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Organic Synthesis with Carbohydrates

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and
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Organic Synthesis with Carbohydrates

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Geert-Jan Boons and Karl J. Hale

Preface

The carbohydrates or saccharides constitute the most abundant group of compounds found in nature. They are structurally very diverse and are endowed with a wealth of stereochemical properties. Saccharides are available in cyclic and acyclic forms, can have different chain lengths and oxidation and reduction states, and can be substituted with a wide range of functionalities. Furthermore, monosaccharides can be linked together through glycosidic linkages to give oligo- or polysaccharides. Many saccharides are readily and cheaply available and provide an attractive, renewable source of material.

Not surprisingly, these compounds are important starting materials in organic synthesis, and there are thousands of research papers and numerous industrial processes in which carbohydrates feature prominently.

This book provides broad coverage of the use of carbohydrates in organic synthesis, at postgraduate student level. Each chapter describes established and widely used methods and approaches, but also covers recent and promising reports. Many citations to the primary literature are provided. It is hoped, therefore, that this book will also be of use to synthetic organic chemists and carbohydrate chemists in academic and industrial laboratories.

The authors recognise that one book cannot cover all aspects of synthetic carbohydrate chemistry. Part A focuses on monosaccharide chemistry, complex oligosaccharides and glycoconjugate synthesis. For a long time, this area of chemistry was the domain of a small and specialised group of researchers. In the early eighties, it became apparent that oligosaccharides are involved in many important biological processes, such as cell-cell recognition, fertilisation, embryogenesis, neuronal development, viral and bacterial infections and tumour cell metastasis. Consequently, the preparation of complex glycoconjugates became part of mainstream organic chemistry and it is now part of the undergraduate or postgraduate chemistry curriculum in many universities. Chapter one covers important properties of saccharides, such as configuration, conformation, the anomeric effect and equilibrium composition in solution. This basic knowledge is key to many of the discussions that follow. The next two chapters detail the use of protecting groups in carbohydrate chemistry and the preparation of functionalised monosaccharides. Chapters four and five deal with glycosidic bond chemistry, preparation of complex oligosaccharides and the synthesis of glycopeptides.

Part B discusses enantioselective natural product synthesis from monosaccharides. Nowadays, most natural product syntheses are performed in an asymmetric manner. This development is due principally to the realisation

that enantiomers may have very different biological properties: one of them may have the desired property, while the other may be potentially harmful, or at least undesirable. Many methods are available for obtaining compounds in an optically pure form. However, each method involves, at a particular stage, a chiral molecule obtained from a natural source, either by using a chiral starting material or chiral auxiliary, or by employing a chiral catalyst. Carbohydrates have been used extensively as chiral starting materials but they have also been utilised as chiral auxiliaries and ligands of chiral catalysts. The examples covered in chapters six to eighteen illustrate the use of carbohydrates in the synthesis of a wide range of natural products. In many cases, the origin of the starting material cannot be recognised in the final product. These chapters demonstrate how the rich stereochemistry of carbohydrates can be used efficiently to install chiral centres into target compounds. To ensure that this material is suitable for teaching, emphasis is placed on retrosynthetic analysis as well as on mechanistic explanations for key and novel reactions.

Geert-Jan Boons and Karl J. Hale

Contents

PART A: STRUCTURE AND SYNTHESIS OF SACCHARIDES AND GLYCOPROTEINS

1	Mono- and oligosaccharides: structure, configuration and conformation	1
1.1	Introduction	1
1.2	Configuration of monosaccharides	2
1.3	Conformational properties of monosaccharides	7
1.3.1	Ring shapes of pyranoses and furanoses	7
1.3.2	The anomeric effect	10
1.3.3	The equilibrium composition of monosaccharides in solution	15
1.4	Conformational properties of oligosaccharides	18
1.5	Acid-catalysed glycoside bond formation and cleavage	19
	References	24
2	Protecting groups	26
2.1	Introduction	26
2.2	Ether protecting groups	27
2.2.1	Benzyl ethers	27
2.2.2	<i>p</i> -Methoxybenzyl ethers	33
2.2.3	Allyl ethers	34
2.2.4	Triphenylmethyl ethers	37
2.2.5	Silyl ethers	38
2.3	Acetal protecting groups	41
2.3.1	Benzylidene acetals	41
2.3.2	Isopropylidene acetals	43
2.3.3	Dispirodiketal and cyclohexane-1,2-diacetal groups	45
2.4	Ester protecting groups	46
2.5	Anomeric protecting groups	49
2.6	Amino protecting groups	51
2.6.1	Phthalimides	52
2.6.2	Azides	52
	References	53
3	Functionalised saccharides	56
3.1	General introduction	56
3.2	Deoxyhalogeno sugars	56
3.2.1	Introduction	56
3.2.2	Direct halogenation of alcohols	56

3.2.3	Displacement reactions	60
3.2.4	Miscellaneous methods	63
3.3	Unsaturated sugar derivatives	65
3.3.1	Introduction	65
3.3.2	Glycals	66
3.3.3	Isolated double bonds	69
3.3.4	6-Deoxy-hex-5-enopyranose derivatives	69
3.4	Deoxy sugars	71
3.4.1	Introduction	71
3.4.2	Reduction of halides, sulfonates and epoxides	72
3.4.3	Radical deoxygenation of thiocarbonyl derivatives	74
3.5	Amino sugars	76
3.5.1	Introduction	76
3.5.2	The preparation of amino sugars by nucleophilic displacement	77
3.5.3	Addition to glycals	81
3.5.4	Reduction of oximes	82
3.5.5	Intramolecular substitutions	84
3.6	Epoxy sugars	84
3.7	Sulfated saccharides	87
3.7.1	Introduction	87
3.7.2	O and N sulfation	89
3.8	Phosphorylated saccharides	89
3.8.1	Introduction	89
3.8.2	Non-anomeric sugar phosphates	90
3.8.3	Anomeric phosphates	94
References		96

4 Oligosaccharide synthesis 103

4.1	Introduction	103
4.2	Chemical glycosidic bond synthesis	103
4.2.1	Glycosyl halides	105
4.2.2	Trichloroacetimidates	107
4.2.3	Thioglycosides	109
4.3	Stereoselective control in glycosidic bond synthesis	110
4.3.1	Neighbouring-group-assisted procedures	111
4.3.2	<i>In situ</i> anomerisation	112
4.3.3	Glycosylation with inversion of configuration	114
4.3.4	Solvent participation	118
4.3.5	Intramolecular aglycon delivery	120
4.4	Preparation of 2-amino-2-deoxy-glycosides	122
4.5	Formation of glycosides of <i>N</i> -acetyl-neuraminic acid	124
4.6	The introduction of 2-deoxy glycosidic linkages	127
4.7	Convergent block synthesis of complex oligosaccharides	131
4.8	Chemoselective glycosylations and one-pot multistep glycosylations	135
4.9	Solid-phase oligosaccharide synthesis	139
4.10	Enzymatic glycosylation strategies	144
4.10.1	Glycosyl transferases	146
4.10.2	Glycosyl hydrolases	148
References		150

5	The chemistry of <i>O</i>- and <i>N</i>-linked glycopeptides	155
5.1	Introduction	155
5.2	Strategies for the chemical synthesis of glycopeptides	156
5.3	Protecting groups in glycopeptide synthesis	160
5.4	Chemical synthesis of serine <i>O</i> -glycoside derivatives	161
5.5	The synthesis of <i>N</i> -glycopeptides	166
5.6	Solution-phase and solid-phase glycopeptide synthesis	167
5.7	Enzyme-mediated glycopeptide synthesis	171
	References	172
 PART B: NATURAL PRODUCT SYNTHESIS FROM MONOSACCHARIDES		
6	(-)-Echinospurin	175
6.1	Introduction	175
6.2	Smith's retrosynthetic analysis of (-)-echinospurin	175
6.3	Smith's (-)-echinospurin synthesis	176
6.4	Mechanistic analysis of some key reactions employed in the Smith (-)-echinospurin synthesis	181
	References	184
7	(+)-Zaragozic acid C	186
7.1	Introduction	186
7.2	Carreira's retrosynthetic analysis of (+)-zaragozic acid C	186
7.3	Carreira's total synthesis of (+)-zaragozic acid C	188
7.4	Mechanistic analysis of some of the key steps in Carreira's synthesis of (+)-zaragozic acid C	194
	References	198
8	(+)-Neocarzinostatin	200
8.1	Introduction	200
8.2	Myers' retrosynthetic planning for the synthesis of (+)-neocarzinostatin	200
8.3	Myers' total synthesis of (+)-neocarzinostatin	206
8.4	Mechanistic analysis of the key steps in Myers' (+)-neocarzinostatin synthesis	211
	References	215
9	(+)-Castanospermine	217
9.1	Introduction	217
9.2	The Pandit retrosynthetic analysis of (+)-castanospermin	217
9.3	Pandit's total synthesis of (+)-castanospermine	218
9.4	Mechanistic analysis of the Pandit synthesis of (+)-castanospermine	221
	References	222

10	(-)-Silphiperfolene	224
10.1	Introduction	224
10.2	The Fraser-Reid retrosynthetic analysis of (-)-silphiperfolene	224
10.3	Fraser-Reid's total synthesis of (-)-silphiperfolene	229
10.4	Mechanistic analysis of the Fraser-Reid (-)-silphiperfolene synthesis	232
	References	232
11	(-)-Allosamizoline	234
11.1	Introduction	234
11.2	The Kuzuhara retrosynthetic analysis of (-)-allosamizoline	235
11.3	The Kuzuhara total synthesis of (-)-allosamizoline	236
11.4	Mechanistic analysis of the Kuzuhara (-)-allosamizoline synthesis	239
11.5	Simpkins' retrosynthetic strategy for (-)-allosamizoline	239
11.6	Simpkins' total synthesis of (-)-allosamizoline	241
11.7	Mechanistic analysis of some key steps in the Simpkins (-)-allosamizoline synthesis	243
11.8	Epilogue	245
	References	245
12	(-)-Reiswigin A	247
12.1	Introduction	247
12.2	The Kim retrosynthetic analysis of (-)-reiswigin A	247
12.3	The Kim total synthesis of (-)-reiswigin A	251
12.4	Mechanistic points of interest in the (-)-reiswigin A synthesis	254
	References	257
13	(-)-Octalactin A	259
13.1	Introduction	259
13.2	The Buszek retrosynthetic analysis of (-)-octalactin A	259
13.3	Buszek's total synthesis of (-)-octalactin A	264
13.4	Items of mechanistic interest in the Buszek (-)-octalactin A synthesis	265
	References	269
14	(-)-ACRL toxin I	270
14.1	Introduction	270
14.2	The Lichtenhaler retrosynthetic analysis of (-)-ACRL toxin I	270
14.3	Lichtenhaler's total synthesis of the (-)-ACRL toxin I	273
14.4	Items of mechanistic interest in the Lichtenhaler synthesis of the (-)-ACRL toxin I	277
14.5	Epilogue	279
	References	279
15	(+)-Gabosine E	280
15.1	Introduction	280
15.2	The Lygo retrosynthetic analysis of (+)-gabosine E	280
15.3	The Lygo synthesis of (+)-gabosine E	282

15.4 Points of mechanistic interest in the Lygo (+)-gabosine E synthesis	284
References	285
16 (–)-Augustamine and (–)-amabiline	286
16.1 Introduction	286
16.2 The Pearson retrosynthetic analysis of (–)-augustamine	286
16.3 The Pearson total synthesis of (–)-augustamine	288
16.4 Pearson's synthesis of (–)-amabiline	290
16.5 Mechanistic analysis of the (–)-augustamine and (–)-amabiline syntheses	290
References	291
17 (–)-FK506	292
17.1 Introduction	292
17.2 The Danishefsky retrosynthetic analysis of (–)-FK506	292
17.3 The Danishefsky formal total synthesis of (–)-FK506	295
17.4 The Merck endgame used in the first total synthesis of (–)-FK506	302
17.5 Smith's retrosynthetic analysis of (–)-FK506	305
17.6 The Smith formal total synthesis of (–)-FK506	308
17.7 Items of interest in the Danishefsky and Smith total syntheses of (–)-FK506	317
References	326
18 (3<i>S</i>,5<i>S</i>)-5-Hydroxypiperazic acid	329
18.1 Introduction	329
18.2 The Hale retrosynthetic analysis of (3 <i>S</i> ,5 <i>S</i>)-5-hydroxypiperazic acid	329
18.3 The Hale total synthesis of (3 <i>S</i> ,5 <i>S</i>)-5-hydroxypiperazic acid	331
18.4 Points of mechanistic interest in the Hale (3 <i>S</i> ,5 <i>S</i>)-5-hydroxypiperazic acid synthesis	332
References	333
Index	334

1 Mono- and oligosaccharides: structure, configuration and conformation

G.-J. Boons

1.1 Introduction

Carbohydrates constitute the most abundant group of natural products. This fact is exemplified by the process of photosynthesis, which alone produces 4×10^{14} kg of carbohydrates each year. As their name implies, carbohydrates were originally believed to consist solely of carbon and water and thus were commonly designated by the generalised formula $C_x(H_2O)_y$. The present-day definition¹ is that 'the carbohydrates' are a much larger family of compounds, comprising monosaccharides, oligosaccharides and polysaccharides, of which monosaccharides are the simplest compounds, as they cannot be hydrolysed further to smaller constituent units. Furthermore, the family comprises substances derived from monosaccharides by reduction of the anomeric carbonyl group (alditols), oxidation of one or more terminal groups to carboxylic acids or replacement of one or more hydroxyl group(s) by a hydrogen, amino or thiol group or a similar heteroatomic functionality. Carbohydrates can also be covalently linked to other biopolymers, such as lipids (glycolipids) and proteins (glycoproteins).

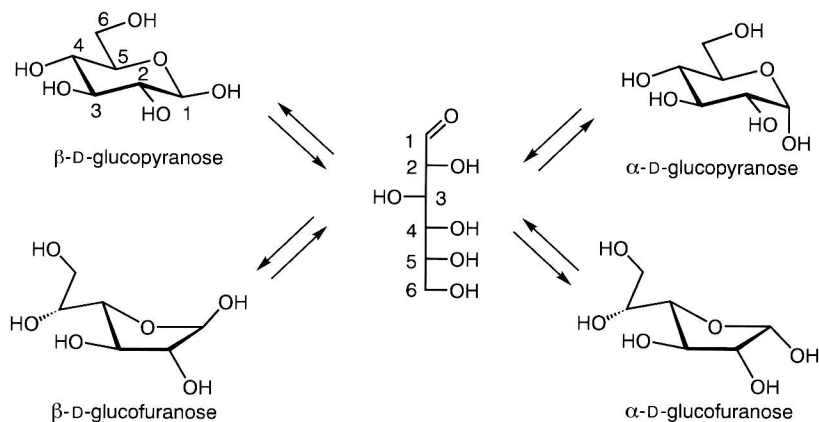
Carbohydrates are the main source of energy supply in most cells. Furthermore, polysaccharides such as cellulose, pectin and xylan determine the structure of plants. Chitin is a major component of the exoskeleton of insects, crabs and lobsters. Apart from these structural and energy storage roles, saccharides are involved in a wide range of biological processes. In 1952, Watkins disclosed that the major blood group antigens are composed of oligosaccharides.² Carbohydrates are now implicated in a wide range of processes³ such as cell-cell recognition, fertilisation, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organisation into specific tissues, viral and bacterial infections and tumour cell metastasis. It is not surprising that saccharides are key biological molecules since by virtue of the various glycosidic combinations possible they have potentially a very high information content.⁴

In this chapter, the configurational, conformational and dynamic properties of mono- and oligosaccharides will be discussed and, in general, reference is made to reviews that cover these aspects. These

properties, as described in the discussion which follows, are not placed in a historical context.

1.2 Configuration of monosaccharides^{5,6}

Monosaccharides are chiral polyhydroxy carbonyl compounds, which often exist in a cyclic hemiacetal form. Monosaccharides can be divided into two main groups according to whether their acyclic form possesses an aldehyde (aldoses) or keto group (ketoses). These, in turn, are further classified, according to the number of carbon atoms in the monomeric chain (3–10) into trioses, tetroses, pentoses, hexoses, etc. and the types of functionalities that are present. D-Glucose is the most abundant monosaccharide found in nature and has been studied in more detail than any other member of the family. D-Glucose exists in solution as a mixture of isomers. The linear form of glucose is energetically unfavourable relative to the cyclic hemiacetal forms. Ring closure to the pyranose form occurs by nucleophilic attack of the C(5) hydroxyl on the carbonyl carbon atom of the acyclic species (Scheme 1.1). Hemiacetal



Scheme 1.1 Different forms of D-glucose.

ring formation generates a new asymmetric carbon atom at C(1), the anomeric centre, thereby giving rise to diastereoisomeric hemiacetals which are named α and β anomers depending on whether the C(1) substituent resides on the bottom or top of the sugar ring. Cyclisation involving O(4) rather than O(5) results in a five-membered ring structurally akin to furan and is therefore designated as a furanose.

Accordingly, the six-membered pyran-like monosaccharides are termed pyranoses.

All the common hexoses contain four asymmetric centres in their linear form and therefore 2^4 (16) stereoisomers exist which can be grouped into eight pairs of enantiomers. The pairs of enantiomers are classified as D and L sugars. In the D sugars the highest numbered asymmetric hydroxyl group [C(5) in glucose] has the same configuration as the asymmetric centre in D-glyceraldehyde and, likewise, for all L sugars the configuration is that of L-glyceraldehyde (Figure 1.1). The acyclic and pyranose forms of the D-aldoses are depicted in Figures 1.2 and 1.3, respectively.

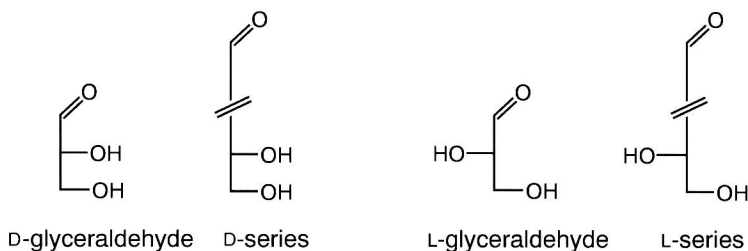


Figure 1.1 D and L sugars.

Monosaccharides have been projected in several ways, the Fischer projection being the oldest (Figure 1.4). In the Fischer projection, the monosaccharides are depicted in an acyclic form and the carbon chain is drawn vertically, with the carbonyl group (or nearest group to the carbonyl) at the top. Each carbon atom is rotated around its vertical axis until all of the C—C bonds lie below a curved imaginary plane. It is only when the projection of this plane is flattened that it can be termed a Fischer projection. In the α anomer the exocyclic oxygen atom at the anomeric centre is formally *cis*, in the Fischer projection, to the oxygen of the highest-numbered chiral centre [C(5) in glucose]; in the β anomer the oxygens are formally *trans*.

Haworth introduced his formula to give a more realistic picture of the cyclic forms of sugars. The rings are derived from the linear form and drawn as lying perpendicular to the paper with the ring oxygen away from the viewer and are observed obliquely from above. The chair conformation gives a much more accurate representation of the molecular shape of most saccharides and is the preferred way of drawing these compounds. It has to be noted that the Mills formula and zig-zag depiction are particularly useful for revealing the stereochemistry of the carbon centres of the sugars.

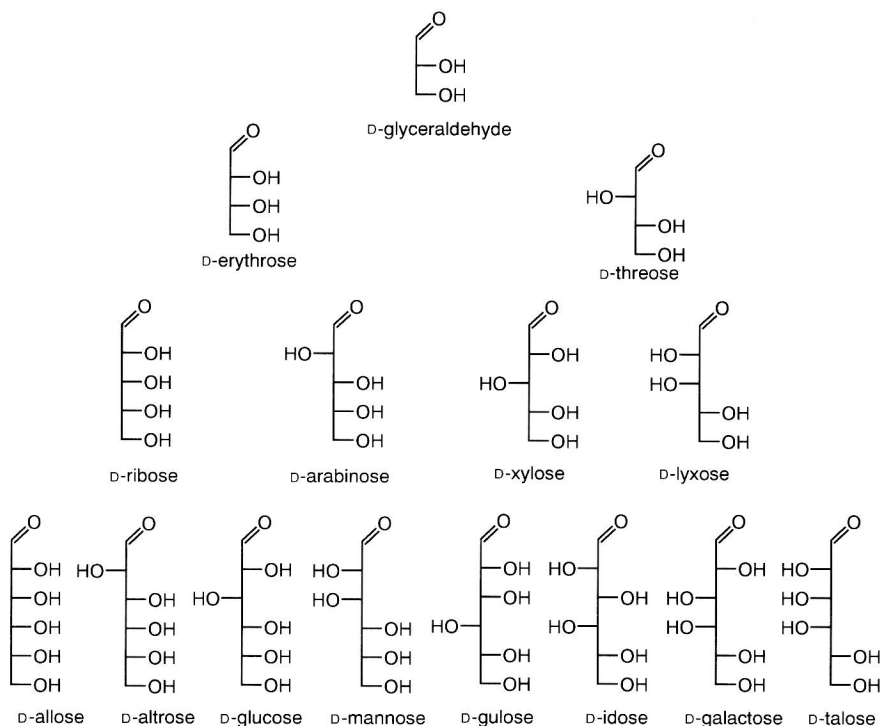


Figure 1.2 Acyclic forms of the D-aldoses.

Apart from the monosaccharides depicted in Figure 1.3, many other types are known. Several natural occurring monosaccharides have more than six carbon atoms and these compounds are named the higher carbon sugars. L-Glycero-D-manno-heptose is such a sugar and is an important constituent of lipopolysaccharides (LPS) of Gram-negative bacteria (Figure 1.5).

Some saccharides are branched and these types are found as constituents of various natural products. For example, D-apiose occurs widely in plant polysaccharides. Antibiotics produced by the micro-organism *Streptomyces* are another rich source of branched chain sugars.

As already mentioned, the ketoses are an important class of sugars. Ketoses or uloses are isomers of the aldoses but with the carbonyl group occurring at a secondary position. In principle, the keto group can be at each position of the sugar chain, but in naturally occurring ketoses the keto group, with a very few exceptions, is normally at the 2-position. D-Fructose is the most abundant ketose and adopts mainly the pyranose form.

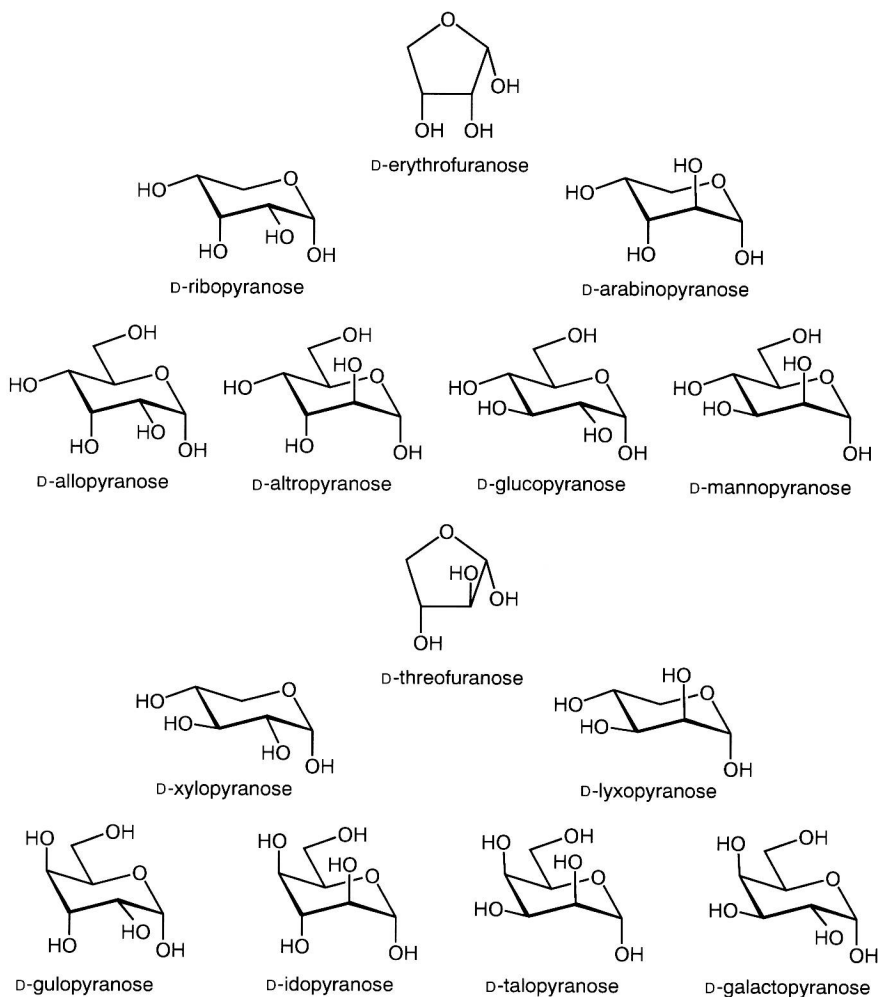


Figure 1.3 Cyclic forms of α -D-aldoses.

The uronic acids are aldoses that contain a carboxylic acid group as the chain-terminating function. They occur in nature as important constituents of many polysaccharides. The ketoaldonic acids are another group of acidic monosaccharides, and notable compounds of this class are 3-deoxy-D-manno-2-octulosonic acid (Kdo) and *N*-acetyl neuraminic acid (Neu5Ac). Kdo is a constituent of LPS of Gram-negative bacteria and links an antigenic oligosaccharide to Lipid A. *N*-Acetyl-neuraminic acid is found in many animal and bacterial polysaccharides and is critically involved in a host of biological processes.