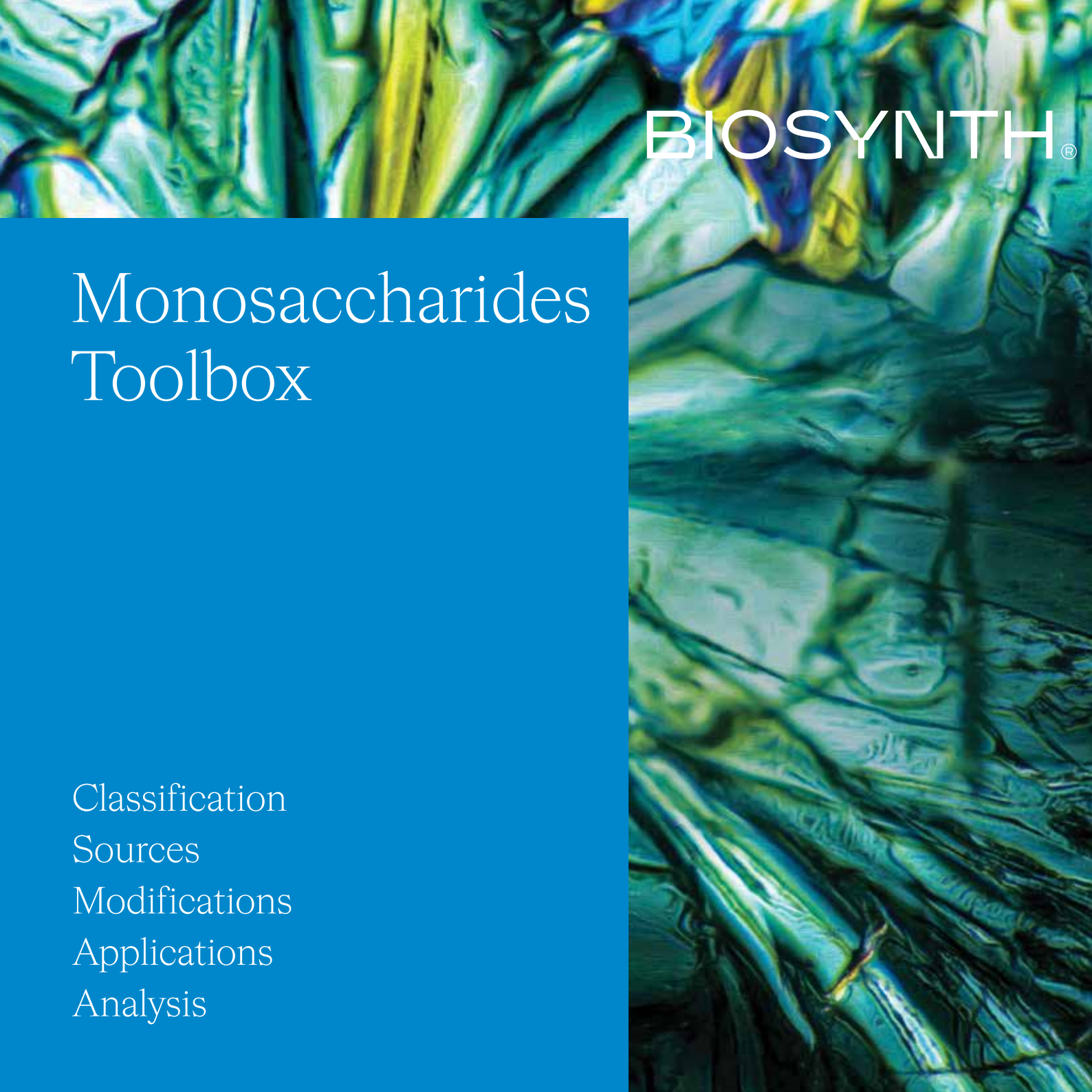

BIOSYNTH®

Monosaccharides Toolbox

Classification
Sources
Modifications
Applications
Analysis

Global Reach

The Netherlands - Lelystad
Synthetic laboratories
Peptide manufacture

Switzerland - Staad
Synthetic laboratories
Large-scale manufacture
Distribution hub

United Kingdom - Compton
Synthetic laboratories
Distribution hub

Austria - Vienna (EUCODIS Bioscience)
Enzyme Engineering and Manufacturing
Biocatalysis

Ireland - Dublin (Aalto Bio Reagents)
Biologics for IVD
Antibodies and antigens

Slovakia - Bratislava
Synthetic laboratories
Large-scale manufacture
Distribution hub

China - Beijing, Jinan, Suzhou
Synthetic laboratories
Large-scale manufacture
Distribution hub

United States - Gardner, Louisville
Synthetic laboratories
Peptide synthesis

South Korea - Seoul
Sales office

United States - San Diego
Distribution hub

Japan - Tokyo
Sales office

India - Chennai
Sales office

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About Biosynth

Biosynth is an innovative life sciences reagents, custom synthesis and manufacturing services company. We are by scientists, for scientists, securing supply chains with consistent quality, across the globe. We manufacture and source a vast range of chemical and biochemical products, and take pride in delivering products that others cannot. We are experts in complex chemistry, peptides and key biological raw materials. We provide a full range of products and services to support life science research and development, with more than half a million products in our research catalog and hundreds of complex manufacturing service projects. Our complex chemistry specialties include enzyme substrates, carbohydrate and nucleoside chemistry, with manufacturing services from the first idea to the finished product, from route scouting to GMP or ton scale production. For peptides, we also have a full end-to-end offering, from lead discovery and optimization, library production, through to GMP NCE or Neoantigen projects.

Biosynth's mission is to be the leading life sciences platform for scientists developing revolutionary medicines and diagnostics.

The trusted supplier, manufacturer and partner for the pharmaceutical, life science and diagnostic sectors, along with customers across food, agrochemistry and cosmetics, we have facilities across three continents and a rapid global distribution network. Our main chemical research and manufacturing laboratories are in Switzerland, the United Kingdom, Slovakia and China, with peptide production in the USA and the Netherlands. Enzyme projects are based in Austria and biological IVD reagents in Ireland. Our R&D resources and production facilities are modern and versatile, allowing us to produce chemicals on the milligram to ton scale, and at ISO 9001 and GMP, with peptides at mg to multikilogram scale.

Four Areas of Focus

Research Products	Complex Chemicals	Quality Peptides	Key Biologics
• Over 500,000 Products • Small Scale • Rapid Distribution • Retail Chemicals	• Custom Synthesis • Optimization • Large Scale Production • GMP Manufacture	• Custom Synthesis • Neoantigen Peptides • GMP Production • End to End Services	• Custom Antibodies • Reagents for IVD • Enzyme Development • Epitope Mapping

Development of Innovative New Products

Chemical Manufacturing Capabilities

- Custom Synthesis
- Large-Scale Manufacturing
- GMP Manufacturing
- Quality Control and Quality Assurance
- CDMO Services
- Custom Filling and Packaging
- Logistics and Warehousing
- Sourcing

Biosynth History

Biosynth was founded in 1966 by Hans Spitz, and has grown to a global products and services business. Biosynth merged with Carbosynth in 2019 to form Biosynth Carbosynth, creating a world leader in carbohydrates, nuclesosides and enzyme substrates. In 2022 Biosynth Group acquired both vivitide and Pepscan, which strengthened the offering in peptide manufacturing services and catalog products. Also in 2022 Biosynth Group acquired Aalto Bio Reagents, expanding the range of biological products and key raw materials for clinical diagnotics including antigens and antibodies, as well as EUCODIS Bioscience, experts in Enzyme development. Following these acquisitons, the company returned to the Biosynth brand. Biosynth is owned by KKR, Ampersand and senior management.

Ordering

You can conveniently order products online at www.biosynth.com

You can also place an order or make a product inquiry at sales@biosynth.com

For more information, please visit www.biosynth.com

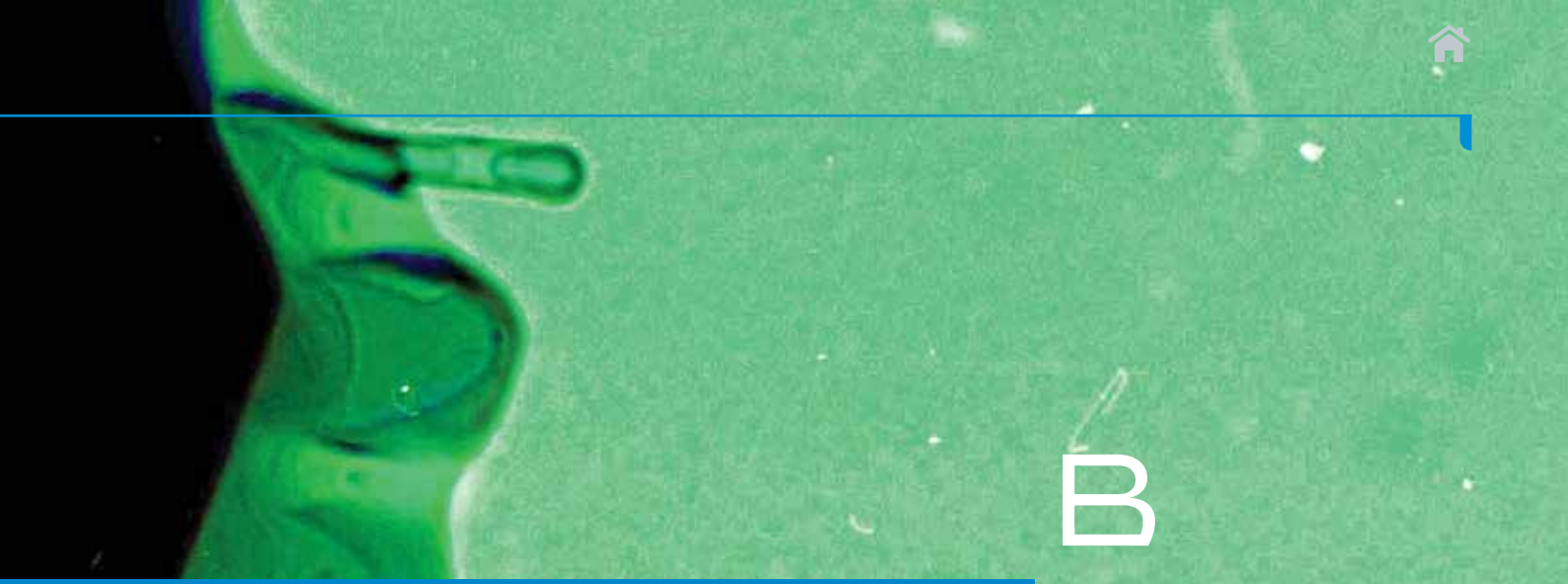
Monosaccharides are produced by photosynthesis, the process by which plants, some bacteria and some protistans use the energy from sunlight to produce glucose from carbon dioxide and water. Glucose is then converted into pyruvate which releases adenosine triphosphate (ATP) by cellular respiration. Oxygen is also formed. Photosynthesis may be summarised by the following word equation:

$$6CO_2 + 6H_2O \xrightarrow[\text{Chlorophyll}]{\text{Sunlight}} C_6H_{12}O_6 + 6O_2$$

Carbon Dioxide + Water → Carbohydrate + Oxygen

The conversion of usable sunlight energy into chemical energy is associated with the action of the green pigment chlorophyll.

Monosaccharides are the basic carbohydrate building units that when joined together give rise to oligosaccharides or polysaccharides. Thus, the relationship of monosaccharides to oligosaccharides or polysaccharides is analogous to that of amino acids and proteins, or nucleotides and nucleic acids (polynucleotides).



B

Section 2

Classification of Monosaccharides

2 Classification of Monosaccharides

The two main classes of monosaccharides are the aldoses and ketoses where the carbonyls are aldehydes and ketones respectively. In the case of aldoses, the aldehyde group occurs at chain ends whereas for ketoses, the carbonyl group is within the chain (Fig I1).

Monosaccharides with three carbon atoms are called trioses and these are the smallest monosaccharides, such as glyceraldehyde (aldoses) (Fig I2) and dihydroxyacetone (ketoses) (Fig I3). Those composed of four carbon atoms are called tetroses, those with five carbons are called pentoses, those that have six carbons are hexoses, and so on.

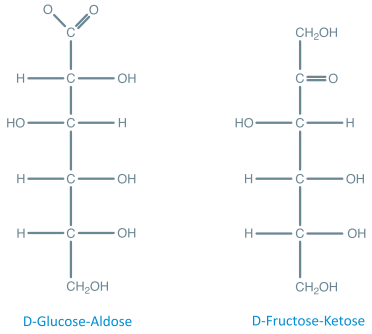


Fig I1 Aldose and ketose structures

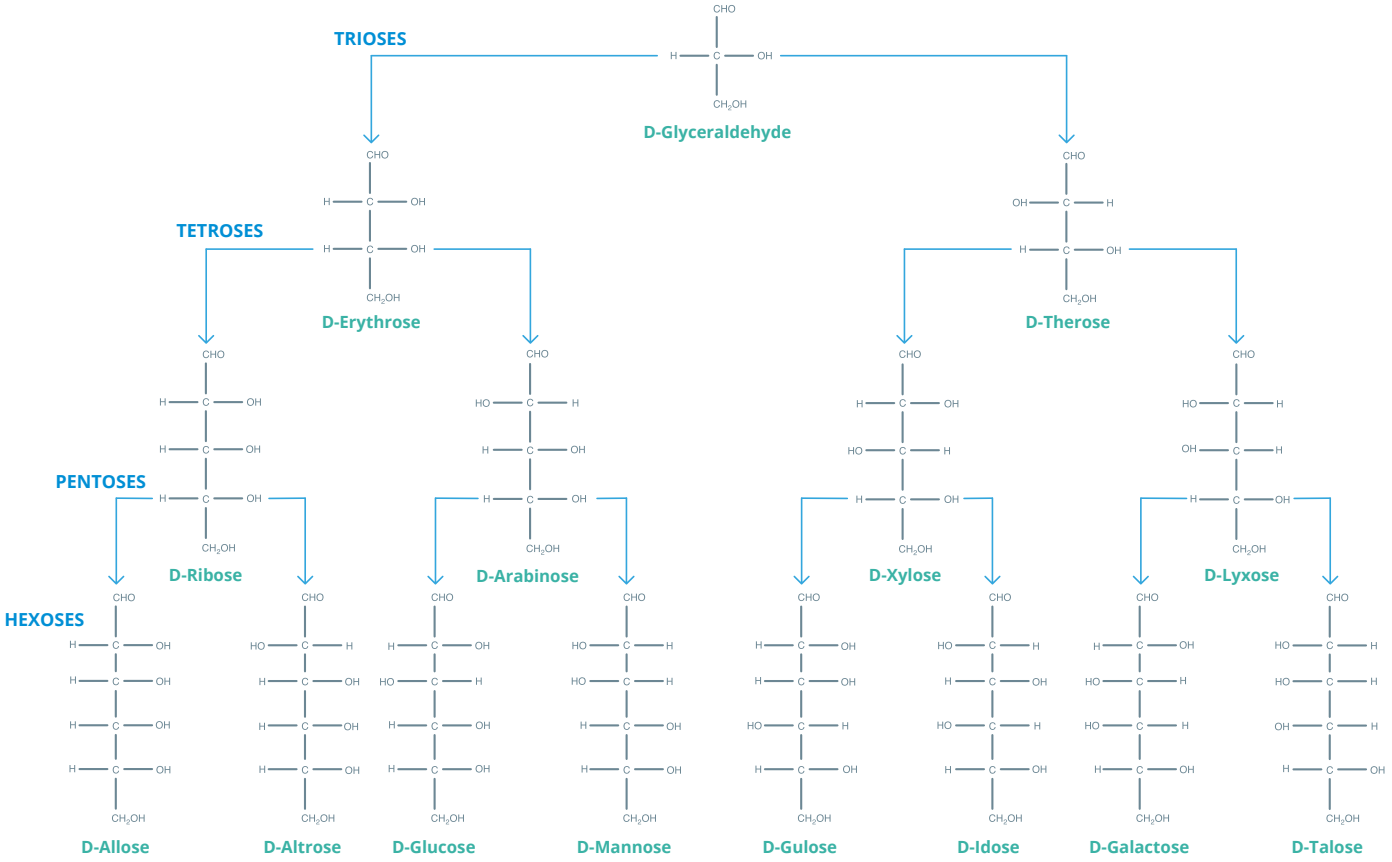


Fig I2 The eight possible D-aldohexoses

The most common aldohexose is glucose with galactose and mannose occurring in many plant and animal tissues and body fluids.
Of the aldopentoses, the most common are arabinose and xylose with ribose being part of the ribonucleotides from which RNA is formed.

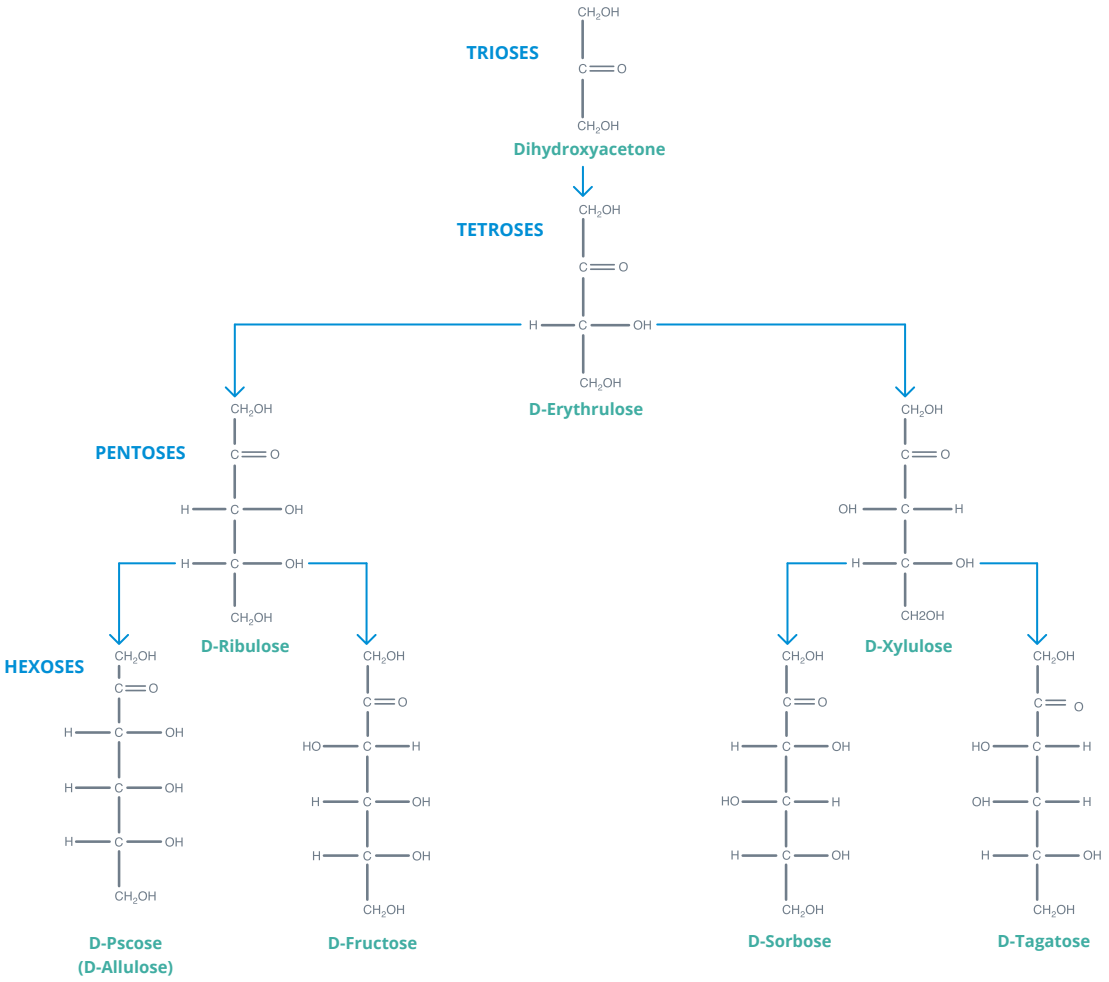
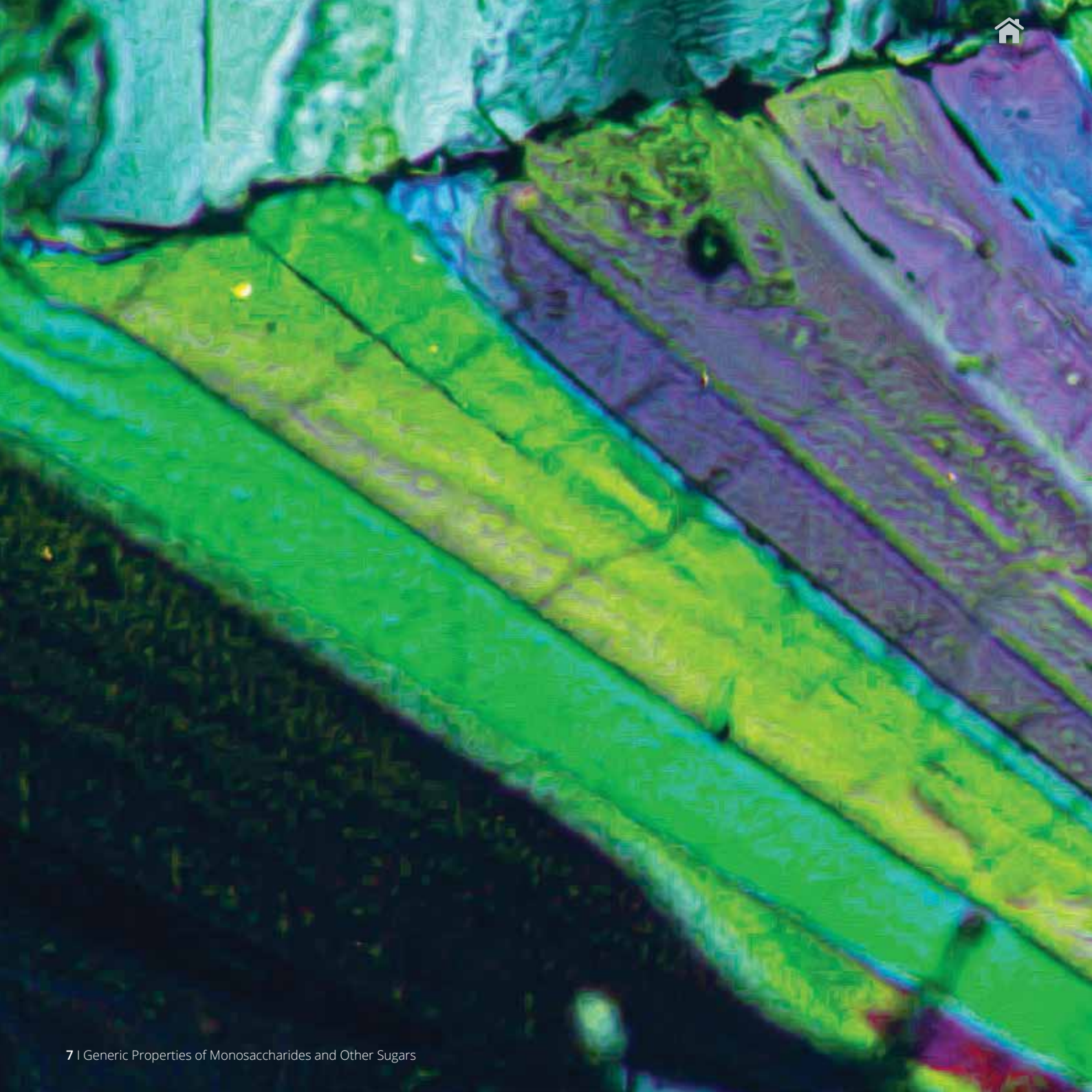
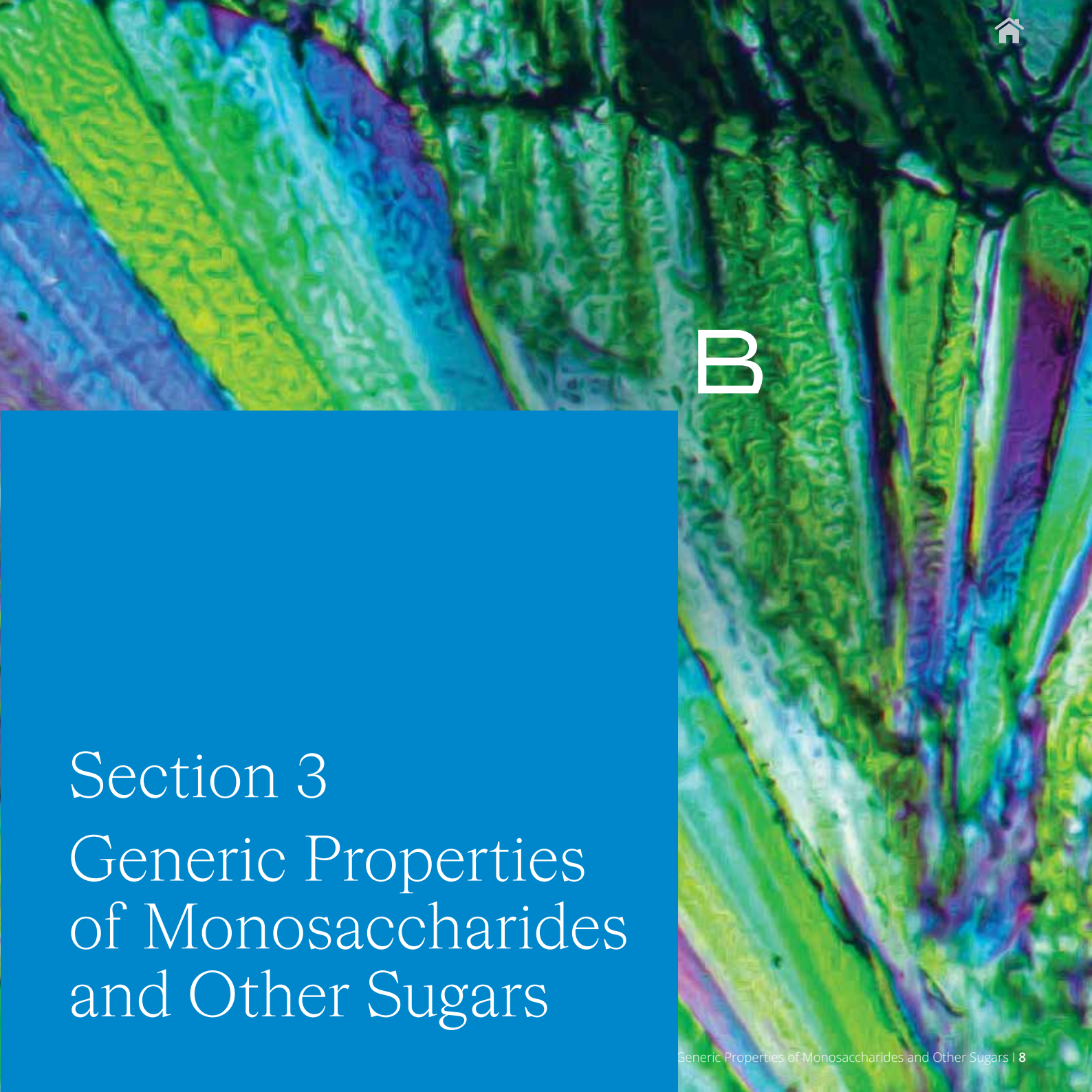


