Marco Brito-Arias

Synthesis and Characterization of Glycosides

Second Edition

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To Carmina Daniela BR and Iryna K

Preface

There is no doubt that glycoside chemistry continues to be a dynamic and exciting field of organic chemistry. Within sugar chemistry, glycosides are of special interest not only because of the challenges represented by their synthesis and structural characterization, but also due to their important biochemical relevance, and hence their applications in a number of essential disciplines, such as pharmaceuticals, food, and biotechnology.

Important biomolecules such as DNA and RNA, or cofactors such as ATP and NAD are some of the natural glycosidic structures that play key roles at a biochemical level. Also, a considerable number and variety of natural and synthetic glycosides are being extensively used as antibiotics, antiviral, and antineoplastic agents.

There are also a significant number of chromophoric glycosides being used in molecular biology as substrates for detection of enzymatic activity of gene markers.

Solid-phase oligosaccharide synthesis despite the great progress recently reported by different groups continues to be a challenging task considering the diversity and complexity of glycosides, especially those present in cellular membranes. However, based on the satisfactory evolution of this approach, there is confidence that many complex molecules will be prepared just in the same way that solid-phase chemistry is currently used to prepare oligopeptides and oligonucleotides.

The aim of this book is to provide methods and strategies for the formation of glycosides, illustrated by the synthesis of important biologically active glycosides, and also to present an overview of the basic tools needed for the characterization of glycosides through NMR spectroscopy, X-ray diffraction, and mass spectrometry.

From the overwhelming number of excellent articles related to glycoside chemistry, it has not been an easy task to select those that are biologically important, and perhaps most importantly serve as didactic models for understanding more about the process of glycoside bond formation.

The book should also serve as a helpful guide to those professionals interested in sugar chemistry, especially regarding the design of synthetic routes, by evaluating suitable protecting and leaving groups, and the best reaction conditions needed for the preparation of glycosides.

la Laguna Ticomán cp., Mexico Marco Brito-Arias

Preface for Second Edition

The second edition is designed to serve as a textbook on glycoside chemistry with the main goal to provide updated information about the methods considered classical or of primary significance as well as novel variations or new methods for achieving glycosylation processes. This applies to glycosyl donors, promoters or activators, and protecting groups that have been currently reported as more efficient or with significance for preparing active substances of glycosidic nature with important implications in pharmaceutical, food, environmental, and biotechnological related disciplines. The second edition provides updated information on chemical shifts, and coupling constant data for complete structure assignment of glucopyranoses and pyranosyl disaccharides, as well as the main fragmentation pattern observed in mass spectrometry. I hope this new edition will expand its usefulness to those professionals involved in glycoside chemistry and will provide support in design of suitable methodologies in a novel or more efficient way. Finally the author would be grateful for receiving any comment intended to improve the quality of the material included.

Acknowledgments

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Contents

Chapter 1
Glycosides, Synthesis and Characterization

1.1 Introduction

Monosaccharides are generally defined as aldoses and ketoses connected to a polyhydroxylated skeleton [1]. In an aqueous solution, monosaccharides are subject to internal nucleophilic addition to form cyclic hemiacetal structures. When addition occurs between -OH at C(4) or -OH at C(5), and the carbonyl group, a five- or a six-member ring is formed called a furanose or a pyranose respectively. It is also known that an equilibrium exists between the open and the cyclic form, being displaced to the latter by more than 90 %. Therefore, in aqueous solution, it is more accurate to consider that most sugars are present as cyclic molecules and behave chemically as hemiacetals.

The Haworth structure is a useful way to represent sugars. However, as it is known that for any six-membered rings a nonplanar conformation is assumed. The conformation exclusively preferred is called chair and the two possible conformations are $^4C_1$ and $_4C^1$. The first conformation is used for the D enantiomeric form and the second for the L form (Scheme 1.1).

On a chair conformation type $^4C_1$, an α anomeric hydroxyl group is positioned in the axial orientation while a β hydroxyl lies equatorial (Scheme 1.2).

As a result of this reversible ring formation process, a diastereomer mixture of anomers α and β is produced as indicated in Table 1.1 for some of the most common monosaccharides [1, 2].

