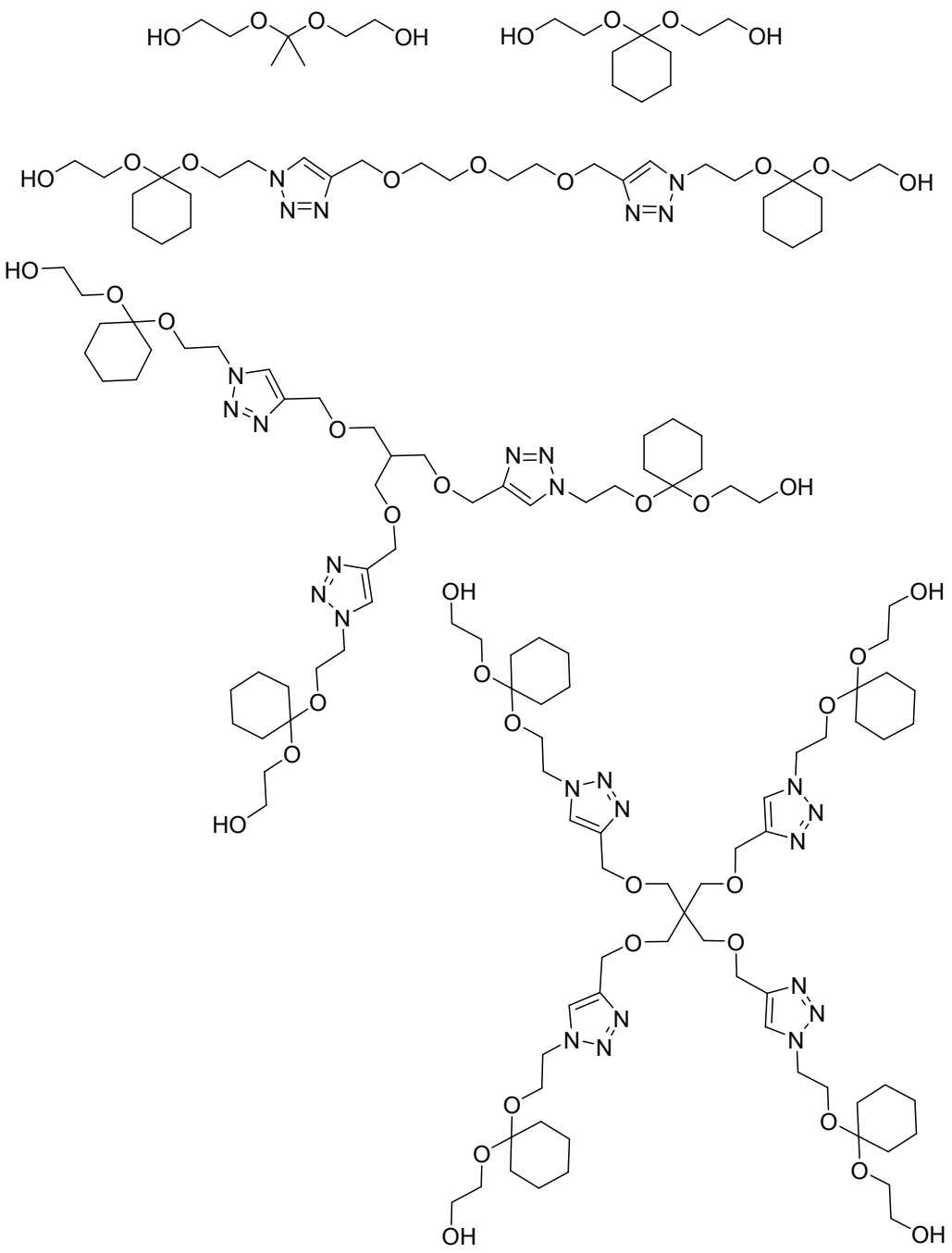
Quinic acid is a natural cyclitol found in coffee beans and other plants. Their protected *tert*-butyldimethylsilyloxy (TBS) 1,4- and 1,5-diol monomers afforded polycarbonates (Scheme 55) with high-temperature thermal transitions and enhanced mechanical properties.[222] Both diol monomers were polymerized with trichloromethyl chloroformate, yielding two TBS-protected polycarbonates. Removal of the TBS-protecting groups under mild conditions was investigated to achieve a good control over the deprotection process, although full deprotection was not achieved without some degree of degradation.



