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ROYAL SOCIETY
OF **CHEMISTRY**

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Sustainability Spotlight Statement: “Isohexides can be used in production processes and synthetic transformations as sustainable alternatives for those currently employed derived from crude oil. In fact, these compounds respect at least 7 of the 12 principles of Green Chemistry. Especially isosorbide can be extracted from renewable feedstocks, preventing the waste of precious resources and following the atomic economy, it can be used as benign solvent leading to less hazardous syntheses, and can be employed in catalytic quantities or as chiral auxiliaries in processes that traditionally require toxic organocatalysts. These are bicyclic compounds that can be isolated from sugar wastes that do not compete with the agri-food supply chain, namely low-cost materials that are capable of undergoing even complex transformations with harsh reaction conditions that push to produce highly performing polymeric materials. The reader is therefore shown the real possibility of ubiquitous application of compounds with an isohexidic structure in very different but fundamental areas of the new sustainable transition.“

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REVIEW

Synthetic routes and fields of application of isohexides: ubiquitous perspective of relevant industrial compounds

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Isohexides are a class of compounds that can be obtained from natural sources with simple processes and with interesting properties. Among these, the intrinsic chirality of the rigid bicyclic structural cavity and the presence of two hydroxyl groups in positions 3 and 6 available for functional group interconversion, appeared as the most interesting characteristics for real innovative applications. In this review, the strategies for the synthesis of isohexides from polysaccharides and biomasses of different complexities have been analyzed and the alternative processes to the traditional synthetic routes in terms of sustainability have been discussed. Secondly, the properties that make isosorbide the most suitable isohexide compound in terms of availability, stability and scalability for innovative production processes have been highlighted. The fields of application of these extremely interesting compounds have been investigated, proceeding with a discussion in which the areas of exploitation of isohexides are analyzed as building blocks, chiral auxiliaries or constituents of chiral ionic liquids. Finally, the numerous applicative possibilities of isosorbide as monomer or co-monomer of a wide range of polymeric materials of different nature have been thoroughly investigated. This review represents a first investigation into the possible uses of isohexidic-based compounds by analyzing the positive and negative aspects of their exploitation as ubiquitous alternatives to replace current oil-based intermediates. Certainly, future studies on the optimization of those production processes that occupy a large share of the chemical products market will lead to the confirmation of the synthetic potential of compounds with an isohexidic structure.

1. Introduction

Only in the United States, 400 million tons of sugar-based dry biomass are generated annually from the corn, soybean, flour, and sorghum production industries.rmous scale of fuel consumption and the market demand. For these reasons, biomass is currently more effectively used in the conversion to chemical feedstocks and chemical precursors.(2) However, the high market value of these products sometimes requires the use of expensive unit operations for pre-treatment, processing, and separation, completely *ex novo* compared to traditional industrial precursor plants.

The growing interest in circular economy and environmental sustainability has increased the search for renewable sources and their conversion into products, which include chemical reagents, energy resources and materials,(3) to replace the enormous demand for fossil fuels (**Figure 1**).

Given the abundance of these materials and the lack of competition with the agri-food sector, during the current century a market segment dedicated exclusively to the valorization of waste biomass was successfully established.

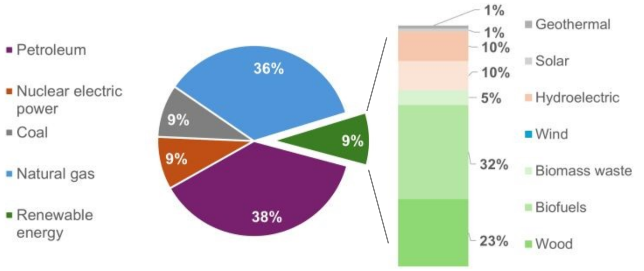

Figure 1: US primary energy consumption by energy source in 2023, only 9% is renewable.(3)

Therefore, the research is evolving towards the formulation of integrated processes that can lead to new products with high added value, starting precisely from the mentioned biomasses. Due to the promising background, many scientists from all over the world have dedicated their research to the extraction and separation of high added value components from wastes of different natures.

This has opened new frontiers in different areas of the chemical industry, allowing components deriving from petrochemicals (used in already consolidated processes) to be replaced with interesting and more sustainable alternatives.(1)

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In this context, agricultural raw materials come into play as a natural, renewable and sustainable resource to produce a large variety of biopolymers, bio-chemicals and bioenergy.(4,5)
For example, cellulose can be obtained mainly from agricultural residues and is one of the largest sources of organic raw materials in the world. It is in fact considered a promising resource that can be transformed into sustainable fuels and chemicals.(6)
Since the 1990s, there has been a growing research in isolation, synthesis and innovative use of numerous sugar-based products.(7,8) As can be seen from the graph shown in **Figure 2**, interest in this sector and the related scientific publications has witnessed an exceptional increase over the last decades.(9)

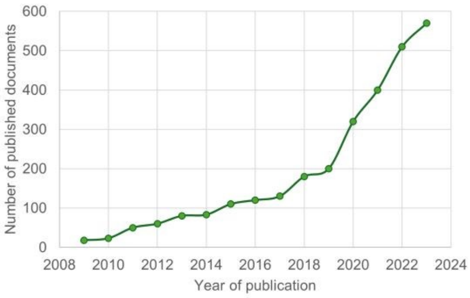


Figure 2: Number of documents published on biomass valorisation per year, data from cited Scopus database.(9)

Alcohols derived from C_5 and C_6 sugars obtained from cellulose or hemicelluloses are considered as sustainable building blocks and important synthons in organic synthesis.(10)
Among these, the hexitols are a class of polyols with six hydroxyl groups that can be obtained fr(10)
Among these, the hexitols are a class of polyols with six hydroxyl groups that can be obtained from the corresponding hexoses (**Figure 3**).(11)

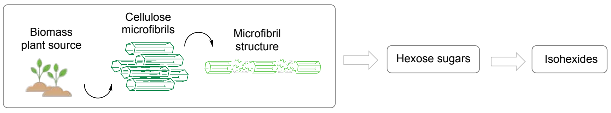


Figure 3: Synthetic scheme to produce isohexides precursors starting from agro-food waste biomass.(11)

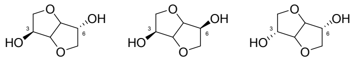
In fact, from plant-based biomasses rich in fibers (such as rice husk, wood pulp, banana peel, coffee husk, wheat straw, sisal fibers, sugarcane bagasse) it is possible to isolate cellulose microfibrils with recently consolidated processes.(12)
Crystalline structures that can be isolated from cellulose constitute one of the optimal precursors for the synthesis of hexose sugars from natural sources. The interconversion of functional groups starting from the OH present on the sugar-based carbon skeleton opens the door to different classes of compounds. Isohexides, for example, are compounds with a 6-carbon skeleton and 2 hydroxyl groups linked to different carbons that are extremely interesting.