The pioneering work in 1890 by Fischer [3] allowed him to determine the relative configuration and the synthesis of the most known aldohexoses. Based on the assumption that in D-glyceraldehyde, the hydroxyl group is placed to the right, he proposed correctly the structure of tetroses, pentoses, and aldohexoses (Scheme 1.3). The relative configuration of D-glyceraldehyde was later confirmed by X-ray diffraction by Bijvoet in 1951. Consequently, all the resulting biologically active distereoisomeric aldoses derived from D-glyceraldehyde conserve

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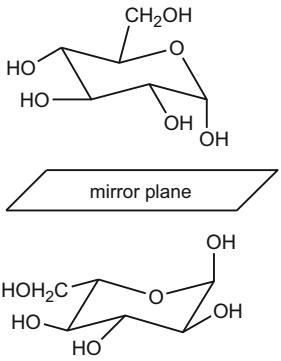


Scheme 1.1 α-D-glucopyranose-$^4C_1$ and α-L-glucopyranose-$^1C_4$

always the secondary alcohol next to the primary one to the right side in the Fischer projection. Ketoses with 3–6 carbons are naturally produced from 1,3-dihydroxyacetone, according to the tree shown in Scheme 1.4.

1.2 Reactions of Monosaccharides

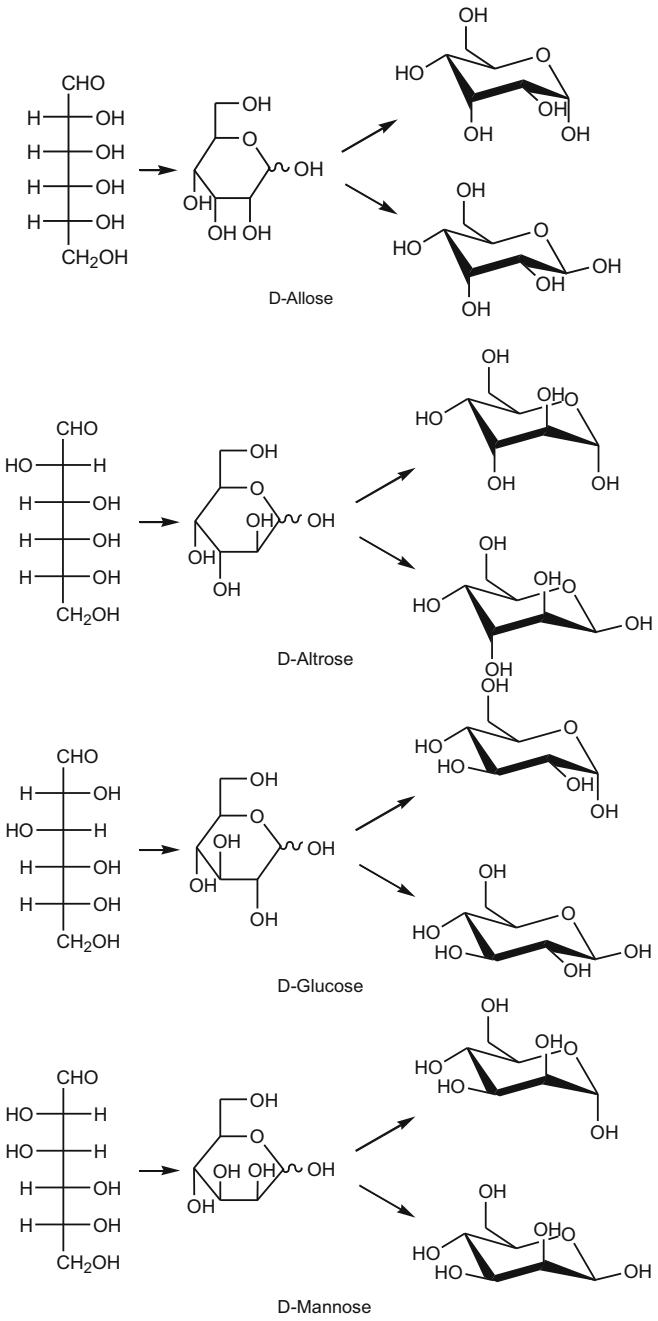
Carbohydrates own their reactivity to the hemiacetalic center and to the hydroxyl groups, with the primary group being more reactive than the secondary group. Aldoses and ketoses are susceptible to nucleophilic addition and the latter is less reactive due to steric hindrance. The cyclic forms are adopted when the hydroxyl group positioned at C-5 verifies an intramolecular nucleophilic addition to the carbonyl group producing an anomeric mixture of pyranosides (Scheme 1.5).

1.3 Chemical Modifications

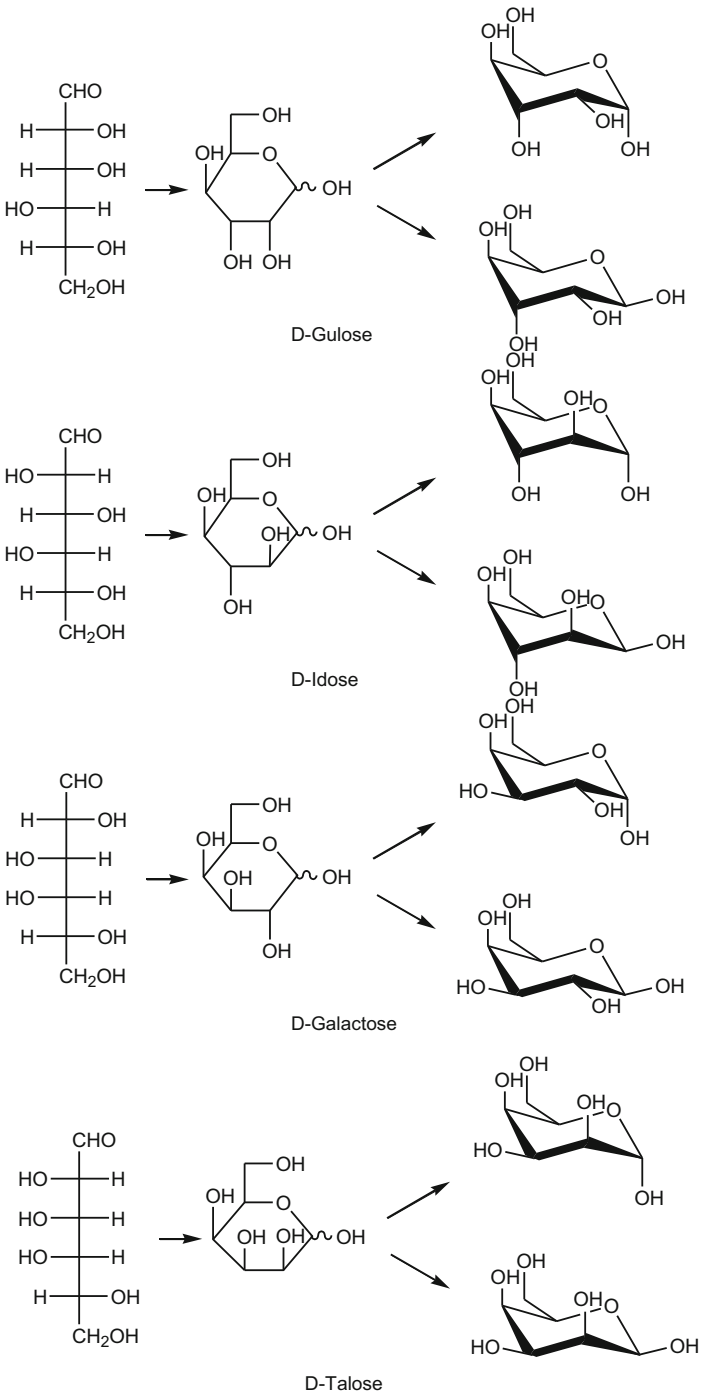
The classical reactions on monosaccharides are used initially for identification or sugars or to distinguish between aldoses and ketoses. They are also very useful for preparing key intermediates in the construction of glycosides. Some of the common reactions used to identify monosaccharides are:

1.3.1 Oxidations

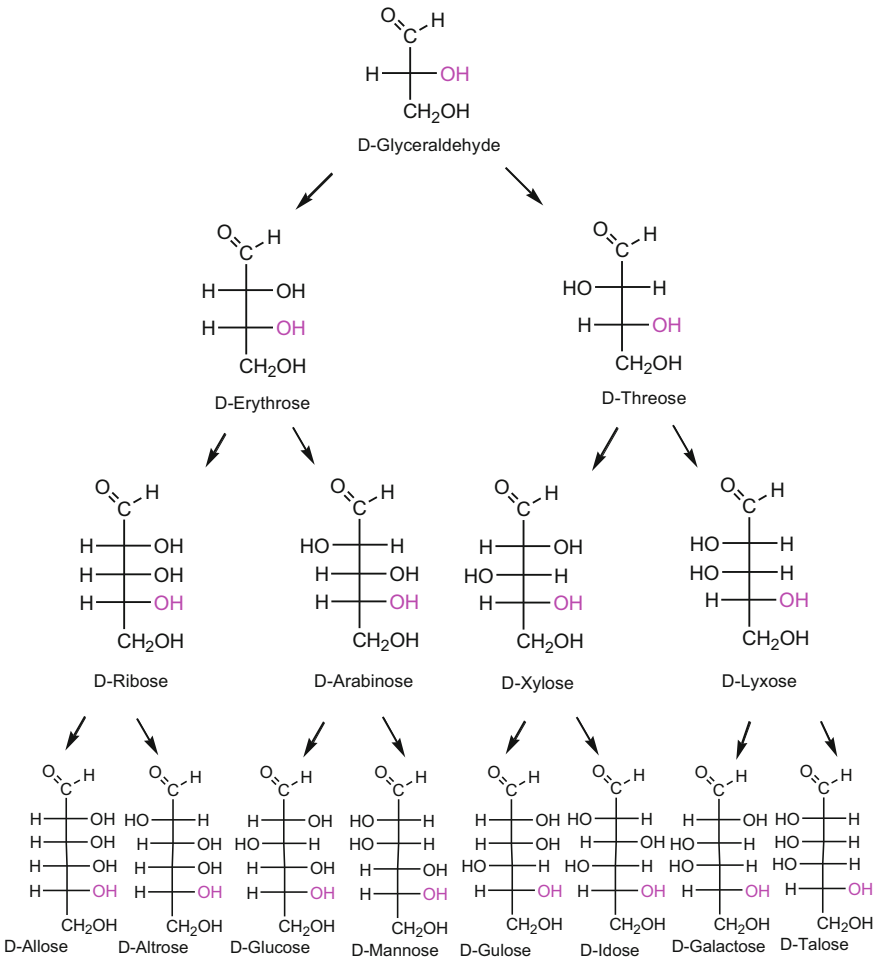
The oxidation of non-protected aldoses may result in carboxylic acid formation depending on the reaction conditions. Thus, with aqueous bromine a monocarboxylic acid (aldonic acid) is formed, whereas with nitric acid a dicarboxylic acid is favored (aldaric acid) (Scheme 1.6).



Scheme 1.2 Fischer projections, Haworth structures, and $^4C_1$ chair conformation of D-aldohexoses



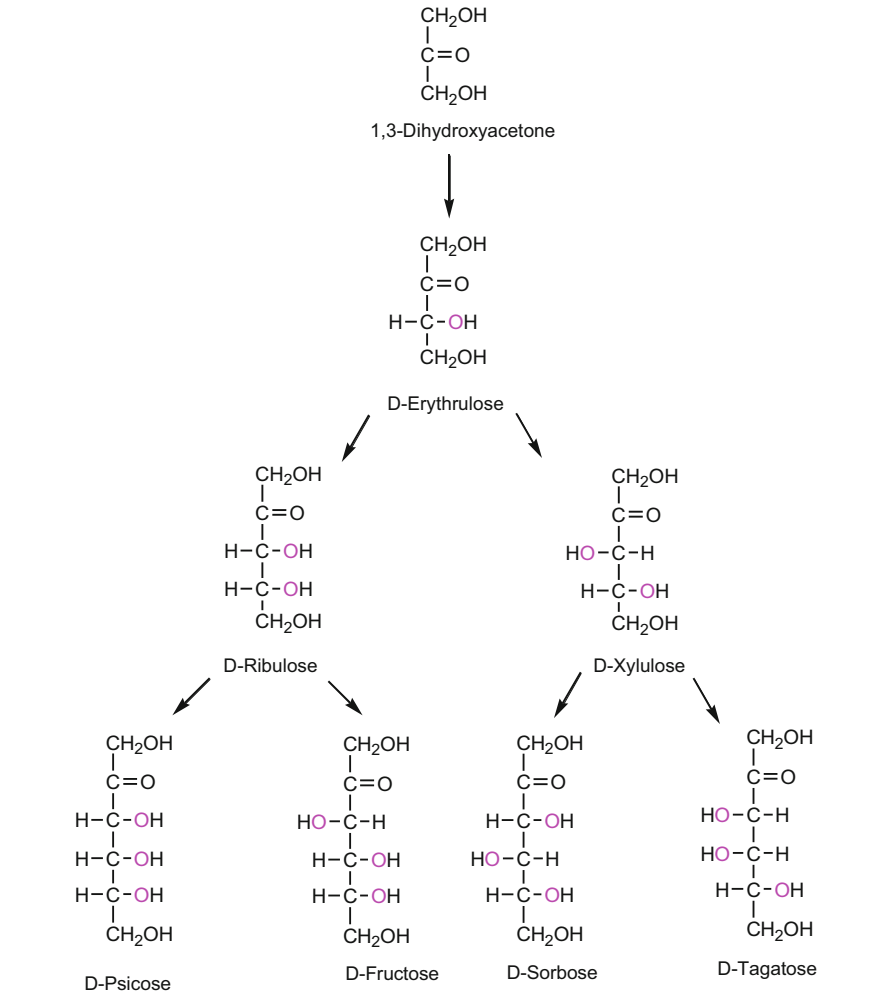
Scheme 1.3 Fischer projections of D-aldoses



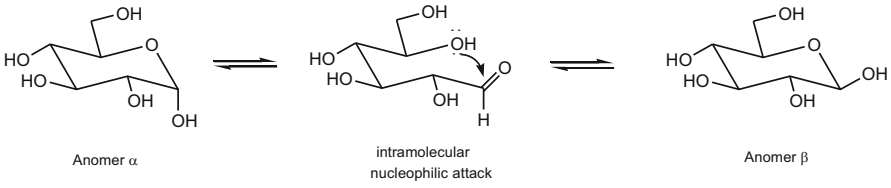
Scheme 1.3 (continued)

Table 1.1 Distribution of α β of some D-monosaccharides in solution at 31 °C

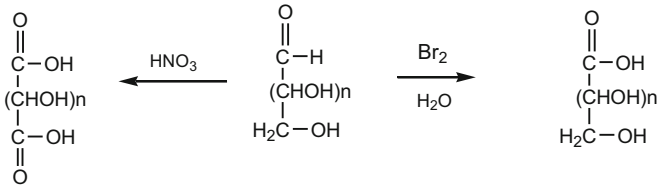
	% Pyranose		% Furanose	
Carbohydrate	α	β	α	β
Glucose	38	62	0.1	<0.2
Galactose	30	64	3	4
Mannose	65.5	34.5	0.6	0.3
Rhamnose	65.5	34.5	0.6	0.3
Fructose	2.5	65.0	6.5	25
Ribose	21.5	58.5	6.4	13.5
Xylose	36.5	63.0	0.3	0.3



Scheme 1.4 Fischer projections of the 2-ketoses

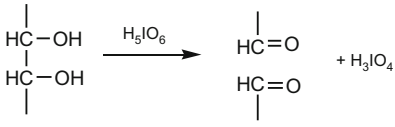


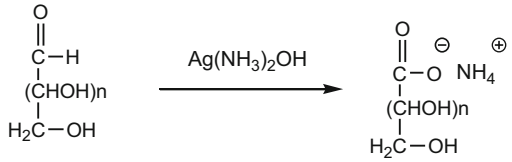
Scheme 1.5 Pyranose ring formation



Scheme 1.6 Oxidative aldose transformation into monocarboxylic and dicarboxylic acids

Scheme 1.7 Oxidative cleavage of diol by periodic acid





Scheme 1.8 Tollens reaction

1.3.2 Periodate Oxidation

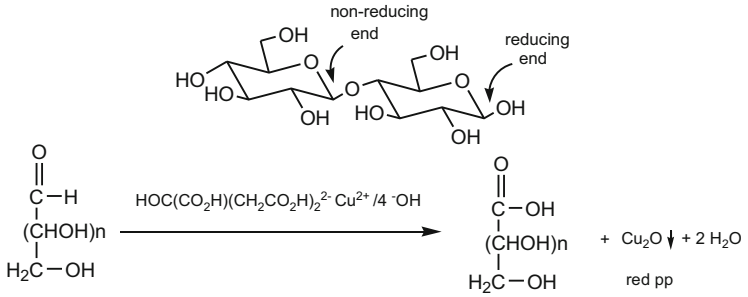
Periodic acid is an strong oxidizing agent and is capable of breaking 1,2-cis diols to generate carbonyl fragments after cleavage of the C–C bond (Scheme 1.7).

1.3.3 Tollens Reaction

This classical reaction is very useful for aldose identification and consists in the oxidation of the aldehyde function with a moderate oxidative agent (a silver ammonium salt) to form the glucuronide ammonium salt and metallic silver which produce the silver mirror effect (Scheme 1.8).

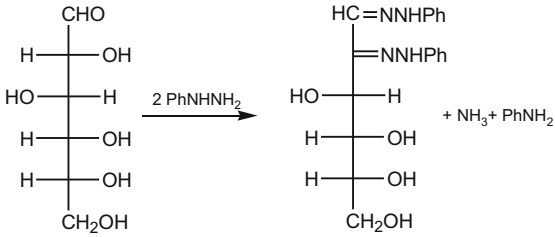
1.3.4 Benedict and Fehling Test

The test consist in the use of a copper citrate (Benedict reagent) or copper tartrate complex (Fehling reagent), which upon treatment with the sugar under study produces the glucuronide ion along with copper (I) oxide which is detected as a brick-red precipitate (Scheme 1.9).



Scheme 1.9 Benedict and Fehling test

Scheme 1.10 Osazone formation



Based on Tollens, Benedict, or Fehling test, sugars are classified into reducing when positive or non-reducing sugars if negative. Reducing sugars are hemiacetals in equilibrium with small amounts of open forms. Under basic conditions, aldoses and ketoses are positive for Tollens and/or Benedict/Fehling test as result of an aldose–ketose equilibrium via enediol intermediates.

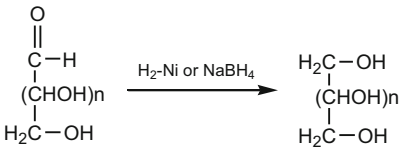
1.3.5 Nucleophilic Addition

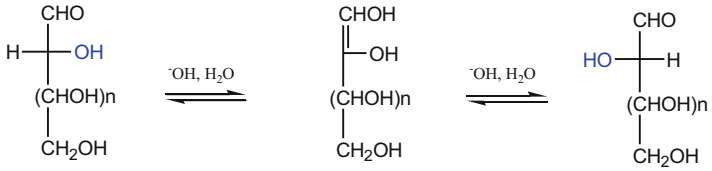
Aldoses and ketoses may react with a variety of nucleophiles, giving rise to addition/elimination products such as osazones and oximes, or addition products such as reduced derivatives when reacted with hydrides.

The reaction that allowed E. Fischer to determine the structure of common aldoses is the osazone formation and consisted in the reaction between hydrazine and aldoses (Scheme 1.10) to yield crystalline derivatives that can be identified through their melting point values.

The carbonyl group can be reduced by hydrogenation or hydride addition to produce corresponding alditols (Scheme 1.11). These reduced sugars are present in various fruits such as cherries, pears, and apples and are used as sugar substitutes for diabetics.

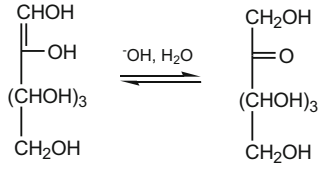
Scheme 1.11 Carbonyl reduction for the preparation of sorbitols





Scheme 1.12 Enediol rearrangement

Scheme 1.13 Enediol rearrangement



1.3.6 Enediol Rearrangement

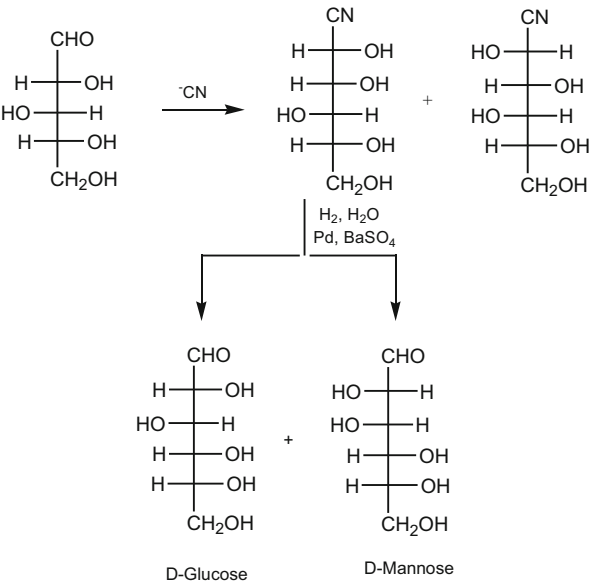
This transformation occurs in a basic medium and allows the conversion of epimers, defined as isomeric forms that differ in the position of the hydroxyl group at C-2. In this way it is possible to transform glucose to mannose through the enediol intermediate and vice versa (Scheme 1.12).

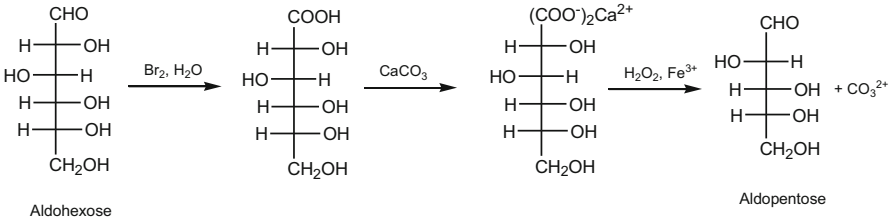
Another important isomerization process through the enediol rearrangement is the interconversion of glucose and fructose. Thus, the enolization proceeds by migration of proton at position 2, to carbon at 1 (Scheme 1.13).

1.3.7 Kiliani–Fischer Synthesis

This sequence was used to increase the number of carbons in a sugar. The reaction involves cyanohydrin formation by nucleophilic addition of cyanide to the aldehyde. The diastereoisomeric mixture of cyanohydrins obtained is partially reduced to produce the epimeric forms (Scheme 1.14).

Scheme 1.14 Kiliani–Fischer synthesis





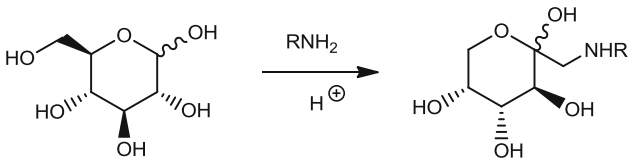
Scheme 1.15 Ruff degradation

1.3.8 Ruff Degradation

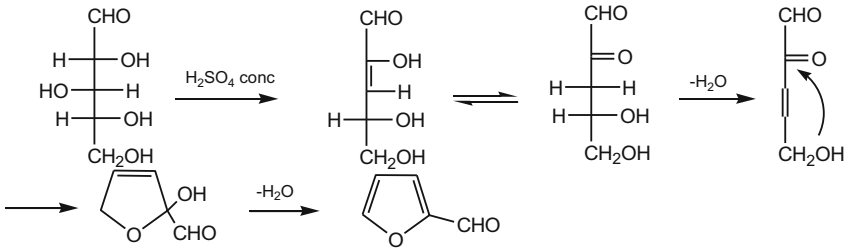
The process of reducing the monosaccharide skeleton in one carbon is known as Ruff degradation and consists in the oxidation of the aldehyde to the carboxylic acid through the use of calcium salt and subsequent peroxide treatment in the presence of ferric salts to produce the aldose reduced in one carbon (Scheme 1.15).

1.3.9 Amadori Rearrangement

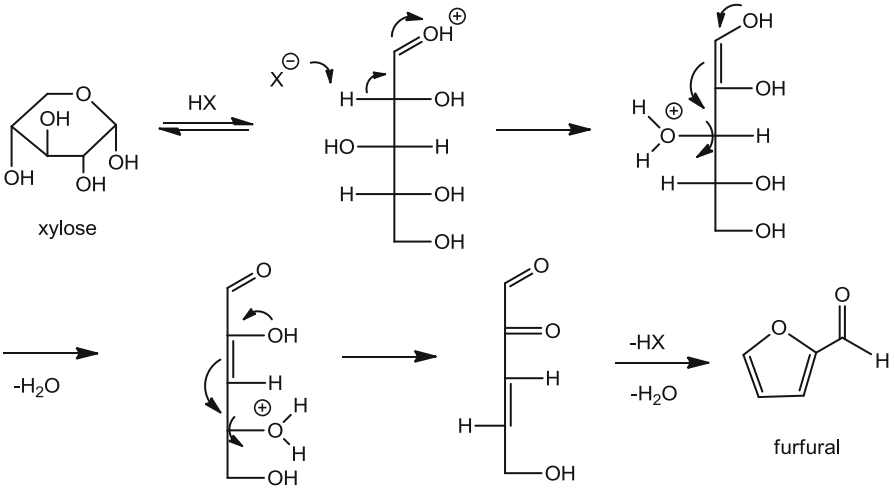
This reaction occurs between an unprotected aldose such as D-glucose and suitable amines, producing 1-amino-1-deoxy ketoses as a mixture of anomers. When the amino group comes from an amino acid the reaction is known as the Maillard reaction, which is an important modification in food science (Scheme 1.16) [4].



Scheme 1.16 Amadori rearrangement



Scheme 1.17 Conversion of pentoses to furfural



Scheme 1.18 Conversion of xylose to furfural

1.3.10 Conversion to Furfural Derivatives

Pentoses subjected to high acid concentrations can be transformed to furfural in quantitative yields. The sequence involves a tautomeric keto-enol equilibrium, dehydration, and intramolecular nucleophilic addition of the primary alcohol to the aldehyde to generate furfural (Scheme 1.17).

The main pentose source used for preparing furfural is xylose which under acidic medium is subjected series of dehydrations, enolization and intramolecular cyclization as shown in Scheme 1.18. Some of the conditions reported for preparing furfural are described in Table 1.2.

Table 1.2 Reaction conditions for preparation of furfural

Sugar source	Catalyst	Reference
Xylose	Solid acid/ZrO_2–Al_2O_3	[5]
Xylose	Atmospheric pressure by dilute sulfuric	[6]
Xylose	Halides in dilute aqueous acidic	[7]
Xylose	Vanadyl pyrophosphate	[8]
Xylose	Formic acid	[9]
Pentosan	Acid hydrolysis	[10]

Table 1.3 Reaction conditions for the preparation of hydroxymethylfurfural

Sugar source	Catalyst	Reference
Starch-rich acorn biomass	Chromium halides	[13]
Rice straw	Single-phase and biphasic systems	[14]
High fructose	Ionic liquids	[15]
Fructose	Inorganic salt in alcohol	[16]
Fructose and sucrose	Protic ionic liquids	[17]
Fructose or glucose	Imidazolium ionic liquids with and without a catalyst	[18]
Alditols and ketohexoses	Polymer-mediated cyclodehydration	[19]
Fructose	Acidic resin-catalyzed	[20]
Glucose	Co-catalysts and solvents	[21]
Fructose	Phosphorous pentoxide in ionic liquid	[22]
Cellulose	Zinc chloride, MW	[23]
Sucrose	Ammonium halides	[24]
Fructose	Mesoporous SBA-15-SO_3H in ionic liquid BmimCl	[25]
Glucose	$SnCl_4$-tetrabutyl ammonium bromide	[26]

1.3.11 Preparation of 5-Hydroxymethylfurfural (HMF)

This valuable derivative is subjected to intensive studies since it can be used in the preparation of pharmaceuticals, liquid fuels, plastics, and other fine chemicals. The common sugar source is fructose and glucose, although starch, cellulose, and sucrose have been examined as a natural source for the preparation of HMF (Table 1.3) [11, 12]. The mechanism involves enol formation after the first dehydration, and two further dehydrations to furnish the furan ring (Scheme 1.19).

1.4 Biosynthesis of Sugars

Synthesis of carbohydrates in plants occurs through a mechanism of carbon dioxide fixation, and was understood through the use of long-lived radioactive isotope of carbon ^{14}C. After considerable investigations it was found that the initial CO_2 acceptor