Scheme 55. Polycarbonates based on the quinic acid

Hyperbranched and micellar structures are target systems not only in polymer chemistry but also in carbohydrate-based polymers. For example, the synthesis of biodegradable hyperbranched polyglycerols (BHPGs) with acid-cleavable core structures has been

described.[223] The new materials were synthesized by anionic ring-opening multi-branching polymerization of glycidol using initiators bearing dimethyl and cyclohexyl ketal groups (Scheme 56). The polymers were relatively stable at physiological pH but degraded at acidic pH values. The polymer degradation was dependent on the type of ketal structure present in the BHPG; polymers with cyclohexyl ketal groups degraded at much lower rates than those with dimethyl ketal groups at a given pH. Thus, good control of polymer degradation was achieved under mild acidic conditions by changing the structure of ketal linkages. A precise control of the molecular weight of the degraded HPG was achieved by controlling the number of ketal groups within the core, as revealed from the gel permeation chromatography (GPC) analyses. The decrease in the polymer molecular weights upon degradation correlated well with the number of ketal groups in their core structure.



Scheme 56. Functionalized ketal initiators containing one to four ketal groups per molecule

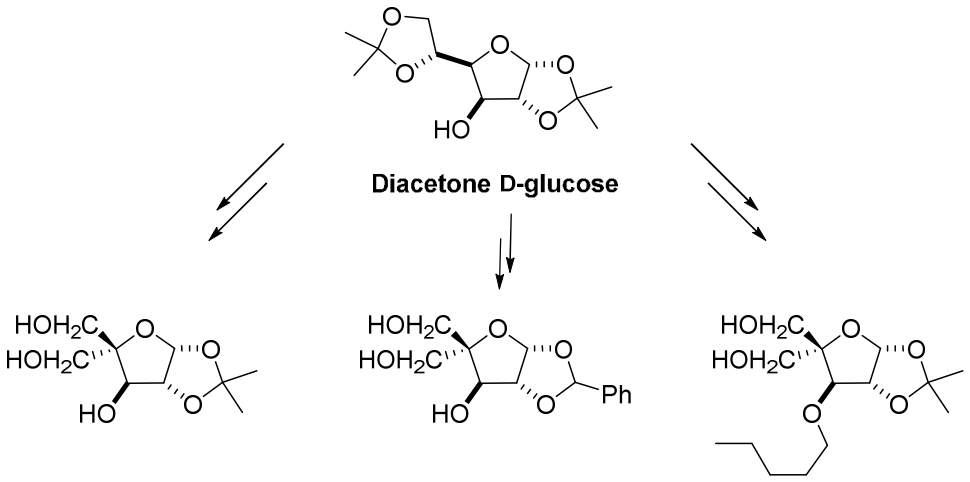
Other saccharide-based superstructures have been reported: a unimolecular reversed micelle consisting of a lipophilic poly(L-lactide) (PLA) shell and a hydrophilic hyperbranched D-mannan (HBM).[224] HBM was synthesized from 1,6-anhydro-β-D-mannopyranose, and the synthesis of PLA–HBM was carried out by the polymerization

of L-lactide (LA) in a solution of HBM in dry DMSO using 4-(dimethylamino)pyridine (DMAP) as catalyst. The generated macrostructure exhibited the ability to encapsulate hydrophilic molecules such as the water-soluble dye rose bengal and slowly release it from the core. The release rate was enhanced when an enzyme-catalyzed hydrolysis of the shell was accomplished.

Of the synthetic procedures to produce polysaccharides from mono- and disaccharides, Daines *et al.* [225] exemplified the utility of melt polymerization catalyzed by citric acid to generate amorphous polymers from a series of monosaccharides (glucose, galactose, fucose, and xylose). Characterization of the new materials revealed similar branched-degree polymerization and differences in the overall molecular weight of the polymers produced. Attempts to directly polymerize lactose itself by microwave irradiation in the presence of sorbitol, citric acid, and a small amount of water, were fruitless. Lactose was hydrolyzed under these conditions very efficiently (almost complete hydrolysis in less than 15 min) and the isolated oligosaccharides were generated by the melt polymerization of monomers from lactose hydrolysis. The as-described polymers displayed similar chemical properties to those synthesized from mixtures of galactose and glucose. The ability of bifidobacteria to utilize these polysugars as substrates for growth suggested they might be useful as novel prebiotics.