Fig I3 The four possible D-2-ketohexoses

In the ketose series, the most common member is fructose, a ketohexose found in many plant tissues.





B

Section 3
Generic Properties of Monosaccharides and Other Sugars

3.1 The Anomeric Effect

The anomeric effect in carbohydrate chemistry refers to the preference of a hydroxyl substituent attached in the anomeric position (the carbon with a hemiacetal or acetal-C1 for aldoses, and C-2 for ketoses – see Fig I4 opposite for the numbering convention) to favour an axial orientation rather than an equatorial one, despite the increased 1,3-diaxial interactions.

The equatorially positioned substituents of a carbohydrate ring are, for steric reasons, the most energetically favoured, compared to their axial counterparts, as is the case in every molecule with a chair conformation. However, the anomerically bound groups in carbohydrates do not follow this rule completely: Thus as shown in Fig I5, the top structure represents a cyclohexane ring in which any substituent favours the equatorial position. However, in the bottom structure of a stylised monosaccharide where there is a ring oxygen atom, the axial position is favoured.

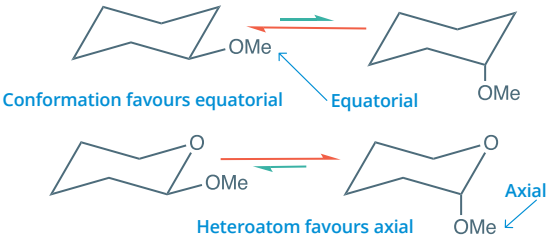


Fig I5 Schematic showing the influence of a heteroatom (oxygen) over conformation only

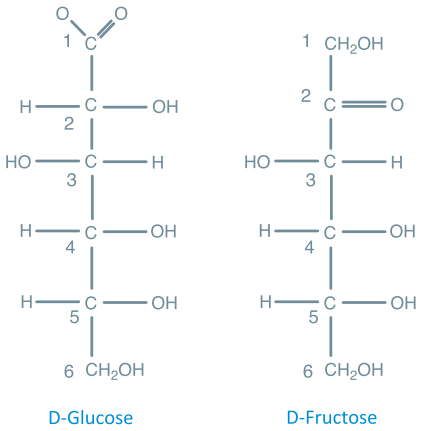
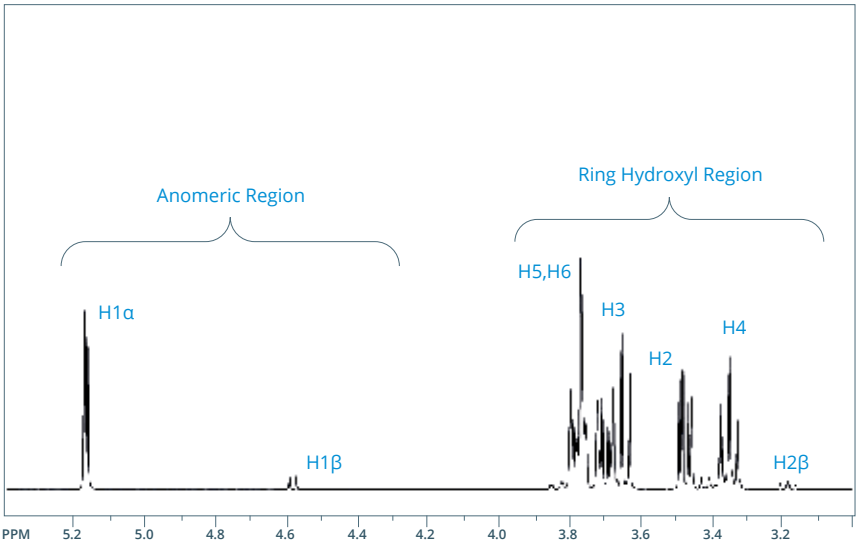


Fig I4 Numbering convention for aldoses and ketoses

An aqueous solution of D-glucose, for example, contains a higher proportion of the β-form than would be expected. This behaviour is demonstrated by a proton NMR experiment in which the α-anomer predominates at the start of the experiment but after several hours, the β-anomer has increased to nearly 50% of the mixture (Fig I6).



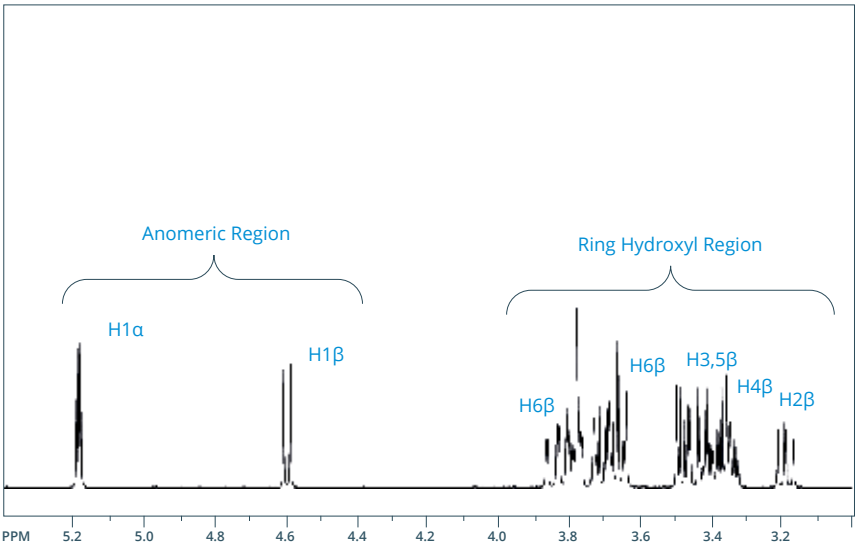


Fig I6 Anomeric effect demonstrated by NMR spectroscopy

This unusual preference of the sterically unfavoured axial position over the equatorial position at the anomeric center was named the 'anomeric effect' by the Canadian chemist Raymond Lemieux (Lemieux, 1975) (Fig I7).

> *This phenomenon, resulting from the operation of the anomeric effect, is of the greatest significance in carbohydrate chemistry since it contributes importantly to the free energies of many pyranoid compounds and hence to their preferred conformations and reactivities and also to the compositions of isomeric mixtures at equilibrium.*
>
> **(Collins, 1995)**

Fig I7 Raymond Lemieux

3.2 Mutarotation

In aqueous solution, monosaccharides undergo a complex series of reactions consequently producing a mixture of products that are in equilibrium. In the case of glucose, the [α]D 20 of this mixture is +52.7° and represents the resulting optical rotation of the following five compounds: 37% α-D-glucopyranose, 67% β-D-glucopyranose, 0.5% α-D-glucofuranose, 0.5% β-D-glucofuranose, and 0.002% of the open chain free aldehyde (Fig I8). This transformation is called mutarotation and takes place through the open chain form. The importance of mutarotation is that many reactions of carbohydrates both chemical and enzymatic involve C1 and take place via the open chain form.

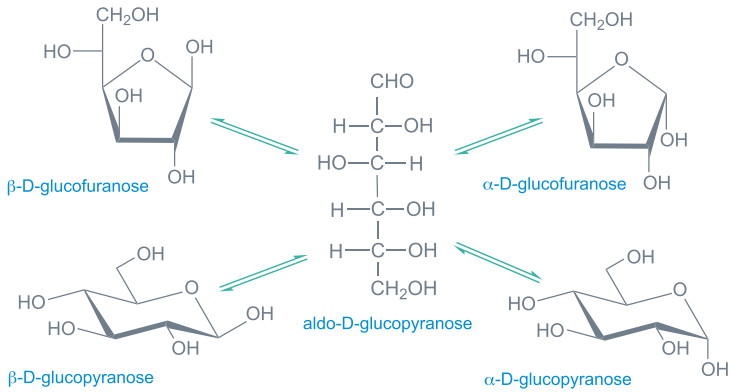


Fig I8 Mutarotation

3.3 Stability Considerations

The most stable or most favourable conformation usually is the one that places the majority of the bulky substituents (for most carbohydrates a bulky substituent is a hydroxyl group or a hydroxymethyl group) in an equatorial position, and, likewise, the least favoured conformation is the one that places the majority of the bulky groups in an axial position. The placing of the bulky groups in the plane of the ring, or equatorial position, puts the bulky groups as far apart from each other as possible, creating a low-energy form with a minimum of bulky group interactions. Placing the bulky groups perpendicular to the ring, in an axial position, puts the bulky groups as close together as possible, creating a higher energy form with a maximum of interaction. This can be illustrated for α-D-glucopyranose in which all of the bulky groups are equatorial when the molecule in the *C (C1). Mannose contains one axial group (2) and gulose contains two axial groups (3, 4) (Fig I9). It is interesting to note that in nature the predominance glucose-mannose-gulose decreases in that order.

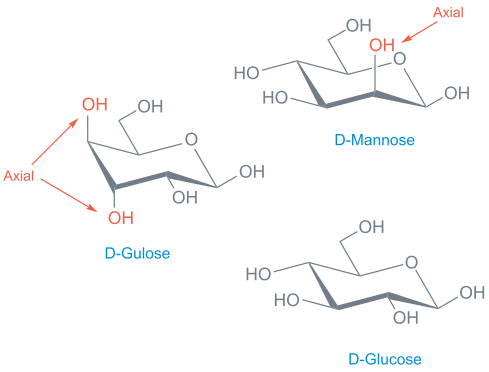


Fig I9 Glucose, mannose & gulose showing axial hydroxyl groups

3.4 The D/L Notation

Monosaccharides are given the notation D- and L-, relating to whether the molecule rotates the plane of polarised light to the right (Dextro) or to the left (Levo); they are mirror images.

The D/L system (named after Latin dexter and laevus, right and left) names molecules by relating them to the two chiral molecules of glyceraldehyde. Certain chemical manipulations can be performed on glyceraldehyde without affecting its configuration, and its historical use for this purpose (possibly combined with its convenience as one of the smallest commonly used chiral molecules) has resulted in its use for nomenclature. In this system, compounds are named by relating the structure to glyceraldehyde, which, in general, produces unambiguous designations, but is easiest to see in small biomolecules analogous to glyceraldehyde (Fig I10).

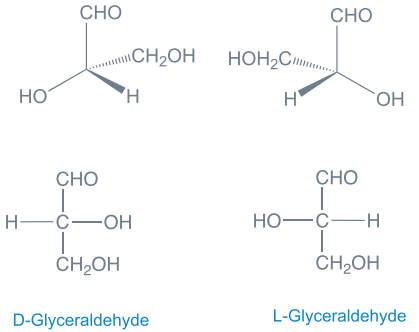


Fig I10 Representations of glyceraldehyde

A Fischer projection is used to differentiate between L- and D- carbohydrates. On a Fischer projection of a monosaccharide, the penultimate ("next-to-last") carbon (alternatively, the last stereogenic carbon) of D sugars are depicted with hydrogen on the left and hydroxyl on the right. L sugars will be shown with the hydrogen on the right and the hydroxyl on the left. In a standard Haworth projection of the cyclohexane structures of hexoses, D-carbohydrates have the terminal carbon (typically -CH_2OH) pointing up (Fig I11).

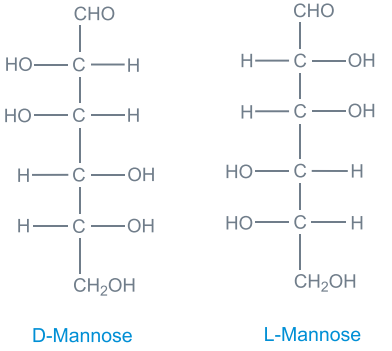


Fig I11 Fischer projections of D & L mannose

The conformational representation of D & L is given as an example by Glucose (Fig I12)

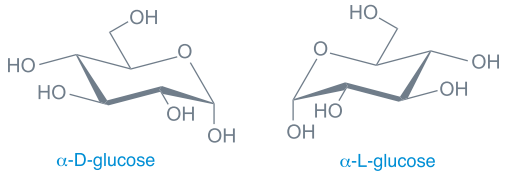


Fig I12 Conformational representation of D & L glucose

3.5 Structural Conventions

3.5.1 Fischer

The classification of monosaccharide structures began in the late 19th century with the pioneering work of Emil Fischer who published three papers in 1891 describing the structures of glucose, fructose, mannose and arabinose (Fischer, 1890). Together with his work on carbohydrate enzymes, it is generally accepted that he is the father of both carbohydrate chemistry and biochemistry (Fig I13).

The Fischer structure (projection) for glucose is shown opposite (Fig I14):

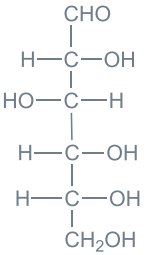


Fig I14 The Fischer projection for glucose

Fig I13 Emil Fischer in his laboratory

3.5.2 Haworth

In the 1920's the research group of Sir Norman Haworth at The University of Birmingham expanded on the work of Fischer, characterising many more carbohydrates and vitamin C. Howarth and (Sir) Edmund Hirst (Fig I15) developed the Howarth projection which differs from the Fischer projection in that it is used to represent the carbohydrate in its cyclical form and addresses a number of questions that could not be answered by the Fischer projection (Charlton, 1926).

The Haworth projection is now one of the standards in organic chemistry for stereochemical carbohydrate illustrations, thicker bonds between carbon atoms represent those closest to the viewer, and the hydrogen/hydroxyl bonds below the plane of the carbon atoms represent those on the right in a Fischer projection (Fig I16). Both Fischer and Haworth (for vitamin c) received the Nobel Prize.

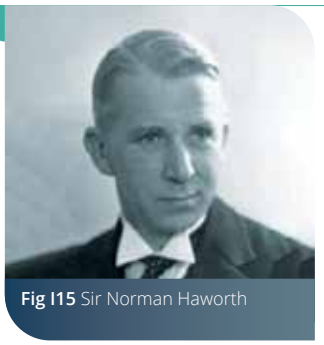


Fig I15 Sir Norman Haworth

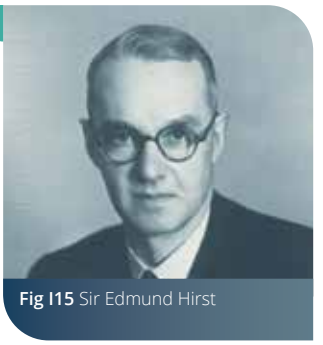


Fig I15 Sir Edmund Hirst

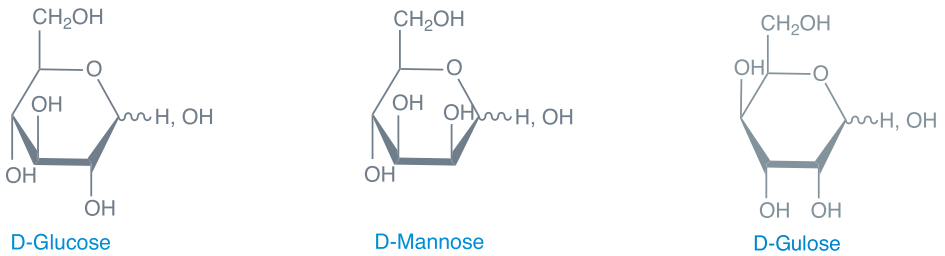


Fig I16 The Howarth projection

3.5.3 Isbell

Pyranose ring (six membered) structures are conformationally represented more accurately in two chair, six boat, six skew, and twelve half-chair conformations. In practice, chair conformations strongly dominate and the $^4C_1$ conformation is the most important (Fig I17). It is energetically the most favoured chair with the fewest non-bonded interactions as all OH groups and the CH_2OH group are equatorial. This conformation is also adopted by the α/β-anomers of D-galactose and D-mannose, each having a single axial OH group (Isbell, 1960).

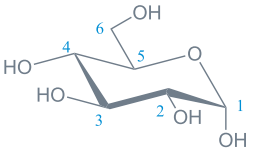


Fig I17 Glucose in the favoured 4C1 conformation

The ring numbering shown for aldoses is from the anomeric carbon to position six of the primary hydroxyl group. For ketoses, it is the lowest number that can be reached in the linear (Fischer) projection (for fructose this is 2). The rest of the carbons are numbered accordingly (Robyt, 2012).

3.5.4 From Howarth to Isbell (Rings to Chairs and Boats)

Monosaccharides can adopt different forms of ring structure – such as chair, boat and half chair conformations. These are important for stability and are also relevant for understanding enzymatic mechanisms and in synthetic work.

Pyranose (six membered forms)

For hexoses the name derives from the pyrans, which also contain five carbon atoms and one oxygen in a six membered ring and the most common hexose example is β-D-glucopyranose. β-D-glucopyranose can exist in alternative conformations which convert to each other by rotation about the bonds within the closed ring and the conformation with lowest energy is normally favoured. From the fundamental chemistry of carbon and oxygen that all bond angles in the structure will be close to tetrahedral. These bond angles can be altered only at the expense of introducing *angle strain*, which would increase the energy of the molecule and therefore the preferred conformations are those which are free from angle strain. In these, the ring cannot be flat, it must be puckered with the approximate shape of a chair or boat and all the hydroxyl groups are pointing away from each other *equatorially*. Fig I18 shows the favoured equatorial *chair conformation* and a possible but less favoured *boat conformation* where two hydroxyl groups are parallel to the plane of the ring or *axial*.

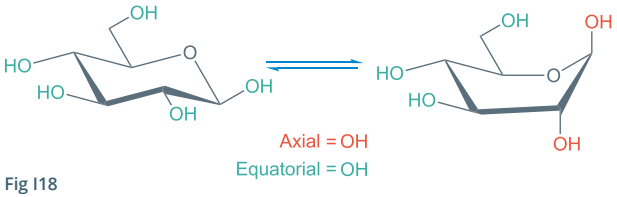


Fig I18

Furanose (five membered) **forms**

Although six-membered ring forms are most often found in nature and are usually the most chemically stable, the five-membered ring is also biologically important, derived from the furans and known as *furanose*.

Chains of carbohydrate units in the five-membered ring form, have a source of flexibility which is not shared by chains of six-membered chair forms. Five-membered sugar rings can interconvert without distortion of bond angles, and therefore they are flexible in a way that six-membered chair forms are not. In solution they can pass more smoothly and continuously between low and high energy forms (Fig I19).

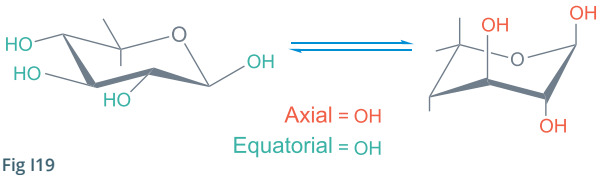


Fig I19

3.5.5 Glycobiology

Synthetic chemistry requires the full molecular structure for each sugar residue so that detailed manipulations can be described. However, this presents difficulties for the biological sciences due to the large number of monosaccharides that often make up the complex carbohydrate structures that decorate glycoproteins and other important biological molecules. Thus, symbols have been designed to replace monosaccharides so that complete oligosaccharides can be represented with sufficient simplicity to allow for pictorial representation in publications as diverse as glycoprotein analysis by mass spectroscopy or the description of the active site of an enzyme (Varki, 2015) (Fig I20).

Thus:

Fig I20 Examples of monosaccharide symbols used in glycobiology

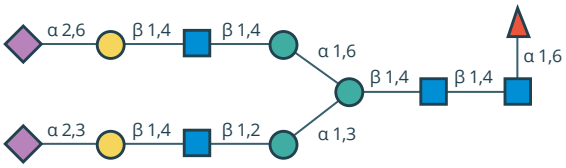


Fig I21 *N*-linked oligosaccharide

An illustration of the use of the symbols is the representation of a N-linked oligosaccharide shown above (Fig I21):

3.5.6 SMILES

SMILES (simplified molecular-input line-entry system) is a specification in the form of a line notation for describing the structure of chemical species using short ASCII (American Standard Code for Information Interchange) strings. The figure (Fig I22) below demonstrates the conversion of SMILES strings into key monosaccharides associated with glycoproteins.