Therefore, the different configurations of the stereogenic centers define the structural divergences of the isohexidic spatial isomers and their further chemical modification.
These differences will be highlighted throughout the manuscript and the important asymmetric reactivity of the two OH groups will be especially emphasized.

In this review, the synthetic strategies for isohexides will be thoroughly discussed, focusing the reader's attention on the comparison between the processes traditionally used in industry or laboratory scale and the possible paths recently identified as greener alternatives.
Subsequently, the possible application of isohexides in the organic synthesis of discrete molecules such as chiral auxiliaries and macromolecular materials with a polymeric structure will be discussed, demonstrating the suitability of the use of compounds with an isohexidic structure in various industrial sectors.

1.1. Structure of isohexides

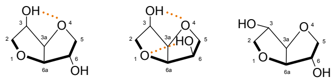
The term isohexides refers to a class of diol compounds whose structure is characterized by the presence of two tetrahydrofuran rings fused with a *cis*-type junction.
Isosorbide (1,4:3,6-dianhydro sorbitol **1**), isomannide (1,4:3,6-dianhydro mannitol **2**) and isoidide (1,4:3,6-dianhydro iditol **3**), are three of the main isomers in this category of natural sugar-based compounds. They are distinguished by their different stereochemistry of the hydroxyl groups in position 3 and in position 6: the two OH groups of isosorbide **1** are in *endo-exo*, in isomannide **2** and in isoidide **3** they are oriented in *endo-endo* and in *exo-exo* respectively.(13)
The chemical structure of the three main isohexidic isomers is shown below (**Figure 4**).



1 **2** **3**

Figure 4: Chemical structure of isohexides: isosorbide **1**, isomannide **2**, isoidide **3**.

The type of junction present between the two rings gives a concave vaulted structure to the isohexides, with a dihedral angle between the two tetrahydrofuran rings of about 120°.
As can be observed in **Figure 5**, in isosorbide the concavity of the structure offers the possibility of forming intramolecular hydrogen bonds between the hydrogen of the hydroxyl group in position 3 and the oxygen of the adjacent ring.(4)



1 **2** **3**

Figure 5: Three-dimensional structure of isohexides with possible hydrogen bond enhanced.(4)

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In compound **1** the two hydroxyl groups occupy different stereochemical surroundings furthermore, we could deduce that they also show different degrees of reactivity.

In isomannide the hydroxyl groups have the same stereochemistry, thus making **2** a highly symmetric derivative with the possibility of forming two intramolecular hydrogen bonds, thanks to the *endo* arrangement of both hydroxyl groups facing the inside of the chiral cavity.

In isoidide **3**, no intramolecular hydrogen bond can occur due to the orientation of the two OH groups towards the outside of the cavity.

1.2. Properties of isohexides

Regardless of the *endo* or *exo* position of the hydroxyl groups, for the same compound the reactivity of the two substituents in 3 and 6 are affected by the nearby chemical environment.

The structural difference between the three isohexides can be also predicted by the wavelengths at which the maximum of the different peaks relating to the stretching of the O-H bonds can be observed by IR spectroscopy (**Figure 6**).(14,15)

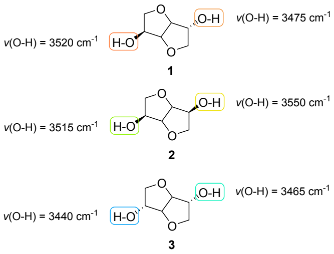

Figure 6: Open-source FT-IR simulation data for O-H stretching of isohexides.(16)

Even the literature ^{1}H-NMR spectra(14,15) of isohexides demonstrate the non-equivalence of the above-mentioned groups, if all other assumptions can be considered equal.

Table 1: ^{1}H-NMR simulation data for isohexides.(17)

Compound	δ [ppm]	H	Multiplicity	J [Hz]
1	3.65-3.95	8H	dd	7.0, 5.9
	3.81		dd	12.9, 6.8
	8.87		dd	12.9, 4.7
	3.88		ddd	6.8, 5.9, 4.7
2	3.65-4.00	8H	dd	7.3, 6.7
	3.77		dd	10.4, 6.1
	3.90		ddd	6.7, 6.1, 5.5
	3.93		dd	10.4, 5.5
3	3.66	2H	dd	7.0, 3.8
	3.82-4.00	6H	ddd	7.8, 6.8, 3.8
	3.91		dd	10.5, 7.8
	3.93		dd	10.5, 6.8

The data and deductions shown in **Table 1** have been obtained from theoretical simulations while at the experimental level these differences are rarely observed through the most common techniques of characterization of organic compounds performed in standard conditions.

The structural difference of the three isomers clearly implies differences in their chemical-physical properties, such as their melting temperature (**Table 2**) and the different reactivity of the hydroxyl groups.

Table 2: Melting temperature of isohexides.

Compound	Melting Temperature [°C]
1	60-63
2	80-85
3	50-56

As discussed before, the difference in melting temperature ranges can be attributed to the presence or absence of intramolecular hydrogen bonds. Considering the steric effects and the establishment of hydrogen bonds, isomannide **2** with the two *endo* hydroxyl groups is certainly the least reactive isomer, and isoidide **3** with the two *exo* groups is more reactive than isosorbide **1**.

Therefore, it could be deduced that isoidide **3** is the most attractive isomer on the market but, unfortunately, it is the rarest in nature and remains the most expensive for many industrial applications.

For the above-mentioned reasons, research attention in the field of isohexides derived from renewable sources and in their applications, is mainly directed to the *endo-exo* isosorbide **1** and in recent years has witnessed a notable increase.

The interest in isosorbide lies both in the possibility of selective derivatization of the OH groups and in the presence of the cavity-like structure. This cavity constitutes a true chiral confined system, within which molecules of appropriate size and stereochemistry can be hosted or converted, thus favouring enantioselection.

While the selective derivatization of the hydroxyl groups of the isomannide **2** is possible only through the control of the stoichiometry of the reagents. Based on a statistical approach, a 2:1 ratio between isomannide and the derivatizing agent is usually employed, which often leads to the formation of a mixture of mono-derivatized product, disubstituted derivative and unreacted reagent.

On the other hand, the non-equivalence of the OH groups of isosorbide **1** enables its selective functionalization and hence the production of mono-substituted and non-symmetric composites with great industrial relevance.