Enzymatic polymerization has also been demonstrated to be an effective method for producing natural and non-natural polysaccharides. Sugar-PEG-based polyesters were synthesized by enzymatic polymerization of 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-β-L-threo-pentofuranose, 4-*C*-hydroxymethyl-1,2-*O*-benzylidene-β-L-threo-pentofuranose, and 4-*C*-hydroxymethyl-1,2-*O*-isopropylidene-3-*O*-pentyl-β-L-threo-pentofuranose (Scheme 57) with PEG-600 dimethyl ester using Novozyme-435 (*Candida antarctica* lipase immobilized on polyacrylate).[226] Carbohydrate monomers

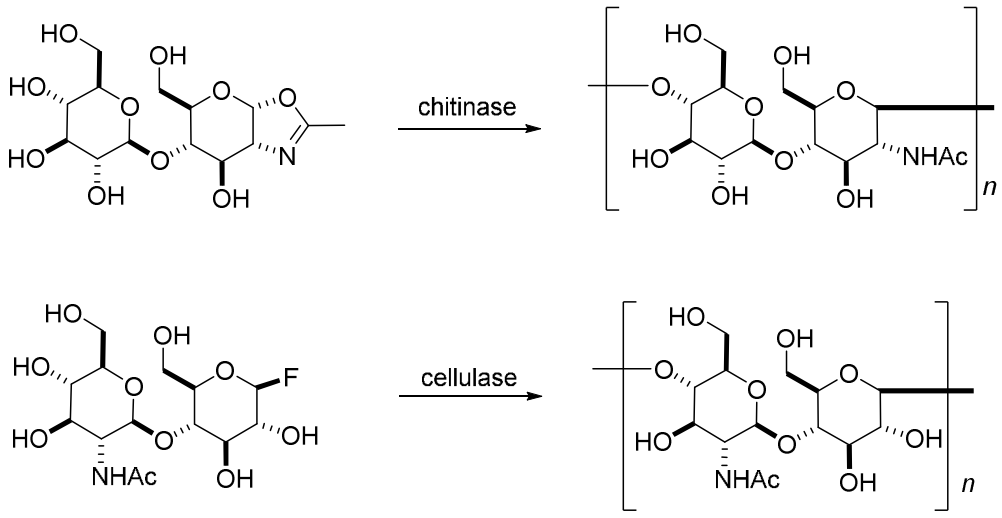
were obtained by a multistep synthesis starting from diacetone-D-glucose. Aggregation studies on the copolymers revealed that, in aqueous solution, those polymers bearing the hydrophobic pentyl/benzylidene moieties spontaneously self-assembled into supramolecular aggregates. The polymeric aggregates were further explored for their drug encapsulation properties in buffered aqueous solution of pH 7.4 (37 ºC) using nile red as a hydrophobic model compound.



Scheme 57. Chemical structure of the β-L-threo-pentofuranose-based monomers prepared from diacetone-D-glucose

Another example of enzymatic polymerization is the synthesis of a cellulose-chitin hybrid polysaccharide having alternatingly β(1-4)-linked D-glucose and *N*-acetyl-D-glucosamine, which was carried out *via* two different enzymatic polymerizations: chitinase-catalyzed ring-opening polyaddition of a sugar oxazoline monomer and cellulase-catalyzed polycondensation of a sugar fluoride monomer (Scheme 58).[227] Both monomers were polymerized under total regio- and stereoselective control, leading to amorphous, low-molecular-weight cellulose-chitin hybrid polysaccharides in good yields. The polysaccharides obtained by the two methods differed only in the polymer chain ends. It was demonstrated that lysozyme can catalyze the hydrolysis *in vitro* of the

new materials. Similarly, the synthesis of natural and non-natural polysaccharides (hyaluronan, chondroitin, and their derivatives belonging to glycosaminoglycans) was achieved by enzymatic polymerization using sugar oxazoline monomers and a glycoside hydrolase as catalyst.[228]