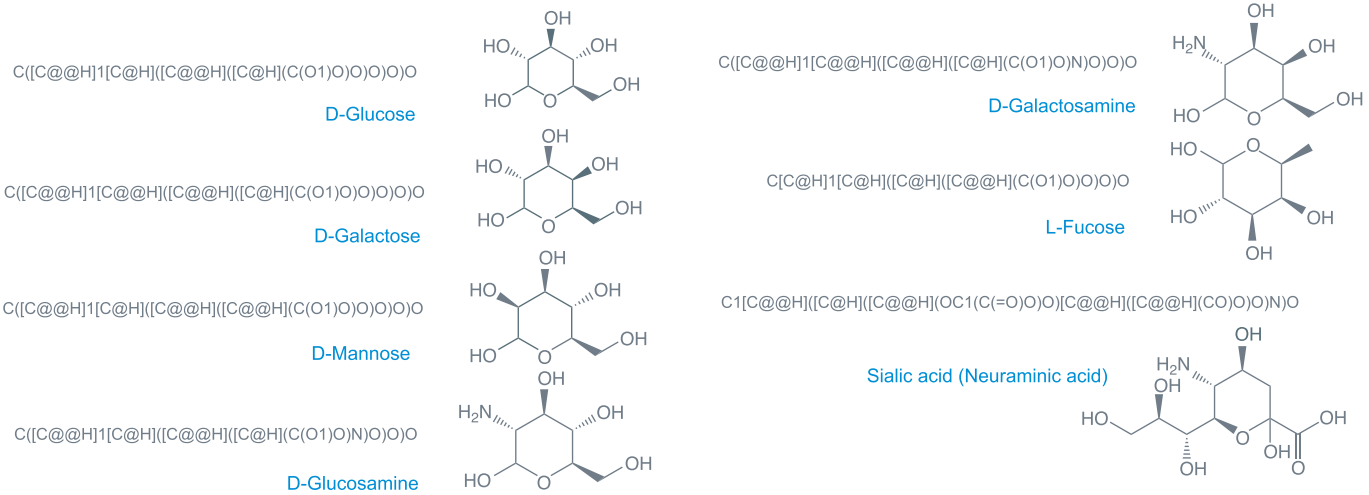


Fig I22 Some monosaccharide structures represented by SMILES strings

Thus, Sialyl-Lewis x is represented with the following SMILES string (Fig I23).

C[C@H]1[C@H]([C@H]([C@@H]([C@@H](O1)O[C@H]([C@H](C=O)NC(=O)C)[C@@H]([C@@H](CO)O)O[C@H]2[C@@H]([C@H]([C@H](O2)CO)O)O[C@@]3(C[C@@H]([C@H]([C@@H](O3)[C@@H]([C@@H](CO)O)O)NC(=O)C)O)C(=O)O)O)O)O)O

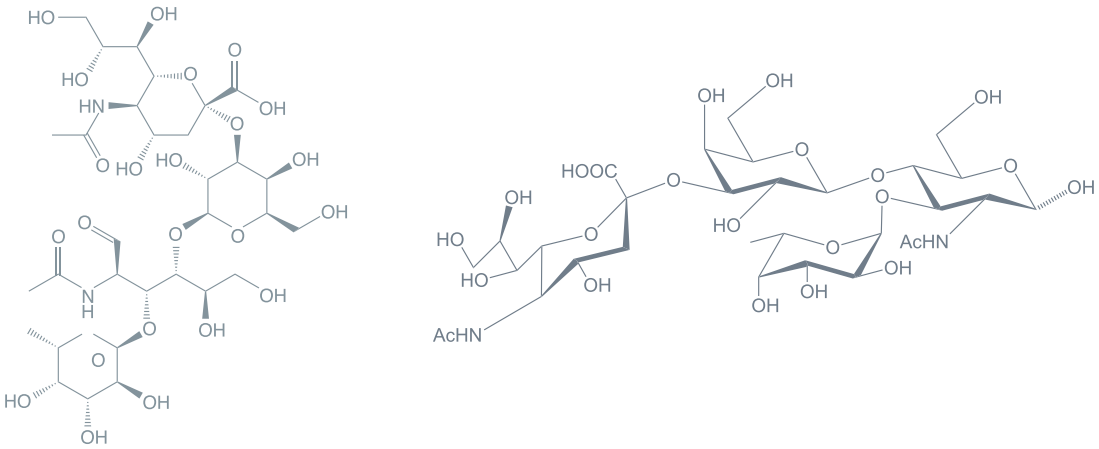
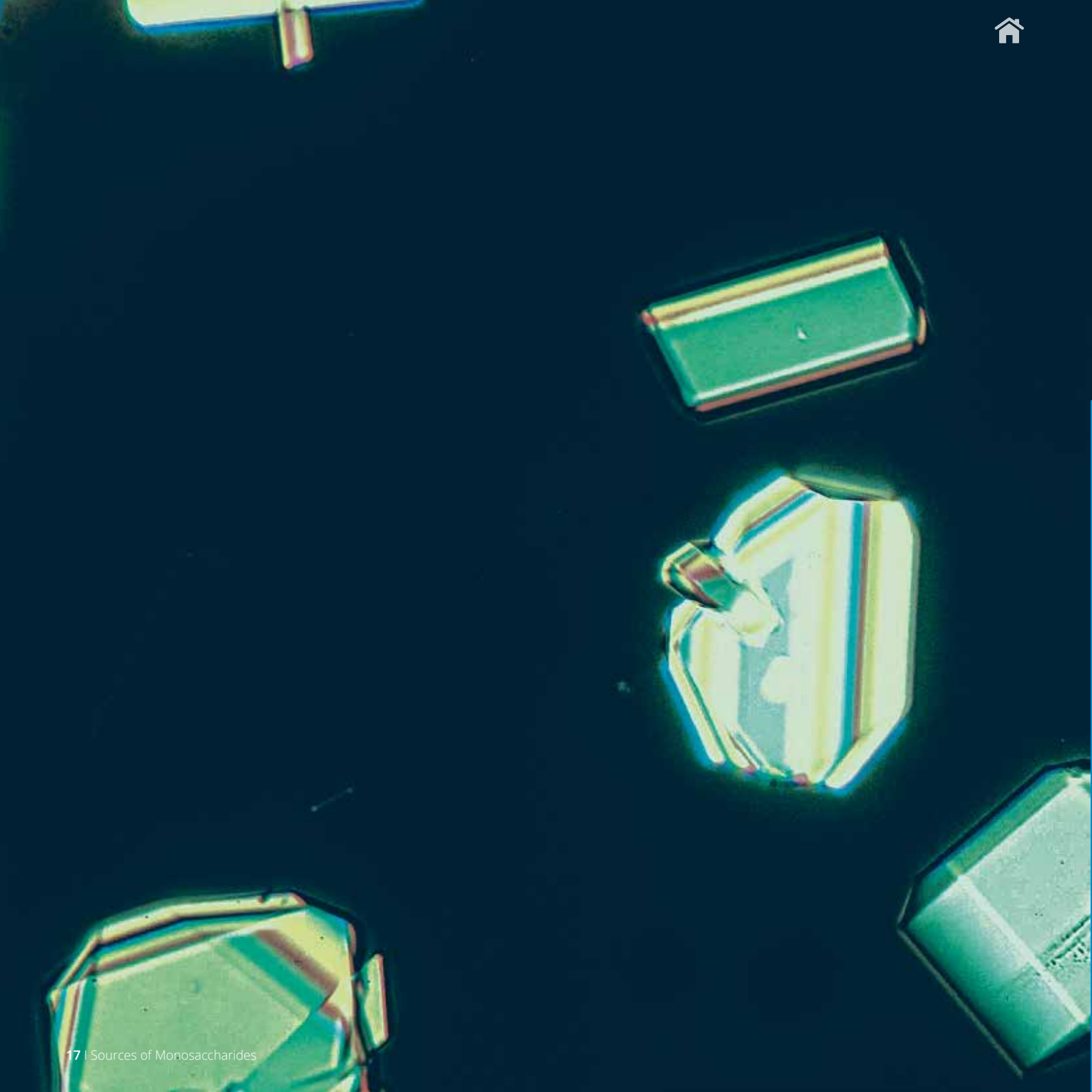


Fig I23 Conformational structure of SiaLex compared with its SMILES counterpart

This convention has proved very successful for chemists working on synthetic carbohydrate strategies such as in oligosaccharide synthesis (Sarkar, 2015).



Section 4
Sources of Monosaccharides

4 Sources of Monosaccharides

The source of a number of key monosaccharides is described in detail in section 5, but in overview, monosaccharides occur both free and bound in plant and animal tissues. When they are free (e.g. glucose, fructose), they occur in the sap of plants but they are also covalently attached to proteins and lipids (Gabius, 2009). This is exemplified by the glycoprotein shown below (Fig I24):

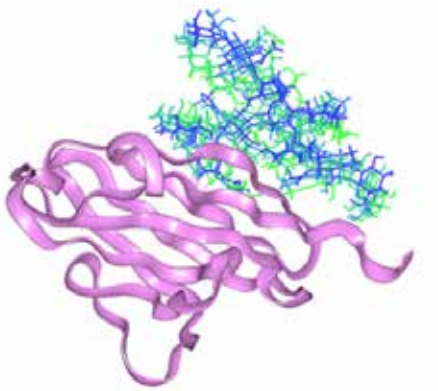


Fig I24 A glycoprotein structure with glycosylation shown in blue

As previously described, monosaccharides are produced by photosynthesis. The generation of monosaccharides is normally due to the breakdown of larger carbohydrates, including oligosaccharides - such as the production of galactose from lactose (Bailey, 1965) (Fig I25).

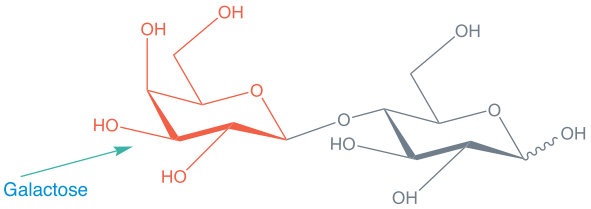


Fig I25 Galactose from Lactose

Mannose is produced by hydrolysis of the mannan (vegetable ivory) from a species of the genus *Phytelephas* ("elephant plant"), native to South America (Collins, 2006) (Fig I26).

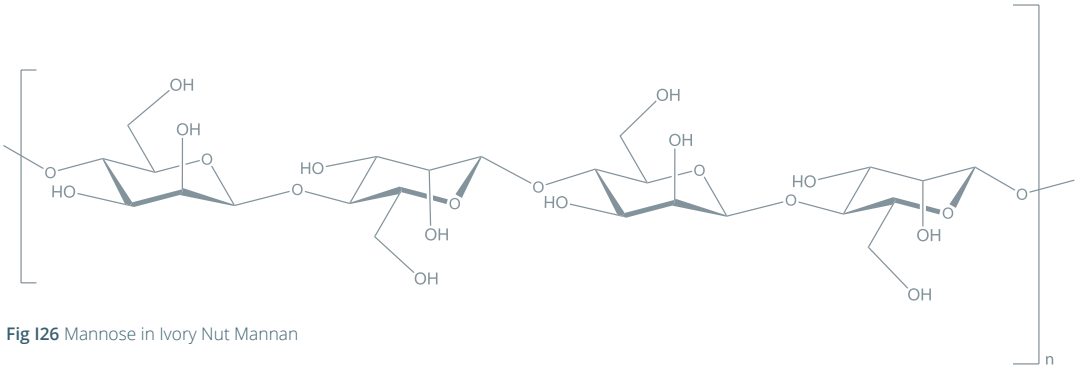
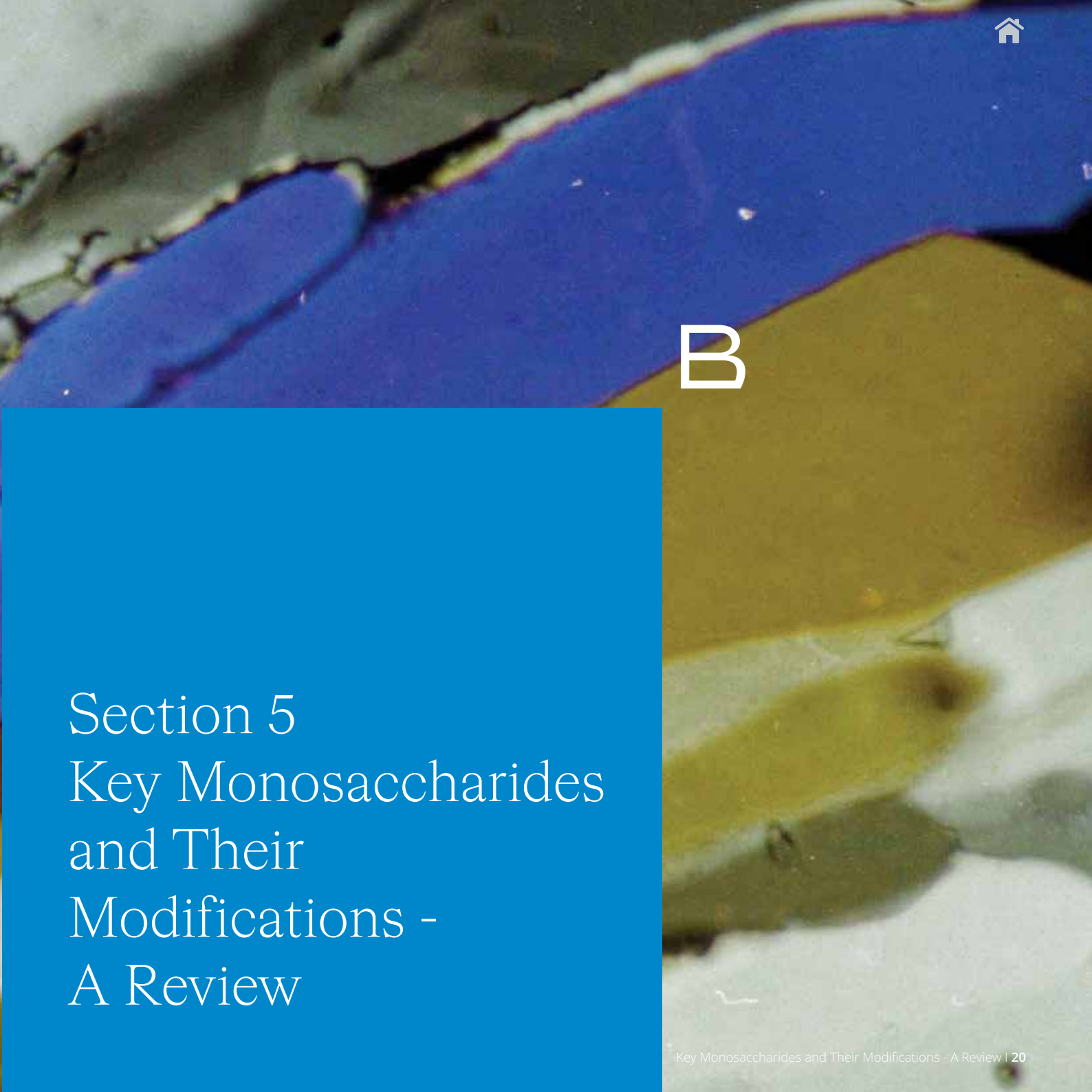


Fig I26 Mannose in Ivory Nut Mannan



B

Section 5
Key Monosaccharides and Their Modifications - A Review

5 Key Monosaccharides and Their Modifications - A Review

5.1 Introduction

The hexose aldoses, glucose, galactose and mannose, and the ketose, fructose are the most common monosaccharides (Isbell, 1940). In the pentose series arabinose and xylose predominate. Many other monosaccharide modifications based upon the parent aldoses and ketoses are found in nature including fucose and rhamnose and other natural monosaccharides are found that contain functional groups such as acetate, sulphate and phosphate. Other important monosaccharide analogs that include the inositols and glycosidase inhibitors (monosaccharides with the ring oxygen replaced with nitrogen) are reviewed.

5.2 The Commodity Monosaccharides Glucose & Fructose

The energy providing hexoses, glucose and fructose, are found in the cytosol (plant cell sap) with concentrations that can be very high in fruits and vegetables such as corn, peas and sweet potatoes (Kirk, 1991) (Fig R1).

Fig R1 Maize

Fig R1 Peas

Fig R1 Potato

Sucrose, an equimolar combination of glucose and fructose, is produced from sugar beet in temperate climates and from sugar cane in the tropics (Fig R2). However, glucose and fructose are not produced from sucrose as the cost is prohibitive.

Another source of glucose, fructose (and sucrose) is nectar and the honey derived from it (Crane, 1975) (Fig R3).

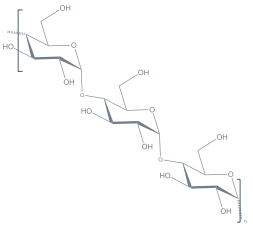
Fig R2 Sugar beet

Fig R2 Sugar cane

Fig R3 Honeycomb

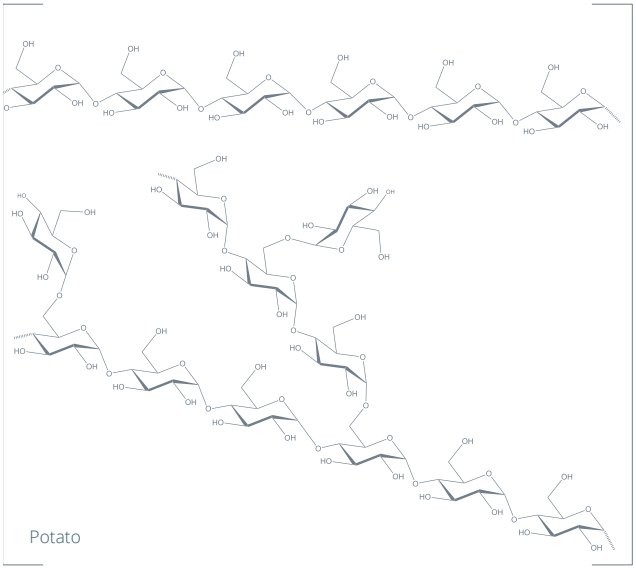
The major commodity monosaccharides are glucose and fructose. By far the largest market for these sugars is the food industry and due to the complexity of their production and use, it is difficult to produce exact figures for volumes of the pure monosaccharides. The species used for glucose production (e.g. corn, potato, waxy maize) contains high levels of starch (the linear glucan amylose and the branched glucan amylopectin in different proportions) (Fig R4). These glucans are hydrolysed (acid/enzyme) to produce glucose syrups (Fig R5) and depending on the hydrolysis conditions, the resulting (non-crystallising) syrups contain glucose and a range of glucose polymers known as maltooligosaccharides (Sihui, 2017; Eggleston, 2003). In 2018, it is estimated that in The European Union ~4.8x106 tonnes of glucose syrup was produced.

Fig R4 Corn



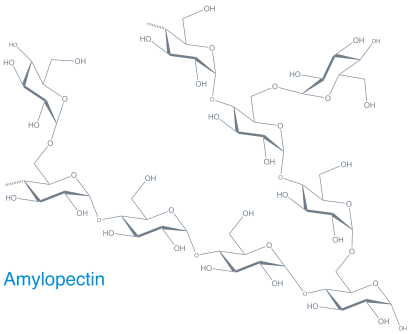
Corn (high amylose)

Fig R4 Potato



Potato

Fig R4 Waxy maize



Amylopectin

Waxy maize (α1,4, α1,6)

A semisynthetic product, High Fructose Corn Syrup (HFCS) contains both fructose (55%) and glucose (45%) (Fig R6).

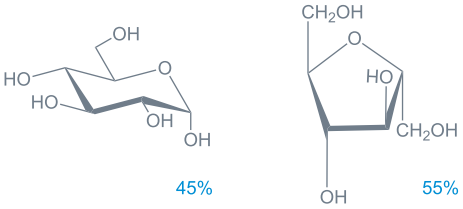


Fig R6 Constituents of HFCS

Fig R5 Glucose syrup

HFCS is produced from Corn Syrup by the action of the enzyme glucose isomerase (Bae 2018) (Fig R7). Glucose isomerase (also known as xylose isomerase, EC 5.3.1.5), produced intracellularly by *Streptomyces, Bacillus and Arthrobacter* species, converts glucose into fructose to exploit the greater sweetness of fructose over glucose and sucrose.

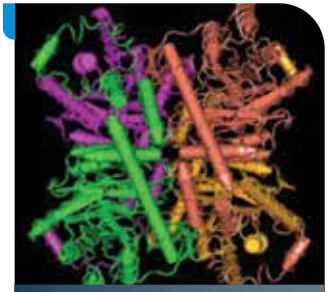
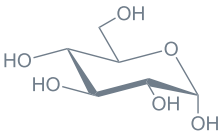


Fig R7 Glucose isomerase

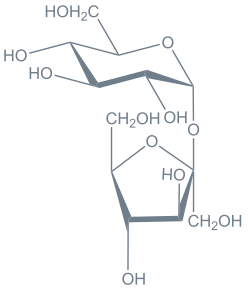
The steps involved in the conversion of starch into HFCSs using glucose isomerase, the largest biocatalytic process in current practice with millions of tons of HFCS produced annually, in 2019 ~7x10^6 tonnes of HFCS were produced in the US (Saha, 2009). Glucose syrup and HFCS are used in confectionery, beverages, bakery, sauces and pharmaceuticals.

HFCS competes directly with a product from the sugar industry known as partially inverted refiner's syrup, a mixture of sucrose, glucose and fructose (e.g. Golden Syrup) (Fig R8). The proportions of sucrose to glucose and fructose are arranged to prevent crystallisation of the syrup while preserving the sweetness of sucrose. As HFCS is cheaper to produce than the sucrose-based product many sugar producers have struggled to compete. In the US, this has resulted in the insolvency of several inefficient producers while in Europe until recently (2017) the quantity of HFCS (GFS) was limited through production and import quotas to protect the beet sugar industry.

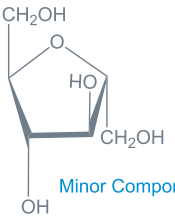
Fig R14 Partially inverted refiners syrup (Golden Syrup)



Minor Component



Major Component



Minor Component

Octyl glucoside (C8), Decyl Glucoside (C10), and Lauryl Glucoside (C12) were developed some years ago as biodegradable surfactants mainly for use in cosmetics and personal care products such as baby, skin care, eye makeup and hair care products, including hair dyes and colours (Holmberg, 2001). More recently these products have been formulated in household products, such as, washing up liquids. The global demand for alkyl polyglucoside surfactants is estimated to be valued at US$ 902.1M by the end of 2018 and registered a 6.8% annual growth rate over the period of 2018 to 2028 (Fig R9).

Various glycosides have been evaluated as polyols in the manufacture of urethanes and alkyds. These include methyl glucoside (Fig R10), ethylene glycol glucoside (Fig R11) and glycerol glucoside (Fig R12). The most promising was methyl glucoside, a simple adduct of methanol and glucose (Frisch, 1977). These polyols were evaluated in the production of rigid urethane foams but the major drawback to large scale use has been the economics compared with pentaerythritol. In the future this may change due to environmental arguments against the use of fossil fuels.