2. Synthesis of isohexides

2.1. From biogenic polysaccharides

Polysaccharides are a class of macromolecules that are widespread in nature among animals, plants, microorganisms and algae. These polymeric materials are commonly characterized by high molecular weight and complex structural features that determine their biological functions.(18)

The performance of these functions can be crucial for the survival, the growth and the health development of the organism that synthesizes them or that exploits their metabolism. In recent years, there have been increasing attempts to study natural biomaterials based on polysaccharides. The enhanced properties of polysaccharides have been extended to various applications, including biomedical engineering, human drug delivery, food packaging, biofuel isolation from biomasses, contaminated wastewater treatment and even textile fiber production.(19)

Due to their biodegradable and biocompatible characters, bioactive polysaccharides have been largely used in the hexitols production processes according to the synthetic scheme shown in **Figure 7**.

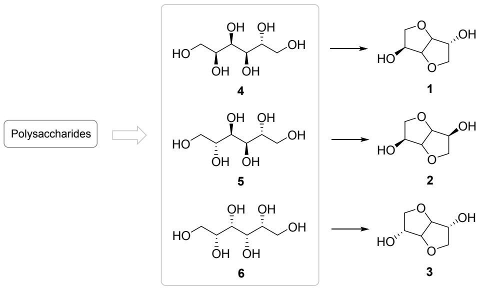

Figure 7: Scheme of isohexides production from hexitols.(19)

As previously mentioned in the introduction (Section 1), hexitols are C_6 polyols: organic compounds with various hydroxyl groups present in the structure with a skeleton composed of six carbon atoms.

Therefore, starting from polysaccharides it is possible to isolate hexitols, thus obtaining the precursors for isohexides directly from sustainable sources.

In fact, isohexides have been known since 1880 and their synthesis commonly involved the dehydration of the corresponding hexitols (sorbitol, mannitol and iditol) in an acid environment and in the presence of a solvent.

2.1.1. Synthesis of isosorbide from sorbitol

In the 1990s, the industrial synthesis of isosorbide involved a homogeneous batch process at atmospheric pressure and catalyzed by sulfuric acid, with water as a solvent medium.(20)

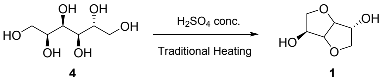

Figure 8: Isosorbide synthesis starting from sorbitol, using an acid aqueous medium and traditional reaction conditions.(20)

The main drawbacks of the process shown in **Figure 8** included the need for separation of the products by neutralization, the elimination of sulfur compounds, the required distillation stage (energy-demanding for each production batch and inerting for the acid catalyst) and finally the recovery of the product with a yield that not exceeded 65% by weight.

The desire for the combination of the Green Chemistry principles and industrial progress has led to the development of new production methods for this isohexidic intermediate.

For example, in 2013 an innovative catalytic dehydration strategy of sorbitol **4** to isosorbide was proposed,(21) which employed microwaves (MWs) as a heating method and Amberlyst 35 as an acid catalyst (**Figure 9**).

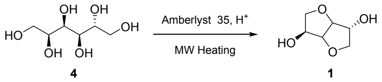

Figure 9: Isosorbide synthesis starting from sorbitol, using Amberlyst 35 in acid aq. medium and MWs heating system.(21)

This research led to the optimization of the reaction conditions, the efficient recovery of energy and the increase in isosorbide yield.

Following the principles of atomic efficiency and the good compromise between yield and purity of the product, this strategy is still nowadays the most widely used to produce isosorbide from hexitols.

2.1.2. Synthesis of isomannide from mannitol

As seen for isosorbide, isomannide **2** can also be produced from the respective hexitol, *i.e.* mannitol.

As an example, the data relating to the conditions used in the synthesis of isomannide starting from mannitol **5** and the relative yields are reported in **Figure 10** and in **Table 3**, respectively.

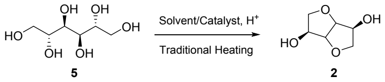

Figure 10: Isomannide synthesis starting from mannitol, using different solvent - catalyst systems and a traditional heating.(20)

The main disadvantages of these synthetic methods included the requirement of solvents, the commonly unsatisfactory yield achieved, the obtaining of a large amount of resinous distillation residues and the long reaction times often required, reaching over 85 hours for complete substrate-to-product conversion.

Table 3: Reaction conditions and yields obtained in the isomannide synthesis starting from mannitol.

Solvent/Catalyst	2 Yield [wt%]
Ethyl acetate/Dioxane	35
Dichloroglycerol	36
Conc. Hydrochloric acid	25-40

The issues also highlighted in Section 1.1.1, exclude the possibility of preparing both isosorbide **1** and isomannide **2** on a large scale with these methods. In addition, the cost of the starting material (for example pure mannitol and sorbitol) is considerably high compared to the normal cost of the precursors used in the chemical industry to produce intermediates intended for commodities.

Subsequently, an innovative synthetic route for isohexides was proposed where the authors obtained high yields in isomannide with a selective reaction, in the absence of solvent and treating the crystalline hexitol with gaseous hydrogen halide (preferably $HCl_{(g)}$) as shown **Figure 11**.

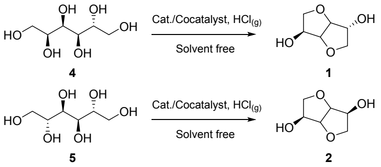

Figure 11: Solvent-free isomannide synthesis starting from mannitol, using catalysts and gaseous hydrogen halide.(20)

To date, these are the most used dehydration reaction conditions at the laboratory level to produce **1** and **2** from hexitols **4** and **5**, respectively.

2.1.3. Synthesis of isoidide from iditol

Isoidide can also be synthetized by dehydration of the corresponding hexitol. In fact, **3** can be produced starting from iditol **4**, a water-soluble C_6 sugar polyol that can be industrially obtained from biomasses such as agricultural wastes.

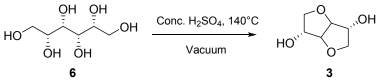

Figure 12: Isoidide synthesis starting from iditol, using concentrate sulfuric acid and a traditional heating system.(20)

The reaction conditions shown in **Figure 12**, were analogous to those traditionally used, therefore an acidic medium in which the acid functionalities catalyze the dehydration reaction and consequent intramolecular closure of the bicyclic structure were successfully employed.

2.1.4. Synthesis of isoidide from isosorbide

An interesting synthetic strategy proposed by Saska *et al.*(22) involved the synthesis of isosorbide through the epimerization of isosorbide.

The term epimerization refers to the stereochemical process by which a diastereomer can be converted into another diastereomer by changing just one chiral center in the entire structure.(23)

The authors were able to propose a reaction mechanism that involved the two steps shown in **Figure 13**: a catalytic dehydrogenation hydrogenation reaction and the hydride abstraction/re-addition step.