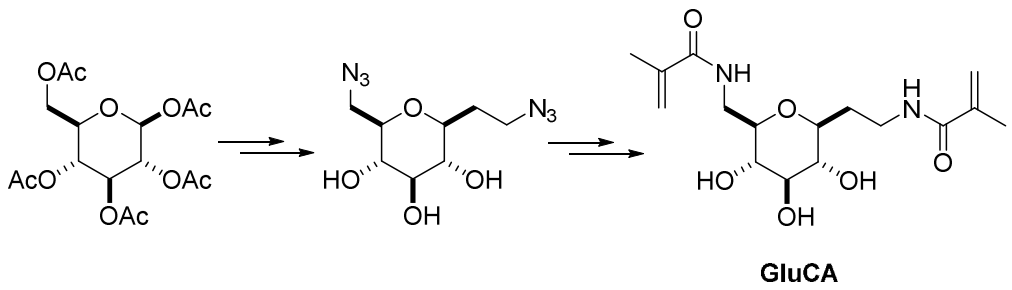


Scheme 58. Enzymatic preparation of cellulose-chitin hydrid polysaccharides

Grimaud *et al.* [229] have designed a smart procedure to synthesize α-glucans from the sole substrate sucrose by the tandem action of two bacterial enzymes, *i.e.* the amylosucrose from *Neisseria polysaccharea* and the branching enzyme from *Rhodothermus obamensis*. The biomimetic system reproduced *in vitro* and in a single step the activities involved in the formation of α(1,4) and α(1,6) glycosidic linkages during glycogen biosynthesis. The influence of the ratio between elongating and branching enzymes, as well as that of the initial sucrose concentration, on the product structure was investigated.

A multistep synthetic route to glycosylpyranose-based cross-linking agent (GluCA) (Scheme 59) has been developed from penta-*O*-acetyl-β-D-glucopyranose to be used in the preparation of poly(2-hydroxyethyl methacrylate) (PHEMA) -based hydrogels.[230]

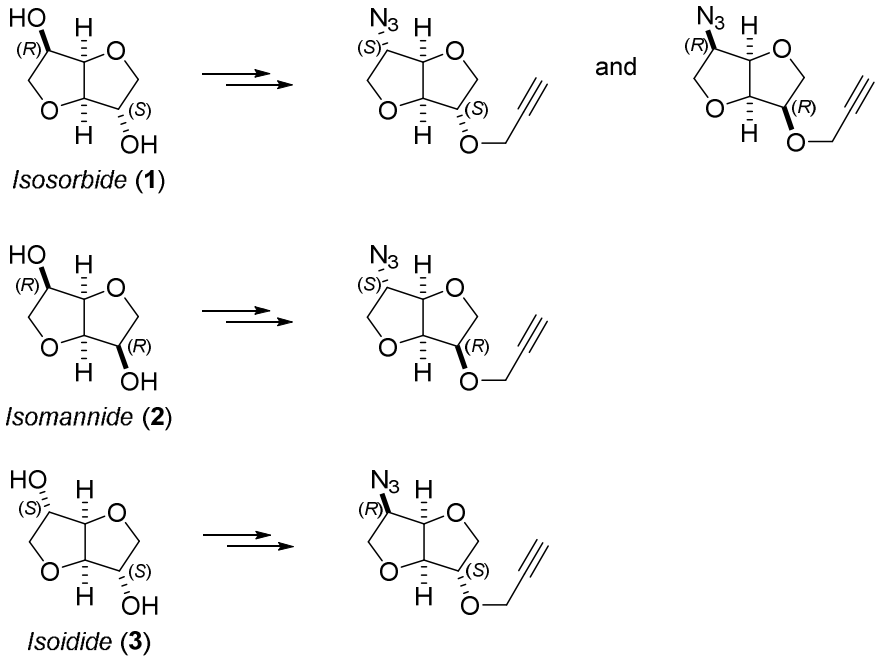
The route can be easily adapted to the synthesis of other cross-linking agents with azido groups that can undergo 1,3-cycloaddition with alkynes in click chemistry. Cross-linker GluCA was successfully incorporated into PHEMA sponges by copolymerization with HEMA under conditions that induce phase separation. The resulting PHEMA sponges exhibited morphologies based on polymer droplets that were larger than those seen for otherwise similar sponges cross-linked with tetraethylene glycol dimethacrylate. A review with a broad description of the structures and properties of the most-important polycacharide-based hydrogel systems, the methods of preparation, as well as an overview of their applications in the field of tissue engineering has been published.[231]