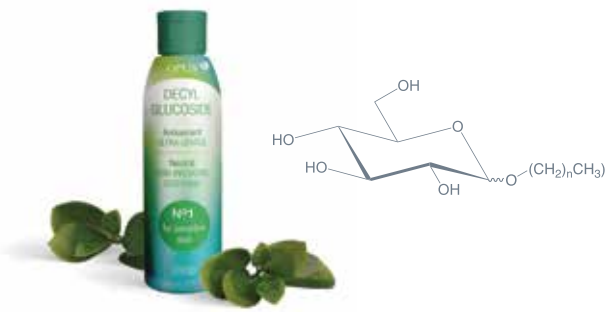


Fig R9 Alkyl polyglucoside surfactant, n= 8, 10, 12

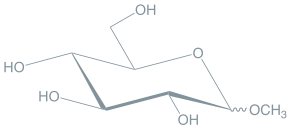


Fig R10 Methyl glucoside

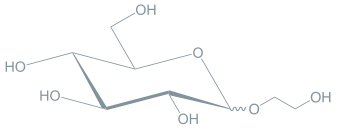


Fig R11 Ethylene glycol glucoside

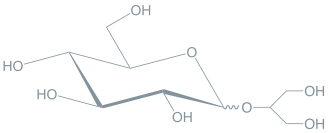


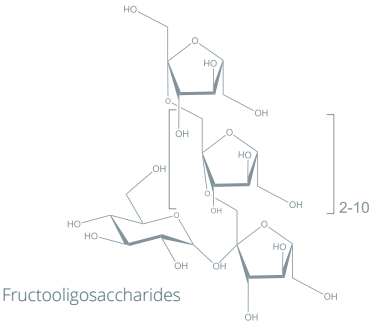
Fig R12 Glycerol glucoside

Finally, a crystalline fructose product (Fig R13) was developed some years ago from inulin using strictly controlled hydrolysis conditions and the major producer Tate & Lyle manufactured ~120x10^3 tonnes in 2015, approximately 31% of the total world production.

Inulin, obtained from Tubers such as Jerusalem artichoke and Chicory contains fructose plus a range of fructooligosaccharides (Ganaie, 2014) (Fig R14). Fructo-oligosaccharides have found application as pre and probiotics, and are sold in quantity for this use.

Fig R13 Crystalline fructose

Fig R14 Jerusalem artichoke



Fructooligosaccharides

Agave syrup contains a mixture of fructose and fructans, commonly used in Southern USA and Latin America and contains typically about 85% fructose. The carbohydrate composition in agave syrup depends on the species from which the syrup was made. Tequilana (blue agave), the syrup contains some 56% to 60% fructose, 20% glucose, and trace amounts of sucrose, whereas in *A. salmiana*, sucrose is the main sugar (Velázquez Ríos IO, 2019).

The mirror image of D-glucose, L-glucose was found to be a laxative, and has been proposed as a colon-cleansing agent which would not produce the disruption of fluid and electrolyte levels associated with the significant liquid quantities of bad-tasting osmotic laxatives conventionally used in preparation for colonoscopy (Raymer, 2003). L-glucose has very similar properties of sweetness to D-glucose and has been evaluated as a low calorie sweetener. However, production costs have precluded its commercialisation (Fig R15).

In addition to its commercial use, glucose is a major component of the oligosaccharides that are found in milk and are important constituents of many plant, algal and bacterial polysaccharides (e.g. starch, cellulose, β-glucan, xanthan gum). It is a key component of immunological determinants, hormones, cell membrane structures, endogenous lectins, and glycoproteins. Apart from commerce and in inulin, fructose is not found in other polysaccharides or biomolecules.

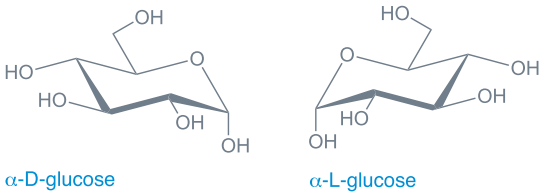


Fig R15 D- and L-Glucose

5.3 Other Common Hexoses and Pentoses

5.3.1 Deoxy hexoses (L-Fucose, L-Rhamnose)

Galactose, the C4 (axial) epimer of glucose (Fig R16) is uncommon in nature as the free sugar and by far the largest source is lactose, the disaccharide of glucose and galactose found in human and animal milks (Fig R16).

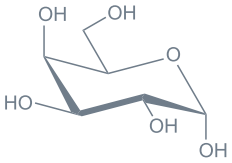


Fig R16 α D-galactose

The name galactose is derived from Greek galaktos (milk), and it is readily derived from lactose by hydrolysis. Galactose is also found in plant and algal polysaccharides such as carrageenan, hemicelluloses and other gums. It is synthesized by the body, where it is present in glycolipids and N- and O- linked glycoproteins. Galactose is a component of blood group oligosaccharides, gangliosides, other milk oligosaccharides and Galili antigens. Galactose is about as sweet as glucose and enters glycolysis by its conversion to glucose-1-phosphate. This occurs through a complex series of steps that is referred to as the Leloir pathway, named after Luis Federico Leloir who determined the overall process of galactose utilization (Caputto, 1949) (Fig R18).

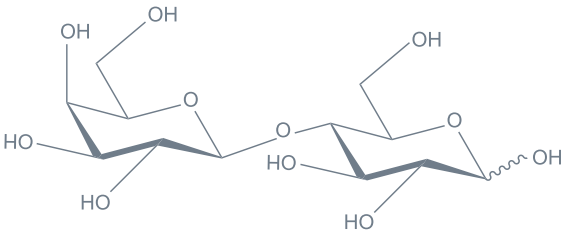


Fig R17 Lactose

The Leloir pathway is the conversion of α-D-galactose to UDP-glucose via three principal enzymes: Galactokinase, Galactose-1-phosphate uridyltransferase and finally, UDP galactose-4'-epimerase. The above mechanisms for galactose metabolism are necessary because the human body cannot directly convert galactose into energy, and must first go through one of these processes in order to utilise the sugar in the gut (Berg, 2013). Galactosemia is an inability to properly break down galactose due to a genetically inherited mutation in one of the enzymes in the Leloir pathway. As a result, the consumption of even small quantities is harmful to galactosemics (Elsas-Louis, 1998).

A number of companies have produced syrups and crystalline galactose, but the volume usage has not developed, probably due to several competing products such as the glucose/fructose sweeteners as discussed previously. An enzyme-derived mixture of randomly linked galactose residues (galactooligosaccharides-GOS) was developed as a prebiotic and is now offered as a healthfood (Rastall, 2015) (Fig R19).

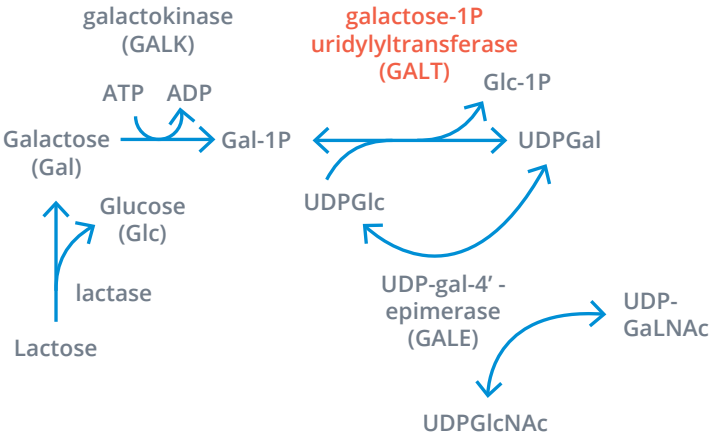


Fig R18 The Leloir pathway

Beverages and foods rich with GOS significantly increase the health and numbers of bifidobacteria

Fig R19 Galactooligosaccharide probiotics

5.3.2 Mannose

Mannose, is the C2 (axial) epimer of glucose (Fig R20):

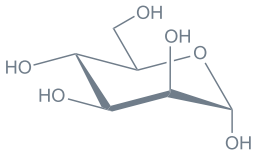


Fig R20 α D-mannose

Mannose occurs in microbes, plants and animals. Free mannose is found in small amounts in many fruits such as oranges, apples and peaches (Herman, 1971) and in mammalian plasma at 50-100 μM (Alton, 1998). More often, mannose occurs in polysaccharides such as yeast mannans (α-mannose) where it can account for nearly 16% of dry weight or in galactomannans. Ivory nuts from the custard apple tree, composed of β-mannans (sometimes called vegetable ivory) are quite hard and used for carving and manufacturing buttons, and were the original industrial source of mannose (Kusakabe, 1983) (Figs R21, R22).

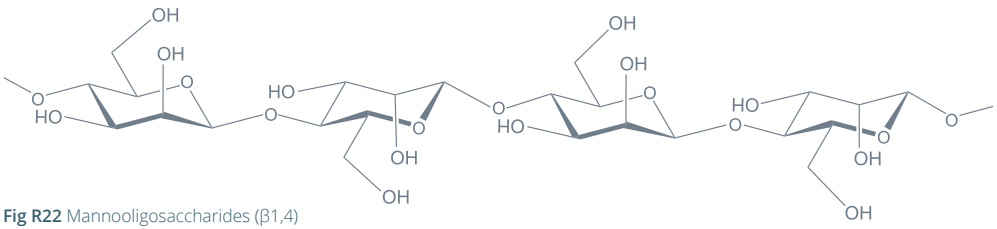


Fig R22 Mannooligosaccharides (β1,4)

Fig R21 Ivory Nut Mannan (custard apple, ebony and palm trees)

Coffee beans, fenugreek and guar gums are rich sources of galactomannans (Whistler, 1993), but these plant polysaccharides are not degraded in the mammalian GI tract and, therefore, provide very little bio-available mannose for glycan synthesis.

In animal tissues, mannose is found in *N*- and *O*- linked protein glycosylation. In *N*-glycosylation, the core glycan contains two GlcNAc residues and three mannose residues; in *O*-glycans, the glycans can contain *O*-linked mannose, that occurs in specific proteins or protein domains, such as, epidermal growth factor repeats, thrombospondin type I repeat or dystroglycan (Reily, 2019).

The major use for free mannose is in the treatment and/or prevention of acute and recurrent urinary tract infections (UTI) caused by uropathogenic *Escherichia coli* and is an alternative to antibiotics, reducing the burden of antibiotic resistance and associated side effects (Scribano, 2020) (Fig R23).

Fig R23 Mannose for UTI

5.3.3 Arabinose

Arabinose is the aldopentose analogue of glucose or mannose that has been evaluated by the food and flavour industry as a natural sweetener with a very similar taste profile to sucrose but only half the sweetness. In nature the L- form is most common (Fig R24) and is found in polysaccharides such as the hemicelluloses (Holtzapple, 2003) (Fig R25) and mustard seed araban (Rees, 1966).

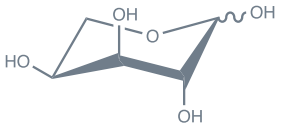
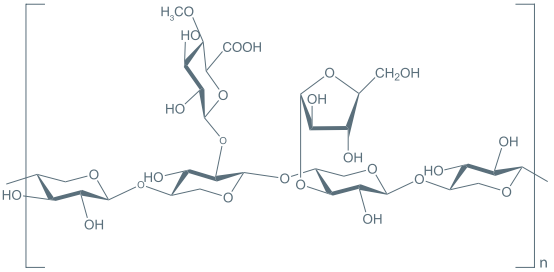


Fig R24 L- Arabinopyranose

Fig R25 L-Arabino *(methyl-D-glucurono)*



Xylooligosaccharides *(hemicellulose)*

L-Arabinose is also useful in the Maillard Reaction to produce meaty flavours and will react with amino acids to create flavours found naturally in cooked or roasted meats (Fig R26).

Fig R26 Maillard Reaction

Treatment with L-Arabinose has been reported to influence blood sugar reduction in the treatment of human diabetes. In vitro studies performed with porcine intestinal mucosa (Seri, 1996) and in vivo studies in rats (Osaki, 2001), mice (Seri, 1996) and pigs (Preuss, 2007) fed by sucrose in combination by L-arabinose revealed the inhibitory effect of L-arabinose on intestinal sucrase activity resulting in a delayed digestion of sucrose, and consequently a slower absorption of glucose that leads to a delayed and decreased blood glucose and insulin responses.

Unlike other L-sugars, L-arabinose is relatively available from natural sources. L-ribose is a rare and expensive sugar that can be used as a precursor for L-nucleoside analogue production which are used as antiviral drugs. L-arabinose has been shown to be a promising raw material for L-ribose production (Hu, 2011).

The potential use of L-arabinose as the starting material in the synthesis of non-ionic surfactants has been reported (Bouquillon, 2011). Due to the increasing importance of carbohydrates as cheap and renewable starting materials, this is of interest for the production of biodegradable, non-ionic surfactants. An example is the enzymatic synthesis of L-arabinose laurate (Méline, 2018) (Fig R27).

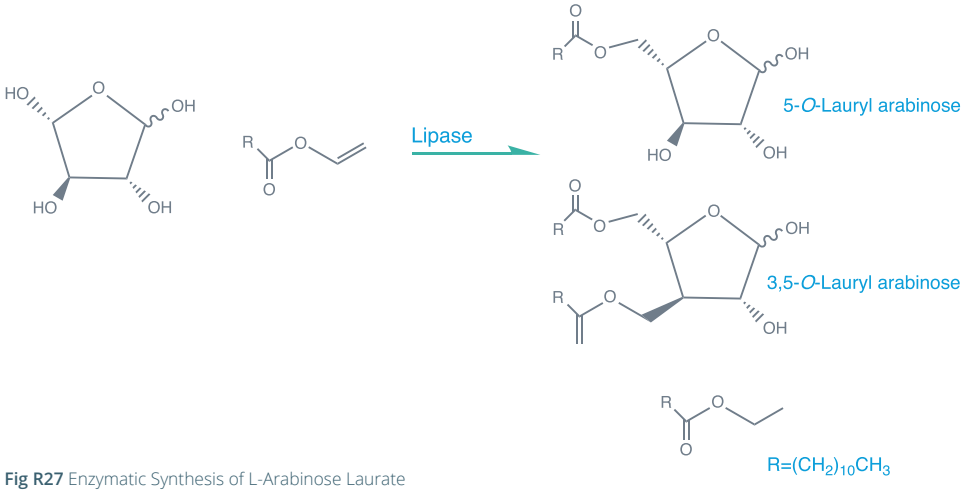


Fig R27 Enzymatic Synthesis of L-Arabinose Laurate

A process for the synthesis of arabitol by hydrogenation of arabinose on a supported ruthenium catalyst has been described (Murzin, 2020). Arabitol can also be produced by yeasts in the processes of bioconversion or biotransformation of waste materials from agriculture, the forest industry (l-arabinose, glucose) and the biodiesel industry (glycerol) (Kordowska-Wiater, 2015). Arabitol is used in the food industry as a sweetener and in the production of human therapeutics as an anticariogenic agent and an adipose tissue reducer. It can also be utilised as a substrate for chemical products such as arabinoic and xylonic acids, ethylene glycol, xylitol and others. It is included on the list of 12 building block C3-C6 compounds, designated for further biotechnological research (Fig R28).

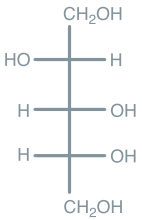


Fig R28 Arabitol

5.3.4 Xylose

Xylose is the aldopentose analogue of gulose and idose and is the second most abundant monosaccharide in nature, being major constituents of the hemicelluloses from wood and some algal polysaccharides (Fig R29).

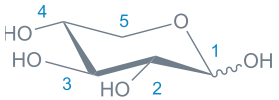


Fig R29 Xylose

The hemicelluloses have amorphous structures and can be easily degraded by acid or enzymatic hydrolysis (Amorim, 2019) to release xylose. An important xylan is the linear xylan that can be obtained from certain hardwoods such as Beech or Birch as this is employed in the drug pentosan polysulfate (Fig R30, Fig R31).

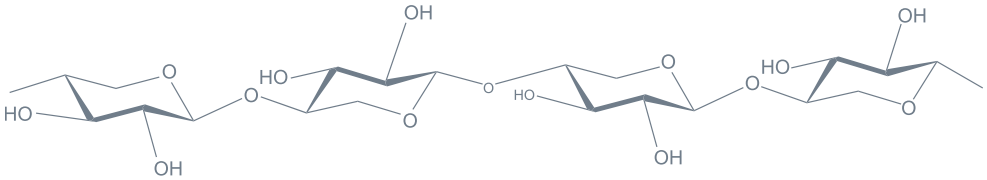


Fig R31 Llinear xylooligosaccharides, (1,4 xylooligosaccharides)

Fig R30 Beechwood-hardwood source of Linear Xylan

Xylose is the first monosaccharide added to serine or threonine in proteoglycan *O*-glycosylation and is the first sugar residue in the biosynthetic pathways of most anionic polysaccharides such as heparan sulfate and chondroitin sulfate.

Xylitol is obtained by the catalytic hydrogenation of xylose (Fig R32). It is used as a sugar substitute in various products such as drugs, dietary supplements, confections, toothpaste, and chewing gum, but is not a common household sweetener. It is possible to obtain various products from xylitol such as polyethylene glycol and ethylene glycol as a substitute to fossil-based raw materials (Arcaño, 2020).

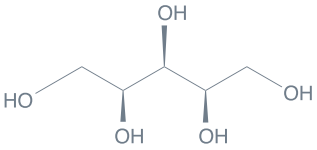


Fig R32 Xylitol

Xylose is still little explored for biosurfactant production but the production of biosurfactants from hemicellulosic hydrolysates is promising. However, there is need for further investigations, because few microorganisms have been found to metabolise xylose to produce surfactants (Vieira Neta, 2021). However, Xylolipid surfactants based on C8-C14 fatty acids have recently become available (Fig R33).

β-carotene is a natural pigment and health-promoting metabolite, and has been widely used in the nutraceutical, feed and cosmetic industries. The GRAS yeast *Saccharomyces cerevisiae* is reported to produce β-carotene from xylose and it was found to produce this pigment at a titer three-fold higher than from glucose. These results suggest that xylose utilisation is a promising strategy for the overproduction of carotenoids and other isoprenoids in engineered *S. cerevisiae* (Sun, 2020).

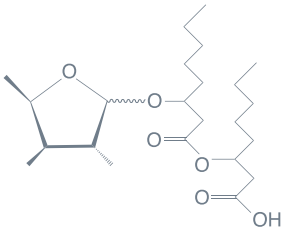


Fig R33 C8/C8 Xylolipid surfactant

5.4.1 Deoxy hexoses (L-Fucose, L-Rhamnose)

L-Fucose, (6-deoxy-L-galactose) (Fig R34) is not found in the free state but is a constituent of *N*- and *O*-linked glycans, the oligosaccharides found in human milk, blood group determinants and sulphated fucoidans found in brown algae (*Phaeophyceae*) (Percival, 1967) (Fig R35, Fig R36). Fucose is released by partial acid hydrolysis (Daniel, 2007).

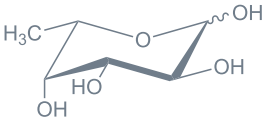


Fig R34 L-Fucose

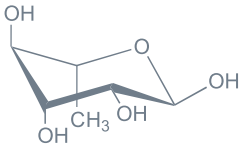


Fig R37 L-Rhamnose

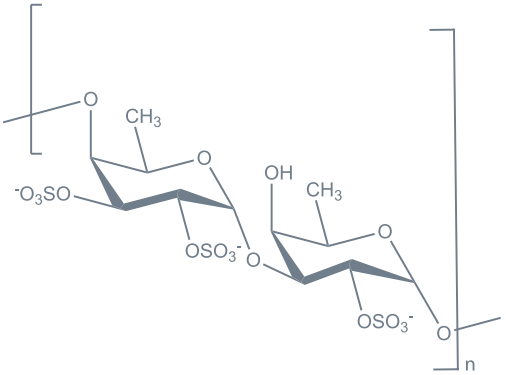


Fig R36 Structure of Fucoidan

Fig R35 *Ascophyllum nodosum*, a source of fucoidan

A recent study has described how algal supplements can be an excellent source of vitamin B12 and fucose for fortified food and beverages. Fucose is one of the eight essential mammalian sugars required for cellular structure and function (Castillejo, 2018).

L-Rhamnose (6-deoxy-L-mannose) (Fig R37) is widely distributed in bacteria and plants but is rare in animals. Glycans containing rhamnose residues play critical roles in diverse pathogenic bacteria as well as exhibiting various biological functions in plants (Giraud, 2000). Rhamnose is mainly found in plant cell wall pectic polysaccharides, a group of complex polysaccharides that form a gel-like matrix for embedding cellulose microfibrils and hemicelluloses (Rhamnogalacturon I and Rhamnogalacturonan II) (Yapo, 2011, Atmodjo, 2013). L-Rhamnose is also found in several plant glycosides, such as, Solamargine from *Solanum sodomaeum* (Friedman, 1999) (Fig R38, Fig R39).

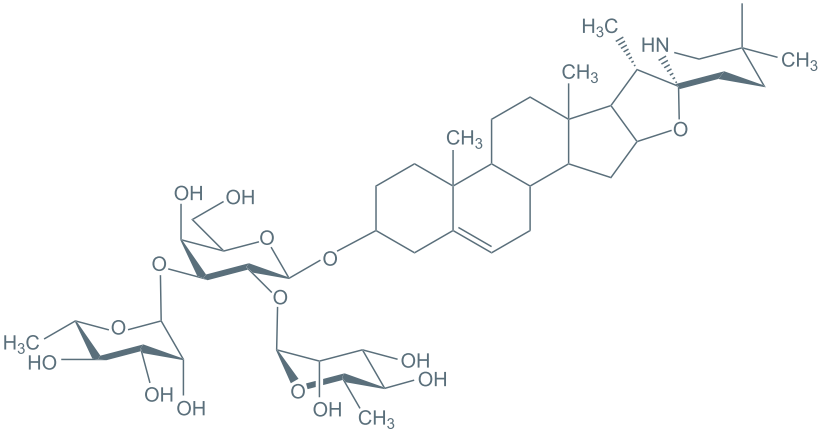


Fig R38 Solamargine

Fig R39 *Solanum sodomaeum* (the devils apple)

5.4.2 D-Ribose

D-Ribose is a naturally occurring monosaccharide within the pentose pathway that assists with ATP production and as the 2-deoxy derivative is a key component of DNA, ribonucleic acid (RNA) and acetyl coenzyme A (Pauly, 2000) (Fig R40).

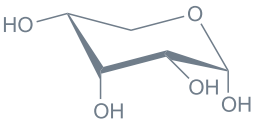


Fig R40 D-Ribose

5.4.3 Acid Derivatives of Monosaccharides (-onic, -uronic, -aric)

The carboxylic acid formed by oxidation of the aldehyde in an aldose is referred to as a glyconic acid (e.g. gluconic acid is the oxidation product of glucose). Gluconic acid is not very common in nature but is a metabolite of *Aspergillus niger* in an aerobic fermentation with a high oxygen demand. The process resembles more an enzymatic conversion rather than a microbial process. Gluconic acid, its delta-lactone and salts are used as a flavoring agent in a variety of food items such as meat, wine, and dairy products (Ramachandran, 2006) (Fig R41).

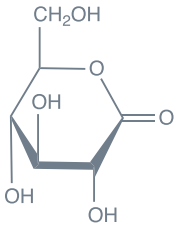


Fig R41 Gluconic acid

By oxidising the primary OH group (C6), glycuronic acids are produced and the most common are glucuronic, galacturonic, mannuronic, guluronic and iduronic acids, mostly found in polysaccharides (Fig R42).

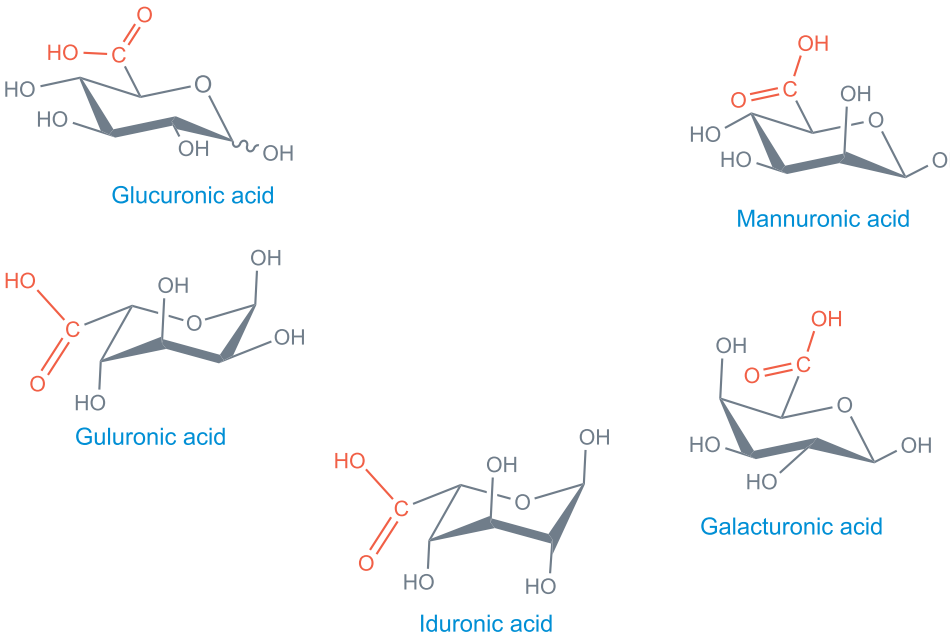


Fig R42 The five common uronic acids

Galacturonic acid is the major component of pectic acid (Fig R43), a polygalacturonan that is found in citrus fruits such as limes and lemons (Gullón, 2013) (Fig R44), and mannuronic and guluronic acids occur in alginates from brown seaweeds (*Phaeophyceae*) (Percival, 1967) (Fig R45, Fig R46), as well as in gram negative bacteria (*Pseudomonas aeruginosa, Azotobacter vinelandii*) (Deavin, 1977). The individual monosaccharides can be released by enzymatic hydrolysis (Heyraud, 1998).

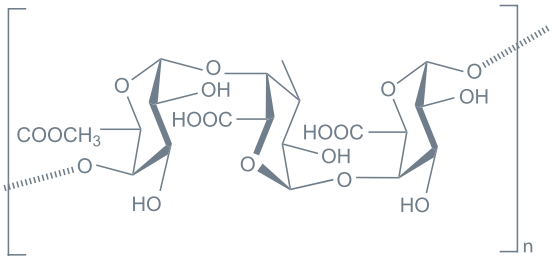


Fig R43 Pectic acid (*Galacturonooligosaccharides* (α1,4))

Fig R44 Citrus fruits

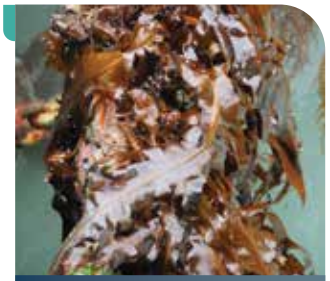
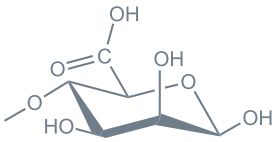
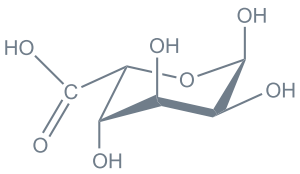


Fig R45 Brown seaweed (*Macrocystis pyrifyra*)



Mannuronic acid



Guluronic acid

Fig R46 Mannuronic & guluronic acid

Glucuronic acid was first isolated from urine where it functions to solubilise toxins and remove them from the body. It is found in many polysaccharides such as gum arabic, xanthan gum (Fig R47), and Kombucha tea, and is important for the metabolism of microorganisms, plants and animals (Dutton, 2012).

Iduronic acid is a major uronic acid component of the glycosaminoglycans (GAGs), dermatan sulfate (Thelin, 2013) (Fig R48), and heparin. It is also present in heparan sulphate (Casu 1985, 1990).

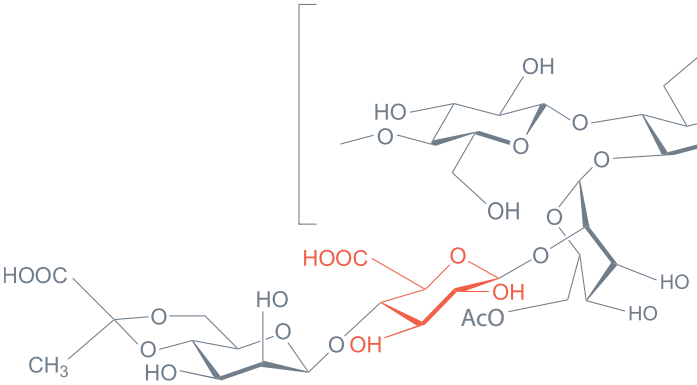


Fig R47 Xanthan gum (glucuronic acid in red)

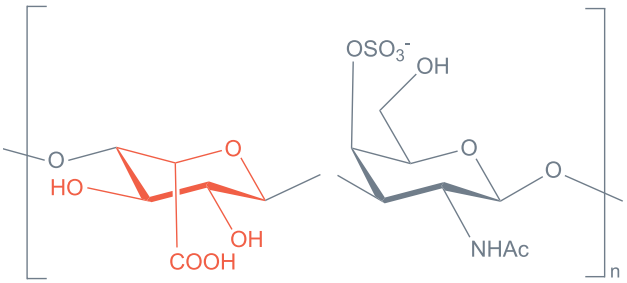
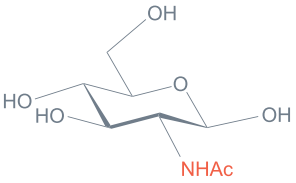
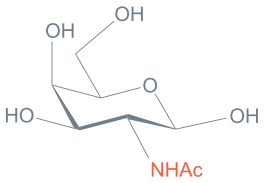


Fig R48 Dermatan sulfate (iduronic acid in red)

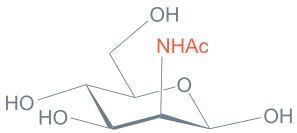
Amino sugars are obtained by replacing a hydroxyl group of a monosaccharide by an amino group. The most common amino sugars are the 2-aminoaldohexoses, namely, D-glucosamine, D-galactosamine and D-mannosamine (Fig R49). However, amino sugars are unstable due to the formation of imines and aminoacetals with the monosaccharide aldehyde as soon as they are released as free sugars. In order to preserve stability, they are converted to salts or are often found in nature as *N*-acetates.



N-Acetyl glucosamine



N-Acetyl galactosamine



N-Acetyl mannosamine

Fig R49 N-Acetyl glucosamine, N-Acetyl galactosamine and D-mannosamine

As the *N*-acetates, they are components of polysaccharides such as the insect and crustacean structural polysaccharide chitin (Shamshina, 2019) (Fig R50, Fig R51).

Fig R50 Crustacians

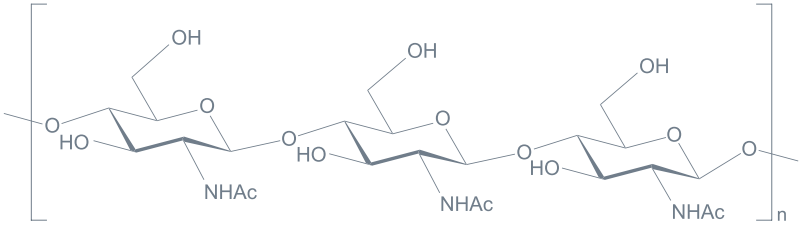


Fig R51 Chitin, (β-1,4 poly N-Acetyl glucosamine)

They are also components of glycosphingolipids (e.g. ganglioside GM1) (Aureli, 2016) (Fig R52).

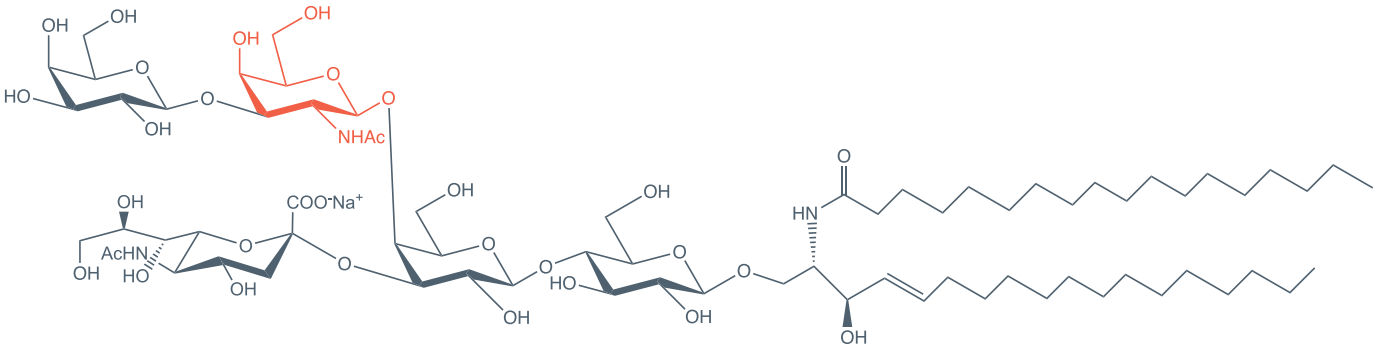


Fig R52 Ganglioside GM1 (N-Acetyl galactosamine red)

Amino sugars are important constituents of blood groups, *N*- and *O*-linked glycans (Varki, 2017). *N*-acetyl-galactosamine (GalNAc) is transferred from UDP-GalNAc to the hydroxy group of protein serine or threonine forming the Tn antigen (Fig R53).

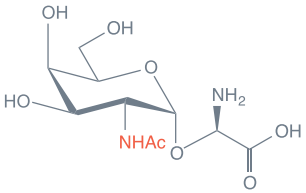


Fig R53 TN Antigen

N-Acetylmuramic acid, a constituent of bacterial cell wall polysaccharides, has a lactyl side chain linked to C3 of glucosamine through an ether linkage (Fig R54).

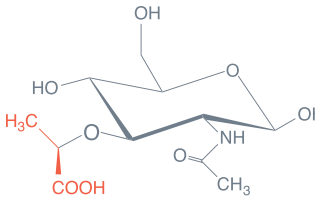


Fig R54 *N*-Acetylmuramic acid

Sialic acids are abundant on vertebrate glycoproteins and have diverse functional roles. They exert many functions through their electronegative charge, such as repulsion of cell–cell interactions, protein stabilisation, ion binding, and ion transport. They are among the most rapidly evolving classes of glycans in nature. Although 5-*N*-acetylneuraminic acid is the most common sialic acid in humans (Fig R55, the Sialic acid family is comprised of related structures that vary at the C-5 carbon, including 5-N-glycolylneuraminic acid and 2-keto-deoxynonulosonic acid, with a hydroxyl group at C-5 (Tanner, 2005).

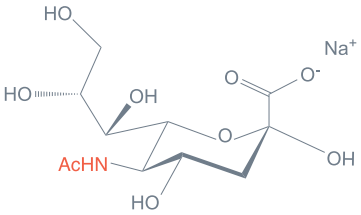


Fig R55 Sialic acid

The sialic acids are unique among the monosaccharides found in Nature as a family of over 50 structural types. They are nine carbon α-keto acids formed through the condensation of pyruvate with *N*-acetyl-D-mannosamine, having six-membered pyranose rings and adopting a $^{2}C_{5}$ chair conformation. They occur widely in cellular tissues and body fluids including *N*- and *O*-Linked glycans, Gangliosides, human milk oligosaccharides and blood group antigens.

The polysaccharide Colominic acid is composed exclusively of sialic acid residues that can be released by neuraminidase from gram negative bacteria, such as, E. coli (Fig R56).

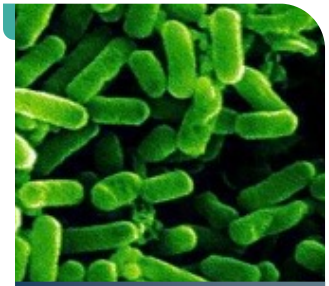
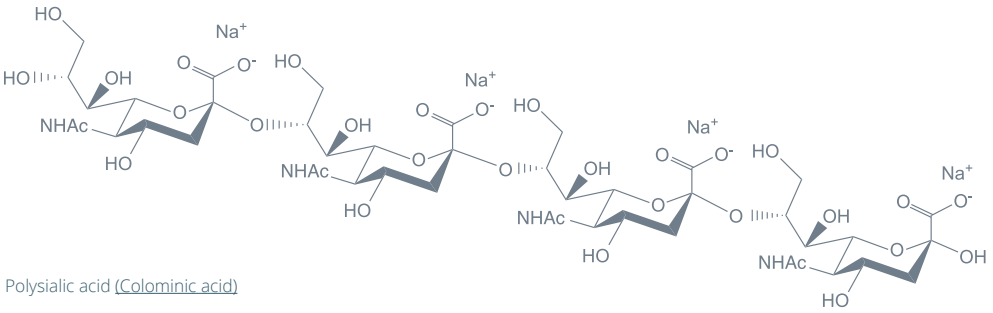


Fig R56 *E. Coli*



Polysialic acid (Colominic acid)

Another related sialic acid derivative of significance is 2-keto-3-deoxy-D glycero-D-galacto-nononic acid (kdn), found in most eukaryotes (Pavlova, 1999) (Fig R56a).

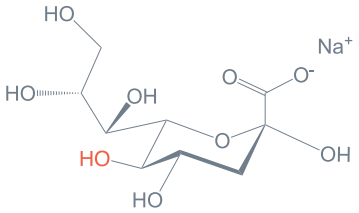


Fig R56a kdn

5.5.1 Esters

Esters are important derivatives. These include phosphates (including diphosphate esters) with perhaps glucose 6-phosphate a phosphomonoester formed from glucose by transfer of phosphate from Adenosine triphosphate with hexokinase- an important intermediate in the glycolytic pathway being the best known (Berg, 2002) (Fig R57).

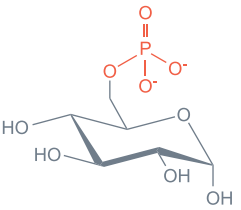
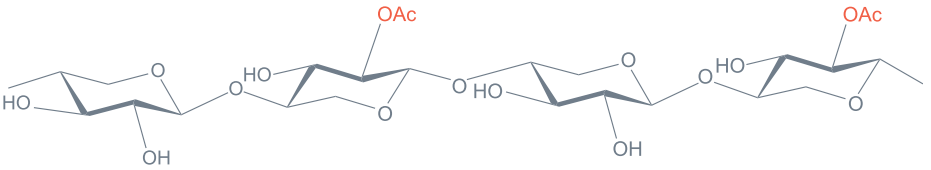


Fig R57 Glucose 6-phosphate

The acyl esters (with acetic acid or fatty acids) include acetates that can be found in the acetylated xylans from beech or birchwood (Telemana, 2002) (Fig R58) and bacterial alginate (Davidson, 1977).

Fig R58 Silver Birch



Acetylated xylan

Sulfate half esters are found in several polysaccharides including Fucoidan, Carrageenan (Whistler, 1993) and Heparin (Casu, 1985) (Fig R59).

Sulphated monosaccharides can be released from Heparin by enzymatic or partial acid hydrolysis (Zhang, 2019).

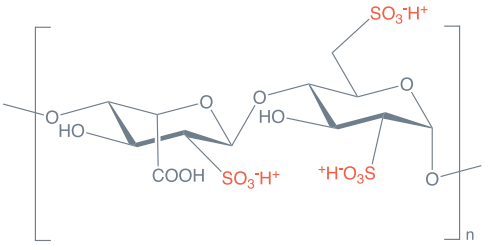


Fig R59 Heparin

5.5.2 Reduced monosaccharides

When the carbonyl group of a monosaccharide is reduced to a hydroxyl group (Fig R60) an alcohol is produced. As an example, Sorbitol is synthesized from glucose-6-phosphate by the action of a glucose-6-phosphate reductase and a sorbitol (glucitol)-6-phosphate phosphatase. Thus reduction of glyceraldehyde or dihydroxyacetone yields glycerol. Sorbitol, mannitol and xylitol are formed when glucose, mannose and xylose are reduced. Keto sugars of more than three carbons can yield more than one sugar alcohol. For example, the chemical reduction of D-fructose yields a mixture of D-sorbitol and D-mannitol (Awuchi, 2017).

Sorbitol and mannitol are found naturally in fruits and vegetables such as pineapples, olives, asparagus, sweet potatoes and carrots. Xylitol also called “wood sugar”, occurs naturally in straw, corncobs, fruit, vegetables, cereals, mushrooms and some cereals (Schiweck, 2005) (Fig R56). The sugar alcohols are used as reduced-calorie sweeteners and are not as sweet as white sugar and provide

approximately half of the calories of white sugar. Sugar alcohols are poorly absorbed into the bloodstream from the small intestine, a useful feature for the control of diabetic blood sugar.

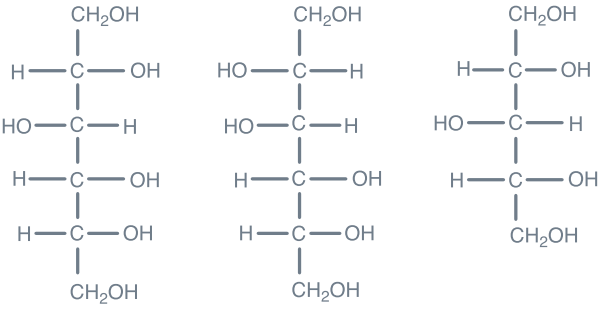


Fig R60 The common sugar alcohols

5.5.3 Deoxy sugars

Monosaccharide residues with hydroxyls replaced by hydrogen are deoxysugars. Nature has evolved reductases to perform this reaction in one step, whereas chemically multistep procedures are required. Several deoxy sugars, notably 2-deoxy-D-erythro-pentose (2-deoxy-D-ribose) and deoxygenation of ribose within a ribonucleotide to form the 2-deoxyribonucleotide is a critical reaction in DNA biosynthesis. The sugar components of DNA, 6-deoxy-L-mannose (L-rhamnose), 6-deoxy-L-galactose (L-fucose), 6-deoxy-D-glucose (quinovose) (Fig 61), and their derivatives, occur very widely in natural products (de Lederkremer, 2007).

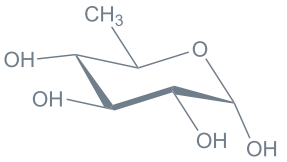


Fig R61 6-deoxy-D-glucose (Quinovose)

5.5.4 Anhydro sugars

The best known anhydro monosaccharides are the D & L 3,6-anhydrogalactoses (Fig R62). They occur naturally in red algae in the D- form as a component of carrageenan (Hirase, 1958) and furcellaran (Fig R63), and in the L- form as a component of agaropectin (Jouanneau, 2010) and porphyran. (Percival, 1967) (Fig R64).

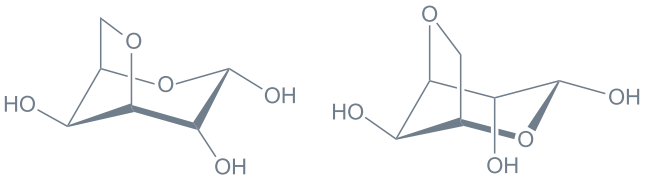
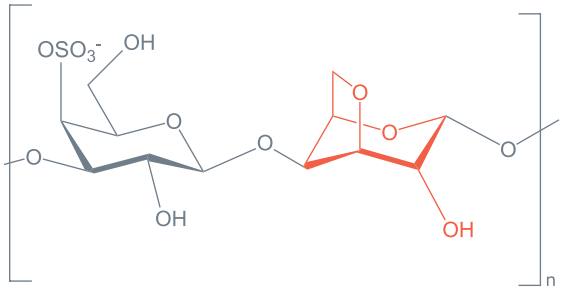


Fig R62 3,6 Anhydro D-galactose

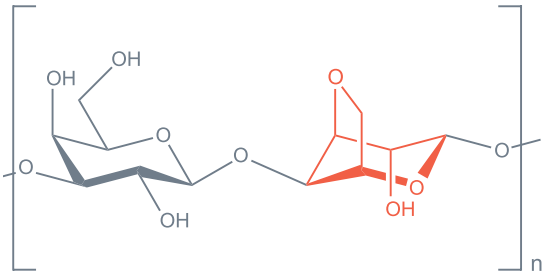
3,6 Anhydro L-galactose

Fig R63 The red alga (*Chondrus crispus*)



Source of 3,6 Anhydro D-galactose

Fig R64 The red alga-agar (*Gracilaria)*



Source of 3,6 Anhydro L-galactose

5.5.5 Two Other Modifications, Pyruvate & Succinate

Pyruvate and succinate are found as natural substituents attached to monosaccharide residues in algal and bacterial polysaccharides. Examples are agaropectin (Percival, 1967), xanthan gum from *Xanthomonas campestris* (Rees, 1976), colanic acid from *E. coli* (Lawson, 1969) and succinoglycan (Zevenhuizen, 1997) (Fig R65).

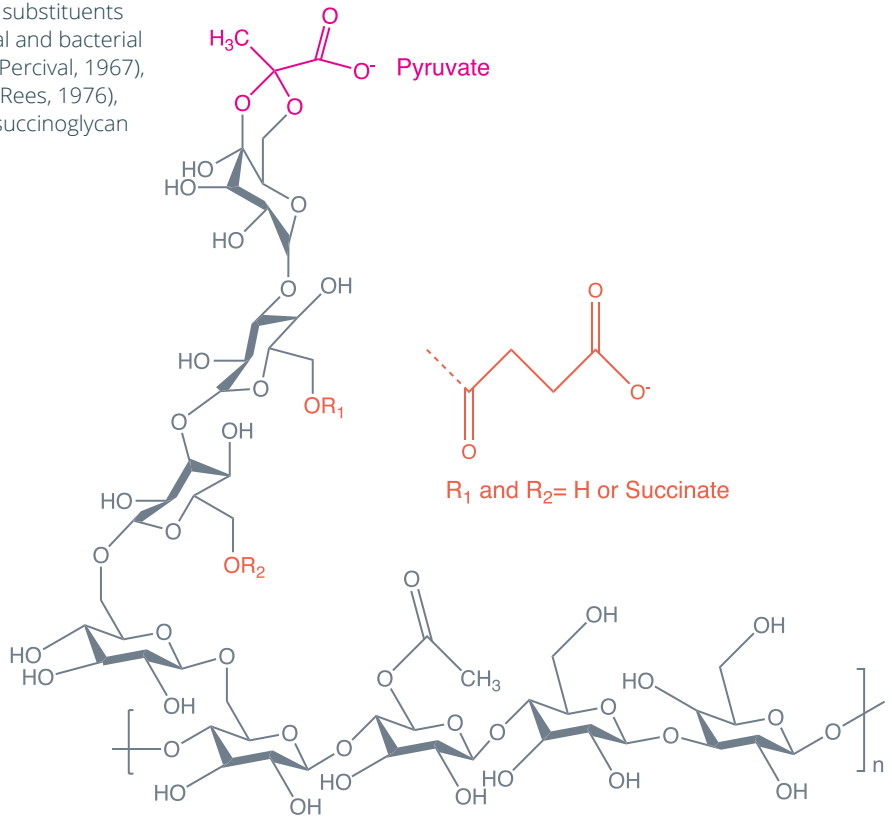


Fig R65 Succinoglucan showing pyruvate and succinate substituents

5.6 Glycosidase Inhibitors (Imino Sugars)

5.6.1 Introduction

Imino sugars are examples of naturally occurring monosaccharide analogs found in plants and microbes with the ring oxygen replaced by nitrogen (or sulphur). They inhibit glycosidases associated with a range of diseases and a number have been developed by scientists to produce useful drugs.

5.6.2 Nojirimycin

The first natural iminosugar, nojirimycin (Fig R66), was discovered in Japan in 1966 from the broth containing a *Streptomyces* species. Castanospermine (Fig R67) is another effective glycosidase inhibitor that can be isolated from the Australian tree *Castanospermum* (Fig R68). Research into modifying nojirimycin, Castanospermine and related analogs has resulted in new inhibitors with improved selectivities, activi¬ties and solubilities. These analogs have been marketed for the treatment of many diseases including diabetes (miglitol was the first iminosugar drug to reach the market).

Fig R68 *Castanospermum*

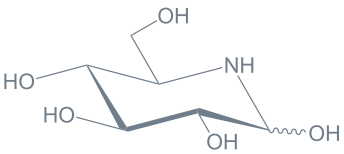


Fig R66 Nojirimycin

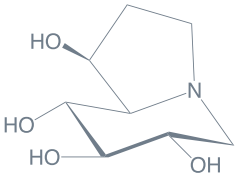


Fig R67 (+)-*Castanospermine*

5.6.3 Swainsonine

The α-Mannosidase Inhibitor, Swainsonine (Fig R69) was first isolated from the Australian plant *Swainsona canescens* (Colegate, 1979) (Fig R70), and soon thereafter isolated with its N-oxide from locoweeds (Molyneux and James, 1982). It has been a valuable therapeutic in the treatment of Gauchers disease (Fig R71).

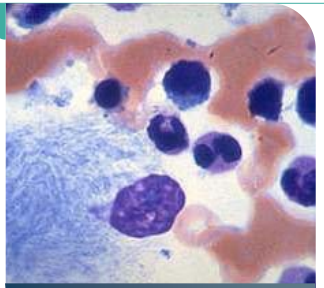


Fig R71 Gaucher's disease cells

Fig R70 *Swainsona canescens*

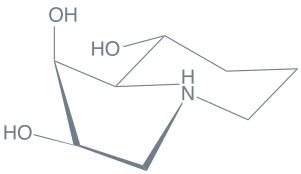


Fig R69 (-)-Swainsonine

5.6.4 Siastatin

The potent neuraminidase (Sialidase) inhibitor Siastatin B is derived from *Streptomycetes* culture media (Fig R72). This iminosugar antibiotic showed inhibitory activity for tumour metastasis and may be a useful tool in cancer research (Umezawa, 1974).

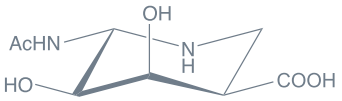


Fig R72 Siastin

5.6.5 Salacinol

A most potent natural α-glucosidase inhibitor named salacinol (Fig R73) was isolated from the antidiabetic Ayurvedic traditional medicine, *salacia reticulata* (wight) through bioassay-guided separation (Fig R74). The structure of salacinol was determined by chemical and X-ray crystallographic analysis. This revealed a unique spiro-like configuration comprising a 1-deoxy-4-thioarabinofuranosyl cation and 1'-deoxyerythrosyl-3'-sulfate anion (Yoshikawa, 1997).

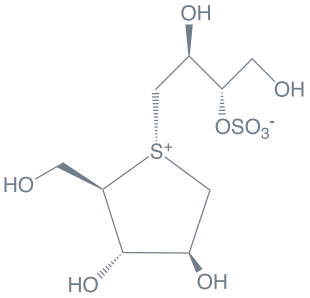


Fig R73 Salacinol

Fig R74 *Salacia reticulata (wight)*

5.6.6 Isofagomine

Isofagomine (Fig R75) is one of several "chaperone therapeutics" helping proteins to fold correctly. These therapies which bind to folding proteins allow correct folding, preventing them from misfolding. Isofagomine (strictly not natural) is a dideoxy analog of glucose and binds to the active site of beta-glucocerebrosidase helping the enzyme to fold correctly, overcoming problems caused by gene mutations. Isofagomine may also cross the blood-brain barrier, which may allow it to treat neurological conditions (Khanna, 2010).

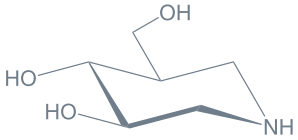


Fig R75 Isofagomine

5.6.7 Australine

Australine (Fig R76) is a polyhydroxylated pyrrolizidine alkaloid that was isolated from the seeds of the Australian tree *Castanospermum australe* (Fig R77) and was characterized by NMR and X-ray diffraction analysis (Tropea, 1989). This alkaloid proved to be a good inhibitor of the α-glucosidase amyloglucosidase, but it did not inhibit β-glucosidase, α- or β-mannosidase, or α- or β-galactosidase. However, it has been shown to reduce the ability of the human immunodeficiency virus (HIV) to infect cultured cells, and thus has potential for treating AIDS (Thawabteh, 2019).

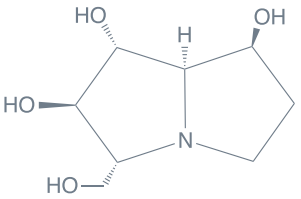


Fig R76 Australine

Fig R77 *Castanospermum australe*

5.6.8 (+)-Casuarine

The alexines and australines are a growing subclass of pyrrolizidine alkaloids, many of which display potent glycosidase activity. (+)-Casuarine (Fig R78) is the most recently isolated member of this class. It was obtained from 75% aqueous ethanolic extract of the bark of *Casuarina equisetfolia L. (Casuarinaceae)* (Fig R79) in 0.013% yield. The structure and the absolute configuration of Casuarine were established unambiguously by single-crystal X-ray spectroscopy as (+)-. Casuarine is an effective inhibitor of glucosidase I rivalling that of the indolizidine alkaloid castanosperime (Denmark, 2000).

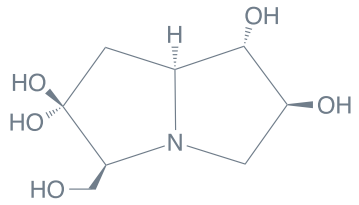


Fig R78 (+)-Casuarine

Fig R79 *Casuarina equisetfolia*

5.7 The Inositols

An important group of monosaccharide-analogs with no hetero atom in the ring are the inositols, or more precisely myo-inositols, carbocyclic residues that are abundant in the brain and other mammalian tissues. In humans, most inositol is synthesized in the kidneys, followed by testicles, typically in amounts of a few grams per day. They mediate cell signal transduction in response to a variety of hormones, neurotransmitters, and growth factors and participate in osmoregulation (Majumder, 2006).

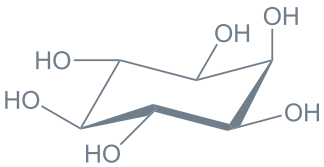


Fig R80 *Myo*-inositol

The *Myo*-isomer is the most abundant in nature (Fig R80). It occupies a unique position in inositol metabolism because this is the only isomer synthesised *de-novo* from D-glucose-6-phosphate. All the other known isomers are derived from myo-inositol (Loewus, 1990; Loewus & Murthy 2000).

Many cellular functions are regulated by calcium (Ca^{2+}) signals that are generated by different signalling pathways. One of these is the inositol 1,4,5-trisphosphate/calcium ($InsP_3/Ca^{2+}$) signalling pathway that operates through either primary or modulatory mechanisms. Its primary role is evident in nonexcitable cells where it generates the Ca^{2+} signals to control processes as diverse as metabolism, secretion, fertilisation, proliferation, and smooth muscle contraction. Inositols appear to be involved in a large number of human diseases such as Alzheimer's disease, asthma, cancer, congestive heart failure, diabetes, Duchenne muscular dystrophy and Huntington disease (Berridge, 2016).

Myo-Inositol hexaphosphate (Fig R81), also called phytic acid or IP6, is the principal storage form of phosphorus in many plant tissues, especially bran and seed. Phosphorus and inositol in phytate form are not generally bioavailable to non-ruminant animals because these animals lack the digestive enzyme phytase required to remove the phosphate groups.

Ruminants are readily able to digest phytate because of the phytase produced by rumen microorganisms. Moreover, phytic acid also chelates important minerals such as calcium, magnesium, iron, and zinc, making them unabsorbable, and contributing to mineral deficiencies in people whose diets rely highly on bran and seeds for their mineral intake, such occurs in developing countries.

Six isomers of inositol have been found in nature to date in addition to *Myo*-Inositol (Majumder, 2006, Chapter 1) (Fig R82, Fig R83 see opposite).

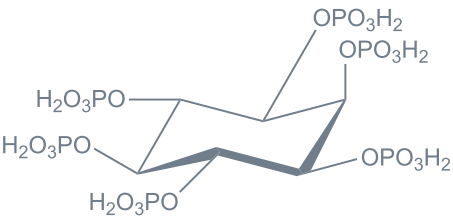
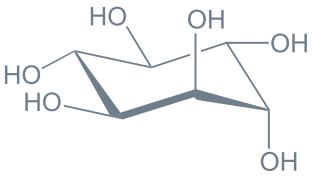


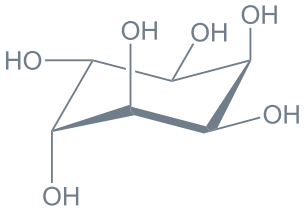
Fig R81 *Myo*-inositol hexaphosphate

However, other than *Myo*-inositol, these isomers only occur in very small quantities.

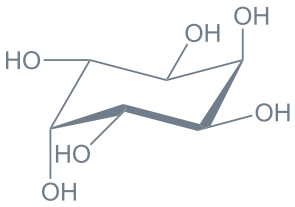
Inositol is a safe and effective treatment for polycystic ovary syndrome (PCOS) by increasing insulin sensitivity. As a follicle stimulating hormone second messenger (FSH), myo-inositol is effective in restoring menstrual cycle regularization. *Myo*-Inositol's role as FSH leads to a correct ovarian follicle maturation and consequently to a higher oocyte quality (Unfer, 2012).



L-chiro inositol

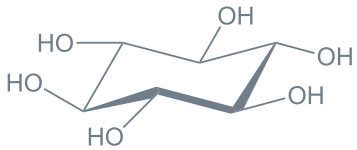


D-chiro inositol

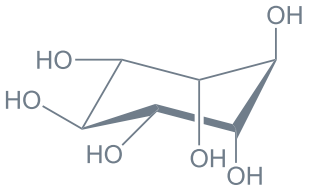


Neo-inositol

Fig R82



Scyllo-inositol



Muco-inositol

Fig R83

5.8 Monosaccharides in Synthesis

5.8.1 Protecting Groups in the Functionalisation of Monosaccharides

As synthetic carbohydrate chemistry is part of organic chemistry, many of the selective and reversible protecting groups employed are the same for both monosaccharide and oligosaccharide synthesis (see for instance, Wuts, 2014). In oligosaccharide synthesis there is less distinction therefore between permanent and temporary protecting groups as the number of overall synthetic steps is generally lower.

Examples of common protecting groups are:

a) Esters, in particular acetates and benzoates:

Standard conditions for their introduction are the reaction of a monosaccharide with active esters such as acyl chlorides or anhydrides in pyridine or under acidic conditions (Levy, 2006). The 'Zemplen method' namely a catalytic amount of sodium methoxide in methanol is considered particularly useful for ester removal. The stability of the protecting group can be adjusted by substitutions e.g. with a pivaloyl (2,2,2-trimethylacetyl) group. This confers orders of magnitude higher resistance to attack than the parent acetyl group. Similarly, the susceptibility of a benzoate to hydrolysis can be adjusted with electron withdrawing or -donating substituents on the phenyl ring.

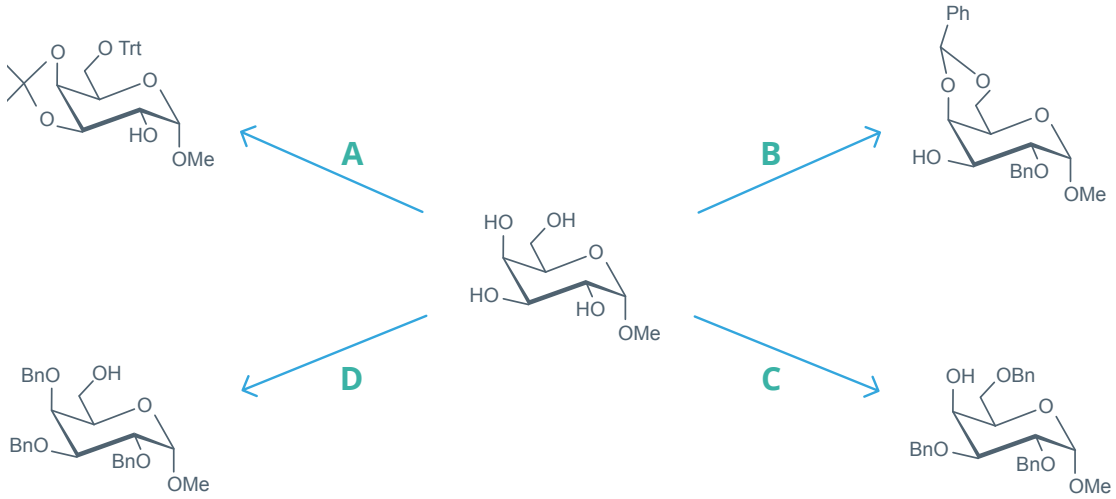
b) Ethers, in particular benzyl ethers and some acid-labile ethers:

Methyl ethers themselves are too stable chemically to find much use as protecting groups in sugars. This is due to the high energy of the methyl cation (which does not fulfill the octet rule, see Gillespie and Robinson, 2007) and the corresponding harsh conditions required for its formation during the transition state of acid-mediated methyl ether cleavage. This situation changes when the methyl cation becomes stabilised through delocalisation of adjacent π–electrons, e.g. from a phenyl ring or an oxygen atom. Consequently, substituted methyl ethers such as the trityl (triphenylmethyl) ether or the methoxymethyl (MOM) ether (an open-chain acetal) that form stabilised carbocations (a carbon atom having a degree of positive charge) under acidic conditions are widely used acid-labile protecting groups.

Fine tuning can be achieved by further substitution and in particular the dimethoxytrityl (DMT) ether has become the dominant protecting group for the primary hydroxy group of ribofuranoses in the vast field of nucleotide synthesis (Schaller, 1963). These types of ether protecting groups are commonly introduced by reaction of a corresponding alkyl halide with the hydroxyl group under basic conditions or promoted by silver salts. However, derivatisation can also allow for other means of introduction.

For more permanent protection of hydroxy groups, benzyl ethers are a very common solution due to their broad chemical stability. They are formed by reaction with benzyl chloride or bromide in strong alkali and are removed by hydrogenation over a palladium catalyst and solvent evaporation (traceless).

Protection of monosaccharides for selective functionalisation



Scheme 1: Protecting group manipulations to allow for selective chemical manipulations at various positions in a monosaccharide
A: 1. Dimethoxypropane, H+; 2. Trityl chloride, H+.
B: Benzaldehyde dimethylacetal, H+; 2 . Benzyl bromide, tetrabutylammonium bromide, aq. NaOH, DCM.
C: Benzaldehyde dimethylacetal, H+; 2. Benzyl bromide, NaH; 3. Sodium cyanoborohydride, H+.
D: Benzaldehyde dimethylacetal, H+; 2. Benzyl bromide, NaH; 3. Aluminium chloride, LAH.

For a representative example how such protecting group strategies are used in the synthesis of e.g. the Galα3Gal disaccharide epitope, (see Plaza-Alexander, 2013).

c) Silyl ethers:

The high affinity of silicon to the fluoride ion, thus allowing for selective removal in the presence of most other common protecting groups has led to the rise of silyl ether protection. Popular representatives are the tert.butyldimethylsilyl (TBS, TBDMS) ether or the tert.butyldiphenylsilyl (TBDPS) ether, the latter for selective primary hydroxyl group protection due to its bulkiness. Here too, substitution has resulted in a library of available silyl ethers with finely tuned susceptibility to fluoride, acid or base. Generally, silyl ethers are introduced via the silyl chloride in the presence of a base such as pyridine or imidazole (Crouch, 2013).

d) Acetals, in particular cyclic acetals:

Cyclic acetals such as the isopropylidene and benzylidene acetals are long established protecting group tools in carbohydrate chemistry. There are several factors besides the chemical stability that influence the choice of a cyclic acetal. Both of these examples favour ring formation with a vicinal cis-diol in a sugar but they do favour different ring sizes. For instance, if only one equivalent of acetal is introduced into a galactoside, a 3,4-acetal will form preferably in case of the isopropylidene group and a 4,6-acetal will form preferably in case of the benzylidene group.

This is due to steric effects with the phenyl group in the former ending up in the equatorial position of the 6-membered ring but the methyl groups escaping unfavourable 1.3-diaxial interactions when remaining in the 5-membered ring in the latter (see Wuts and Greene, 2007). Many variations of these two systems exist with some of them not only tuning the stability but also adding novel means of cleavage.

Importantly, these vicinal diol protecting group options are now accompanied by substituted dispiroketals such as the butane-2,3-diacetal (BDA) group, which favour trans-diols. *Silyl acetals/ketals* are another attractive alternative with the 1,3-(1,1,3,3-tetraisopropyl-disilyloxanylidene (TIDPS) acetal being a common, selective protection option for the 3.5-diol in riboses which is cleaved, like silyl ethers, by fluoride.

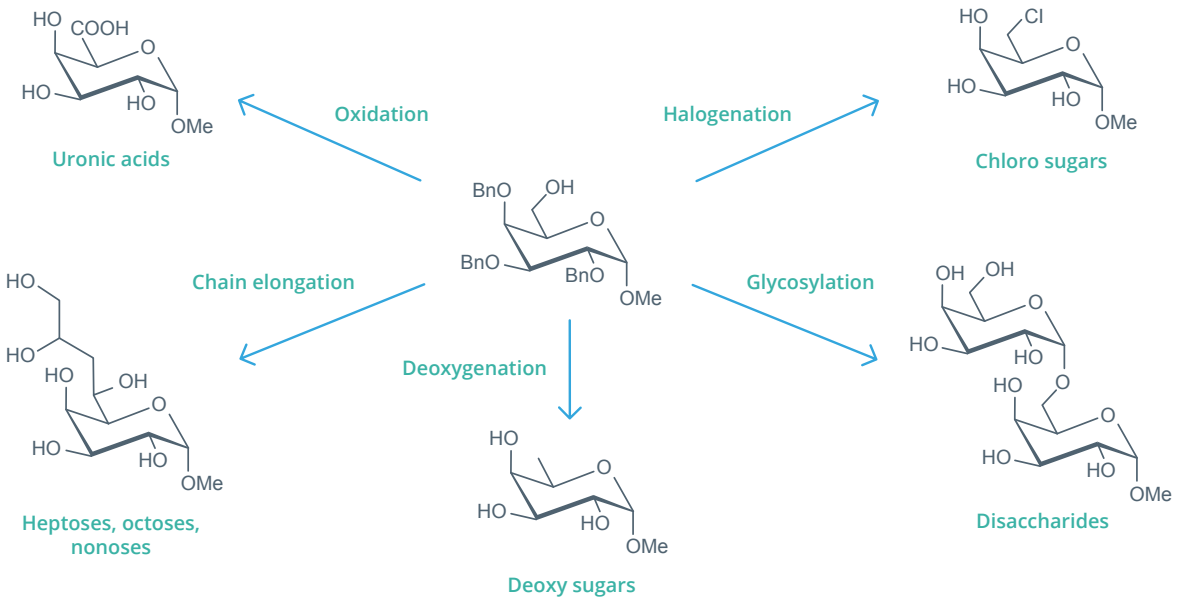
e) Protection of other heteroatom groups:

Nitrogen is by far the most common substituent on naturally occurring monosaccharides besides oxygen, e.g. in hexosamines. Many *N*-protecting groups in sugar chemistry take advantage of the enhanced stability towards hydrolysis of carbamates and amides over their *O*-counterparts, esters and carbonates.

5.8.2 Functionalisation of monosaccharides

Some chemical modification reactions in monosaccharides can be carried out selectively based on the difference in reactivity of the hydroxy groups, meaning only some or even none require protection. A widely used example would be the TEMPO (2,2,6,6-tetramethylpiperidinyloxyl radical) reagent which catalyses oxidation of primary hydroxy groups to the carboxylic acid in the presence of secondary and tertiary hydroxy groups. This is particularly useful in carbohydrate chemistry as oxidation of the primary hydroxy group e.g. leads from hexoses to hexuronic acids, another important group of natural monosaccharide units.

Functionalisation of monosaccharides



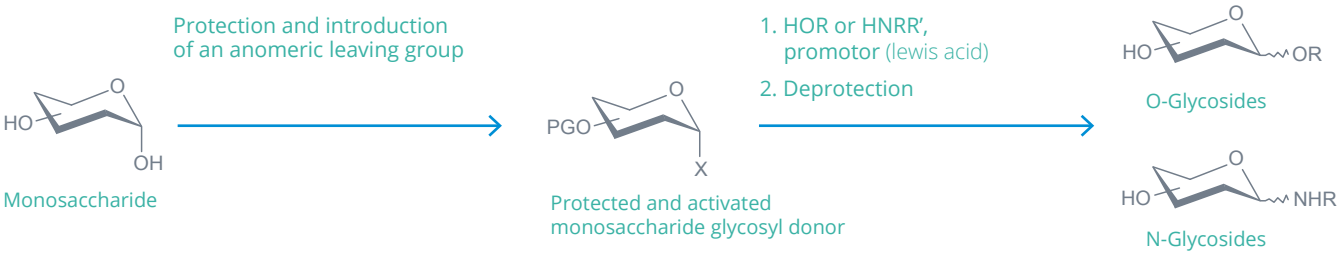
Scheme 2 : Functionalisation of a monosaccharide

Some of the reactions described in Scheme 2 will require protection to afford selective accessibility. Examples of modification reactions can be drawn from all areas of organic chemistry, but will depend on the intended purpose of the target sugar and as an example a uronic acid accessible by oxidation (see Scheme 2) is such a target.

Deoxygenation sequences lead to deoxy sugars, halogenations such as chlorination towards sweeteners or fluorination to alter binding properties are commonplace and substitution and chain-elongation or -shortening reactions convert sugars into each other to name a few examples.

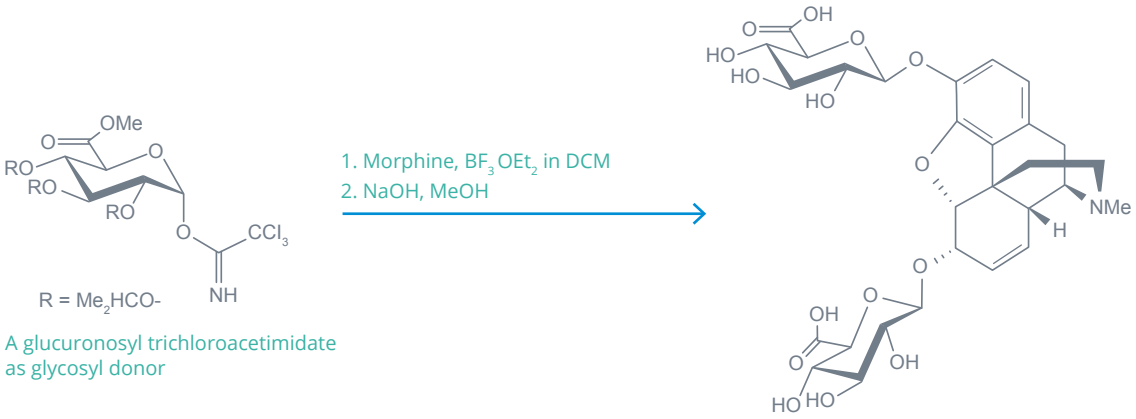
Reactions at the anomeric centre of monosaccharides, especially *glycosylation* leading to glycoconjugates and oligosaccharides, are of huge interest and have been the subject of intense research for many years. For more detail, the reader is referred to the Biosynth publication 'Oligosaccharide Toolbox' and more specialised literature (Levy and Fügedi, 2006). Examples of chemical glycosylation sequences are shown in schemes 3a and 3b.

Glycosylation of monosaccharides towards natural poducts and analogues



O-and N-Glycosides make up groups of natural products such as for instance glycolipids glycosteroids, oligosaccharides, N- and O-linked glycopeptides, glycoproteins and glycosides formed during phase II metabolism such as glucuronides.

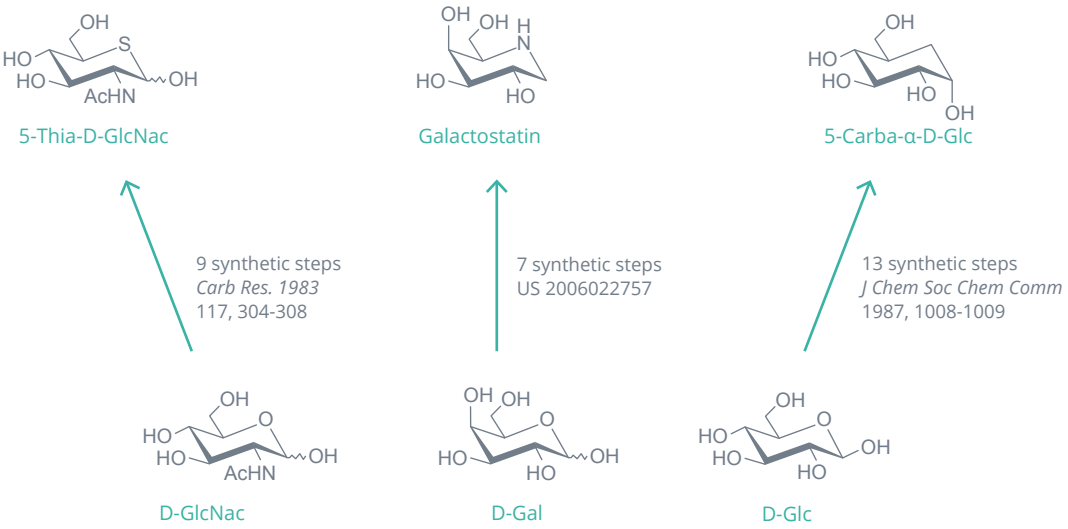
Scheme 3a : Chemical glycosylation sequence. The monosaccharide, typically in protected form, is converted into a glycosyl donor by introduction of a leaving group at the anomeric centre. Following activation with a suitable promotor/catalyst, the monosaccharide reacts with a glycosyl acceptor, via an oxocarbenium ion intermediate, to form the saccharide acetal (or *O,N*-acetal).



Scheme 3b : Glycosylation of morphine and deprotection to obtain phase II-type metabolites.

If the ring oxygen of a monosaccharide is replaced by another heteroatom or carbon, the resulting analogue *sterically* still very closely resembles the parent sugar and is therefore often able to substitute the latter in, for instance, biological interaction events.

Sugar mimetics where the ring-oxygen is replaced by carbon or another heteroatom



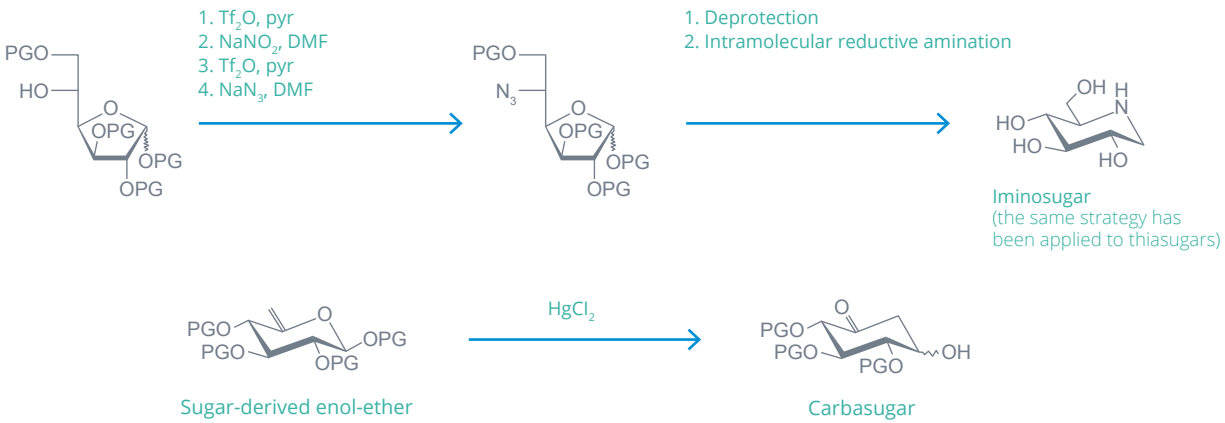
Scheme 4 : Syntheses of sugar mimetics with replaced ring oxygen from readily available monosaccharides.

However, this is not the case *electronically*, such substitutions (for examples see scheme 4) lead to entirely different physicochemical properties and have therefore been exploited in the development of many drugs:

Acarbose (Glucobay™) contains the carbasugar unit valienamine, the anti-HIV agent carbovir contains a cyclopentane as ribose mimetic and the validamycins, a class of antibiotics, even contain disaccharide-type carbasugar structures (see scheme 5). Examples for iminosugar drugs are *N*-hydroxyethyl-deoxynojirimycin (miglitol, Glyset™, see section 5.6.2) in the treatment of diabetes and *N*-butyldeoxynojirimycin (miglustat, Zavesca™) for the treatment of Gaucher's disease.

5-Thiosugars feature less prominently as drugs but are in use as glycosidase inhibitors and investigated as, for instance, antithromboticagents (Bellamy, 1995).

Classical approaches to 5-thia-, 5-aza- and 5-carbasugars: The double-displacement strategy and the Ferrier rearrangement



Scheme 5 : Two classical strategies for the replacement of the ring oxygen by carbon (Ferrier rearrangement) or sulfur/nitrogen (double displacement).

Section 6
Analytical Aspects

6 Analytical Aspects

6.1 Introduction

The analytical methods used for monosaccharides are very similar to those outlined in the recently published Oligosaccharide Toolbox (Lawson, 2021). However, the emphasis is different due in part to the lower molecular weight profile of monosaccharides compared to oligosaccharides.

6.2 Release from Polysaccharides and Oligosaccharides

Monosaccharide residues are normally bound within the structures of carbohydrate polymers and oligomers. Several methods are available for their release.

6.2.1 Acid Hydrolysis

The two most popular methods are by hydrolysis with trifluoroacetic acid (TFA) (typically, 3h. at 100 °C with 2M TFA) that will release all the neutral monosaccharides and if harsher conditions are required (perhaps to completely remove the core N-acetylhexosamines attached to proteins) 6M HCL can be used (Churms, 1982). However, there may be degradation under these conditions, including removal of the *N*-Acetyl groups present on GlcNAc and GalNAc. The use of acid hydrolysis for the release of uronic acids such as from pectins (galacturonic acid) or alginates (mannuronic and guluronic acid) is difficult due to the electron-withdrawing carboxyl group making the initial protonation of the glycosidic oxygen atom more difficult. The published methods employ very harsh conditions to release the uronic acid residues (Haug, 1962).

The synthesis of N-Acetyl mannosamine can be accomplished by:

ManNAc can be synthesised 1. by aldolase treatment of sialic acid to produce ManNAc and pyruvic acid; 2. by base catalysed epimerization of N-acetyl glucosamine. 3. by rhodium (II)-catalyzed oxidative cyclization of glucal 3-carbamates.

6.2.2 Enzymatic Hydrolysis

Many enzymes are available for the hydrolysis of polysaccharides. These include the amylases that will degrade amylose (α1,4-linked glucan) to glucose. Pectinase will release galacturonic acid from pectic acid and xylanase will release xylose from hemicellulose material. Enzymes are available for the degradation of Glycosaminoglycans but these are lyases producing 4-5 unsaturation in the resulting fragments (Heparinase, Chondroitin B lyase) (Karaki, 2016). Other enzymes of importance include the glycosidases, glycosulphatases, phosphatases and esterases as these are important for the release of monosaccharides from glycoconjugates and some polysaccharides.

6.3 Colorimetric Methods

There are many colorimetric methods for determining the concentration of carbohydrates in solution. The best known of these is the phenol-sulphuric-acid test for carbohydrates (Churms, 1982; Dubois, 1956).

Another useful method is the resorcinol-HCl test for anhydro sugars (Yaphe, 1960).

The carbazole-sulfuric acid colour test method is used for the determination of hexuronic acids such as galacturonic acid in pectins and mannuronic acid/guluronic acid in the alginates and producing a purple colour that is stable for about 1hr (Dische, 1962).

Fig A1 Phenol-sulphuric acid test for monosaccharides

Fig A2 Resorcinol-HCl test for anhydro sugars

The initial requirement will be to identify and quantify monosaccharide residues that make up mixtures released from polysaccharides and oligosaccharides by chemical or enzymatic degradation or the separation of products from intermediates in a synthetic strategy. The process of hydrolysis or product formation can be followed in a rapid and simple manner by thin layer chromatography on glass plates lined with a layer of silica gel. Possibly the most common visualisation technique is achieved by dipping the plates into a solution of concentrated sulfuric acid (5%) in methanol followed by heating on a hotplate until the monosaccharide chars to black/brown colloidal carbon (Churms, 1982).

More comprehensive analysis is undertaken by quantitative chromatography with known internal standards (White, 1991).

Fig A3 Thin layer separation of monosaccharides

Methods

The most popular systems are ion-exchange, ion-exclusion, ion-pair, hydrophilic interaction, and reverse-phase chromatography. For carbohydrates, hydrophilic interaction based on chromatography (HILIC) and ion-exchange chromatography (Dvořáčková, 2014) are widely used. Both hydrophilic interaction and ion exchange are effective in the separation, the former is more commonly used in the separation of mono- and oligosaccharides, and the latter for mono- and disaccharides.

Stationary Phases

The stationary phases that are most often used in bonded-phase chromatography in its reversed-phase mode are based on octyl (C8 columns) and octadecyl (C18 columns) functionality. Porous graphitic carbon columns have been useful due to the difference in relative retention times that these stationary phases show (Knox, 1986).

Detectors

The detectors most frequently used in HPLC for analysis of carbohydrates are pulsed amperometric (PAD), refractive index (RI), evaporative light scattering detector (ELSD), and mass spectrometric (MS) detectors.

PAD operates using a triple-step potential waveform to combine amperometric detection with alternating anodic and cathodic polarisation to clean and reactivate the electrode surface (Haddad, 1990).

Refractive index (RI) detection is less popular today due to lack of sensitivity, response to fluctuation in temperature and difficulties in gradient elution due to baseline drift.

Evaporative light scattering detection (ELSD) works by nebulising the column effluent, forming an aerosol that is further converted into a droplet cloud for detection by light scattering. Therefore, ELSD requires the vaporisation of the compounds analysed. Consequently, the chromatography eluent is dependent of the detection system.

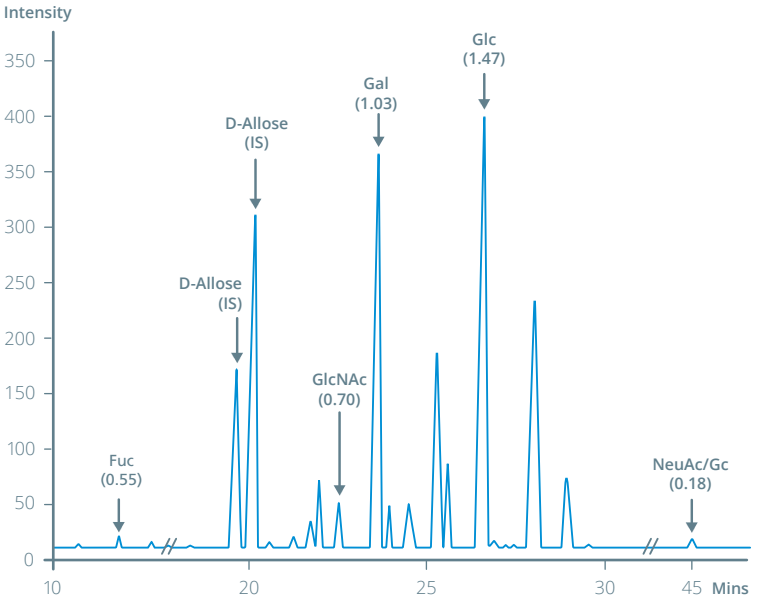


Fig A4 Monosaccharide chromatography with reversed phase and PAD detection.

The mass spectrometric detector (MS) is the most sophisticated hyphenated HPLC detector in use today ("hyphenated" refers to the coupling of an independent analytical instrument to provide detection). For complex samples, mass spectrometry coupled with liquid chromatography is a powerful technique, due to its high sensitivity and selectivity (Chen, 2007; Xu, 2018).

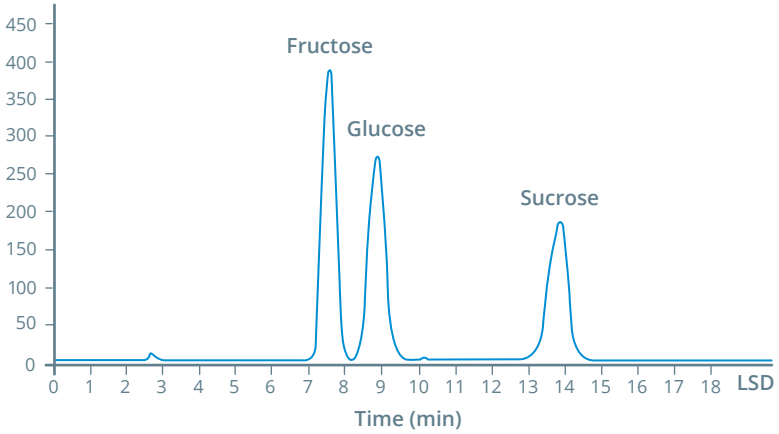


Fig A5 ELSD detection of glucose, fructose and sucrose

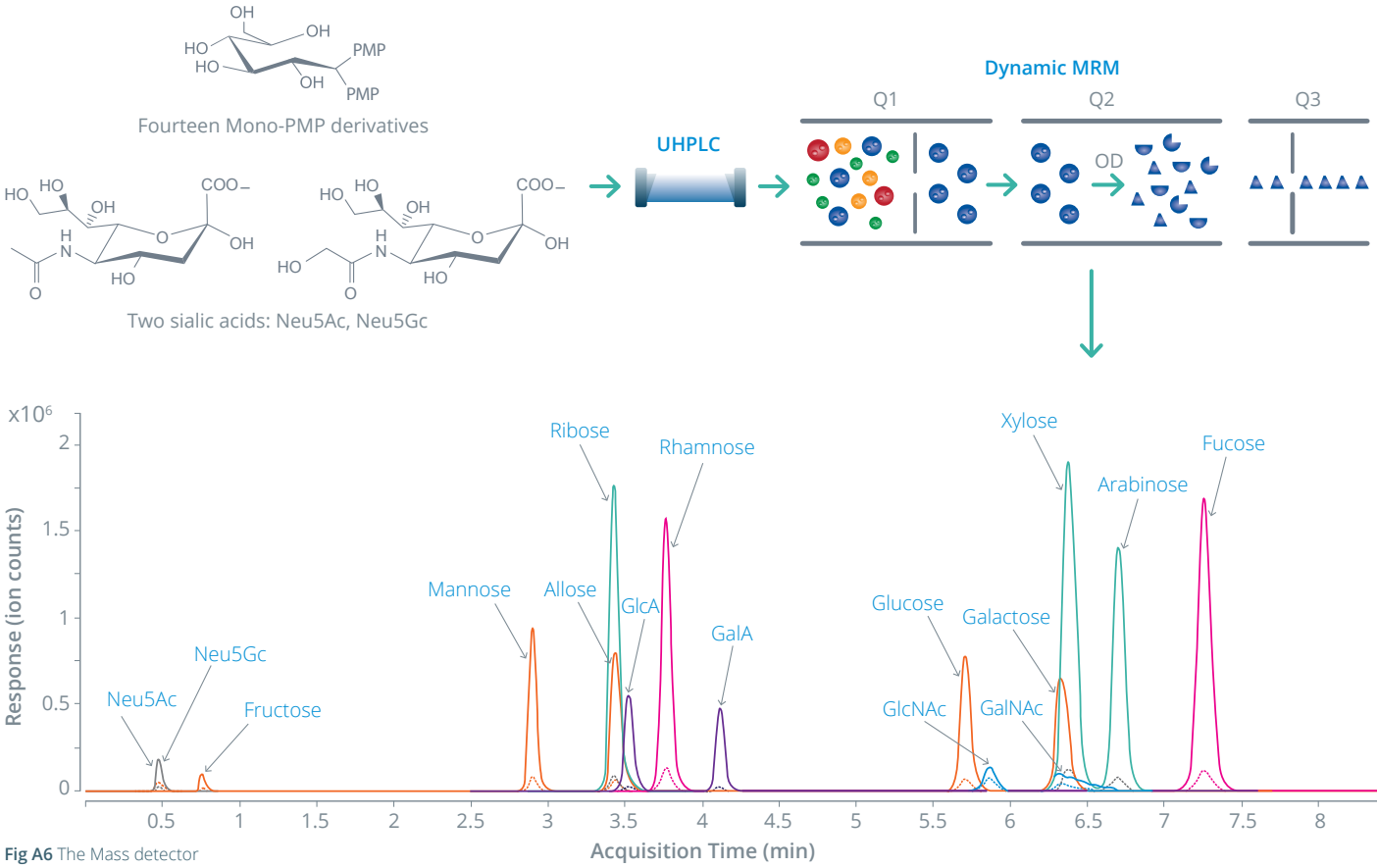


Fig A6 The Mass detector

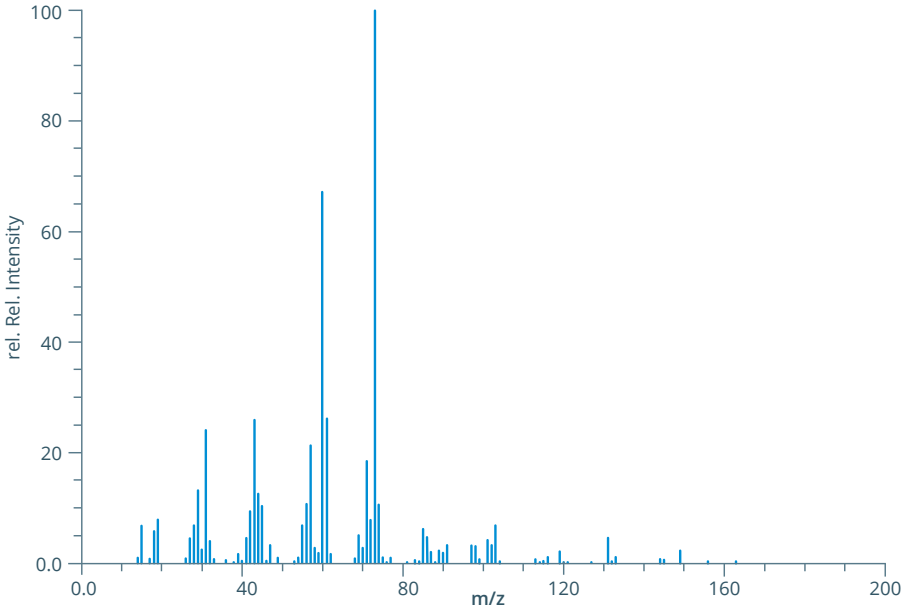


Fig A11 Typical CI spectrum of Glucose

Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) spectra for several monosaccharides have recently been published. Examples shown below are Glucose and Rhamnose (Bernard, 2019) (Fig A12).

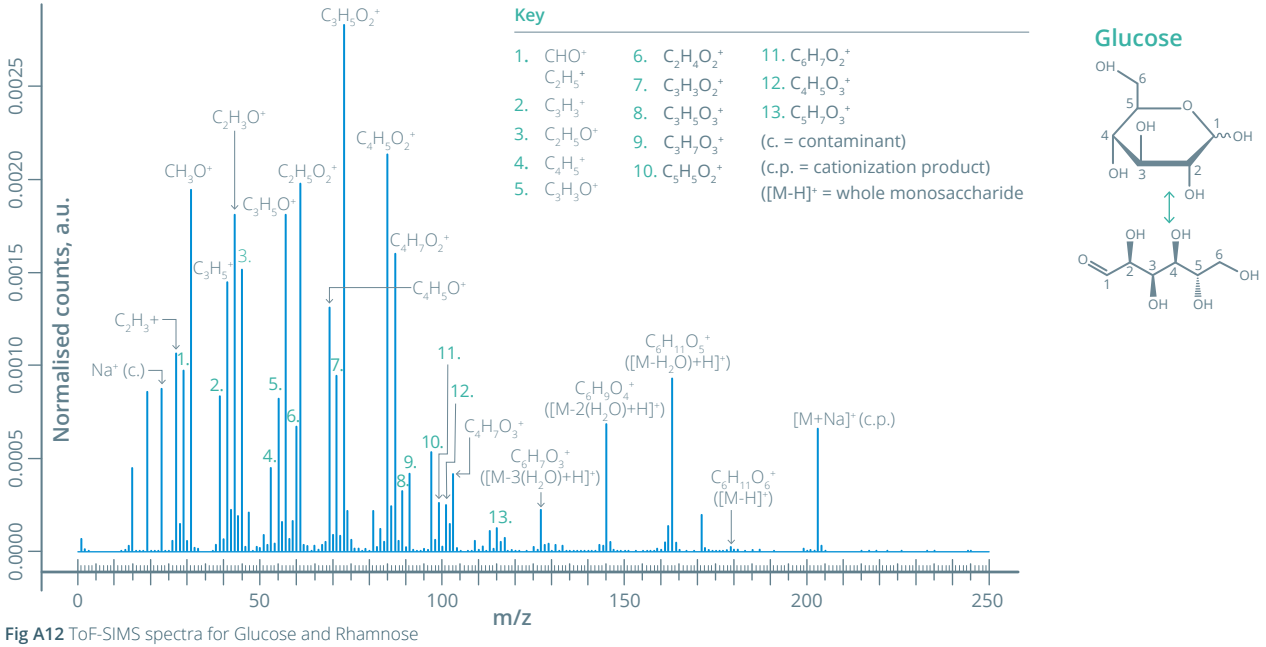


Fig A12 ToF-SIMS spectra for Glucose and Rhamnose

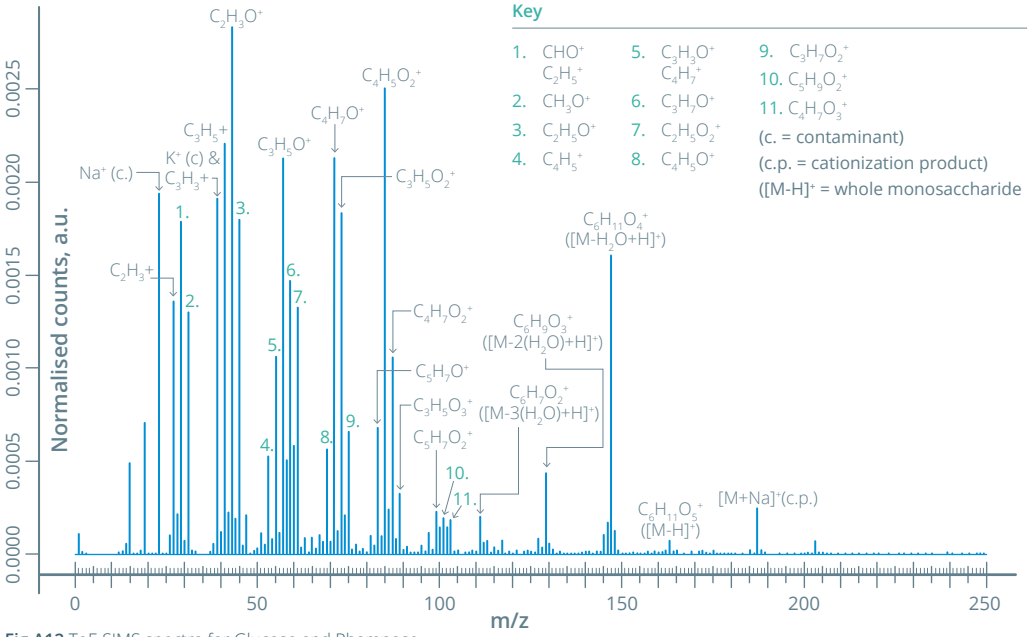


Fig A12 ToF-SIMS spectra for Glucose and Rhamnose

6.6 Spectroscopy

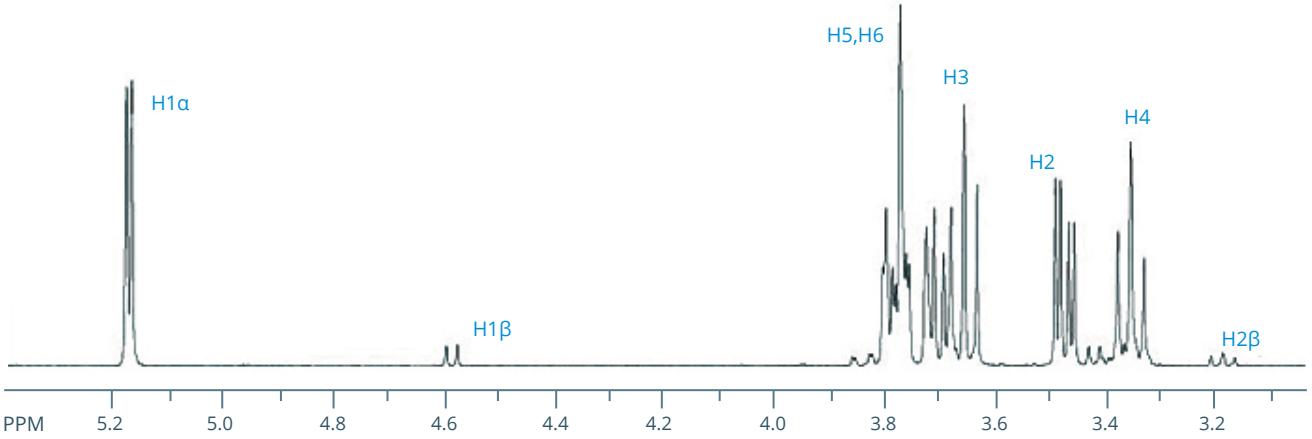
6.6.1 NMR Spectroscopy

NMR spectroscopy is one of the most important techniques in the elucidation of monosaccharide structure (Hounsell, 1995). Both proton ^{1}H and carbon ^{13}C spectra are of value as are 2D experiments such as NOESY for long range coupling analysis (Hounsell, 1990; Donald, 1986). The technique has greatest value for pure samples >~1mg for ^{1}H spectra and >~10mg for 13C spectra (Robyt, 1998).

Fig A7 NMR spectroscopy

Proton Spectra

Spinworks 4: 20210806_Glucose_HNMR_RS
Proton.icon D20 {C:\Bruker\TopSpin3.2pl7} QC 15



file: ...se\20210806_Glucose_HNMR_RS\10\fid expt: <zg30>
transmitter freq.: 400.132471 MHz
time domain size: 131072 points
width: 12019.23 Hz - 30.0381 ppm = 0.091699 Hz/pt
number of scans: 16

freq. of 0 ppm: 400.130000 MHz
processed size: 131072 complex points
LB: 0.100 GF: 0.0000
Hz/cm: 38.457 ppm/cm: 0.09611

Fig A8 Proton spectrum of glucose

The 1D ^{1}H-NMR spectrum can be used to fingerprint a monosaccharide (Fig A8). If the spectrum of an unknown monosaccharide matches the spectrum of a known one, the two monosaccharides must be identical although mirror images (D- and L-) will be the same. This requires a database of spectra from known structures against which an unknown can be matched. Care has to be taken to record spectra of the unknown monosaccharide under the same conditions (for example, pH, temperature, solvent, ionic strength) as those used in the spectral database. The technique is fast, requires about 50 nanomoles of material, and is very widely used.

In practice, it is not usually necessary to match the entire monosaccharide spectrum, but only to concentrate on specific regions that contain particular diagnostic signals from “structural reporter groups” (Vliegenthart, 1983).

The most important regions are the anomeric (C1H) region from about 4.2 to 5.5 ppm (fig A8) ring protons from 3.2-4.0 ppm and the lowfield region from about 1.0 ppm to 3.0 ppm containing methyl resonances.

A further use of the “fingerprint” method is to identify known structural features within a novel structure, but this must be done with care.

As the NMR spectrum of any given nucleus depends on the local structure around that nucleus, a given structural unit is likely to give a similar contribution to the overall spectrum in any compound. For example, certain monosaccharides can be easily identified by the presence of well-resolved, characteristic signals in the 1D spectrum (e.g. fucose gives a three-proton doublet at 1.2 ppm, while sialic acid gives two one-proton multiplets at 2.7 and 1.8 ppm).

Carbon Spectra

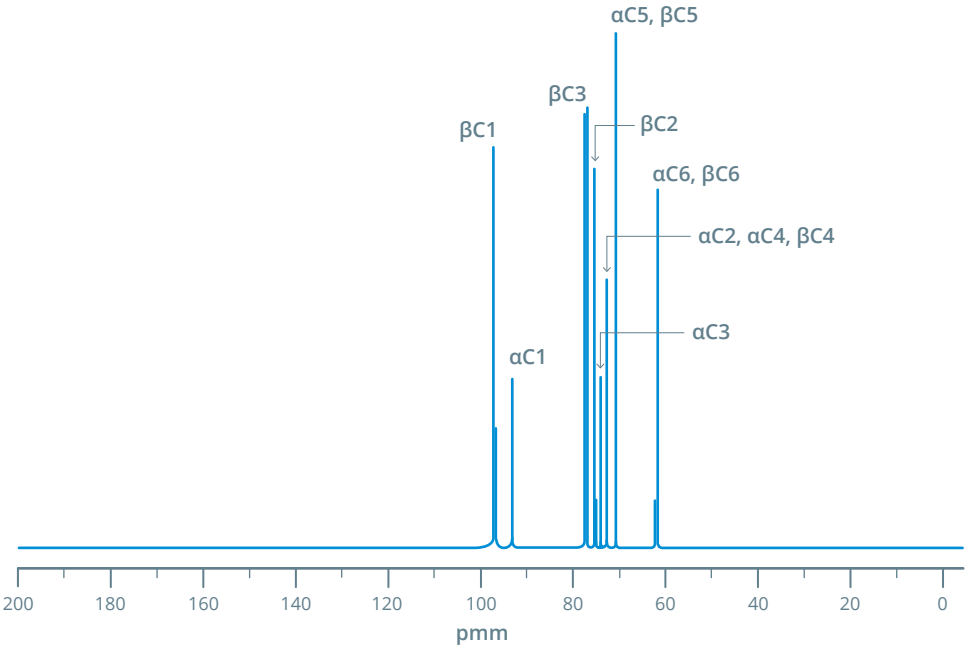


Fig A9 Carbon NMR spectrum of α/β glucose

The carbon spectrum of glucose shown above shows the α/β annotations in a similar fashion to the proton spectrum (Fig A9). Interestingly, the carbon spectrum for mannitol is very simple due to its symmetry (Fig A10).

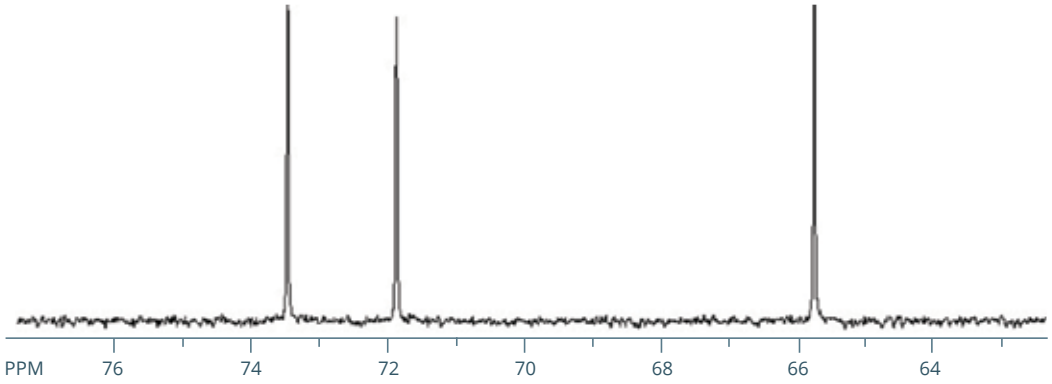
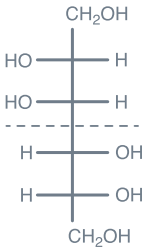


Fig A10 Carbon spectrum of mannitol



Mannitol

The infrared spectrum of monosaccharides (e.g. glucose) (Fig A13) is a useful additional technique that supports other methods such as NMR and Mass spectroscopy (Kacurakova, 2001).

An example of the infrared spectrum providing specific information is in the case of the uronic acid composition of alginates where a semi-quantitative estimation of the mannuronic acid to guluronic acid ratio can be measured (Mackie, 1971; Sellimia, 2015). The resonances are at 1083.5 cm-1 for mannuronic acid and 1024 cm-1 for guluronic acid-shown in (Fig A14).

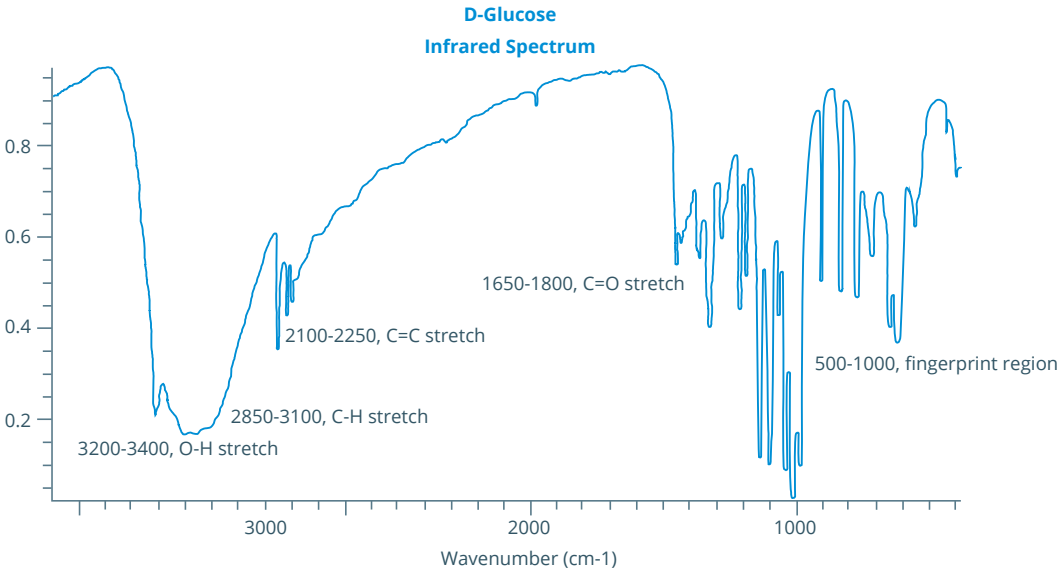


Fig A13 FTIR infrared spectrum of glucose (annotated)

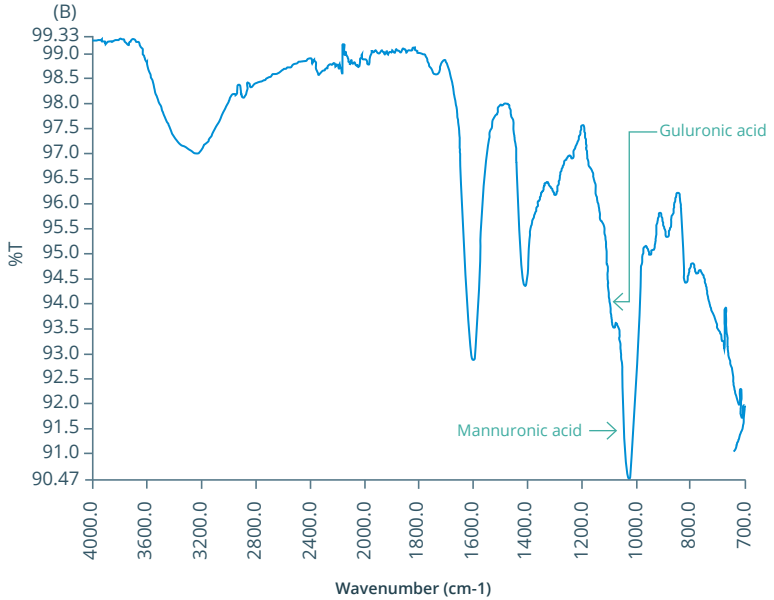


Fig A14 Determination of Alginate M/G ratio by Infrared Spectroscopy

Monosaccharides are non-superimposable on their mirror images and are thus chiral and optically active. A monosaccharide causes rotation of the plane of polarisation of plane-polarised light because the two circularly polarised components travel at different speeds through it or a solution of it (Fig A15).

The optical activity of an asymmetric sample in solution is usually expressed as the *specific rotation* [α] measured at temperature *T* and wavelength λ with $[\alpha]^{T}_{\lambda} = 100\alpha/lc$, where α is the observed rotation (in degrees, the sign of α being important), l is the length of the sample tube (in dm) and c is the solution concentration (in g per 100 ml). The *specific rotation* of a monosaccharide is regarded as a fundamental unit in the same way as melting point. Some examples of the *specific rotation* of monosaccharides are:

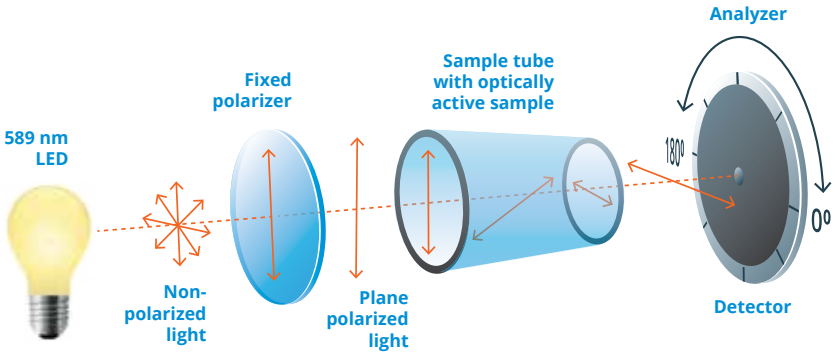
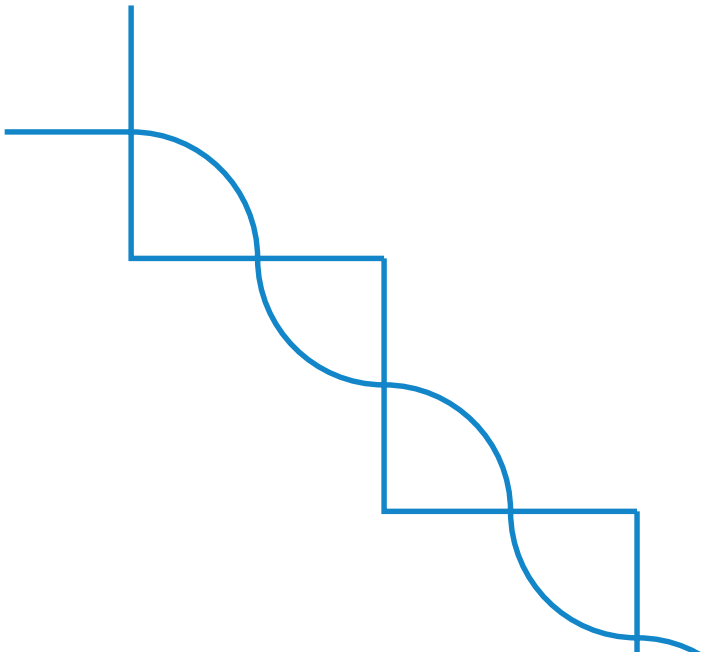


Fig A15 Polarimeter diagram

D-Glucose	+52.7
D-Galactose	+80.2
D-Fructose	-92.4
D-Mannose	+14.2
D-Arabinose	-105.0
L-Arabinose	+104.5



B

Section 7
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About the authors

Chris Lawson, Ph.D.

Ph.D. in Carbohydrate Chemistry & Enzymology (Edinburgh, 1969) with Prof. Sir Dai Rees FRS who discovered that polysaccharides form double helices in plant and animal tissues with profound effects on structure, biological function and texture. He has published over 35 papers, patents and book chapters.

Fellow of the Royal Society of Chemistry, member of The Biochemistry Society, The American Chemical Society and the Society of Glycobiology.

In 1969 he joined Tate & Lyle to manage a research team developing microbial polysaccharides resulting in the commercialisation of Xanthan Gum. He then helped to commercialise sucrose ester surfactants and Sucralose. In 1989, he founded Dextra Laboratories with a colleague and developed it into a successful glycobiology company with a catalogue of key research carbohydrates and a specialist custom synthesis business. In 2006 he founded Glycomix Ltd to focus on polysaccharide structure and function and in 2016 having sold the company to Carbosynth he became Scientific Advisor to help develop their carbohydrate business.

Hansjorg Streicher, Ph.D.

Ph.D. in Chemistry in Konstanz, Germany (1995) with Prof. R. R. Schmidt on Transition-State Analogues for the Antibody-Catalysed Glycosyltransferase.

He holds a habitation in organic chemistry and has published around 30 papers and book chapters.

Has held various academic positions at the Weizmann Institute of Science (Rehovot, Israel), University of Konstanz and University of Sussex (Brighton, UK) with a scientific focus on lectins and carbohydrate mimetics.

Established as a consultant in the life science sector since 2014 works with Biosynth as a Scientific Advisor.

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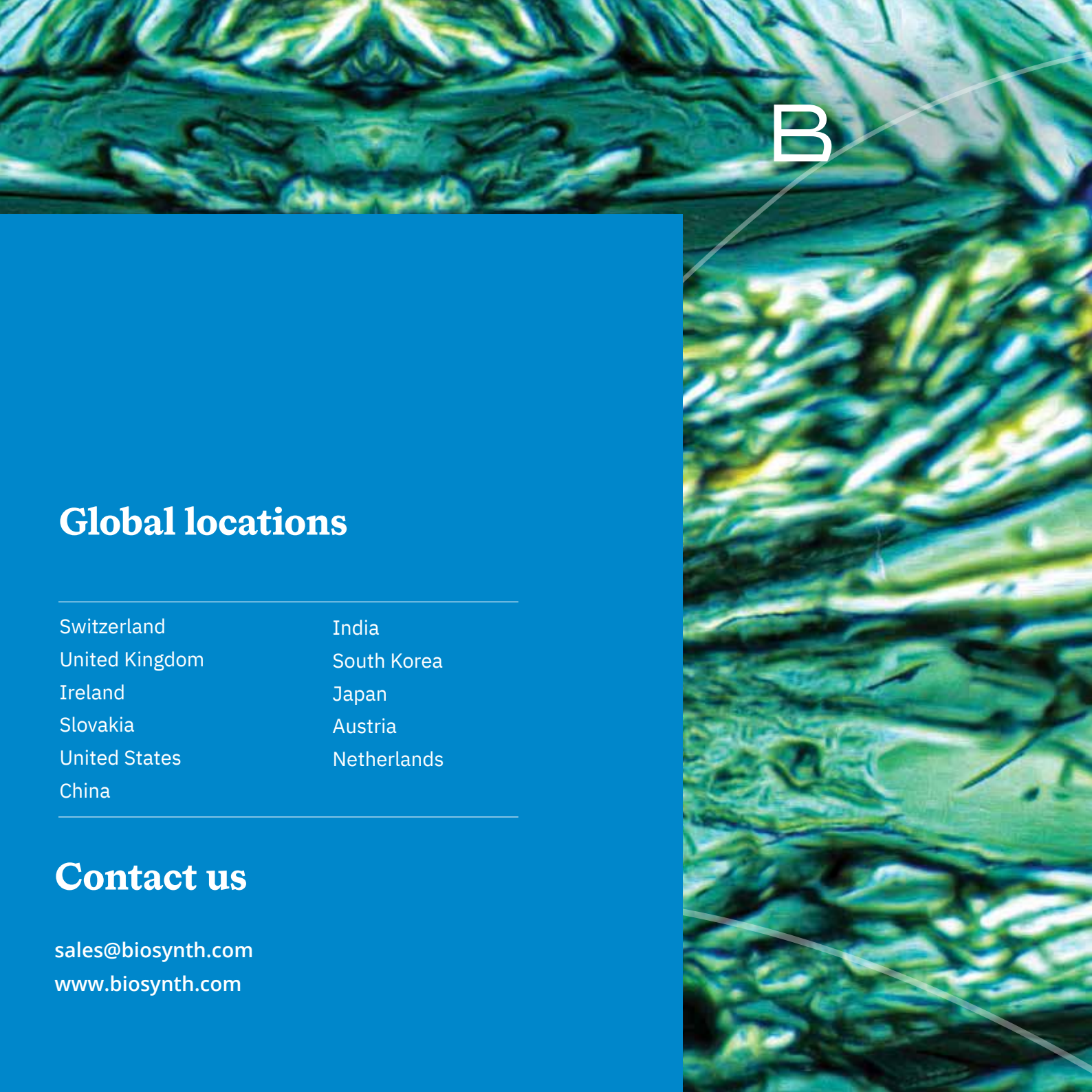

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