The first step included the use of Ru/C as catalyst in 2-propanol, while the hydride subtraction was performed with $Pb(OAc)_2$ in acetic anhydride, leading to an overall isoidide purity with a value higher than 99%.

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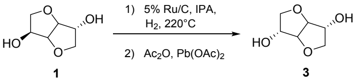

Figure 13: Isoidide synthesis starting from isosorbide, using a two-step chemo-catalytic process.(22)

In fact, a few years earlier, the optimized conditions for the synthesis reaction of isoidide from isosorbide had been developed by the group of La Notre *et al.*,(14) highlighting the potential applications of epimerization reactions of isohexides.

As demonstrated by the survey discussed in Section 1, isohexide **1** has the greatest applicative possibilities and the most abundant availability in nature.

Therefore, the discussion will focus on the industrial and laboratory perspectives of using isosorbide as a building block in the applied fields of organic synthesis.

2.2. Synthesis of isosorbide from raw biomasses

A more complex but more abundant sugar source than simple biogenic polysaccharides is constituted by cellulosic and lignocellulosic biomass. This type of biomass does not compete with the agri-food sector and often constitutes a waste volume that aggravates the down-stream of industrial production processes of products such as paper, pulp, cellulose etc.

To date, studies have been carried out on the possibility of obtaining isosorbide by means of a one-pot synthesis starting from cellulose or lignocellulosic biomasses.

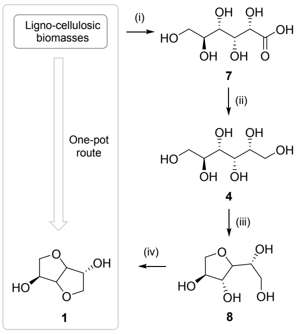

Figure 14: One-pot isosorbide synthesis starting from biomasses.(13)

The synthesis shown in **Figure 14** involved in cascade: (i) the hydrolysis of cellulose or starch to glucose **7**, (ii) the hydrogenation of glucose to sorbitol **4**, (iii) the dehydration of sorbitol to sorbitan **8** and lastly (iv) the dehydration of sorbitan to isosorbide **1**.

The one-pot process requires both an acidic environment and a hydrogenation catalyst. The medium acidity, crystallinity and particle size of the cellulose, as well as the nature and therefore the origin of the raw materials, significantly influenced the yield of the isosorbide production process.

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The deactivation of the catalyst in the presence of lignin (present in most cellulosic raw material stocks) and its non-recyclability in aqueous environment, were considered the main problems of this synthetic path proposal.

In these studies, the possibility of formulating a sustainable and interesting way for the design of a heterogeneous catalyst composed of a supported metal, designed to be stable in water and tolerant to the presence of lignin was hypothesized.

Carrying this reaction in continuous flow using two alternating catalytic beds (suitable for the regeneration of the catalyst) could constitute alternative solutions for the synthesis of isosorbide from raw biomasses.

There was recent experimental evidence of a certain success for the synthesis of **1** starting from lignocellulosic biomass, which employed a heterogeneous Ruthenium-based hydrogenation catalysts supported on carbon.(24)

Table 4: Reaction conditions and yield results for the isosorbide synthesis starting from lignocellulosic biomass.(24)

Dehydrating agent	T [°C]	H_2 [bar]	Time [h]	Ru/C [mg]	1 Yield [wt%]	Ref
[HCl]=0.1M	215	60	0.5	20	50	(25)
[H_2SO_4]=0.5M	220	40	2	40	50	(26)
[BPO_4]=0.1M	230	60	24	20	28	(27)
[$H_4SiW_{12}O_{40}$]=55M	160	50	7	100	13	(28)
[$H_4PW_{12}O_{40}$]=55M	160	50	7	100	17	(28)
[$H_4SiW_{12}O_{40}$]=3M	210	50	7	1000	65	(29)

Unfortunately, the reaction conditions shown in **Table 4** led to the synthesis of isosorbide with low yields that do not exceed 65% by weight, value that can be traced back to the phenomenon of deactivation of the hydrogenation catalyst which significantly lowers the product yield.

Research in this area is moving towards the design of a heterogeneous catalyst composed of a transition metal supported on a carrier with acid moieties, stable in water and tolerant to the presence of the lignin contained in the starting material. In this way it would be possible to overcome the difficulties encountered to date in undertaking a synthesis with a very complex matrix such as lignocellulosic biomasses.

Certainly, the choice of synthesizing di-anhydrous hexitols starting from biomass of vegetal origin represents the most complex strategy at laboratory level, but it could constitute the scalable innovation process suitable for the industrial production of important intermediates such as isosorbide.

3. Isohexides as building blocks

In the chemical field, the term “Building Blocks” refers to a virtual molecular fragment or a real chemical compound that possesses reactive functional groups. Building blocks are used for the upward pyramidal assembly of molecular architectures: nanoparticles, metal-organic structures, organic compounds with high molecular complexity and supra-molecular complexes.(30)

The selective reactivity of the two hydroxyl groups, the chirality, the controlled stereochemistry and the performance of its derivatives, elect isosorbide as a promising “green fine chemical”. In fact, isohexides in general are considered fine chemicals as they are produced in limited quantities and at a high market price and are therefore destined to be converted into value-added products.

3.1. Chiral intermediates based on isohexides

Di-anhydrous hexitolic derivatives have been successfully employed in asymmetric catalysis.(31) Asymmetric catalysis is the most widely used method for carrying out an asymmetric synthesis, *i.e.* the conversion of a prochiral substrate into a chiral product with preferential formation of one of the possible enantiomers.(32) To perform a reaction within the asymmetric catalysis, a chiral catalyst is commonly needed. Usually, a transition metal complex coordinated by chiral ligands is employed and when it is formed of purely organic chiral ligands, the reaction can be named as asymmetric organocatalysis.(33)

The efficiency of an enantioselective synthesis process can be very high, but each stage of the synthesis influences the final product yield therefore, an industrial design suitable for the purpose will be required. This approach is particularly important in the field of pharmaceutical synthesis, since different enantiomers or diastereomers of a molecule often have different biological activities.(34)

Among the many possible synthetic intermediates that can be produced from isohexides, the chiral derivatives are of vital importance and given the exceptional properties and advantages mentioned above, the mono- and disubstituted derivatives of isosorbide will be mainly discussed.

At first glance, some of the isosorbide derivatives worth mentioning are reported in **Figure 15**.

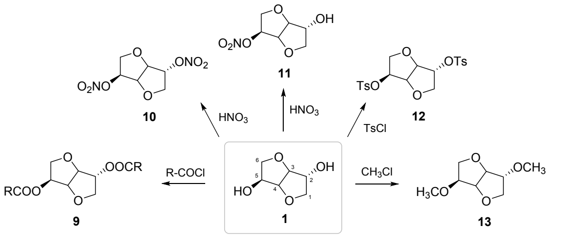

Figure 15: Industrial relevant derivatives of isosorbide.(35)

The synthesis of a wide spectrum of mono- and di-esters, mono and di-nitrates, mono- and di-tosilates of isosorbide such as compounds **9**-**13** were reported by Bhat et al.,(36) expanding the chiral intermediates that can be obtained from biomass-derived isosorbide. For example, most of the amino derivatives of isosorbide are designed for the polymer field (*e.g.* polyurethanes and polyamides) as will be discussed in Section 3.3, but the role of isosorbide-based building blocks has grown a large curiosity especially in the chemical industry for the asymmetric synthesis of enantiopure compounds.(37)

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In fact, in recent years the call for sustainable transition of well-known polluting and hazardous reactions and the upgrade on large-scale synthesis of intermediates such as ligands and chiral auxiliaries, has found an outlet in asymmetric structure based on isosorbide derivatives.

For instance, Wu et al.(38) developed a novel isosorbide-based dinitrile synthesis procedure leading to the production of compounds with one extra carbon atom for each hydroxyl group by the isosorbide epimerization under mild and base-catalyzed reaction conditions (**Figure 16**).

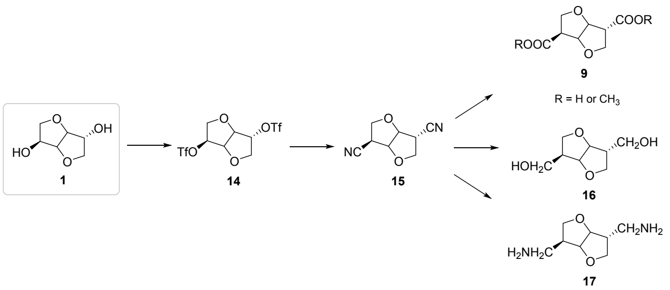

Figure 16: Synthesis of 1-carbon-extended isosorbide-based compounds through epimerization reaction.(38)

The author proposed a detailed reaction mechanism through a structural analysis of the possible dinitrile isomers by DRX analysis(39) and DFT calculations,(40) demonstrating that different characteristic structural parameters of the chiral cavity, such as dihedral angles and torsion angles, can vary over a wide range and modify the outcome of the reaction.

The concept of structural rigidity of the bicyclic cavity was overcome by the authors, proposing a lesser conservative torsion possibility and were consequently able to demonstrate access to an interesting class of building blocks in which the substituent orientation effects the yield of the extended C_2/C_5 isohexidic compounds.(38)

Isohexidic derivatives have been used in asymmetric catalysis, as chiral metal ligands for the asymmetric reduction of alkenes, ketones, imines and for the formation of C-C bonds by allylic substitution, alkylation and hydroformylation.(31,41)

They have been employed also as chiral auxiliaries in Diels-Alder reactions (**Figure 17**), affording products with enantiomeric excesses of up to 99% for the desired product.

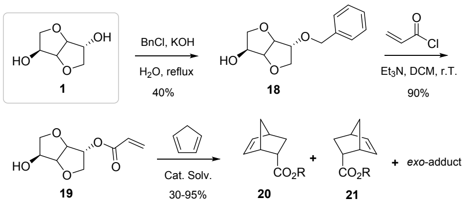

Figure 17: Diels-Alder reaction of an acrylate derived from *exo*-mono-benzylated isosorbide and cyclopentadiene.(42)

The authors were able to fully demonstrate the efficiency of using isosorbide-based compounds as chiral auxiliary leading to comparable or even improved results with respect of the more traditional auxiliar compound based on natural sources such as camphor and menthol derivatives.

Isosorbide has also been employed as a starting material for the synthesis of many novel chiral amino alcohols and diamines, as shown in **Figure 18**.

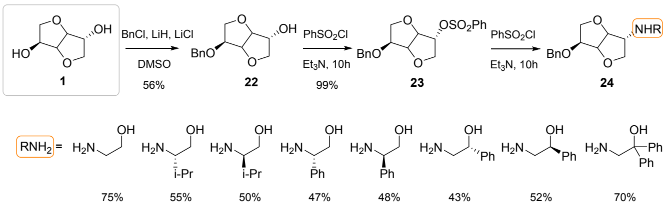

Figure 18: Synthesis of some amino derivatives of isosorbide.(43)

These derivatives have been synthesized in moderate to good yields (43-75%), depending on the RNH_2 reagents used. The above-mentioned study demonstrated the potential use of the obtained products as chiral ligands for Asymmetric Transfer Hydrogenation (ATH) reactions of aromatic ketones catalyzed by Ruthenium, providing chiral alcohols with enantiomeric excesses up to 91%.(43)

The exploitation of the biomass-based starting materials can also be applied in the case of isosorbide itself and not only for its derivatives,(44) whose interconversion has appeared very attractive in recent years.

In fact, the *endo-exo* spatial arrangement of the two hydroxyl groups in position 3 and 6 of the isosorbide skeleton have been successfully converted to synthesize a wide range of organo-catalysts and chiral auxiliaries.(45)

Zullo *et al*.(46) were able to synthesize an amino alcohol with an isohexide structure by subjecting isosorbide to various reactive steps, including the innovative selective acetylation of the *endo*-OH group through a protection performed by a biocatalyst in heterogeneous form (**Figure 19**).(46)

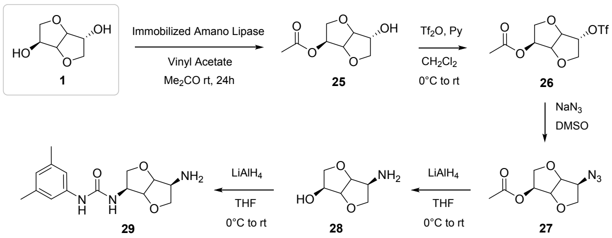

Figure 19: Synthesis of hydroxyurea from isosorbide used as chiral discrimination agent.(46)

Starting from the amino alcohol in question, they were able to successfully use this compound as a chiral solvating agent in the enantio-discrimination of complex aromatic structures, demonstrating the possibility of using the functionality of asymmetric induction from chiral pool.(47)

Recently, the Mitsunobu reaction(48) has also been successfully performed on isosorbide, leading to the synthesis of some bioactive intermediates with improved pharmacodynamic and pharmacokinetic properties.(49)

In fact, conjugates containing isohexidic moieties have been synthesized that confer improved solubility and permeability properties to the structure compared to bare scaffold compounds towards target compounds. Only a few of the possible examples of isosorbide-based compounds with high added value in the field of enantioselective and asymmetric synthesis have been mentioned, but the research has witnessed a large increase in possible chiral discriminants based on the strategies discussed in Section 3.1.

3.2. Chiral Ionic Liquids based on isohexides

The efficiency of using isosorbide and isomannide in the synthesis of Chiral Ionic Liquids (CILs) has been widely demonstrated and discussed in literature. CILs are a subset of Ionic Liquids (ILs), namely salts that are liquid in a temperature range close to the room temperature.(50)

In ionic liquids, the nature of the ions plays a fundamental role in their efficiency as solvents and the presence of a strong ionic interaction within these substances is reflected in their chemical-physical properties. Different ions impart different behavior in the final IL, but the most common characteristics comprehend low vapor pressure, relatively non-flammability, good thermal and mechanical properties and electrochemical stability.(51) For the synthesis of high-value chemical products, such as fine chemicals and pharmaceuticals, the replacement of conventional processes with processes based on the use of an ionic liquid is interesting only if the following requirements are satisfied: the IL allows a high degree of recyclability, high yields and easy separation of products.

Studies carried out in recent years have led to the statement that not all ionic liquids are intrinsically green solvents since some are considered extremely toxic. However, the ability to modify their properties through molecular design by their intrinsic versatility and their correct use, can contribute to the development of processes with significantly higher sustainability levels with respect with the twelve principles of the Green Chemistry.(52)

Chiral ionic liquids (CILs) have gained considerable potential in asymmetric synthesis, stereoselective polymerization, chiral chromatography and production of different liquid crystals.

In the last decades, the ammonium and imidazole salts of isosorbide have been studied thoroughly.

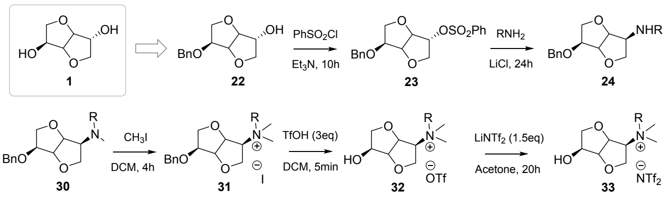

Figure 20: Example of synthesis of CILs from isosorbide *endo*-mono-benzoate.(53)

As shown in **Figure 20**, with simple methods it was possible to synthesize a new family of ammonium-based CILs containing a chiral moiety due to the presence of the isosorbide structure and a hydroxyl functionality free for further modifications.(53)

Chiral ammonium-based Ionic Liquids are just one example of possible CILs that are being widely studied.(54)

Chirality to ILs can also be imparted by the anion to form protic and protic ILs based on production needs and surely a new range of isosorbide-based ions will soon be expanded.

3.3. Isohexides in Polymer Science

Since isosorbide has been classified by the FDA as a GRAS ("General Recognized As Safe") compound, it constitutes the most available di-anhydro hexitol on the market.

Therefore, isosorbide can be used as a greener alternative to petroleum-derived and oil-based chemicals in industrial polymerization processes. The molecular structure of isosorbide and the possibility of derivatization with appropriate functionalities provide excellent characteristics of compatibility with many commercial polymeric materials and additives for special uses.(55) Indeed, it can be used in the synthesis of low molecular weight compounds that can act as plasticizers,(56) stabilizers or compatibilizers and in the synthesis of thermosetting materials such as epoxy resins.(57)

3.3.1. Epoxy Resins

Epoxy resins were developed in the 1940s by CIBA as thermosetting adhesive materials.(58)

They can be obtained from epichlorohydrin or allyl bromide and Bisphenol A (BPA) in a two-stage process: a pre-polymerization process in which oligomers are formed and a crosslinking stage in the presence of crosslinking agents.

The epoxy resins can also be sold as two component solutions which can be crosslinked upon application to the chosen solid substrate.

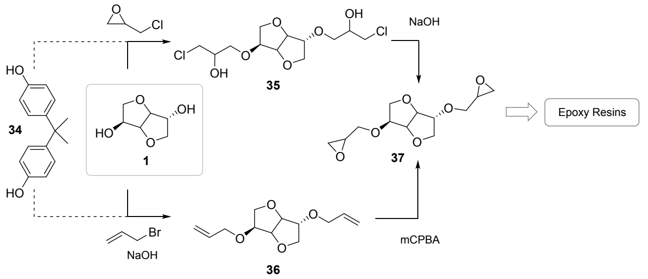

Figure 21: Isosorbide as a substitute of BPA in the production of epoxy resins.(13)

Since BPA is a compound recognized as toxic, it is sought to be replaced especially in cases of use in the food packaging or biomedical industries.

In fact, in recent years alternative glycidyl ethers have been synthesized such as those resulting from resorcinol or from simple sugars and carbohydrates of natural origin.

The use of isosorbide as a substitute for BPA fits perfectly into this context and Rose *et al.*(13) were able to successfully employ **1** as an alternative di-glycidyl ether for the preparation

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of epoxy resins (**Figure 21**). With this synthetic strategy it was possible to obtain epoxy resins with a behavior typical of a material with a high rubbery modulus thanks to the low molar mass and high percentage of functionalization of the formed oligomers.(13,59) By the comparison of different studies, it emerged that the inclusion of isosorbide functionalities can lead to oligomers with a molar mass of 260-770 g/mol with an increased impact and tensile strength.

The mentioned results were obtained despite the characteristic lower glass transition temperature of di-glycidyl ether based on isosorbide compared to traditional epoxy resin which use BPA as a reagent.(60)

3.3.2. Polyesters

Considering its nature of diol, isohexide **1** can also be used in the synthesis of polyesters. Polyesters are a class of polymers characterized by the presence of the ester bond (-CO-O-) in the main chain of the macromolecule and they can be obtained by the reaction of diols with diacids or diesters.(61)

Nevertheless, isosorbide was successfully employed as a monomer in the production of thermoplastic materials, specifically in the synthesis of polyester.(62–64)

On an industrial scale, polyesters can be obtained from carboxylic acids or derivatives and diols with a two-stage polycondensation process that involves the release of a low molecular weight by-product. They can be either aromatic or aliphatic based on the nature of the monomers used in the production process.

Among the most common aromatic polyesters we can find poly(ethylene terephthalate) PET, poly(butylene terephthalate) PBT, poly(cyclohexylene dimethylene terephthalate) PCT and poly(ethylene naphthenate) PEN, while among the aliphatic ones we can find poly(butylene succinate) PBS, poly(ethylene succinate) PES, poly(lactic acid) PLA and poly(Ɛ-caprolactone) PCL, etc.(61)

Promising results have been obtained in the synthesis of a polyester based on the structure of PET, in which however the ethylene glycol has been replaced with isosorbide.

The polycondensation of isosorbide with terephthalic acid and its acid dichloride led to the production of poly(isosorbide terephthalate) PIsT, as shown in **Figure 22**.(65)

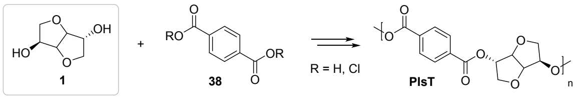

Figure 22: Isosorbide as monomer for the synthesis of PET analogue PIsT.(65)

Given the versatility of the hydroxyl groups, **1** can also be converted into the respective diacids and/or diesters and used in the formulation of ester-based copolymers with innovative and interesting structures.(66)

Recently, Wu et al.(67) were able to synthesize and thoroughly characterize the class of polyesters (shown in **Figure 23**) which were completely based on the carbon skeleton of isosorbide, for both the diol and the diester components named poly(isosorbide isosorbate) PIsI.

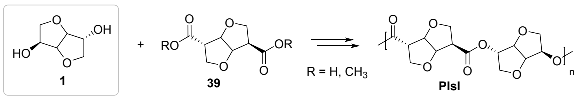

Figure 23: Fully isosorbide-based polyesters.(67)

This review demonstrated the possibility of optimizing the atom economy of polyesters production processes and the sustainable derivation of the raw materials used to obtain polymeric products, with characteristics comparable to those currently on the market for that specific commercial use.(68,69)

Still in the field of aliphatic polyesters, Wu *et al.*(70) have been able to carry out a CALB-catalyzed enzymatic polymerization (EP) of diethyl succinate, 1,4-butanediol (1,4-BDO) and isosorbide, obtaining in good yields copolyesters of poly(butylenisosorbide-*co*-succinate) PBIsS.

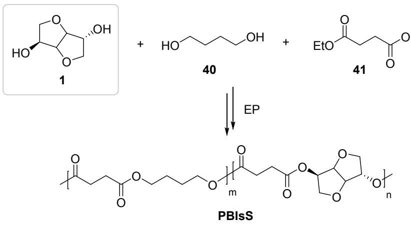

Figure 24: Fully aliphatic isosorbide-based copolyester *via* enzymatic polymerization using Lipase.(70)

The polymeric materials produced by the authors (**Figure 24**) showed tunable temperature of glass transition and crystallinity in a wide range, which could elect them to new fields of applications such as textile fibers or engineering plastic materials.(71,72)

The most relevant scientific cases concerning the use of isosorbide derivatives in the innovative polymer industry will be discussed below, starting from aliphatic copolyesters based on **39**, methyl diester of isosorbide.

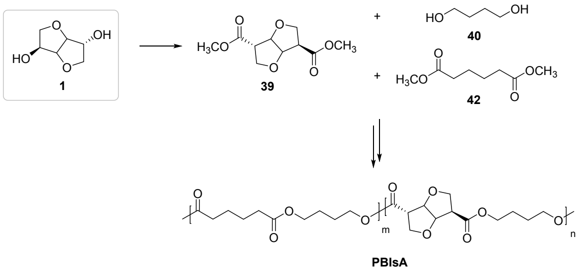

Figure 25: Fully aliphatic isosorbide-based copolyester *via* melt polycondensation process.(73)

As shown in **Figure 25**, the methyl diester of isosorbide has been successfully employed as one of the two diacid-reagent in a polycondensation process which included the employment

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of dimethyl adipate and 1,4-BDO.(73) The authors were able to fully demonstrate the production of novel systems with improved viscoelastic properties with an average molecular weight of approximately 24000-47600 g/mol, as well as surprising self-adhesion capabilities and consequent industrial weldability. Thiyagarajan *et al.*(74) reported the synthesis of an AB-type homo polyesters based on *exo* OH monomers of isohexides with molecular weights comparable to those witnessed from the BB or AA-type analogues.(75) With the same molecular weight of 2500 g/mol, the thermal properties of the produced samples were found to be suitable for application at higher temperatures. Poly(isoidide-*co*-isoidide dicarboxylic acid) PIiI and poly(isosorbide-*co*-isoidide dicarboxylic acid) PIsI were the references and the samples proposed by the authors consisted of a set of six composition of isohexides and their respective methylcarboxylates.(74) The various bifunctional derivatives of isosorbide, isomannide and isoidide, also have a high application potential in the polymer industry as well.(76) They were successfully included in the production of biobased polymers, solvents, fuel additives, nitrogenous plastics such as polyamides, polyimides and polyurethanes, and many others.(13)

3.3.3. Polyimides

For example, polyimides PIs are polycondensation polymers characterized by the presence of an imide bond (-CO-NR-CO-) and they are synthesized starting from dianhydrides and dianilines whereas PIs based on aromatic structures have shown a wider spectrum of application.(77)

Isohexidic functionalities were successfully inserted into the structures of partially biobased polyimide monomers by Thiyagarajan *et al.*(78) The presence of isosorbide in the repeating chain resulted in polymeric samples exhibiting higher mechanical stiffness and thermal stability comparable to their petrochemical counterparts. In fact, the innovation resided in their excellent optical transparency and optical activity properties attributable to the chiral cavities of isosorbide.(79) Poly(ether imine)-based polymers PEIs that exploit the structure of isosorbide as co-monomer to impart special properties to the produced materials have been successfully synthesized and fully characterized (**Figure 26**).(80)

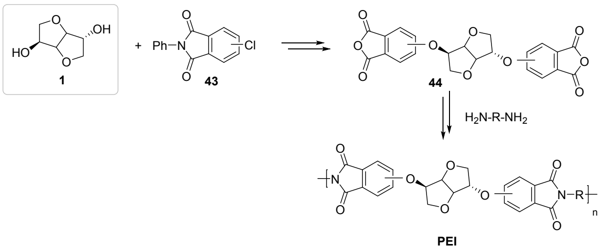

Figure 26: Poly(ether imides) PEIs synthetized starting from isosorbide-derived dianhydrides.(80)

The authors were able to demonstrate that most of the samples derived from isosorbide possessed thermal properties of glass transition temperatures, tensile strengths and Young's moduli comparable to petroleum-based poly(ether imine)s.

3.3.4. Polyurethanes

On the other hand, polyurethanes Pus are polymers characterized by the urethane group (R-NH-CO-O-) that can be obtained by polyaddition reaction generally starting from a diol and a diisocyanate even if in most cases the starting material is made up of polyfunctional monomers.(81)

Polyurethanes have a very diversified field of application but are commonly used to produce both flexible and rigid foams.(82) An important structure-property correlation study of innovative polymers within the class of sustainable polyurethanes was carried out by the Kieber *et al.*(83)

The authors provided an interesting screening on the possibility of employing different stereochemical isomers of isohexides in the synthesis of polymeric material with molecular weight between entanglements of 6-34 kDa.

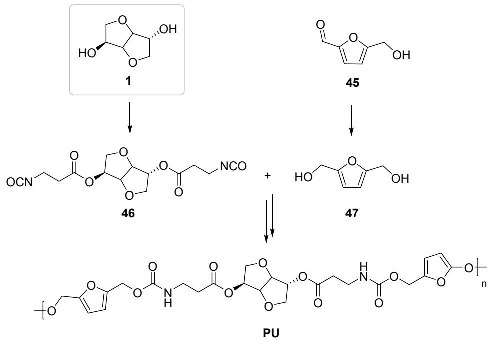

Figure 27: Polyurethane synthesis starting from biomass-derived monomers.(83)

The isosorbide-based PU showed in **Figure 27** the best results in terms of mechanical strength, higher density, reduced free volumes and good thermal stability compared to the counterpart considered,(84,85) always based on biomass-derived diols(86) of hydroxymethyl furfural (HMF).

3.3.5. Polyacetals

An interesting strategy was developed by Rajput *et al.*(87) for the synthesis of a narrow range of diacetal isohexides intended to produce chiral building blocks for the polymer industry to be used in pharmaceuticals and medicine.(87)

Polyacetals are polymeric materials with simple bond repeating units (-CH2-O-) and are commonly used in the production of components for household appliances, gears, bearings and automotive parts, and components for biomedical devices.(88)

They are used as commodities and, given the large market demand, the possibility of replacing oil-based components with more sustainable solutions appears to be an excellent starting point for the green transition of the economy in the context of polyacetals. Isosorbide-based diacetals were

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subjected to acid-catalyzed polycondensation (**Figure 28**) under mild conditions.

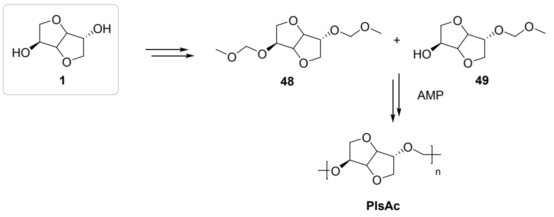

Figure 28: Isosorbide-based polyacetals synthetized through Acetal Metathesis Polymerization (AMP).(87)

The authors were able to synthesize innovative materials with good yields, appearance and intrinsic characteristics such as molecular weight of 3200-27600 g/mol of the isolated product. This publication led several groups of researchers to investigate the possibility of using isosorbide in this field.(89,90)

3.3.6. Polyamides

Another class of polymeric materials in which the typical functionalities of isohexides can be exploited to obtain innovative materials is constituted by polyamides.

Polyamides PAs are macromolecular materials characterized by an amide bond (-CO-NH-) in the main chain.

In polymers this bond is established by a reaction of polycondensation of a -COOH terminal of a carboxylic acid and a -NH_2 terminal of an amine.(91) The amide bond can resonate between two limit structures and can assume a partial double bond character, thus giving the bond a planar geometry, a certain rigidity and a non-negligible Debye dipole moment. Commonly, these characteristics allow macromolecules to be organized in trans-planar linear structures.

In addition, the spatial arrangement of the chains allows for effective overlap and the possibility of forming hydrogen bonds translates into a high degree of crystallinity that reaches values of up to 40-50%, and molecular weights of 10^4 g/mol.(92)

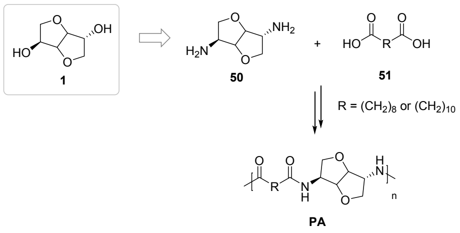

Figure 29: Polyamide synthesis starting from isosorbide-based diamine and aliphatic natural dicarboxylic acids.(93)

Jasinska-Walc *et al.*(93) were able to synthesize fully biobased polyamides from diamino-isosorbide and sebacic or brassylic acid, C_{10} and C_{13} aliphatic diacids deriving from castor oil as shown in **Figure 29**. To date, all polyamides produced on an industrial scale from monomers derived from biomass are based on monomers derived from castor oil.(94) A problem that has not yet been addressed is the competition with the food supply chain for the use of building blocks of natural origin to produce polymeric commodities. The use of isohexides such as isosorbide could constitute the green breakthrough so sought after by many researchers in the sector of macromolecular products.(95)

In Section 3, the current discussion on the sustainability of the monomer feedstock supply chain and on the main potential application fields of isosorbide-based compounds in the polymeric materials industry was thoroughly highlighted.

4. Conclusions

In this review, a comprehensive survey of peculiar compounds with isohexidic structure was performed with a focus on isosorbide **1**, a di-anhydro hexitol with two *endo-exo* OH groups in position 3 and 6, respectively. The main properties that distinguish isohexides from any other reactant class have been addressed in Section 1, with particular attention to the correlations between molecular structure and properties of the final product. In Section 2 it was discussed how isosorbide can be successfully synthesized by common dehydration of hexitols or separated from vegetable waste biomasses that do not compete with the agri-food industry. The isosorbide's interesting characteristics which can be exploited for the replacement of different diol compounds commonly derived from the crude oil sector, have been emphasized starting from Section 3. The singular structure of isosorbide is based on two tetrahydrofuran rings fused with a *cis*-type junction and the spatial arrangement of the two hydroxyl substituents allow this isohexide to be used for its intrinsic chiral property as chiral auxiliary and/or proper reactant.

In the last part of the review, the reader can find an in-depth bibliographic research with salient examples of uses of isosorbide in the synthesis of polymeric materials with a high percentage of biobased, thanks to its high reactivity and the possibility of forming intramolecular hydrogen bonds.

For instance, the use of isosorbide as a monomer, comonomer and precursor has been demonstrated in the production processes of different types of polymers, such as epoxy resins, polyesters, polyimides, polyurethanes, polyacetals, and polyamides with good to excellent yields and high average molecular weights.

Overall, this review has shown how and why isosorbide can be considered a compound of great industrial relevance in many chemical sectors. The reader will be able to recognize the potential exploitation of isosorbide in the fields of asymmetric synthesis, realization of chiral ionic liquids and production of polymeric materials with high applicative potential. Following the author's personal interpretation of the cited literature, the differences that can be encountered when isosorbide is used as reactant or auxiliar diols instead of the traditional diols deriving from the petrochemical chain, will be clarified.

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5. Conflicts of interest

There are no conflicts of interest to declare.

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