Scheme 59. Glucosylpiranose-based crosslinking agent

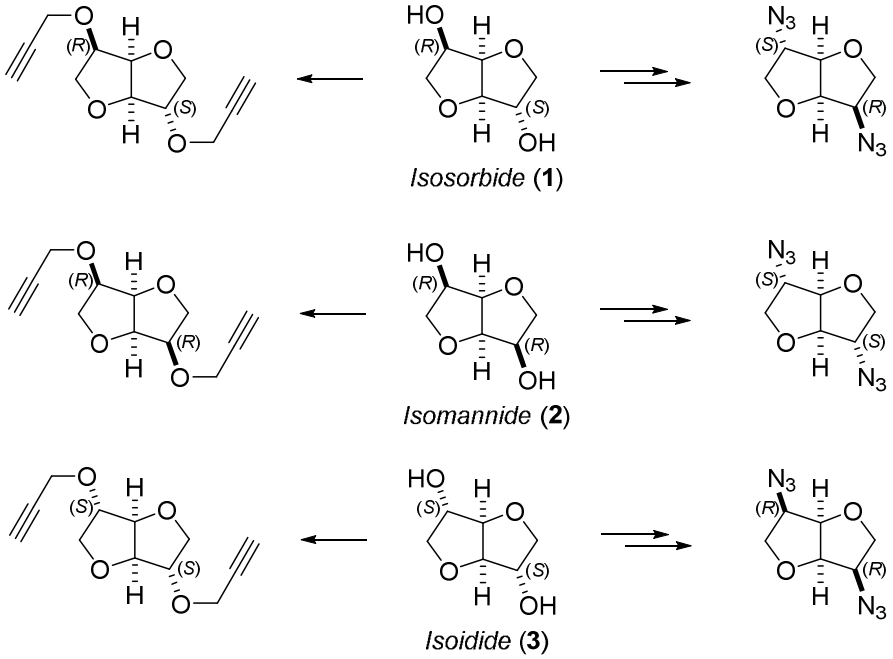
A set of α-azide-ω-alkyne-1,4:3,6-dianhydrohexitol AB-monomers has been prepared from the isohexides (**1**-**3**) using a three-step synthetic pathway (Scheme 60), and their copper(I)-catalyzed azide-alkyne (CuAAC) and solvent-free 1,3-dipolar Huisgen cycloaddition reactions were studied.[232,233] The CuAAC step-growth polymerization was completely regioselective, as was demonstrated by ^{1}H NMR; however, the solvent- and catalyst-free polymerization yielded mixtures of regioisomers. Nevertheless, the thermal properties of the resulting polytriazoles were only slightly affected by the loss of regioselectivity. In addition, while CuAAC polyaddition in solution produced poorly soluble polytriazoles with low values of Mn and required several purification steps,

thermal polyaddition in bulk gave polytriazoles with enhanced solubility, higher Mn values, and comparable thermal properties.



Scheme 60. AB-Monomers from isohexides for azide-alkyne cycloaddition polymerizations

The AB-monomer (2*S*,5*R*) was copolymerized with the symmetrical heterofunctional A_2B_2 aliphatic cross-linker 2,2-bis(azidomethyl)-1,3-bis(O-propargyl) propanediol, through the thermal Huisgen polyaddition reaction.[234] The formation of polytriazole networks was evidenced by rheological studies. The same group[233,235] has described the synthesis of a series of dialkyne and diazide functionalized dianhydrohexitol stereoisomers (Scheme 61), which afforded a new set of isohexide-based polytriazoles with defined stereochemistry through AA + BB CuAAC step-growth polymerization.[234] They obtained amorphous materials, which displayed high glass-transition temperatures (Tg = 125-166 °C) and high thermal stability (Td_{10} = 325-347 °C). Optimal thermal properties were obtained with monomers having (2*S*,5*R*) configuration.



Scheme 61. AABB-Monomers from isohexides for azide-alkyne cycloaddition polymerizations

10. Conclusions

Polymer syntheses from renewable and biomass resources constitute a steadily growing field of interest and monosaccharide-based polymers can be prepared that are analogous to the technologically more established polymers —polyamides, polyesters, polyurethanes — with an enhanced hydrophilicity and degradability. Nevertheless, there are some issues. One is that their water uptake is much higher than that of the monomers derived from petrochemical feedstock, which could be a drawback in certain applications. Also, in order to control the reactivity of many different hydroxyl groups, selective protection-deprotection chemistry would be required. So, in most of the cases, the high costs involved in the preparation of the monomers limit the application of these polymers within the biomedical and other specialized fields. The extension of this kind of polymer to more-conventional domains, making them competitive with the

petrochemical-based polymers requires more intense and systematic efforts in the search for new more-available monomers and simpler polymerization processes.

Sugars, as well as their natural oligomers and polymers, also play a fundamental role as precursors to other monomers, namely furan derivatives and lactic acid.

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Biographies

Juan A. Galbis studied chemistry at the University of Seville, Spain, and received his Ph.D. in the research group of Prof. F. García-González at the same University with a work on the synthesis of polyhydroxyalkyl-pyrroles. He gained an Associate Professorship at the University of Extremadura in Badajoz, Spain, where he developed the syntheses of new aminosugars and *C*-glycosides. He moved to the Chemistry Department of The Ohio State University as Research Fellow working on the synthesis of double-headed *C*-nucleosides with Prof. Derek Horton. He returned to the University

of Seville as Full Professor of Organic Chemistry and Head of the Department of Organic and Pharmaceutical Chemistry. His research interests include the development of novel synthetic methodologies, carbohydrate-based monomers, novel biobased polymers, and medicinal chemistry.

M. de Gracia García-Martín received her Ph.D. degree in Pharmacy from the University of Seville (Spain) in 1985, in the carbohydrate chemistry field. She got a Fulbright Postdoctoral Fellowship to join Professor Derek Horton´s Carbohydrate Group at Ohio State University (USA), where she worked on the synthesis of aminoglycoside antibiotics from1986-88. She was appointed Tenure Professor in the Department of Organic and Pharmaceutical Chemistry of the University of Seville in 1990, and accredited as Full Professor in 2014. In 1989, she started working in the group led by Professor Juan A. Galbis, on the synthesis of sugar-based monomers for the synthesis and characterization of biodegradable polyamides, polyesters, and polycarbonates. Her current research interest focuses on the preparation of biodegradable carbohydrate-based polymers for biomedical applications.

M. Violante de Paz gained her Ph.D. degree in Pharmacy in 1997 from the University of Seville (Spain), where she worked on sugar-based polymer synthesis. She later spent two years with Prof. Steven P. Armes at the University of Sussex (UK, 1998–2000) as Research Fellow, working on living polymerizations of methacrylate derivatives. She later returned to Spain to join the University of Huelva as a lecturer and, in 2004, she moved to the University of Seville. She is currently a member of the research group headed by Prof. Juan A. Galbis, and her research activity is now focused on the preparation and characterization of biodegradable and functionalized sugar-based polyurethanes and polyureas. She is also interested in the preparation of new biomaterials from renewable resources.

Elsa Galbis studied Chemistry at the University of Seville and obtained her Ph.D. on Physical Chemistry at the same University in December 2010. During her Ph.D. she performed several stays in different research centers, including the Max Planck Institute for Polymer Research (Mainz, Germany). She got a Postdoctoral CNRS contract for two years (2011-2013) at the "Centre de Recherche sur les Ions, les Matériaux et la Photonique" (CIMAP) in Caen, France. She returned in 2013 to the University of Seville as a post-doctoral researcher in the Department of Organic and Pharmaceutical Chemistry. Her current research interests are focused on the synthesis and characterization of methacrylate derivatives, hydrogels, and biodegradable carbohydrate-based polymers.

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TOC graphic: