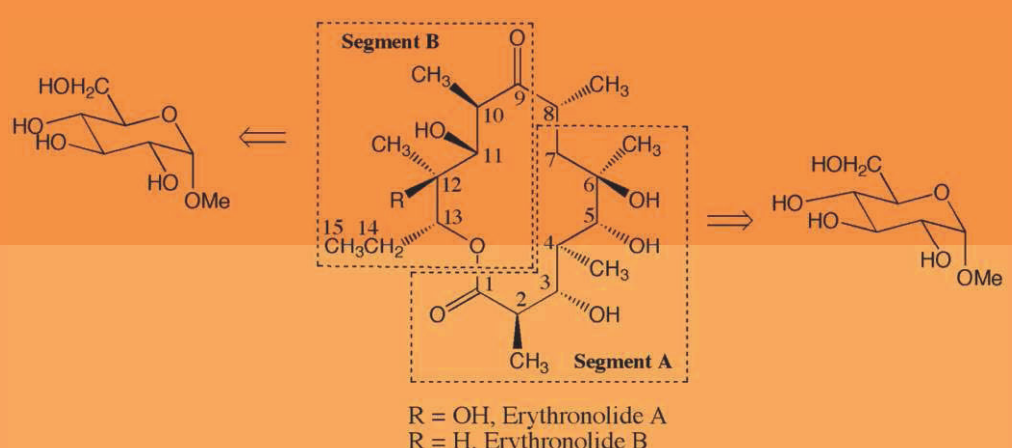
Momčilo Miljković

Carbohydrates

Synthesis, Mechanisms, and Stereoelectronic Effects



Springer

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Synthesis, Mechanisms, and Stereoelectronic Effects

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ISBN 978-0-387-92264-5 e-ISBN 978-0-387-92265-2
DOI 10.1007/978-0-387-92265-2
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2009933276

Dedicated to the memory of Professors Milivoje S. Lozanić and Djordje Stefanović University of Belgrade, Serbia

Foreword

The development of organic chemistry over the last 40 years has been absolutely phenomenal, particularly the deepened understanding of chemical reactivity, molecular construction, and tools for analysis and purification. Without doubt, carbohydrate chemistry has played a major role in this historic advance and in the future will have crucial ramifications in most areas of biomedical research into the functioning of Nature at the molecular level.

This book covers all basic carbohydrate chemistry, including most important synthetic methods and reaction mechanisms and notably takes into account the principle of stereoelectronic effect which has played a key role in understanding the conformation and chemical reactivity of this important class of natural product. Even nomenclature has been properly covered and it is fair to say that all the key references of carbohydrates have been cited. Such a book could only have been written by an expert who has spent his entire research career in this area.

This book of Momčilo Miljković will be of interest not only to specialists in the field, but also to synthetic chemists in general. This book also contains most of the material needed for a graduate course in carbohydrate chemistry. Furthermore, it should be particularly valuable for investigators working in various aspects of bioorganic chemistry including the discovery of new medicines.

Quebec, Canada — Pierre Deslongchamps, FRS, FRSC

Preface

Carbohydrates are one of the three most important components of living cells (the other two being amino acids and lipids). In order to understand their biochemical behavior one must understand steric and electronic factors that control their reactivity and chemistry. Two properties of carbohydrates that are most important for their chemical behavior are their shape (conformation) and stereoelectronic interactions that are unique and characteristic for each carbohydrate structure.

So chapters on anomeric effect, a very important electronic effect first discovered in studies of carbohydrates and later found to be of general importance in many other organic molecules, glycosidic bond hydrolysis, isomerization of free carbohydrates in aqueous solution, relative reactivity of hydroxyl groups in a carbohydrate molecule, nucleophilic displacement with or without change of the configuration at the reacting carbon atom, addition of nucleophiles to glycopyranosiduloses, etc., are all to a various extent related to stereoelectronic effects that exist in carbohydrate structures.

Cyclic acetals and ketals and anhydrosugars are both very important intermediates in synthetic carbohydrate chemistry, first being used for protection of hydroxyl groups that are not supposed to take part in further chemical transformation of the intermediate and second being used as synthetic intermediates in carbohydrate chemistry because they can serve as starting materials for the synthesis of many different carbohydrate derivatives, for example, the amino sugars, the branched chain sugars, oligosaccharides. The amino sugars, being important components of many biomolecules such as glycosaminoglycans, heparin, chondroitin as well as many natural products, such as sugar-based antibiotics, macrolide antibiotics, are discussed in a separate chapter.

The last three chapters of the book deal with topics not usually found in carbohydrate chemistry texts like this one, although according to the author's opinion they are very important and they are unjustly neglected. These are carbohydrate-based antibiotics, synthesis of polychiral natural products from carbohydrates, and chemistry of higher-carbon carbohydrates.

Much attention has been paid to the mechanisms of various carbohydrate reactions as well as to the role of stereoelectronic effects that they play in the reactivity of carbohydrates and the stereochemical outcome of various carbohydrate reactions.

In the end, I wish to express my deep gratitude to Professor Pierre Deslongchamps for taking time to read the entire book and provide me with invaluable comments and critique. I would also like to thank my wife, Irina Miljković, for her patience and understanding throughout my scientific life.

Contents

Chapter 1
Introduction

Monosaccharides are polyhydroxy aldehydes or ketones having four to nine carbon atoms in their carbon chains – most often, five or six (Fig. 1.1).

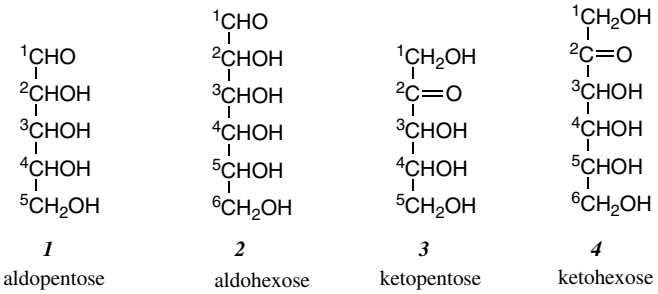


Fig. 1.1

Depending on the number of carbon atoms in their skeleton, monosaccharides are named tetroses (four carbon atoms), pentoses (five carbon atoms), hexoses (six carbon atoms), heptoses (seven carbon atoms), etc., and depending on the nature of their carbonyl group, they are named *aldoses* (when their carbonyl group is an aldehydo group) or *ketoses* (when their carbonyl group is a keto group). Hence, there are aldo-tetroses, aldopentoses, aldo-hexoses, aldo-heptoses, etc. and keto-tetroses, keto-pentoses, keto-hexoses, keto-heptoses, etc.

The simplest monosaccharides consist of carbon, hydrogen, and oxygen and have the general molecular formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ (hence the name *carbohydrates – hydrates* of carbon). However, they may often have fewer hydrogen and/or oxygen atoms or more oxygen atoms than required by the above general formula (e.g., unsaturated sugars, deoxy sugars, aldonic acids, uronic acids, aldaric acids), or they may also contain, in addition to carbon, hydrogen and, oxygen atoms, other elements such as nitrogen, sulfur, halogen.

The carbon atoms of a monosaccharide chain are numbered in such a way that the carbonyl carbon has always the lowest possible number, i.e., # **1** in aldoses (since the aldehydo group always occupies the terminal position) and # **2** (or higher) in ketoses (since the keto-group can occupy any position in a carbohydrate chain, except the terminal position).

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_1,

Stereochemistry

Monosaccharides are *polychiral* molecules, i.e., they have two or more chiral carbon atoms in their skeleton, which are most often, but not always, hydroxymethylene carbons. The term *chiral* carbon (from the Greek word *chiros* = *hand*) has replaced the older term *asymmetric* carbon for practical reasons [1]. The configuration of the highest numbered chiral carbon of a monosaccharide (i.e., the chiral carbon) that is furthest away from the carbonyl (*anomeric*) carbon determines whether the monosaccharide belongs to a D- or to an L-series (Fig. 1.2). If the configuration of this carbon (e.g., *5* in Fig. 1.2) is identical to the configuration of D-glyceraldehyde (*6* in Fig. 1.2), the monosaccharide belongs to D-series; if it is identical to the configuration of L-glyceraldehyde (*8* in Fig. 1.2), the monosaccharide belongs to L-series (*7* in Fig. 1.2).

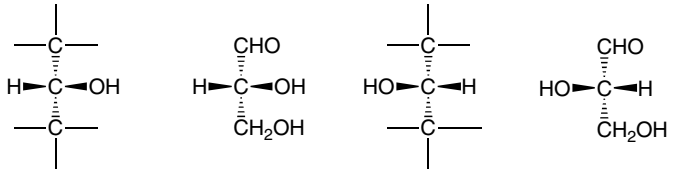


Fig. 1.2

Structures in Fig. 1.2 are drawn in a special way: the chiral carbon is placed in the plane of the paper so that the heavy tapered horizontal lines are projected above the plane of the paper (toward an onlooker) and represent the valences linking a chiral carbon to its substituents (H, OH, etc.); the vertical dotted tapered lines are projected below the plane of the drawing (away from an onlooker) and represent the valences linking that chiral carbon to the two neighboring carbon atoms of a carbohydrate carbon chain (vide infra).

Representation of Monosaccharides

Acyclic Form of Monosaccharides

In 1891 Emil Fischer [2] proposed an ingenious method for accurate two-dimensional representation of polychiral monosaccharide molecules by projecting their three-dimensional structures onto the plane of paper. In order to draw these, so-called, *Fischer's projections*, the following rules must be observed. A chiral carbon atom of a monosaccharide carbon chain must be placed in the plane of paper, with the two neighboring carbons that are *positioned below the plane of the paper*, i.e., away from an onlooker projected on a vertical line. The hydrogen atom and the hydroxyl group positioned *above the plane of paper* and toward an onlooker are

projected on a horizontal line as illustrated for D- and L-glyceraldehyde in Fig. 1.3. So the vertical line contains the chiral carbon and the two adjacent carbon atoms of a monosaccharide chain, whereas the horizontal line that is perpendicular to the vertical line contains the chiral carbon and its two substituents: the hydroxyl group and the hydrogen atom. The chiral carbon lies at the intersection of these two perpendicular lines, and it is customary not to write the symbol for this carbon. This operation has to be repeated for each chiral carbon up or down the monosaccharide chain in exactly the same manner as described above. The result of these operations is an

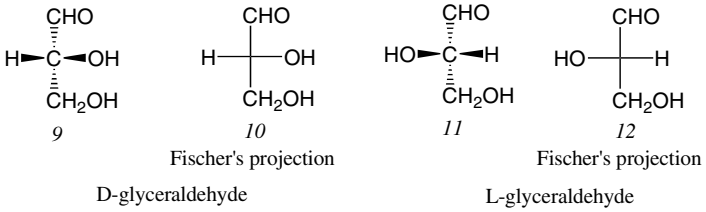


Fig. 1.3

elongated vertical line intersected by two or more perpendicular horizontal lines, whose number depends on the length of a monosaccharide chain (tetrose, pentose, hexose, etc.).

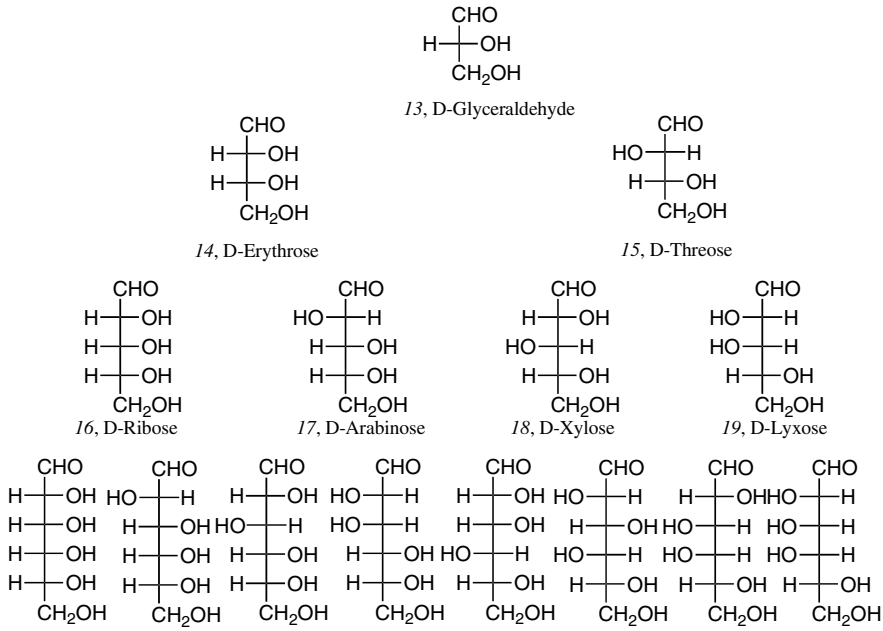


Fig. 1.4

At the intersections of vertical and horizontal lines lie the chiral carbons and at the end of horizontal lines are placed ligands (hydrogen atoms, hydroxyl groups, amino group, etc.). The Fischer projection must be so oriented that the *anomeric* (carbonyl) carbon is always at the top (or near the top) of the vertical line, whereas the hydroxymethyl group is at the bottom. Figure 1.4 illustrates Fischer projections of aldoses in their *acyclic* (*aldehydo*) forms having three to six carbon atoms in their carbon skeleton. Only D-forms are shown; the L-forms are the mirror images of shown Fisher projections.

If transposition of a substituent must be performed in order to compare the Fischer projections of different stereoisomers, a number of rules must be obeyed, or otherwise the configurational change may take place and erroneous conclusions may be drawn.

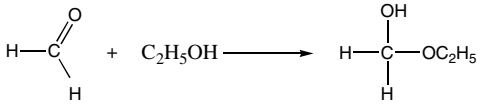
1. The Fischer projection must never be taken out of the plane of drawing for manipulation, since this operation may result in change of the configuration of chiral carbons.
2. The rotation of a Fischer projection in the plane of drawing by 180° does not change the configuration of chiral carbons in a molecule.
3. The rotation of a Fischer projection in plane of drawing by 90° converts a given chiral carbon to its enantiomer.
4. One interchange of two chiral carbon ligands converts that chiral carbon to its enantiomer.
5. Two consecutive interchanges of two pairs of ligands do not change the configuration of that carbon

Cyclic Forms of Monosaccharides

The existence of cyclic forms of sugars was recognized very early because some of the observed chemistry of monosaccharides could not be explained by the open-chain structure. Thus, the acetylation of aldoses gave two isomeric penta-*O*-acetyl derivatives [3, 4] whereas the acyclic form should give only one penta-*O*-acetyl derivative. The reaction of methanolic hydrogen chloride with aldoses produced two isomeric mono-methoxy derivatives; so these compounds were not dimethyl acetals [5]. Further, the reactivity of the aldehydo group of aldoses was unusually low. For example, aldoses do not react with Schiff reagent (fuchsin-sulfurous acid), a reaction typical for aldehydes [6] except under special conditions and with a specially adjusted reagent [7, 8]. Finally, Tanret was able to isolate two forms of D-glucose that interconverted in aqueous solution [9].

The unusually low reactivity of the carbonyl group of aldoses is explained by Tollens [10] by postulating cyclic structure, and proposed, without any proof, the existence of tetrahydrofuran ring. Haworth later corrected this tetrahydrofuran formula [11] to a tetrahydropyran and introduced a new way for representation of cyclic structures (vide infra).

This early conclusion that monosaccharides exist in cyclic form was fully substantiated a half century later. In 1949, it was determined that the molar heat of reaction of gaseous monomeric formaldehyde (*28*) with alcohol vapors (*29*) is about 14.8 kcal/mol [12], indicating that in mixtures of alcohols and carbonyl compounds there indeed exist a strong tendency for the formation of hemiacetal structure (*30*). Contrary to expectation that substitution of a hydrogen atom of formaldehyde with a larger group would hinder the hemiacetal formation, due to steric reasons, the trichloroacetaldehyde (chloral) that contains a large trichloromethyl



28 *29* *30*

Fig. 1.5

group, forms a very stable hemiacetal. Further, both, the 4-hydroxybutanal and the 5-hydroxypentanal exist predominantly as cyclic hemiacetals (*lactols*) [13] suggesting that there is indeed a strong driving force for the hemiacetal formation in mixtures of alcohols and aldehydes or ketones [14] (Figs. 1.5, 1.6).

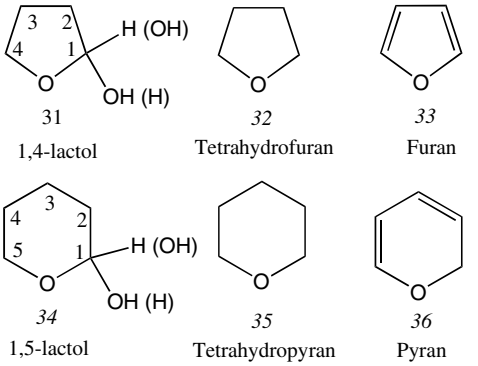


Fig. 1.6

It is therefore no surprise that intramolecular formation of hemiacetal (*lactol*) ring is so much favored in aqueous solutions of free monosaccharides since they have in the same molecule both the electrophilic *anomeric* (carbonyl) carbon and the C4 and/or the C5 nucleophilic hydroxyl groups. It has been polarographically determined that an aqueous solution of D-glucose (at pH = 6.9) contains, at equilibrium, only 0.0026% of the acyclic (aldehydo) form; the rest of the sugar is in cyclic (lactol) form [15].

The addition of C4 hydroxyl group to the anomeric carbonyl carbon of an acyclic aldose results in the formation of a five-membered ring, whereas the addition of C5 hydroxyl group to the anomeric carbonyl carbon of an acyclic aldose results in the

formation of a six-membered ring. In Fig. 1.7, the cyclic forms of monosaccharides are represented using Fischer projections.

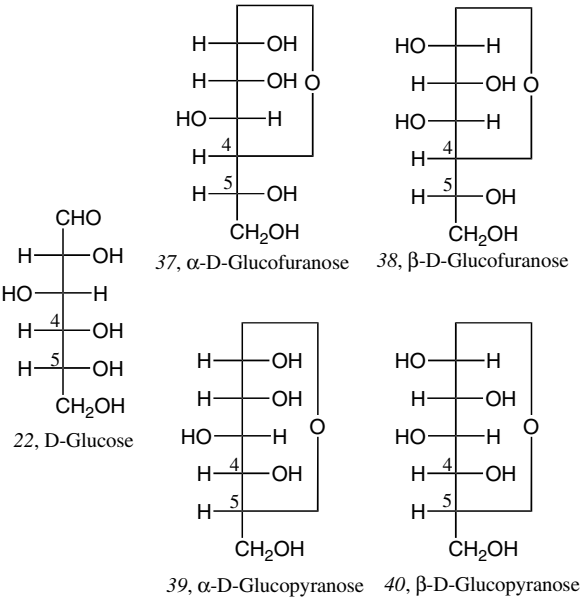


Fig. 1.7

Haworth proposed the terms *furanoses* and *pyranoses* [11] for these two monosaccharide forms due to their apparent similarity to furan and pyran molecules (Fig. 1.6) and at the same time introduced also a different way of representing the cyclic structures of monosaccharides.

In Fig. 1.8, the two cyclic forms of D-glucose are represented with the so-called *Haworth projection* formulae (β-D-glucopyranose *41* and α-D-glucofuranose *42*), which are still in use today despite their serious and obvious shortcomings (in these representations the carbon valence angle of 109° is totally ignored since the C–C bond angles in carbohydrate ring are 120°, and the C–H and the C–OH bond angles

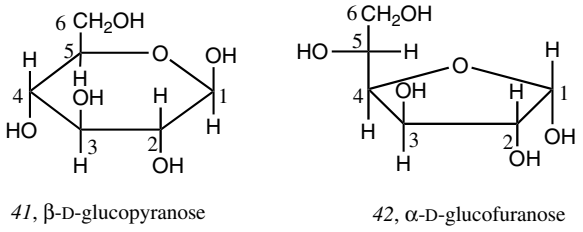
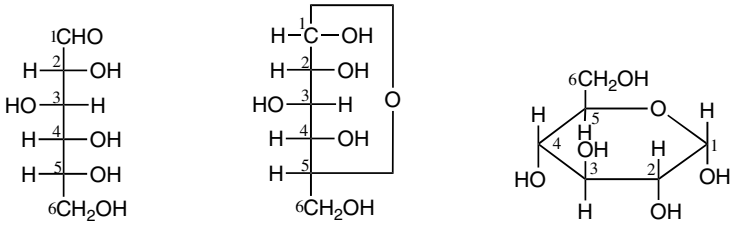


Fig. 1.8

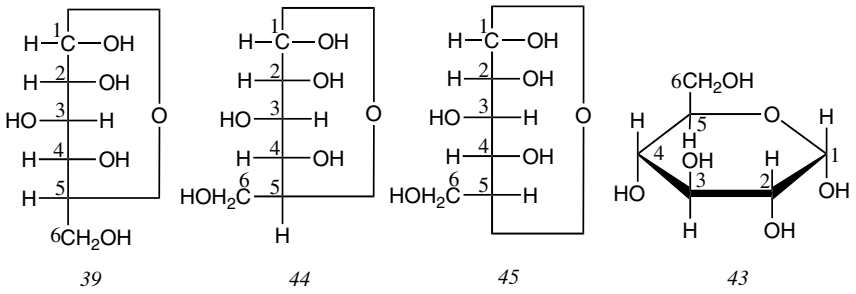
are 90°). However, Haworth, like Fischer before him, never intended to represent the actual shape of a molecule, but rather to accurately describe the configurations of individual chiral carbons and their configurational relationships. In Fig. 1.9, D-glucose is represented in the acyclic form *22*, in the cyclic pyranose form using Fischer projection *39*, and in the cyclic pyranose form using Haworth projection *43*. It is obvious that the Haworth projection of cyclic pyranoses has fewer shortcomings than Fischer projection, but it is nevertheless still very far from realistic representation.



22, aldehydo D-Glucose *39*, α-D-glucopyranose Fischer Projection *43*, α-D-glucopyranose Haworth Projection

Fig. 1.9

The Haworth projection can be obtained from a Fischer projection in the following way. The C5 hydrogen exchange with the C5 hydroxymethyl group of α-D-glucopyranose written as Fischer projection (*39* in Fig. 1.10) will produce *44* (Fig. 1.10), whereas the C5 hydrogen exchange with the C5 ring oxygen will produce *45* (Fig. 1.10). Since described operation consisted of two consecutive sub-



39 *44* *45* *43*

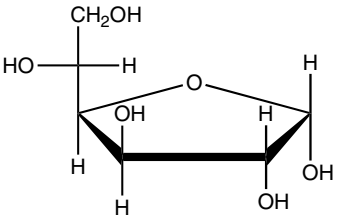
Fig. 1.10

stituent exchanges at the C5 carbon atom, the configuration of the C5 carbon atom did not change (vide supra, Rule 4 in handling the Fischer projections). In this way, the Fischer projection *39* is easily converted into Haworth projection *43*.

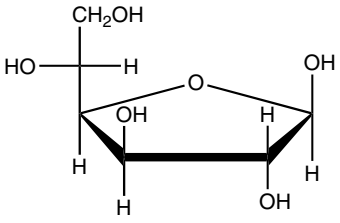
In Haworth projection the six-membered pyranose ring is written in such a way that the plane of the *planar* six-membered ring is positioned perpendicularly to the plane of paper with carbon atoms 1 and 4 lying in the plain of paper. The ring

oxygen and the C5 carbon are placed behind the plane of paper so that the ring oxygen is placed on the right and the C5 carbon on the left side; the C2 and C3 carbons are projected above the plain of the paper. The C1–C2–C3–C4 bonds are represented with heavy lines (indicating that they are closer to an onlooker) and the C1–O5–C5–C4 bonds are represented with lighter lines (indicating that they are away from an onlooker). Ligands that are in the Fischer projection on the right-hand side from the vertical line representing the carbon skeleton are written in Haworth projection below the plane of the six-membered pyranose ring, and the ligands that are, in Fischer projection, on the left-hand side from the vertical line representing the carbon skeleton of a monosaccharide are written above the six-membered pyranose ring of Haworth projection (*45* and *43* in Fig. 1.10).

The Haworth projection of furanose form of a monosaccharide is obtained from Fischer projections similarly to pyranoses, namely the planar five-membered ring is again positioned perpendicularly to the plane of paper with the C1 and the C4 carbon atoms lying in the plane of a paper. The carbon atoms 2 and 3 are placed above the plane of the paper whereas the ring oxygen is placed behind the plane of the paper. The atoms positioned above the plane of the paper are connected with heavy lines (C1–C2–C3–C4 bonds) indicating that they are oriented toward an onlooker; C1–O5–C4 bonds are represented with lighter lines indicating that they are positioned behind the plane of the paper, and away from an onlooker (see Fig. 1.11). The ligands that are in the Fischer projection positioned on the right-hand side from the vertical line representing the carbon skeleton of a monosaccharide are again written in Haworth projection below the furanose five-membered ring, and the ligands that are in the Fischer projection positioned on the left-hand side from the vertical line representing the carbon skeleton of a monosaccharide are written in Haworth projection above the furanose five-membered ring (Fig. 1.11)



42, α-D-Glucofuranose



46, β-D-Glucofuranose

Fig. 1.11

The conversion of the Fischer projection of a furanose to Haworth projection is accomplished similarly as described for pyranoses, just the two consecutive substituent exchanges are taking place at the C4 carbon atom of the monosaccharide chain.

The cyclization of an acyclic sugar, in addition of converting the acyclic chain of a polyhydroxy aldehyde or ketone into a five-membered tetrahydrofuran or six-membered tetrahydropyran ring, introduces yet another very important structural

change in a monosaccharide molecule and that is that the achiral carbonyl carbon becomes a chiral *hemiacetal* (*lactol*) carbon, adding thus two more stereoisomers to the parent monosaccharide. These two stereoisomers are called *anomers* and are referred to as α- and β-isomers.

The configuration of this new chiral carbon, the anomeric carbon, is determined by the orientation of its hydroxyl group with regard to the orientation of hydroxyl group at the highest numbered chiral carbon in Fischer's projection (Fig. 1.7). If the two oxygen atoms are positioned on the same side relative to the vertical line representing the carbon skeleton (*cis*), the anomer is α (*37*); if they are positioned on the opposite side (*trans*), it is β (*38*). It should be noted that the ring oxygen, although written in Fischer projection in the middle of a long line shaped like a rectangle and connecting the C5 and the C1 carbon atoms is nevertheless the oxygen linked to the highest numbered chiral carbon of D-glycopyranose (C5), and it is projected to the right of the vertical line (carbon chain).

The Nomenclature of Carbohydrates

For a comprehensive description of the nomenclature of carbohydrates, see Reference [16].

The nomenclature described here is based on these rules, but it is significantly abbreviated and limited only to monosaccharides and some of their derivatives.

Trivial Names

The trivial names of the acyclic aldoses with three, four, five, or six carbon atoms are preferred to their systematic (IUPAC) names. The trivial names of most common aldoses are

Triose: glyceraldehyde
Tetroses: erythrose, threose
Pentoses: ribose, arabinose, xylose, lyxose
Hexoses: allose, altrose, glucose, mannose, gulose, idose, galactose, talose

Stem and Systematic Names

The *stem name* indicates the *length of the carbon chain of a monosaccharide*. Thus the acyclic aldoses having three, four, five, six, seven, eight, nine, ten, etc., carbon atoms in the chain are *triose, tetrose, pentose, hexose, heptose, octose, nonose, decose, etc.*

The *stem names* of the acyclic ketoses having four, five, six, seven, eight, nine, ten, etc. carbon atoms in the chain are *tetrulose, pentulose, hexulose, heptulose, octulose, nonulose, deculose, etc. Systematic names* are formed from a stem name and a configurational prefix, which are always written in italicized lower case letters.

Each prefix is preceded by configurational symbol D or L. Configurational prefixes are obtained from trivial names of sugars by omitting the ending -se. Examples: D-*ribo*-pentose for D-ribose; D-galacto-hexose for D-galactose.

Conventions

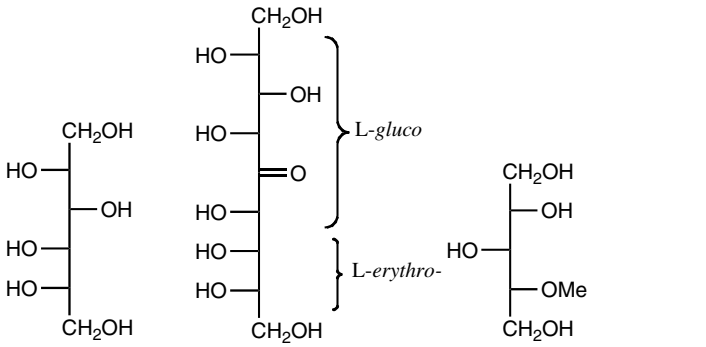
The following abbreviations are commonly used for substituents in carbohydrate structures: Ac (acetyl), Bn (benzyl), Bz (benzoyl), Et (ethyl), Me (methyl), Me_3Si (trimethylsilyl), Ms (mesyl = methanesulfonyl), Ph (phenyl). Tf (triflyl = trifluoromethanesulfonyl), Tr (trityl = triphenylmethyl), Ts (tosyl = *p*-toluenesulfonyl).

Choice of Parent Monosaccharides

In cases where more than one monosaccharide structure is embedded in a larger molecule, a *parent structure* is chosen on the basis of the following *order of preference*.

(a) The *parent* with the greatest number of carbon atoms in the chain has the preference, e.g., heptose rather than hexose.
(b) The *parent*, of which: the first letter of the trivial name or of the configurational prefix occurs earliest in the alphabet (e.g., *47* in Fig. 1.12). If two possible parents have the same initial letter, then the choice will be made according to the letter at the first point of difference in the trivial name. Examples: allose before altrose, galactose before glucose, glucose before gulose and mannose, *allo*- before *altro*-, *gluco*- before *gulo*- (*47* in Fig. 1.12).
(c) The configurational symbol D- before L- (*49* in Fig. 1.12).
(d) The anomeric symbol α- before β-

Examples:



47, L-Glucitol not D-gulitol

48, L-*erythro*-L-*gluco*-Non-5-ulose not D-threo-D-allo-Non-5-ulose

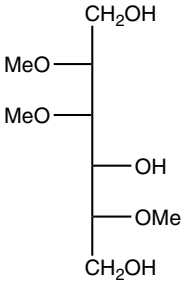
49, 4-O-Methyl-D-xylitol not 2-O-Methyl-L-xylitol

Fig. 1.12

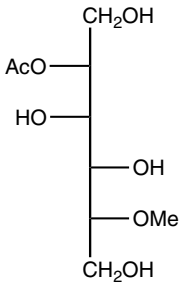
Choice Between Alternative Names for Substituted Derivatives

When the parent structure is symmetrical, preference between alternative names for derivatives should be given according to the following criteria, taken in order:

(a) The name that includes the configurational symbol D rather than L as is for example shown with *49* in Fig. 1.12.
(b) The name that gives the lowest set of locants to the substituents present (see 50 in Fig. 1.13)



50, 2, 3, 5-Tri-O-methyl-D-mannitol
not 2, 4, 5-Tri-O-methyl-D-mannitol



51, 2-O-Acetyl-5-O-methyl-D-mannitol
not 5-O-acetyl-2-O-methyl-D-mannitol

Fig. 1.13

Configurational Symbols and Prefixes

Configurational prefixes are given in Figs. 1.14 and 1.15.

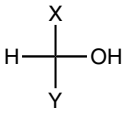
Each prefix is D or L according to whether the configuration at the reference carbon atom in the Fischer projection is the same as, or opposite of, that in D(+)-glyceraldehyde. Only Fischer projections of D-prefixes are given above; X is the group with the lowest numbered carbon atom.

The configuration of >CHOH group or a set of two, three, or four contiguous >CHOH groups (fully or partially derivatized, such as >CHOMe, >CHOAc, etc., or fully substituted hydroxyl groups, such as $>CHNH_2$, >CHCl) are designated by one of the following configurational prefixes which are derived from the trivial names of the aldoses (Fig. 1.14 and 1.15).

A monosaccharide is assigned to the D or to the L series according to configuration of the highest numbered chiral carbon atom (configurational carbon atom). This was discussed earlier (vide supra).

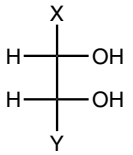
Configurational classification is denoted by the symbols D and L which in print will be small capital roman letters and which are unrelated to terms *dextro* and *levo* that denote the sign of optical rotation of a sugar. Racemic forms are indicated by DL. Such symbols are affixed by a hyphen immediately before the monosaccharide trivial name. If the sign of optical rotation is to be indicated, this is done by adding

One >CHOH group

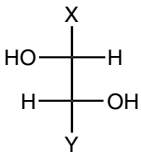


52, D-*glycero*

Two >CHOH groups

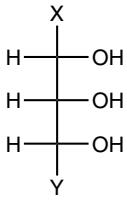


53, D-*erythro*

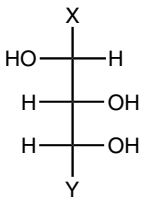


54, D-*threo*

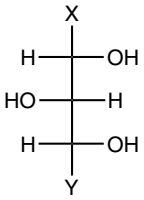
Three >CHOH groups



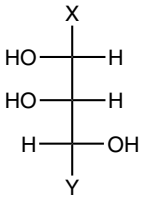
55, D-*ribo*-



56, D-*arabino*-



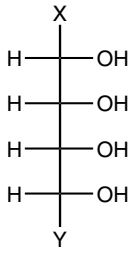
57, D-*xylo*-



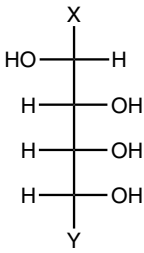
58, D-*lyxo*-

Fig. 1.14

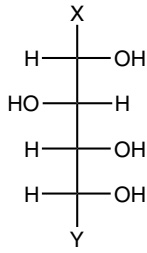
Four >CHOH groups



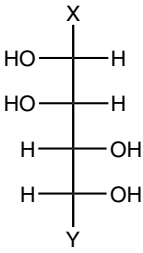
59, D-*allo*-



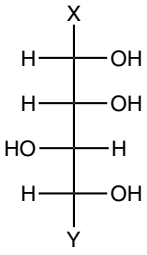
60, D-*altro*-



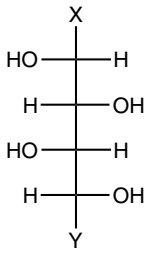
61, D-*gluco*-



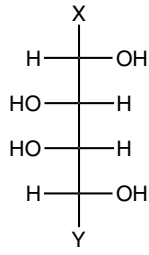
62, D-*manno*-



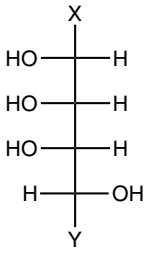
63, D-*gulo*-



64, D-*ido*-



65, D-*galacto*-

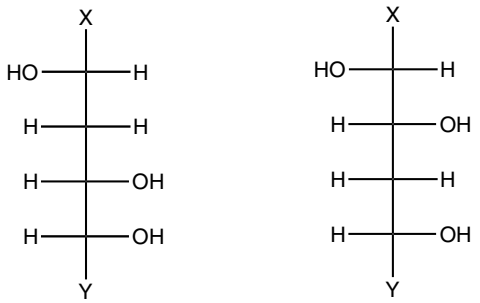


66, D-*talo*-

Fig. 1.15

(+) or (–) immediately after the configurational symbols D and L. Racemic forms may be indicated by (±). Examples: D-glucose or D (+)-glucose, D-fructose or D (–)-fructose, DL-glucose or (±)-glucose.

When monosaccharides have a plane of symmetry as a consequence of which they are optically inactive, the prefix *meso* is used where appropriate.



67 *68*

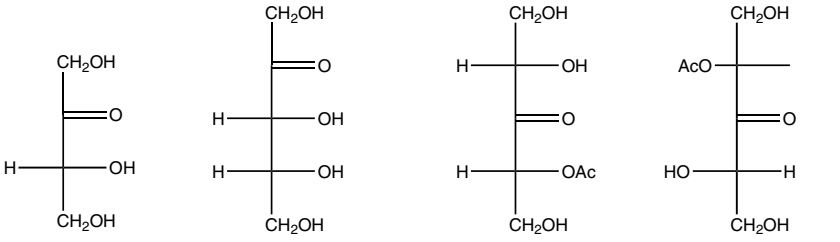
both D-*arabino*

Fig. 1.16

The monosaccharides that have a sequence of consecutive but not contiguous chiral carbons are named so that the interrupting achiral carbons are ignored as if they are not there (for examples see Fig. 1.16). The achiral carbon can be methylene carbon (as in case of deoxy-sugar), but it can also be a keto group of a ketose containing not more than four chiral carbons (see Fig. 1.17).

Ketoses

Ketoses are classified as 2-ketoses, 3-ketoses, etc., according to the position of the carbonyl or potential carbonyl group. When the carbonyl group is at the middle



69 D-*glycero*-2-tetrulose

70 D-*erythro*-2-pentulose

71 4-O-acetyl-D-*erythro*-3-pentulose

72 2-O-acetyl-L-*erythro*-3-pentulose

Fig. 1.17

carbon atom of a ketose containing an uneven number of carbon atoms in the chain, two names are possible. The name that will be selected must be in accordance with the order of precedence given in rule on *parent names*. For example, the rotation by 180° of the 4-*O*-acetyl-D-*erythro*-3-pentulose (*71*, Fig. 1.17) in the plane of the paper will give the 2-*O*-acetyl-L-*erythro*-3-pentulose *(72*, Fig. 1.17). However, the 4-*O*-acetyl-D-*erythro*-3-pentulose will be the correct name for this ketose, since the prefix D has the preference over the prefix L. Some other examples for naming ketoses are given in Fig. 1.17.

Deoxy-monosaccharides

The replacement of an alcoholic hydroxyl group of a monosaccharide, or a monosaccharide derivative, by a hydrogen atom is expressed by using the prefix *deoxy*, preceded by the locant and followed by a stem or trivial name separated by a hyphen. The stem name must include configurational prefixes necessary to describe the configurations of the chiral carbons present in the deoxy-compound. The order of citation of the configurational prefixes starts at the end farthest from the carbon atom number one (See Fig. 1.15). "Deoxy" is regarded as a detachable prefix, i.e., it is placed in alphabetical order with other substituent prefixes – for example, acetyl before anhydro, benzyl before benzoyl, deoxy before fluoro. Several examples for naming deoxy sugars are given in Fig. 1.18.

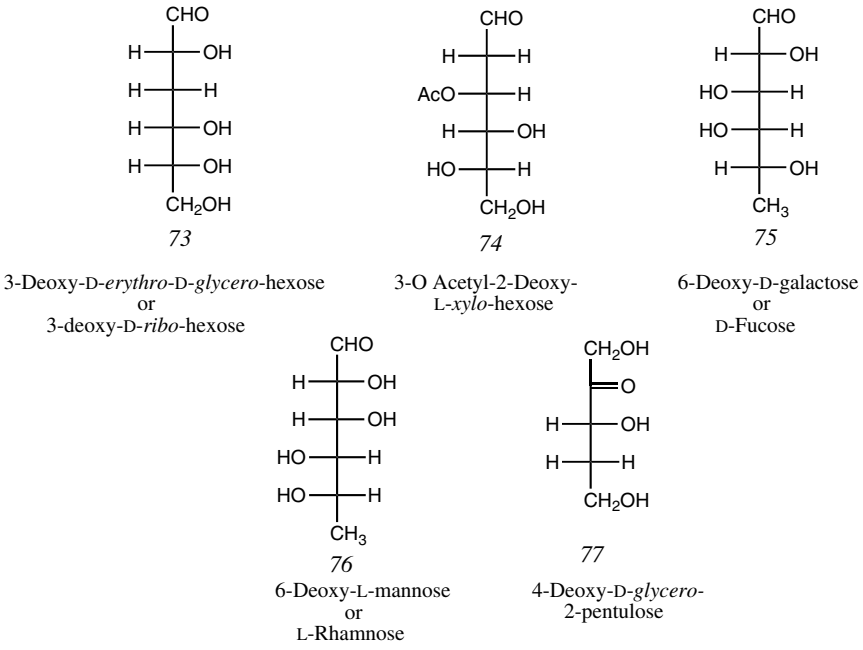
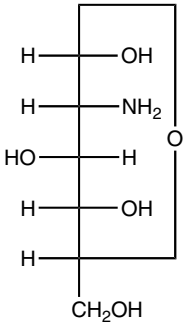


Fig. 1.18

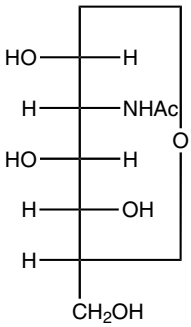
Amino-monosaccharides

The replacement of an alcoholic hydroxyl group of a monosaccharide, or a monosaccharide derivative, by an amino group is treated as substitution of the appropriate hydrogen atom of the corresponding deoxy-monosaccharide by the amino group (Fig. 1.19).



78

2-Amino-2-deoxy-
α-D-glucopyranose



79

2-Acetamido-2-deoxy-
β-D-glucopyranose

Fig. 1.19

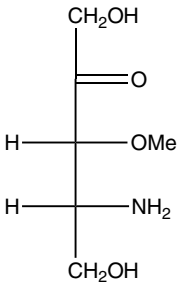
Substitution in the amino group is indicated by use of the prefix N unless the substituted amino group has a trivial name (for example, CH_3CONH-, acetamido). The trivial names accepted for biochemical usage are D-galactosamine for 2-amino-2-deoxy-D galactopyranose, D-glucosamine for 2-amino-2-deoxy-D-glucopyranose, D-mannosamine for 2-amino-2-deoxy-D-mannopyranose, etc.

When the complete name of a derivative includes other prefixes, *deoxy* takes its place in the alphabetical order of detachable prefixes; in citation the alphabetical order is preferred to numerical order – for example, 4-amino-4-deoxy-3-*O*-methyl-D-*erythro*-2-pentulose *80* and 4-deoxy-4-(ethylamino)-D-*erythro*-2-pentulose *81* (see Fig. 1.20).

O-Substitution

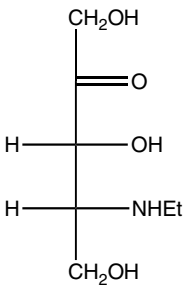
Replacement of a hydrogen atom of an alcoholic hydroxyl group of a monosaccharide or its derivative by another atom or group is denoted by placing the name of this atom or group before the name of the parent monosaccharide. The name of the atom or group is preceded by an italic capital letter *O* (for oxygen), followed by a hyphen in order to make clear that substitution is on oxygen. The *O* prefix need not be repeated for multiple replacements by the same atom or group. Instead a prefix, di- tri-, etc., is used.

Replacement of hydrogen attached to nitrogen or sulfur by another atom or group is indicated in a similar way with the use of italic capital letters *N* or *S*.



80

4-amino-4-deoxy-3-O-methyl-
D-*erythro*-2-pentulose

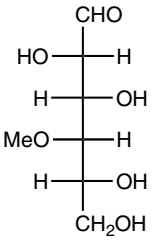


81

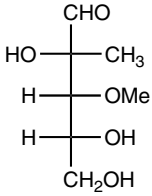
4-deoxy-4-(ethylamino)-
D-*erythro*-2-pentulose

Fig. 1.20

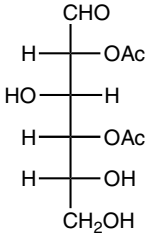
The italic capital letter *C* may be used to indicate replacement of hydrogen attached to carbon (for example in branched chain monosaccharides), to avoid possible ambiguity. Examples are given in Fig. 1.21.



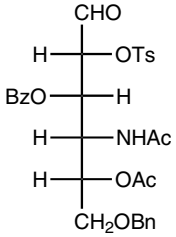
82, 4-O-Methyl-D-idose



83, 3-O-Methyl-2-C-methyl-
D-arabinose



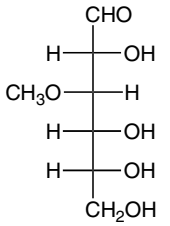
84, 2,4-Di-O-acetyl-D-glucose



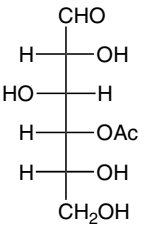
85, 4-acetamido-5-acetyl-3-O-benzoyl-
6-O-benzyl-4-deoxy-2-O-tosyl-D-glucose

Fig. 1.21

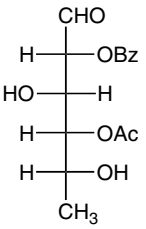
O-Substitution products of monosaccharides or their derivatives may be named as esters, ethers, etc., following the procedures presented for that purpose in IUPAC Nomenclature for Organic Chemistry, Section C, 1963. Examples are given in Fig. 1.22.



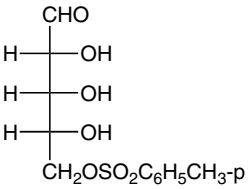
86, D-Glucose 3-O-methyl ether



87, D-Glucose 4-acetate



88, 6-Deoxy-D-gulose 2-benzoate

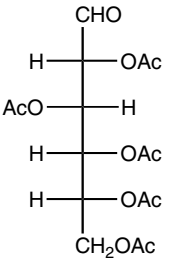


89, D-Ribose 6-p-toluenesulfonate (not 6-tosylate)

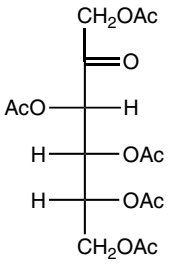
Fig. 1.22

Acyclic Forms

The acyclic nature of a monosaccharide or monosaccharide derivative containing an uncyclized carbonyl group may be stressed by inserting the italicized prefix *aldehydo* or *keto* respectively, immediately before the configurational prefix(es) or before trivial name. These prefixes may be abbreviated to *aldehydo* and *keto*. Examples are given in Fig. 1.23.



90, 2,3,4,5,6-Penta-O-acetyl-aldehydo-D-glucose, *or aldehydo*-D-Glucose 2, 3, 4, 5,6-pentaacetate



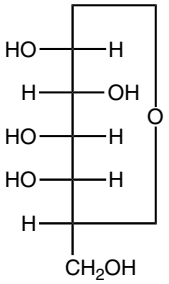
91, 1,3,4,5,6-Penta-O-acetyl-*keto*-D-fructose or *keto*-D-Fructose 1,3,4,5,6-pentaacetate

Fig. 1.23

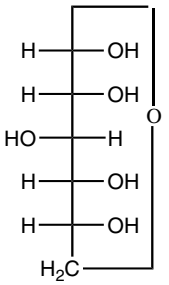
Anomers and the Anomeric Configurational Symbols ("α" or "β").

The free hemiacetal hydroxyl group of a cyclic form of monosaccharide or monosaccharide derivative is termed the *anomeric* or *glycosidic* hydroxyl group (the word *anomer* comes from the Greek words ανω = *ano* and μερωσ = *meros*. The first word means *up, top* and the second word means *part*, or in this case *position*).

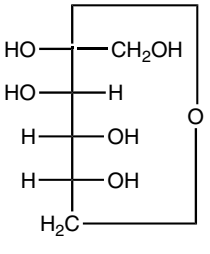
The two stereoisomers of an aldose or ketose, or their derivatives that differ in the configuration of anomeric hydroxyl group (termed *anomers*), are distinguished with the aid of the two anomeric prefixes α and β, relating the configuration of the anomeric carbon to that of the reference chiral carbon atom of the monosaccharide;



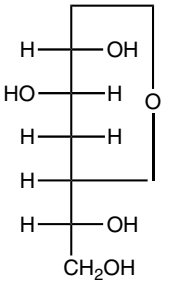
92, β-D-Galactopyranose
or
β-D-Galactose-(1,5)



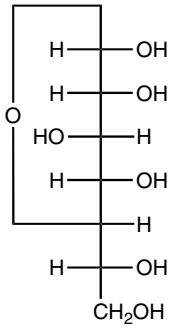
93, α-D-Glucoseptanose
or
α-D-Glucose-(1,6)



94, β-D-Fructopyranose
or
β-D-Fructose-(2,6)



95, 3-Deoxy-α-D-*erythro*-L-*glycero*-hexofuranose
or
3-Deoxy-α-D-*erythro*-L-*glycero*-hexose-(1,4)



95, α-D-*glycero*-L-*ido*-Heptopyranose
or
α-D-*glycero*-L-*ido*-Heptose-(1,5)

Fig. 1.24

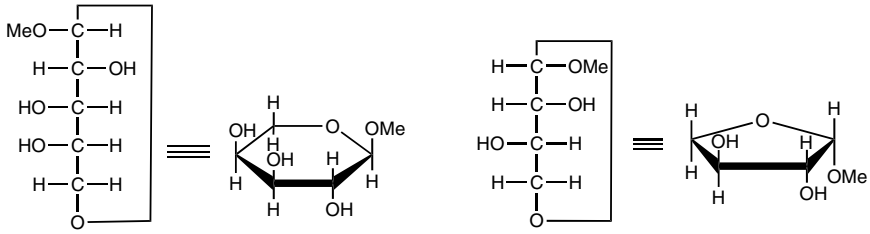
the anomer having the same configuration, in the Fischer projection, at the anomeric and the reference carbon atom is designated α. In the α-anomer, the exocyclic oxygen atom at the anomeric center is formally *cis*, in the Fischer projection, to the oxygen atom attached to the anomeric reference atom; in the β anomer, these oxygen atoms are formally *trans*.

The anomeric prefix, α or β, followed by a hyphen, is placed immediately in front of the configurational symbol, D or L, of the trivial name, or of the configurational prefix denoting the group of achiral carbon atoms that include the reference carbon atom.

Examples are given in Fig. 1.24.

Glycosides

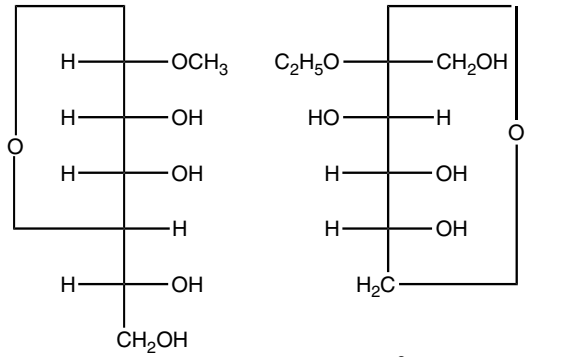
Mixed acetals, resulting from replacement of the hydrogen atom of the anomeric or glycosidic hydroxyl group by a group R, derived from an alcohol or phenol (ROH), are named *glycosides*. The term glycoside is used in a generic sense only and may not be applied to specific compounds. Glycosides are named by replacing the terminal "e" of the name of the corresponding cyclic form of the saccharide derivative by "ide" and placing before the word thus obtained, as a separate word, the name of the group R. Examples are given in Figs. 1.25, 1.26, and 1.27.



97, Methyl α–L-arabinopyranoside

98, Methyl β-L-threofuranoside

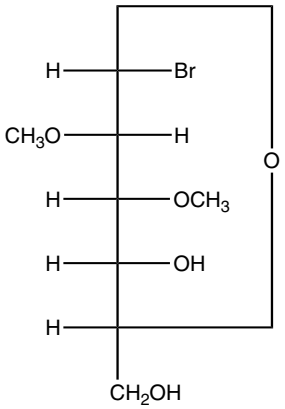
Fig. 1.25



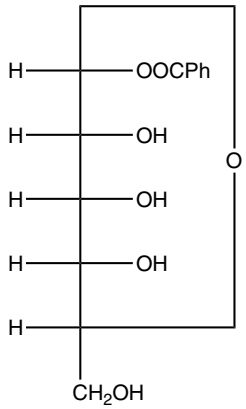
99, Methyl α-L-gulofuranoside
or
Methyl α-L-gulosiode-(1,4)

100, Ethy β-D-fructopyranoside
or
Ethyl β-D-fructoside-(2,6)

Fig. 1.26



101, 2,3-Di-O-methyl-α-D-altropyranosyl bromide
or
2,3-Di-O-methyl-α-D-altrosyl-(1,5) bromide

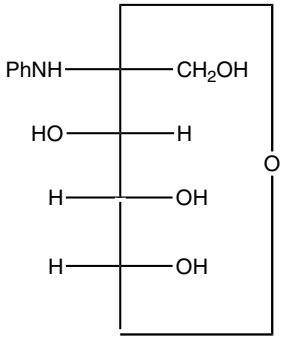


102, α-D-Allopyranosyl benzoate,
1-O-Benzoyl-α-D-allopyranose
or
α-D-allosyl-(1,5) benzoate.
1-O-Benzoyl-α-D-allose-(1,5)

Fig. 1.27

Glycosyl Radicals and Glycosylamines

(a) The radical formed by detaching the anomeric or glycosidic hydroxyl group from the cyclic form of a monosaccharide or monosaccharide derivative is named by replacing the terminal "e" of the name of the monosaccharide or monosaccharide derivative by "yl." The general name of these radicals is *glycosyl* (glucofuranosyl, glucopyranosyl, mannopyranosyl, galactopyranosyl, fructofuranosyl, etc.) radical (Fig. 1.28).



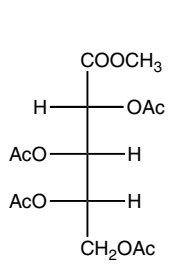
103, N-Phenyl-β-D-fructopyranosylamine
or
N-Phenyl-β-D-fructosyl-(2,6) amine

Fig. 1.28

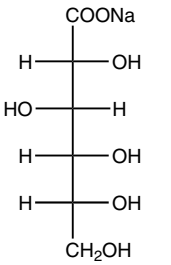
(b) The replacement of the glycosidic hydroxyl group of a cyclic form of a monosaccharide derivative by an *amino* group is indicated by adding the suffix "amine" to the name of the glycosyl radical (Fig. 1.28).

Aldonic Acids

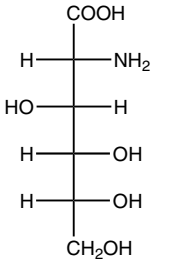
Monocarboxylic acids formally derived from aldoses having three or more carbon atoms in the chain, by oxidation of the aldehydic group, are named *aldonic acids* and are divided into aldotrionic acids, aldotetronic acids, aldopentonic acids, aldohexonic acids, etc., according to the number of carbon atoms in the chain. Names of the individual compounds of this type are formed by replacing the ending "ose" of the systematic or trivial name of the aldose by "onic acid" (Fig. 1.29).



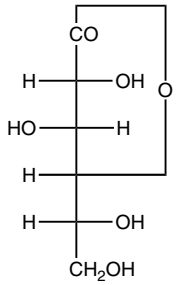
104, Methyl tetra-O acetyl-L-arabinonate
or
Methyl L-arabinonate tetraacetate



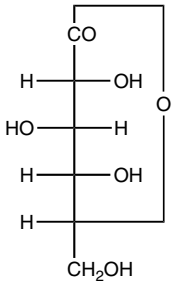
105, Sodium D-gluconate



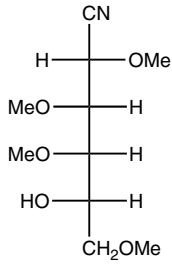
106, 2-Amino-2-deoxy-D-gluconic acid
or
D-Glucosaminic acid



107, D-Glucono-1,4-lactone
or
D-Glucono-γ-lactone



108, D-Glucono-1,5-lactone
or
D-Glucono-δ-lactone



109, 2,3,4,6-Tetra-O-Methyl-
L-altrononitrile

Fig. 1.29

Derivatives of these acids formed by change in the carboxyl group (salts, esters, lactones, acyl halides, amides, nitriles, etc.) are named according to the IUPAC Nomenclature of Organic Chemistry, Section C, 1965, Rules C-4. Examples are given in Fig. 1.29.

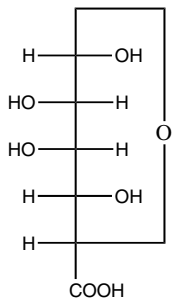
Uronic Acids

The monocarboxylic acids formally derived by oxidation of the terminal CH_2OH group of aldoses having four or more carbon atoms in the chain, or of glycosides derived from these aldoses, to a carboxyl group are named "uronic acids." The names of the individual compounds of this type are formed by replacing the (a) ending "ose" of the systematic or trivial name of the aldose by "uronic acid" or (b) ending "oside" of the name of the glycoside by "osiduronic acid."

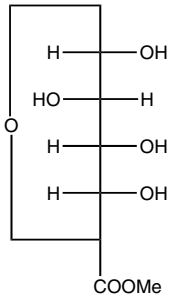
The carbon atom of the (potential) aldehydic carbonyl group (not that of the carboxyl group) is numbered 1.

Derivatives of these acids formed by change in the carboxyl group (salts, esters, lactones, acyl halides, amides, nitriles, etc.) are named according to the IUPAC Nomenclature of Organic Compounds, Section C, 1965, Rules C-4.

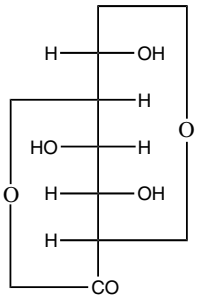
Examples are shown in Fig. 1.30.



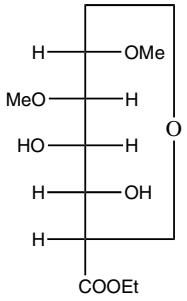
110, α-D-Mannopyranuronic acid



111, Methyl β-L- galactopyranuronate



112, α-D-Mannopyranurono-6,2-lactone



113, Ethyl (methyl 2-O-methyl-α-D-mannopyranosid)uronate

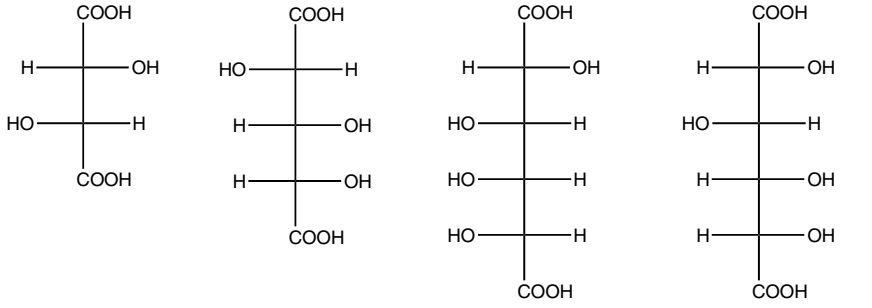
Fig. 1.30

Aldaric Acids

The dicarboxylic acids formed by oxidation of both terminal groups of an aldose to carboxyl groups are called "aldaric acids." Names of individual components of this

type are formed by replacing the ending "ose" of the systematic or trivial name of the corresponding aldose by "aric acid." Choice between the several possible names is based on the order of precedence given in Rule 3. Examples:

a) Names requiring D or L:



114, L-Trearic

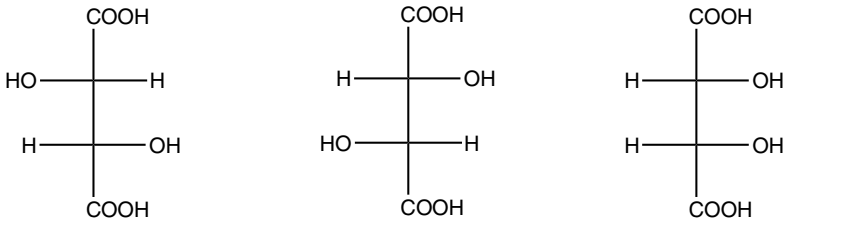
115, D-Arabinaric acid
not
D-lyxaric acid

116, L-Altraric acid
not
L-talaric acid

117, D-Glucaric acid
not
L-gularic acid

Fig. 1.31

b) To the names of aldaric acids optically compensated intramolecularly, which therefore have no D or L prefix, the prefix *meso-* may be added for the sake of clarity. Examples: *meso*-erythraric acid, *meso*-ribaric acid, *meso*-xylaric acid, *meso*-allaric acid, *meso*-galactaric acid.



118, (–)-Tartaric acid
D-Threaric acid
(RR-Tartaric acid)

119, (+)-Tartaric acid
L-Threaric acid
(SS-Tartaric acid)

120, meso-Tartaric acid
(Erythraric acid)
RS-Tartaric acid

Fig. 1.32

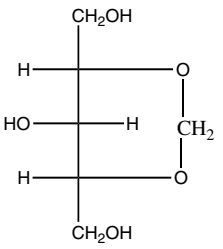
The D and L prefix must however be used when *meso*-aldaric acid has become asymmetric as a result of substitution (Fig. 1.31).

c) The trivial names that are preferred to the systematic names are given in Fig. 1.32.

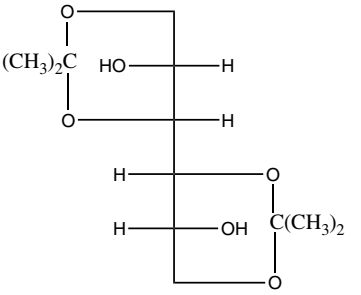
Cyclic Acetals

Cyclic acetals formed by reaction of monosaccharides or their derivatives with aldehydes or ketones are named in accordance with Rule 7 for O-substitution, bivalent radical names being used as prefixes, the names of such radicals following the rules of general organic chemical nomenclature. In indicating more than one cyclic acetal grouping of the same kind, the appropriate pairs of locants are separated typographically when the exact placement of the acetal groups is known (Fig. 1.33).

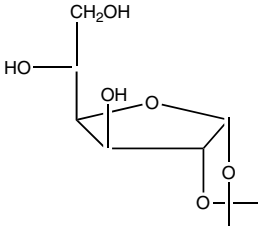
Examples:



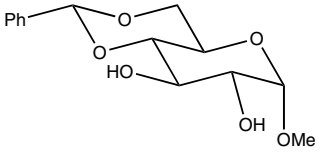
121, 2,4-O-Methylenexylitol



122, 1,3:4,6-Di-O-isopropylidene-D-mannitol



123, 1,2-O-Isopropylidene-α-D-glucofuranose

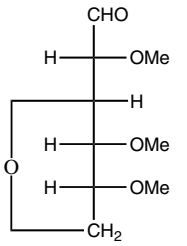


124, Methyl 4,6-O-benzylidene-α-D-glucopyranoside

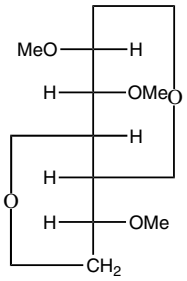
Fig. 1.33

Intramolecular Anhydrides

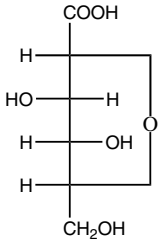
An intramolecular ether (commonly called an intramolecular anhydride), formed by elimination of water from two alcoholic groups of a single molecule of a monosaccharide (aldose or ketose) or monosaccharide derivative, is named by attaching the (detachable) prefix “anhydro” by a hyphen before the monosaccharide name; this prefix, in turn, is preceded by a pair of locants identifying the two hydroxyl groups involved. Examples are given in Fig. 1.34.



125, 3,6-Anhydro-2,4,5-tri-O-methyl-*aldehydo*-D-glucose



126, Methyl 3,6-anhydro-2,5-di-O-methyl-β-D-glucofuranoside



127, 2,5-Anhydro-D-gluconic acid

Fig. 1.34

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Chapter 2
Conformational Analysis of Monosaccharides

Molecules are dynamic assemblies of atoms chemically linked by single or multiple bonds. Hence, all atoms as well as groups of atoms are in perpetual motion, vibrating and rotating about chemical bonds. The deformation of chemical bonds due to vibration (stretching, wagging, etc.) of atoms is quantized and it is not the subject of conformational analysis. However, the rotation of atoms about the single bonds is the subject of conformational analysis.

Conformation of a molecule can be defined as a spatial arrangement of its atoms (or ligands) in a molecule that is obtained by free rotations about single bonds. Hence, the conformations are interconvertible by rotation about the single bonds.

When an atom that carries no substituent rotates about a single bond that links it to another atom, which does or does not carry a substituent, the rotation will not change the spatial arrangement of atoms in that molecule and therefore there will be no change in conformation due to rotation, as shown in Fig. 2.1 for molecules of hydrogen (*1*), chlorine (*2*), and water (*3*).

1 *2* *3*

Fig. 2.1

Hence, these rotations of atoms in a molecule are not the subject of conformational analysis.

The rotation of two atoms about a single bond that connects them will, however, result, in the course of time, in formation of many nonidentical spatial arrangements of atoms in a molecule, if both atoms carry at least one substituent. Each individual spatial arrangement of atoms or group of atoms in a molecule obtained *via* the free rotation is called the *conformation* of that molecule.

Thus, for example, in hydrogen peroxide (Fig. 2.2) the rotation of oxygen atoms about the oxygen–oxygen single bond could theoretically produce an "infinite" number of conformations. However, even though the hydrogen atom is very small, some conformations will be favored over the others because the rotational barrier is not small (1.1 kcal/mol [1, 2]). Various conformations of hydrogen peroxide in

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_2,

Fig. 2.2 are represented with the so-called "sawhorse" (perspective) formulas (upper raw) and with the so-called Newman′s projections (lower raw) (the relative position of the two hydrogen atoms is looked upon along the oxygen–oxygen bond). It was found by millimeter-wave spectroscopy [3] and by ab initio calculation [4] that the gauche coformation *6* is the favored conformation (dihedral angle between the hydrogens is ca. 120°).

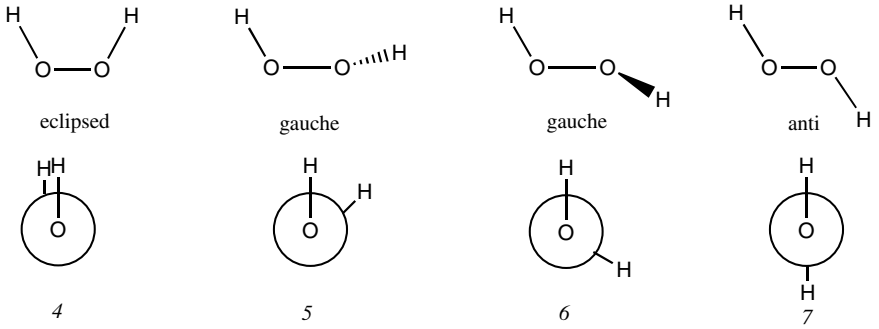


Fig. 2.2

Conformational Analysis of Acyclic Hydrocarbons

The rotation of two methyl groups of ethane about the C–C single bond (Fig. 2.3) should theoretically produce also an "infinite" number of conformations if the rotation about the C–C bond was completely free. However, due to a nonbonded interaction between the hydrogen atoms on two adjacent methyl groups (known as

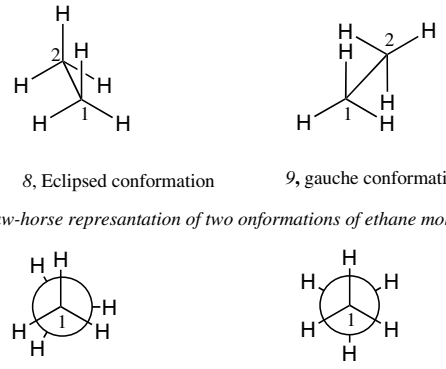
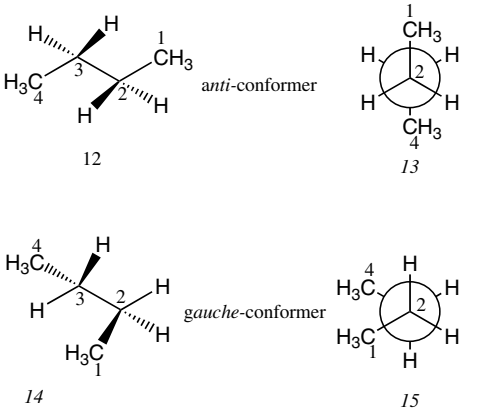


Fig. 2.3

torsional or *Pitzer strain* [1]) the rotation about the C–C bond in ethane molecule is not completely free [3] because in the *eclipsed* conformation the interaction between the hydrogen atoms is larger (ca. 2.89–2.93 kcal/mol [1–8]) than in the *gauche* conformation, since the inter-atomic distance between the vicinal hydrogen atoms of the two neighboring methyl groups in eclipsed conformation (torsional angle 0°) is significantly shorter (2.26 Å) than in the gauche conformation (torsional angle 60°) (2.50 Å). Since the conformational energy of *8*, *10* is higher than that of *9*, *11* the *gauche* conformation will be preferred in the conformational equilibrium mixture of ethane. In Fig. 2.3 only two conformations of ethane molecule are shown – the least stable *eclipsed* conformation (*8* and *10*) (it has the highest internal energy of all possible ethane conformations because the hydrogen atoms are closest to each other) and the most stable *gauche* (*9* or *11*) conformation because it has the lowest internal energy of all possible ethane conformations (the hydrogen atoms are at the greatest distance from each other).

It should be, however, noted that the steric (van der Waals) interactions actually account for less than 10% of the rotational barrier in ethane, since the hydrogen atoms of two methyl groups are barely within the van der Waals distance. Electrostatic interactions of the weakly polarized C–H bonds are negligent, too. The principal interaction responsible for the rotational barrier in ethane is, according to Pitzer [9], the overlap resulting in repulsion [10] of bond orbitals in the eclipsed conformation; changes in electronic structure other than those required by the changes in C–H bond overlaps are of minor importance for the existence of the barrier [9]. The existence of rotational barrier in ethane, according to Bader et al. [11] is explained by the increase of the C–C bond length during the transition from the gauche (staggered) conformation to the eclipsed one; this increase is more than 10 times larger than the accompanying decrease in the C–H separation.



12 13 14 15

Fig. 2.4

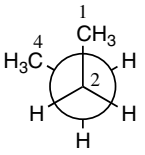
When two carbon atoms linked by a single bond carry larger atoms or group of atoms as substituents, then the conformational energy difference of *gauche* and

eclipsed conformations becomes much larger. This difference becomes even greater if substituents are polar or if they are even electrically charged, because in addition to the nonbonded (van der Waals) interactions there now will also be present dipolar and/or electrostatic interactions between the neighboring substituents.

Since, it is well established that molecules tend to assume their most stable conformations in which the magnitude and the number of unfavorable stereoelectronic interactions are at the minimum, then all possible *eclipsed* conformations may be safely eliminated from discussions because they will not be present in conformational mixtures in significant amounts to influence the chemical behavior of a given molecule.

It should be pointed out that of all possible *gauche* conformations there is only one in which the dihedral angle between the two largest substituents is 180°. This conformation is called *anti* or antiperiplanar [12] (*ap*) conformation and is always the preferred conformation.

This is now a good place to briefly describe Klyne–Prelog proposal [12] for describing the stereochemistry across a single bond in terms of torsional angle, τ, between the ligands such as, for example, between the two methyl groups in *n*-butane. When $\tau = 60°$ the conformer is *gauche* (*staggered* or *skewed*) but according to Klyne–Prelog proposal it is either ±*syn*-clinal (±sc) *(16*, *17*) or ±*anti*-clinal (±ac)(*18*, *19*) (Fig. 2.5). When torsional (dihedral) angle between the two methyl groups is between +30° and +90° the conformer is +*syn*-clinal (+sc), and if it is between –30° and –90°, the conformer is –*syn*-clinal (–sc). When the torsional (dihedral) angle between the two methyl groups is between +90° and +150° the conformer is +*anti*-clinal (+ac) and if it is between –90° and –150° the conformer is –*anti*-clinal (–ac). When torsional angle between two methyl groups is between



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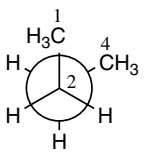

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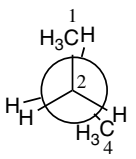

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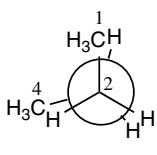

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–*syn*-clinal conformer + *syn*-clinal conformer + *anti*-clinal conformer –*anti*-clinal conformer

All four conformers are *gauche*, *staggered*, or *skew* conformers

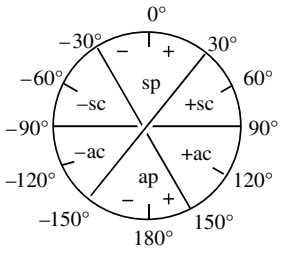
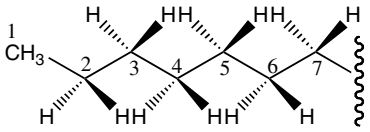


Fig. 2.5

–30° and +30° the conformer is ±*syn*-periplanar (±sp) and if it is between –150° and +150° the conformer is ±*anti*-periplanar (±ap). When torsional (dihedral) angle between two methyl groups is 0° the conformer is eclipsed and when the torsional (dihedral) angle between two methyl groups is 180° the conformer is *trans* or *anti*.

In aliphatic hydrocarbons, such as *n*-butane, for example, where only steric (van der Waals) interactions are involved, the *anti*-conformer is significantly preferred, over the *gauche* conformers, since the two methyl groups (the largest substituents on the C2 and C3 carbon atoms) are furthest apart (Fig. 2.4). The *anti*/*gauche* conformer ratio in *n*-butane is, at room temperature, almost 2:1 as determined by NMR spectroscopy.

Consequently, the polymethylene hydrocarbons tend to adopt planar *zigzag* conformation in which all carbon atoms lie in one plane (Fig. 2.6). In this conformation, all carbon atoms (the largest "substituents" in *n*-butane subunits) are in the *anti*-orientation (C1–C4, C2–C5, C3–C6, etc.). The small 1,3-nonbonding interactions between the hydrogen atoms (C_2H-C_4H, C_3H-C_5H, etc.) are the only destabilizing interactions. Unlike the acyclic hydrocarbons, each carbon atom of an acyclic monosaccharide has in addition to a hydrogen atom one large substituent which is most often hydroxyl group, but it can also be an amino, thio, or other group or an atom. In this case, if the acyclic form of a carbohydrate adopts the *zigzag* conformation then depending on a monosaccharide one or more 1,3-nonbonded interactions are possible between two larger ligands (oxygen atoms, for example).



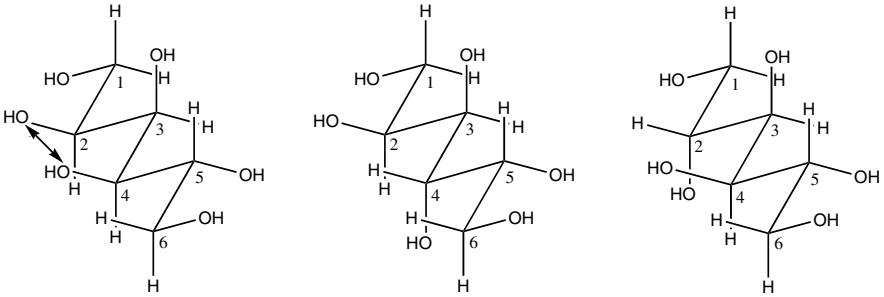
20

Fig. 2.6

Conformational Analysis of Acyclic (Aldehydo) Forms of Monosaccharides

The conformation of acyclic aldehydo sugars cannot be studied in solutions due to their spontaneous cyclization and formation of hemiacetals. However, derivatization of the C4 and the C5 hydroxyl groups (by alkylation or acylation) or derivatization of the aldehydo group of a monosaccharide (by formation of dialkylacetals or dialkyldithioacetals) prevents the hemiacetal formation permitting thus the conformational studies to be conducted in solution. To avoid derivatization the carbonyl group of a monosaccharide can simply be reduced with complex metal hydrides and the obtained sugar alcohol – *alditol* can then be used for conformational studies.

If D-glucitol (*21*), D-galactitol (*22*), and D-mannitol (*23*) (the alditols obtained by reduction of D-glucose, D-galactose, and D-mannose) are represented in their zigzag conformations (Fig. 2.7) it can be seen that only in D-glucitol there is one large 1,3-nonbonded interaction (both steric and dipolar) between the C2 and the C4 hydroxyl groups. This interaction destabilizes this conformation by 1.5 kcal/mol. In all three *zigzag* conformations there is present a number of much weaker 1,3-*syn*–axial interactions (we will explain the term "1,3-*syn*–axial interac-



21, D-Glucitol *22,* D-Galactitol *23,* D-Mannitol

Fig. 2.7

tion" when we discuss the conformational analysis of pyranoid forms of monosaccharides). In D-glucitol there are four 1,3-*syn*–axial interactions (two between the C3 oxygen and the C1 and C5 hydrogens, one between the C5 oxygen and the C3 hydrogen, and one between the C4 oxygen and the C6 hydrogen) that destabilize this conformation by additional 1.8 kcal/mol (one *syn*–axial interaction between an oxygen and hydrogen atom destabilizes the given conformation by 0.45 kcal/mol). In D-galactitol (*22*) there are six 1,3-*syn*–axial interactions between the oxygen and hydrogen atoms (two between the C3 oxygen and the C1 and C5 hydrogens, two between the C4 oxygen and the C2 and C6 hydrogens, one between the C5 oxygen and the C3 hydrogen, and one between the C2 oxygen and C4 hydrogen destabilizing this conformation by a total of 2.70 kcal/mol). In D-mannitol (*23*) there are also six such interactions present (one between the C2 oxygen and the C4 hydrogen, two between the C3 oxygen and the C1 and C5 hydrogens, two between the C4 oxygen and the C2 and C6 hydrogens, and one between the C5 oxygen and C3 hydrogen) destabilizing this conformation by 2.70 kcal/mol.

Unlike D-galactitol and D-mannitol, which in solution exist predominantly in planar *zigzag* conformation, as shown [13] by ^{1}H NMR spectroscopy and in crystalline state by X-ray crystallography [14–18] D-glucitol adopts the so-called *sickle* (bent) conformation [14], in which the C2 and the C5 carbon atoms are in the *gauche* rather than in the *anti*-orientation (Fig. 2.8), to avoid the destabilizing *syn*–axial interaction between the C2 and the C4 hydroxyl groups (*21* in Fig. 2.7).

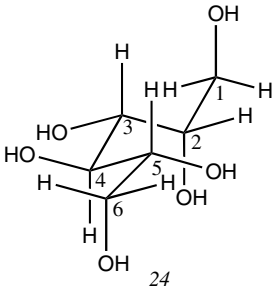


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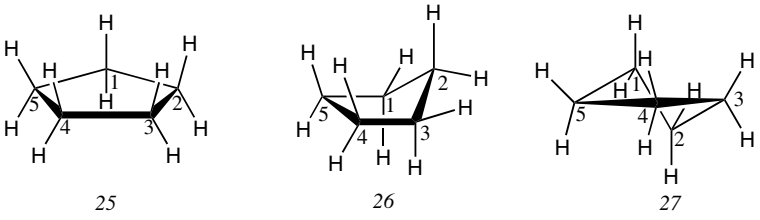
Fig. 2.8

Conformational Analysis of Cyclic (Lactol, Hemiacetal) Forms of Monosaccharides

Furanoses

The conformational analysis of furanoid forms of sugars is closely related to the conformational analysis of substituted cyclopentanes because they are both five-membered ring systems. For that reason we will start our discussion on conformational analysis of furanoid form of monosaccharides by briefly discussing the conformational analysis of cyclopentane first.

The cyclopentane can assume three distinct conformations: planar *25*, envelope *26*, and twist *27* conformation (Fig. 2.9), together with an infinite number of conformations that lie in the conformational interconversion path of cyclopentane.



25 planar *26* enevelope *27* twist

Fig. 2.9

The deviation of the endocyclic C–C bond angle of 108° in planar conformation of cyclopentane (*25* in Fig. 2.9) from tetrahedral valence angle of 109.5° of a carbon atom is relatively small (1.5°) and cannot have noticeable effect on the energy content of cyclopentane due to the Baeyer ring strain. Yet if one compares the heat of combustion per CH_2 group of acyclic hydrocarbons (157.5 kcal/mol) [19] and cyclohexane (157.4 kcal/mol) with that of cyclopentane (158.7 kcal/mol) it is

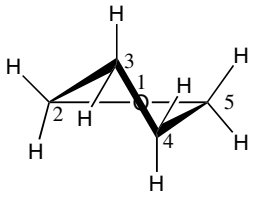
estimated that the energy content of cyclopentane is higher by 6–7 kcal/mol than that of both *n*-pentane or the five-carbon fragment of cyclohexane. Since this higher internal energy of cyclopentane cannot be related to Baeyer ring strain, it was suggested by Pitzer [20–22] that the energy content of cyclopentane must be due to sterically unfavorable arrangement of adjacent methylene groups. As can be seen from Fig. 2.9 in the planar conformation *25* all 10 hydrogen atoms are completely eclipsed as well as all five-ring carbons. If one accepts the value of ca. 1 kcal/mol as the magnitude of unfavorable interaction energy between two eclipsed hydrogen atoms in ethane molecule, the internal energy of the planar conformation of cyclopentane should be greater than 10 kcal/mol. However it is 6–7 kcal/mol suggesting that in order to minimize these destabilizing interactions the cyclopentane adopts a *puckered* (a nonplanar) conformation which can be either the *envelope 26* conformation (also called the C_2 conformation – named after the symmetry point group) or the *twist* conformation *27* (also called the *half-chair* or the C_s conformation – named after symmetry point group) (Fig. 2.9). By adopting the envelope conformation the total torsional strain is only 60% of total torsional strain of planar conformation because of the presence of only six pairs of eclipsed hydrogens. According to Pitzer the cyclopentane ring is puckered to such an extent that one carbon sticks out about 0.2 Å from the plane containing the other four carbon atoms [20, 21]. The more recent calculations [22, 23] have shown that the energy minimum of cyclopentane molecule is attained when one carbon atom takes up the position 0.5 Å out of plane containing the other four carbon atoms. The carbon atom protruding from the plane is not fixed in that position [20, 21] but it "rotates around the ring" by an up and down motion of all five methylene carbons; this motion has been termed "*pseudorotation*" the result of which is the adoption of an infinite number of intermediate conformations.

In twist conformation the three neighboring carbons lie in one plane, while the other two are twisted, one lies below and the other above that plane, and they are equidistant from the plane containing the other three carbons. Since the twist conformation has only four pairs of eclipsed hydrogen atoms the total torsional strain of this conformation is 40% of the torsional strain of planar conformation. Difference in energy between the envelope and the twist conformations is very small, the envelope form being more stable by 0.5 kcal/mol.

Puckering of cyclopentane ring has been experimentally confirmed (a) thermodynamically from entropy measurements [24–27] and (b) by electron scattering [28]. Since the puckering of cyclopentane ring is not fixed and the energy barrier for conformational inter-conversions via pseudorotation is small (less than 0.6 kcal/mol at room temperature) no definite conformational energy minima and maxima can be observed for cyclopentane.

Most of what is said for cyclopentane is applicable to the conformational analysis of tetrahydrofuran. Calculation on tetrahydrofurans suggests [22] that the molecule exists in *twist* (half-chair) form with the maximum puckering occurring at carbon atoms 3 and 4, away from the heteroatom (*28* in Fig. 2.10). The replacement of one cyclopentane carbon with an oxygen atom decreases the Pitzer strain but introduces additional Baeyer strain into the molecule because the valence

angle of oxygen atom is 104.45°, whereas the endocyclic valence angle of planar cyclopentane ring is 108°.



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Tetrahydrofuran in twist conformation

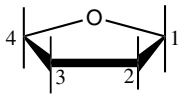
Fig. 2.10

The introduction of substituents into either cyclopentane or tetrahydrofuran dramatically limits the number of possible conformations that they may adopt due to the increase of energy barriers for conformational interconversions.

The proof that furanoses do exist in nonplanar conformations has been obtained from X-ray crystallographic studies as well as from NMR spectroscopy studies in solutions.

Depending on the nature and location of its substituents, the furanose ring was shown to adopt both the C_s and the C_2 conformation [29–33]. Bulky substituents are taking up the most staggered ("equatorial") position, at the most staggered carbon atom. The oxygen atom most likely takes up the least staggered position in the furanose ring. Lemieux [34] has discussed, in considerable depth, the conformational behavior of furanoses based on the assumption that they adopt the C_s conformations.

Nonbonded interactions between the *cis*-1,2-substituents on furanoid ring are relieved by puckering of a planar conformation to the C_2 conformation by displacing the C_2 or C_3 carbons from the plane containing the other four atoms [35–40] (Fig. 2.11) or to the C_s conformation (Fig. 2.10). Hence it may be concluded that E conformations with the C_2 or C_3 carbons displaced from the plane of the ring (i.e., ^2E, E_2, ^3E, E_3) are the most stable conformations (for instance, *31* corresponds to ^2E conformation). In addition, electronegative substituents at carbon atoms other than C_1 will prefer to take up quasi-equatorial or isoclinal orientations. The C_1 electronegative substituents will tend to assume quasi-axial orientation.



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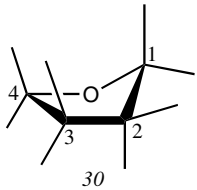

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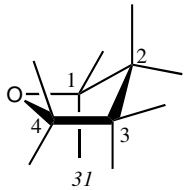


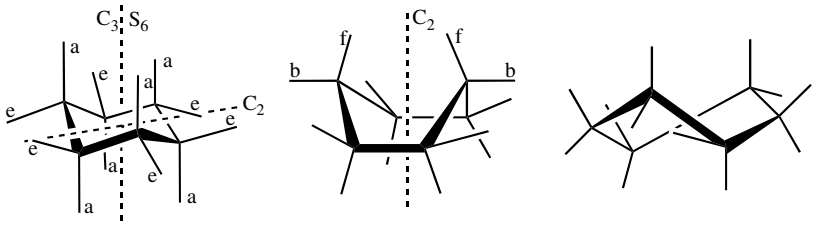
31

Fig. 2.11

The conformational analysis of furanoses is plagued by two insurmountable difficulties: (a) the flexible nature of the five-membered ring which is not allowing the accurate evaluation (or calculation) of interaction energies between the ring substituents and (b) difficulties in accurately determining the concentration of furanose forms in solutions at equilibrium.

Pyranoses

Although carbohydrate pyranoid rings are slightly flattened compared to cyclohexane rings and have no elements of symmetry, the conformational analysis of pyranoses is intimately related to the conformational analysis of cyclohexane. Therefore, we will begin our discussion of conformational analysis of pyranoses by briefly discussing the conformational analysis of cyclohexane first.



32 chair conformation

33 boat conformation

34 Skew-boat conformation

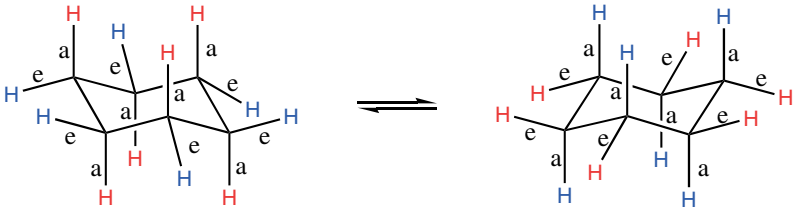
Fig. 2.12

Cyclohexane may exist in three distinct conformations (Fig. 2.12): *chair 32*, *boat 33*, and *twist-boat* (or *skew-boat*) *34* conformations. The *chair* conformation is relatively stiff and has the following elements of symmetry: C_3 axis of symmetry that coincides with the S_6 rotation–reflection axis of symmetry, three C_2 axis of symmetry, three planes of symmetry, and a center of symmetry. The *boat* conformation is flexible and has one C_2 axis of symmetry and two planes of symmetry, whereas the *skew-boat* (or *twist-boat*) *conformation* is flexible and has no symmetry elements.

Cyclohexane in chair conformation *32* has two geometrically different sets of hydrogens: six hydrogens are oriented parallel to the S_6 (that is also the C_3) axis of the molecule and are called *axial* (*a*) hydrogens and the six hydrogen atoms that alternate about the so-called "equatorial" plane that is a plane perpendicular to the S_6 (C_3) axis and are called *equatorial* (*e*) hydrogens. In the boat conformation (*33* in Fig. 2.12) there are two pairs of hydrogens that are very different from the other eight. These are the four hydrogens that are attached to two carbons that lie out of the plane of other four carbons of the boat conformation. The two hydrogens that point away from the ring and are almost parallel to the plane containing the four carbon atoms are said to be in *bowsprit* (*b*) orientation; the two hydrogens that are pointed toward the ring are said to be in *flagpole* (*f*) orientation. From other eight

hydrogens four are equatorial and the other four pseudo-axial. Although the boat conformation is free from Baeyer (ring) strain, there is eclipsing of eight hydrogen atoms that are part of the planar part of the six-membered ring causing elevated torsional strain; in addition to that there is also a severe van der Waals interaction between two hydrogen atoms in the *flagpole* orientation. As a result, the boat conformation is calculated to be 6.9 kcal/mol less stable than the chair conformation [41]. To avoid these unfavorable interactions the boat adopts the *skew-boat* conformation *34* by pseudo-rotation around its ring C–C bonds (Fig. 2.12). Its energy has been calculated to be 5.3 kcal/mol, i.e., 1.6 kcal/mol less than the boat conformation, but still 5.3 kcal/mol higher than the energy of the chair conformation.

Although relatively rigid, the cyclohexane *chair* conformation *35* is able to *flip* over to the alternate chair conformation *36*, as illustrated in Fig. 2.13. After flipping over, the hydrogen atoms of a cyclohexane that were axial (red in the left conformation) became equatorial and vice versa, the hydrogens that were equatorially oriented in the left conformation (blue hydrogens) became axial in the right conformation.



35 Interconversion of two alternate chair conformations *36*

Fig. 2.13

The interconversion of the two-cyclohexane chair conformations (*37* ⇌ *42*) (Fig. 2.14) involves the formation of a *half-chair conformation 38* in the transition state (first step), which (in the second step) collapses either into flexible twist-boat conformation (*39*, *40*) or back to the initial conformation *37*. The *twist-boat* conformation 39 is in dynamic equilibrium with the boat conformation *40*; in this conformational mixture the *twist-boat* conformation is at the energy minimum and the boat conformation is at the energy maximum (energy difference between these two forms is estimated to be 1.0–1.5 kcal/mol). The conversion of a *twist-boat* conformation into an alternate chair conformation *42* requires the formation of the corresponding alternate *half-chair* conformation *41* in the second transition state. Figure 2.14 illustrates the chair–alternate chair (*37* ⇌ *42*) interconversion via the half-chair *38* and alternate half-chair *41* transition state intermediates.

The activation energy of chair-to-chair interconversion (the barrier of the ring inversion in cyclohexane) has been experimentally determined by variable temperature NMR studies [42, 43] and calculated by force field method [42, 44, 45]. The obtained $\Delta G^{\#}$ values for the barrier was found to vary from 10.1 to 10.25 kcal/mol at temperatures between –50 and –70°C. Calculated and experimentally determined values are in good agreement.

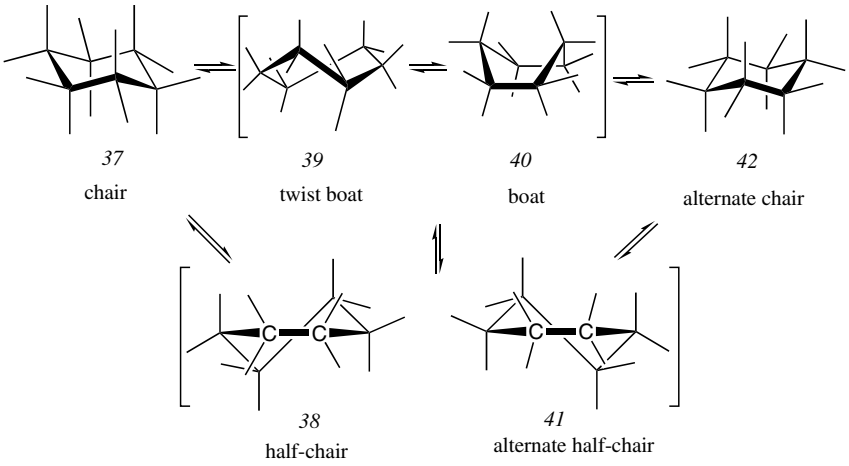


Fig. 2.14

Substitution of one hydrogen atom in cyclohexane with a "bulky" substituent dramatically changes the described situation. The most stable chair conformation of a mono-substituted cyclohexane is the one in which the substituent takes up the equatorial orientation.

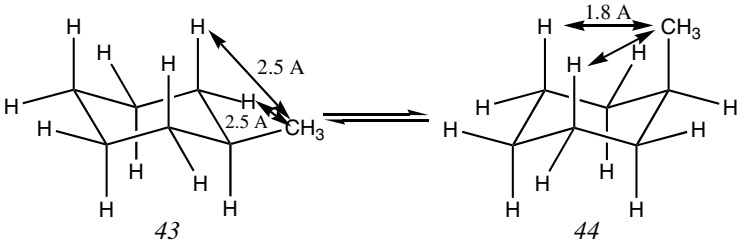


Fig. 2.15

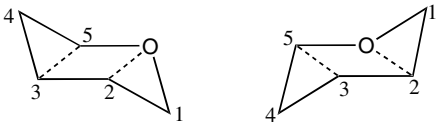
The reason for this is the unfavorable nonbonding interaction between the axial substituent and the two 1,3-*syn*–axial hydrogen atoms. For example 1,3-*syn*–axial interaction between an axial methyl group and the two axially oriented hydrogen atoms in methylcyclohexane (*44* in Fig. 2.15) is 1.6–1.8 kcal/mol suggesting that at conformational equilibrium (Fig. 2.15) the conformation having methyl group equatorially oriented (*43* in Fig. 2.15) will strongly predominate (*43*:*44* = 19:1; i.e., 95:5%). Disubstituted and polysubstituted cyclohexanes are even more restrictive in number of possible conformations.

Replacing one carbon atom of a cyclohexane ring with an oxygen atom, converting thus the cyclohexane to tetrahydropyran, introduces several very important changes. First, the six-membered ring of a pyranoid sugar is somewhat flattened compared to the cyclohexane due to the shorter C–O bond as compared to C–C

bond (1.43 Å vs. 1.53 Å, respectively) and due to the larger endocyclic C–O–C valence angle (112–114°) as compared to C–C–C valence angle (109°) of cyclohexane. Consequently the nonbonding interactions in pyranoid forms of sugars are slightly different than in cyclohexane. Second, the chair conformers of pyranoid rings are asymmetric. Third, for all pyranoid forms of sugars two distinct chair conformations are possible whereby very often one is much more stable than the other.

When describing various pyranoid conformations the following conventions are commonly used:

1. Conformations are designated: C, for the chair, B for the boat, S for the twist-boat, and H for the half-chair conformation.
2. A reference plane must always be chosen so that it contains four of the ring six atoms. If an unequivocal choice is impossible, as with the chair and twist-boat conformers, the reference plane is chosen so that the lowest numbered carbon in the ring is displaced from this plane.
3. Ring atom(s) that lie(s) above the reference plane (numbering clockwise from above) is/are written as superscript(s) and precede(s) the letter designating the conformation, while the ring atom(s) that lie(s) below the reference plane is/are written as subscript(s) and follow the letter designating the conformation.



45 $^4C_1$ conformation

46 $^1C_4$ conformation

Fig. 2.16

Thus as shown in Fig. 2.16, the reference plane for the two possible chair conformations of a pyranoid ring is chosen so that they contain O, C2, C3, and C5 atoms. When the C1 atom is below and the C4 atom above the reference plane the chair conformation is designated as $^4C_1$; when the C1 atom is above and the C4 atom below the reference plane, it is designated as $^1C_4$. Since enantiomeric conformers have different descriptors the $^4C_1$ (D) conformer is the enantiomer of $^1C_4$ (D) conformer. For this reason conformational descriptors should always be used in reference to either the D- or the L-series. This can be illustrated with the $^4C_1$ and $^1C_4$ conformers of methyl α-D- and α-L-ribopyranosides (*47* and *48*, respectively) (Fig. 2.17).

An alternative method to ascribe the descriptors $^4C_1$ and $^1C_4$ to two pyranoid conformers is as follows: when the atom numbering is clockwise (looking from the above) and the plane containing the C2, C4, and O5 (ring oxygen) is above the plane containing C1, C3, and C5 carbons, the ring conformer is $^4C_1$ (*49*); similarly, when the atom numbering is anticlockwise (looking from the above) and the plane

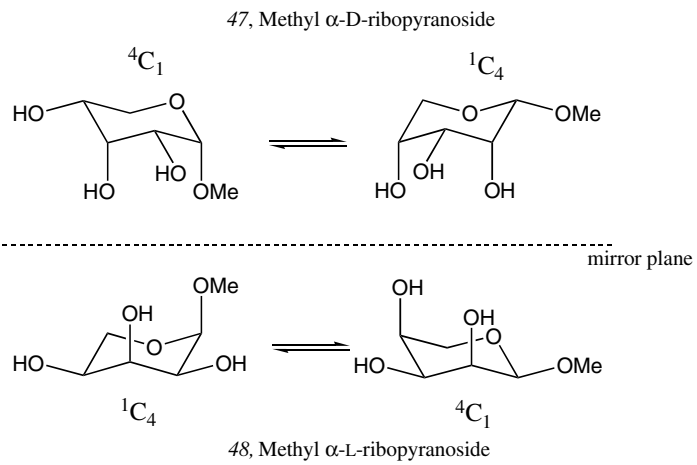


Fig. 2.17

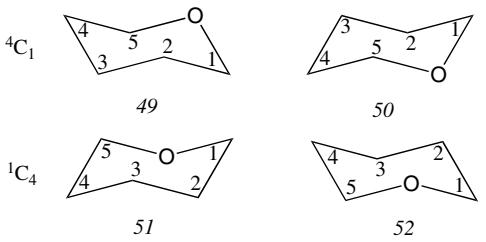
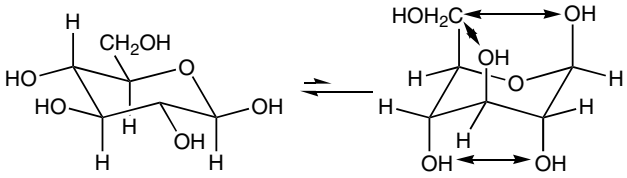


Fig. 2.18

containing the C2, C4, and O5 (ring oxygen) is below the plane containing the C1, C3, and C5 carbon atoms, the conformer is again $^4C_1$ (*50*). However, when the atom numbering is clockwise (looking from above) and the plane containing the C1, C3, and C5 carbon atoms is above the plane containing the C2, C4, and O5 (ring oxygen) the conformer is $^1C_4$ (*51*). The conformer is again $^1C_4$ (*52*), when numbering is anticlockwise and the plane containing the C1, C3, and C5 carbon atoms is below the plane containing C2, C4, and O5 (ring oxygen) (Fig. 2.18).

The hydroxymethyl group (the C6 carbon) of a hexopyranose will always assume the equatorial orientation because it is, as the largest substituent on a pyranoid ring, subjected to largest nonbonded steric interactions with other ring substituents. Consequently, whether a glycopyranose will adopt the $^4C_1$ or the $^1C_4$ conformation will depend on in which conformation the hydroxymethyl group is equatorially oriented. Thus, in D-series the hydroxymethyl group is oriented equatorially in $^4C_1$ conformation, whereas in L-series the hydroxymethyl group is oriented equatorially in $^1C_4$ conformation.

For example, β-D-glucopyranose normally exists in $^4C_1$ conformation, with the largest substituent (hydroxymethyl group) equatorially oriented (*53* in Fig. 2.19). In

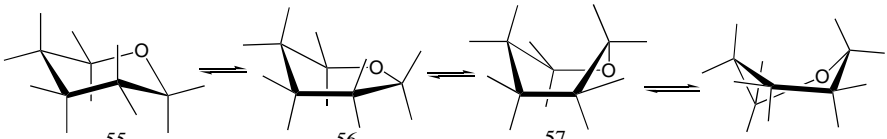


53 *54*

$^4C_1$ Conformation of β-D-glucopyranose $^1C_4$ Conformation of β-D-glucopyranose

Fig. 2.19

the $^1C_4$ conformation the hydroxymethyl group of β-D-glucopyranose will be axially oriented and subjected to two strong 1,3-*syn*–axial interactions with the C1 and the C3 hydroxyl groups (*54*); in addition, the axially oriented C2 hydroxyl group will be involved in 1,3-*syn*–axial interaction with the C4 hydroxyl group additionally destabilizing this conformation (Fig. 2.19).



55 *56* 57 *58*

Fig. 2.20

By analogy to conformational interconversions of cyclohexane rings, the $^4C_1$ and the $^1C_4$ conformers of a pyranoid sugar can also undergo interconversion. This is shown in Fig. 2.20. The rigid $^4C_1$ chair pyranoid conformer converts, via a transition state that resembles a half-chair conformation, to flexible boat and twist-boat conformations which can then either convert back, via the same transition state, to initial $^4C_1$ conformation or to a rigid $^1C_4$ conformation. Six different twist-boat conformers and six different boat conformers may be identified in the course of boat/twist-boat pseudorotation pathway of a pyranoid ring (Fig. 2.21). However, similar to the cyclohexane ring, twist-boat conformers are found to be much less stable than $^4C_1$ and $^1C_4$ chair conformations and their presence in conformational equilibria can be considered in most instances negligible.

Calculation of Conformational Energies of Pyranoses

The prediction of conformational properties of pyranoid form of a monosaccharide can be done only if the relative free energies of two chair forms are known. Angyal [35, 46, 47] has developed a semiempirical method for obtaining the values of these relative free energies by taking both steric and electronic interactions into consideration [48].

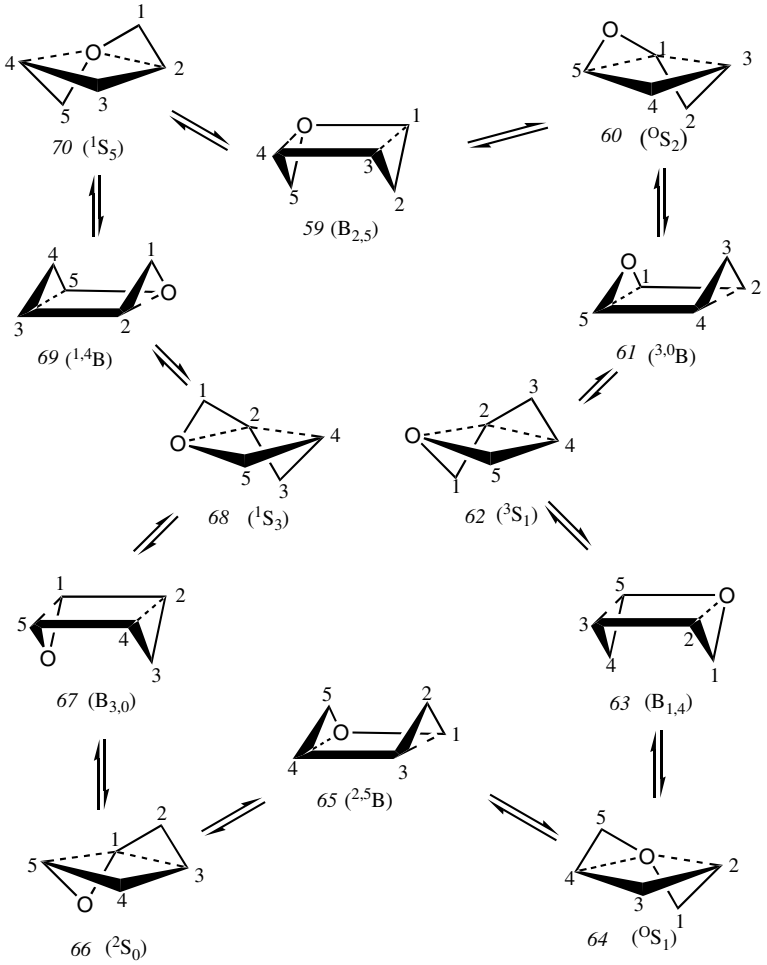


Fig. 2.21

The numerical values for nonbonding interactions in pyranoid structures of monosaccharides were obtained from conformational studies of cyclitols and some model pyranose sugars.

However, this semi-quantitative calculation of relative free energy of cyclitols and pyranoses in aqueous solutions is based on a number of assumptions, of which the following three are the most important.

1. *The pyranose and the cyclohexane rings have the same geometry*. This is only partially true since the replacement of one ring carbon with an oxygen results in considerable flattening of the six-membered ring due to (1) shorter C–O bonds (they are ca. 10% shorter than C–C bonds, i.e., 1.42 Å vs. 1.54 Å, respectively)

and (2) due to larger endocyclic O–C–O bond angle (112–114°) with regard to the endocyclic C–C–C bond angle (109°).

2. *In aqueous solutions the intramolecular hydrogen bonds do not play any role in conformational equilibria.*
3. *The relative free energy of conformers can be obtained by simple addition of (1) energies of various nonbonded interactions between ligands, (2) energies of electronic interactions, and (3) entropy differences*. The assumption is made that *the contributions of these individual thermodynamic quantities are independent of each other.*

Although none of the above assumptions is strictly true, the success of this approach in practice suggests that the errors introduced by making these assumptions are quite small.

If the energy contributions due to bond length deformation strain and bond angle bending strain are considered to be negligible, then only two types of nonbonded interactions are important for the conformational analysis of hexopyranoses:

(1) 1,3-*Syn*–axial nonbonded interactions between *syn*–axial ligands (excluding the *syn*–axial interaction between two hydrogen atoms). This interaction is designated as X_a:Y_a.
(2) 1,2-Nonbonded interactions between ligands on two vicinal (adjacent) carbon atoms that are in *gauche* conformation (again excluding the *gauche* interaction between two hydrogen atoms). This interaction is designated as X_1:Y_2.

The standard conformational free energy difference between two conformers can be calculated from the conformational equilibrium constant according to the equation:

$$\Delta G_X^0 = -RT \ln K \tag{1}$$

where ΔG_X^0 is the standard conformational free energy difference, R is the universal gas constant (1.98726 cal/deg mol), T is the absolute temperature in Kelvin, and K is the equilibrium constant.

The most of interaction energies in pyranoid forms of sugars were determined by studying the equilibrium composition of tridentate borate complexes of cyclohexitols having three hydroxyl groups in *cis*-1,3,5 relationship (this arrangement is not possible in sugar pyranoid forms (Fig. 2.22)).

The formation of tridentate complex involves the initial inversion of more stable chair form *71*, in which the three hydroxyl groups are equatorially oriented, to the alternative chair conformation *72*, in which they are all axial (Fig. 2.22). This conformation is then capable to form the borate complex. Tridentate complexes are formed in the 1:1 ratio from their components (cyclitols and borate) and are strong acids, unlike borate complexes with vicinal diols that are weak acids (the acid strength of the latter complexes is comparable to boric acid). Consequently, the formation of tridentate complex lowers the pH of borate solutions. The boric

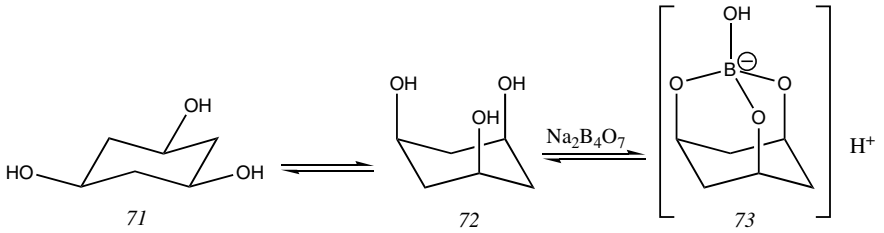


Fig. 2.22

acid itself is a weak Lewis acid with little tendency to form tetrahedral borate anion $B(OH)_4^-$, because its planar form is considerably stabilized by resonance involving the limiting structures $H^+O{=}B^-(OH)_2$. From the change in pH of the borate solution caused by successive addition of a cyclitol, the equilibrium constant K of complex formation can be calculated (Equation (1)) [49]

$$K = [\text{Complex}^-]/[\text{Borate}^-][\text{Cyclitol}] \tag{2}$$

The equilibrium constants for the formation of borate complexes with *scyllo*-quercitol *74, myo*-inositol *75*, *epi*-quercitol *78, epi*-inositol *79*, *cis*-quercitol *82*, and *cis*-inositol *83* are shown in Figs. 2.23 and 2.24.

Since the equilibrium constants of tridentate borate formation depend on nonbonded interactions in the complex, the values of interaction energies can be calculated from K. In order to do so, two assumptions were made:

(1) Free energy of formation of tridentate anion from axial *cis*-1,3,5-hydroxyl groups and borate ion is independent of the nature of other substituents on cyclohexane ring
(2) Free energies of conformational isomers are additive functions of energy terms associated with the presence of nonbonded interactions, that is, the occurrence of one interaction in a molecule does not affect the magnitude of another one

The stability of the complex depends on steric orientation of free hydroxyl groups in the complex: the more these are in the axial position, the less stable the complex is. Since the equilibrium constants of tridentate borate formation depend on nonbonded interactions of the free hydroxyl groups, the values of these interaction energies were calculated from equilibrium constants (Figs. 2.23, 2.24, and 2.25).

The interaction energies are calculated in the following way. The energies of each nonbonded interaction in individual cyclitols, and in the tridentate borate complexes, are listed and separately added up. For borate complexes a term is added to account for the free energy change on formation of the tridentate borate complex from the three hydroxyl groups; and the difference between the totals for each cyclitols and for its borate complex is equated with the experimentally determined free energy

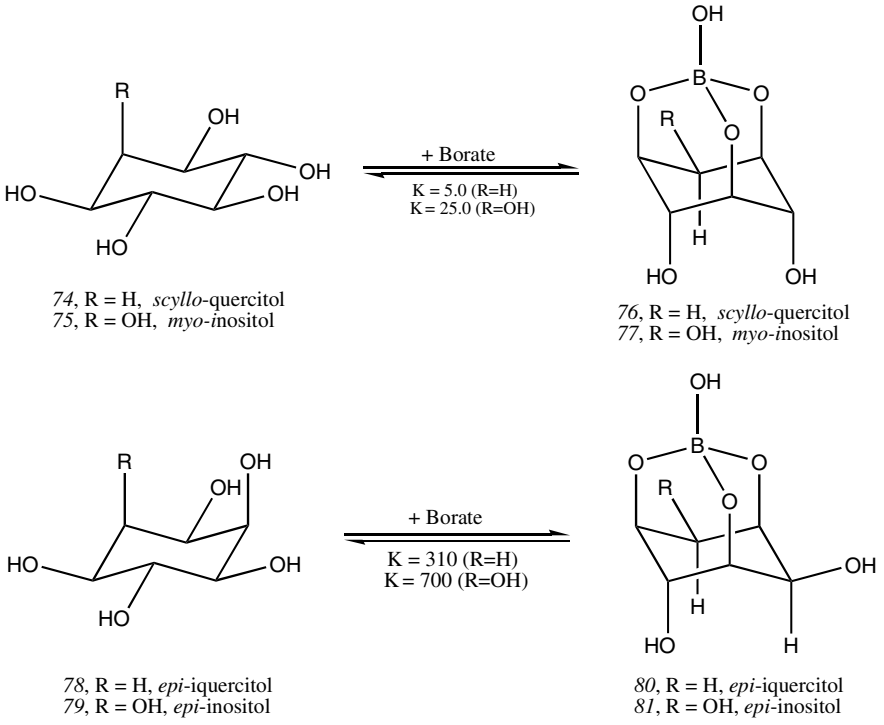


Fig. 2.23

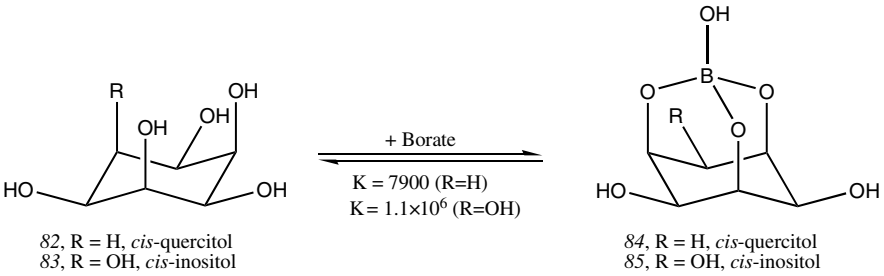


Fig. 2.24

difference (calculated from $\Delta G^0 = -RT\ln K$). A series of equations resulted from which all unknown quantities were calculated [50, 51] (Table 2.1).

Thus, for example, from Fig. 2.23 we see that for *scyllo*-quercitol *74* the equilibrium constant K for the complex formation with borate is 5. This corresponds to ΔG^0 value of –0.95 kcal/mol. Since ΔG^0 is equal to the difference between the sum of nonbonded interactions in the complex *76* which is $2(O_a{:}H_a) + (O_a{:}O_a)$ and the

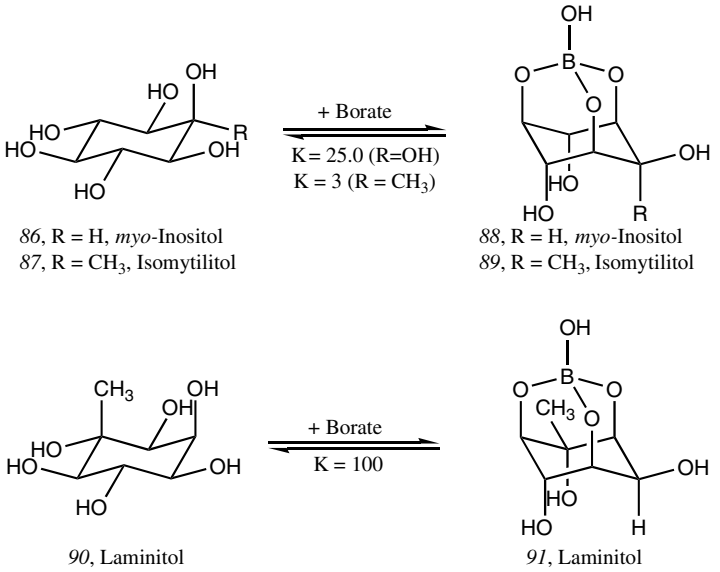


Fig. 2.25

Table 2.1 The values for 1,2-*gauche* and 1,3-*syn*–axial interactions between the ligands on a pyranoid ring (excluding the interactions between hydrogen atoms)

Interaction	ΔG^0 (kcal/mol at 25°C)
O_1:O_2	0.35
C_1:O_2	0.45
O_a:H_a	0.45
C_a:H_a	0.9
O_a:O_a	1.9
C_a:O_a	2.5*
Anomeric effect	0.55–3.2**
Δ2 effect	1.36

* Determined at 40°C

** Value of 0.55 kcal/mol is for free sugars; for OMe it is 0.9 kcal/mol, and for 1-halogens higher.

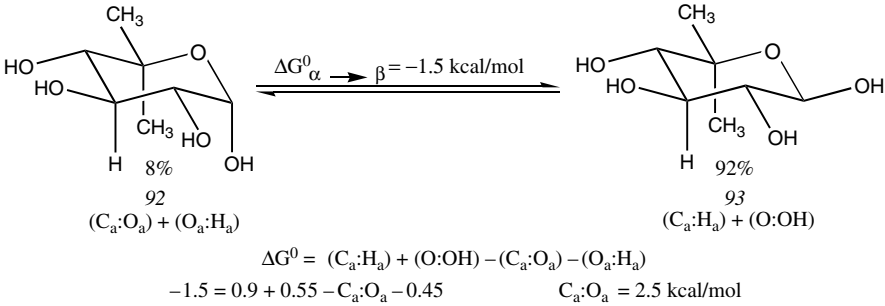
sum of nonbonded interactions in *scyllo*-quercitol *74* which is $4(O_1{:}O_2)$, one can write

$$\Delta G^0 = 2(O_a{:}H_a) + (O_a{:}O_a) + \Delta G^0_F - 4(O_1{:}O_2) = -0.95\,\text{kcal/mol}$$

In analogous fashion, another five equations can be written for the other five cyclitols from Figs. 2.23 and 2.24, and the set of six simultaneous equations can be solved for $(O_1{:}O_2)$, $(O_a{:}H_a)$, $(O_a{:}O_a)$, and $\Delta G^0{}_F$. The value found for $\Delta G^0{}_F$ is –2.5 kcal/mol.

In order to determine the interaction energies of hydroxymethyl group that is needed for the calculation of conformational energies in pyranoid rings, it was assumed that conformational energy of hydroxymethyl group is not very different from conformational energy of methyl group in aqueous solvents. Preliminary experiments [52] have indicated that interactions of the methoxymethyl group are approximately of the same value as those of methyl group. Based on this one can safely assume that this would also apply to the hydroxymethyl group.

The values for carbon–oxygen [(C_a:O_a) and (C_1:O_2)] and carbon–hydrogen (C_a:H_a) interactions were determined similarly as was done previously, only the methyl cyclitols were used for the formation of tridentate borate complexes such as *myo*-inositol *86*, isomytilitol *87*, and laminitol *90* (Fig. 2.25). From equilibrium constants and the sums of nonbonded interactions in cyclitols and their corresponding tridentate borate complexes conformational free energies were again calculated. The obtained values are listed in Table 2.1.



92 (C_a:O_a) + (O_a:H_a)

93 (C_a:H_a) + (O:OH)

$$\Delta G^0 = (C_a{:}H_a) + (O{:}OH) - (C_a{:}O_a) - (O_a{:}H_a)$$

$$-1.5 = 0.9 + 0.55 - C_a{:}O_a - 0.45 \qquad C_a{:}O_a = 2.5 \text{ kcal/mol}$$

Fig. 2.26

It should be noted that the 1,2-interactions between the two vicinal oxygen atoms (equatorial–equatorial or axial–equatorial) are considered to be identical.

Alternatively, from a study of the equilibrium in aqueous solution between the α- and β-anomers of 6-deoxy-5-C-methyl-D-*xylo*-hexopyranose value of 2.5 kcal/mol was obtained for the (C_a:O_a) (Fig. 2.26).

The value for (C_a:H_a) is assumed to be one-half the conformational energy of a methyl group, i.e., 0.9 kcal/mol ($-\Delta G^0_{\text{methyl}} = 1.8$ kcal/mol [52]).

In addition to nonbonding interaction energies that have been so far determined there is another stereoelectronic interaction that has to be taken into account when calculating the free energies of pyranoses and that is the so-called "anomeric effect." The existence of this stereoelectronic effect was first recognized by Edwards [53] but it was given its name and exhaustively studied by Lemieux [54] and has become the subject of study of many investigators (this topic will be discussed later to a much greater detail). It is related to the composition of equilibrium mixtures of free sugars in aqueous solutions which seemed to be in violation of the classical postulates of conformational analysis of cyclohexane. The aqueous solution of D-glucose, for example, contains at equilibrium 36% of α-D-glucose and 64% of the

β-D-glucose, corresponding to a free energy difference of only 0.35 kcal/mol, in spite of the fact that there are in α-D-glucose two O_aH_a interactions each one raising the free energy of α-D-glucose by 0.45 kcal/mol for a total of 0.9 kcal/mol. Furthermore, the conformational mixture of cyclohexanol at equilibrium contains 77% of conformer with equatorial hydroxyl group *94* and 23% of conformer with axially oriented hydroxyl group *95* corresponding to a free energy difference of 0.8 kcal/mol [55] (Fig. 2.27).

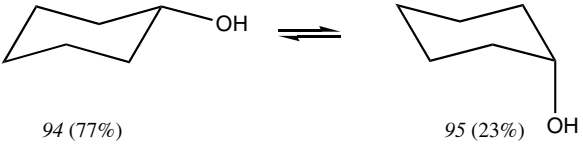


Fig. 2.27

It should be noted that the reported *A*-values in the literature for the hydroxyl group vary significantly and depend upon the method used for its determination. Thus for example, from esterification studies Eliel [56] determined that the *A*-value for OH is 0.5 kcal/mol, whereas Subotin et al. [57] found from ^{13}C NMR studies of cyclohexanol equilibrium at low temperatures (–80°C) the *A*-value for hydroxyl group to be 1.02 kcal/mol.

Figure 2.28 illustrates how the value for the anomeric effect (O:OH) was determined. As can be seen the anomeric effect is lowest for sugars having the C2 hydroxyl group equatorially oriented and highest for sugars having the C2 hydroxyl group axially oriented. The 2-deoxy sugars have the anomeric effect between these two extremes.

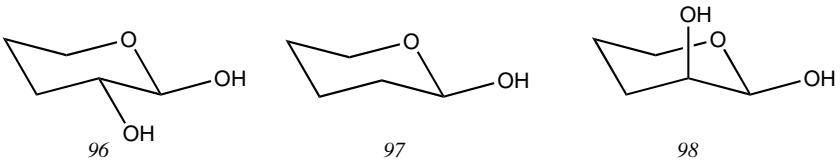
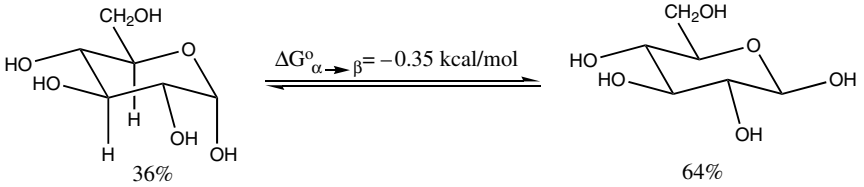


Fig. 2.28

Since the C2 carbon of 2-deoxy sugars bears no electronegative substituent (hydroxyl oxygen) which can interfere with the electronic properties of the C1 carbon and thus with the anomeric effect, then 0.85 kcal/mol can be taken as the value for the anomeric effect. The introduction of an equatorial electronegative substituent at the C2 carbon (hydroxyl group) decreases the value of anomeric effect (O:OH = 0.55 kcal/mol), whereas the introduction of an axial electronegative substituent (hydroxyl group) at the C2 carbon of a hexopyranoside increases the value of the anomeric effect (O:OH = 1.0 kcal/mol) (Fig. 2.30).

D-Glucopyranose

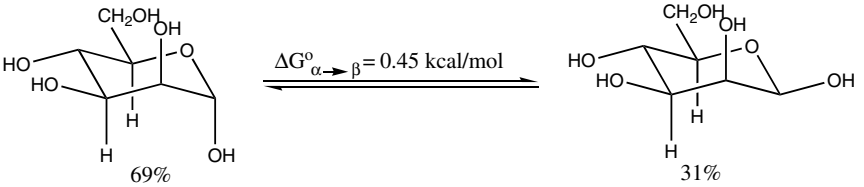


36% 64%

Interactions: 2 (O_a:H_a) Interactions: (O:OH)

ΔG^o = (O:OH) – 2 (O_a:H_a) –O.35 = (O:OH) – 0.9 (O:OH) = 0.55 kcal/mol

D-Mannopyranose

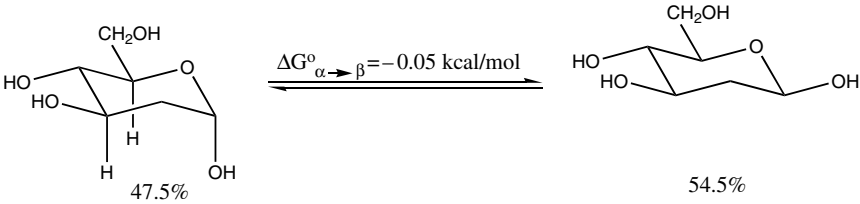


69% 31%

Interactions: 2 (O_a:H_a) Interactions: (O:OH) + (O_1:O_2)

ΔG^0 = (O:OH) + (O_1:O_2) – 2 (O_a:H_a) 0.45 = (O:OH) + 0.35 – 0.9 (O:OH) = 1.0 kcal/mol

2-Deoxy-D-glucopyranose



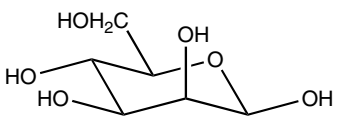
47.5% 54.5%

Interactions: 2 (O_a:H_a) Interactions: (O:OH)

ΔG^0 = (O:OH) – 2 (O_a:H_a) – 0.05 = (O:OH) – 0.9 O:OH) = 0.85 kcal/mol

Fig. 2.29

The increased values for the anomeric effect of sugars having the C2 hydroxyl group axially oriented, as, for example, in D-mannose, was originally considered as a separate electronic interaction and was named by Reeves [58, 59] Δ2 effect. The originally suggested explanation for the high value of the anomeric effect of D-mannose was that the C2 axial hydroxyl group in β-D-mannopyranose lies parallel and coplanar with the resultant dipole of the C1–O5 and the C1–O1 oxygens (*100* in Fig. 2.30) introducing thus an additional destabilization.



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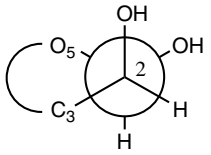

100

Fig. 2.30

If both the C2 and C3 carbons bear an axial hydroxyl group they are considered [47] to cancel out each other and the value of 0.85 kcal/mol is used for the anomeric effect.

In Table 2.2 are given the compositions of the equilibrium mixtures of aldoses after dissolution in water as determined by NMR [61].

The equilibrium compositions of the sugars in solutions are affected by temperature, by the nature of solvent, and by the presence of substituents. In less polar solvents than water, the anomeric effect increases favoring the α-pyranose over the β-pyranose form if the sugar belongs to D-series and is in $^4C_1$ conformation. Aldoses with an axial C2 hydroxyl group (mannose, lyxose) contain much higher proportion

Table 2.2 Predominant conformations of D-aldohexo- and D-aldopentopyranoses in aqueous solution

Aldose	Conformation found by		Calculated interaction energies (kcal/mol)	
	NMR [63–65]	Calculation [66]	C1	1C
α-D-Allose	C1	C1	3.9	5.35
β-D-Allose	C1	C1	2.95	6.05
α-D-Altrose	C1, 1C	C1, 1C	3.65	3.85
β-D-Altrose	C1	C1	3.35	5.35
α-D-Glucose	C1	C1	2.4	6.55
β-D-Glucose	C1	C1	2.05	8.0
α-D-Mannose	C1	C1	2.5	5.55
β-D-Mannose	C1	C1	2.95	7.65
α-D-Gulose		C1	4.0	4.75
β-D-Gulose	C1	C1	3.05	5.45
α-D-Idose	C1, 1C	C1, 1C	4.35	3.85
β-D-Idose		C1	4.05	5.35
α-D-Galactose	C1	C1	2.85	6.3
β-D-Galactose	C1	C1	2.5	7.75
α-D-Talose	C1	C1	3.55	5.9
β-D-Talose		C1	4.0	8.0
α-D-Ribose	C1, 1C	C1, 1C	3.45	3.55
β-D-Ribose	C1, 1C	C1, 1C	2.5	3.1
α-D-Arabinose	1C	1C	3.2	2.05
β-D-Arabinose		C1, 1C	2.9	2.4
α-D-Xylose	C1	C1	1.95	3.6
β-D-Xylose	C1	C1	1.6	3.9
α-D-Lyxose	C1, 1C	C1, 1C	2.05	2.6
β-D-Lyxose	C1	C1	2.5	3.55

of the α-pyranose form in dimethyl sulfoxide than in water, whereas sugars with an equatorial C2 hydroxyl group (glucose, xylose) have approximately the same equilibrium composition in both solvents [62, 63].

The conformations of aldohexopyranoses, in aqueous solutions, are, as seen from the data in Table 2.2, controlled mainly by the orientation of hydroxymethyl group, which is the bulkiest substituent and as such tends to assume the equatorial position. Hence, all of the β-D-anomers are predominantly in the C1 ($^4C_1$) conformation, because in the 1C ($^1C_4$) form there is a large *syn*–axial interaction between the axial hydroxymethyl and the axial anomeric hydroxyl groups, as shown in Fig. 2.18. This interaction is absent from 1C conformation of α-anomers but most of them also prefer the C1 conformation; only α-D-idopyranose exists predominantly in the 1C form; the aqueous solutions of α-D-altropyranose and α-D-gulopyranose have substantial proportions of both chair forms at equilibrium.

In the absence of a hydroxymethyl group at C5, the conformations of the aldopentopyranoses are controlled by the orientation of the hydroxyl groups. Thus, the D-arabinopyranoses favor the 1C form, α-D-lyxopyranose and α-D-ribopyranose are conformational mixtures, and the other pentoses are predominantly in the C1 form.

A relationship between the percentage of the more stable conformer at equilibrium, equilibrium constant K, and standard free energy difference at 25°C for an equilibrium of isomers A ⇌ B is given in Table 2.3.

Table 2.3 Relationship between the % of the morer stable isomer in equilibrium, the equilibrium constant and the conformational energy difference

% of more stable isomer	K	ΔG^0 (kcal/mol)
50	1.00	0
60	1.50	0.119
70	2.33	0.502
80	4.00	0.973
90	9.00	1.302
95	19.00	1.744
98	49.00	2.306
99.9	999.0	4.092
99.99	9999	5.456

As it can be seen the difference in free energies between two conformers of 0.973 kcal/mol results in fourfold excess of the more stable isomer in the equilibrium mixture.

Computational studies of carbohydrate structures were reported by many groups [67–78]. The early studies were based partly on experimental data, and partly on ab initio calculations, usually at the Hartree–Fock level. The experimental data, though reliable, were normally determined in solutions, very often in water, or some other hydroxylic solvents, with sugar concentrations most often unknown. Hence, one must be concerned about solvation effects in the interpretation of these data. An additional difficulty was that ab initio calculations of carbohydrates required the use of a fairly large basis set in order to obtain what is hoped to be the chemical accuracy.

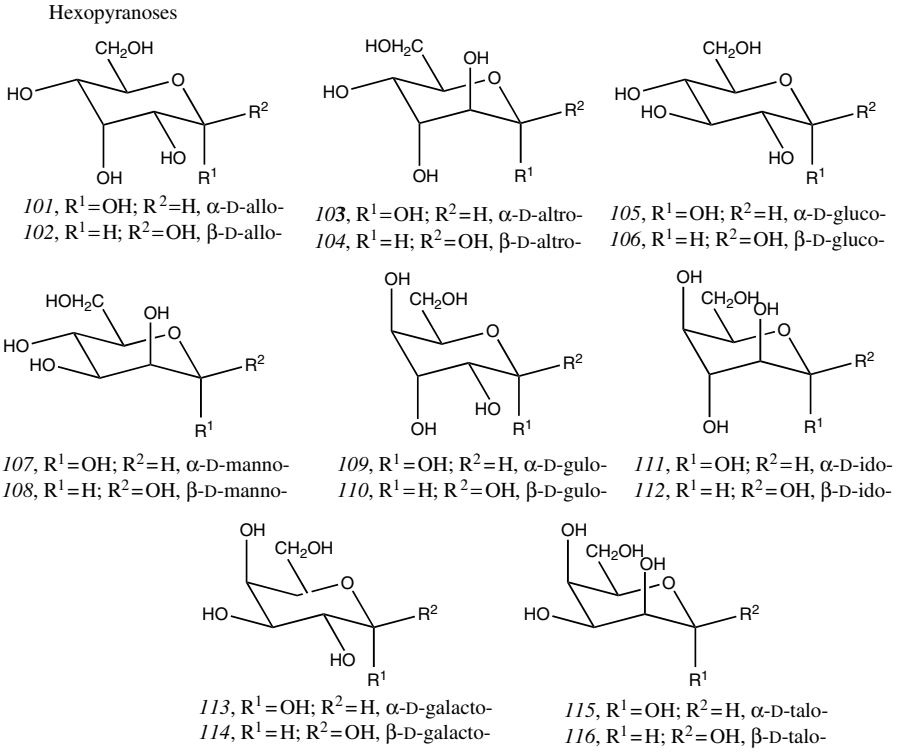

Fig. 2.31 Structures of hexopyranoses depicting the orientations of their secondary hydroxyl groups

Figure 2.31 shows the preferred conformations for aldohexopyranoses in aqueous solution as determined by NMR spectroscopy [60]. Allinger et al. [79] have reported the ab initio calculations of 84 conformations of 12 different sugars (hexoses), in both pyranose and furanose forms. They used the same MM4 force field calculation that they used for the calculation of simple alcohols and ethers, but for carbohydrates they had to make some important additions to take into the account the anomeric affect, gauche effect, and the Δ2-effect which are all present in sugars but not in simple alcohols and ethers (Fig. 2.32).

Fig. 2.32

The Δ2-effect is energetically important only in a few sugars, such as β-D-altropyranose *104*, β-D-mannopyranose *108*, β-D-idopyranose *112,* and β-D-talopyranose *116* (Fig. 2.31) and tends to stabilize the α anomer relative to β, by about 1.36 kcal/mol. It should be noted that a recent study found no evidence that Δ2-effect plays an important role in determining the conformational properties of sugars [80].

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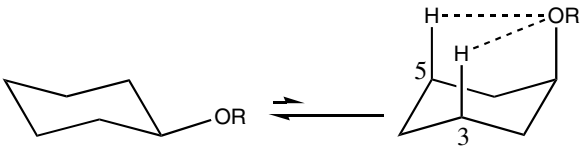
Chapter 3
Anomeric Effect

In substituted cyclohexanes, such as cyclohexanol or its methyl ether, the substituent will preferably assume the equatorial position as opposed to the axial one, due to fewer nonbonded interactions with other ligands (in this case the C3 and the C5 hydrogen atoms) on the cyclohexane ring [1–5]. Thus, the conformational mixture of cyclohexanol or its methyl ether contains, at equilibrium, 89% of the conformer with equatorially oriented hydroxyl or methoxy group and 11% of the conformer with axially oriented hydroxyl or methoxy group, indicating clear preference for the equatorial conformer (Fig. 3.1).



89%
1

11%
2

R = H, CH_3

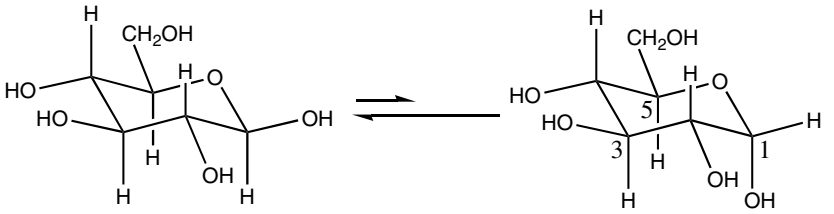
Conformational equilibrium of cyclohexanol

Fig. 3.1

Endo-anomeric Effect

The equilibrium mixture of two D-glucopyranose anomers contains 63% of equatorial (β) and 36% of axial (α) anomer (Fig. 3.2). Thus, in spite of the presence of two O_a:H_a 1,3-*syn*–axial interactions between the anomeric oxygen and the C3 and C5 hydrogens present in α-anomer that destabilize this isomer by 0.9 kcal/mol the amount of the α-anomer in equilibrium mixture is significantly higher than in cyclohexanol. It should be noted that this amount of destabilization energy would require that the equilibrium mixture of two D-glucopyranose anomers does not contain more than ca. 20% of α-anomer.

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_3,



63%(β) 36%(α)

3 *4*

Anomeric equilibrium of D-glucopyranose

Fig. 3.2

The studies of conformational equilibria of anomers of other glycopyranoses have shown that monosaccharides with the axial anomeric oxygen (conformationally less favored than equatorial ones) are also present in higher percentages than expected (Tables 3.1 and 3.2).

Table 3.1 Composition of aqueous solution of some monosaccharides at equilibrium [6]

	Estimated from oxidation[a] (%)		Calculated from optical rotation[b] (%)	
Sugar	α	β	α	β
D-Glucose	37.4	62.6	36.2	63.8
D-Mannose	68.9	31.1	68.8	31.2
D-Galactose	31.4	68.6	29.6	70.4

[a]Oxidation of sugar solutions at 0°C with bromine water in the presence of $BaCO_3$
[b]Calculated from optical rotation, assuming that only two constituents are present in the solution.

Table 3.2 Relative free energies (kcal/mol) and the percentage of α-anomer for selected D-aldohexo- and D-aldopentopyranoses in aqueous solution at equilibrium[a]

				α-Anomer (%)	
Pyranose	$G^0{}_\alpha$	$G^0{}_\beta$	G^0_{pyranose}	Calculated	Experimental
Glucose	2.4	2.05	1.8	36	36
Galactose	2.85	2.5	2.25	36	27
Mannose	2.5	2.95	2.25	68	67
Idose	3.65	4.0	3.4	64	46
Ribose	3.1	2.3	2.15	20.5	26
Arabinose	1.95	2.2	1.65	60	63
Xylose	1.9	1.6	1.35	37	33
Lyxose	1.85	2.4	1.65	72	71

[a]By ^{1}H nuclear magnetic resonance [7, 8].

In the case of D-glucose and D-galactose the anomer with the equatorial C1 hydroxyl group (β) is, as expected, more stable; D-mannose represents a special case and will be discussed later.

The preference for axial orientation of the C1 substituent in D-glucopyranose was found to increase with the increase of electronegativity of the C1 substituent (Table 3.3).

Table 3.3 Anomeric equilibria of 1-*O*-substituted D-glucopyranoses

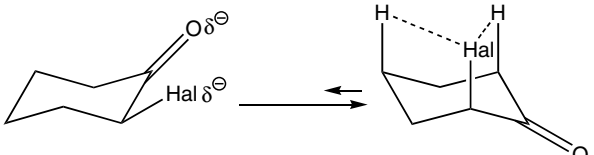
Compound	C1 substituent	Axial isomer (%)
D-Glucopyranose[a]	OH	36
Methyl D-glycopyranoside[b]	OMe	67
Penta-*O*-acetyl-D-glycopyranose[c]	OAc	86
Tetra-*O*-acetyl-D-glucopyranosyl chloride[d]	Cl	94

[a]In water at 25°C.
[b]In methanol at 25°C.
[c]In acetic acid–acetic anhydride at 25°C using perchloric acid as catalyst [9, 10].
[d]In acetonitrile [11] at 30°C.

In 1928 Pacsu discovered [12] that the β-anomers of acetylated alkyl glycopyranosides anomerize in the presence of stannic chloride or titanium tetrachloride in chloroform to α-anomers suggesting the greater thermodynamic stability of anomeric alkoxy group in the axial orientation. A possibility that the driving force for anomerization is somehow related to complexing reaction involving the Lewis acid catalysts (including boron trifluoride [13]) was excluded by observing the extensive β- to α-anomerization of several acetylated methyl glycopyranosides also during sulfuric acid catalyzed acetolysis [14, 15].

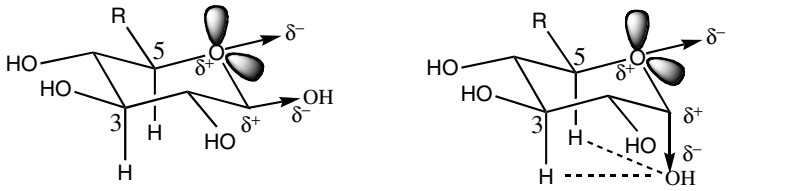
Detailed study of anomerization of peracetylated pento- and hexopyranoses [16] suggested that the preference for the axial orientation of aglycon could only be explained if one assumes that there is a special driving force which forces the 1-acetoxy group to take a *syn*-clinal orientation relative to the C5 of the pyranose ring. This driving force, named "anomeric effect" [17], was estimated to be about 1.5 kcal/mol and depended on the sugar (Fig. 3.3).

The first rationalization of a tendency for aglycons of alkyl glycopyranosides to assume axial orientation was proposed by Edward [18] and was inspired by a Corey study [19] on stereochemistry of some α-halocyclohexanones in which it was



5 *6*

Fig. 3.3



7, R = H, β-D-xylopyranose
8, R = CH_2OH, β-D-glucopyranose

9, R = H, α-D-xylopyranose
10, R = CH_2OH, α-D-glucopyranose

Fig. 3.4

determined by IR spectroscopy that the most stable conformation of α-chloro- and α-bromocyclohexanone is that chair form (*6*) in which the halogen substituent is axial. This was explained to be a consequence of dipole–dipole interaction between the C–halogen and the C=O group when halogen atom is equatorially oriented which is considered to be more important than the steric interactions in the axial conformer. By analogy, Edward proposed that the equatorially oriented electronegative aglycon group such as *O*-alkyl, halogen, etc., is subjected to energetically unfavorable dipolar interaction with the resultant dipole of two unshared electron pairs of the ring oxygen atom since these two dipoles are coplanar and equally oriented (*7* and *8*, in Fig. 3.4). This destabilization was considered to be larger than the two *syn*–axial interaction between the axially oriented aglycone (in the α-D-anomer) and the C3 and C5 hydrogen atoms and as a result the electronegative substituents such as Cl, OH, and OR at C1 of pyranosides preferred an axial orientation (*9* and *10* in Fig. 3.4). Thus the *anomeric effect was originally considered to be an electrostatic effect that destabilizes the equatorially oriented C1 electronegative substituent through dipolar interaction with the two pairs of nonbonding electrons on the ring oxygen* (Fig. 3.4)

Although recognizing that the anomeric effect is the preference of glycosides to assume that conformation in which the number of interactions between opposing unshared pairs of electrons should be at minimum (which he called e//e component of anomeric effect) [20] Lemieux [16, 17, 20] offered no explanation for the anomeric effect but did point out that the simple consideration of the effect on charge distribution arising from a change of the polar bonds from the antiperiplanar to the *syn*-clinal orientation provides a change in energy which is close to the experimentally observed value for the anomeric effect.

Thus the anomeric effect was originally considered to be an electrostatic effect that destabilizes equatorially oriented C1 electronegative substituent through dipolar interaction with the pair of nonbonding electrons on the ring oxygen (Fig. 3.4).

Comparison of two anomeric structures of D-glucopyranose (Fig. 3.4) shows that, except for the two 1,3-*syn*–axial interactions between the axial O1 and the axial H3 and H5 atoms, which are present only in α-anomer, both anomers have all other nonbonded interactions identical, including the gauche interaction between the C1 and the C2 hydroxyl groups. Consequently, the study of interconversion of two anomers

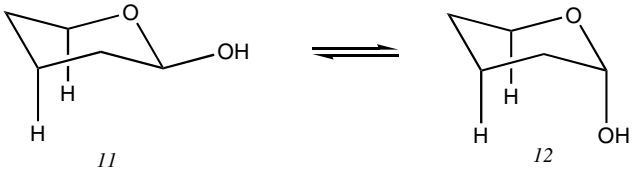


Fig. 3.5

of D-glucopyranose (*anomerization*, the isomerization of anomeric carbon) can be simplified by substituting D-glucopyranose with the 2-hydroxy-tetrahydropyran as model compound for the anomerization studies (Fig. 3.5). The free-energy difference between *11* and *12* defines the conformational free energy of hydroxyl group (the so-called *A*-value [21, 22] $= -\Delta G^0$) in 2-hydroxy-tetrahydropyran (Fig. 3.5). The *A*-value is significantly greater in protic (aqueous) solution than in aprotic solutions, possibly because of hydroxyl group solvation via hydrogen bonding that increases its effective size.

The quantitative estimate of the magnitude of anomeric effect must take into account the steric preference for equatorial orientation of an electronegative group larger than hydrogen in the corresponding cyclohexane compound. In order to do this it must be assumed that the conformational energies of hydroxyl group in 2-hydroxy-tetrahydropyran and in cyclohexanol are of the same magnitude. Although this assumption ignores the difference in geometry between cyclohexane and tetrahydropyran ring, in most cases this does not lead to significant discrepancy.

The magnitude of the anomeric effect is thus defined as the difference between the conformational free energy $(-\Delta G^0{}_X)_O$ for the equilibrium of two 2-substituted tetrahydropyran conformers (Fig. 3.6) and the conformational free energy $(\Delta G^0{}_X)$ for the equilibrium of the two analogously substituted cyclohexane (Fig. 3.7) [23].

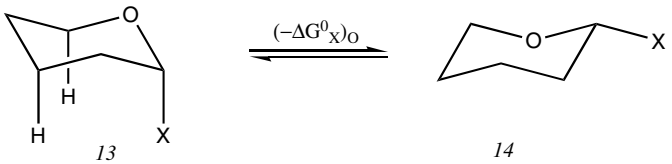


Fig. 3.6

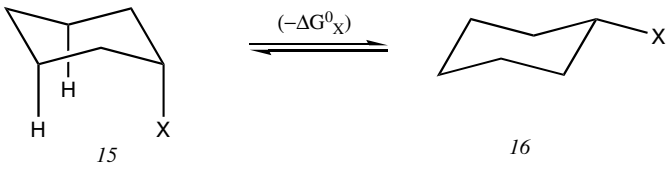


Fig. 3.7

Thus, the anomeric effect (AE or O:X, where X = OH or any other electronegative substituent such as OMe, OAc, Cl, Br, etc.) can be expressed as

$$(\text{O:X}) = (-\Delta G^0_{\text{X}}) - (-\Delta G^0_{\text{X}})_{\text{O}} \tag{1}$$

Rewriting the above equation gives the following expression for the magnitude of anomeric effect:

$$(\text{O:X}) = (\Delta G^0_{\text{X}})_{\text{O}} - (-\Delta G^0_{\text{X}}) \tag{2}$$

The value of anomeric effect in D-glucopyranose was determined in the following way. The internal energies of D-glucopyranosyl residues in both α- and β-anomer are identical since they have identical number and types of nonbonded interactions. The introduction of an electronegative anomeric substituent (hydroxyl group, halogen, etc.) into these two residues introduces the difference between their respective internal energies, depending on whether the electronegative substituent is equatorially or axially oriented. Therefore, the internal energy of α-anomer will be the sum of internal energy of D-glucopyranosyl residue, E^0, and the two *syn*–axial interactions between the axial anomeric hydroxyl group and the C3 and C5 axial hydrogen atoms of the pyranoid ring (2×0.45 kcal/mol = 0.9 kcal/mol). The internal energy of β-anomer will be the sum of internal energy E^0 of D-glucopyranosyl residue and the anomeric effect (AE). The number of gauche 1,2-interactions is identical in both α- and β-D-glucopyranose. From the composition of equilibrium mixture of α- and β-D-glucopyranose (36% vs. 64%, respectively) one can calculate that the β-anomer has lower free energy than the corresponding α-anomer by 0.35 kcal/mol [24].

Therefore,

$$E_\alpha - E_\beta = 0.35 \text{ kcal/mol}$$

If E_α is now substituted with (E^0 + 0.9) and E_β with (E^0 + AE), the following expression is obtained:

$$(E^0 + 0.9 \text{ kcal/mol}) - (E^0 + \text{AE}) = 0.35 \text{ kcal/mol}$$

Solving this equation for AE (O:OH) gives

$$0.9 \text{ kcal/mol} - (\text{O} + \text{OH}) = 0.35 \text{ kcal/mol}$$

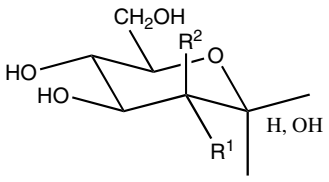
$$(\text{O:OH}) = 0.9 - 0.35 \text{ kcal/mol} = 0.55 \text{ kcal/mol}$$

Hence, the difference of 0.55 kcal/mol between 0.9 kcal/mol and 0.35 kcal/mol corresponds to the anomeric effect (O:OH) and represents the electronic stabilization of the axially oriented hydroxyl group in the α-anomer. Thus, in other words, this electronic interaction was thought to be responsible for the higher percentage

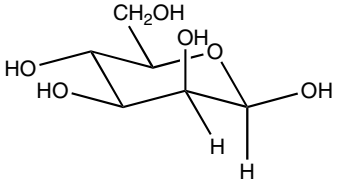
of axial anomer in an equilibrium mixture in spite of the unfavorable steric 1,3-*syn*–axial interactions between the C1 substituent and the C3 and the C5 hydrogens present in such anomers. This is in contrast to the Edward explanation for the anomeric effect as the electronic destabilization of the equatorially oriented anomer due to dipolar interaction between the equatorially oriented electronegative substituent and the resultant dipole of the two pairs of nonbonding electrons on the ring oxygen.

Similar calculations for the D-mannopyranose which at equilibrium contain 69% of α-anomer and 31% of β-anomer [25] gave the value for (O:OH) of 1.0 kcal/mol and for the 2-deoxy-D-arabino-hexopyranoses which at equilibrium contain 47.5% of α-anomer and 52.5% of β-anomer [25, 26] gave the value for (O:OH) of 0.85 kcal/mol.

Thus, the magnitude of *anomeric effect* determined in this way depends, among other factors, on the nature and on the configuration of substituent at the C2 carbon atom. In the case of β-D-mannopyranose, the C2–oxygen bond bisects the torsional angle between the C1–O1 and C1–O5 bonds (Fig. 3.8) and this dipolar interaction seems to introduce an additional electronic destabilization which is evident from the increased value for anomeric effect(1.0 kcal/mol). This interaction was considered as a separate electronic interaction and was named by Reeves [27–29] the Δ2 effect. It is now regarded as simpler to take as the base value for anomeric effect the value of 0.85 kcal/mol which is the value for 2-deoxy-arabino-hexopyranose and then when an elecronegative substituent at the C2 carbon is axial to increase this value by 0.15 kcal/mol and when the C2 substituent is equatorial to decrease it by 0.3 kcal/mol.



17, $R^1 = H$; $R^2 = OH$
18, $R^1 = R^2 = H$



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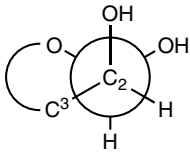
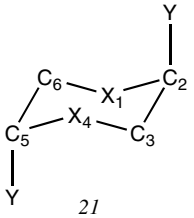


20

Fig. 3.8

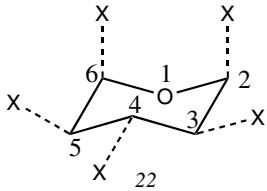
The Quantum-Mechanical Explanation

In halogeno-1,4-dioxanes ($X_1 = X_4 =$ oxygen), halogeno-1,4-thioxanes ($X_1 =$ oxygen, $X_4 =$ sulfur), and halogeno-1,4-dithianes ($X_1 = X_4 =$ sulfur; Y = Cl, Br) *21* (Fig. 3.9), the halogen atoms were found to occupy preferentially the axial orientation, which was in contradiction to the well-known situation in monohalogenocyclohexanes [30, 31]. Similarly, in 2- or 6-monochloro or monobromo tetrahydropyran (X = Cl, Br) (*22* in Fig. 3.10) the halogen atom takes up the axial



21

Fig. 3.9

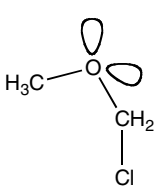


22

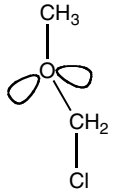
Fig. 3.10

orientation, whereas the halogen bonded to the C3, C4, or C5 carbon has a great preference for the equatorial orientation [32–34].

Study of a simple acyclic compound such as monochloromethoxymethane (*23, 24*) by electron diffraction [35, 36] (Fig. 3.11) has shown that the molecule does not exist in conformationally more stable *anti* conformation *24* (Fig. 3.11) but in *gauche* conformation *23* which is equivalent to the axial orientation in a six-membered ring. This suggests that the anomeric effect or the preference of the C–O–C–Hal system for the gauche conformations is a general phenomenon. The most intriguing finding was that the anomeric effect for Cl or Br as substituents amounts to several kcal/mol.



23, *gauche* conformation



24, *anti* conformation

Fig. 3.11

The anomeric effect has been defined as the sum of free-energy difference between the axial (favored) and the equatorial anomer plus the conformational preference (the *A*- value) for the same substituent in cyclohexane [37]. Thus the anomeric effect measures the stability of axial over an equatorial substituent in 2-substituted tetrahydropyran relative to the expected value in cyclohexane (where the equatorial substituent is favored). The anomeric effect for chlorine, bromine, and

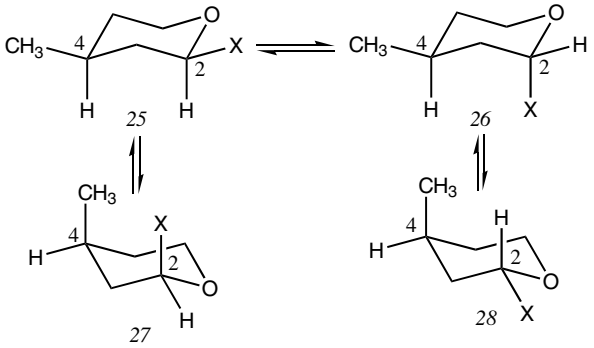


Fig. 3.12

iodine in 2-halo-4-methyl-tetrahydropyrans (Fig. 3.12) was found (by NMR) to be 2.65, > 3.2, and > 3.1 kcal/mol, respectively [34]. In polar solvents, such as acetonitrile, the value for chlorine seems to be smaller (2.0 kcal/mol) than in neat liquid (2.65 kcal/mol) [34]. However, all these values are much higher than those for the anomeric effect of hydroxy, alkoxy, or acyloxy groups in the 2-substituted tetrahydropyrans (0.9–1.4 kcal/mol); the values for the anomeric effect of these substituents were also found to be significantly solvent dependent [23, 38–41].

The initially proposed explanation for the anomeric effect [18] as a simple dipole–dipole interaction accounts therefore only for a part of the effect, but it does not represent the whole story. If one calculates the electrostatic interaction energy in *trans*-2,5-dichloro-1,4-dioxane (Fig. 3.13) (the molecular geometry of which is known from the X-ray analysis) using the values of $\mu = 2.2$ and 1.4 D for the dipole moments of C–Cl and C–O bonds and $\epsilon = 2.3$ for the dielectric constant, one arrives at the energy difference of about 1 kcal/mol in favor of the diaxial form [42]. This difference is clearly too small to account for a strong preference for diaxial conformation [43]. Consequently, it was proposed [44] that the *anomeric effect consists of two contributing components.* One substantial component is that in conformer with two axially oriented chlorine atoms (*29*) there are two gauche halogen–oxygen lone pair electron interactions (Figs. 3.13 and 3.14) (one at the C2 and one at the C5 carbon), whereas in the conformer having two chlorine atoms equatorially oriented

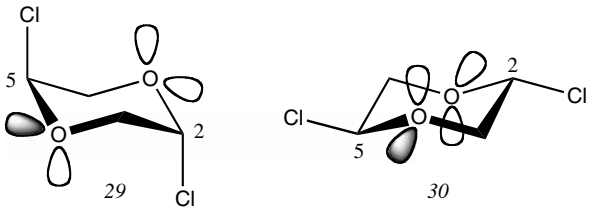
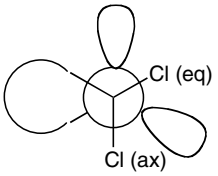


Fig. 3.13



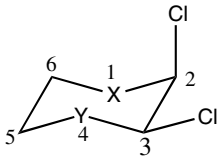
31

Fig. 3.14

(*30*) there are four gauche halogen–oxygen lone pair electron interactions (two at the C2 and two at the C5 carbon) (Figs. 3.13 and 3.14).

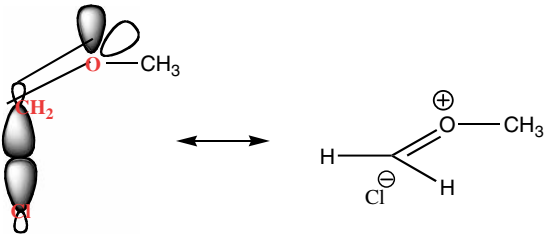
The other contributing component emerged from a study of geometry of halogenodioxanes *32*, halogenothioxanes *33*, and halogenodithianes *34* (Fig. 3.15) by X-ray crystallography and of chloromethoxymethane (*23, 24* in Fig. 3.11) by electron diffraction. The result of studies of *32* and *33* was that in all cases where the accuracy of measurements was good, the C_2–O distance is significantly shorter than the C_6–O distance (*32* in Fig. 3.15). When compared to the lengths of C–O bonds in aliphatic ethers, the C_6–O_1 bond appears to be normal, whereas the O_1–C_2 bond appears to be shorter (*32* in Fig. 3.15). A second observation was that the axial C_2–Cl bond is somewhat longer than the corresponding equatorial C_3–Cl bond [in *cis*-2,3-dichloro-1,4-dioxane (Fig. 3.15)]. The axial C_2–Cl bond was measured to be 1.819 Å, and the equatorial C_3–Cl bond 1.781 Å; the accepted values for the aliphatic C–Cl bond is 1.79 Å. These bond length abnormalities in the system C–X–C–Y suggested [45–48] that the one nonbonding electron pair of the ring oxygen is delocalized by orbital mixing with a suitably oriented σ* antibonding orbital of the C–Hal bond. As a result of this delocalization (Fig. 3.16) the C–O bond between the carbon bearing the halogen and oxygen will be strengthened (shortened) and the C–Hal bond weakened (elongated). In Fig. 3.16 two resonance forms of this structure are shown using the concept "double bond–no bond resonance." Table 3.4 lists bond distances in the C_6–X–C_2–Y system.

In Fig. 3.17 are compared the electronic distributions in chloromethoxymethane *38* and in the partial structure of *cis*-2,3-dichloro-1,4-dioxane *32* (Fig. 3.15).



32, X = Y = O
33, X = O, Y = S
34, X = Y = S

Fig. 3.15

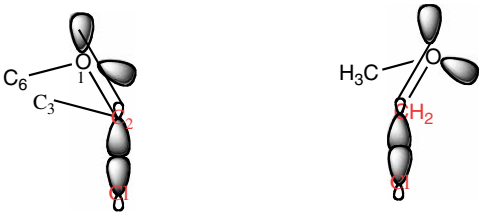


35 36

Fig. 3.16

Table 3.4 Bond distances in the group C_6–X–C_2–Y (in Angstroms) [44]

Compound	X	Y	C_6–X	C_2–X	C_2–Y
trans-2,3-Dichlorodioxane	O	Cl	1.43	1.38	1.84
cis-2,3-Dichlorodioxane	O	Cl	1.466	1.394	1.819
trans-2,5-Dichlorodioxane	O	Cl	1.428	1.388	1.845
Chloromethoxymethane	O	Cl	1.414	1.368	1.813



37 38

C_6-O-C_2-Cl fragment of cis-2, 3-dichloro-1, 4-dioxane

chloromethoxymethane

Fig. 3.17

Exo-anomeric Effect

The *exo*-anomeric effect [49] relates to the preference of the aglycon (e.g., methyl group of a methyl glycopyranoside) to be in near *syn*-clinal orientation to both the ring oxygen and the anomeric hydrogen, whereas the anomeric effect which should be more correctly called *endo-anomeric effect* relates to the preference for the axial orientation of the glycosidic oxygen of glycopyranosides. In Fig. 3.18 this is illustrated by using the C2–methoxy oxygen bond rotamers of 2-methoxy-tetrahydropyran with the methoxy group equatorially or axially oriented (*39, 41*, *43* and *40, 42*, *44*, respectively). The eclipsing of unshared electron pairs on glycosidic oxygen with the nonbonding electrons on the ring oxygen giving rise to destabilizing

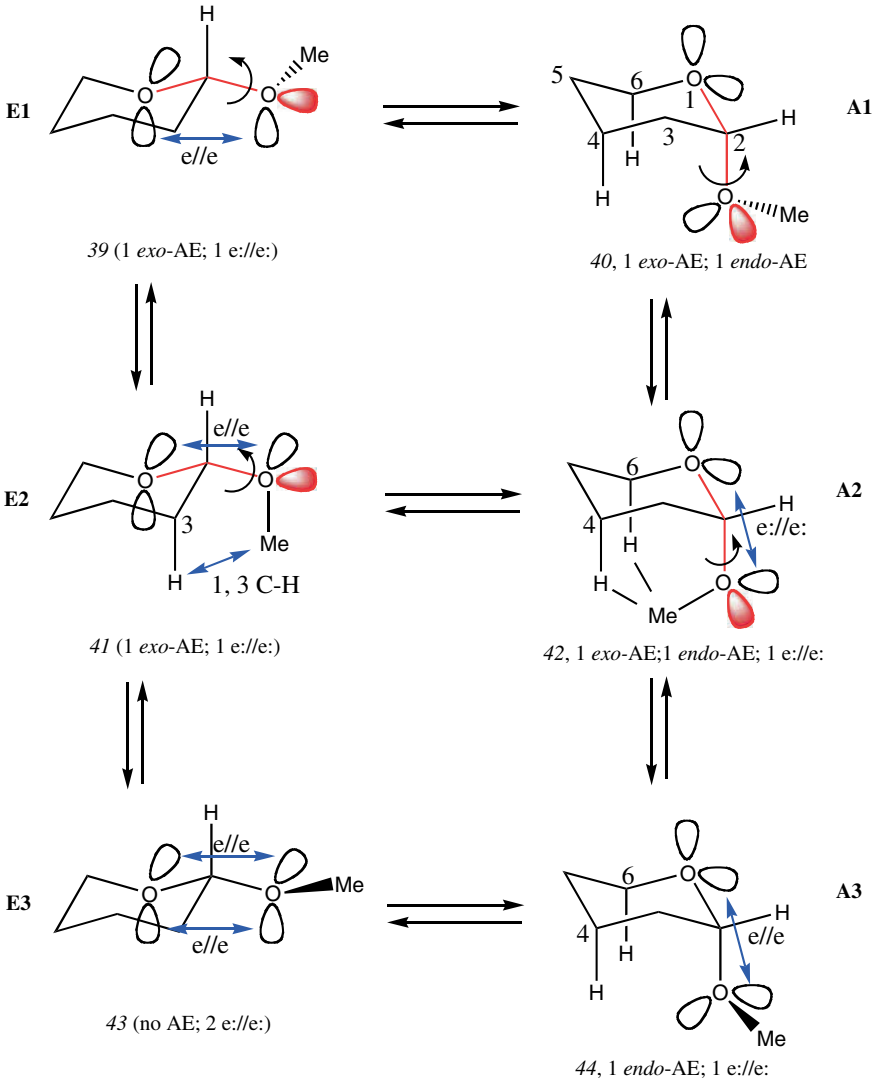


Fig. 3.18

syn–axial lone electron pair interactions is shown with a blue double-headed arrow and denoted e://e:. The *exo*-anomeric effect is shown by red bonds.

Three staggered conformations are possible for the rotation about the C1–O1 bond in both equatorial and axial conformers of a 2-methoxy-tetrahydropyran (Fig. 3.18). These are referred to as E1–E3 (*39*, *41*, *43*) and A1–A3 (*40*, *42*, *44*). In the E1 conformer (*39*) there are no *syn*–axial steric interaction but there is one *exo*-anomeric effect (stabilizing interaction) and one destabilizing *syn*–axial lone

pair (electronic) interaction. In conformer E2 (*41*) there are several steric and electronic interactions: one 1,3-*syn*–axial interaction between the methyl group and the axial C3 hydrogen atom (steric interaction), one *endo*-anomeric effect (stabilizing electronic interaction), and one destabilizing *syn*–axial interaction between two lone pair electrons (one on the glycosidic oxygen and the other on the ring oxygen). In the conformer E3 (*43*) there are only two destabilizing *syn*–axial interaction between the four lone pair electrons (two on the glycosidic oxygen and two on the ring oxygen). In axial conformer *40* there are two stabilizing electronic interactions (one *endo*- and one *exo*-anomeric effect). In conformer *42* there is one severe steric interaction between the methyl group and the two axially oriented hydrogen atoms, one at the C3 and the other at the C5 carbon. In addition to that there is one destabilizing electronic *syn*–axial interaction between the two lone pair electrons (one on the glycosidic oxygen and the other on the ring oxygen). Finally there is one stabilizing electronic interaction: the *endo*-anomeric effect. In conformer *44* there is only one destabilizing *syn*–axial electronic interaction between two lone pair electrons (one on the glycosidic oxygen and the other on the ring oxygen).

Based on the above discussion from the three equatorial conformers E1 conformer should be favored, and from the three axial conformers the conformer A1 should be favored. Thus the *exo*-anomeric effect controls the conformation of the aglycon group.

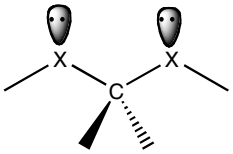
The experimental evidence, for the *exo*-anomeric effect although initially difficult to obtain, has gradually accumulated over the years and today this phenomenon is fully accepted.

For molecules in crystalline state the evidence is unequivocal. It was determined that alkyl pyranosides adopt either the A1 or the E1 conformation [41] and analysis of over 50 carbohydrate structures reveals the following regularities: for axial methyl pyranosides the torsional angle O_5–C_1–O-CH_3 (which should be 60° in A1 conformer) lies between 61 and 74° and for equatorial anomers the range is 68–87°.

There is conflicting evidence for whether the *exo*-anomeric effect is larger for the axially or equatorially oriented groups. Even the analysis of crystal structures quoted above does not give a clear answer for glycopyranosides in the solid state, and the results in solutions are equally ambiguous, particularly for oligosaccharides. One thing is, however, clear: it is dominant short-range interaction that controls the conformation about the glycosidic linkage in both α- and β-linked oligosaccharides and therefore it is important for conformational analysis of these molecules.

Generalized Anomeric Effect

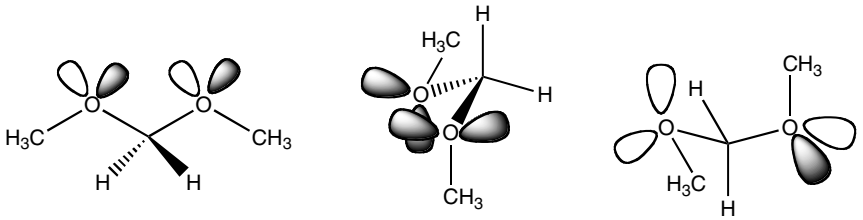
In 1968 Hutchins et al. [50] reported that there is a widespread phenomenon in structural chemistry that the conformations are strongly disfavored if the unshared electron pairs on nonadjacent atoms are parallel or *syn*-axial, as is the case for example in Fig. 3.19. This effect is thought to be the result of the repulsion of electric dipoles engendered by the unshared electron pairs. For obvious reasons Eliel



45

Fig. 3.19

proposed to call this phenomenon the "rabbit-ear effect." Although the existence of this effect has been pointed out earlier when we discussed the anomeric effect [it is the destabilizing component of the anomeric effect consisting of electrostatic repulsion of 1,3-*syn*–diaxial or 1,3-parallel unshared pairs of electrons (e://e: interaction)]. Support for this came from the finding that dimethoxymethane would tend to exist in the *gauche–gauche* conformation *48* (Fig. 3.20) rather than in the extended *trans–trans* conformation *46* with all large groups in *anti*-orientation or in *gauche–trans* conformation *47*. There are two reasons for this: the first destabilizing one is that there are two *syn*-parallel interactions between the four pairs of unshared electrons on two oxygen atoms (rabbit-ear effect) and in the *gauche–gauche* conformation there are two stabilizing *endo*-anomeric effects.



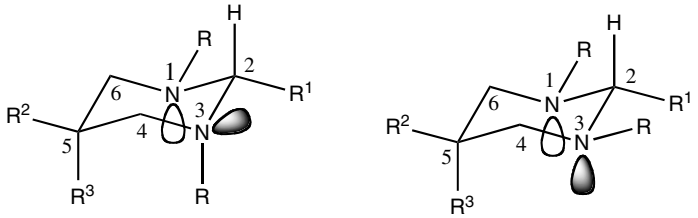
46, trans-trans *47, gauche-trans* *48, gauche-gauche*

Fig. 3.20

Kubo [51] obtained evidence through dipole-moment measurements that dimethoxymethane exists in *gauche–gauche* (+sc, +sc) conformation *48*. This conclusion was later substantiated by electron diffraction studies [52, 53].

By using NMR Hutchins et al. [50] studied the conformations of variously substituted 1,3-diazanes and found a striking support for the rabbit-ear effect (Fig. 3.21).

The introduction of one (equatorial) methyl group at the C5 carbon of *N*,*N*,2-trimethyl-1,3-diazane *49* giving the *N*,*N*,2,5-tetramethyl-1,3-diazane *50* slightly affects the position of the H2 chemical shift. However, the introduction of the second (axial) methyl group at the C5 carbon of *49* dramatically affects the position of the H2 chemical shift. This large upfield shift of H2 in *N*,*N*,2-trimethyl-1,3-diazane upon introduction of geminal methyl groups at the C5 carbon (*N*,*N*,2,5,5-pentamethyl-1,3-diazane *51*) was explained by assuming that in *N*,*N*,2-trimethyl-1,3-diazane *49* one *N*-methyl group is oriented axially and the other equatorially as



49, $R = R^1 = CH_3$; $R^2 = R^3 = H$
50, $R = R^1 = R^2 = CH_3$; $R^3 = H$

51, $R = R^1 = R^2 = R^3 = CH_3$

Fig. 3.21

shown in Fig. 3.21. Introduction of an equatorial C5 methyl group in *N*,*N*-trimethyl-1,3-diazane *49* does not significantly increase the conformational energy, whereas the introduction of the second axial methyl group in the *N*,*N*,2,5-tetramethyl-1,3-diazane encounters a very severe nonbonding steric interaction with one of the two methyl groups on the nitrogen atom suggesting that in *N*,*N*,2-trimethyl-1,3-diazane one methyl group must be oriented axially and the other equatorially, in spite of the 1,3-*syn*–diaxial interaction of the axially oriented *N*-methyl group and the axial C5 hydrogen. This suggests that the 1,3-*syn*–diaxial interaction of two nitrogen unshared electron pairs must exist and that is larger than the 1,3-*syn*–diaxial interaction of the axially oriented *N*-methyl group and the axial C5 hydrogen. It should be noted that the conformer *49* has also one *endo* N-anomeric effect that additionally stabilizes the axial orientation of the C3 methyl group.

Booth and Lemieux [54] have studied the conformations of six-membered perhydro-1,3-oxazoline and 1,3-diazine compounds (Fig. 3.22) with NMR and found that the conformer which avoids placing the unshared electron pair orbitals of both heteroatoms in axial orientation is more stable. This conclusion was drawn in view of the magnitude of the coupling constant between the *N*-hydrogens and the vicinal hydrogen in the axial orientation.

For historical reasons Lemieux proposed the term *generalized anomeric effect* for the general preference for the *gauche* conformation about the carbon-hetero atom bond in systems R-X-C-Y which are the results of the same kind of interactions as were proposed for explaining the anomeric effect but present in noncarbohydrate structures. This proposal has now been universally adopted.

Many cases are known where substituents on six-membered rings prefer an axial orientation [55], and not all of these are the consequence of the anomeric effect: for example, the 2-halocyclohexanone system [56] where the axial preference decreases in the order Br > Cl > F and can be explained as a combination of steric effect and dipole–dipole interactions (Fig. 3.23) and in 2-alkoxycyclohexanones [57] where the effect is comparable in magnitude to that caused by anomeric effect in 2-alkoxytetrahydropyrans (Table 3.5).

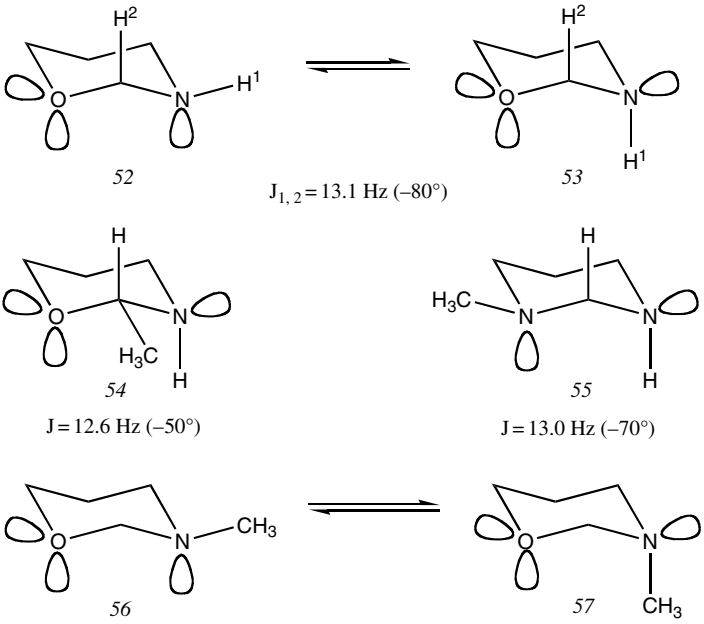


Fig. 3.22

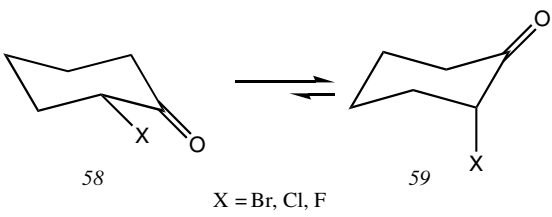
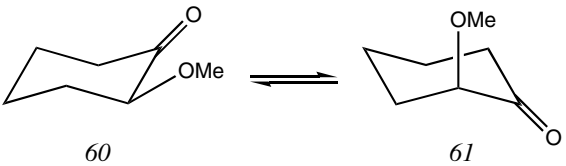
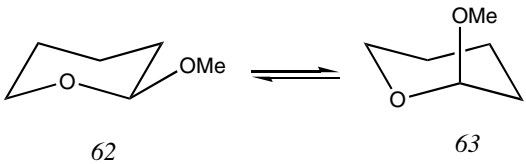
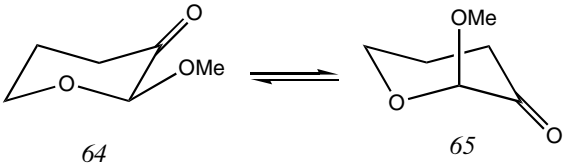
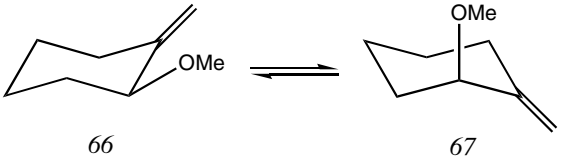


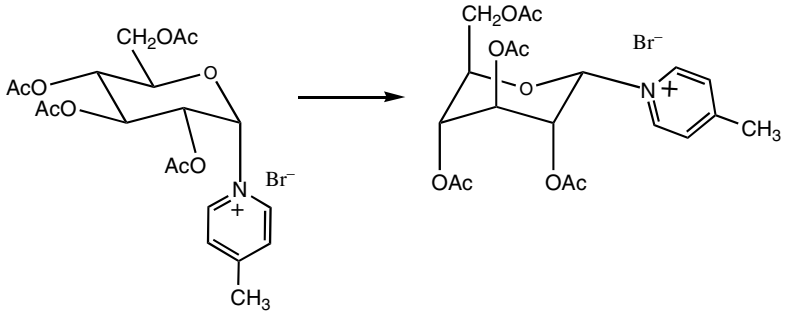
Fig. 3.23

Reverse Anomeric Effect

In 1965, Lemieux and Morgan [58] studied the conformation of *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methyl-pyridinium bromide *68* by NMR spectroscopy and found that the 4-methyl-pyridinium group is equatorially oriented and have suggested that *68* exists in $^1C_4$ conformation *68e* (Fig. 3.24), forcing thus all other substituents to assume the axial orientation despite the presence of one O//O 1,3-*syn*–axial interaction between the C2 and the C4 acetyl groups and one O//C 1,3-*syn*–axial interaction between the C3 acetyl and the C5 acetoxymethyl group amounting to 1.5 + 2.5 = 4.0 kcal/mol.

Table 3.5 Axial preference for methoxyl groups adjacent to sp^2-hybridized ring carbon

	% of axial isomer in CCl_4
 *60* *61*	63
 *62* *63*	69
 *64* *65*	100
 *66* *67*	78



68a, aglycon axial (in the $^4C_1$conformation) *68e*, aglycon equatorial (in the $^1C_4$ orientation)

Fig. 3.24

James has, however, found [59] that the compound *68* in crystalline state does not exist in the $^1C_4$ conformation (*68e* in Fig. 3.24) but in the $B_{2,5}$ conformation *69* as shown in Fig. 3.25 with the methyl-pyridinium group quasi-equatorially oriented.

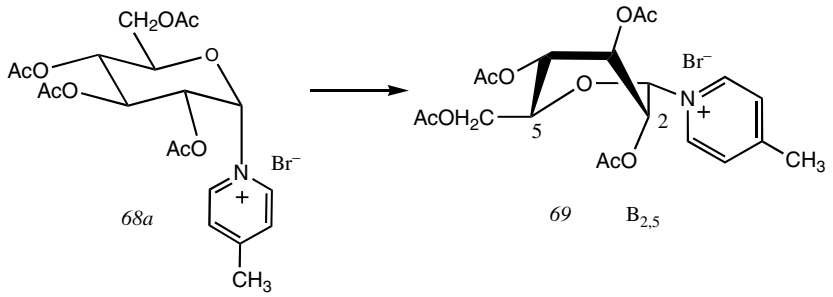


Fig. 3.25

Since both NMR and crystallographic studies showed that the conformations of aminoglycosides with anomeric nitrogen in axial orientation are strongly disfavored, particularly in cases where the nitrogen carries a positive charge, Lemieux concluded [20, 60, 61] that there must exist a powerful driving force for the pyridinium group to adopt an equatorial orientation.

Lemieux named as *reverse anomeric effect* (RAE) this driving force for the electropositive aglycon in hexopyranosides to assume the equatorial orientation. Since the reverse anomeric effect could be either the result of steric interactions due to the bulkiness of pyridinium group or due to electronic interactions stemming from the presence of positively charged nitrogen, or both, Lemieux and Saluja [20, 62] suggested that the existence of (polar) *reverse anomeric effect* can be established only if a clear distinction between the steric and polar effects can be made.

Soon thereafter two groups (Lemieux et al. [20, 62] and Paulsen et al. [63]) independently concluded that the glycosyl imidazoles (Fig. 3.26) would be more suitable substrates for these studies than pyridinium glycosides since the protonation of an imidazole ring is not expected to significantly change its size and therefore any conformational change due to protonation could be attributed to polar effect (i.e., to the reverse anomeric effect). While this argument seems likely, it is still uncertain to what extent the association of a counterion with the positively charged imidazolium

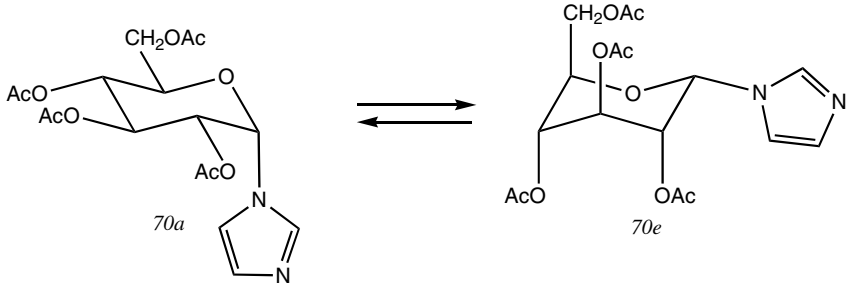


Fig. 3.26

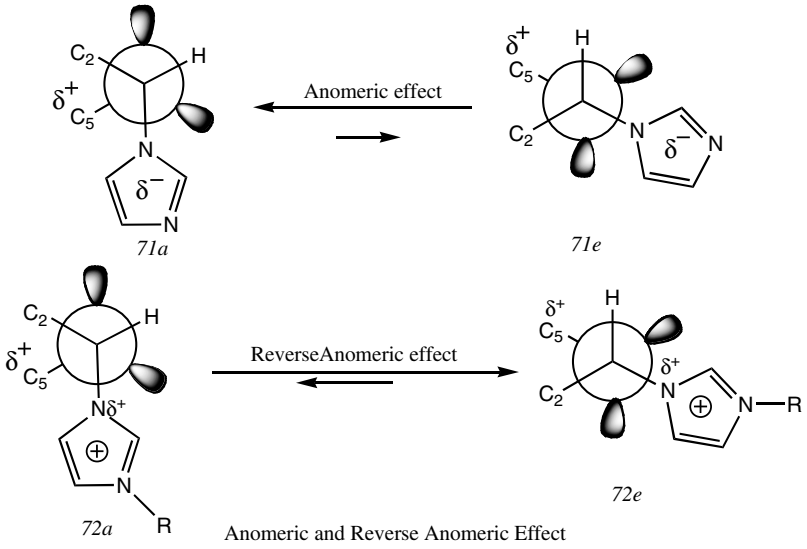


Fig. 3.27

ion affects the **A**-value of the imidazolium group, as well as what effect has the solvation of the imidazolium salt on the *A*-value of the imidazolium group.

Lemieux and Saluja [20, 62] studied the protonation of imidazole ring of *N*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)imidazole *70* (Fig. 3.26) in deuterochloroform and found that the addition of equimolar amount of a weak acid (acetic acid) produced a much smaller effect on the NMR spectrum than the addition of equimolar amount of a strong acid such as trifluoroacetic acid. The addition of a strong acid had an effect upon decreasing the magnitudes of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ coupling constants that is nearly equivalent to the methylation of the imidazole group.

The distribution of electrical charge is more favorable with the imidazole group in the axial orientation when the nitrogen attached to the anomeric carbon carries a partial negative charge and this is the anomeric effect (Fig. 3.27). However, the distribution of electrical charge is more effective in the anomer with the imidazole group in equatorial orientation when the imidazole ring has a positive charge that did acquire either through protonation or alkylation, and this is reverse anomeric effect.

Deslongchamps and Grein [64, 65] suggested that the equatorial orientation of aglycon is favored because of electronic stabilization via dipolar interaction of the positively charged aglycon (N^+) with the two unshared pairs of electrons on the hexopyranose ring oxygen as shown in Fig. 3.28. Apparently, the lp-N^+ electrostatic attraction exceeds the desire of lp delocalization, corresponding to the *endo*-anomeric effect (Fig. 3.28).

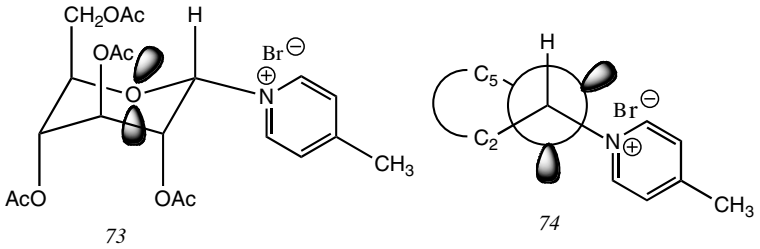


Fig. 3.28

Figure 3.28 illustrates the Deslongchamps and Grein [64, 65] explanation of the reversed anomeric effect. The imidazole ring is an electron-rich group due to the presence of two nonbonding *p*-electron pairs on nitrogen and therefore tends to adopt, due to anomeric effect, the axial orientation. However, the imidazole ring on protonation becomes positivelycharged and consequently adopts the equatorial orientation because in this conformation the positively charged imidazole ring is in gauche orientation relative to two nonbonding *p*-electrons on the ring oxygen that stabilizes the positive charge of imidazole.

The strongest support for the existence of reverse anomeric effect (RAE) comes from ^{1}H NMR study of conformational equilibrium of *N*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)imidazole in $CDCl_3$ solution in the absence and presence of trifluoroacetic acid (TFA) conducted by Paulsen et al. [63]. It was found that in the absence of acid the equilibrium mixture contained 65% of the $^1C_4$ conformer *76* with imidazole aglycon equatorially oriented and 35% of the $^4C_1$ conformer *75* with imidazole aglycon axially oriented (Fig. 3.29). In the presence of acid the proportion of the $^1C_4$ conformer *77* with the imidazole aglycon equatorially oriented increased to more than 95%. This difference corresponds to free-energy change >1.4 kcal/mol. The authors [63] attributed the shift of conformational equilibrium to the presence of positive charge on imidazolium ring due to protonation assuming that N-protonation did not significantly change the size of the imidazolyl group. Thus they completely excluded steric effects as the possible cause for the observed conformational change.

Finch and Nagpurkar [66] studied the population of equatorial conformer in an equilibrium mixture of *N*-(α-D-glycopyranosyl)imidazole of D-glucose,

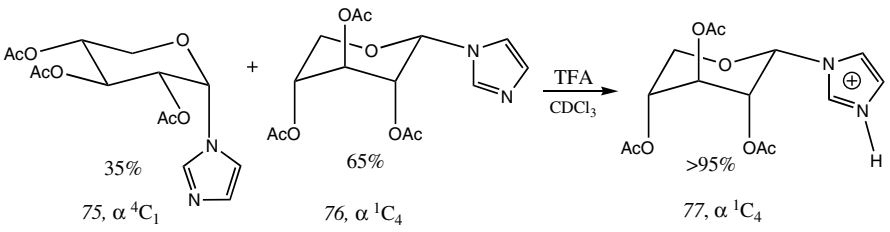


Fig. 3.29

D-mannose, and D-galactose in D_2O, of *N*-(α-D-glycopyranosyl)imidazole of D-glucose, D-mannose, and D-galactose tetraacetate in $CDCl_3$, and of *N*-(α-D-xylopyranosyl)imidazole triacetate in $CDCl_3$ in the absence and presence of acid and found that both steric factors and polar factors (reverse anomeric effect) are likely to be involved in determining the relative percentages of the two conformations at conformational equilibrium. The obtained results could in large part be accounted for by steric factors, but the operation of additional polar factors was also likely (Table 3.6).

The concept of reverse anomeric effect (RAE) has been subject to much controversy and skepticism, because the positively charged anomeric nitrogen ought to lower the energy of the $\sigma_{C-X}{}^*$ orbital and enhance the stabilization of the axial conformer, not to destabilize it.

One of the first reports [67] that challenged the existence of RAE was the stereospecific formation of α-D-glucopyranosylacetonitrilium ion *79* when α- and β-anomers of pent-4-enyl D-glucopyranoside *78* reacted with *N*-bromosuccinimide in dry acetonitrile (68% from β-anomer and 64% from α-anomer). The anomeric configuration of *79* was determined by trapping the acetonitrilium ion *79*, in situ, with 2-chlorobenzoic acid and by subsequent conversion of the obtained α-imide *81* with sodium methoxide to α-2-chlorobenzamide *82* (Fig. 3.30). The exclusive formation of axially oriented α-acetonitrilium ion *79* is clearly in contrast to what would be predicted by the reverse anomeric effect.

Since both RAE and steric repulsions favor the equatorial conformer, it was essential to quantitatively assess steric factors and to determine whether the preference of pyridinium and imidazolium groups to adopt the equatorial orientation is predominantly due to steric interactions of these two groups. Since pyridinium and imidazolium groups were too bulky for this assessment to be made reliably,

Table 3.6 Population of equatorial conformer in equilibrium mixture of *N*-(α-D-glycopyranosyl) imidazoles of D-glucose, D-mannose, D-galactose, and D-xylose and their tetra and triacetyl derivatives, respectively

Glycon residue	Conformation	X	Solvent	Average % of $^1C_4$ conformer
Gluco	$^4C_1$	N	D_2O	0
Gluco	$^4C_1$	NH^+	D_2O + TFA	0
Manno	$^4C_1 + {}^1C_4$	N	D_2O	30.4
Manno	$^4C_1 + {}^1C_4$	NH^+	D_2O +TFA	31.3
Galacto	$^4C_1$	N	D_2O	0
Galacto	$^4C_1$	NH^+	D_2O + TFA	0
Ac_4Gluco	$^4C_1$	N	$CDCl_3$	0
Ac_4Gluco	$^4C_1 + {}^1C_4$	NH^+	$CDCl_3$ + TFA	27.4
Ac_4Manno	$^4C_1 + {}^1C_4$	N	CDC_3	Not given
Ac_4Manno	$^4C_1 + {}^1C_4$	NH^+	$CDCl_3$ + TFA	67
Ac_4Manno	$^4C_1 + {}^1C_4$	N	$(CD_3)_2CO$	51.1
Ac_4Manno	$^4C_1 + {}^1C_4$	NH^+	$(CD_3)_2CO$+TFA	71.8

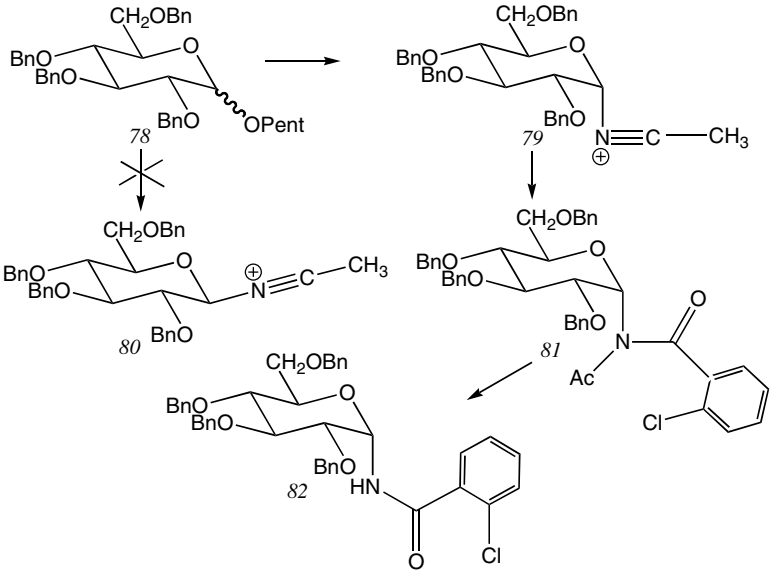


Fig. 3.30

a protonable cyclohexyl substituent whose steric size is known in both protonated and unprotonated forms seemed to be more suitable for probing RAE. One such substituent is NH_2 (Fig. 3.31). The conformational energy ($-\Delta G^0$ or *A*-value) [21] for NH_3^+ was found to be larger (2.15 kcal/mol in D_2O) than the *A*-value for NH_2 (1.7 kcal/mol in D_2O and 1.65 in aprotic solvents, e.g., cyclohexane) [68–70]. The increase of *A*-value on protonation is a measure of the increase in size of the protonated substituent, relative to the unprotonated substituent. This extra bulk is due to the additional proton itself and also to the additional solvent molecules attached to the positive charge needed to stabilize it. (The increase in protic solvent is due to hydrogen bonding, which clusters solvent molecules around the polar group [71, 72].) Since the C–O bond is shorter than C–C bond, steric repulsions in tetrahydropyran system with axially oriented 2-amino group are greater than in cyclohexane system with axially oriented amino group and should be corrected to 2–2.5 kcal/mol for aprotic solvents and 2.4–2.9 kcal/mol for protic solvents.

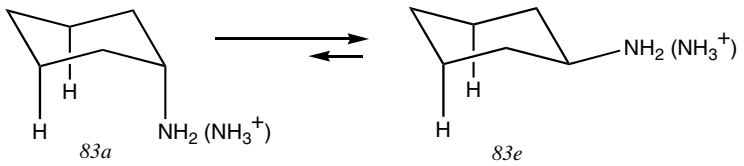


Fig. 3.31

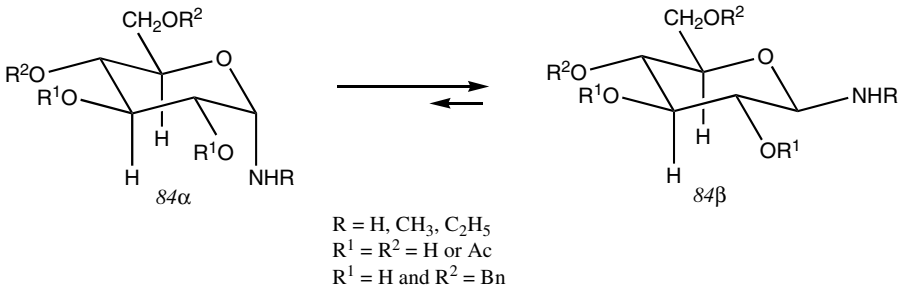


Fig. 3.32

Unlike previous experimental investigations of the reverse anomeric effect that involved the study of conformational equilibrium between the unprotonated and protonated aminoglycosides, Perrin and Armstrong [73] carried out a ^{1}H NMR study of composition of equilibrium mixture obtained by acid-catalyzed anomerization of glycosylamines of a wide variety of glycopyranosylamine derivatives along with their conjugate acids (Fig. 3.32).

This interconversion is known to proceed in four steps [74]: (1) the reversible protonation of the ring oxygen 84α, (2) the pyranoid ring opening to the imminium ion intermediate *85*, (3) the rotation about the C1–C2 bond *85*→*86*, and (4) reclosure of the pyranoid ring *86*→*84*β (Fig.3.33). The greatest experimental difficulties encountered in this work were the sensitivity of glycosylamines to hydrolysis and

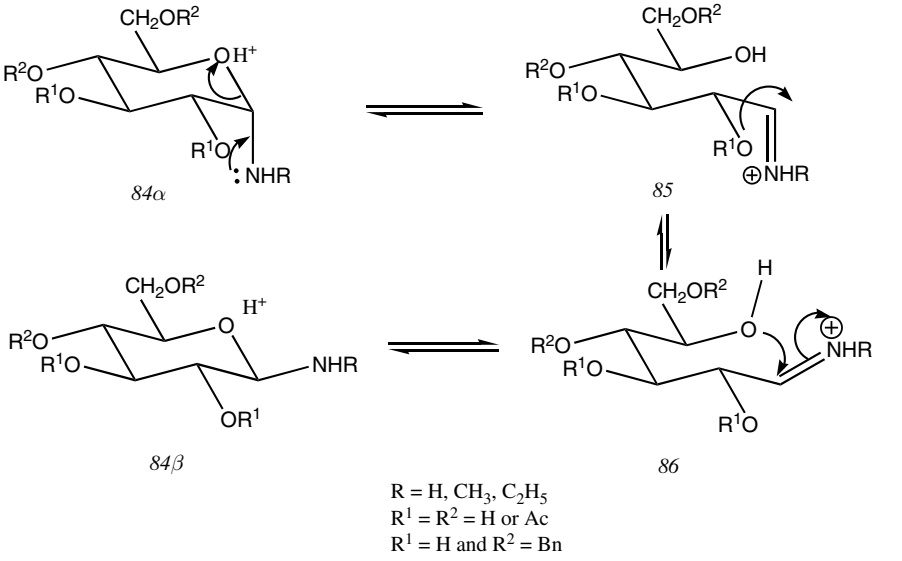


Fig. 3.33

the problem of assignment of ^{1}H NMR signals to the axial stereoisomer which was present only in low concentration.

The *84*α/*84*β ratio was measured by integration of corresponding ^{1}H NMR signals for the anomeric protons across a range of solvents, for both the unprotonated and protonated glycosylamines, and the obtained results are given in Table 3.7.

Table 3.7 Average percentage of α-anomer, free-energy change $\Delta G^0(\beta \rightarrow \alpha)$ (kcal/mol), $A(NH_2)$ or $A(NH_3^+)$ (kcal/mol) in glycopyranosylamines and glycopyranosylammonium ions

Amine	α-Anomer (%)	ΔG^0 β→α	*A* Cyclohexane	*A* THP	α–Anomer (%) estimated
$-NH_2$	10	1.6 ± 0.4	1.6 or 1.3	2.5 or 2.0	–
–NHR	13	1.5 ± 0.3	1.6 or 1.3	2.5 or 2.0	–
$:H^+$, aq.	3.5	2.0 ± 0.1	1.9	2.9	0.8
$:H^+$, nonaq.	7.5	1.5 ± 0.1	Ca. 1.6	Ca. 2.4	1.7

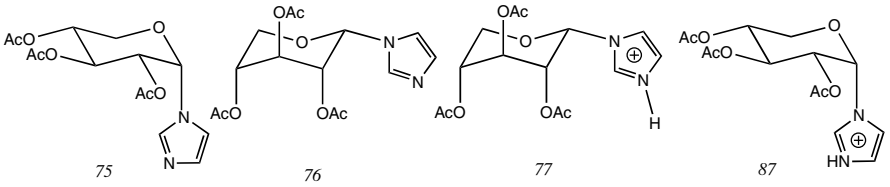
The most important result of these studies is that the axial anomer *82*α is present in appreciable amounts even in acid solution; it is present in smaller percentage in aqueous solution perhaps because in water, the $-NH_3^+$ or $-NH_2R^+$ group is bulkier due to solvation. The fact that the $\Delta G^0(\beta \rightarrow \alpha)$ values (the free-energy change for the conversion of equatorial *84*β to the axial *84*α isomer) are considerably lower than *A*-values for $-NH_3^+$ or $-NH_2R^+$ in THP (Table 3.7) indicates that the preference of the $-NH_3^+$ for equatorial orientation can be accounted for chiefly by the steric effect. These results also suggest the existence of a weak anomeric effect, but not of a reverse anomeric effect.

The reverse anomeric effect can also be determined from a difference in anomerization free-energy changes between the protonated and unprotonated glycosylamines, as shown in Equation (3):

$$\Delta\Delta G^0(N \rightarrow N^+) = \Delta G^0(\beta \rightarrow \alpha)(NH^+) - \Delta G^0(\beta \rightarrow \alpha)(N) \qquad (3)$$

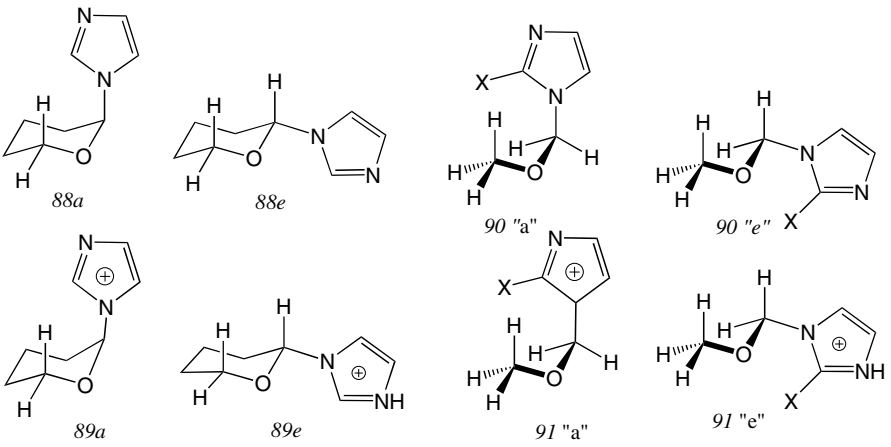
$\Delta\Delta G^0$ is the extent to which the N-protonation increases the preference of amino substituent for the equatorial orientation. Across all the glycosylamines examined the average $\Delta\Delta G^0(N \rightarrow N^+)$ is found to be 0.1 ± 0.1 kcal/mol [73] which is not significantly different from zero. Furthermore this value is definitely smaller than $A(NH_3^+) - A(NH_2)$ which is what would be expected from the increase in steric bulk. Even though NH_3^+ is certainly bulkier than NH_2, the proportion of axial isomer *83*α does not decrease on N-protonation. Therefore, Perrin and Armstrong [73] concluded that there is probably no reverse anomeric effect present with any cationic nitrogen substituent.

Several computational studies on reverse anomeric effect have been published [64, 65, 75–77]. Thus, conformational equilibrium of 2,3,4-tri-*O*-acetyl-D-xylopyranosylimidazol *75*⇌*76* (Fig. 3.34) was subjected to ab initio calculation. In order to simplify the calculations, the axial and equatorial conformers of unprotonated and protonated 2,3,4-tri-*O*-acetyl-D-xylopyranosylimidazoles (*75*, *76*, *77*, and *87*, respectively) were substituted with unprotonated and protonated model



75 *76* *77* *87*

Fig. 3.34



88a *88e* *90* "a" *90 "e"* *89a* *89e* *91* "a" *91* "e"

Fig. 3.35

substrates (*88a*, *88e*, and *89a* and *89e*) (Fig. 3.35) whose conformational energies were then calculated. Also the conformational energies of truncated acyclic models of *88a*, *88e*, *89a*, and *89e* (the structures *90*"a", *90*"e", *91*"a", and *91*"e" with X = H, F, and CH_3) were calculated [78].

From the results of calculations it was concluded that the dominant contributions to the conformational equilibrium of *N*-pyranosylimidazoles were stabilizing anomeric hyperconjugation and destabilizing steric 1,3-interactions in the axial unprotonated conformer (*88a*). Both effects increase on N-protonation (*89a*). It was also concluded that the fine balance between these opposing contributions would allow small intramolecular electrostatic interactions to control the position of equilibrium. Stabilizing electrostatic interactions in N-protonated equatorial conformers were identified and found to be associated with ImH2–O (ring) hydrogen bonding (Type 1) and dipole–dipole electrostatic stabilization between the nonbonding electrons on ring oxygen and the cationic imidazolium dipole (Type 2) (see Deslongchamps and Grein's proposal [64, 65]). An equatorial shift on N-protonation of 0.4–2.4 kcal/mol was predicted using models *89a* and *89e*. Since Perrin [73] suggested that only 0.024–0.089 kcal/mol should result from the steric effect related to imidazole N-protonation, it was concluded that reverse anomeric effect for the *N*-(xylopyranosyl)imidazoles is approximately 0.8–1.4 kcal/mol.

Since the anomeric effect is known to be sensitive to solvent polarity Vaino et al. [79] have reexamined the conformational equilibrium of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosylimidazole *75* and 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl-2-methylimidazole *92* in the presence of trifluoroacetic acid (TFA) because protonation of imidazole by TFA increases the ionic strength of solution. The ^{1}N NMR titration of the glycosides *75* and *92* with varying amounts of TFA and/or tetra-*N*-butyl-ammonium bromide (TBAB) were undertaken in order to account for the effects of solvent ionic strength change upon equilibrium (Fig. 3.36).

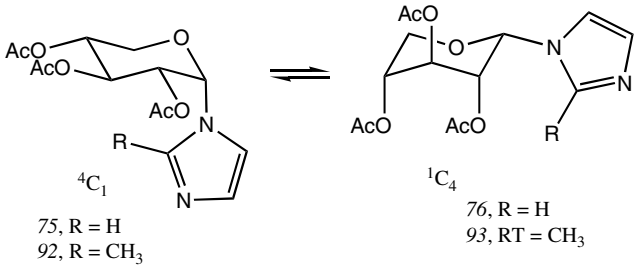


Fig. 3.36

From the results obtained it was concluded that the large equatorial shifts observed for *75* and *92* on N-protonation are not the results of solvent and ionic strength effects. Interestingly the effect of increasing solution ionic strength with TBAB produces a small axial shift for *75*. The authors suggest that RAE does exist and that it is the result of stabilizing intramolecular electrostatic contributions to the $^{1}C_4$ conformer on N-protonation [64, 78]. The size of the effect in the two xylopyranosyl systems studied is quantified as 0.8–1.4 kcal/mol. Since contributions from this electrostatic RAE may be small, there may be other contributions to conformational energy and will be diminished on transferring to solvents more polar than chloroform.

Fabian et al. [80] used an ^{1}H NMR titration method to measure with high precision the shift of anomeric equilibrium on protonation of *N*-(D-glucopyranosyl)imidazole *94* and its tetraacetyl derivative *95* (Fig. 3.37) and found that $\Delta\Delta G^{0}_{\beta\rightarrow\alpha} = \Delta G_{\text{N-ImidazolylH+}} - \Delta G_{\text{N-Imidazolyl}} = -0.018$ to -0.368 kcal/mol.

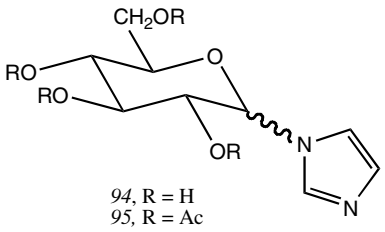
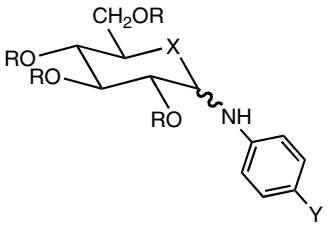


Fig. 3.37

This result means that the protonated imidazolyl group has a small but significantly greater preference for the axial position than does the unprotonated group. This is exactly opposite to what is expected from the existence of the reverse anomeric effect. This led authors to conclude that RAE does not exist [2, 5, 81].

Additional experimental evidence is sparse [82–86]. The geometric changes are consistent with an enhanced anomeric effect, not a reverse one [87, 88]. Molecular orbital calculations are not conclusive because it is difficult to separate the RAE from steric effects and hydrogen bonding, which also favor the equatorial conformer [76, 78, 89–91].



96, R = Ac; X = S; Y = OCH_3
97, R = Ac; X = S; Y = H
98, R = Ac; X = S; Y = CF_3
99, R = Ac; X = S; Y = NO_2
100, R = H; X = S; Y = OCH_3
101, R = H; X = S; Y = H
102, R = H; X = S; Y = CF_3
103, R = H; X = S; Y = NO_2

104, R = Ac; X = O; Y = OCH_3
105, R = Ac; X = O; Y = H
106, R = Ac; X = O; Y = NO_2

Fig. 3.38

The question of the existence of a generalized RAE was addressed by systematic examination of substituent and solvent effects on the configurational equilibria of *N*-aryl-5-thioglucopyranosylamines *96–103* and *N*-arylglucopyranosylamines *104–106* (Fig. 3.38) and the corresponding protonated species [92] (Fig. 3.38).

The equilibrium populations of the 5-thio compounds *96–99* and their protonated derivatives were determined by ^{1}H NMR spectroscopy at 294 K. Equilibration of neutral species *96–99* (Fig. 3.39) was achieved by the $HgCl_2$ catalysis of the

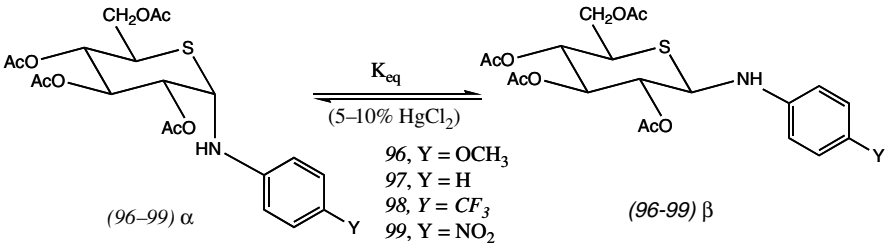


Fig. 3.39

individual isomers in polar solvents CD_3OD, CD_3NO_2, and $(CD_3)_2CO$ only, because of the limited solubility of β-anomers, to ensure that the true equilibrium had been reached.

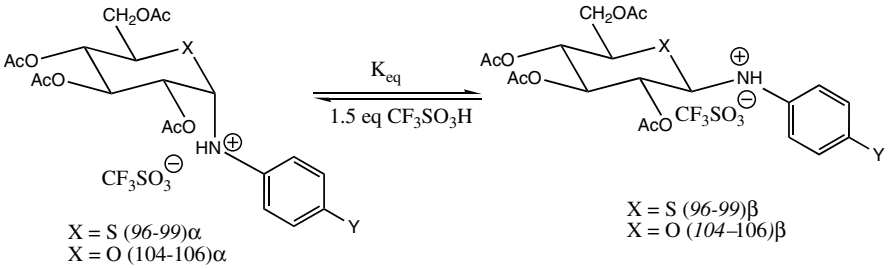


Fig. 3.40

The corresponding equilibrations of the protonated species *104–106* (Fig. 3.40) were studied in the presence of 1.5 equivalents of triflic acid, in polar and nonpolar solvents. The addition of 1.5 equivalents of triflic acid would ensure the complete protonation of amines since the pK_a of triflic acid is –5.9 [93] while the p*K*as of the isolated aglycons are 5.31 for *p*-anisidine (Y = CH_3O), 4.60 for aniline (Y = H), 2.45 for *p*-trifluoromethyl-aniline (Y = CF_3), and 1.00 for the weakest base, *p*-nitroaniline (Y = NO_2).

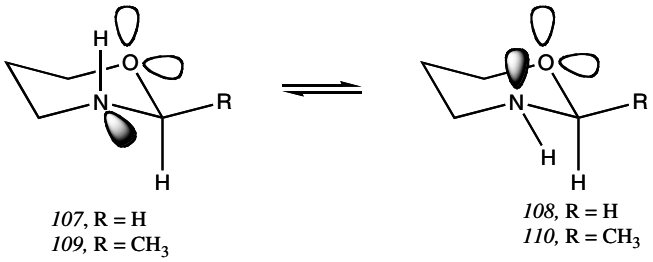
The equilibration of the oxygen analogs *104–106* (Fig. 3.40) was achieved by addition of catalytic amounts of triflic acid to the solution of individual anomers and was performed at 230 K in CD_2Cl_2 and CD_3OD. In this series the choice of solvents was restricted because of the instability of compounds or line broadening effects in the spectra that did not permit unambiguous assignment of signals or their accurate integration.

The conclusion based on the obtained results is that there is no evidence to support the existence of generalized reverse anomeric effect in neutral or protonated *N*-aryl-5-thioglucopyranosylamines and *N*-arylglucopyranosylamines.

For the neutral compounds, the anomeric effect ranges from 0.85 kcal/mol in *95* to 1.54 kcal/mol in *106*. The compounds *96–99* and *104–106* show an enhanced anomeric effect upon protonation. The anomeric effect in the protonated derivatives ranges from 1.73 kcal/mol in *98* to 2.57 kcal/mol in *105*. The values of K_{eq} in protonated *96–99* increase in the order OMe < H < CF_3 < NO_2, in agreement with the dominance of steric effects (due to counterion) over the *endo*-anomeric effect. The values of K_{eq} in protonated *104–106* show the trend OMe < H < NO_2 that is explained by the balance of the anomeric effect and steric effects in the individual compounds.

Anomeric Effect in Systems O–C–N

The NMR studies at low temperature of unsubstituted and C2 substituted 1,3-diazines such as *107* (R = H) and *109* (R_1 = CH_3) [94] strongly suggest that



107, R = H
109, R = CH_3

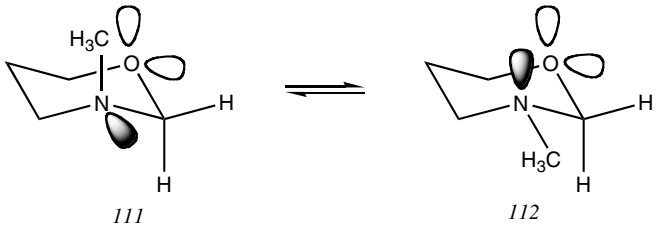
108, R = H
110, R = CH_3

Fig. 3.41

the conformers *107* and *109* are the major components of the equilibrium mixtures *107* ⇌ *108* and *109* ⇌ *110* (Fig. 3.41).

These results were explained in the following way. Two anomeric effects are possible for conformers *107* and *109* (one anomeric effect where the equatorial nitrogen lone pair of electrons mixes with the antibonding C–O orbital and the other where the equatorial oxygen lone pair of electrons mixes with the antibonding C–N orbital). In conformers *108* and *110* there is only one anomeric effect possible and that is where the equatorial oxygen lone pair of electrons mixes with the C–N antibonding orbital. It should be, however, noted that because the nitrogen is less electronegative than oxygen, it is a better electron donor than oxygen and σ*C–N a weaker acceptor of electrons than σ*C–O bond. Consequently the O- and N-anomeric effects are not of equal energy. In addition, in the conformers *108* and *110* ring nitrogen and oxygen atoms would have their axially oriented lone pairs of electrons in 1,3-syn-axial orientation, which will further destabilize this conformation due to the generalized anomeric effect.

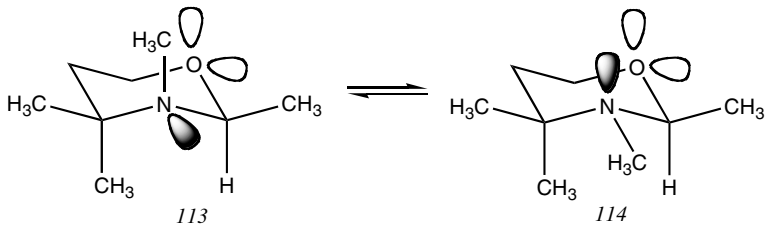
The NMR study of *N*-methyl tetrahydro-1,3-oxazine such as *111* suggested that the conformer *111* with the *N*-methyl group in the axial orientation is more stable than conformer *112* wherein the methyl group is equatorially oriented for the same reasons given above [95] (Fig. 3.42).



111 *112*

Fig. 3.42

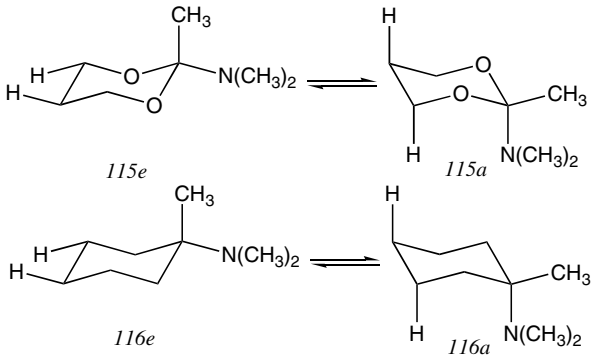
Similarly it was found that the conformer *113* is present in appreciable concentration in conformational equilibrium *113* ⇌ *114* (Fig. 3.43) again for the same reasons given above [95, 96].



113 *114*

Fig. 3.43

Kirby and Wothers [98] studied conformational equilibrium of amide acetal *115e* $\rightleftharpoons$ *115a* to determine the magnitude of the anomeric effect of dimethylamino group, by comparing ΔG^0 for ring inversion with that of its cyclohexyl analog *116e* $\rightleftharpoons$ *116a* (Fig. 3.44).



115e *115a*

116e *116a*

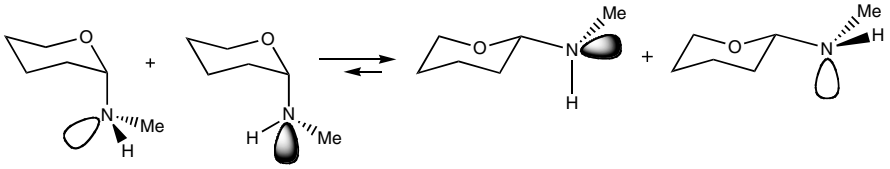
Fig. 3.44

On cooling a sample of amide acetal *115* to 140 K (in 70:30 CBr_2F_2–CD_2Cl_2), not a trace of conformer with the NMe_2 group equatorial (*115e*) was detected. It was concluded that the amide acetal exists as a single conformer *115a* and this conclusion was confirmed by NOE experiments.

If steric repulsion experienced by the methyl and dimethylamino groups increases by the same factor on going from the cyclohexane to dioxane, then the equilibrium constants for the ring inversion of the two compounds should be the same. At 185 K, the cyclohexane conformation in which the NMe_2 is axially oriented is more favorable by $\Delta G^0 = 1.59$ kJ/mol, whereas in dioxane analog the axial orientation of NMe_2 group is favored by $\Delta G^0 \geq 4.5$ kJ/mol. Thus, the conformation *115a* is at least 3 kJ/mol more stable at 185 K than what would be expected from steric factors alone.

This result can be used to shed some light on the *exo/endo*-anomeric effect in the 2-aminotetrahydropyrans studied extensively by Booth et al. [99, 100]. Because nitrogen is less electronegative than oxygen it is a better donor, and the antibonding σ^*C–N orbital a weaker acceptor of electrons than the antibonding σ^*C–O orbital.

Consequently it could be expected that 2-methylaminotetrahydropyran exhibits a stronger *exo*-anomeric effect (n_N-σ^*_{C-O}) than *endo*-anomeric effect (n_O-σ^*_{C-N}). Thus, as shown by Booth et al. (loc. cit.) 2-methylaminotetrahydropyran prefers the equatorial conformation (Fig. 3.45).



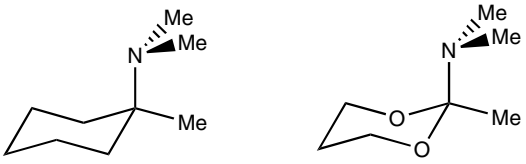
117a (1) *117a (2)* *117e (1)* *117e* (2)

Fig. 3.45

With the NHMe group equatorial rotamer *117e(1)* is stabilized by *exo*-anomeric effect and is preferred. With NHMe axial the preference is for rotamer *117a(2)*.

In contrast to the *N*-methyltetrahydropyrans, no *exo*-anomeric effect is expected when dimethylamino group is axial in the 2-position on dioxane ring, because in order for the nitrogen lone pair to be *anti* to the C–O bond one methyl group would be subjected to severe steric interaction with the axially oriented C4 and C6 hydrogen atoms. This is possible for the hydrogen but the steric demands of a methyl group are prohibitive.

Calculations of the energies of different conformers of *118* and *119* (Fig. 3.46) by using MM2 and 6–31G* basis set have shown that the conformer with the dimethylamino group axially oriented as shown in Fig. 3.46 is preferred.



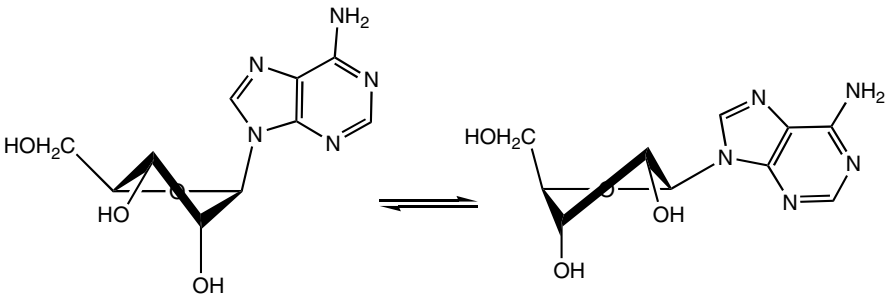
118
0 kJ/mol

119
0 kJ/mol

Fig. 3.46

The pseudorotation concept was introduced to describe the continuous interconversion of puckered forms of the cyclopentane ring [101]. The same concept is applied to furanose geometry where the C1, C4, and O4 atoms lie in one plane and the C2 and C3 atoms lie above and below that plane. A statistical analysis of X-ray crystal structures of nucleosides and nucleotides has shown that North (N) (*120*) and South (S) (*121*) conformations are the most dominant forms, which has been the basis of the assumption of the two-state N $\rightleftharpoons$ S pseudorotational equilibrium in solution (Fig. 3.47).

The two-state N $\rightleftharpoons$ S pseudorotational equilibrium of the sugar moiety of β-D-ribofuranosyl-*N*-nucleosides in solution is energetically controlled by various



North (N) conformation
($C_{3'}$-*endo*-$C_{2'}$-*exo*)

120

South (S) conformation
($C_{2'}$-*endo*-$C_{3'}$*exo*)

121

Fig. 3.47

stereoelectronic gauche and anomeric effects [102–107]. The gauche effects [107, 108] of O4′–C4′–C3′–O3′ and O2′–C2′–C1′–N fragments drive the sugar pseudorotational equilibrium toward S[102] whereas it is driven to N by the gauche effect of O4′–C1′–C2′–O2′ (Fig. 3.43).

The X-ray crystal structure of *N*-nucleosides shows the shortening of the O4′–C1′ bond relative to C4′-O4′ by about 0.03 Å which has been considered as a manifestation of the anomeric effect.

The preference of 5′-CH_2OH group to occupy the pseudoequatorial orientation is manifested in the positive $\Delta H^{\#}$ value for the pseudorotational equilibrium [108] (Fig. 3.47). From the determination of energetics of the two-state pseudorotational equilibrium in 36 nucleosides it was found that the combined stereoelectronic and steric contributions in the anomeric effect of the nucleobases increases in the following order: adenine ≈ guanine < thymine < uracil < cytosine. One reason for the stronger anomeric effect in pyrimidine than in purine nucleosides could be that the $n(O4') \rightarrow \sigma^*_{C1'\text{-}N}$ delocalization is more effective in the π-deficient pyrimidine moiety compared to relatively more electron-rich purine [109–111].

The strength of the anomeric effect was enhanced upon protonation (evident by the increase in N-type sugar population) relative to the neutral state. These results are consistent with the favorable $n(O4') \rightarrow \sigma^*_{C1'\text{-}N}$ delocalization in the electron-deficient protonated aglycone at the acidic pH and unfavorable $n(O4') \rightarrow \sigma^*_{C1'\text{-}N}$ delocalization in the electron-rich anionic aglycone at the basic pH, compared to the neutral state, as the origin of the anomeric effect.

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Chapter 4
Isomerization of Sugars

Mutarotation

In 1846 Dubrunfaut [1] observed that the optical rotation of a freshly dissolved α-D-glucose in water was changing with time and that after several hours it became constant.

$$\alpha\text{-D-glucose} \rightleftharpoons \gamma\text{-glucose} \rightleftharpoons \beta\text{-D-glucose}$$
$$+112^\circ \rightarrow +52.7^\circ \leftarrow +18.7^\circ$$

The same equilibrium rotation of 52.7° was attained regardless of whether the starting sugar was α- or β-D-glucose. Initially, this "new form" of glucose, having the optical rotation of +52.7°, was named "γ-glucose," but very soon it was realized that the "γ-glucose" was not a new form of glucose but simply an equilibrium mixture of α- or β-D-glucose. Similar behavior was later observed with all other sugars.

This interconversion of α- and β-D-glucose (Equation 1) was named *mutarotation*, and it was kinetically described [2] with Equation 2:

$$\alpha \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \beta \tag{1}$$

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_1[a-x] - k_2[x] \tag{2}$$

where k_1 is the rate constant for α → β conversion, k_2 is the rate constant for β → α conversion, "a" is the initial concentration of α form, "x" is the concentration of β form at time t, and [a–x] is the concentration of α form at time t. The integration of (2) gives after rearrangement

$$k_1 + k_2 = \frac{1}{t} \ln \frac{K_\mathrm{a}}{K_\mathrm{a} - (1+K)x} \tag{3}$$

where $(k_1 + k_2)$ is *mutarotation constant*, and $K = k_1/k_2$. Equation (3) can also be expressed in terms of optical rotation [2] if the sugar concentrations are substituted with concentration-dependent optical rotations:

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_4,

$$k_1 + k_2 = (1/t) \ln [(r_0 - r_{eq})/(r_t - r_{eq})] \quad (4)$$

where r_0 is the initial rotation, r_{eq} is the rotation at equilibrium, and r_t is the rotation at time t.

This type of mutarotation is called *simple mutarotation* since the result of this isomerization is the formation of another anomer (*anomerization)* of the parent sugar. The simple mutarotation is observed in solutions of gluco-, manno-, gulo-, and allopyranoses, hence in the solution of sugars that contain practically only α- and β-pyranose forms, with very small proportions of other forms of sugars (e.g., furanoses).

α-pyranose ⇌ acyclic form ⇌ β -pyranose

Scheme 4.1

It has been suggested that simple mutarotation takes place via an acyclic intermediate (Scheme 4.1) as shown in Fig. 4.1. In the first step, the lactol ring of β-D-glucopyranose *1* opens with the formation of the acyclic D-glucose conformer *2* in which the carbonyl oxygen is pointed outward. The acyclic conformer *2* can then either cyclize back to the starting β-D-glucopyranose *1* or it can, prior to cyclization, be converted by a free rotation about the C1-C2 bond into the conformer *3* of the acyclic D-glucose intermediate in which the carbonyl oxygen is pointed down. The cyclization of this acyclic conformer will then give the α-anomer *4*. The participation of water molecules as general acid–general base catalysts is essential for this reaction.

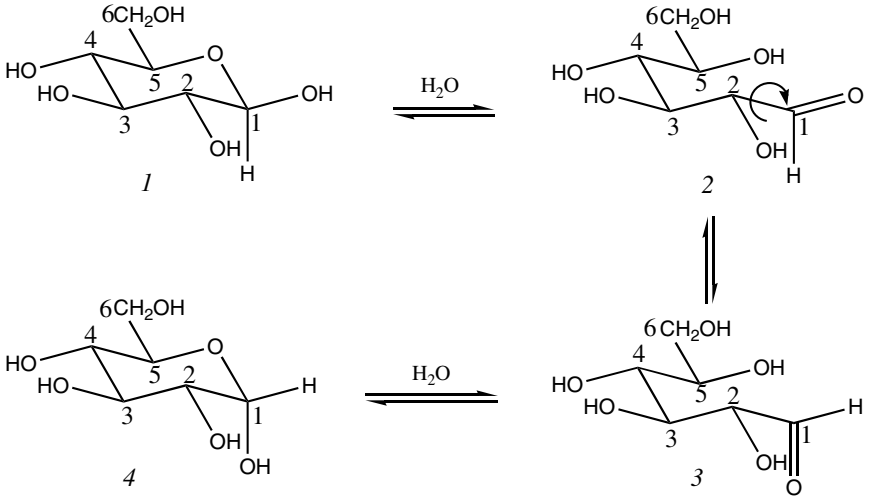


Fig. 4.1

The equilibrium solutions of galacto-, talo-, altro-, and idopyranoses have much more complex composition because they contain, in addition to α- and β-pyranose forms, substantial amounts of furanose and other forms of sugars. Apparently these sugars undergo besides anomerization also the ring isomerization. This ring isomerization, observed also in solutions of gluco-, manno-, gulo-, and allopyranoses, although to a much smaller extent, was explained in the following way.

If, after opening of the pyranose ring and after the formation of the corresponding acyclic conformer of D-glucose (*2* in Figs. 4.1 and 4.2), the rotation about the C3-C4 single bond takes place prior to cyclization, the conformation *5* of acyclic glucose will be formed (*2*→5) (Fig. 4.2), which upon cyclization will give the α-D-glucofuranose.

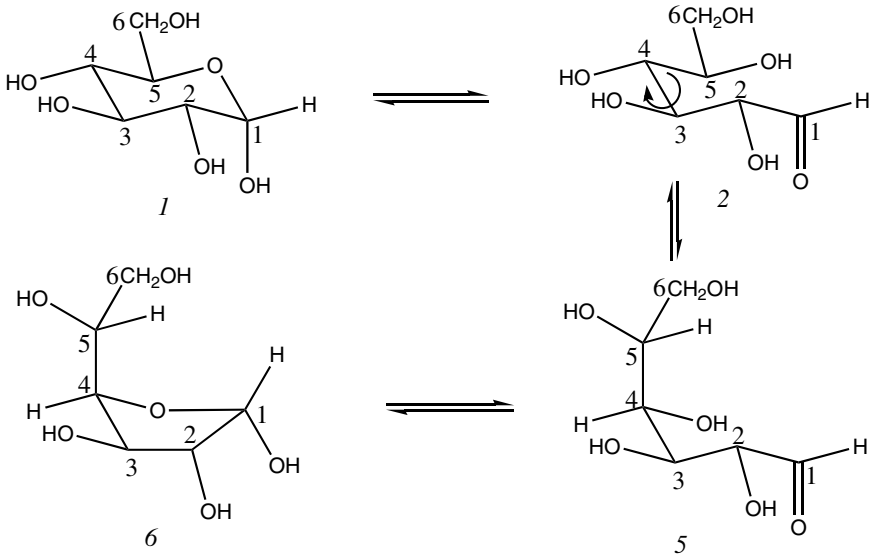


Fig. 4.2

If after rotation about the C3-C4 bond rotation about the C1-C2 bond also takes place prior to cyclization, the acyclic conformer *7* (Fig. 4.3) will be formed which on cyclization will give the β-anomer of D-glucofuranose *8* (Fig. 4.3). The ring isomerization, i.e., the interconversion of pyranose and furanose ring forms is called *complex mutarotation*.

The mutarotation of reducing sugars is catalyzed by both acids and bases. The increase of rate of mutarotation by acids was first reported by Erdmann [3] and catalysis by both acids and bases was described by Urech [4]. Hudson [5] has shown that mutarotation is catalyzed by water molecules. Lowry and coworkers [6–8] studied mutarotation of tetra-*O*-methyl-α-D-glucopyranose and found that the rate of mutarotation is low in dry pyridine or in dry cresol, but that it is high in the

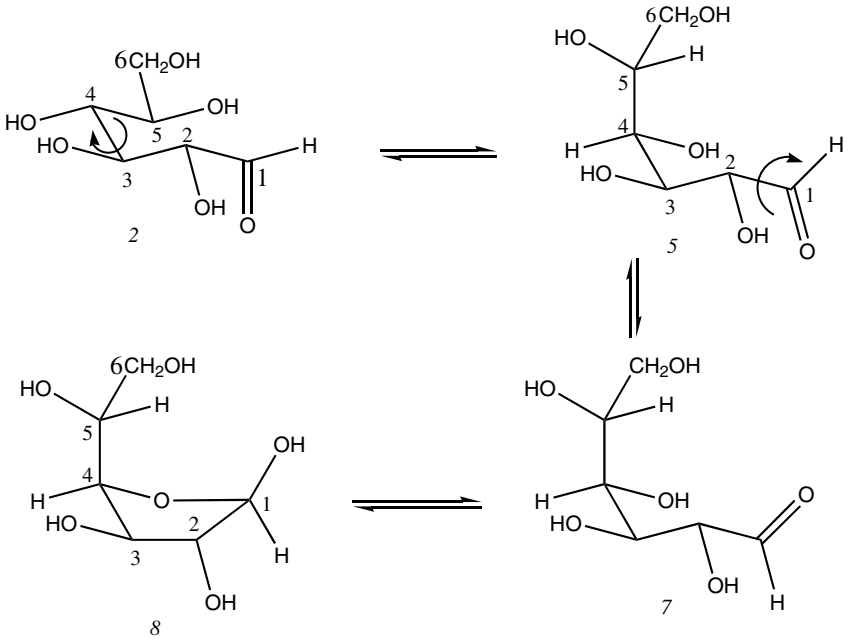


Fig. 4.3

mixture of these two solvents, or in each one of them when moist. Lowry and Smith [9] concluded that *mutarotation requires both an acid and a* base catalyst and that amphoteric solvents are perfect catalysts for mutarotation, whereas the aprotic solvents are not.

Since mutarotation is catalyzed by both acids and basis, Swain and Brown [10] designed the first bifunctional catalyst, 2-pyridinol *10*, which on its two adjacent ring atoms has an acidic and a basic functional group. It was found that the rate of mutarotation catalyzed by 2-pyridinol in benzene, as solvent, is 7000 times faster than mutarotation calculated for analogous concentration of pyridine or phenol alone. The action of bifunctional catalyst is explained by postulating a concerted mechanism that involves the formation of an eight-membered cyclic transition state, as illustrated in Fig. 4.4.

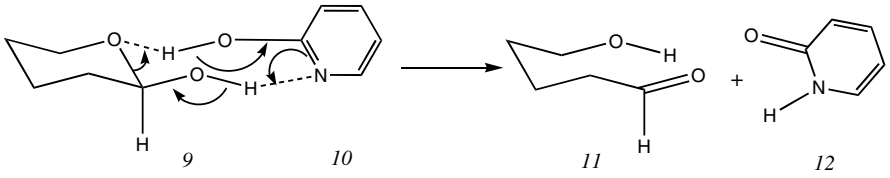


Fig. 4.4

Carboxylic acids also act as bifunctional catalysts for mutarotation because the carbonyl oxygen is a hydrogen acceptor (base) whereas the carboxylic hydrogen is an acid, and they, too, are able to form an eight-membered cyclic transition state similar to the one formed by 2-pyridinol (Fig. 4.5).

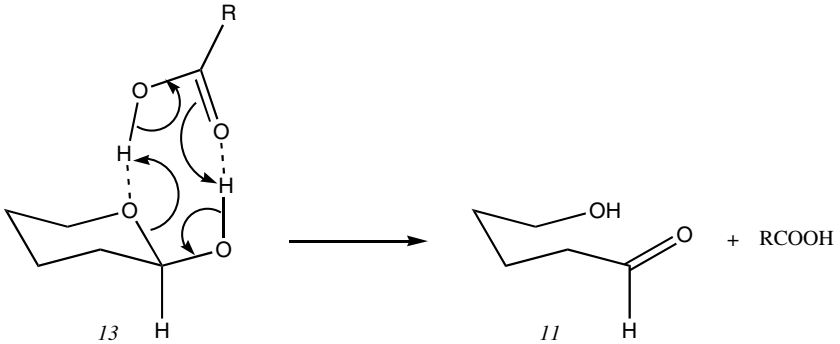


Fig. 4.5

Studies of mutarotation in water and in deuterium oxide have shown that the reaction is faster in water than in deuterium oxide, regardless of the catalyst. It was found [11] that the k_H/k_D value is 1.37 for catalysis by specific acids (H_3O^+) and 3.80 for catalysis by water molecules. From a study of large number of sugars, Nicolle and Weisbuch [12] determined that the k_H/k_D ratio lies in the range of 3.0–3.8 and is independent of pH.

Several interpretations have been put forward to explain this observation. All of them agree in the assumption that the opening of the pyranose ring with formation of the corresponding acyclic intermediate is the rate-determining step. The contested part of the mechanism is whether the formation of a pre-equilibrium state precedes the ring rupture or not. According to Bonhoeffer et al. [13, 14], Bell [15], and Purlee [16], an intermediate *15* (Fig. 4.6) is formed prior to proton transfer from an acid to the ring oxygen (protonation of the pyranose ring oxygen) and the ring cleavage (Fig. 4.7). This intermediate then undergoes slow pyranose ring opening with simultaneous proton transfer from the acid H–A and simultaneous cleavage of the H–A bond (protonation step), in aqueous solution, and D–A bond in deuterium

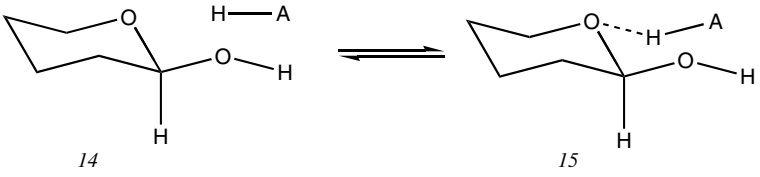


Fig. 4.6

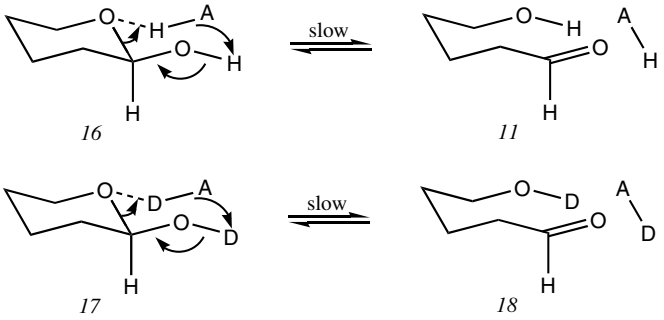


Fig. 4.7

oxide. Since the D–A bond is stronger than the H–A bond, the reaction in deuterium oxide will be slower than in H_2O and k_H/k_D will be greater than 1.

Challis et al. [17] and Long and Bigeleisen [18] suggested that the pre-equilibrium proton transfer (cleavage of H–A or D–A bond) takes place prior to the pyranose ring rupture, whereas the second proton transfer (proton from the anomeric hydroxyl group to the base) occurs simultaneously with the ring rupture (Fig. 4.8). If this were so, then a higher concentration of conjugate acid can be expected to be found in deuterium oxide than in water, which should result in k_H/k_D ratio less than 1. However, in D_2O, the hydrogen atom of the anomeric hydroxyl group (as well as of all other hydroxyl groups in carbohydrate molecule) will be almost instantaneously replaced by deuterium. In the subsequent simultaneous opening of the pyranose ring, the cleavage of C1–O–H in water or C1–O–D bond in deuterium oxide, which is the rate limiting step, will be slower in deuterium oxide, because the O–D bond is stronger than OH bond, and k_H/k_D ratio will be greater than 1 (Fig. 4.9).

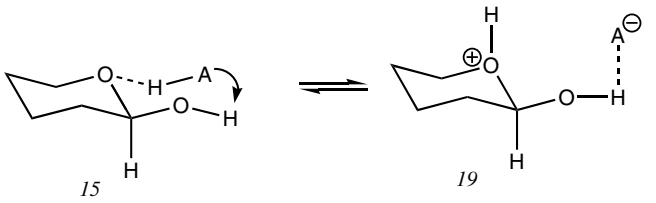


Fig. 4.8

The high value of k_H/k_D for the observed mutarotation in water was explained by postulating a *concerted mechanism* proposed by Lowry [7, 19] (Fig. 4.10) in which water acts as the general acid and the general base catalyst. Two slightly different transition state intermediates can be written for the mutarotation of sugars in water:

According to one mechanism, two molecules of monomeric water are required – one water molecule acts as the general acid and the other as the general base (Fig. 4.10) – and according to the other mechanism, one molecule of dimeric water molecule is required, in which case an eight-remembered cyclic transition state

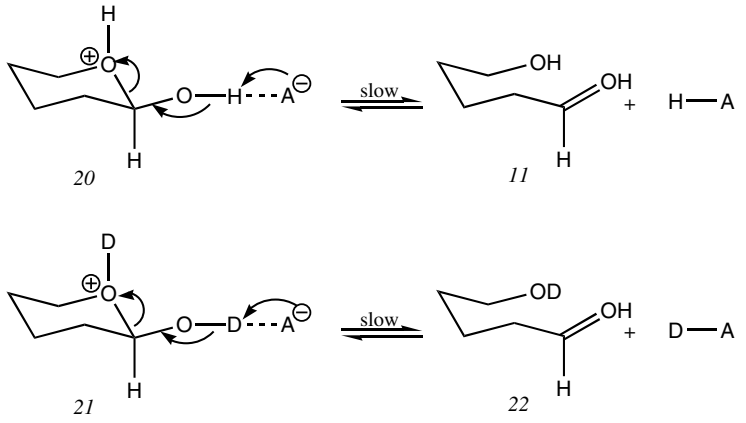


Fig. 4.9

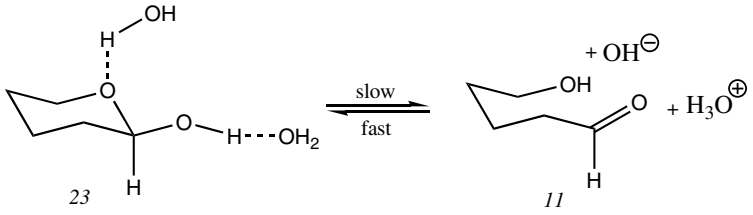


Fig. 4.10

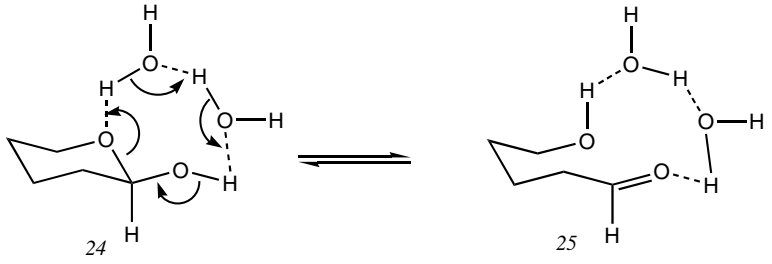


Fig. 4.11

intermediate is formed in which one part of the water dimer acts as a general acid and the other part as a general base (Fig. 4.11). Thus in the second mechanism, water dimer acts as a *bifunctional catalyst*, and the reaction is a concerted one.

The mutarotation of sugars in aqueous solutions catalyzed by acid–base catalysts involves two proton transfers (one from the acid catalyst to the sugar-ring oxygen and the second proton from the sugar anomeric hydroxyl group to the base catalyst) and the pyranose ring rupture. The reaction can start with either proton transfer.

Before we discuss these issues, let us take a brief look at how the charges are distributed in a pyranose or a furanose ring (Fig. 4.12). Zhdanov et al. [20] have calculated the electronic structures and charge distributions of nonspecified pentoses in their furanose and pyranose forms using the LCAO-MO method of inductive parameters, in the form derived by Del Re [21]. The results of their calculations are given in Tables 4.1 (for pentofuranoses) and 4.2 (for pentopyranoses).

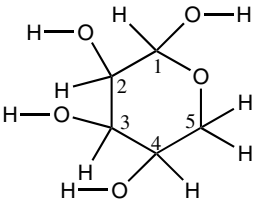
Table 4.1 Electronic distribution in pentofuranoses

Pentofuranose							
C5	+0.0467	O5	–0.4731	(C)H5	+0.0530	(O)H5	+0.3164
C4	+0.0964	O4	*–0.2642*	(C)H′5	+0.0530		
C3	+0.1068	O3	–0.4748	(C)H4	+0.0507	(O)H3	+0.3161
C2	+0.1160	O2	–0.4734	(C)H3	+0.0518	(O)H2	+0.3164
C1	*+0.1926*	O1	*–0.4627*	(C)H2	+0.0529	(O)H1	+0.3184
				(C)H1	+0.0610		

Table 4.2 Electronic distribution in pentopyranoses

Pentofuranose							
C5	+0.0362	O5	*–0.2631*	(C)H5	+0.0518		
C4	+0.1069	O4	–0.4747	(C)H′5	+0.0518	(O)H4	+0.3161
C3	+0.1079	O3	–0.4746	(C)H4	+0.0518	(O)H3	+0.3161
C2	+0.1162	O2	–0.4734	(C)H3	+0.0520	(O)H2	+0.3164
C1	*+0.1929*	O1	*–0.4629*	(C)H2	+0.0529	(O)H1	+0.3166
				(C)H1	+0.0611		

As one can see from the results of these calculations, the electronegativities of all hydroxyl oxygens are practically identical except for the ring oxygen and the C1 oxygen of the anomeric hydroxyl group. The anomeric oxygen is slightly less electronegative (ca. –0.01) than other hydroxyl group oxygens, whereas the ring oxygen, in both pyranose and furanose rings, is significantly less electronegative (by –0.2) than other hydroxyl group oxygens. The small electronegativity of the ring oxygen (–0.2642 for pentofuranoses and –0.2631 for pentopyranoses) as compared to the



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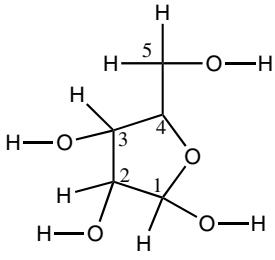

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Fig. 4.12

electronegativity of the anomeric oxygen (–0.4627 for pentofuranoses and –0.4629 for pentopyranoses) immediately raises the question of why would the protonation of the ring oxygen as the first step of mutarotation be favored over the protonation of the anomeric or any other oxygen of the sugar molecules, since all of them are more electronegative.

Aside of this controversy, the mechanism for the simple mutarotation described in Fig. 4.13 is accepted as the most plausible one.

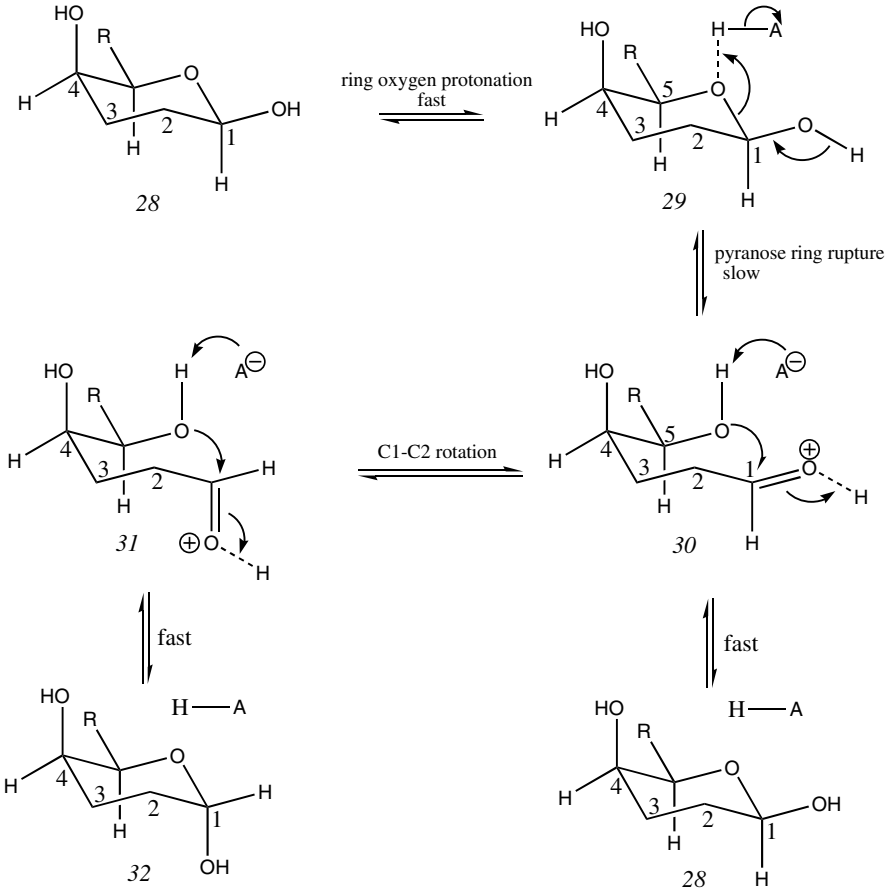

Fig. 4.13 Acid catalyzed simple mutarotation

The first step is assumed to be the fast formation of an adduct between an acid and the ring oxygen (*28* → *29*) which is followed by a slow (rate determining) ring rupture with the simultaneous formation of the C5–OH and a protonated carbonyl oxygen, *29* → *30*. The acyclic intermediate *30* then undergoes either a fast recyclization, back to the starting β-D-pyranose, or, prior to recyclization, a rotation about the C1–C2 carbon, which takes place giving the acyclic conformer *31,* which on recyclization gives the α-anomer *32*.

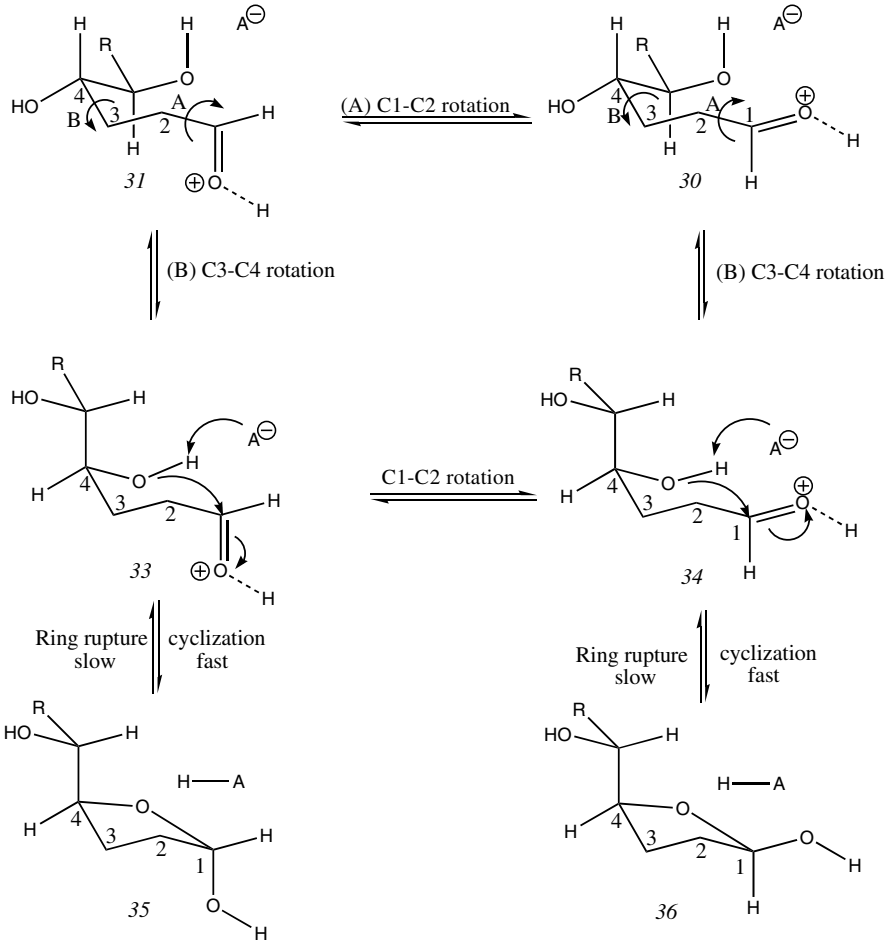

Fig. 4.14 Acid catalyzed complex mutarotation

However, an additional step can be involved in the mutarotation of sugars (Fig. 4.14). Namely, the intermediate *30* (or *31*) can, either before or after the C1–C2 rotation, undergo another rotation about the C3–C4 bond giving the conformer *33* or *34* which after recyclization is converted to the α- and β-furanoid forms of the sugar (*35* or *36*). This is the accepted mechanism for the *complex mutarotation.*

The mechanism of mutarotation of sugars catalyzed by bases differs from the one catalyzed by acids in the site of initial attack of the catalyst. Whereas the acid catalyzed mutarotation begins with the attack of an acid to the ring oxygen, in the base catalyzed mutarotation the first step is deprotonation of the anomeric hydroxyl group. The sugar anion then undergoes slow opening of the pyranose ring, with the participation of water. Closure of the ring without prior conformational change of the acyclic intermediate produces the starting material. However, the rotation about

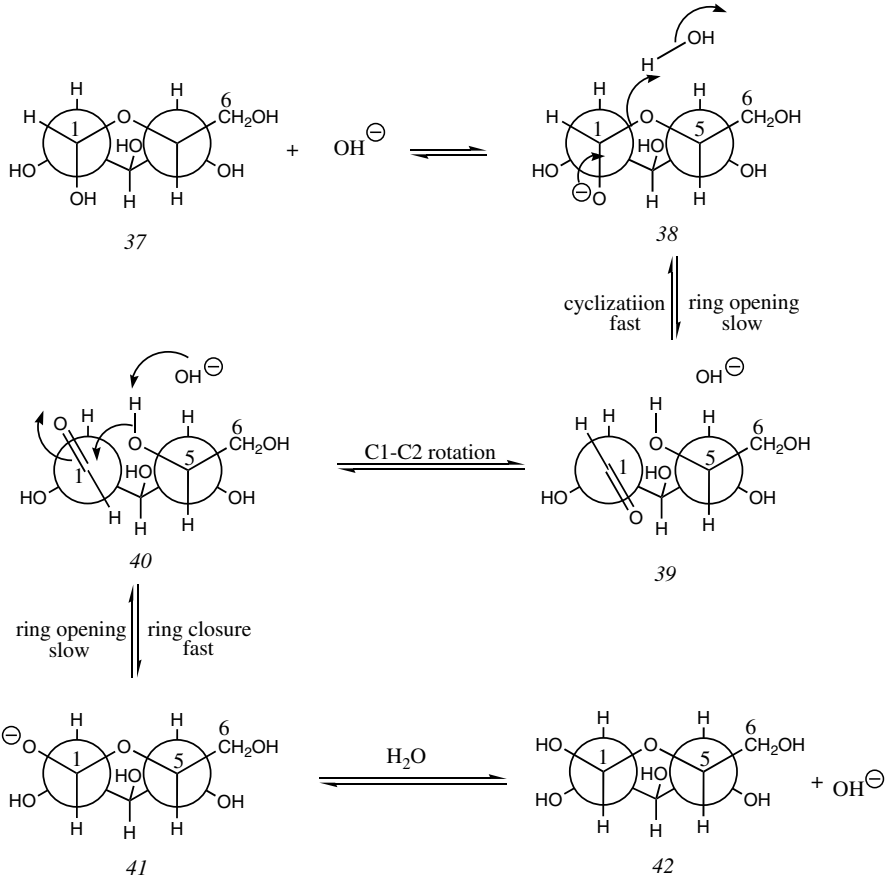

Fig. 4.15 Base catalyzed mutarotation

the C1–C2 bond prior to the ring closure gives another acyclic conformer of the parent sugar, which upon cyclization gives the anomer of starting glucopyranose (*simple mutarotation*) (Fig. 4.15).

Anomerization

The *simple* and *complex mutarotation* is typical behavior for the so-called reducing sugars, i.e., sugars with underivatized anomeric hydroxyl group. The epimerization of the C1 carbon of pento- and hexofuranoses and pento- and hexopyranoses, i.e., the α- to β-isomer conversion, and vice versa, without a ring isomerization, was named *anomerization*. An important difference between *simple mutarotation* and the *anomerization* is that the mutarotation requires presence of both an acid and a

base catalyst, whereas for the anomerization only an acid catalyst is needed. In addition to that, *simple mutarotation* can take place only in protic (aqueous) solutions whereas the *anomerization* can also take place in aprotic (nonaqueous) solutions [22]. Consequently, the reaction mechanisms of *simple mutarotation* and *anomerization* are similar and different at the same time. Glycopyranosyl or glycofuranosyl derivatives that undergo anomerization are glycofuranosyl or glycopyranosyl 1-acetate, 1-amines, alkyl (or aryl) glycosides, 1-halogen derivatives, etc.

Although anomerization of glycofuranosyl or glycopyranosyl derivatives can proceed via several routes, the following four pathways are probably the most plausible.

(1) The anomerization can take place by the cleavage of C1-O5 (ring oxygen) bond when catalyzed by specific acid, followed by the C1-C2 rotation of obtained acyclic intermediate *44* and its cyclization into the C1 epimer *46* of the starting material *43* (Fig. 4.16).

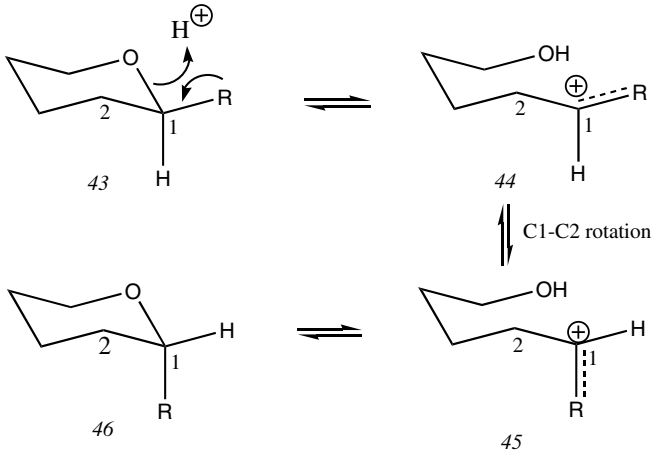

Fig. 4.16

Similar reaction pathway has been postulated for the simple mutarotation.

(2) The anomerization can take place via a complete dissociation of the C1-X bond (X = aglycon[1]) after protonation of the aglycon, followed by recombination of ions to form the starting sugar or its anomer, as shown in Fig. 4.17.

[1] Alkyl, aryl groups in an aglycon X are referred to as "aglycon groups." Hence the aglycon is the aglycon group and glycosidic oxygen linked together.

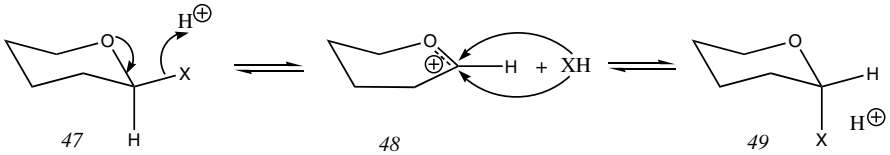

Fig. 4.17

(3) The anomerization may occur by migration (without complete dissociation) of the aglycon group (R) from one side of the ring to another, by way of an intermediate molecular complex (Fig. 4.18).

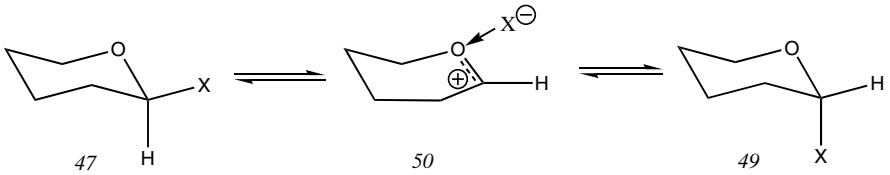

Fig. 4.18

(4) The anomerization may proceed by a way of bimolecular displacement, under the conditions where solvent supplies the aglycon group (solvolysis) (Fig. 4.19).

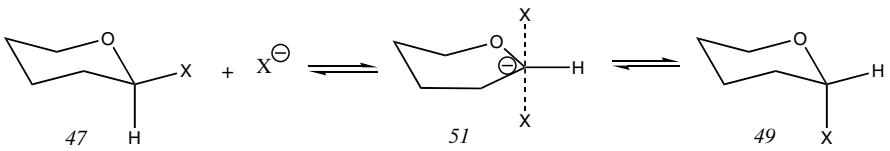

Fig. 4.19

Evidence obtained from a study of methanolysis of a number of methyl glycosides, by paper chromatography and isotope exchange, suggests that the anomerization can proceed via both acyclic (*44* and *45* in Fig. 4.16) and cyclic (*48* in Fig. 4.17) oxo-carbenium intermediate [23, 24]. Thus, from equilibration of methyl α-D-gluco- and α-D-mannopyranosides in anhydrous ^{14}C-labeled methanol containing 1% of anhydrous HCl, it was concluded that the anomerization proceeds via cyclic oxo-carbenium ion (*51* in Fig. 4.19). The same mechanism was considered to be the principal pathway for acid-catalyzed anomerization of ethyl D-xylopyranosides [25]. However, it was concluded that the anomerization of methyl β-D-glucopyranoside, methyl α- and β-D-galactopyranoside, and methyl β-D-mannopyranoside proceeds via acyclic oxo-carbenium ion (*44* and *45* in Fig. 4.16).

Some substituents of the C2 hydroxyl group of glycopyranoses, having the C1 hydroxyl group already derivatized (alkyl, acetyl, etc.), strongly favor the axial anomer in the anomeric equilibrium. Thus equilibration of methyl tetra-*O*-methyl-α

and β-D-glucopyranosides in 5% methanolic HCl yields about 3:1 mixture α- to β-anomers [26].

The mechanism of anomerization has been most extensively studied with peracetylated glycopyranoses and acetylated alkyl glycopyranosides. Due to the presence of acetyl group at the C2 carbon of these substrates, the reaction mechanism is slightly different from unprotected glycopyranosides since the acetyl group is known to participate in the stabilization of oxo-carbenium ion intermediate (there will be more discussion on the neighboring group participation later).

It has been found [27] that the furanoside to pyranoside conversion proceeds predominantly with the retention of configuration at the anomeric carbon. The suggested explanation for this observation was that the acyclic ion formed on opening of the furanoside ring underwent the ring closure to the pyranoside with the same anomeric configuration at a much greater rate than that for the conformational change required to produce the other anomeric configuration (C1-C2 rotation).

Two excellent reviews on mutarotation of sugars have been published by Isbel and Pigman [28, 29].

Lobry de Bruyn–Alberda van Ekenstein Transformation

Lobry de Bruyn–Alberda van Ekenstein transformation is acid–base catalyzed aldose–aldose and ketose–ketose epimerization, and aldose–ketose isomerization [30–40] (Fig. 4.20). The reaction is essentially an enolization of an aldose or a ketose having a hydrogen at the α-carbon to the carbonyl group and proceeds via a common "enediol" *53* intermediate.

These reactions are usually base catalyzed and proceed readily in alkaline solution; however, they can also take place under acid or even neutral conditions [40]. 2-Deoxy aldoses and 2-deoxy-2-acetamido-hexoses understandably do not undergo

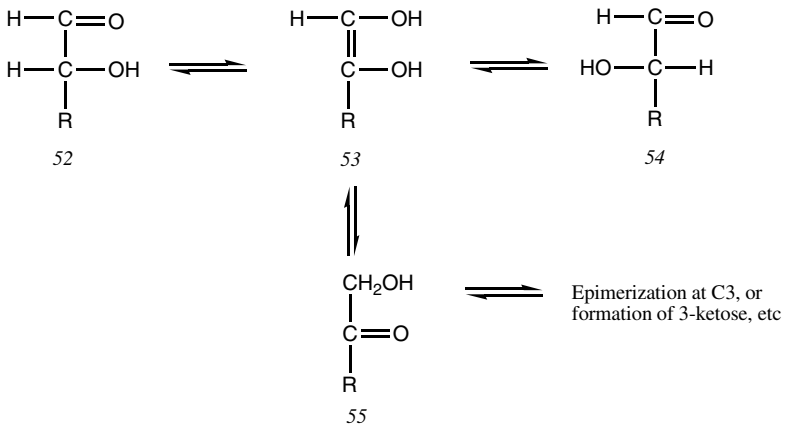

Fig. 4.20

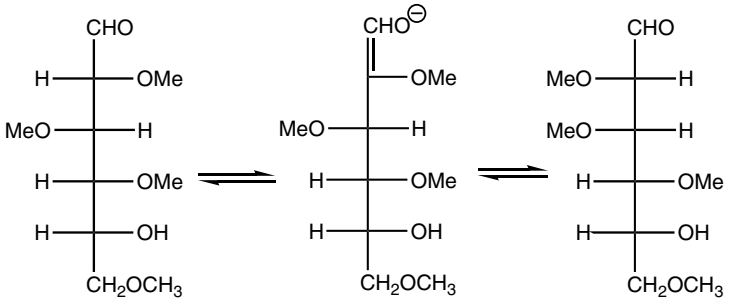

Fig. 4.21

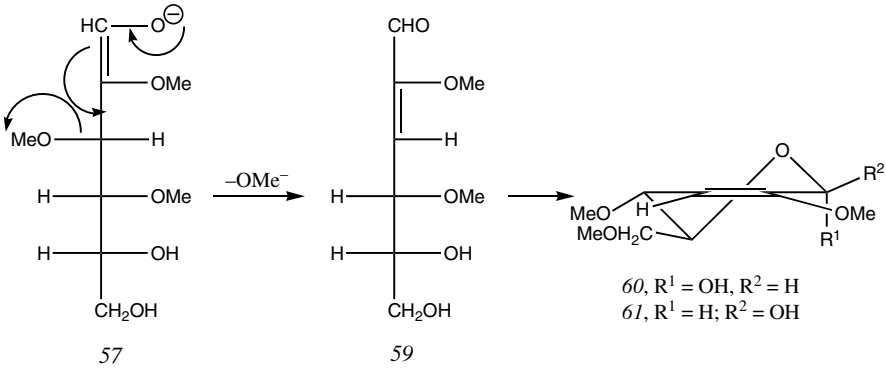

Fig. 4.22

Lobry de Bruyn–Alberta van Ekenstein transformation [41, 42]. Aldoses with their hydroxyl groups protected with alkali-stable protecting groups, such as methyl groups, on reaction with bases undergo only epimerization giving a mixture of C2 epimers (Fig. 4.20). Thus, forexample, reaction of 2,3,4,6-tetra-*O*-methyl-D-glucose *56* and 2,3,4,6-tetra-*O*-methyl-D-mannose *58* with a base (saturated lime water) gives a mixture of these two epimeric aldoses in the same proportion [43, 44] (Fig. 4.21).

The enolate *57* initially obtained by treating 2,3,4,6-tetra-*O*-methyl-D-glucose or 2,3,4,6-tetra-*O*-methyl-D-mannose with lime water slowly eliminates the C3 methoxy anion to form the unsaturated sugar *59,* which cyclizes to 3-deoxy-2,4,6-tri-*O*-methyl-α,β-D-*erythro*-hex-2-enopyranose *60, 61* [45, 46, 47] (Fig. 4.22).

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Chapter 5
Relative Reactivity of Hydroxyl Groups in Monosaccharides

Introduction

The furanoid and pyranoid cyclic structures of monosaccharides generally may have four types of chemically distinguishable hydroxyl groups: (1) the *anomeric* (*hemiacetal, lactol*) hydroxyl group and (2) three types of alcoholic hydroxyl groups: (a) the *primary hydroxyl group*, which is always *exocyclic* with regard to the carbohydrate ring and is found in both hexopyranoses and pento- or hexofuranoses, (b) the *endocyclic secondary hydroxyl* groups found in both hexopyranoses and pento- or hexofuranoses, and (c) the *exocyclic* secondary hydroxyl groups found in hexofuranoses or in higher sugars containing hexopyranose ring.

The reactivity of hydroxyl groups, excluding the anomeric hydroxyl group, is controlled by several factors. First, it depends on whether the hydroxyl group is a primary or a secondary one. In general, the *primary hydroxyl group* is *more reactive* than the secondary one suggesting that the difference in reactivity is most likely due to steric control. The steric factor is probably also responsible for the *exocyclic secondary hydroxyl groups* being more reactive than *endocyclic ones.* The difference in the reactivity among the endocyclic secondary hydroxyl groups is most likely controlled by stereoelectronic factors and by the ability of individual hydroxyl groups to form the intramolecular hydrogen bonds with neighboring hydroxyl or alkoxy oxygen. This difference is evident from dependence of reactivity of a given hydroxyl group on its position in a furanoid and/or pyranoid ring. Finally, the reactivity of a hydroxyl group depends on its configuration, i.e., on whether it is in the axial or in the equatorial orientation on a pyranoid ring.

The chemical behavior of the anomeric hydroxyl group, which is a hemiacetal or lactol hydroxyl group, is in many respects very different from all other hydroxyl groups of a monosaccharide. Thus (1) it can be easily oxidized (in both aldopyranoses and aldofuranoses) with aqueous bromine solution to a corresponding glyconolactone, whereby the other hydroxyl groups of a carbohydrate remain unchanged and (2) it can be replaced with an alkoxy group by treating a monosaccharide with an alcohol in the presence of an anhydrous mineral acid. Thus, for example, reaction of a furanoid or pyranoid form of a monosaccharide with anhydrous methanol and catalytic amounts of anhydrous HCl (gas) will result in

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_5,

replacement, with the methoxy group, of only the anomeric hydroxy group giving the so-called *methyl glycoside* as the product; all other hydroxyl groups will remain unchanged under the reaction conditions. The ability of monosaccharides to undergo this, so-called, *glycosidation* reaction is by far the most important property of carbohydrates and has found an extensive use in living organisms for the synthesis of biologically important carbohydrate oligomers and polymers, as well as in the glycosylation of other bio-molecules, such as proteins, lipids, that perform specific biological functions.

The relative reactivity of individual sugar hydroxyl groups depends also on the type of the reagent that is used for their transformation to corresponding derivatives. Thus in the case of acylation it often depends upon the nature of acylating agent (acyl chloride, acyl anhydride, etc.) and in case of alkylation upon the nature of alkylating agent.

Selective Acylation (Esterification)

Discussion of selectivity of acylation of hexo- and pentopyranoses will be first focused on acyl chlorides and acyl anhydrides as acylating agents because they are the most widely studied. At the end of discussion, a select number of other acylating agents will be described, which were developed to either improve the regioselectivity or to increase the yield of acylation.

The readers are referred to three very informative reviews dealing with this topic [1–3].

Our discussion on selectivity of sugar hydroxyl groups toward acylation will be limited to the following monosaccharides: α- and β-anomers of alkyl and/or aryl D-gluco- (*1*), D-manno- (*2*) and D-galactopyranosides (*3*) among hexopyranosides and α- and β-anomers of alkyl D-xylopyranoside (*4*) among pentopyranoses. The reason for this choice is that none of these glycopyranoses has either the O:O or the C:O 1,3-*syn*–axial interaction (the O:H 1,3-*syn*–axial interaction that are present in *2* and *3* are presumed to have no influence upon the final conclusions) (Fig. 5.1). In all other hexopyranoses there is at least one 1,3-*syn*–axial interaction between the axial hydroxyl groups and the presence of these interactions may adversely interfere with the interpretation of obtained results.

For example, α-anomers of D-allopyranose *5*, D-altropyranose *6*, and D-gulopyranose *7* (Fig. 5.2) all have one 1,3-*syn*–axial interaction between the axial anomeric hydroxyl group and the axial 3-OH group. The β-anomers of these hexoses have no 1,3-*syn*–axial interactions. There is one 1,3-*syn*–axial interaction between the 2-OH and the 4-OH present in both α- and β-D-talopyranose (*8* and *9*, respectively) as well as in β-D-idopyranose *11*, whereas in the α-D-idopyranose *10*, there are two *syn*–axial interactions, one between the anomeric hydroxyl group and the C3 hydroxyl group and the other between the 2-OH and the 4-OH (Fig. 5.3).

It must be emphasized that relative reactivity of hydroxyl groups in carbohydrates is, in addition to being of theoretical interest, also of great practical importance [1].

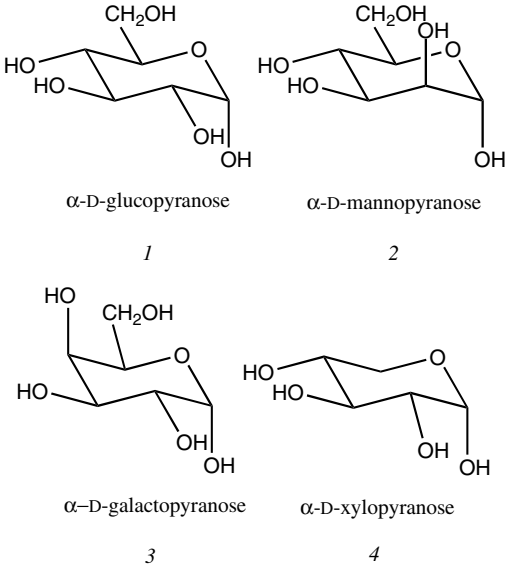


Fig. 5.1

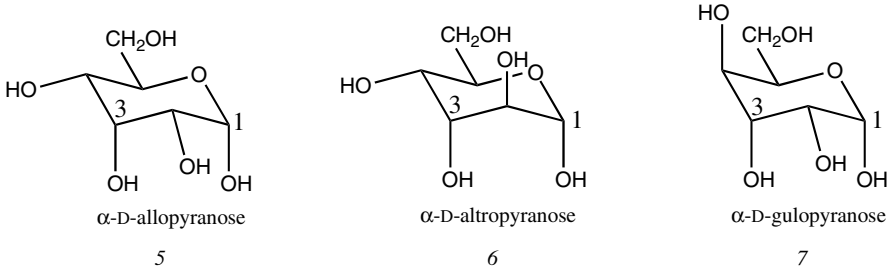


Fig. 5.2

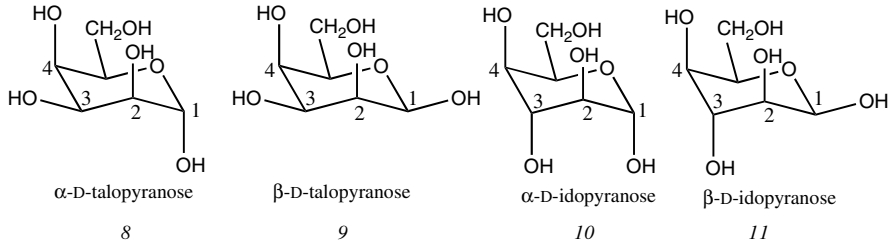


Fig. 5.3

A good overall picture of relative reactivity of C2, C3, C4, and C6 hydroxyl groups in methyl α-D-glycopyranosides can be obtained by studying the partial acylation using 1, 2, and 3 mol equivalent of acylating reagent to 1 mol of methyl

α- or β-D-glycopyranoside. The study of acylation of partially blocked glycopyranose derivative such as methyl 4,6-*O*-benzylidene-α-D-glycopyranoside permits determination of relative reactivity of the C2 and C3 hydroxyl groups.

The selective alkyl- or arylsulfonylation (methanesulfonylation – *mesylation* or *p*-toluenesulfonylation – *tosylation*) and benzoylation are the most extensively studied selective acylation reactions of monosaccharides.

Selective p-Toluenesulfonylation (Tosylation) and Methanesulfonylation (Mesylation)

Tosylation of methyl α-D-glucopyranoside *12* at 0°C with 1 mol equivalent of *p*-toluenesulfonyl (tosyl) chloride in pyridine [4] gives a mixture of tosyl esters in which the 6-*O*-tosylate *13* was a preponderant product (36%) (Fig. 5.4).

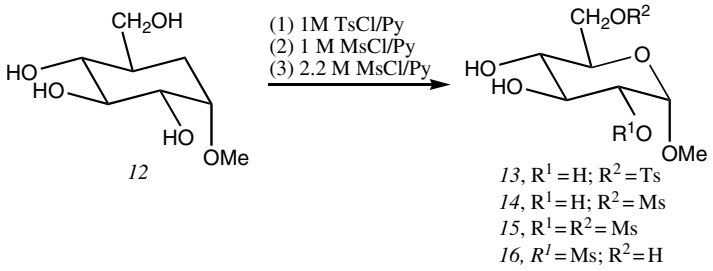
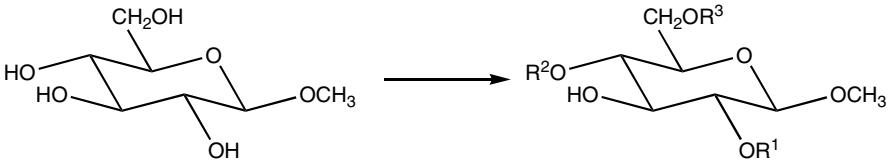


Fig. 5.4

The methanesulfonylation [5] (mesylation) of methyl α-D-glucopyranoside *12* with 1 mol equivalent of methane sulfonyl (mesyl) chloride in pyridine at –20°C gave the 6-*O*-mesyl derivative *14* with a considerably higher yield (67%) (Fig. 5.4).

However, in another study [6] the monomesylation of methyl α-D-glucopyranoside *12* with mesyl chloride in pyridine below –20°C was reported to give a complex mixture of products: the 6-*O*-mesyl ester *14* was obtained in only 20% yield, the 2,6-di-*O*-mesyl ester *15* was obtained in 10% yield, and 2-*O*-mesyl ester *15* in 2.5% yield. When mesylation was conducted with 2 mol equivalent [6] or 2.2 mol equivalent [7] of mesyl chloride in pyridine at –20°C, 2,6-di-*O*-mesyl derivative was obtained in 51% yield indicating that the C6 primary hydroxyl group and the C2 equatorial hydroxyl group are the most reactive hydroxyl groups in *12* (Fig. 5.4) and that the C2 hydroxyl group is more reactive toward mesylation than both the C3 and the C4 hydroxyl groups (Fig. 5.5).

The tosylation of methyl β-D-glucopyranoside [4] *17* with 1 mol equivalent of *p*-toluenesulfonyl chloride in pyridine gave 41% of 6-*O*-tosyl ester *18* indicating that the primary C6 hydroxyl group is the most reactive hydroxyl group toward tosylation also in β-anomers.



17

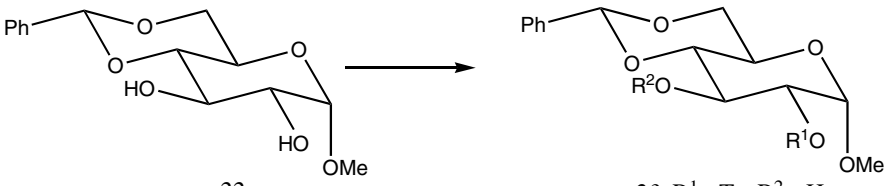
18, $R^1 = R^2 = H$; $R^3 = Ts$
19, $R^2 = R^3 = Ms$; $R^1 = H$
20, $R^1 = R^3 = Ms$; $R^2 = H$
21, $R^3 = Ms$; $R^1 = R^2 = H$

Fig. 5.5

Dimolar mesylation of methyl β-D-glucopyranoside [6] *17* was much less selective than the dimolar mesylation of α-isomer. Now the major product was methyl 4,6-di-*O*-methanesulfonyl-β-D-glucopyranoside *19* (13%), whereas the methyl 2,6-di-*O*-methanesulfonyl-β-D-glucopyranoside *20* and methyl 6-*O*-methanesulfonyl-β-D-glucopyranoside *21* were obtained with 4% yield each (Fig. 5.5).

These results show that selectivity of mesylation of endocyclic hydroxyl groups does not depend only on the type and the position of a hydroxyl group in the ring but also on the anomeric configuration. In β-D-glucopyranoside the relative reactivity of the C2 and the C4 hydroxyl groups seems to be reversed.

Tosylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside [8] *22* in pyridine with 0.74 mol equivalent of TsCl for 24 h gives the 2-*O*-tosyl ester *23* with 64.30% yield. Tosylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside *22* in pyridine with 1.3 mol equivalent of TsCl at room temperature for 12 h [9] gives 64.46% of 2-*O*-tosyl ester *23* (Fig. 5.6). Small amounts of starting material and the 2,3-ditosyl ester *24* were also isolated.



22

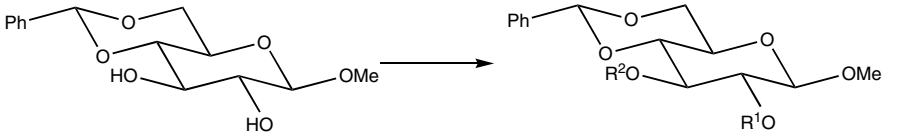
23, $R^1 = Ts$; $R^2 = H$
24, $R^1 = R^2 = Ts$
25, $R^1 = Ms$; $R^2 = H$
26, $R^1 = R^2 = Ms$

Fig. 5.6

The mesylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 22 with 1.1 mmol of methanesulfonyl chloride in pyridine gave the 2-*O*-mesyl derivative *25* with 68% yield [10] together with 16% of 2,3-dimesylate *26*.

These results are in full accord with the previous conclusion that the 2-OH is more reactive than 3-OH group in methyl α-D-glucopyranoside. This study also indicated that the selectivity of these two hydroxyl groups toward mesylation and tosylation is identical.

The tosylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside [11] *27* with 1.1 mol equivalent of tosyl chloride in pyridine gave 2-*O*-tosyl ester *28* with 21% yield, 3-*O*-tosyl ester *29* with 28% yield, and 2,3-di-*O*-tosyl ester *30* with 4% yield (Fig. 5.7).



27

28, R^1 = Ts; R^2 = H
29, R^1 = H; R^2 = Ts
30, R^1 = R^2 = Ts
31, R^1 = R = Ms
32, R^1 = Ms; R^2 = H
33, R^1 = H; R^2 = Ms

Fig. 5.7

In another study [12] tosylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside *27* with 1 mol equivalent of TsCl was conducted at 4°C for 6 days (pyridine solution of TsCl and the pyridine solution of sugar were pre-cooled with dry ice–acetone prior to mixing), 3-*O*-tosyl ester *29* was obtained with 8% yield, 2-*O*-tosyl ester *28* with 2–5% yield, and 2,3-di-*O*-tosyl ester *30* with 40% yield (20% of the starting material *26* was recovered after the reaction) (Fig. 5.7).

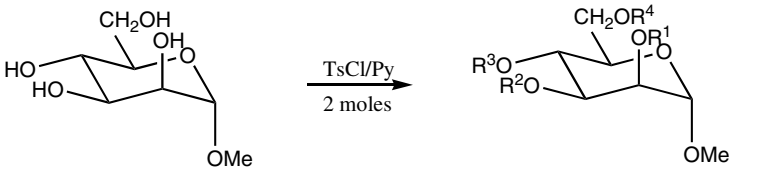
Thus, the tosylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside has shown (1) a much lower selectivity from that found in the corresponding α-anomer and (2) the relative reactivity of the C2 and the C3 hydroxyl groups appears to be reversed.

Selective mesylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside [12] with 1 mol equivalent of methanesulfonyl chloride in pyridine (pyridine solution of MsCl and the pyridine solution of sugar were pre-cooled with dry ice-acetone prior to mixing) by keeping the reaction mixture at 4°C overnight gave 2,3-di-*O*-mesylate *31* with 41% yield, 2-*O*-mesylate *32* with 6% yield, and 3-*O*-mesylate *33* with 17% yield (Fig. 5.7).

From these, as well as from other studies, it was concluded [1] that the primary hydroxyl group of both α- and β-D-glucopyranoses is more reactive toward alkyl or arylsulfonyl chlorides than any of the secondary hydroxyl groups, thus permitting the selective esterification of the terminal hydroxyl group in methyl glucopyranosides.

Kondo [13] studied selective tosylation of methyl α-D-mannopyranoside *34* using 2 mol equivalent of *p*-toluenesulfonyl chloride and found that two major products were 6-*O*-tosylate *35* (35%) and 3,6-ditosylate *36* (35%). The mixture of minor

products consisted of 4,6- (*37*) and 2,6-ditosylate (*38*) (14%), 2,3,6-tri-*O*-tosylate *39* (3%) and 3,4,6-tritosylate *40* (1%) (Fig. 5.8).



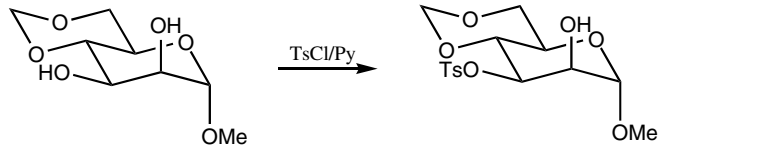
34

35, $R^1 = R^2 = R^3 = H$; $R^4 = Ts$
36, $R^2 = R^4 = Ts$; $R^1 = R^3 = H$
37, $R^1 = R^2 = H$; $R^3 = R^4 = Ts$
38, $R^1 = R^4 = Ts$; $R^2 = R^3 = H$
39, $R^1 = R^2 = R^4 = Ts$; $R^3 = H$
40, $R^1 = H$; $R^2 = R^3 = R^4 = Ts$

Fig. 5.8

Mesylation of methyl α-D-mannopyranoside with the 3 mol equivalent of MsCl gave methyl 2,3,6-tri-*O*-methanesulfonyl-α-D-mannopyranoside with 41% yield together with some other unidentified mesylation products [6].

The tosylation of methyl 4,6-*O*-ethylidene-α-D-mannopyranoside *41* with 1.0 mol equivalent of TsCl (2 days at –5°C and 1 day at 0°C) gave the 3-*O*-tosylate *42* in good yield (59.16%), whereas the 2-*O*-tosyl derivative was not detected indicating that the equatorial 3-OH is sulfonylated much more readily than the axial 2-OH group [14] (Fig. 5.9).



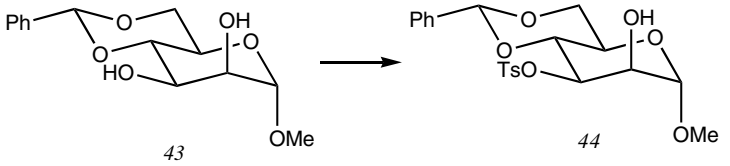
41, Methyl 4,6-ethylidene-α-D-mannopyranoside

42, Methyl 4,6-ethylidene-3-O-tosyl-α-D-mannopyranoside

Fig. 5.9

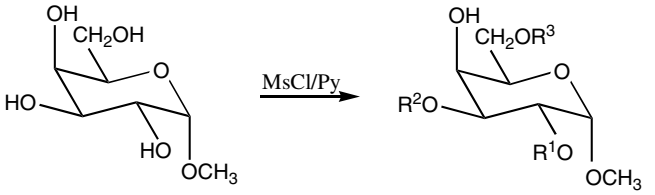
Tosylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside *43* with 1.1 mol equivalent of TsCl in pyridine at 0°C for 24 h [15] gave the 3-*O*-tosylate *44* with 35.9% yield together with small amount of 2,3-di-*O*-tosyl derivative (4.3%) (Fig. 5.10).

The mesylation of methyl α-D-galactopyranoside [6] *45* with 2 mol equivalent of methane sulfonyl chloride gave 2,6-di-*O*-mesyl ester *46* with 20% yield, 2,3,6-tri-*O*-mesyl ester *47* with 10% yield, and 3,6-di-*O*-mesyl ester *48* with 4% yield. The mesylation of *45* with 3 mol equivalent of methanesulfonyl chloride [6] gave 2,3,6-tri-*O*-mesyl ester *47* with 30% yield (Fig. 5.11).



43 *44*

Fig. 5.10

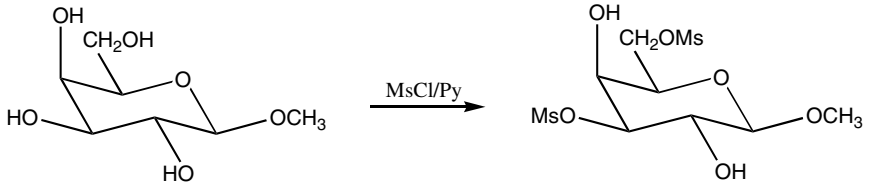


45

46, $R^1 = R^3 = Ms$; $R^2 = H$
47, $R^1 = R_2 = R_3 = Ms$
48, $R^2 = R^3 = Ms$; $R^1 = H$

Fig. 5.11

Mesylation of methyl-β-D-galactopyranoside [6] *49* with 2 mol equivalent of methanesulfonyl chloride gave the 3,6-di-*O*-mesyl ester *50* with 26% yield (Fig. 5.11).

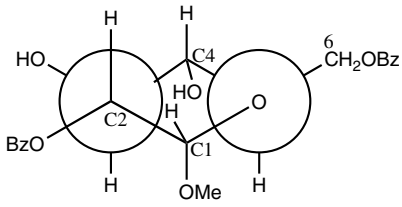


49 *50*

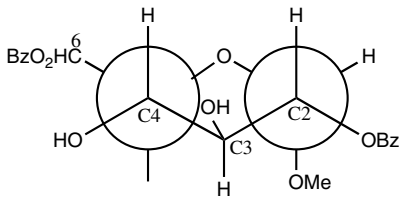
Fig. 5.12

Selective Benzoylation

Williams and Richardson [16] studied the selective benzoylation of methyl α-D-gluco-, α-D-manno-, and α-D-galactopyranoside with benzoyl chloride in pyridine. The benzoylation of methyl α-D-glucopyranoside *12* with 3.1 mol equivalent of benzoyl chloride gave a reaction mixture containing predominantly two tribenzoates: 2,3,6-tribenzoate *51*, which was the major product (67% yield), and 2,4,6-tribenzoate *52* which was the minor product (28% yield) (in pure form, *51* was isolated with 49% yield and *52* with 19% yield). Dibenzoylation of methyl α-D-glucopyranoside *12* gave 2,6-di-*O*-benzoate *53* with the 50% yield (Fig. 5.13).



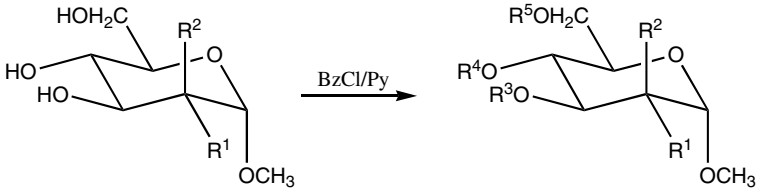
56, Methyl 2,6-di-O-benzoyl-α-D-glucopyranoside



57, Methyl 2,6-di-O-benzoyl-α-D-glucopyranoside

Fig. 5.13

The lower reactivity of the C4 hydroxyl group compared to 3-OH (2,3,6-tri-*O*-benzoyl derivative *51* was obtained with 2.4 times greater yield than 2,4,6-tribenzoate *52*) was explained by steric hindrance (Fig. 5.14), namely it is known that the C6 primary hydroxyl and the C2 hydroxyl groups are the two most reactive hydroxyl groups in *12* toward acylation. Therefore, it can be expected that the 2,6-dibenzoate will be formed first. The tribenzoates are actually then formed by benzoylation of 2,6-dibenzoate. In 2,6-dibenzoate the C3 hydroxyl group is *gauche* to the 2-*O*-benzoate and to the C4 hydroxyl group *56* (Fig. 5.14) and the C4 hydroxyl group is *gauche* to the C6 hydroxymethyl group and to the C3 hydroxyl group *57* (Fig. 5.14). Therefore due to steric constraint of the C4 hydroxyl group, the C3 hydroxyl group is more available for acylation and thus will be benzoylated at a faster rate than the 4-OH, thus explaining the preponderance of 2,3,6-tribenzoate (67%) over the 2,4,6-tribenzoate (28%).



12, R^1 = OH; R^2 = H
34, R^1 = H; R^2 = OH

51, R^1 = OBz; R^3 = R^5 = Bz; R^2 = R^4 = H
52, R^1 = OBz; R^4 = R^5= Bz; R^2 = R^3 = H
53, R^1 = OBz; R^2 = R^3 = R^4 = H; R^5 = Bz
54, R^2 = OBz; R^3 = R^5 = Bz; R^1 = R^4 = H
55, R^1 = R^4 = H; R^2 = OH; R^3 = R^5 = Bz

Fig. 5.14

Lieser and Schweizer [17, 18] obtained methyl 2,6-di-*O*-benzoyl-α-D-glucopyranoside *53* with 50% yield on benzoylation of methyl α-D-glucopyranoside *12* with 2.0 mol equivalent of benzoyl chloride in pyridine. It is interesting that the benzoylation of phenyl β-D-glucopyranoside with equimolar amount of benzoyl chloride in pyridine gave phenyl 6-*O*-benzoyl-β-D-glucopyranoside with 73% yield,

indicating an unusual high selectivity of the primary hydroxyl group for benzoylation compared to mesylation or tosylation.

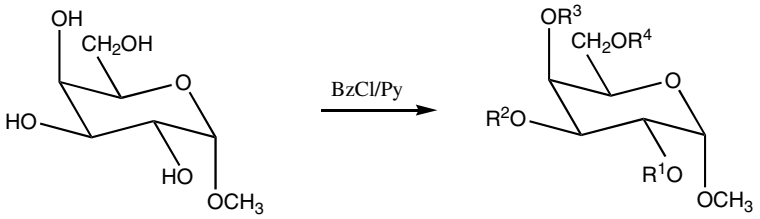
The order of reactivity of secondary hydroxyl groups in methyl α-D-glucopyranoside toward benzoylation with benzoyl chloride in pyridine is thus 2-OH > 3-OH > 4-OH.

Benzoylation of methyl α-D-mannopyranoside *34* (Fig. 5.13) with 3.1 M equivalent of benzoyl chloride in pyridine [16] gave 2,3,6-tri-*O*-benzoate *54* as the major product (56%) and methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside *55* as the minor product (26%).

Benzoylation of methyl α-D-mannopyranoside *34* with 2 M equivalent of benzoyl chloride in pyridine [16] gave methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside *55* with 62% yield (Fig. 5.13) suggesting that in methyl α-D-mannopyranoside the C3 hydroxyl group is the most reactive secondary hydroxyl group. The lesser reactivity of the 2-OH is probably due to its unfavorable axial orientation, since it is known [18], from conformational analysis, that axial hydroxyl groups are considerably less reactive (3.69 times) toward acylation than equatorial ones.

The fact that tribenzoylation of methyl α-D-mannopyranoside gave the 2,3,6-tribenzoate *54* as the predominant product shows that the C4 hydroxyl group is the least reactive of the three secondary hydroxyl groups. Thus the order of reactivity of secondary hydroxyl groups in methyl α-D-mannopyranoside is 3-OH > 2-OH > 4-OH. The greater reactivity of the C2 hydroxyl group compared with the C4 hydroxyl group is difficult to rationalize. Perhaps, the C2 hydroxyl group experiences less unfavorable *gauche* interactions than the 4-OH and/or is somehow activated by the anomeric group.

The benzoylation of methyl α-D-galactopyranoside *45* with 4.2 mol equivalent of benzoyl chloride in pyridine [16] at –30°C gave 2,3,6-tri-*O*-benzoate *58* with 65% yield, 3,6-di-*O*-benzoate *59* with 6% yield, and 2,3,4,6-tetra-*O*-benzoate *60* with 2% yield (Fig. 5.15).



45

58, $R^1 = R^2 = R^4 = Bz$; $R^3 = H$
59, $R^1 = R^3 = H$; $R^2 = R^4 = Bz$
60, $R^1 = R^2 = R^3 = R^4 = Bz$

Fig. 5.15

The proposed explanation for the predominant formation of *58* (Fig. 5.15) is again that the axial C4 hydroxyl group is considerably less reactive than equatorial ones (C2 and the C3) [19].

Benzoylation of methyl 6-deoxy-α-L-galactopyranoside *61* (methyl α-L-fucopyranoside) with 2.1 M equivalent of benzoyl chloride in pyridine [20] at –40°C gave 2,3-di-*O*-benzoate *62* with 80% yield (Fig. 5.16).

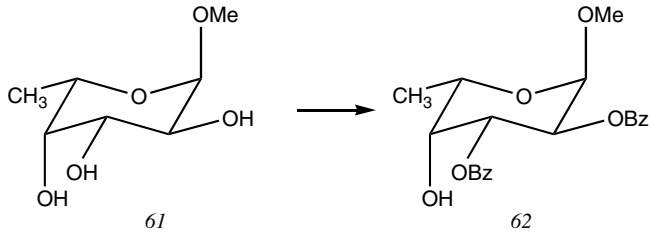


Fig. 5.16

Benzoylation of methyl 6-deoxy-α-L-mannopyranoside (methyl α-L-rhamnopyranoside) *63* with 2.0 M equivalent of benzoyl chloride at room temperature [20] gave 2,3-dibenzoate *64* with 50% yield (Fig. 5.17).

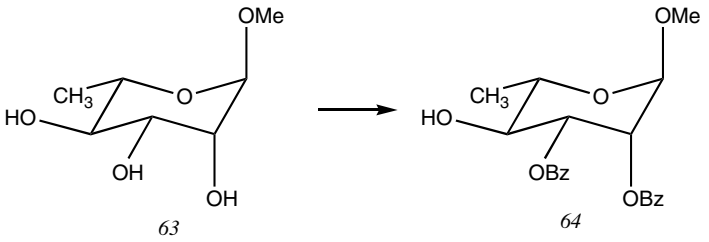


Fig. 5.17

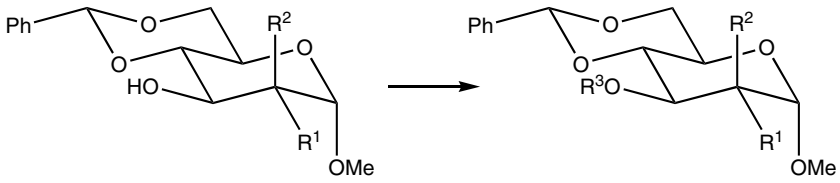
The obtained results are similar to those obtained for benzoylation of methyl α-D-manno- and α-D-galactopyranoside. Consequently the absence of hydroxyl group at the C6 carbon appears to have little or no effect upon the reactivity of the C4 hydroxyl group [20]. With the exception of the C4 hydroxyl group, the relative reactivity of the C2 and the C3 hydroxyl groups of methyl α-D-galactopyranoside cannot be predicted from the above results. The high selectivity toward tribenzoylation only shows that the axial C4-OH is the least reactive one.

It is clear that the order of reactivity of secondary OH groups is different for each glycoside, thus it is 2-OH> 3-OH> 4-OH for the glucoside, 3-OH> 2-OH> 4-OH for the mannoside, and 2-OH, 3-OH> 4-OH for the galactoside.

In conclusion, the most reactive hydroxyl group in methyl α-D-glucopyranoside, α-D-mannopyranoside, and α-D-galactopyranoside is the primary C6 hydroxyl group whereas the least reactive hydroxyl group is the secondary C4 hydroxyl group. The reactivity of the C2 and C3 hydroxyl groups depends upon whether the C2 hydroxyl group is equatorial or axial. If it is equatorial and *cis* to the C1 methoxy group, as is the case in methyl α-D-glucopyranoside, it is more reactive

than the C3 hydroxyl group; if it is axial (*trans* to C1 methoxy group) as in methyl α-D-mannopyranoside, the C3 hydroxyl group is more reactive.

Benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside *22* with 1 mol of benzoyl chloride under phase-transfer conditions [21] (dichloromethane, aqueous 40% sodium hydroxide, tetrabutylammonium chloride) in the presence of sodium iodide or perchlorate gave 2-benzoate *65* as the major product (72% after chromatography, 62% after crystallization). 3-Benzoate *66* and 2,3-dibenzoate *67* were obtained in 4% each. Benzoylation of methyl 4,6-benzylidene-α-D-mannopyranoside *43* with 1 mol of benzoyl chloride under phase-transfer conditions [21], a ~ 1:1 equilibrium mixture of the 2-(*68*) and 3-(*69*) benzoates was obtained. If acylation was performed in the presence of sodium iodide or perchlorate, 2-benzoate *65* was obtained in 52% and 3-benzoate *66* in 11% (both after chromatography (Fig. 5.18)).



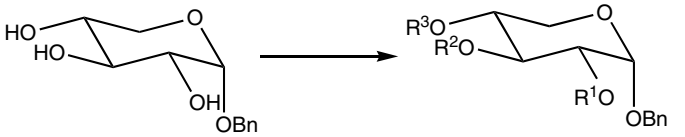
22, R^1 = OH; R^2 = H
43, R^1 = H; R^2 = OH

65, R^1 = OBz; $R^2 = R^3$ = H
66, R^1 = OH; R^2 = H; R^3 = Bz
67, R^1 = OBz; R^2 = H ; R^3 = Bz
68, $R^1 = R^3$ = H; R^2 = OBz
69, R^1 = H; R^2 = OH; R^3 = Bz

Fig. 5.18

The acylation of benzyl or methyl α-D-pentopyranosides shows different relative reactivities of secondary hydroxyl groups presumably due to the absence of exocyclic hydroxymethyl group at the C5 carbon.

Thus, dibenzoylation of benzyl α-D-xylopyranoside [22] *70* gave preponderance of the 2,4-dibenzoate *71* over the 2,3-isomer *72*. The reason for this could be steric; namely the C4 hydroxyl group is *gauche* just to the C3 hydroxyl group (the C5 has



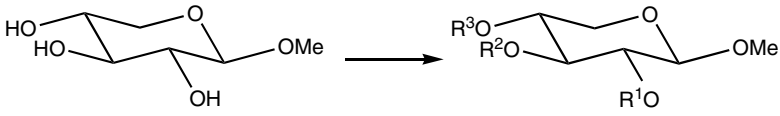
70

71, $R^1 = R^3$ =Bz; R^2 = H
72, $R^1 = R^2$ = Bz; R^3 = H
73, $R^1 = R^2 = R^3$ = Bz
74, R^1 = Bz; $R^2 = R^3$ = H

Fig. 5.19

only hydrogen atoms), whereas the C3 hydroxyl group is *gauche* to both the C4 and the C2 hydroxyl groups (Fig. 5.19).

These results were confirmed by Kondo [23] who repeated the selective benzoylation of methyl α-D-xylopyranoside *60* with 2 M equivalents of benzoyl chloride in pyridine at –40°C and obtained 2,4-dibenzoate *71* in 45%, 2,3-dibenzoate *72* in 39%, 2,3,4-tribenzoate *73* in 11%, and 2-benzoate *74* with 5% yield (Fig. 5.19).



75

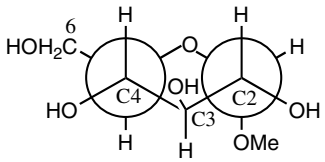
76, $R^1 = R^2 = Bz$; $R^3 = H$
77, $R^2 = R^3 = Bz$; $R^1 = H$
78, $R^1 = R^3 = Bz$; $R^2 = H$
79, $R^1 = R^3 = R^2 = Bz$
80, $R^1 = R^3 = H$; $R^2 = Bz$
81, $R^1 = R^2 = H$; $R^3 = Bz$
82, $R^1 = Bz$; $R^2 = R^3 = H$

Fig. 5.20

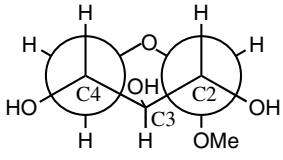
Benzoylation of methyl β-D-xylopyranoside *75* with 2 mol equivalent of benzoyl chloride in pyridine [23] gave a mixture of 2,3-dibenzoate *76* and 3,4-dibenzoate *77* with 53% yield, 2,4-dibenzoate *78* (22%), tribenzoate *79* (17%), the 3-benzoate *80* (4%), and a mixture of 4-benzoate *81* and 2-benzoate *82* (4%) (Fig. 5.20).

Benzoylation of methyl β-D-xylopyranoside *75* with 1 M equivalent of benzoyl chloride in pyridine [23] gave 2-benzoate *82* (26%), 3-benzoate *80* (25%), 4-benzoate *81* (20%), 2,4-dibenzoate *78* (8%), a mixture of 2,3-dibenzoate *76* and 3,4-dibenzoate *77* (19%), and tribenzoate*79* (2%) (Fig. 5.20).

The higher reactivity of 2-OH group in methyl α-D-xylopyranoside was explained by intramolecular hydrogen bonding between the 2-OH group and the *cis*-oriented C1-OR substituent. The lowest reactivity of the 3-OH group in methyl α-D-xylopyranoside is in accord with the results obtained for selective benzoylation of benzyl α-D-xylopyranoside and the C4 carbon. Thus the 3-OH group has *gauche* interactions with the C2 benzoyl and the C4 hydroxyl group, whereas 4-OH has interactions with the C3 benzoyl and the C5 hydrogen atom. Therefore,



83, methyl α-D-glucopyranoside



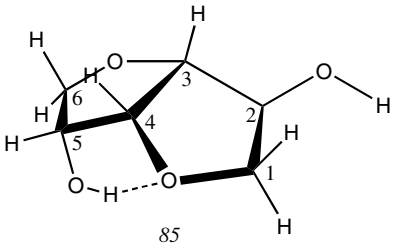
84, methyl α-D-xylopyranoside

Fig. 5.21

4-OH group is less sterically hindered, thus causing the preponderance of the 2,4-dibenzoate over 2,3-dibenzoate. However, the preponderance of 2,3-dibenzoate over 2,4-dibenzoate in selective benzoylation of methyl β-D-xylopyranoside cannot be similarly explained [23] (Fig. 5.21).

The hypothesis that the activation of an equatorial C2 hydroxyl group toward acylation is due to the ability of this hydroxyl group to enter the hydrogen bonding with the neighboring C1 oxygen was questioned, since the IR spectra of pyridine solution of free sugars provide no evidence for intramolecular hydrogen bonding [24]. However, this may not be a valid criticism at all because the 2-OH can form the hydrogen bond with the solvent or the hydrogen bond between the 2-OH and the C1 methoxy group can be destroyed by the solvent.

Support for the rationalization that the activation of a hydroxyl group toward acylation is due to its ability to enter the hydrogen bonding with the neighboring C1 oxygen has been provided by experiments conducted by Lemieux and McInnes [25]. They have tosylated the 1,4:3,6-dianhydro-D-glucitol *85* (Fig. 5.22) with 1 mol equivalent of tosyl chloride and found that the major product was the 5-*O*-tosyl ester



85

Fig. 5.22

(45%), indicating that sterically more hindered *endo*-hydroxyl group is preferably tosylated, whereas the less hindered 2-exo hydroxyl group was tosylated to a much lesser extent (12%). Although the more reactive 5-OH is comparatively shielded, it is significant that it is intramolecularly strongly hydrogen bonded to a ring oxygen atom (C1–O–C4).

Since the selectivity of acylation vary with acylating agent and the catalyst it is important to point out that the relative reactivity of secondary hydroxyl groups in hexopyranoses toward acyl chlorides (tosyl chloride, mesyl chloride, and benzoyl chloride) is not necessarily applicable to acetanhydride, benzoic anhydride, etc., or to some other acylating agents.

Comparison of acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside using acetic anhydride, benzoic anhydride, methanesulfonic anhydride, and *p*-toluene sulfonic anhydride with the acylation using acetyl chloride, benzoyl chloride, and methanesulfonyl chloride in pyridine is given in Table 5.1 [10].

As can be seen from Table 5.1 the product ratio obtained by selective acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with 1 M equivalent of

Table 5.1 Esterification of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in pyridine

Reagent	Molar equivalents of reagent	2-Ester (%)	3-Ester (%)	2,3-Di-ester (%)
$(CH_3CO)_2O$	1.25	3	42	26
$(PhCO)_2O$	1.10	13	25	9
Ms_2O[a]	1.1	40	–	6
Ts_2O[b]	1.1	80–85	–	15
CH_3COCl	1.25	16	–	23
PhCOCl	1.25	24	6	35
CH_3SO_2Cl	1.1	68	–	16

[a] $(CH_3SO_2)_2O$
[b] $(p\text{-}CH_3C_6H_4SO_2)_2O$

acylating reagent in pyridine (Table 5.1) showed a marked dependence on the used reagent [10].

For example, 1 mol equivalent of acetyl chloride and benzoyl chloride in pyridine gives 2-acetyl or 2-benzoyl esters of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside [10] with 16 and 24% yield, respectively.

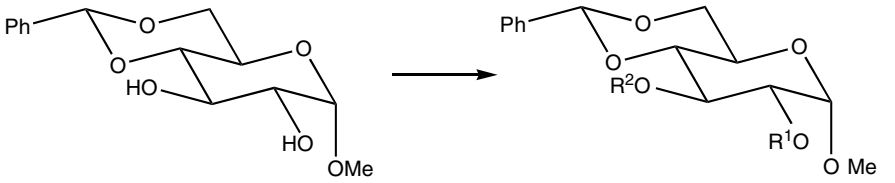
The greater reactivity of the 2-OH group in α-glucopyranoside over that in β-anomer has been attributed [1] to an activating effect of anomeric oxygen. It has been suggested that the activation of the 2-OH by the axially oriented C1 methoxy group in α-anomer takes place via hydrogen bonding between the C1 methoxy oxygen and the C2 hydroxyl hydrogen (they are *cis* oriented in the α-anomer and in β-anomer they are *trans* oriented and thus less likely to form hydrogen bond).

The C3 hydroxyl group is practically in the same steric and electronic environment in both methyl α- and β-D-glucopyranosides. So the difference in the reactivity toward acylation of 2-OH and 3-OH could be due to higher reactivity of the 2-OH in the α-D-glucopyranoside compared to that in β-anomer, rather than to be due to greater reactivity of the 3-OH in the β-anomer compared to that in the α-D-glucopyranoside. Perhaps a better explanation could be that the C3 hydroxyl group is generally more reactive than the C2 hydroxyl group but in the α-anomer the equatorially oriented C2 hydroxyl group is activated via hydrogen bond by the *cis*-oriented C1 methoxy group. However, the greater reactivity of the C2 hydroxyl group over that of the C3 hydroxyl group in β-anomer cannot be rationalized.

Selective Acetylation

Unlike tosylation, mesylation, and benzoylation of carbohydrates that are usually performed by using acyl chloride and pyridine, the acetylation is usually effected by using acetic anhydride in the presence of pyridine, sodium acetate, etc. Thus, the relative reactivity of hydroxyl groups of a pyranoside toward acetylation does not have necessarily to be the same as toward acyl chlorides. For example, the acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside *22* with 1.25 mol equivalent

of acetic anhydride in pyridine at room temperature gave 42% of 3-acetate *86*, 26% of 2,3-diacetate *87*, and 3% of 2-acetate [10] *88*, whereas the acetylation of *22* with 1.1 mol equivalent of acetyl chloride in pyridine at room temperature gave 3-acetate *86* with 6% yield, 2,3-diacetate *87* with 35% yield, and 2-acetate *88* with 6% yield [10] (Fig. 5.23).

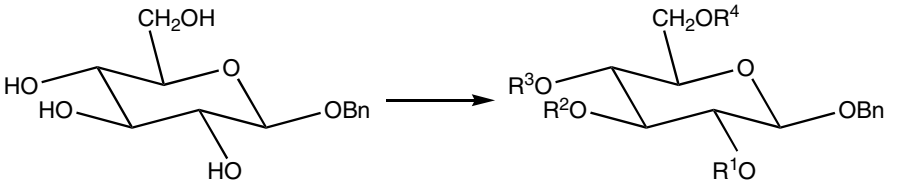


22

86, R^1 = OH; R^2 = Ac
87, R^1 = R^2 = Ac
88, R^1 = Ac; R^2 = H

Fig. 5.23

To the best of our knowledge there are no systematic studies reported on selective acetylation of alkyl or aryl α-D-gluco-, manno-, and galactopyranosides with acetic anhydride in pyridine.



89

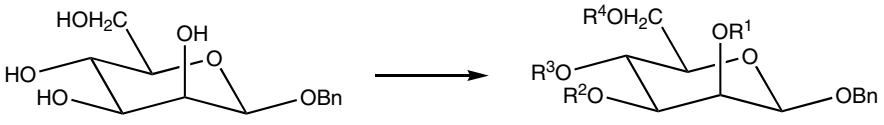
90, R^1= R^2 =R^3 =R^4 = Ac
91, R^1 = R^4 = R^5 = Ac; R^2 = H

Fig. 5.24

However, the selective acetylation of β-anomers of D-gluco- and D-galactopyranosides has been reported. Thus, the acetylation of benzyl β-D-glucopyranoside *89* with 8.5 mol equivalent of acetic anhydride and anhydrous sodium acetate [26], at room temperature gave a mixture of products from which the crystalline tetraacetate *90* and 2,4,6-tri-*O*-acetate *91* were isolated with 32 and 66% yield, respectively (Fig. 5.24).

Acetylation of benzyl β-D-mannopyranoside *92* with 8.5 mol equivalent of acetic anhydride in the presence of anhydrous sodium acetate at room temperature [26] gave a mixture of products consisting of tetraacetate *93* (65%) and 2,3,6-triacetate *94* (25%) (Fig. 5.25).

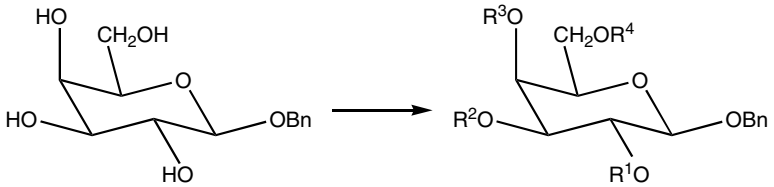
Acetylation of benzyl β-D-galactopyranoside *92* with 5.7 M equivalent of acetic anhydride [26] gave a very complex reaction mixture: tetraacetate *96* was the major



92

93, $R^1 = R^2 = R^3 = R^4 = Ac$
94, $R^1 = R^3 = R^4 = Ac$; $R^2 = H$

Fig. 5.25



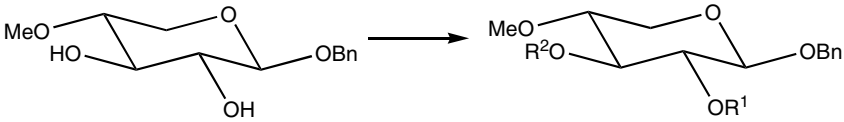
95

96, $R^1 = R^2 = R^3 = R^4 = Ac$
97, $R^1 = R^2 = R^4 = Ac$; $R^3 = H$
98, $R^1 = R^3 = R^4 = Ac$; $R^2 = H$
99, $R^2 = R^3 = R^4 = Ac$; $R^1 = H$

Fig. 5.26

product (38%), 2,3,6-triacetate *97* was obtained with 25% yield, 2,4,6-triacetate *98* was obtained with 9% yield, and 3,4,6-triacetate *99* was obtained with 3% yield (Fig. 5.26).

The partial acetylation of benzyl 4-*O*-methyl-β-D-xylopyranoside [27] *100* was dependent on the reaction conditions: the 2OAc:3OAc (*101:102*) ratio is 1:3 with Ac_2O–$HClO_4$, 1.7:1 with Ac_2O–Py, 2:1 with Ac_2O–CH_3COONa, and 1.1:1 with AcCl–Py (Fig. 5.27).



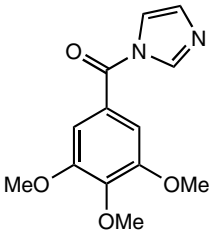
100

101, $R^1 = Ac$; $R^2 = H$
102, $R^1 = H$; $R^2 = Ac$

Fig. 5.27

Other Acylating Reagents

Selective acylation of methyl α-D-glucopyranoside with *N*-3,4,5-trimethoxybenzoyl imidazole [*N*-(tri-*O*-methylgalloyl) imidazol] [28] *103* (Fig. 5.28) in dioxan at 60°C gave methyl 6-*O*-(tri-*O*-methylgalloyl)-α-D-glucopyranoside with 63%

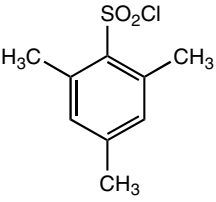


103

Fig. 5.28

yield. In a similar way methyl 2,6-di-*O*-(tri-*O*-methylgalloyl)-α-D-glucopyranoside was obtained with 31% yield and methyl 2,3,6-tri-*O*-(tri-*O*-methylgalloyl)-α-D-glucopyranoside was obtained with 65% yield.

2,4,6-Trimethylbenzenesulfonyl chloride (mesitylenesulfonyl chloride; trimsyl chloride – TmCl) *104* (Fig. 5.29) has been shown [29] to be much more selective for the monosulfonylation of vicinal secondary hydroxyl groups. Thus trimsylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with 1.5 M equivalent in pyridine and at room temperature (6 days) gave 2-*O*-trimsyl ester with 58% yield. The formation of 2,3-di-trimsyl ester was a much slower reaction than monotrimsylation: after treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with 3 M equivalent of trimsyl chloride in pyridine, at room temperature for 4 days, only 7%



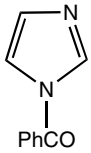
104

Fig. 5.29

of 2,3-di-trimsyl ester was obtained; by allowing reaction to proceed for 30 days, the yield was increased to 25%. Trimsylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside with 1.5 M equivalent in pyridine at room temperature gave after 6 days 11% of 2,3-di-trimsyl ester, 23% of 2-trimsyl ester, and 33% of 3-trimsyl ester.

Benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with benzoylimidazole [30] *105* (Fig. 5.30) in chloroform at reflux gave after 10 h 78% of 2-*O*-benzoyl ester [29].

In monobenzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside using *N*-benzoylimidazole little selectivity between 2-OH and 3-OH was observed since the imidazole formed during the acylations is capable of catalyzing a facile ester migration between the two *cis*-hydroxyl groups, and the product consisted of nearly 1:1 equilibrium mixture of 2- and 3-benzoates, respectively. This contrasts the



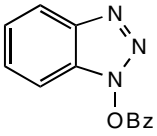
105, Benzoyl imidazole

Fig. 5.30

monobenzoylation of the *trans* orientation of 2-OH and 3-OH groups in a D-glucopyranose derivative in which the acyl migration is much slower under the reaction conditions, and the product is apparently formed under kinetic control.

Benzoylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with 1 M equivalent of benzoyl cyanide in acetonitrile in the presence of a catalytic quantity of triethyl amine [31] yielded 2- and 3-*O*-benzoates in 2.3:1 ratio. The reaction of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside under similar conditions gave 2-*O*-benzoate with 62% yield and 4,6-*O*-benzylidene-β-D-galactopyranoside gave 3-*O*-benzoate with 74% yield [32].

Benzoylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with equimolar amounts of 1-(benzoyloxy) benzotriazole *106* and triethylamine [33] (Fig. 5.31) in methylene chloride at room temperature gave after 5 h 2-*O*-benzoyl ester with 90% yield, together with 2,3-di-*O*-benzoate (2%) and 3-*O*-benzoate (4%). Benzoylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was much less selective but it is not clear if the loss of selectivity was due to the solvent change, namely since methyl 4,6-*O*-benzylidene-β-D-glucopyranoside was insoluble in methylene chloride, the reaction was carried out in tetrahydrofuran; 2-*O*-benzoate was obtained with 50% yield and 3-*O*-benzoate with 43% yield [33]. Very high regioselectivity



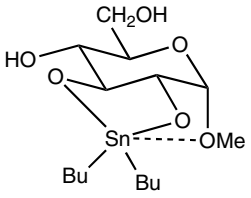
106, 1-(Benzoyloxy)benzotrizole

Fig. 5.31

was also achieved on selective benzoylation of methyl 4,6-*O*-benzylidene-α-D-altropyranoside (90% of 2-benzoate). The 2,3-dibenzoate was not formed [33]. Thus the relative reactivity of 2-OH and 3-OH in α- and β-anomers of D-glucopyranose derivatives could not be compared since they were performed in two different solvents.

Selective benzoylation of some methyl α-D-hexopyranosides was achieved using dibutylstannylene derivatives [34]. Methyl 2,3-*O*- dibutylstannylene-α-D-glucopyranoside, *107* obtained from methyl α-D-glucopyranoside and dibutyltin

oxide, was benzoylated in dioxane by benzoyl chloride and triethylamine whereby 2-*O*-benzoyl ester was obtained with 70% yield, together with 2% of 2,6-dibenzoate. Benzoylation of the analogous tin derivatives of methyl β-D-glucopyranoside *110* and methyl α-D-mannopyranoside *109* failed to be selective.



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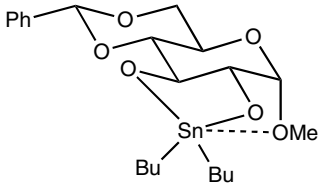
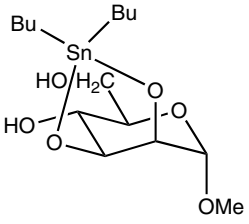


108



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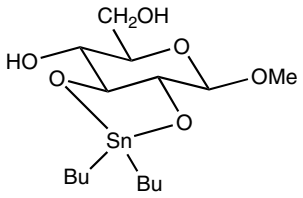


110

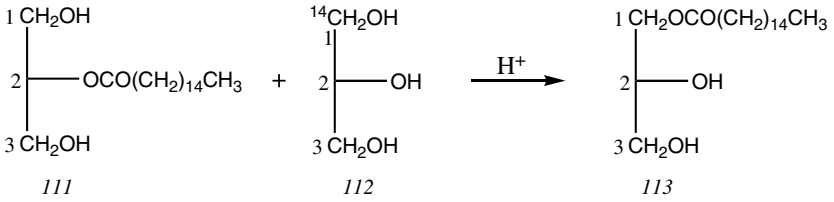
Fig. 5.32

In each case there were obtained approximately equal amounts of 2- and 3-esters in addition to a rather large amount of starting material. This difference in behavior may be due to inability of the respective tin compounds to give coordination between the metal and the α-methoxy group. This explanation is consistent with the fact that the tin compound of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside gives 2-*O*-tosyl ester on treatment with tosyl chloride and triethylamine. Methyl 4,6-*O*-benzylidene-2,3-*O*-dibutylstannylene-α-D-glucopyranoside gave on benzoylation in dioxane with benzoyl chloride and triethylamine 2-*O*-benzoyl ester with 90% yield [34].

In conclusion, all factors that control the selectivity of acylation of secondary hydroxyl groups in glycopyranosides are still not fully understood. In general, the primary hydroxyl group is always the most reactive one; from the secondary endocyclic hydroxyl groups the C2 hydroxyl group is the most reactive but only if it is equatorially oriented and in α-anomers; the C4 hydroxyl group is the least reactive irrespective of the anomeric configuration and regardless whether it is equatorially or axially oriented.

Acyl Migrations

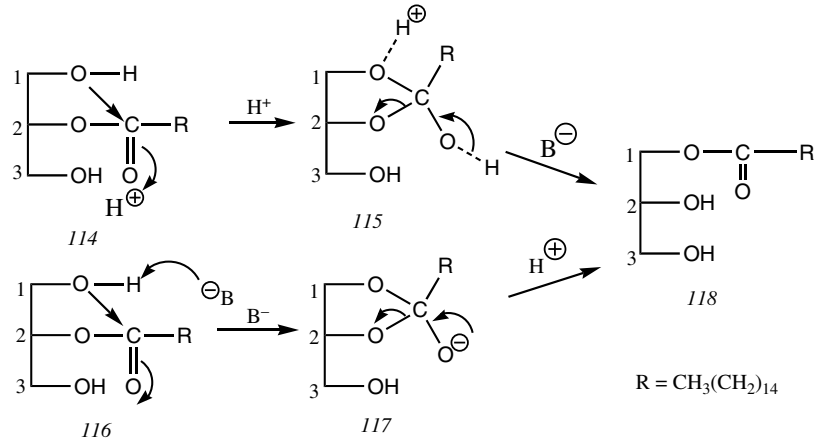
The facile acyl migration in partially acylated polyhydric alcohols was discovered by Fischer [35] who correctly proposed that this rearrangement proceeds via orthoacid intermediate. This proposal was verified by a study of acid catalyzed (0.6 N HCl) rearrangement of unlabeled glycerol-2-palmitate into glycerol-1-palmitate in the presence of 1-^{14}C-labeled glycerol that showed no incorporation of ^{14}C label into the glycerol-1-palmitate [36], thus indicating that the rearrangement is intramolecular and not intermolecular (Fig. 5.33).



111 *112* *113*

Fig. 5.33

The rearrangement is both acid catalyzed and base catalyzed, thus supporting the formation of orthoacid intermediate as shown in Fig. 5.34.



114 *115* *116* *117* *118*

Fig. 5.34

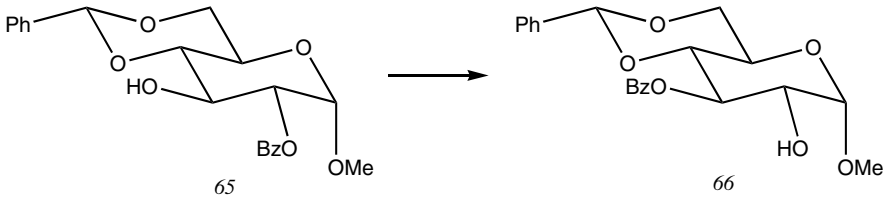
The rate of acyl migration depends on several factors:

(a) The nature of the solvent [37, 38]
(b) The pH of the reaction solution (acidity or alkalinity) [38]
(c) Stereochemistry, i.e., the relative configurations of the two vicinal hydroxyl groups of which one is acylated [38]. The acyl migration occurs more readily in

monoacyl derivatives of vicinal diols if the two oxygen atoms are in *cis* orientation than when they are *trans* disposed, because there is less ring strain introduced into the orthoacid intermediates if they are formed from the *cis*-oriented monoacyl diols than from *trans* monoacyl diols [39]. This is more pronounced in furanose ring structures than in pyranose ring structures

(d) The acyl group generally rearranges from a secondary to the primary carbon atom, probably again due to steric factors

The acyl migration is a reversible process and the composition of equilibrium mixture is most often thermodynamically controlled. However, sometimes the composition of the equilibrium mixture is controlled by external factors, such as, for example, dramatically different solubility of starting material and the product in reaction solvent. For example, dissolution of methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside *65* in acetone–aqueous sodium hydroxide results

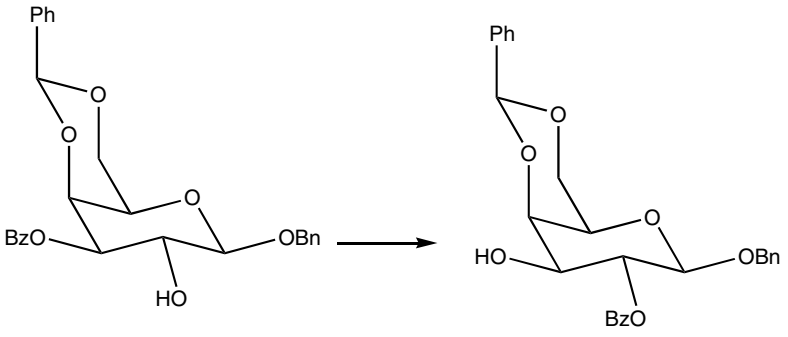


65 *66*

Fig. 5.35

in almost immediate crystallization of the 3-*O*-benzoate *66* with 65% yield [40] (Fig. 5.35).

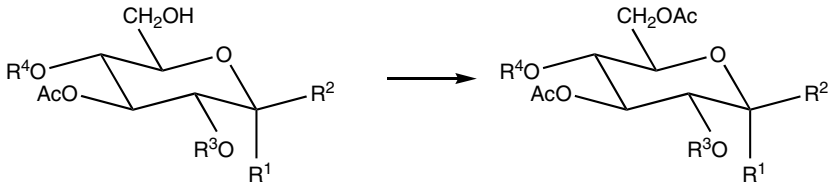
Similarly, benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside *119* gave 2-*O*-benzoate *120* with 81% yield even though the 2-*O*-benzoate is in homogeneous equilibrium solution, only slightly more stable than the 3-*O*-benzoate [41] (Fig. 5.36).



119 *120*

Fig. 5.36

Acyl migrations have often been observed during methylation of partially acylated carbohydrates. For example, methylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside *121* with methyl iodide–silver oxide [42] (Purdie methylation)



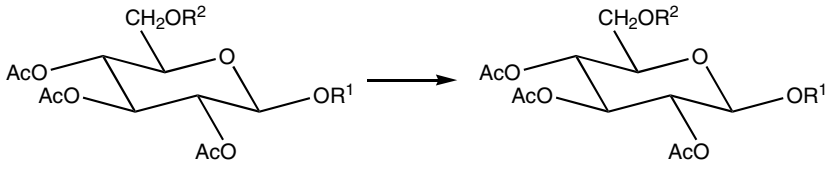
121, $R^1 = OCH_3$; $R^2 = H$; $R^3 = R^4 = Ac$
123, $R^1 = H$; $R^2 = OCH_3$; $R^3 = R^4 = Ac$

122, $R^1 = OCH_3$; $R_2 = H$; $R^3 = CH_3$; $R_4 = Ac$
124, $R^1 = H$; $R^2 = OCH_3$; $R^3 = Ac$; $R^4 = CH_3$
125, $R^1 = H$; $R^2 = OCH_3$; $R^3 = CH_3$; $R^4 = Ac$

Fig. 5.37

gave 2-*O*-methyl ether *122*, whereas the methylation of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside *123* with methyl iodide–silver oxide in *N*,*N*-dimethylformamide [43] (Kuhn methylation) gave 4-*O*-methyl ether *124* with 45% yield. Methylation of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside *123* under the Purdie conditions [44] gave 2-*O*-methyl ether *125* with 66% yield (Fig. 5.37).

Haworth et al. [45] subjected 1:2:3:4-tetraacetyl-β-D-glucopyranose *126* to methylation with methyl iodide and silver oxide and obtained methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside *127* with 19.23% yield. However, methylation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose under the same reaction conditions gave methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside *127* (slightly impure) with 96% yield (Fig. 5.38), indicating that the acetyl group migration goes away from the anomeric carbon and toward the primary C6 hydroxyl group, and not the other way around.



126, $R^1 = Ac$; $R^2 = H$
128, $R^1 = H$; $R^2 = Ac$

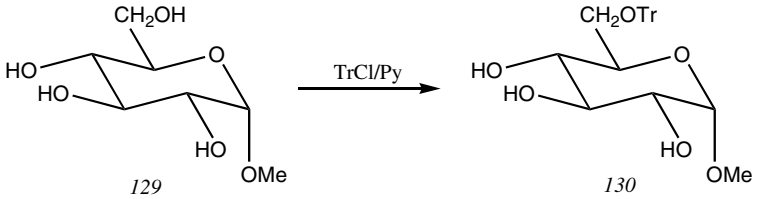
127, $R^1 = CH_3$; $R^2 = Ac$

Fig. 5.38

Selective Alkylation and/or Arylation of Glycopyranosides

Tritylation of Monosaccharides (Triphenylmethyl Ethers)

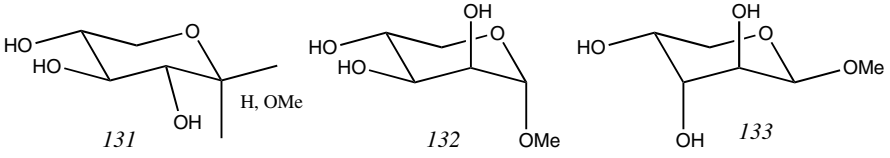
In alkylation reactions the primary hydroxyl group of hexopyranosides is favored over the secondary hydroxyl groups, especially when the alkylating agent is bulky, such as chlorotriphenylmethane (triphenylmethylchloride, trityl chloride, TrCl). Thus reaction of methyl α-D-glycopyranoside *129* with 2 mol of TrCl in pyridine at 30°C gives, after 5–6 h, 6-*O*-trityl ether *130* with 98% yield. The tritylation of any secondary hydroxyl group was not observed [46] (Fig. 5.39).



129 *130*

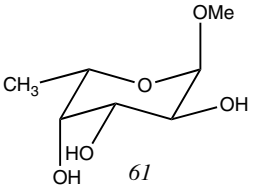
Fig. 5.39

Initially it was believed that tritylchloride, because of its size, can attack exclusively primary hydroxyl group [47–49]. However, Hockett and Hudson [50] have shown that methyl α- and β-D-xylopyranosides *131*, methyl α-D-lyxopyranosides *132*, and methyl β-D-arabinopyranosides *131* also undergo tritylation, despite the absence of an exocylic primary hydroxyl group (the C5 primary hydroxyl group in alkyl pentopyranosides is involved in the hemiacetal ring and thus is not available for tritylation) suggesting that the secondary hydroxyl groups must be the ones that are tritylated (Fig. 5.40).



131 *132* *133*

Methyl α- and β-D-xylopyranoside Methyl α-D-lyxopyranoside Methyl β-D-arabinopyranoside



61

α-L-Fucopyranoside

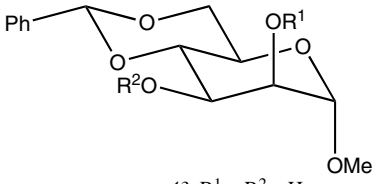
Fig. 5.40

Similar situation exists with methyl α-L-fucopyranoside *61* wherein the C6 carbon has no hydroxyl group. However, tritylation of methyl α-L-fucopyranoside [51] with trityl chloride in pyridine readily gave mono-trityl derivative, the structure of which was not determined; tritylation of methyl β-D-xylopyranoside in pyridine gave two isomeric di-trityl and two mono-trityl derivatives that were isolated as acetates but not identified. However it must be emphasized that all these reactions required a very long time (14 days at 20°C) [51].

Since the rates of tritylation of primary and secondary hydroxyl groups are very different (tritylation of a primary hydroxyl group is usually completed after a few hours) [52], the selective tritylation of primary hydroxyl group of hexopyranosides or hexofuranosides in the presence of free secondary hydroxyl group(s) can be accomplished in high yields.

Selective Benzylation of Monosaccharides

Partial benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside *43* (Fig. 5.32) with 1.2 mol equivalent of benzyl bromide in *N*,*N*-dimethylformamide in the presence of barium oxide and barium hydroxide gave the 3-*O*-benzyl ether *135* as the major product (66%) along with 2,3-di-*O*-benzyl ether *136* (10%), 2-*O*-benzyl ether *134* (16%), and unreacted starting material (8%) [53] (Fig. 5.41). When



43, $R^1 = R^2 = H$
134, $R^1 = Bn$; $R^2 = H$
135, $R^1 = H$; $R^2 = Bn$
136, $R^1 = R^2 = Bn$

Fig. 5.41

benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with benzyl bromide in *N*,*N*-dimethylformamide was performed in the presence of silver oxide, a mixture of products was obtained in which 2-*O*-benzyl ether *134* was the predominant product (55%); 3-*O*-benzyl ether *135* was obtained in 19%, 2,3-di-*O*-benzyl ether *136* with 10% yield, and the starting material was recovered with 16% yield [53] (Fig. 5.40).

The regioselectivity of benzylation was considerably lost when benzylation was conducted in dimethylsulfoxide as the solvent and using sodium hydride as the base. Thus 2,3-di-*O*-benzyl ether *136* was obtained as the major product (65% yield), along with the 2-*O*-benzyl ether *134* (16%), 3-*O*-benzyl ether *135* (7%), and 12% of the starting material [53].

Using the same procedure Boren et al. [54] obtained methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside *134* with 36% yield.

The results of benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside with benzyl bromide in dimethylsulfoxide as the solvent and NaH as the base reported by Srivastava and Srivastava [55] do not agree with the results reported by Kondo [53]. Srivastava and Srivastava [55] reported that 3-*O*-benzyl ether *135* was obtained with 66% yield and the 2,3-di-*O*-benzyl ether *136* with 20% yield, together with small amounts of 2-*O*-benzyl ether and starting material.

From the molar ratios of reaction products it can be concluded that when benzylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside is performed in the presence of barium oxide–barium hydroxide, 3-OH is more reactive than 2-OH. It was, however, shown [56] that the reactivity of hydroxyl groups of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside under the same reaction conditions is 2-OH > 3-OH and for methyl 4,6-*O*-benzylidene-β-D-glucopyranoside 3-OH > 2-OH. From the foregoing findings, it seems that the *cis*-OR substituent activates the adjacent equatorial hydroxyl group also in benzylation in the presence of barium oxide, as it did in acylation of the same substrate. The order of reactivity of hydroxyl groups in benzylation in the presence of silver oxide is 2-OH > 3-OH.

The order of reactivity of the hydroxyl groups in benzylation in the presence of sodium hydride may be 2-OH > 3-OH. However, the high yield of the dibenzyl ether suggests that benzylation occurs very rapidly and that this method is not suitable for regioselective benzylation.

Selective Alkylation of Metal Complexes of Monosaccharides

The initial work of Avela et al. [57–62] showed that copper chelates of vicinal diols prepared from a sugar, sodium hydride, and methyl chloride in the molar ratio 1:2:1 are more regioselective in methylation than any other chelate they investigated.

Eby et al. [63] confirmed Avela′s findings by succeeding to methylate the copper complexes of methyl 4,6-*O*-benzylidene derivatives of α-D-gluco-, α-D-manno-, and α-D-galactopyranosides with methyl iodide, sodium hydride, and copper chloride in the 1:2:1 molar ratio (see Table 5.2). It was found that carbohydrate derivatives having vicinal hydroxyl groups (*e, e* or *a, e*), or those having O-4 and O-5 free, were able to form 1:2:1 copper complexes. All of the complexes were soluble in tetrahydrofuran or 1,2-dimethoxyethane with formation of dark-green solutions.

Benzylation of partially stannylated methyl α-D-glucopyranoside with $(Bu_3Sn_2)_2O$ at 80–90ºC gave 6-*O*-benzyl ether (48.6%), along with 2,6-di-*O*-benzyl ether (30.5%), 3,6-di-*O*-benzyl, ether (4.5%), and 4,6-di-*O*-benzyl ether (6.0%) [64]. The isolation of three dibenzyl ethers in the ratio 3:20:4 together with the 6-*O*-monobenzyl ether showed that the regioselectivity was only moderate, as compared with benzoylation of partially stannylated carbohydrates.

The alcohol hydroxyl groups are relatively unreactive toward diazomethane, but in the presence of certain protic acids, fluoroboric acid [65] and Lewis acids (boron

Table 5.2 Alkylation of 1:2:1 Cu complexes of methyl 4,6-*O*-benzylidene derivatives of α-D-gluco-, manno-, and galactopyranosides

				Composition (%)			
Substrate	Solvent	Metal	Alkyl iodide	2	3	2,3	s.m.
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside	THF	Cu	Methyl	20	66	–	14
	DME	Cu	Benzyl	18	74	–	8
	DME	Cu	Allyl	19	77	–	4
Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside	DMF	Cu	Allyl	19	81	–	–
	THF	Cu	Allyl	20	80	–	–
Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside	DME	Cu	Allyl	29	68	–	–
	DME	Cu	Benzyl	29	68	–	–

trifluoride etherate [66] and aluminum chloride [67]), the reaction is substantially facilitated. The mechanism of methylation of aliphatic alcohols with diazomethane catalyzed by boron compounds has been discussed [68].

The presence of small amounts (10–100 mM equivalents) of stannous chloride dihydrate was found to catalyze the reaction of some D-glucopyranoside derivatives with diazomethane in methanol or methanol-*N*,*N*-dimethylformamide; without this catalyst, little methylation occurred [68]. Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside afforded 93% of the 3-*O*-methyl ether but alkylation of the β-anomer was much less selective giving the 2- and 3-methyl ethers with 34 and 53% yield, respectively. Reaction of methyl and phenyl α-D-glucopyranoside showed the unprecedented selectivity, yield of 74 and 81% of the respective 3- and 2-*O*-methyl ethers being obtained together with the minor amounts of dimethyl ethers. Methyl and phenyl β-D-glucopyranoside gave 3-methyl ethers with 54 and 47% yield, respectively, but with these β-D-glucosides, 2,3-dimethyl ethers were simultaneously obtained in much higher yields (48 and 44%, respectively) than with α-D-glucosides. Other Lewis acids (such as aluminum chloride hexahydrate, magnesium chloride hexahydrate, zinc chloride, and lead acetate trihydrate) were less active in promoting alkylation. The methylation of benzyl 4,6-*O*-benzylidene-β-D-galactopyranoside with diazomethane catalyzed by stannous chloride dihydrate was also highly regioselective [69], the 2-*O*-methyl ether being formed with 91% yield; with boron trifluoride diethyl etherate as the catalyst, 2,3-dimethyl ether was obtained with 84% yield. Involvement of 3-OH in intramolecular hydrogen bonding to 4-OH (which was suggested, is unaffected by stannous chloride, but prevented in the presence of boron trifluoride diethyl etherate) may explain these observations, as the unreactivity of strongly bonded hydroxyl groups toward diazomethane had been noted [70].

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Chapter 6
Cyclic Acetals and Ketals

Cyclic and acyclic carbohydrates react with aldehydes and/or ketones, in the presence of catalysts (hard or Lewis acids), to give cyclic acetals and/or ketals (1,3-dioxolanes *3* or 1,3-dioxanes *5*, respectively) (Fig. 6.1). This reaction is routinely used in carbohydrate chemistry for the protection of hydroxyl groups in a sugar in order to prevent their interference in chemical transformation(s) of other hydroxyl group(s) of that sugar. The reaction of carbohydrates with aldehydes and ketones has been comprehensively reviewed [1–8].

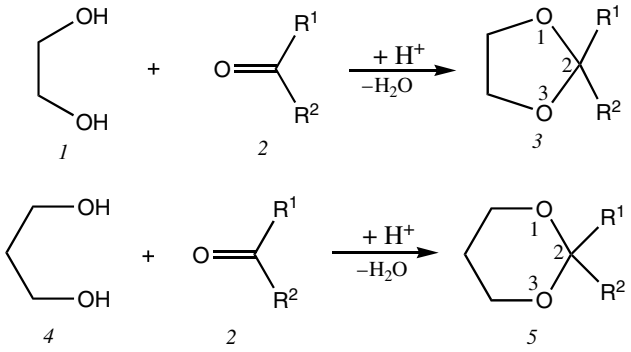


Fig. 6.1

The acetal formation is believed [9] to be a stepwise process that initially involves the hemiacetal formation as represented in Fig. 6.2. The hemiacetal formation and the subsequent proton exchange are considered to be the fast reactions, whereas the formation of oxocarbenium ions *9a*, *b* from *8* (*8* → *9a, b*) and/or the cyclization of *9a, b* → *10* in the subsequent step are assumed to be the rate-limiting reactions. The generally accepted mechanism for the hydrolysis of most simple acyclic acetals [10] and cyclic ketals [11–15] is the S_N1cA or A1 mechanism (Ingold system for naming reaction mechanisms) involving the rate-determining heterolysis of a protonated intermediate. Thus, if the ring opening is the rate-determining step for the

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_6,

hydrolysis of cyclic acetals or ketals, the principle of microscopic reversibility [16] requires that the ring closure *9a, b* → *10* (Fig. 6.2) be the rate-determining step for the formation of cyclic acetals or ketals.

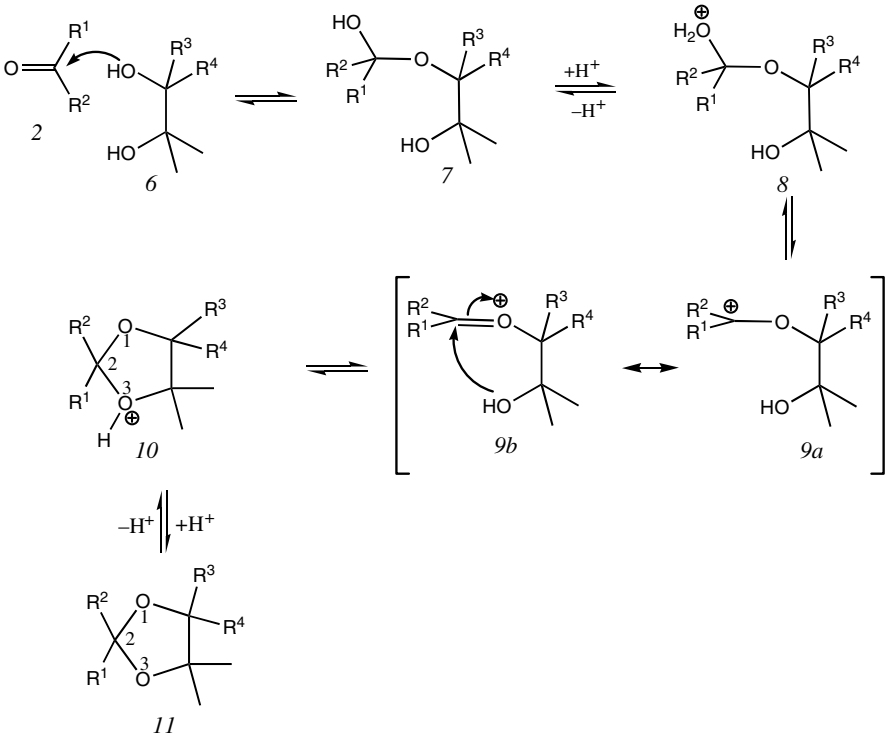


Fig. 6.2

The oxocarbenium ion *9a, b* reacts with the nearest hydroxyl group giving the (kinetic) product *11*, which, after prolonged reaction time, may rearrange to a more stable (thermodynamic) product or to an equilibrium mixture of more stable products; the composition of this mixture is determined by the relative free energies of different isomeric acetals. This is best illustrated by reaction of glycerol and benzaldehyde in anhydrous *N*,*N*-dimethylformamide catalyzed by *p*-toluenesulfonic acid [17]. Since benzyl protons of all four possible acetals (Fig. 6.3) have different chemical shifts, the NMR spectroscopy was ideally suited for monitoring the course of the reaction. Thus it was found that the *cis*- and *trans*-4-hydroxymethyl-2-phenyl-1,2-dioxolanes, *14* and *15*, respectively, are formed first (after less than 2 min). These initial products were then slowly rearranged into *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxanes, *12* and *13*, that were observable after 5 min, and after 12 min the ratio of *12*:*13*:*14*:*15* was ca. 1.1:1.0:6.2:4.0. At equilibrium that was reached after 2 days the ratio of products was 1.8:1.8:1.2:1.0, indicating that the 1,3-acetals are clearly favored products (Fig. 6.3). These results are consistent with

the initial formation of hemiacetal *16* that involves primary hydroxyl group, followed by protonation and formation of oxocarbenium transition state *17* (Fig. 6.4). Subsequent cyclization involving the nearest (the C2) hydroxyl group led to *cis*- and *trans*-4-hydroxymethyl-1,2-dioxolans (*14* and *15*, respectively) (kinetic products).

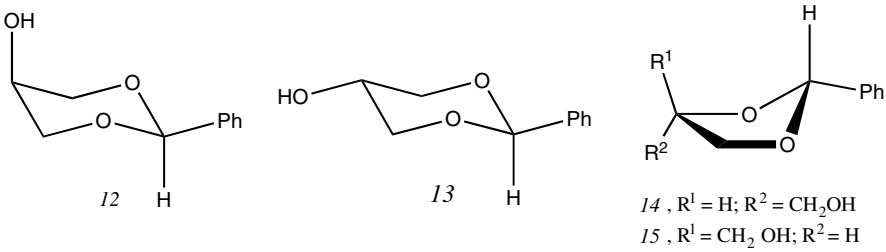


Fig. 6.3

This initial, kinetic phase of reaction is followed by a slow equilibration to give ultimately the thermodynamically more stable 1,3-acetal *19* (i.e., *12* and *13*) as major products (Fig. 6.4).

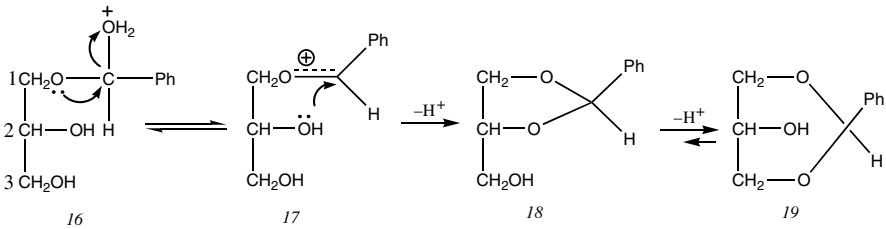


Fig. 6.4

The formation of a single stereoisomer during kinetic phase of reaction has also been demonstrated and this has important mechanistic consequences. Thus, the 1,4-anhydroerythritol *20* (Fig. 6.5) reacts with benzaldehyde giving benzylidene acetal *21* with phenyl group in the *endo*-configuration [18, 19]. Subsequently, equilibration takes place giving ultimately a near-equimolar mixture of *endo*- *21* and *exo*- *22* phenyl isomers. The stereoselective formation of one product in this reaction may

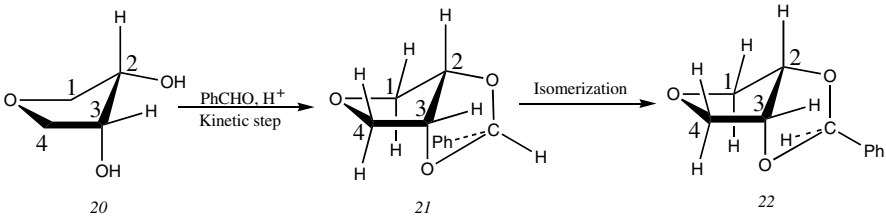
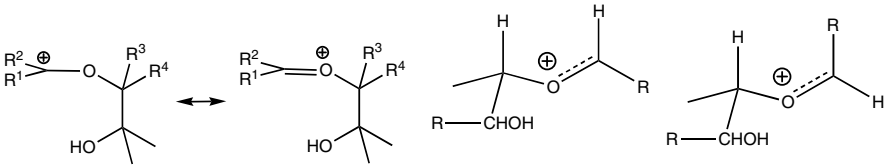


Fig. 6.5

be rationalized [20] by assuming that the oxocarbenium ion (*9a, b*) is highly reactive and thus closely resembles the transition state. The observed relative rates of formation of particular acetals may then be explained by considering the stability or ease of formation of oxocarbenium ion. This approach is, however, valid only if the decomposition of acetal by hydrolysis or its rearrangement is negligible. This requirement is probably fulfilled in the early stages of reaction carried out in anhydrous media.

The stabilization of oxocarbenium cation (*9a, b*) in Fig. 6.2 (and Fig. 6.6) may be accomplished in two ways: (a) carbonium ion *9a* can be directly stabilized by R^1 and R^2 groups or (b) the oxonium ion *9b* can be stabilized by R^3 and R^4 groups and to a lesser extent by a substituent at the carbon atom α to the original hydroxyl group. Effect (a) will, however, not be important when determining the relative rates of formation of isomeric acetals derived from an aldehyde and a polyhydroxy alcohol. Effect (b) is involved in consideration of stabilities of oxocarbenium ions derived from the primary and secondary hydroxyl groups in a polyhydroxy alcohol. The stabilities of these ions are considered to be possible factors in the observed preferential formation of terminal five-membered ring acetals in the kinetic phase of acetal formation.

The preferential formation of a single stereoisomer during kinetic phase of the reaction of an aldehyde with a diol cannot be explained by assuming that the transition state resembles the carbonium ion (*9a*) because if it does two products should be formed from the same intermediate. It is therefore necessary to assume that the transition state resembles the oxonium ion (*9b*) in one of its rotameric forms.



9a *9b* *23* *24*

Fig. 6.6

Provided that the intermediate (*9a, b*) has considerable oxonium ion character, two distinct rotamer forms *23* and *24* (Fig. 6.6) can be recognized and designated as *E* (*23*) and *Z* (*24*), respectively. By analogy with olefins [21] the *E* arrangement should be more stable. Using Newman's projections, the structures *23* and *24* may be depicted by three gauche conformations as shown in Fig. 6.7. The conformations *25* and *28* may be dismissed as possible models for the transition state because the potential acetal carbon atom and the hydroxyl group are not sufficiently close for cyclization. If the oxocarbenium ion is next to a primary hydroxyl group, the rotamers *26* and *27* will have same stabilities. However, if the oxocarbenium ion is next to a secondary hydroxyl group, then the rotamer *30* with the group R and the carbonium carbon in the *anti*-arrangement should be more favorable than rotamer *29* wherein these two substituents are in the *syn*-arrangement. Thus it can be predicted

that for the reaction with a secondary hydroxyl group the most likely transition state will resemble *30*, i.e., the *anti-E* conformation of oxocarbenium ion.

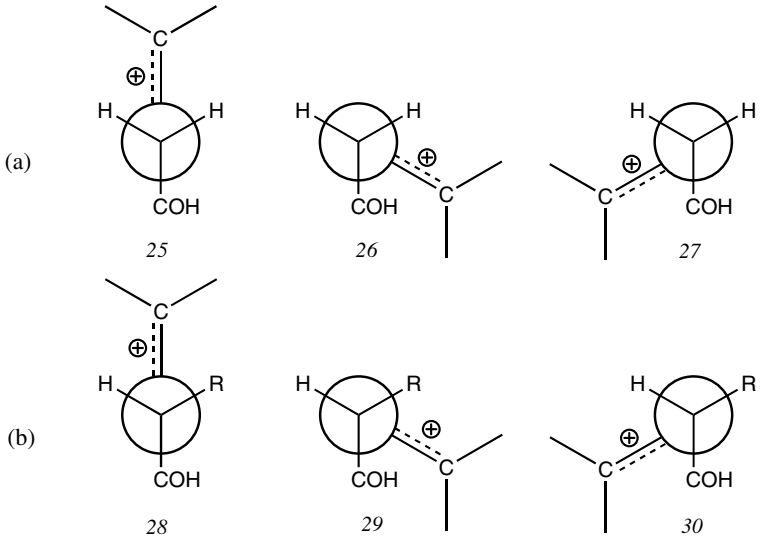


Fig. 6.7 (a) Rotamer forms of the primary oxocarbenium ion and (b) the secondary oxocarbenium ion.

For the reaction between 1,4-anhydroerythritol and benzaldehyde four conformations *31–34* (Fig. 6.8) may be drawn for the oxocarbenium ions, in which the hydroxyl group is well positioned for cyclization, and all four conformations may

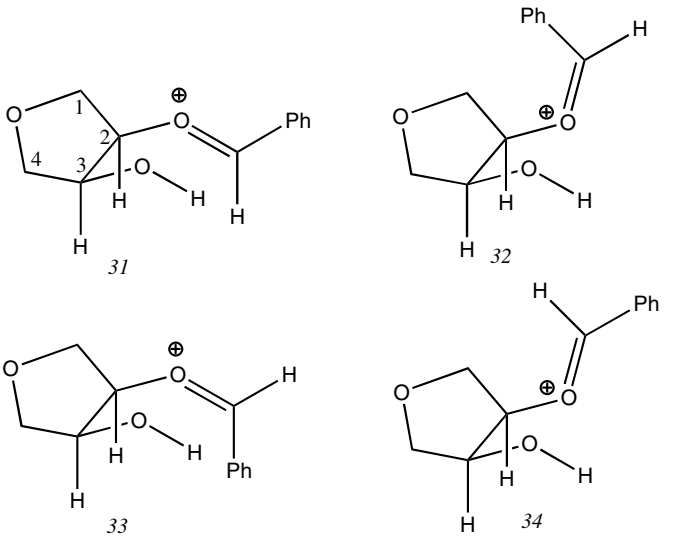


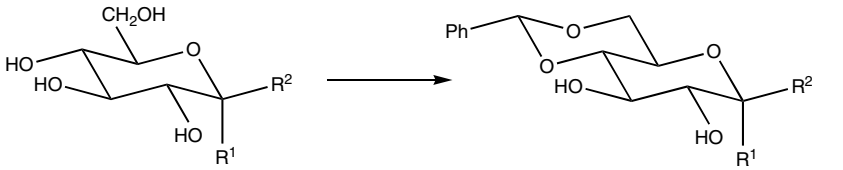
Fig. 6.8

be assumed to resemble the transition state. However, due to steric reasons, the *anti-E* structure *31* should be the most stable one, and a rapid formation of an acetal with an *endo*-phenyl group can be expected. This is in agreement with the experimental observations [18, 19]. The result is quite general and it is expected that the isomer with an *endo*-alkyl group will be the kinetic product in the acetal formation reactions.

Acetalation

Benzylidenation

Benzylidenation [22–25] of anhydrous D-glucose, *35* or *36,* with benzaldehyde in the presence of anhydrous (freshly fused) zinc chloride at room temperature gives 4,6-*O*-benzylidene-D-glucopyranose *39* or *40* with 42% yield (pure product). Similarly, methyl α- or β-D-glucopyranoside (*37* or *38*, respectively) was converted to the corresponding 4,6-*O*-benzylidene acetals [25] with 70% yield (crude product).

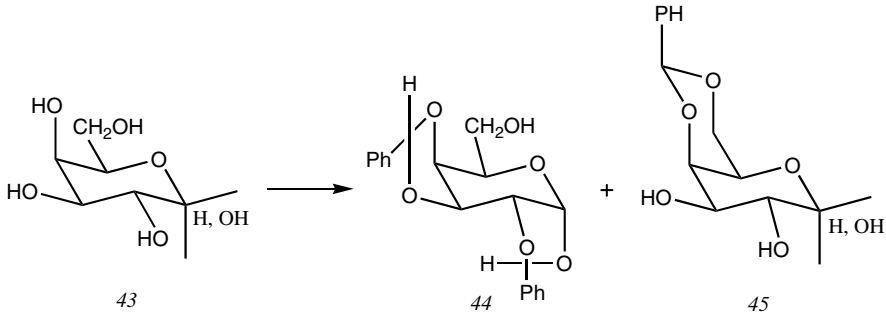


35 , R^1 = OH; R^2 = H *37* , R^1 = OMe; R^2 = H
36, R^1 = H; R^2 = OH *38* , R^1 = H; R^2 = OMe

39 , R^1 = OH; R^2 = H *41* , R^1 = OMe; R^2 = H
40, R^1 = H; R^2 = OH *42* , R^1 = H; R^2 = OMe

Fig. 6.9

Benzylidenation of D-galactose *43* in the presence of anhydrous zinc chloride [26–28] gives the 1,2:3,4-di-*O*-benzylidiene diacetal *44* as the predominant product, whereas the 4,6-*O*-benzylidene acetal *45* is obtained only in negligible amounts.



43 *44* *45*

Fig. 6.10

The benzylidenation may also be carried out with sugars that already contain acetal or ketal group. For example, 1,2-*O*-isopropylidene-α-D-glucofuranose *46* gives with benzaldehyde, in the presence of zinc chloride or phosphorus pentoxide, 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose *47* [29, 30] (Fig. 6.11). However, heating of 1,2-*O*-isopropylidene-α-D-glucofuranose *46* with

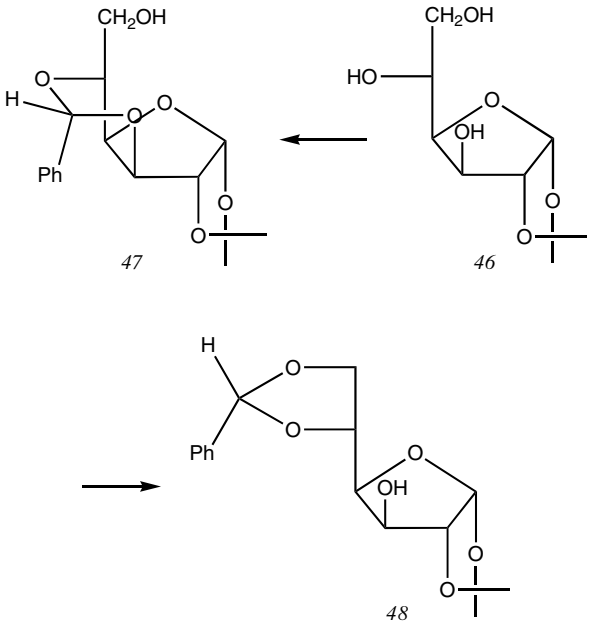


Fig. 6.11

benzaldehyde in the presence of anhydrous sodium sulfate gives 5,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose *48* (Fig. 6.11). The 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose *47* is rearranged by prolonged heating to 5,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose *48* [31] indicating that *48* is more stable than *47*.

Ethylidenation

Reaction of a sugar with acetaldehyde, or paraldehyde, in the presence of sulfuric acid as the catalyst [32–36] gives 4,6-*O*-ethylidene acetal, for example, D-glucose *49* gives the 4,6-*O*-ethylidene-D-glucose *50* (Fig. 6.12).

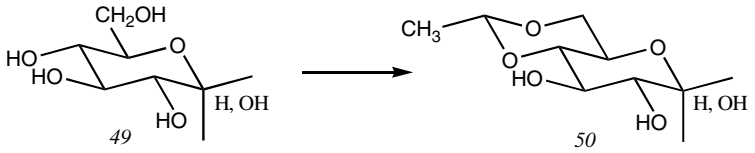


Fig. 6.12

Ketalation

Isopropylidenation (Acetonation)

Isopropylidene acetals are obtained by condensation of monosaccharides or their derivatives with acetone in the presence of mineral acids, such as concentrated sulfuric acid, as the catalysts [37]. The anhydrous acetone serves both as the solvent and as the reagent. Reaction is performed at room temperature and it is usually completed in several hours. Thus, D-glucose *49* and anhydrous acetone give in the presence of concentrated sulfuric acid 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *51* (46.5%) together with some 1,2-*O*-isopropylidene-α-D-glucofuranose *46* (16.8%) (Fig. 6.13).

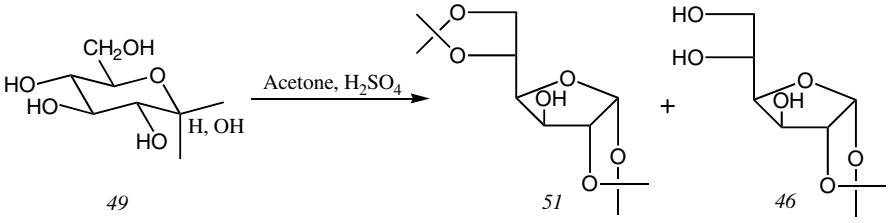


Fig. 6.13

However, when a mixture of anhydrous (freshly fused) zinc chloride and phosphoric acid (85%) is used as the catalyst 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *51* is obtained with 91% yield [38].

Acetonation of D-galactose *43* [39, 40] in the presence of anhydrous $ZnCl_2$ gave 1,2:3,4-di-*O*-isopropylidene-D-galactose *52* (89.9% yield of crude product) (Fig. 6.14). Mixture of concentrated sulfuric acid and anhydrous Cu(II) sulfate can also be used for the synthesis of di-*O*-isopropylidene sugars. Thus, anhydrous galactose *43* reacts with acetone, in the presence of concentrated sulfuric acid and anhydrous Cu(II) sulfate, to give 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *52* with 76–92% yield [41, 42] (Fig. 6.14).

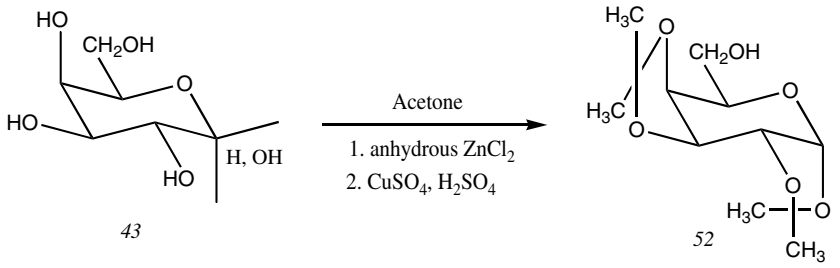


Fig. 6.14

When the use of strong mineral acids is not possible, as is the case, for example, with glycosides, powdered anhydrous Cu(II) sulfate alone can be used as the catalyst. However, the reaction is much slower (it takes several days for completion). Thus acetonation of methyl α-D-mannopyranoside *53* in the presence of anhydrous Cu(II) sulfate gave methyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside *54* (Fig. 6.15) with ca. 11% yield and methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside *55* with ca. 6.6% yield (Fig. 6.15).

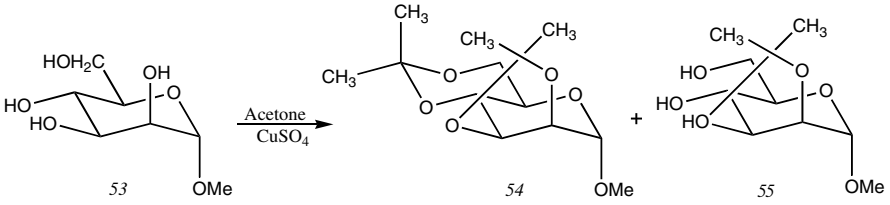


Fig. 6.15

However, methyl β-D-mannopyranoside *56* gave under the same reaction conditions, after 5 months, 45.75% of methyl 2,3:4,6-di-*O*-isopropylidene-β-D-mannopyranoside *57* and 17.86% of methyl 2,3-*O*-isopropylidene-β-D-mannopyranoside *58* [43] (Fig. 6.16).

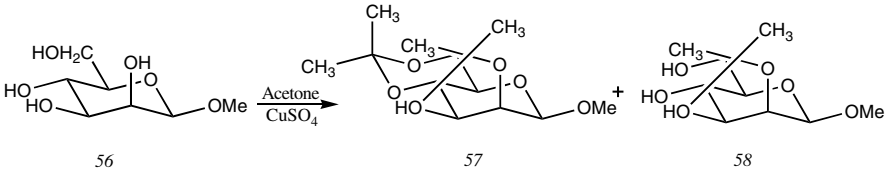
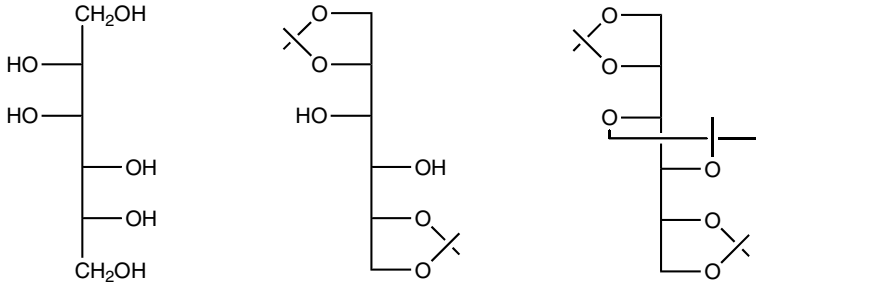


Fig. 6.16

The nature of the catalyst may have a notable effect on acetonation reaction. Thus, for example, in the presence of zinc chloride, D-mannitol *59* affords the



59, D-mannitol

60, 1,2:5,6-di-O-isopropylidene-D-mannitol

61, 1,2:3,4:5,6-tri-O-isopropylidene-D-mannitol

Fig. 6.17

1,2:5,6-di-*O*-isopropylidene ketal *60* [44], whereas when catalyzed by mineral acids 1,2:3,4:5,6-tri-*O*-isopropylidene ketal *61* is obtained [45] (Fig. 6.17). The pattern of acetonation of some glycosides is also influenced by the nature of catalyst [46].

Transacetalation and Transketalation

Acid-catalyzed acetal or ketal exchange, also known as *transacetalation* or *transketalation*, is widely used in carbohydrate chemistry for the synthesis of cyclic acetals and ketals. The mechanism of transacetalation is shown in Fig. 6.18. The protonation of one of the two alkoxy groups of an acetal or ketal donor *63* activates that

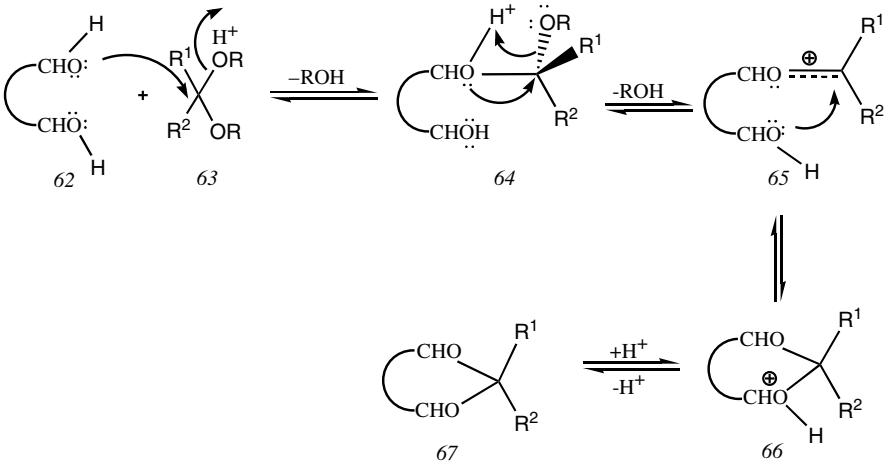
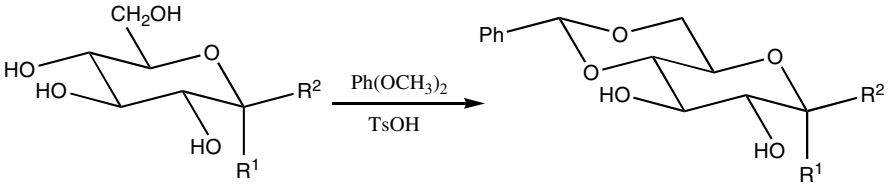


Fig. 6.18

alkoxy group so that it can be displaced by a sugar hydroxyl group and gives a mixed acetal *64*. The protonation of the second alkoxy group of acetal donor and hence the elimination of corresponding alcohol gives oxocarbenium ion *65* that reacts with the second hydroxyl group of a carbohydrate to give first the protonated acetal *66*, which, after deprotonation, yields cyclic acetal or ketal *66*.

Thus, methyl α-D-glucopyranoside *37* reacts with α,α-dimethoxytoluene in anhydrous *N*,*N*-dimethylformamide at 60°C in the presence of *p*-toluenesulfonic acid [47] to give 82.4% of crude (63.5% of pure) methyl 4,6-*O*-benzylidene-α-D-glucopyranoside *41* (Fig. 6.19). This is a significantly improved yield over the condensation of benzaldehyde with methyl α-D-glucopyranoside *37* in the presence of fused zinc chloride. Methyl β-D-glucopyranoside *38* gave under the same reaction conditions 58% of pure methyl 4,6-*O*-benzylidene-β-D-glucopyranoside *42* [47].

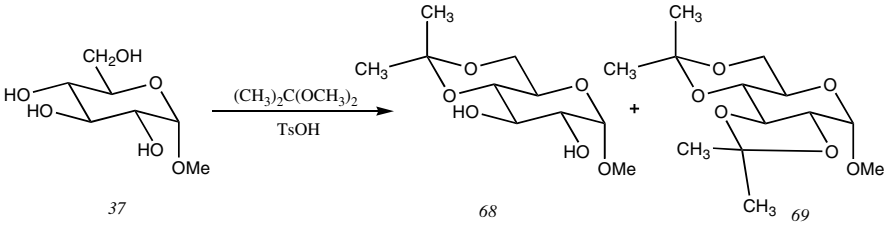
Reaction of methyl α-D-glucopyranoside *37* with 2,2-dimethoxypropane in anhydrous *N*,*N*-dimethylformamide and in the presence of *p*-toluenesulfonic acid [48] gave methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside *68* with 79% yield, together with methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside *69* (1.8%) and some starting material (Fig. 6.20).



37, R^1=OMe; R^2=H
38, R^1=H; R^2=OMe

41, R^1=OMe; R^2=H
42, R^1=H; R^2=OMe

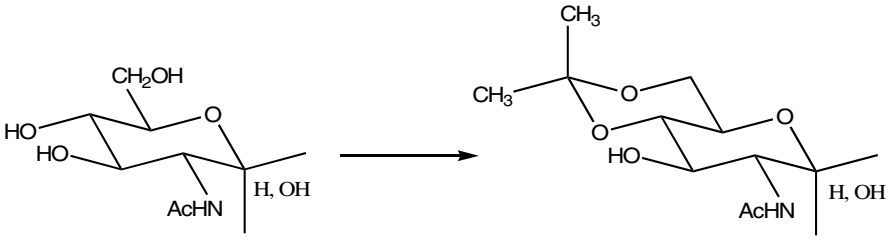
Fig. 6.19



37 *68* *69*

Fig. 6.20

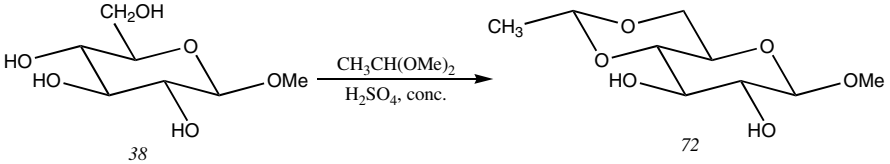
Similarly 2-acetamido-2-deoxy-D-glucopyranose *70* gave with 2,2-dimethoxypropane at 80–85°C in anhydrous *N*,*N*-dimethylformamide in the presence of *p*-toluenesulfonic acid 2-acetamido-2-deoxy-4,6-isopropylidene-D-glucopyranose *71* with 54% yield [49] (Fig. 6.21).



70 *71*

Fig. 6.21

Ethylidene acetals can be obtained by reacting, for example, methyl-β-D-glucopyranoside with 1,1-dimethoxyethane, in the presence of concentrated sulfuric acid, whereby the corresponding 4,6-*O*-ethylidene-acetal is obtained with 59% yield [50–52] (Fig. 6.22).



38 *72*

Fig. 6.22

The isopropylidenation of 2-acetamido-2-deoxy-D-xylose diethyl dithioacetal *73* with 1:1 (v/v) anhydrous acetone-2,2-dimethoxypropane, in the presence of concentrated sulfuric acid, gave the 3,4-*O*-isopropylidene ketal *74*, as the only product,

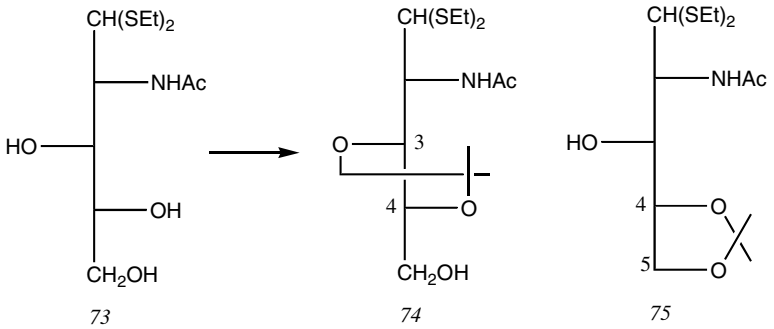


Fig. 6.23

with 90% yield. However, the isopropylidenation of *73* with 1:1 (v/v) anhydrous acetone-2,2-dimethoxypropane in the presence of copper(II) sulfate afforded the 4,5-*O*-isopropylidene ketal *75* with 74% yield [53] (Fig. 6.23).

These results suggest that isopropylidenation of alditols or acyclic sugar derivatives proceeds initially by involving the primary hydroxyl group(s) of a carbohydrate in the ketal formation (due to steric reasons) and if the catalyst is incapable of reversing the ketalation [as is the case with anhydrous copper (II) sulfate], the product is formed under kinetic control. If, however, the catalyst is capable of reversing the ketalation reaction, the end product(s) is (are) thermodynamically controlled.

The Isomerization of Cyclic Acetals and Ketals

Reaction of glycerol with acetone in the presence of acid catalyst should give the equilibrium mixture of two possible cyclic ketals, 1,3-dioxolane *78* and 1,3-dioxane *79* (Fig. 6.24). However, it has been shown that the reaction gives essentially

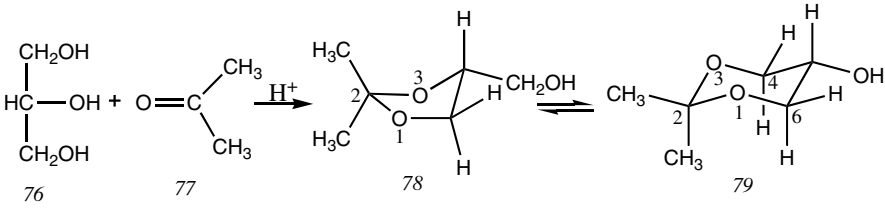


Fig. 6.24

exclusively the 1,2-*O*-isopropylidene glycerol (*78*) [54]. The formation of six-membered *O*-isopropylidene ketal is disfavored [55], because one methyl group must take the axial orientation in the chair conformation of the 1,3-dioxane ring *79*. It has been determined that for the chair form of methylcyclohexane, the conformer with the methyl group axially oriented is about 1.9 kcal/mol less stable than the conformer with the methyl group equatorially oriented due to the *syn*–axial interactions of this methyl group with the axially oriented C3 and C5 hydrogens [56]. For the chair form of 2,2-dimethyl-1,3-dioxane *79* the axially oriented methyl group is even less favorable, since the C–O bonds are shorter (1.43 Å) than the C–C bonds (1.54 Å) and the 1,3-*syn*–axial interactions between the axially oriented C2 methyl group and the axially oriented C4 and C6 hydrogen atoms in *82* will be consequently

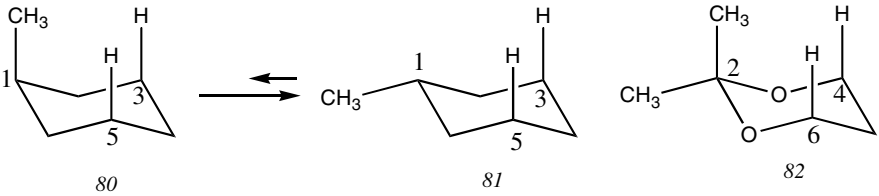


Fig. 6.25

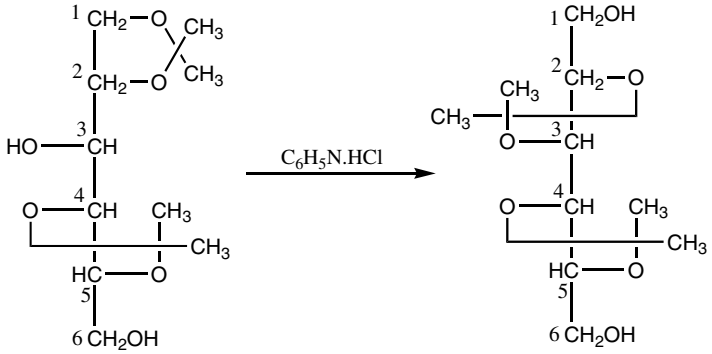
greater than the 1,3-*syn*–axial interactions between the axially oriented C1 methyl group and the two axially oriented C3 and C5 hydrogen atoms in a cyclohexane ring *80* (Fig. 6.25).

The reason that the 2,2-dimethyl-1,3-dioxolane *78* is formed as almost the only product, however, is due not only to destabilizing 1,3-*syn*–axial interactions present in the 2,2-dimethyl-1,3-dioxane ring, but also to the fact that five-membered ring ketal *78* is relatively free from strain in the C_s conformation (shown in Fig. 6.24) wherein the hydroxymethyl group is equatorially oriented. Since the reaction of formaldehyde with glycerol favors only to a slight extent the formation of six-membered dioxane ring [57, 58] it seems that the 1,3-dioxolane ring system is inherently more stable than the 1,3-dioxane ring.

The Migration of Acetal or Ketal Group

An interesting property of isopropylidene derivatives of carbohydrates is the tendency of isopropylidene group to migrate from terminal position wherein the two carbons of isopropylidene group are the primary and secondary carbons of a sugar to a position inside the carbohydrate chain where both carbons of isopropylidene group are secondary carbons.

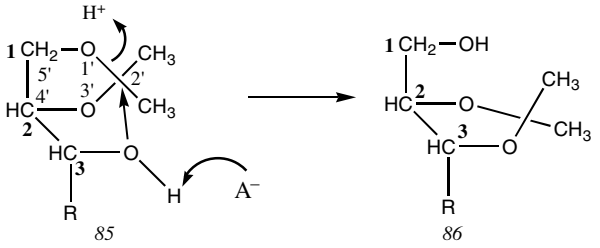
Thus, for example, heating of 1,2:4,5-di-*O*-isopropylidene-D-dulcitol *83* with pyridine hydrochloride smoothly rearranges *83* to 2,3:4,5-di-*O*-isopropylidene-D-dulcitol *84* [59] (Fig. 6.26).



83 *84*

Fig. 6.26

The migration of isopropylidene group takes place via an attack of a proton and an anion according to the so-called push–pull mechanism [60–62]. The protonation of the acetal oxygen linked to the primary carbon (C5) and the simultaneous attack by a base (anion) to the hydrogen atom of the secondary hydroxyl group at the neighboring carbon C**3** results in the simultaneous breakage of the O-H bond and the O1–C2' bond causing the migration of the acetal from the C1–C2 to the C2–C3 carbons.



85 *86*

Fig. 6.27

When working with isopropylidene groups one must always consider the possibility of their migration, particularly in the presence of reagents with strong acid–base properties. Thus, for example, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *51* reacts with triphenyl phosphite iodomethylate in benzene whereby the 5,6-*O*-isopropylidene group migrates to 3,5-position giving 1,2:3,5-di-*O*-isopropylidene-α-D-glucofuranose *87* [63, 64] (Fig. 6.28).

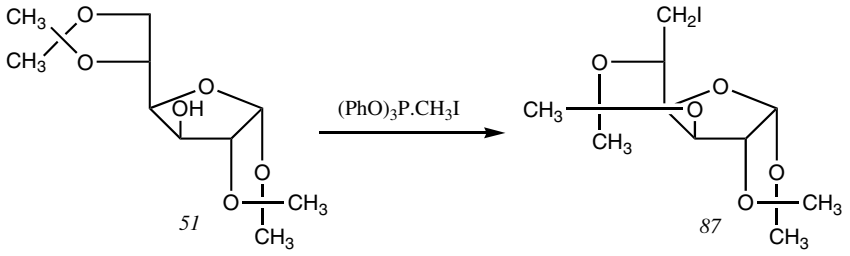
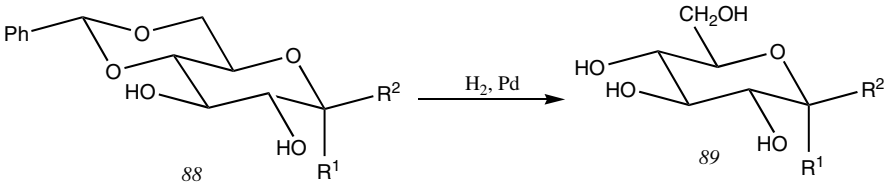


Fig. 6.28

Removal of Acetal and Ketal Groups

Benzylidene Group

The benzylidenation is very often used for protection of 1,2- or 1,3-hydroxyl groups of carbohydrates since it is often regioselective, the yields of benzylidene acetals are high, and the benzylidene group can be easily removed in high yield.



R^1 = OMe, OAc, OBz; R^2 = H
R^1 = H; R^2 = OMe, OAc, OBz

Fig. 6.29

Thus it can be removed by catalytic hydrogenation as from, for example, alkyl 4,6-*O*-benzylidene-α- or β-D-glycopyranoside or 1-*O*-acyl derivatives (acetate, benzoate) by hydrogenation using palladium black as the catalyst and methanol as the solvent [65] (Fig. 6.29). It can also be removed by acid hydrolysis using 9:1 (v/v)

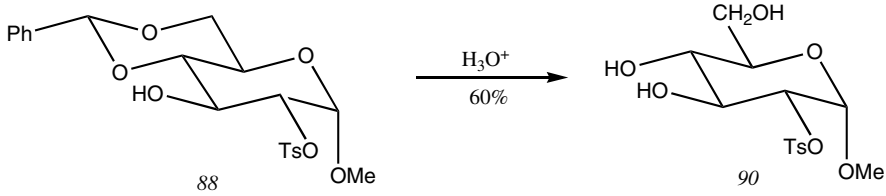
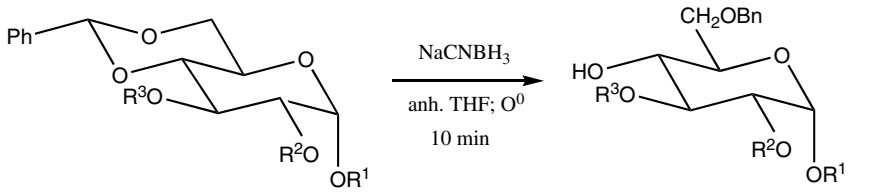


Fig. 6.30

CF_3COOH–water [66] by keeping the mixture for 5–10 min at room temperature (Fig. 6.30).



91, R^1 = OMe; $R^2 = R^3$ = Bn
92, R^1 = OMe; $R^2 = R^3$ = Bn
93, R^1 = OMe; R^2 = NHAc; R^2 = Bn

95, R^1 = OMe; $R^2 = R^3$ = Bn (81%)
96, R^1 = OMe; $R^2 = R^3$ = Bn (95%)
97, R^1 = OMe; R^2 = NHAc; R^2 = Bn (60%)

Fig. 6.31

Sodium cyanoborohydride in dry THF at 0°C converts the 4,6-*O*-benzylidene group to 6-*O*-benzyl group [67] (Fig. 6.31).

The reductive ring cleavage of carbohydrate benzylidene acetals having either the 1,3-dioxane [68–72] or 1,3-dioxolane ring [73–77] proceeds with high regioselectivity giving partially benzylated derivatives. For dioxolane-type benzylidene acetals, the direction of reaction is determined by configuration of the acetal carbon [73–77], whereas the factors that influence the reduction of the 1,3-dioxane acetals are not obvious.

Reduction of several 4,6-*O*-benzylidene derivatives of monosaccharides with $LiAlH_4$–$AlCl_3$ (1:1) [68, 69, 71, 72] gave 4-*O*-benzyl derivative as the major product, in almost every case, accompanied by various amounts of 6-*O*-benzyl ethers. For example, various 4,6-*O*-benzylidene-3-*O*-methyl-glucopyranosides gave the 6-*O*-benzyl ethers as by-products in yields of < 30%, but no 6-*O*-benzyl ethers were detected in the reduction of 3-*O*-benzyl-4,6-*O*-benzylidene glycopyranosides [68–70]. It was suggested [68, 69] that the product ratio is determined by the bulk of the C3-substituent, i.e., by steric accessibility of the acetal oxygen atoms to the chloroalane reagent [78].

A systematic study of the effect of bulkiness of the C3-substituent on the products' ratios of reductive ring cleavage of alkylated alkyl 4,6-*O*-benzylidene-D-glucopyranosides has been published [79].

Benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside was alkylated to give 2,3-di-*O*-methyl (*98*), 2,3-di-*O*-ethyl (*99*), 2,3-di-*O*-propyl (*100*), and 2,3-di-*O*-benzyl (*101*) derivatives as well as 3-deoxy-2-*O*-methyl derivative (*102*), and the reductive ring cleavage of alkylated 4,6-*O*-benzylidene-glucopyranoside derivatives was performed with the $LiAlH_4$–$AlCl_3$ (1:1) reagent in ether–dichloromethane (2:1) at reflux temperature. Reactions were completed within 2 h. The structures are given in Fig. 6.32 and the results are given in Table 6.1.

Considering the product ratios in Table 6.1, it is evident that bulkier the 3-substituent, higher the proportion of the 4-*O*-benzyl ether. This increase in regioselectivity can be explained by postulating the complexation of the Lewis acid

Table 6.1 $LiAlH_4$–$AlCl_3$ reduction of 4,6-*O*-benzylidene-D-glucopyranosides

			Isolated yield (%)	
4,6-Acetal	3-Substituent	Product ratio[a]	4-*O*-Benzyl	6-*O*-Benzyl
98	OMe	77:23	68	14
99	OEt	91:9	75	7
100	OPr	94:6	91	3
101	OBn	93:7	91	4
102	H	53:47	43	41

[a]4-*O*-Benzyl derivative/6-*O*-benzyl derivative.

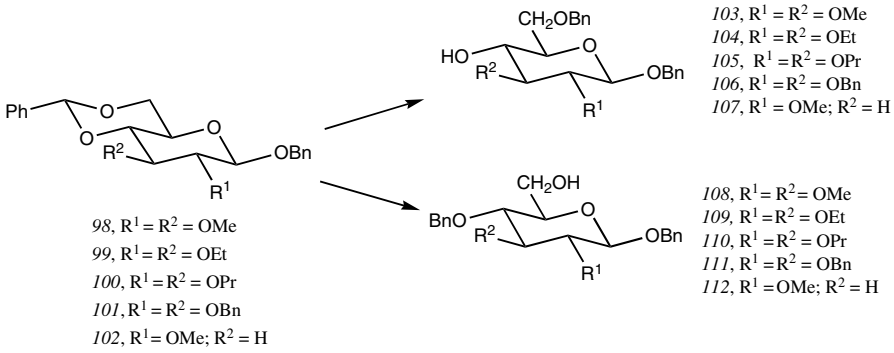


Fig. 6.32

chloroalane with one of the two acetal oxygens [80] (Fig. 6.33). Complex formation at O4 (Path A) is hindered by bulky substituents at the O3 whereas the complexation at O6 (Path B) is not influenced by bulkiness of O3 substituents. Hence, Path B is favored always when the O3 is substituted with bulky substituents, which will result in the greater formation of the 4-*O*-benzyl derivative. It is apparent from Table 6.1 that some of the 4-*O*-benzyl derivative was formed even in the reduction of 3-*O*-propyl (*100*) and 3-*O*-benzyl (*101*) derivatives (Fig. 6.33). These two compounds gave nearly the same product ratios of *O*4/*O*6 benzyl derivatives, indicating that the regioselectivity of this reaction is dependent not just on the length of the *O*-alkyl chain. Perhaps, a better insight could be obtained by comparing the product ratio of the reductive cleavage of 3-*O*-benzyl and 3-*O*-isopropyl ethers.

The proposed explanation is in agreement with earlier findings [69–71] that a higher proportion of 6-*O*-benzyl ethers is obtained by reductive ring cleavage of the 4,6-*O*-benzylidene-D-galactopyranoside derivatives than of the corresponding glucopyranoside derivatives, since steric shielding of the O4 by the 3-substituents is less effective in the former.

The reductive opening of the 4,6-*O*-benzylidene-D-glucopyranoside derivative was examined with various reducing agents [79]. For this purpose benzyl

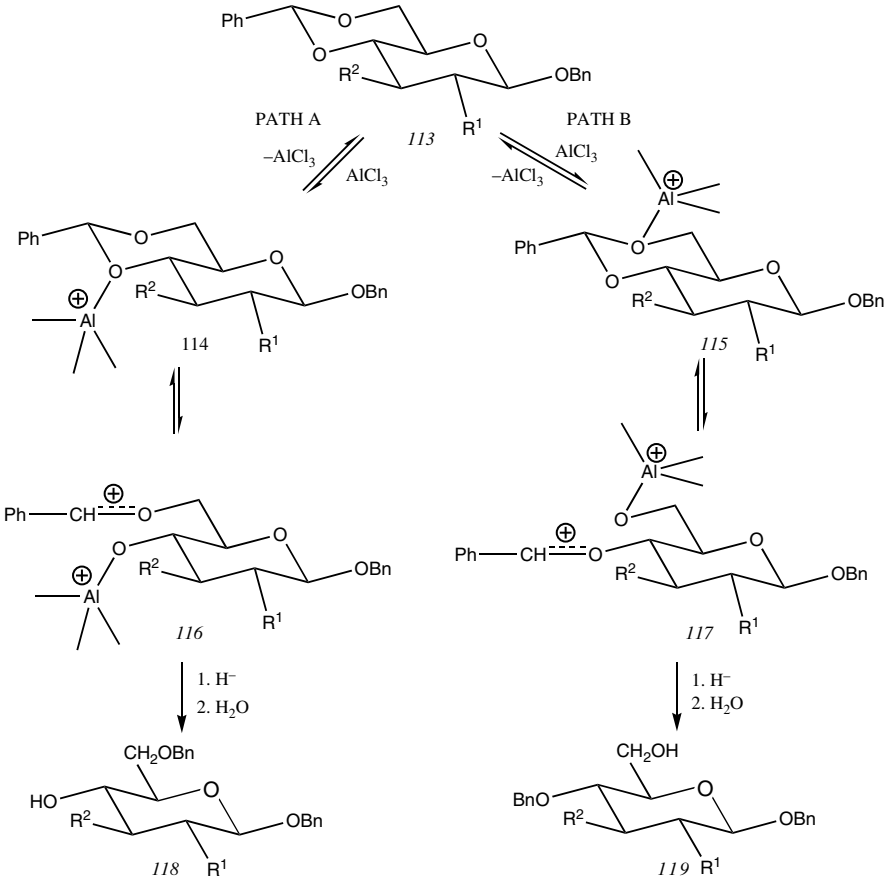


Fig. 6.33

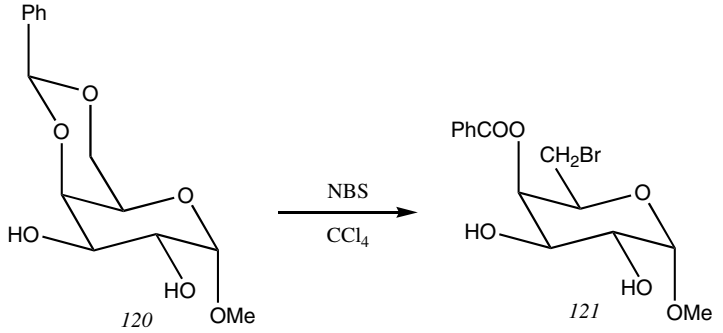
4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside *98* (Fig. 6.32) was chosen, where the steric hindranceis relatively small so that a change in the product ratio should be maximal. The results are summarized in Table 6.2.

Table 6.2 Reductions of *98* with various reducing agents

Reagent	Solvent	Bath temperature (°C)	Reaction time (h)	Product ratios *98*:*103*	Isolated yield (%)	
					98	103
$LiAlH_4$–$AlCl_3$	(2:1) Et_2O–CH_2Cl_2	45	2	77:23	68	14
$LiAlH_4$–$AlBr_3$	(2:1) Et_2O–CH_2Cl_2	45	2	84:16	73	12
$(i\text{-}Bu)_2AlH$	Benzene	0	3	46:54	34	43
$(i\text{-}Bu)_2AlH$	(9:1) Et_2O–CH_2Cl_2	45	8	71:29	68	25
Borane	Tetrahydrofuran	75	72	0:0	–	–
Borane	Benzene	90	120	57:11	46	7

It has been reported [81, 82] that borane in tetrahydrofuran reduces acetals and that it may have some advantages over $LiAlH_4$–$AlCl_3$ system. However, it was found that benzyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside *98* did not react with an excess of borane in tetrahydrofuran after 72 h. Slow reaction also took place in benzene at elevated temperature, so that even after 120 h much of *98* was still present. The major product was the 4-*O*-benzyl ether, formed with a good regioselectivity, but the low reaction rate of this method makes it unsuitable for practical purposes.

Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside *120* reacts with *N*-bromosuccinimide (NBS) in carbon tetrachloride at reflux and in the presence of barium carbonate for neutralizing the generated HBr giving methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-galacto pyranoside *121* with over 60% yield [83] (Fig. 6.34).

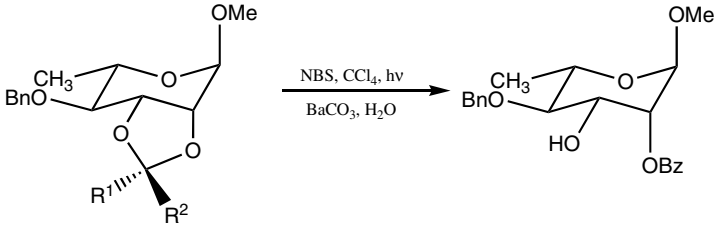


120 *121*

Fig. 6.34

Similarly, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with substituted or unsubstituted C2 and C3 hydroxyl groups gives, with *N*-bromosuccinimide (NBS) in carbon tetrachloride at reflux and in the presence of barium carbonate, 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside [83, 84].

Benzylidene dioxolane derivatives give, under the same reaction conditions except for the presence of water and UV irradiation (low-pressure mercury lamp), the hydroxy benzoates with an axial benzoyl group and the adjacent hydroxyl group equatorially oriented [85] with 72% yield (Fig. 6.35).



122, R^1 = Ph; R^2 = H
123, R^1 = H; R^2 = Ph

124

Fig. 6.35

The oxidative cleavage of acetal rings with ozone to the corresponding esters and alcohols has been studied by Deslongchamps [86, 87].

The ozonolysis of the following methyl α-D-glucopyranosides has been studied: 2,3-di-*O*-methyl *98*, 2,3-di-*O*-acetyl *125*, and 2,3-di-*O*-tosyl *126*. Ozonolysis of *98* in anhydrous carbon tetrachloride gave a mixture of 6-*O*-benzoyl derivative *127* (60%) and 4-*O*-benzoyl derivative *130* (40%) of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside. The ozonolysis of 2,3-di-*O*-acetyl-4,6-*O*-benzylidene derivative *125* in glacial acetic acid gave a mixture of 6-*O*-benzoyl-2,3-di-*O*-acetyl derivative *128* (85%) and 4-*O*-benzoyl-2,3-di-*O*-acetyl derivative *131* (15%). The ozonolysis of 2,3-di-*O*-tosyl-4,6-*O*-benzylidene derivative *126* in glacial acetic acid gave methyl 4-*O*-benzoyl-2,3-di-*O*-tosyl-α-D-glucopyranoside *132* as the only product (Fig. 6.36).

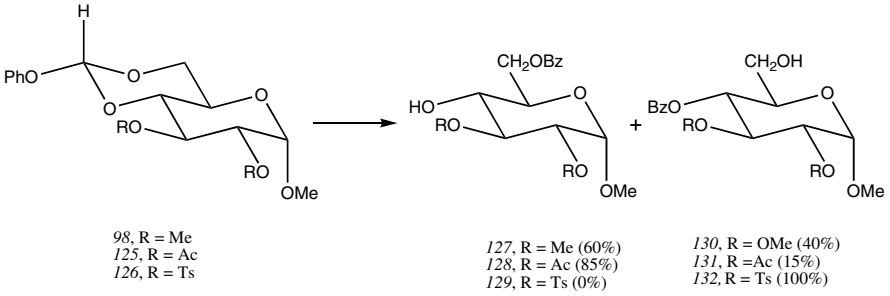


Fig. 6.36

It is known that methyl β-D-glucopyranoside can be oxidized by ozone [86, 87] but this reaction is slow at room temperature. Benzylidene acetals are much more reactive: the oxidation is normally completed within 2 h at –78°C. Therefore the oxidation of benzylidene acetals of alkyl 4,6-*O*-benzylidene-β-D-glycopyranoside can be carried out without oxidation of the anomeric carbon.

The oxidation of methyl 4,6-*O*-ethylidene-2,3-di-*O*-acetyl-α-D-glucopyranoside in acetic acid/ sodium acetate gave methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside with excellent yield (Fig. 6.37). The oxidation was followed by in situ "acetylation" due to use of acetic anhydride/sodium acetate as a solvent.

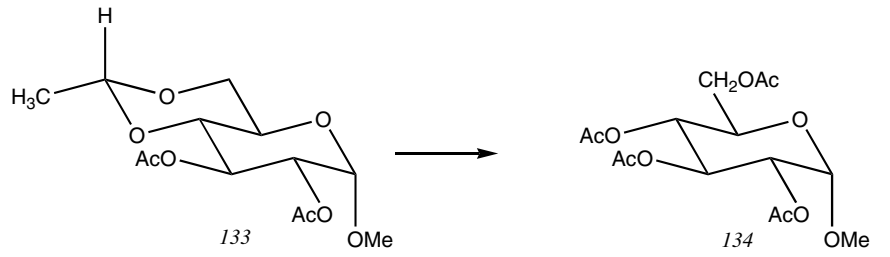
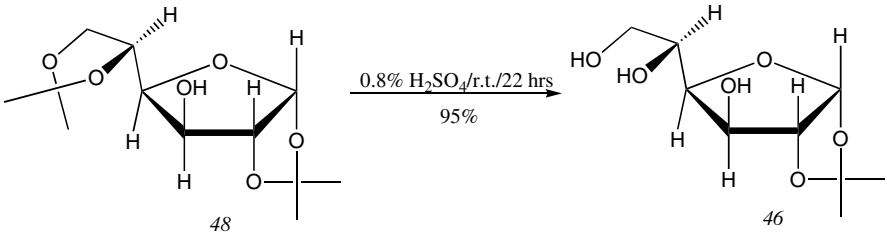


Fig. 6.37

Isopropylidene Group

There is considerable difference in stability between an exocyclic and an endocyclic isopropylidene groups (those that are fused to the furanose ring). Thus, for example, the exocyclic isopropylidene group can be selectively removed from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *48* by acid-catalyzed hydrolysis (Fig. 6.38) giving 1,2-*O*-isopropylidene-α-D-glucofuranose *46* in very high yield [88, 89].



48 *46*

Fig. 6.38

This selective hydrolysis can also be achieved in aqueous acetic acid [90, 91] either by standing at room temperature (several days) or by heating at 100°C for 2 h. Similarly, the D-*ido*- [92] and D-*allo*- [93] isomers may be selectively hydrolyzed to the 1,2-*O*-isopropylidene derivatives. According to crude estimations [90] the 5,6-*O*-isopropylidene group hydrolyses ca. 40 times faster than 1,2-*O*-isopropylidene group.

Under the more vigorous conditions (mineral acid, higher acid concentration, and higher temperature) both isopropylidene groups are hydrolyzed.

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Chapter 7
Nucleophilic Displacement and the Neighboring Group Participation

Nucleophilic Displacement

The nucleophilic substitution reaction of the type S_N2 (bimolecular nucleophilic substitution) proceeds with formation, in a single step, of the trigonal bipyramidal pentacovalent carbon transition state *2* and results in the inversion of configuration at the reacting carbon atom (the configuration of *3* vs. *1*) (Fig. 7.1); it usually follows the second-order kinetics.

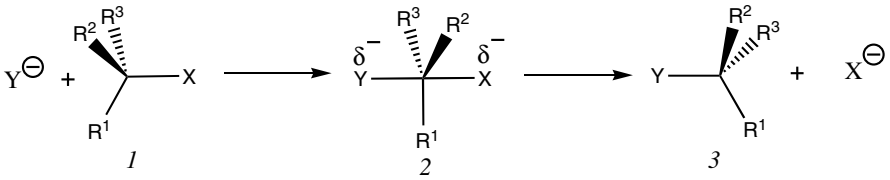

Fig. 7.1

The ligands R^1, R^2, or R^3 can be hydrogen or substituted carbon atoms. In the transition state (*2* in Fig. 7.1) the central carbon is sp^2 hybridized (Fig. 7.3), and the unhybridized *p* orbital, which is perpendicular to the planar sp^2 carbon, is used to form partial bonds with both the entering nucleophile and the leaving group.

The angles between the R groups in transition state are approximately 120° (Fig. 7.2), while the *p* orbital is oriented at an angle of 90° to these three C-R bonds (Fig. 7.3).

Thus during the course of the S_N2 reaction, the reacting carbon atom changes its hybridization from sp^3 to sp^2 and then back to sp^3; the process is accompanied by inversion of configuration.

The S_N2 reaction occurs quite readily. A large variety of nucleophiles and leaving groups are known.

The rate of an S_N2 reaction depends on the nucleophilicity of incoming nucleophile, on the nature of leaving group, on the polarity of solvent (solvation), and on steric and electronic effects. For most S_N2 reactions, steric interactions are the most

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_7,

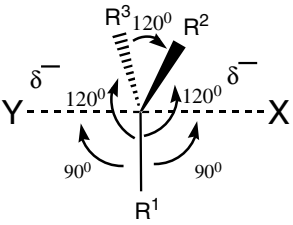

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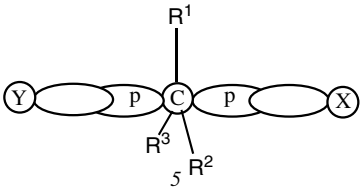
Fig. 7.2



5

Fig. 7.3

important, because the increased crowding about the reacting carbon raises the free energy of transition state, and thus lowers the rate of reaction.

In a nucleophilic substitution, an electron pair is transferred from the nucleophile to the reacting carbon and from the latter to the leaving group. The nucleophiles could be either negatively charged (e.g., $RCOO^-$, OH^-, CN^-) or neutral (e.g., ammonia H_3N:, amines $–RH_2N$:, hydrazine – H_2NNH_2). Since the negatively charged nucleophiles will have their negative charge either destroyed or delocalized in the transition state, the reactants will be more highly solvated than the transition state. If a nucleophile is a neutral molecule that becomes partially positively charged in transition state, then the transition state will be more solvated than the reactants. Consequently, the polar solvent will slow down the reaction of charged nucleophiles and accelerate the reaction of neutral nucleophiles.

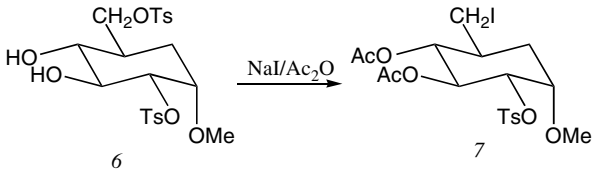
Nucleophilic displacement reaction has been extensively used in carbohydrate chemistry for the synthesis of a particular type of sugar, as for example, amino-, thio-, seleno-, sugar from an appropriately protected monosaccharide that is derivatized with a leaving group at the carbon where the nucleophilic displacements are to take place.

In the absence of neighboring group participation (vide infra) the nucleophilic displacement always proceeds with inversion of the configuration at the reacting carbon. However, if a carbon neighboring to the reacting carbon atom is derivatized by a group that can act as a nucleophile, such as acetate, benzoate, thioacetate, acetamido group, etc., the nucleophilic displacement may proceed with retention of configuration, if the nucleophile on the neighboring carbon is able to displace the leaving group faster than external nucleophile. The intramolecular displacement

reaction is an entropically more favored reaction than intermolecular displacement, provided that the stereochemistry of a neighboring group is favorable, i.e., it is able to form a strainless cyclic transition state.

It has already been said that steric effects exert the greatest influence upon the rate of nucleophilic displacement. For that reason the nucleophilic displacement is fastest at the primary carbon of both hexo- and pentofuranoses and of hexopyranoses.

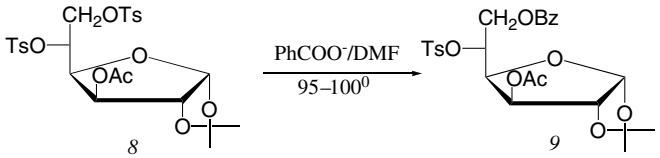
Thus, reaction of methyl 2,6-di-*O*-tosyl-α-D-glucopyranoside *5* with sodium iodide in acetic anhydride gives methyl 3,4-di-*O*-acetyl-6-deoxy-6-iodo-2-*O*-tosyl-α-D-glucopyranoside *6* as the only product, indicating that the primary 6-*O*-tosyl group is much more reactive than the C2 secondary tosyl group [1] (Fig. 7.4).



6 *7*

Fig. 7.4

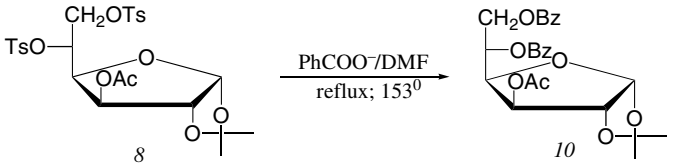
Similarly, treatment of 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *8* with sodium benzoate in *N,N*-dimethylformamide at 95–100°C for 7 h gives in a 64% yield [2] 3-*O*-acetyl-6-*O*-benzoyl-1,2-*O*-isopropylidene 5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *9* (Fig. 7.5).



8 *9*

Fig. 7.5

If *8* is treated with sodium benzoate in *N,N*-dimethylformamide at reflux for 6 h, [2] the 5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose *10* is obtained in 50% yield (Fig. 7.6).



8 *10*

Fig. 7.6

It is interesting that not all primary sulfonates are equally reactive. Thus it is well known that the tosyl group of 1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-α-D-galactose *11* resists the nucleophilic displacement with iodide, fluoride, or methoxide as the nucleophile [3] (Fig. 7.7).

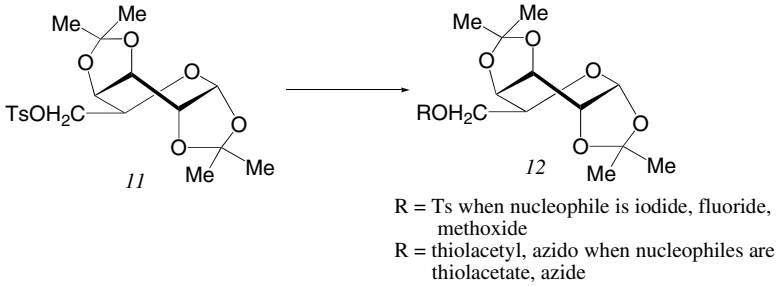


Fig. 7.7

However, this C6 tosyl group can be displaced with some other nucleophiles, such as thiolacetyl and azide.

The nucleophilic displacement of a sulfonyl group attached to a pyranoid or furanoid ring is extremely dependent on steric factors. Thus, the substitution reactions take place readily at the C4 carbon of both α- and β-D-gluco- and α-D-galactopyranosides. For example, the nucleophilic displacement, with benzoate of the axial 4-mesyl-group of methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-mesyl-α-D-galactopyranoside *13* in *N,N*-dimethyl formamide at 140°C for 24 h gives methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside *14* in 49% yield [4] (Fig. 7.8).

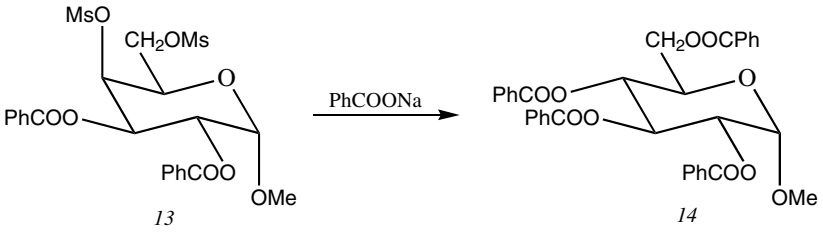
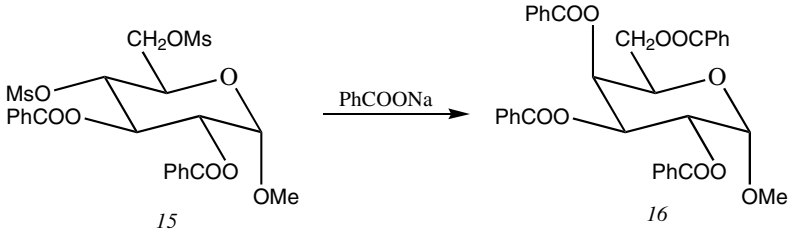


Fig. 7.8

Similarly, the nucleophilic displacement of the equatorial 4-*O*-mesyl group of methyl 2,3-di-*O*-benzoyl-4,6-di-*O*-mesyl-α-D-glucopyranoside *15* with benzoate in *N,N*-dimethylformamide at 140°C for 20 h gave methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-galacto-pyranoside *16* as the only product [5] (Fig. 7.9). It should be noted, however, that an axial leaving group is displaced two to three times faster than the equatorial [4–6].

The attempted displacement with acetate of 4-*O*-mesylate, 4-*O*-tosylate, or 4-*O*-brosylate of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside *17, 18*,

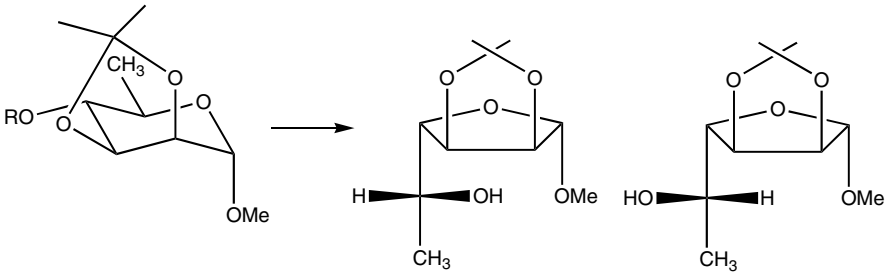


15 *16*

Fig. 7.9

19 resulted in ring contraction giving D-tallo- and L-allo-furanoside products *20* and *21*, respectively, in 7:1 ratio [7] (Fig. 7.10).

The formation of *20* results from inversion at the C4 and retention (or double inversion) at the C5 of *17*, while the formation of *21* is a result of inversion at both C4 and C5.

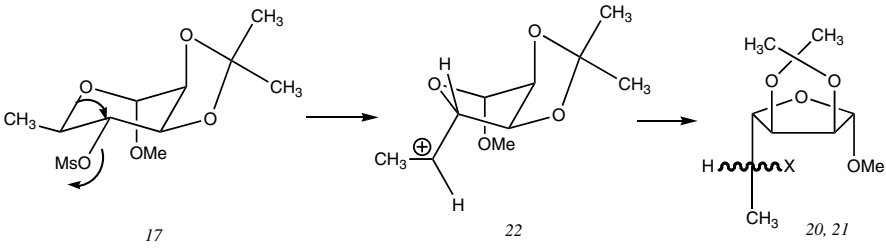


17, R = Ms
18, R = Ts
19, R = Bros

20, α-D-tallo 21, β-L-allo

Fig. 7.10

The following mechanism could be envisioned (Fig. 7.11).

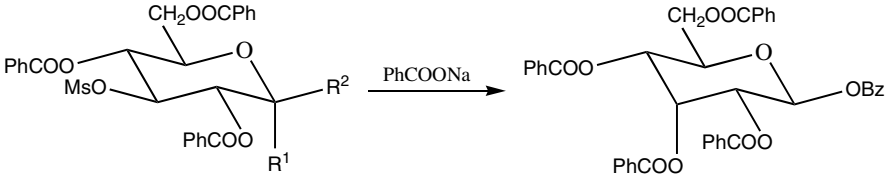


17 *22* *20, 21*

Fig. 7.11

Similar rearrangement was observed by Hanessian [8] using methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside.

The nucleophilic displacement, with benzoate, of 3-*O*-mesyl group of methyl 1,2,4,6-tetra-*O*-benzoyl-3-*O*-mesyl-α- and β-D-glucopyranoses *23* and *24*, respectively, is strongly dependent on the anomeric configuration [9]. Thus, whereas the treatment of methyl 1,2,4,6-tetra-*O*-benzoyl-3-*O*-tosyl-β-D-glucopyranose *24* with sodium benzoate in *N*-methylpyrrolidone at 100°C for 16 h gave the corresponding penta-*O*-benzoyl-β-D-allopyranose *25* in 65% yield (Fig. 7.12), the α-anomer



23, R^1 = OBz; R^2 = H
24, R^1 = H; R^2 = OBz

25

Fig. 7.12

23 failed to undergo the displacement reaction [9]. A possible explanation [9] could be that the approach of the negatively charged nucleophile (benzoate) to the C3 carbon *26* to form the corresponding transition state *27* is impeded by unfavorable 1,3-diaxial electrostatic interaction between the approaching nucleophile (benzoate) and the axially oriented anomeric benzoate (Fig. 7.13).

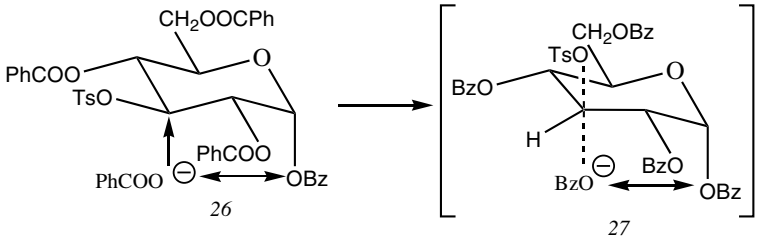
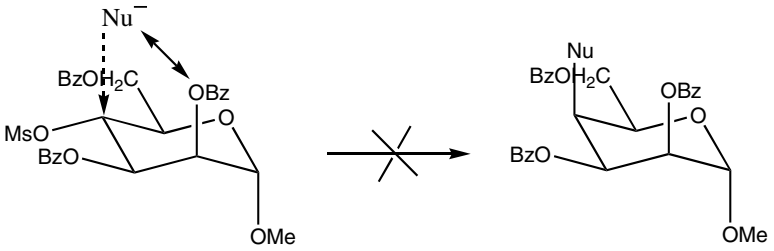


Fig. 7.13

Similarly, solvolysis of methyl 2,4,6-tri-*O*-benzoyl-3-*O-methanesulfonyl*-α-*D*-gluco-pyranoside in wet Cellosolve containing sodium acetate gave no product [10].

The 4-*O*-methanesulfonate of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-mannopyranoside *28* does not undergo direct substitution [11]. This can be again attributed to the presence of the axial 2-*O*-benzoyl group, which may hinder the approach of the nucleophile at the C4 position *28* (Fig. 7.14). This interaction can be electrostatic between the incoming nucleophile and axially oriented benzoate, or it can be the 1,3-*syn*-diaxial interaction between the C2 axial benzoate and the nucleophile in the transition state, or both [12] (Fig. 7.14).

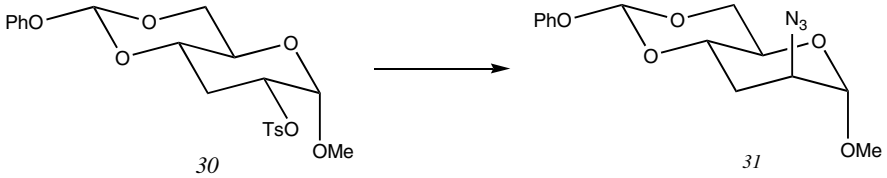
Except for the displacement of *p*-toluenesulfonyl group of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-*p*-toluenesulfonyl-α-D-*ribo*-hexopyranoside *30* with azide [13] (Fig. 7.15), direct displacement of the C2 sulfonyloxy group in a



28 *29*

Fig. 7.14

furanoside or in a pyranoside ring with charged nucleophiles was considered, for a long time, to be very difficult if not impossible.



30 *31*

Fig. 7.15

The use of a neutral nucleophile such as hydrazine did, however, result in displacement of the C2 sulfonate in both furanose [14–16] and pyranose rings [17].

The observed unusually low reactivity of the C2 sulfonyloxy group toward displacement with charged nucleophiles was attributed to electron-withdrawing effect of the anomeric carbon and to unfavorable dipolar interaction in the transition state [18–22]. The greater reactivity of the sulfonyloxy group at the C2 carbon atom with uncharged nucleophiles was ascribed to the reversal of polarity of one of the polar bonds in the transition state resulting in a dipolar attractive force [20].

To examine the stereoelectronic interactions responsible for diminished reactivity of the C2 sulfonyloxy group toward nucleophilic displacement with charged nucleophiles Miljkovic et al. [23] studied displacement of the C2 sulfonate with benzoate in the following substrates: methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α- and β-D-glucopyranosides *32* and *33* and methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methylsulfonyl-α- and β-D-mannopyranosides *34* and *35* (Fig. 7.16 and Table 7.1).

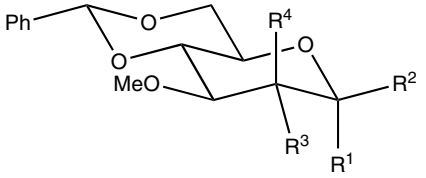
As can be seen from Table 7.1 the nucleophilic displacement of 2-*O*-sulfonate in *35* was considerably faster than displacement of 2-*O*-methanesulfonyl group in *33* (8 h vs. 120 h). The obtained results can be better explained if the partial structures of the C2 sulfonates *32–35* containing only the C1 and C2 carbons with their respective ligands are drawn in Newman's projection (Fig. 7.17).

Thus, in Fig. 7.17 the C1 and the C2 carbon of compounds *32–35* (structures *39–42*) as well as of the corresponding transition states (*43–46*) for the nucleophilic

Table 7.1 Displacement of 2-sulfonate of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methyl-sulfonyl-α- and β-D-gluco- (*32* and *33*) and α- and β-D-mannopyranosides (*34* and *35*)[a]

Sugar	Reaction, *t* (°C)	Reaction time (h)	Yield (%)
Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-glucopyranoside, *32*	153	120	3.5
Methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-glucopyranoside, *33*	153	120	62
Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-mannopyranoside, *34*	153	120	–
Methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside, *35*	153	8	70

[a] Displacement was effected by refluxing an *N,N*-dimethylformamide solution of the corresponding sugar derivative with potassium benzoate.



32, R^1 = OMe; $R^2 = R^4$ = H; $R^3 = CH_3SO_3$
33, $R^1 = R^4$ = H; R^2 = OMe; $R^3 = CH_3SO_3$
34, R^1 = OMe; $R^2 = R^3$ = H; $R^4 = CH_3SO_3$
35, $R^1 = R^3$ = H; R^2 = OMe; $R^4 = CH_3SO_3$
36, R^1 = OMe; $R^2 = R^2$ = H; PhCOO; R^4 = PhCOO
37, $R^1 = R^3$ = H; R^2 = OMe; R^4 = PhCOO
38, $R^1 = R^4$ = H; R_2 = OMe; R^3 = PhCOO

Fig. 7.16

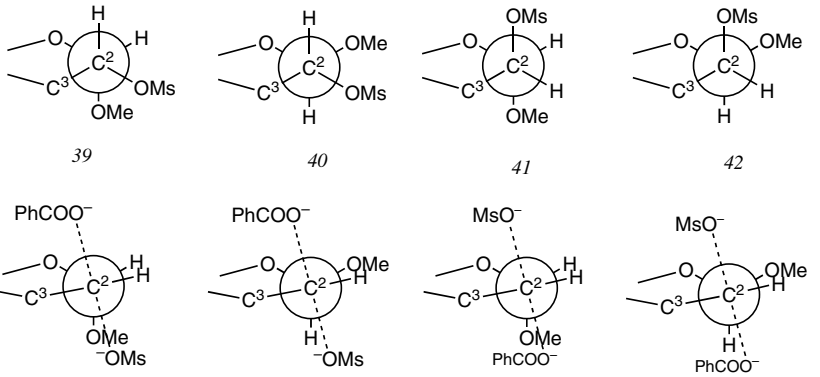


Fig. 7.17

displacements of 2-sulfonates are represented in Newman's projections. Assuming the pentacovalent bi-pyramidal transition state for the nucleophilic displacement of sulfonate, the unfavorable stereoelectronic interactions present in *43–46* are as follows: (a) in *43* there is a Pitzer strain and the electrostatic repulsion between the partially negatively charged leaving methanesulfonyl group and the electronegative C1 methoxy group (they are almost coplanar); (b) in *44* there is only one interaction between the negatively charged nucleophile that approaches the C2 carbon from a direction that bisects the resultant dipole of the β-methoxy group dipole and resultant dipole of the two nonbonding electron pairs on ring oxygen; (c) in *45* there is a Pitzer strain and electrostatic repulsion between the approaching negatively charged benzoate and the electronegative C1 methoxy group (they are almost coplanar); and (d) in *46* there is an unfavorable stereoelectronic interaction between the partially negatively charged leaving methanesulfonyloxy group and the resultant dipole of the β-methoxy group dipole and the resultant dipole of two nonbonding electron pairs on the ring oxygen.

Based on the above considerations one may conclude that the most reactive C2 sulfonate toward nucleophilic displacement will be in *42*, followed by the C2 sulfonate in *40*; the relative reactivity of C2 sulfonates in *39* and *41* is difficult to assess but they should be much lower than in *40* and *42*.

Ishido and Sakairi [24] studied the nucleophilic displacement of 2-*O*-trifluoromethylsulfonyl group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluoromethylsulfonyl-α-D-glucopyranoside *47* with several charged nucleophiles and found that the displacements proceeded relatively fast and the yields of corresponding α-D-mannopyranosides were very good (Table 7.2 and Fig. 7.18).

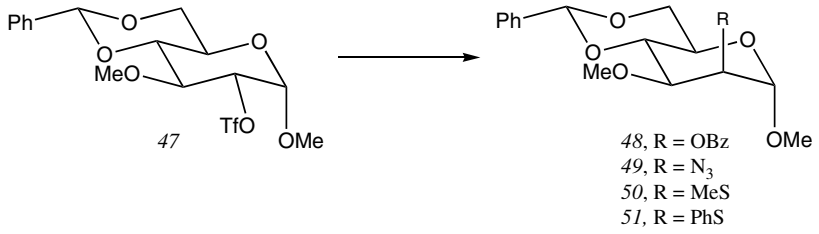


Fig. 7.18

Table 7.2 Displacement of 2-*O*-trifluoromethylsulfonate of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluoromethylsulfonyl-α-D-glucopyranosides *47*

Nucleophile	Temperature (°C)	Reaction time (h)	Yield (%)
$PhCOO^-$	80	5	82
N_3^-	80	2	86
MeS^-	0	1	89
PhS^-	50	6	83

Treatment of benzyl 3,4-isopropylidene-2-*O*-(imidazol-1-sulfonyl)-β-L-arabinopyranoside *52* with sodium azide in refluxing toluene [25] (110°C) gave benzyl 2-azido-2-deoxy-3,4-isopropylidene-β-L-ribopyranoside *53* in 80% yield (Fig. 7.19).

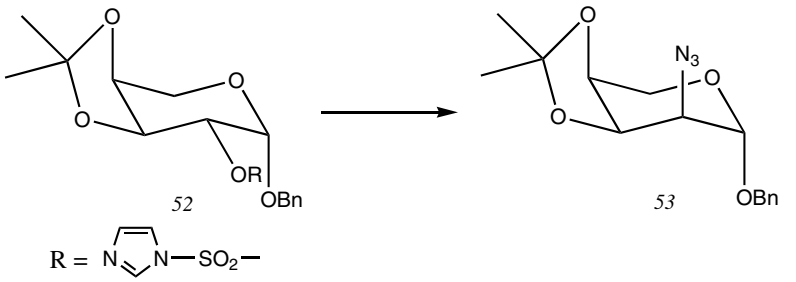


Fig. 7.19

As in the pyranoside series, the nucleophilic displacement at the C2 carbon of furanoside derivatives is also difficult [26]. Treatment of the 2-imidazylate ester of benzyl 5-deoxy-α-D-hexofuranoside derivative *54* with tetrabutylammonium azide or benzoate in refluxing toluene gave the substitution products *55* and *56* in 82 and 53% yield, respectively (Fig. 7.20).

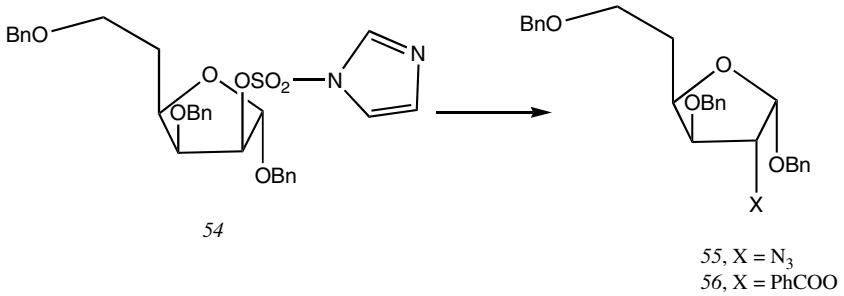
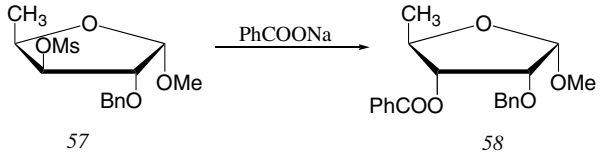


Fig. 7.20

Thus the trifluoromethanesulfonyl group and the imidazol-1-sulfonyl group seem to be very good leaving groups for the displacement of C2 sulfonate in both pyranosides and furanosides (for a good review of nucleophilic displacement of imidazol-1-sulfonates, see [27]).

In general, the nucleophilic displacement of secondary sulfonyloxy groups in a furanoid ring is reported to be slower than nucleophilic displacement of secondary sulfonyloxy groups in a pyranoside ring. The displacement, with benzoate, of the 3-*O*-mesyl group in methyl 2-*O*-benzyl-5-deoxy-3-*O*-mesyl-α-D-xylofuranose *57* can be used as an example where displacement proceeded very sluggishly; methyl 3-*O*-benzoyl-2-*O*-benzyl-5-deoxy-α-D-ribofuranose *58* was obtained in 53% yield,



57 *58*

Fig. 7.21

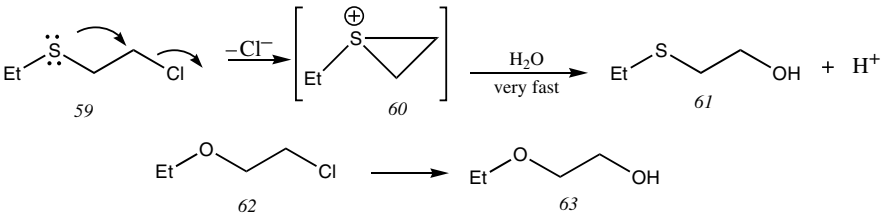
together with several side products, after heating the reaction mixture in DMF at reflux for 40 h [28] (Fig. 7.21).

Nucleophilic Displacements with Neighboring Group Participation

When a rate of nucleophilic displacement in a molecule or the stereochemical outcome of displacement is influenced by a group that lies near the reaction site, but this influence is not a consequence of inductive, conjugative, or steric effects, it was concluded that this group participates directly in the reaction, and this influence is termed the *neighboring group participation.*

There are three types of evidence that support the concept of *neighboring group participation*.

(a) If participation occurs during the rate-determining step of a nucleophilic displacement, the reaction is usually faster than other reactions that are similar but do not involve such participation. For example, the 2-(2-chloroethyl) thioethane $ClCH_2CH_2SCH_2CH_3$ *59* is hydrolyzed over 10,000 times faster than the corresponding ether, $ClCH_2CH_2OCH_2CH_3$ *62* (1-chloro-2-ethoxy-ethane), in aqueous dioxane [29]. This rate difference is far too great to be attributed to differences in inductive, conjugative, or steric effects, but suggests rather that the hydrolysis of the sulfide (but not the ether) proceeds through the participation of sulfur atom via formation of a cyclic sulfonium ion *60*. The intermediate, because of the strained three-membered ring, is readily hydrolyzed to the observed product *61* (Fig. 7.22).



59 *60* *61* *62* *63*

Fig. 7.22

(b) If the nucleophilic displacement occurs at the secondary chiral carbon, then stereochemistry of the reaction may suggest the involvement of a neighboring group. Since nucleophilic displacement at a chiral carbon always proceeds with the inversion of configuration, the retention of configuration would suggest the involvement of the neighboring group in the transition state. It is assumed that two displacements at the reacting carbon take place: first, the leaving group is intramolecularly displaced by a neighboring group then the cyclic transition

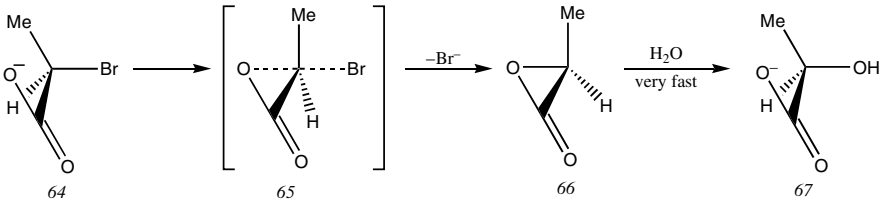


Fig. 7.23

state *65* (or cyclic transition intermediate *66*) obtained by this intramolecular displacement is opened by an external nucleophile. This is illustrated by the hydrolysis of α-bromopropionic acid (Fig. 7.23). In the first step the carboxylate nucleophile displaces the bromine atom with the inversion of configuration at the α-carbon, (*64→65*) to form the nonisolable α-lactone (*66)* which is, in a very rapid step, cleaved by water giving the lactic acid *67* (*66→67*) that has the same configuration as the starting α-bromopropionic acid [30].

(c) Neighboring group participation may lead to a molecular rearrangement when the neighboring group remains bonded to the reaction center but breaks away from the atom to which it was originally attached in the substrate. Thus, chlorinated amine *68* yields on basic hydrolysis, the rearranged aminohydrin *70*, since the diethylammonium intermediate *69* is attacked preferentially at the primary α-carbon rather than at secondary β-carbon atom [31] (Fig. 7.24).

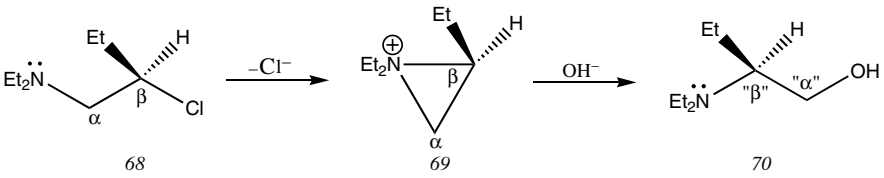


Fig. 7.24

When a transition state or a transition state intermediate is stabilized by a substituent on the same molecule by becoming chemically bonded to the reaction center due to its proximity or to proper orientation this effect is called *neighboring group participation*, and if such participation leads to an enhanced reaction rate, the group

is said to provide *anchimeric assistance* [32, 33] (derived from the Greek: *anchi*, "adjacent"; *meros*, "part").

The most common type of neighboring group participation observed and exploited in carbohydrate chemistry is the participation of a neighboring ester group where the carbonyl oxygen acts as the nucleophile. The first step of such reactions always involves an *intramolecular nucleophilic attack* of the carbonyl oxygen, and if the carbon at which the attack occurs is sp^3 hybridized, the product is usually different from what would be expected in the absence of participation. In the course of neighboring group participation a new ring is formed that may suffer three different fates.

(1) Ring can be opened at the same carbon at which the ring closure took place (e.g., the C1 carbon in Fig. 7.25), leading to an un-rearranged product having the same configuration (β) at the reaction center as the starting material [34, 35].

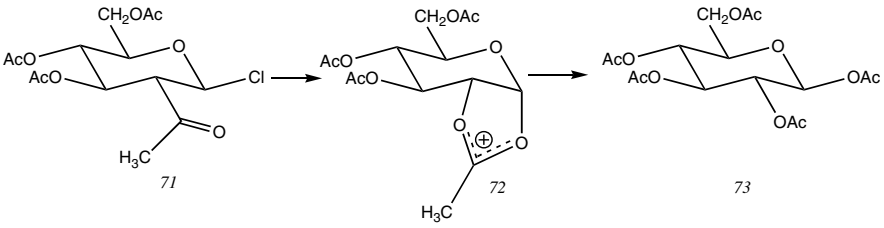


Fig. 7.25

In the absence of neighboring group participation, the direct nucleophilic displacement of C-Cl would take place giving the corresponding α-anomer *74* (Fig. 7.26). However, the direct displacement is not observed in reaction of tetra-*O*-acetyl-β-D-glucopyranosyl chloride with sodium acetate.

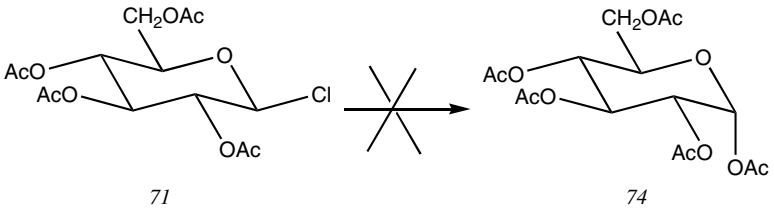


Fig. 7.26

Another example for the nucleophilic displacement with neighboring group participation that results in retention of configuration at the reacting carbon is the reaction of *N,N*-diethyl-1,2-*O*-isopropylidene-3,5-di-*O*-tosyl-α-D-glucofuranuronoamide *75* with the anhydrous Dowex 1 ion-exchange resin in

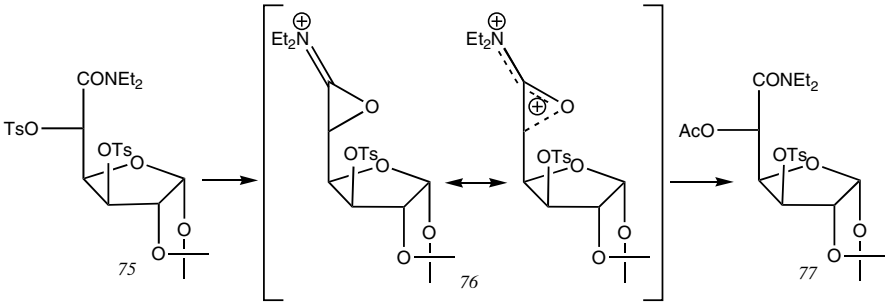


Fig. 7.27

acetate form (refluxing acetic anhydride), whereby the 5-*O*-acetyl-*N,N*-diethyl-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranuronoamide *77* is obtained in 84% yield [36] (Fig. 7.27).

(2) Ring opening may take place at a different carbon from the one where the ring closure took place, leading to a rearranged product. For example, the reaction of 6-*O*-benzoyl-3,5-di-*O*-tosyl-1,2-*O*-isopropylidene-α-D-

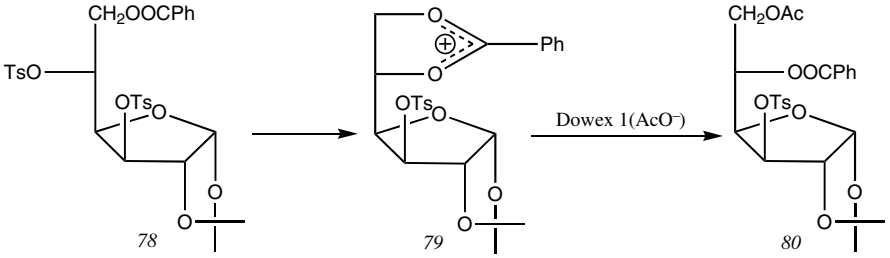


Fig. 7.28

glucofuranose *78* with anhydrous Dowex 1 (X-10, AcO^- form) gave 6-*O*-acetyl-5-*O*-benzoyl-3-*O*-tosyl-1,2-*O*-isopropylidene-β-L-idofuranose [37] *80* in 86% yield (Fig. 7.28). The initial attack of the carbonyl oxygen from the C6 benzoyl group gives as an intermediate the benzoyloxonium cation *79* which opens with the acetate at the C6 carbon atom (less hindered carbon) giving the 6-*O*-acetyl-5-*O*-benzoyl-L-idofuranose derivative *80*.

An interesting neighboring group participation was observed [38] when methyl 4,6-di-*O*-benzoyl-3-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside *81* and methyl 2,6-di-*O*-benzoyl-3-*O*-methyl-4-*O*-methylsulfonyl-β-D-mannopyranoside *82* were treated with potassium benzoate in refluxing *N,N*-dimethylformamide. In both cases the only isolable products were methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside *83* and methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-galactopyranoside *84* (Fig. 7.29).

81, $R^1 = CH_3SO_3$; $R^2 = R^3 = H$; $R^4 = OBz$
82, $R^1 = R^4 = H$; $R^2 = OBz$; $R^3 = CH_3SO_3$

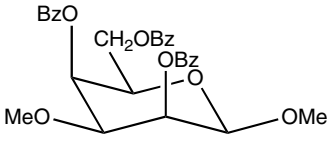
83, $R^1 = R^4 = H$; $R^2 = R^3 = OBz$
84, $R^1 = R^4 = OBz$; $R^2 = R^3 = H$

Fig. 7.29

In the first case the reaction was complete after 120 h, and the products *83* and *84* were obtained in 54 and 18% yield (*83*:*84* ratio was 3:1). In the second case the reaction was complete after 10 h and the products *83* and *84* were obtained in 65 and 20% yield (*83*:*84* ratio was 3.25:1).

Direct displacement of the C2 or the C4 methylsulfonyl group in *81* or *82*, respectively, was excluded since in both cases there is on the β-carbon atom a *trans*-axial substituent that impedes the approach of the nucleophile to the reacting carbon. This argument was supported by a finding [38] that refluxing of an *N,N*-dimethylformamide solution of methyl 3,4,6-tri-*O*-methyl-2-*O*-methylsulfonyl-β-D-galactopyranoside with potassium benzoate for 120 h gave as the only isolable product the starting material.

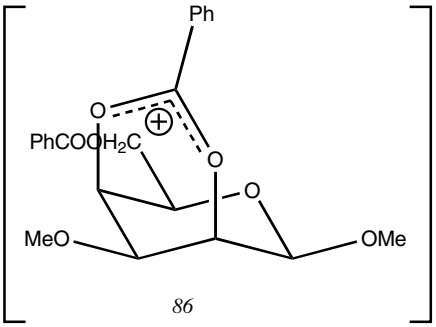
Furthermore, if the direct displacement did take place the *83* and *84* would not be the obtained products but the talo derivative *85* (Fig. 7.30). Therefore, the only possible explanation for the reaction of *81* and *82* with potassium benzoate is that the reaction involves the formation of the six-membered ring acyloxonium transition state intermediate *86* (Fig. 7.31), which is then converted into products *83* and *84* by the nucleophilic attack of benzoate at either the C4 or the C2 carbon atom.



85

Fig. 7.30

The observed higher susceptibility of the C4 carbon of the cyclic six-membered benzoyloxonium intermediate *86* (Fig. 7.31) to the nucleophilic attack is in a good agreement with the observed large difference in reactivity of the C2 mesylate of *81* and the C4 mesylate of *82* (120 h vs. 10 h) and is compatible with the postulated rationalization that the electropositive character of the α-carbon to the reacting carbon atom should decrease the rate of nucleophilic displacement if the amount of

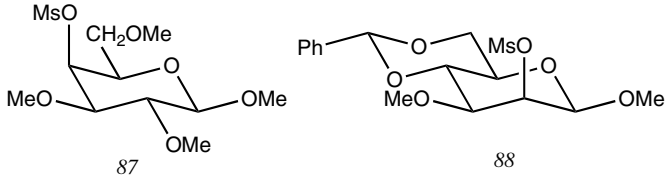


86

Fig. 7.31

positive charge on the reacting carbon atom in the transition state is greater than in the ground state [39].

This is also in a good agreement with previous observation [40] that direct nucleophilic displacement of C4 methanesulfonate of methyl 2,3,6-tri-*O*-methyl-4-*O*-methylsulfonyl-β-D-galactopyranoside *87* is ca. 2.7 times faster than the direct nucleophilic displacement of the C2 methylsulfonyl group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-methanesulfonyl-β-D-mannopyranoside *88* (Fig. 7.32).



87 *88*

Fig. 7.32

There are other functional groups that can act as neighboring groups in nucleophilic displacements. For example, a hydroxyl or an alkoxyl group, alkyl- or arylthio groups, acylamido group (carbonyl oxygen participation or nitrogen participation), dithiocarbamoyl group.

A very nice example for the participation of hydroxyl group in the acid-catalyzed hydrolysis of dimethyl acetal of D-glucose and D-galactose was reported by Capon and Thacker [41]. The rates of hydrolysis of both acetals were substantially higher than that of glyceraldehyde dimethyl acetal where no five-membered ring transition state can be visualized. The following mechanism has been proposed for the acid hydrolysis of these acetals (in Fig. 7.33 dimethyl D-glucose acetal is used).

The above reaction is better described as intramolecular displacement by hydroxyl group of a protonated methoxy group of an acetal than as neighboring group participation by a hydroxyl group. The rate of an unassisted, two-step mechanism would be slower, it would be independent of the configuration at the C4 and the product would be free sugar.

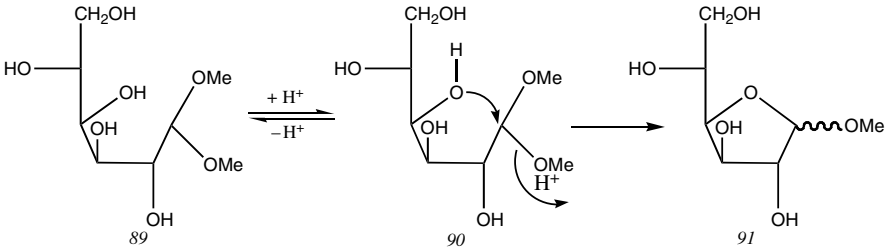


Fig. 7.33

2,3,5-tri-*O*-Benzyl-4-*O*-*p*-toluenesulfonyl-D-ribose dimethyl acetal *92* gives with tetrabutylammonium benzoate in *N*-methylpyrrolidinone the 2,3,5-tri-*O*-benzyl-4-*O*-methyl-L-lyxose hemiacetal benzoate [42] *95*. The formation of *95* could be explained by a nucleophilic displacement of the C4 tosylate by one of

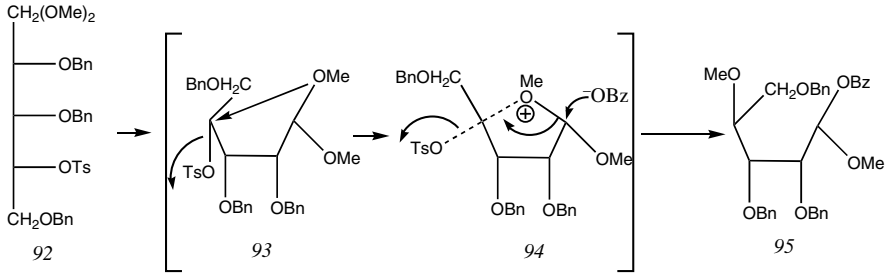


Fig. 7.34

the two methoxy groups of dimethyl acetal with formation of methoxycarbonium ion *94* which with benzoate anion then gives the L-lyxose derivative *95* (Fig. 7.34).

Similarly, 4-*O*-benzyl-1-*O*-*p*-toluenesulfonyl-1,4-pentanediol *96* undergoes a rapid solvolysis in ethanol to give 2-methyltetrahydrofuran, benzyl ethyl, and *p*-toluenesulfonic acid. The rate of the reaction and the products obtained clearly indicate anchimeric assistance from the benzyloxy group via a five-membered, cyclic, oxonium ion intermediate *97* [43] (Fig. 7.35).

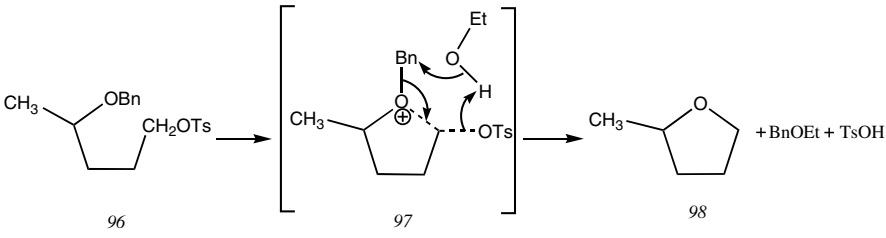


Fig. 7.35

2,3,4-tri-*O*-Benzyl-1,5-di-*O*-*p*-toluenesulfonyl-xylitol solvolyzed in ethanol [43] to give the 1,4-anhydro-2,3-di-*O*-benzyl-5-*O*-*p*-toluenesulfonyl-DL-xylitol *102* (Fig. 7.36). It should be noted that *99* is symmetrical molecule because it has a plane of symmetry passing through the C3 carbon. Consequently, if the C1 tosyl group is intramolecularly displaced, 1,4-anhydro-D-xylitol (*103*) is obtained, but if the C5 tosyl group is intramolecularly displaced the 1,4-anhydro-L-xylitol is obtained (not shown).

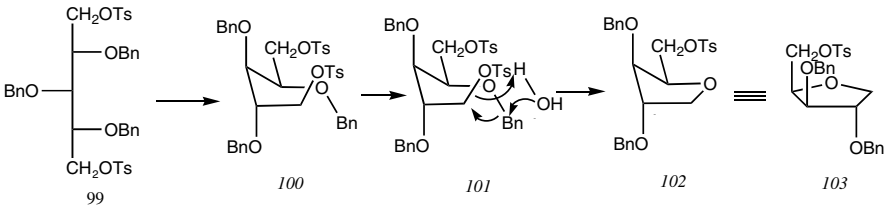


Fig. 7.36

2,3,4-tri-*O*-Benzyl-1,5-di-*O*-*p*-toluenesulfonyl derivatives of D-arabinitol and DL-ribitol underwent smooth solvolysis in ethanol, too. However, the rates of solvolysis of D-xylitol and D-arabinitol were about the same, but larger than that of D-ribitol possibly due to the presence of larger nonbonding interactions in the transition state analogous to *101*.

The acylamido group can participate in nucleophilic displacements with either the carbonyl oxygen or the amino-nitrogen of an amido group acting as a nucleophile.

An example for the first type of participation is described in Fig. 7.27. An example for the participation of nitrogen atom of an amido group is given below. Methyl 4,6-*O*-benzylidene-2-deoxy-2-benzamido-3-*O*-mesyl-α-D-altropyranoside *104* and methyl 4,6-*O*-benzylidene-3-deoxy-3-benzamido-2-*O*-mesyl-α-D-altropyranoside *106* give on treatment with basic reagents the D-manno- and D-allo-aziridines (*105* and *107*), respectively [44] (Fig. 7.37).

Aziridine formation by participation of nitrogen from various neighboring groups occurs only when the reaction conditions are sufficiently basic to convert the neighboring group into its anionic form and if the participating and the leaving groups are in the *trans* orientation (Fürst–Plattner rule [46]).

Treatment of methyl 4,6-*O*-benzylidene-3-deoxy-methyldithiocarbamoyl-2-*O*-mesyl-α-D-altropyranoside *108* (Fig. 7.38) with a hot methanolic solution of sodium methoxide gives the aziridine *109* [46].

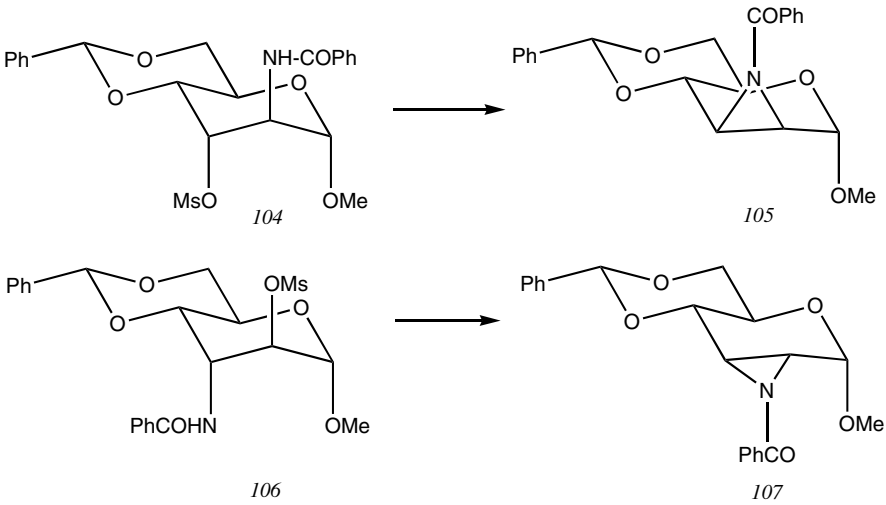


Fig. 7.37

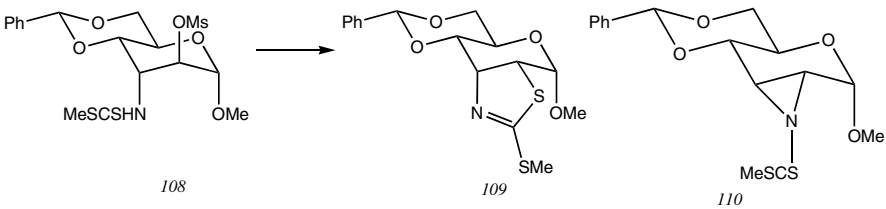


Fig. 7.38

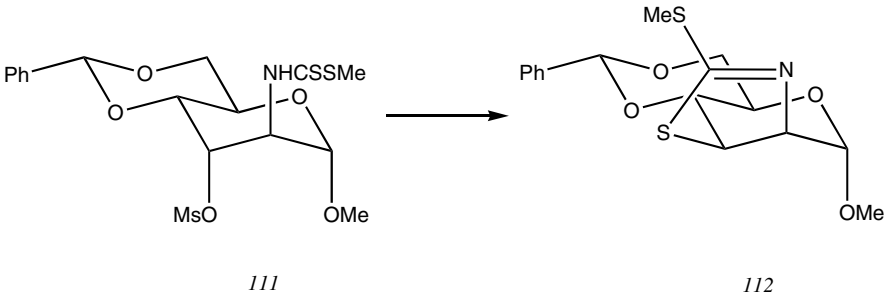


Fig. 7.39

If the 4,6-*O*-benzylidene-3-deoxy-3-methyldithiocarbamoyl-2-*O*-mesyl-α-D-altropyranoside *108* is refluxed in pyridine, the D-allo-thiazoline *109* [47] was obtained, instead of aziridine *110* (Fig. 7.39).

Heating of a pyridine solution of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-2-*N*[(methylthio)thiocarbonyl]-α-D-altropyranoside *111* at 80°C for 2.5 h gave the α-D-manno thiazoline *112* in 71% yield (Fig. 7.39), which can easily be converted to methyl 2-amino-4,6-*O*-benzylidene-3-thio-α-D-mannopyranoside [48].

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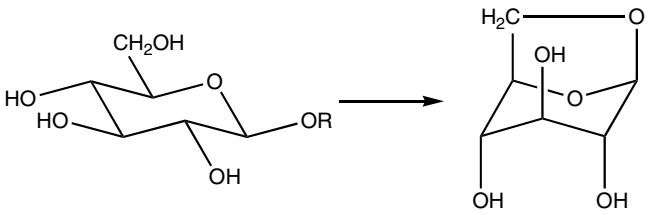
Chapter 8
Anhydrosugars

The monosaccharide derivatives obtained by intramolecular elimination of a molecule of water with simultaneous formation of a new three-, four-, five-, or six-membered heterocyclic ring are called anhydrosugars. The anhydrosugars are subdivided into two groups: (1) the anhydrosugars that involve the anomeric hydroxyl group in their formation resembling thus the intramolecular glycosides; they are called *glycosanes* and (2) the anhydrosugars that do not involve the anomeric hydroxyl group in their formation; they are simply called *anhydrosugar*s. There are several reviews of anhydrosugars [1–3].

The anhydrosugars are not found in the Nature. They are purely synthetic products, and their importance lies exclusively in their use in synthetic carbohydrate chemistry.

1,6-Anhydrosugars (Glycosanes)

In 1894 Tanret [4, 5] prepared the 1,6-anhydro-D-glucose by heating natural aromatic β-D-glucopyranosides (such as picein, salicin, and coniferin) with aqueous barium hydroxide, and he named the obtained product levoglucosan because it was levorotatory (Fig. 8.1).



1 *2*

Fig. 8.1

Levoglucosan is a nice crystalline compound that does not reduce Fehling's solution (aqueous solution of copper (II) sulfate, sodium hydroxide, and sodium

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_8,

potassium tartrate), indicating the absence of free hemiacetal group. Dilute mineral acids convert the levoglucosan back to D-glucose.

The 1,6-anhydrosugars of D-galactose (β-galactosan) and D-mannose (β-mannosane) were obtained in a similar way by treating the phenyl β-D-galacto- and mannopyranoside with a base.

The fact that the phenyl α-D-glucopyranoside is very resistant to alkaline hydrolysis even under drastic conditions suggested that the hydrolysis of β-D-glucoside takes place with the participation of the C-2-oxygen atom [6] (which is not possible for the α-D-anomer). According to this explanation, the β-phenoxy group is intramolecularly displaced by the neighboring alkoxy anion formed by deprotonation of the C-2 hydroxyl group by a base giving the 1,2-anhydro-α-D-glucopyranose *5* in the first step of alkaline hydrolysis of phenyl β-D-glucopyranoside. In the second step of reaction, the C6 alkoxy anion *6* formed by deprotonation of the C6 hydroxyl group opens the 1,2-oxirane ring of *5* by attacking the C1 carbon and giving the 1,6-anhydro-D-glucose as the final product (Fig. 8.2).

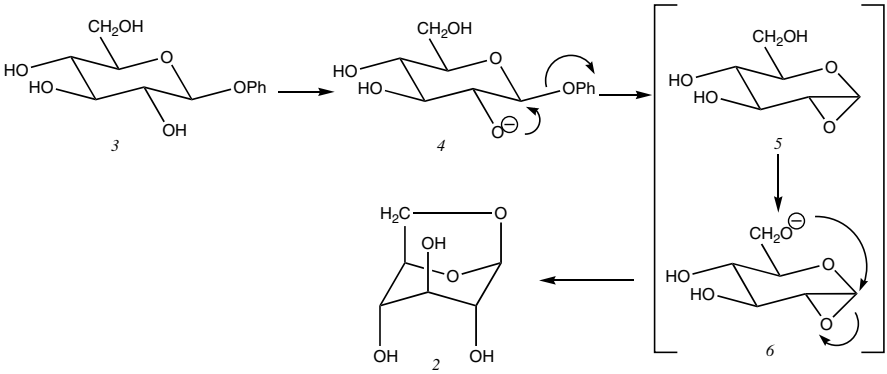


Fig. 8.2

This explanation is supported by the observation that 2-*O*-methyl-β-D-glucopyranoside [7] and 2,3-di-*O*-methyl-β-D-glucopyranoside [6] are highly resistant to alkaline hydrolysis, whereas phenyl 2,4,6-tri-*O*-acetyl-3-*O*-methyl-β-D-glucopyranoside is converted by ethanolic alkali to 1,6-anhydro-3-*O*-methyl-β-D-glucopyranose [7]. Finally, treatment of tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose with alkali gives 1,6-anhydro-β-D-glucopyranose *2* [7, 8].

The reaction mechanism has been discussed in detail by Coleman [6, 7], Lemieux [9], Ballou [10], Micheel [11], and Janson [12].

Over the years, a number of methods have been described for the synthesis of 1,6-anhydrosugars. Thus, for example, β-D-glucosan was synthesized by treating the tetraacetyl-α-D-glucopyranosyl bromide with triethylamine and then by reacting the obtained quaternary ammonium salt with barium hydroxide [13] (Fig. 8.3).

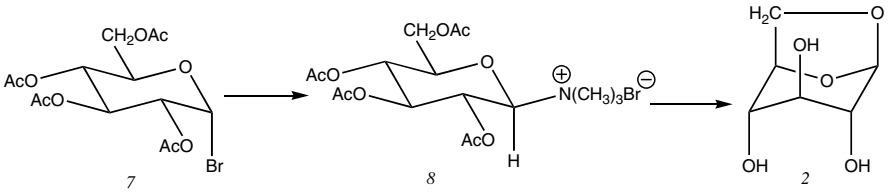


Fig. 8.3

This reaction was successfully used for the synthesis of galactosan [14] from acetobromo-α-D-galactose, though mannosan could not be synthesized in this way from acetobromo-α-D-mannose [15].

1,6-Anhydrosugars have been successfully prepared by action of strong bases on hexopyranosyl derivatives having a good C1 leaving group, such as fluorides [16, 17], bromides, azides [18–21], and tosylates [22] (Fig. 8.4).

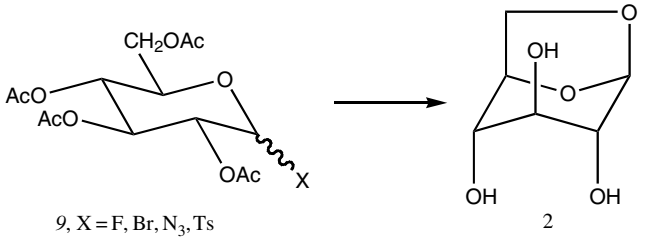


Fig. 8.4

Glycosans have also been prepared by the action of bases (or the ion-exchange resins in OH^- form) upon glycosyl azides [17].

1,6-Cyclization of 6-O-tritylated [23, 24] 4- or 6-O-benzylated [25, 26] hexopyranose 1-acetate in the presence of $SnCl_4$ or $TiCl_4$ (and other Lewis acids [23]) was another approach for the synthesis of 1,6-anhydrosugars (Fig. 8.5).

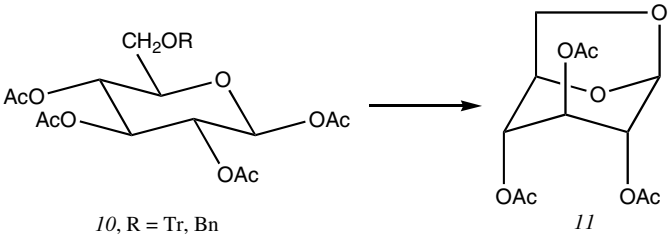
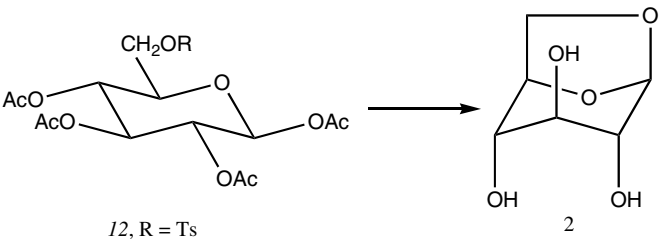


Fig. 8.5

The 1,6-anhydrosugars were also prepared by a base catalyzed cyclization of 6-*O*-tosyl hexopyranoses (for example D-glucose and D-mannose) having a free or

acetylated anomeric hydroxyl group [27–30] (Fig. 8.6). However, this method failed with D-galactose [31].



12, R = Ts 2

Fig. 8.6

There are other methods of preparation of 1,6-anhydrosugars; for a fuller discussion of this topic, the reader is referred to [1, 3, 31–33].

Figure 8.7 gives all 1,6-anhydro-β-D-hexopyranoses that were prepared: *allo* [34–36] (*13*), *altro* [37, 38] (*14*), *gluco* [23] (*2*), *manno* [27, 39–41] (*15*), *gulo* [42] (*16*), *ido* [43] (*17*), *galacto* [19] (*18*), and *talo* [44] (*19*).

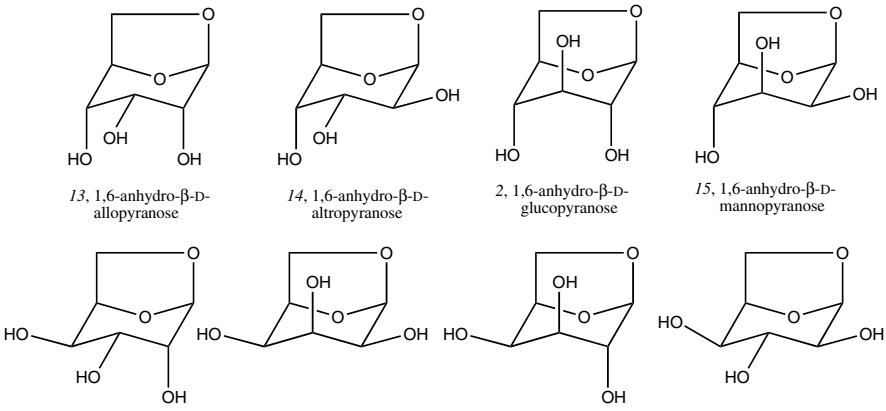


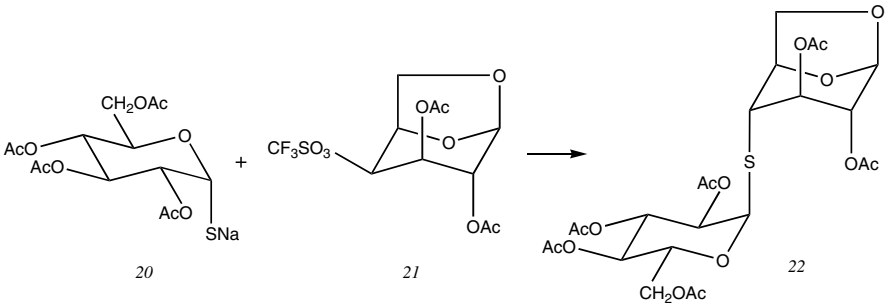
Fig. 8.7

The relative reactivity of individual hydroxyl groups of a number of 1,6-anhydrosugars toward sulfonylation with *p*-toluenesulfonyl chloride has been found to depend upon both the orientation of the hydroxyl group (axial or equatorial) and its position in the pyranose ring [45].

The axially oriented C3 hydroxyl group of a 1,6-anhydrohexopyranose is sterically more hindered than the axially oriented C2 and C4 hydroxyl groups and consequently the least reactive (*15* in Fig. 8.7). This permits selective modifications of axial or equatorial hydroxyl groups at the C2 or the C4 carbon, such as acylation (tosylation, benzoylation), alkylation (benzylation), oxidation [46, 47]. The

equatorially oriented hydroxyl groups of 1,6-anhydrosugars are generally, with a few exceptions [44, 48], more reactive than the axial ones.

Sulfonyloxy groups, both axial and equatorial, may undergo nucleophilic displacement with external or, via neighboring group participation, with internal nucleophiles, depending on their axial or equatorial orientation. Axial or equatorial C4 sulfonyloxy groups can be replaced with inversion of configuration. Thus, for example, the equatorial trifluoromethanesulfonate of 1,6-anhydro-β-D-galactopyranose *21* can be displaced with the sulfide anion of sodium salt of 1-thio-α-D-glucopyranose *20* to give the precursor *22* of thiomaltose in 61% yield [49] (Fig. 8.8).

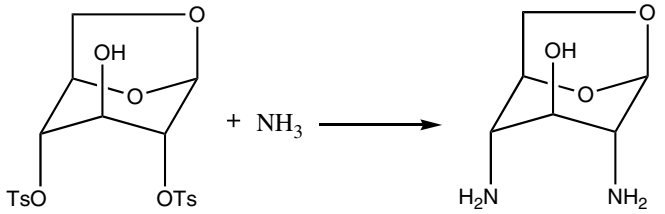


20 *21* *22*

Fig. 8.8

Similarly the S-linked chitobiose has been synthesized [50].

The ammonolysis of 1,6-anhydro-2,4-di-*O*-*p*-toluenesulfonyl-β-D glucopyranose *23* with methanolic ammonia at 0°C gave 1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-glucopyranose *24* together with unidentified monoamino derivatives [51] (Fig. 8.9).



23 *24*

Fig. 8.9

Direct displacement of the C2 and C4 tosyl groups can be excluded since the obtained product was not 1,6-anhydro-2,4-diamino-2,4-dideoxy-β-D-talopyranose as would be expected if the direct displacement took place because this would be accompanied with the inversion of configurations at the C2 and the C4 carbons. The only plausible explanation for the formation of 1,6-anhydro-2,4-diamino-2,

4-dideoxy-β-D-glucopyranose would be that the displacement of these two leaving groups took place via the participation of the C3 hydroxyl anion with formation of the corresponding epoxides as intermediates since the C3 hydroxyl group was left unprotected. The epoxide intermediates were then opened with ammonia (as shown in the Fig. 8.10) to give *24*. There are several reasons for this reaction pathway. First, the C3 hydroxyl group or better alkoxy anion is in the *trans*-diaxial orientation to leaving groups (tosylates) at the C2 and the C4 carbon. Second, intramolecular reactions are thermodynamically more favored than intermolecular reactions, and third the pentacovalent carbon in the SN_2 transition state would place the incoming nucleophile in close proximity with either the ring oxygen or the C6 carbon and thus will be the cause of severe stereoselectronic interactions.

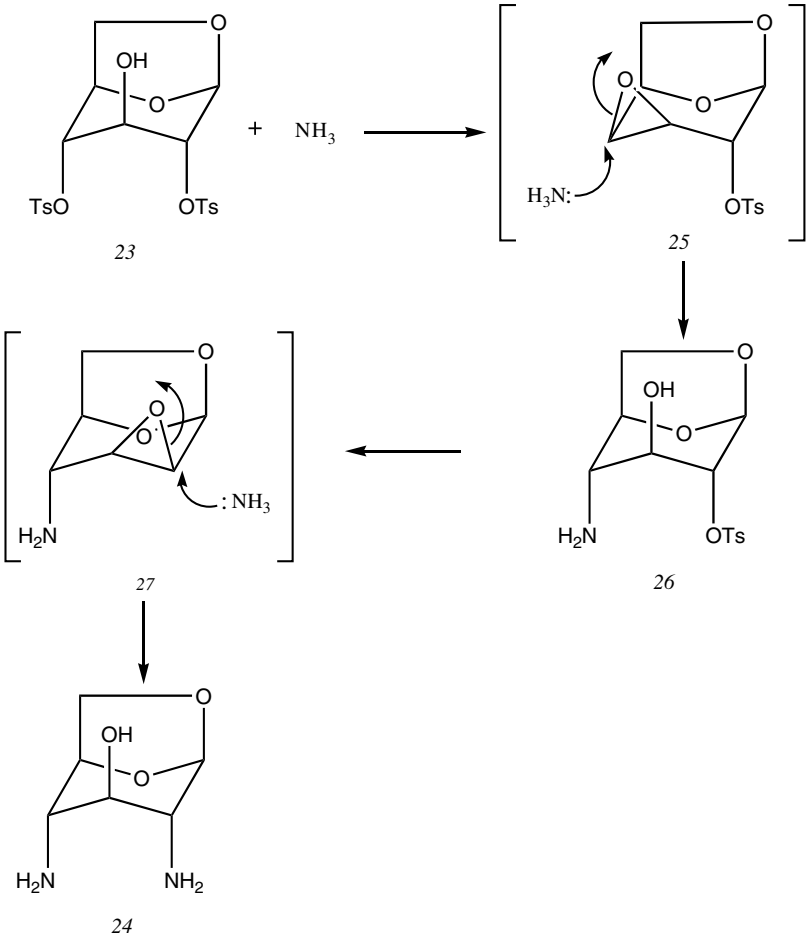
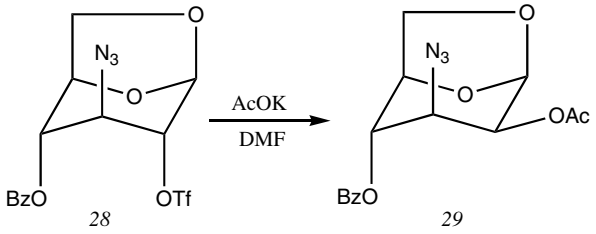


Fig. 8.10

The axial C2 trifluoromethanesulfonylgroup can be, however, directly displaced by acetate [52], under forcing conditions and in the presence of nonparticipating C3 axial azido group (Fig. 8.11).



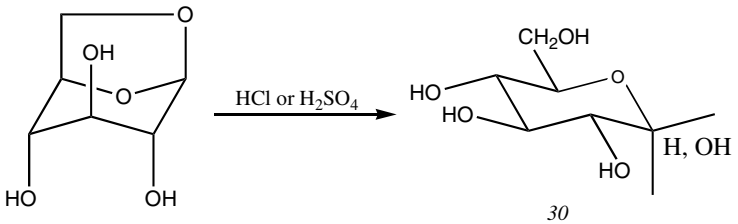
28 *29*

Fig. 8.11

The equatorial C2 trifluoromethanesulfonyl group can be displaced with inversion of configuration by azide [27, 53, 54] and fluoride ions [55].

The axial C3 sulfonyloxy group can be displaced by external nucleophile with inversion of configuration, providing that no axial and nonparticipating substituents are present at the C2 and C4 carbon [56].

The 1,6-anhydrosugars, being actually the intramolecular glycosides, are easily hydrolyzed by mineral acids, such as HCl or H_2SO_4 to their parent sugars (Fig. 8.12). The rate of hydrolysis is higher than with the ordinary glycosides [57, 58]. This increased rate of hydrolysis has been attributed to the ring strain, based on studies of other bicyclic acetals [59].



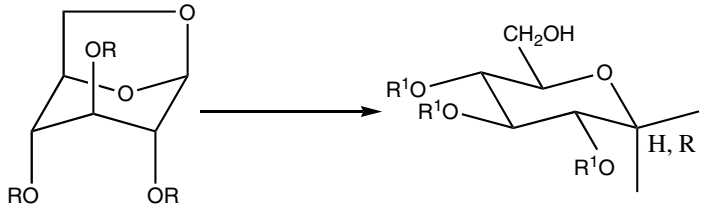
2 *30*

Fig. 8.12

Methanolic hydrogen chloride, at elevated temperatures, converts the 1,6-anhydrohexopyranoses (e.g., *2*) into a mixture of corresponding methyl glycosides *32* [14]. Similarly, ethanethiol and zinc chloride convert the 2,3,4-tri-*O*-benzyl-1,6-anhydro-D-glucopyranose *32* to ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-glucopyranoside *33* [60, 61] (Fig. 8.13).

Treatment of 2,3,4-tri-*O*-acetyl-levoglucosan *11* with hydrogen bromide in acetic acid [62–66], or with hydrogen bromide in acetic anhydride [66, 67] gave 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide *34* (Fig. 8.14).

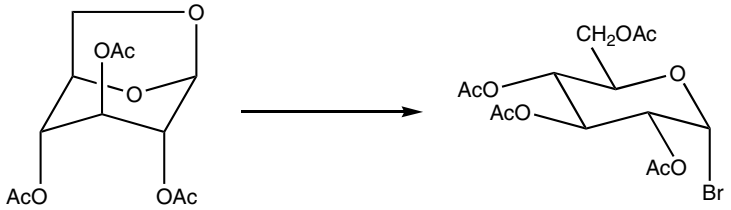
The 1,6-anhydro ring of levoglucosan triacetate can also be cleaved by titanium tetra-chloride [68–70] or tetrabromide [68, 69] in chloroform giving the 2,3,



2, R = H
31, R = Bn

32, R = OCH_3; R^1 = H
33, R = SC_2H_5; R^1 = Bn

Fig. 8.13



11 *34*

Fig. 8.14

4-tri-*O*-acetyl-α-D-glucopyranosyl chloride or bromide. Titanium tetrachloride is also effective with 1,6-anhydro-β-D-galactopyranose derivatives [71, 72], but not with 1,6-anhydro-β-D-manno-pyranose derivatives [73].

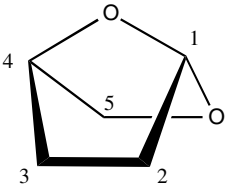
The 1,6-anhydrosugars are useful synthetic intermediates. First, the anomeric and the C6 carbon atom are simultaneously protected and thus excluded from reactions involving other hydroxyl groups of a pyranose ring. Second, there may be considerable differences in reactivities of the remaining hydroxyl groups of the pyranose ring. Third, the stereo-selectivity of nucleophilic addition on the C2, C3, and C4 carbon is considerably increased.

1,4-Anhydrosugars

This class of anhydrosugars (Fig. 8.15) can be regarded as 1,4-glycosans of glyco-pyranoses, or 1,5-glycosans of glycofuranoses. However, according to the Nomenclature of Carbohydrates (IUPAC–IUBMB) recommendations 1996 [74], they should be named 1,4-anhydropyranoses and not 1,5-anhydrofuranoses because the order of preference of ring size designator is pyranose > furanose.

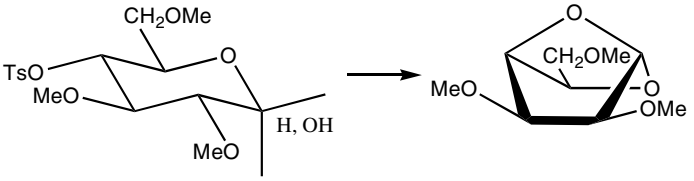
Treatment of 2,3,6-tri-*O*-methyl-4-*O*-*p*-toluenesulfonyl-D-glucose *37* with alkali gives 1,4-anhydro-2,3,6-tri-*O*-methyl-β-D-galactopyranose *38* [75](Fig. 8.16).

6-Azido-2,3-di-*O*-benzoyl-6-deoxy-4-*O*-methanesulfonyl-α-D-glucopyranosyl acetate *39* is converted to 6-azido-2,3-di-*O*-benzoyl-6-deoxy-1,4-anhydro-galactopyranose *44* [76–78]by treatment with sodium azide in *N*,*N*-dimethylamide



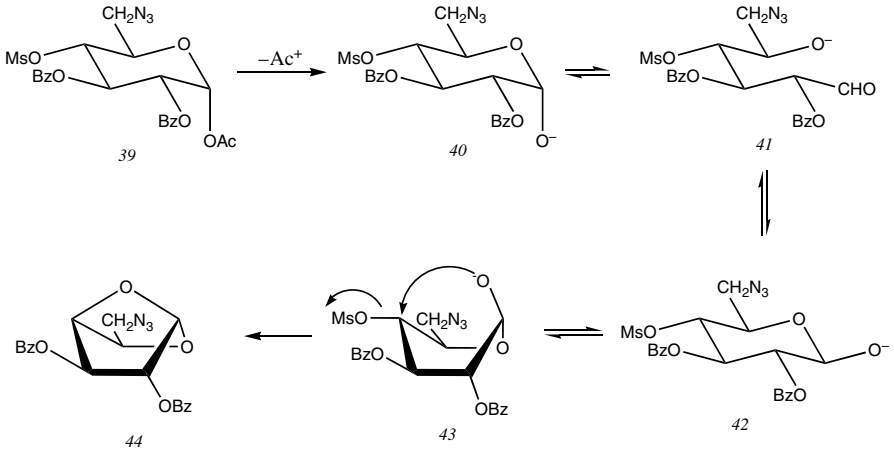
35, 1,4-glycopyranose, or
36, 1,5-glycofuranose

Fig. 8.15



37 *38*

Fig. 8.16

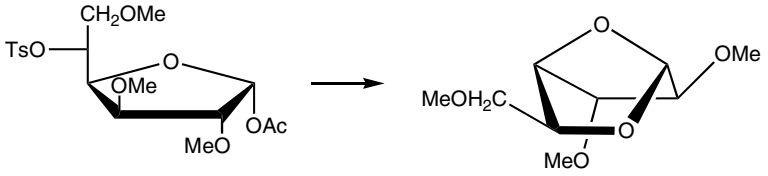


39 *40* *41* *44* *43* *42*

Fig. 8.17

at 140°C (Fig. 8.17). It was surprising that the 4-*O*-methanesulfonate group of *39* did not undergo direct S_N2 displacement with the azide ion, but the deacetylation with the formation of C1 alkoxy anion was the preferred reaction which subsequently led to the formation of a 1,4-anhydro-D-galactose derivative.

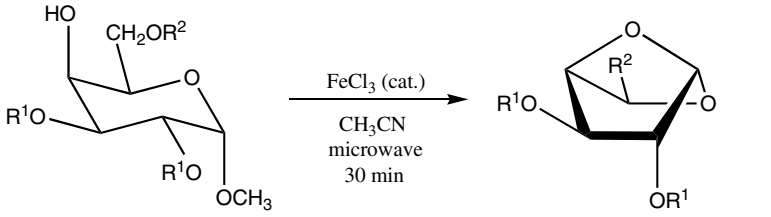
The action of alkali on 1-*O*-acetyl-2,3,6-tri-*O*-methyl-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *45* gave 1,4-anhydro-2,3,6-tri-*O*-methyl-α-L-idopyranose *46* [79] (Fig. 8.18).



45 *46*

Fig. 8.18

Various anhydrosugars have been investigated as monomer units for the synthesis of synthetic polysaccharides and oligosaccharides. Nokami [80] studied the scope and limitations of 1,4-anhydrosugars as glycofuranosyl building blocks for oligofuranoside synthesis. The oligofuranosides are interesting because they constitute a major part of mycolyl-arabinogalactan (AG), a component of the mycobacterial cell wall [81]. The several 1,4-galactopyranoses were prepared by microwave irradiation of acetonitrile solution of substituted methyl α-D-galactopyranosides in the presence of $FeCl_3$ as the catalyst [82] (Fig. 8.19).



47, $R^1 = R^2 = Bn$
48, $R^1 = Bz$; $R^2 = Bn$
49, $R^1 = Bn$; R^2 TBS

50, $R^1 = Bn$; $R^2 = CH_2OBn$ (51%)
51, $R^1 = Bz$; $R^2 = CH_2OBn$ (12%)
52, $R^1 = Bn$; $R^2 = CH_2OTBS$ (25%)

Fig. 8.19

It is interesting that starting galactopyranosides are consumed within 30 min by microwave irradiation, while the same reaction takes several days by conventional heating with comparable yields. As can be seen, the yields are generally poor. As far as the usefulness of 1,4-anhydrosugars as glycofuranosyl building blocks for oligofuranoside synthesis, the results presented are too preliminary and will not be described.

1,2-Anhydrosugars (Brigl's Anhydrides)

The 1,2-anhydrosugars are synthetically very important and useful because they can be easily converted to glycosides or di-, tri-, etc., saccharides because the

1,2-epoxy ring is very reactive and always opens with the attack of a nucleophile at the anomeric (C1) carbon. The configuration of the obtained glycosidic bond is determined by the configuration of the epoxide ring.

The 1,2-anhydrosugars were first prepared by Brigl [83] from penta-*O*-acetyl-β-D-gluco-pyranose as shown in Fig. 8.20. Treatment of penta-*O*-acetyl-β-D-glucopyranose *53* with phosphorus pentachloride gave 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride *54* which on ammonolysis in ether at 0°C gave 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride 55. Further treatment of *55* with ammonia converts *55* to 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose *56*.

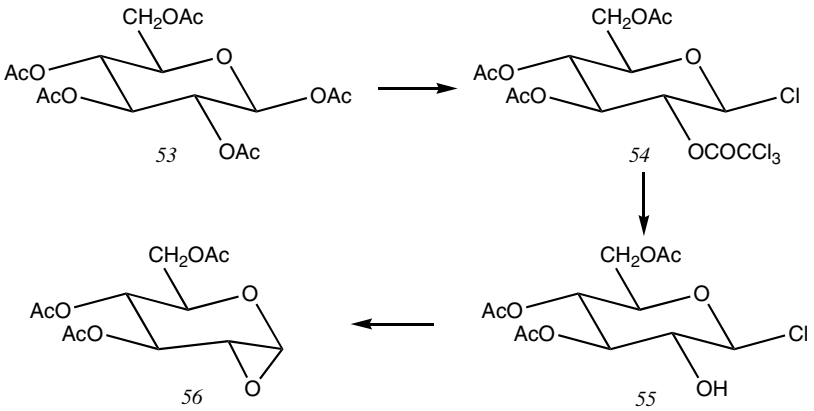


Fig. 8.20

Lemieux and Huber [84, 85] used 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose *57* for the first chemical synthesis of sucrose *59*. Thus heating of *56* with 1,3,4,6-tetra-*O*-acetyl-D-fructofuranose *58* (Fig. 8.21) at 100°C in a sealed glass tube for 104 h gave sucrose derivative in 5.5% yield. The mechanism of this "abnormal" epoxide ring opening to form α-D-glucopyranoside cannot be predicted with certainty, but Lemieux considered as the most plausible route the one which involves the participation of the C6 acetate in the first stage of the reaction to yield the 1,2-diaxial carboxonium ion *57* because the C6-oxygen atom is certainly suitably positioned for such a participation. Hickinbottom et al. [86, 87] have observed that 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose *56* rapidly reacts with methanol at room temperature giving the corresponding methyl β-D-glucoside excluding thus the participation of the C6 acetoxy group as proposed by Lemieux and Huber [84, 85] for the participation of the C6 acetate. However, heating of *55* with phenol at 100°C for 20 h gives exclusively the corresponding phenyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside which is in agreement with Lemieux and Huber [84, 85] proposal for the participation of the C6 acetate. Hardegger and Pascual [88] have reported that the reaction of *56* with isopropanol (16 h at

60°C), benzylalcohol (16 h at 110°C), or *tert*-butyl alcohol (16 h at 60°C) gives, in high yield, the corresponding β-glucosides, excluding thus the participation of the C6 acetoxy group. However, cholesterol (16 h at 120°C) gave, in poor yield, the corresponding α-glucoside again in agreement with the Lemieux and Huber [84, 85] proposal for the participation of the C6 acetate. Finally, the oxygen atom of the C6 acetate group that acts as the nucleophile in Lemieux mechanism is not the carbonyl oxygen but the alkoxy oxygen of the acetate that is not very nucleophilic. The formation of the intermediate *57* thus must be considered not proven.

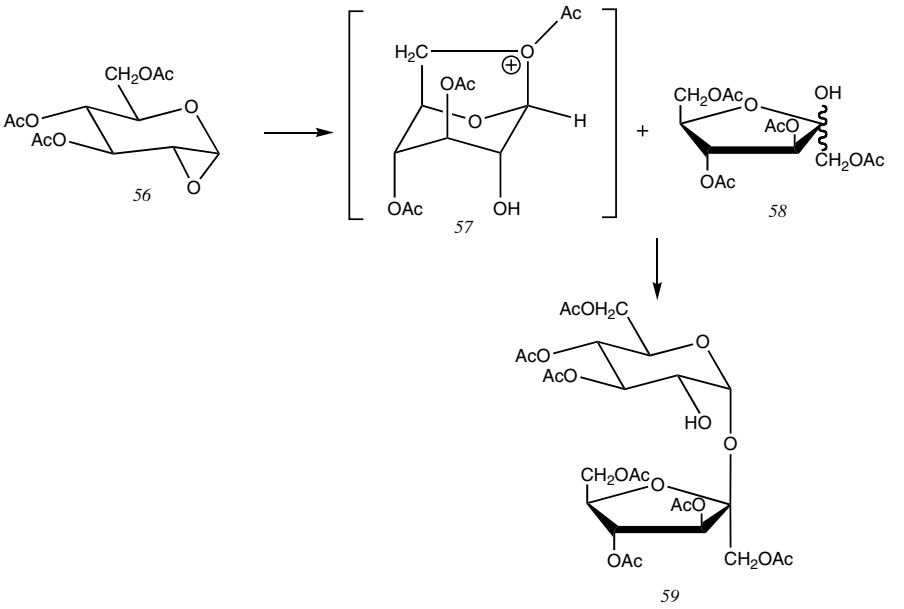


Fig. 8.21

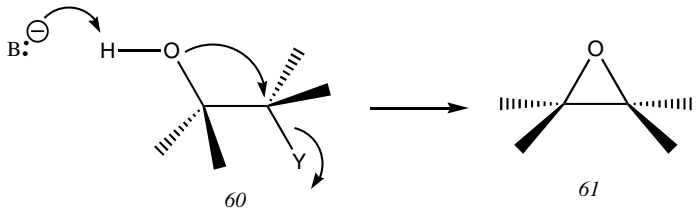
As already stated, Brigl's anhydrides are extremely reactive. Nucleophiles open them by attacking exclusively the anomeric carbon. In case of 3,4,6-tri-*O*-acetyl-1,2-anhydro-α-D-glucopyranose *56*, the Fürst–Plattner rule would be violated if the anomeric hydroxyl group of 1,3,4,6-tetra-*O*-acetyl-D-fructose directly attacked the 1,2-epoxide ring forming the β-glycosidic bond. However, the opening of the 1,2-epoxide ring of *56* takes place by the attack of the C6 oxygen on the anomeric carbon giving the five-membered glucosan *57* as an intermediate, which reaction does not violate the Fürst–Plattner rule; the anomeric hydroxyl group of 1,3,4,6-tetra-*O*-acetyl-D-fructose then opens the acetylium-1,6-anhydro ring of *57* to give the α-glycosidic bond.

Anhydrosugars Not Involving the Anomeric Carbon

Epoxides or Oxiranes

Oxiranes (epoxides) are another synthetically important group of anhydrosugars. They are very valuable intermediates for the synthesis of a wide variety of carbohydrate derivatives.

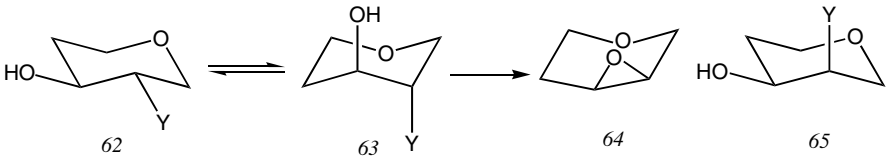
The common strategy employed for the synthesis of this class of anhydrosugars is that all hydroxyl groups of a monosaccharide, except the two hydroxyl groups that are involved in making of the epoxide, must be blocked. Then one of these two hydroxyl groups is derivatized with a good leaving group and the other is left free. Treatment with alkali initiates the intramolecular nucleophilic displacement (S_N2) with the inversion of the configuration at the carbon bearing the leaving group, as shown in Fig. 8.22.



60 *61*

Fig. 8.22

Leaving group Y is most often sulfonic ester, such as *p*-toluenesulfonate or methanesulfonate, but it can also be a halogen (bromide or iodide), sulfate, nitrate, diazonium group, etc. The formation of an epoxide on a pyranoid ring obeys strict stereochemical requirements, i.e., the two reacting groups must be in the antiparallel *trans*-diaxial orientation relative to each other, as shown in Fig. 8.23 (*63*) but not in a *gauche* orientation such as *trans*-diequatorial *62* or in *cis* axial–equatorial *65* orientation.



62 *63* *64* *65*

Fig. 8.23

It has been shown in steroid field that where this requirement is fulfilled without conformational change, the rate of epoxide formation is considerably greater than in cases where a change to a less favorable conformation is required for this condition to be fulfilled [89]. Thus, for example, 1,6-anhydro-2-*O*-mesyl-β-D-galactopyranose *66* and 1,6-anhydro-4-*O*-tosyl-β-D-mannopyranose *68* are readily converted to

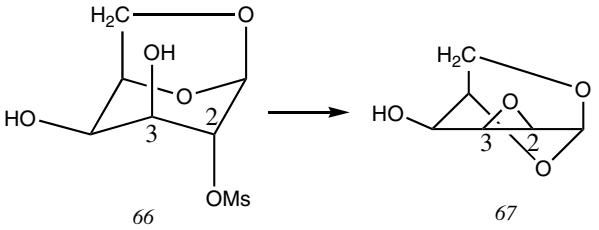


Fig. 8.24

2,3- and 3,4-*talo*-epoxides, *67* and *69*, respectively, since in both of them the hydroxyl and sulfonyloxy groups are in the required coplanar *trans*-diaxial orientation [90, 91] (Figs. 8.24 and 8.25).

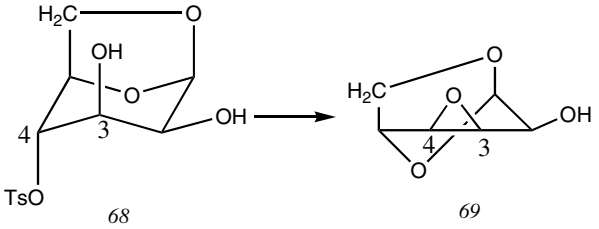


Fig. 8.25

However, in methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside *70* (Fig. 8.26) or methyl 4,6-*O*-benzylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside *73* (Fig. 8.27), the tosyl and the hydroxyl

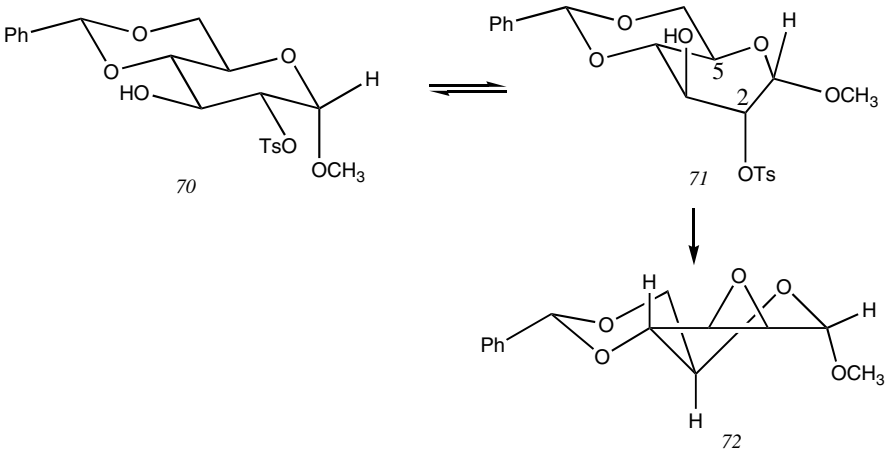


Fig. 8.26

groups are oriented *trans*-diequatorially relative to each other in the preferred $^4C_1$ conformation. In order for these groups to adopt the coplanar *trans*-diaxial arrangement necessary for epoxide formation, the conformation of the pyranoid ring must be changed from $^4C_1$ to $B_{2,5}$ (*71* in Fig. 8.26, or *74* in Fig. 8.27).

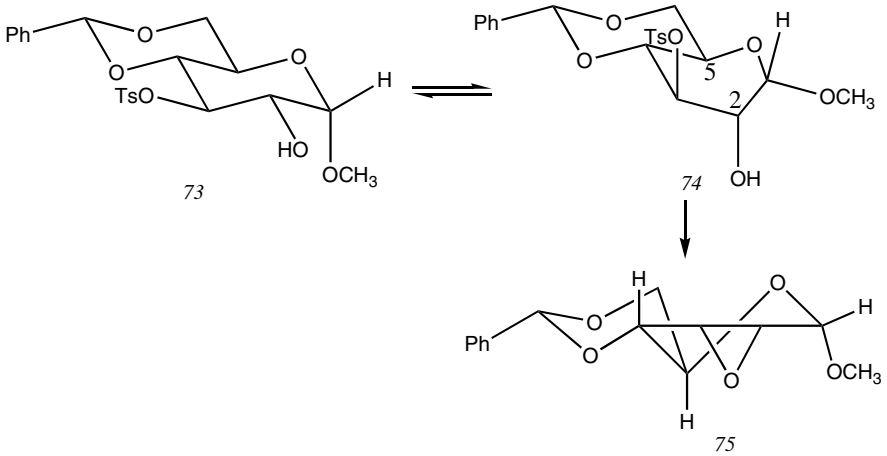


Fig. 8.27

The $^4C_1 \rightarrow B_{2,5}$ conformational change of the α-anomer requires that the 2-tosyloxy and 1-methoxy groups pass each other giving rise to a strong stereoelectronic interaction (Fig. 8.28). This stereoelectronic interaction has been used to explain why the β-anomer of methyl-4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-D-galactopyranoside is more readily converted to the 2,3-oxirane than the α-anomer.

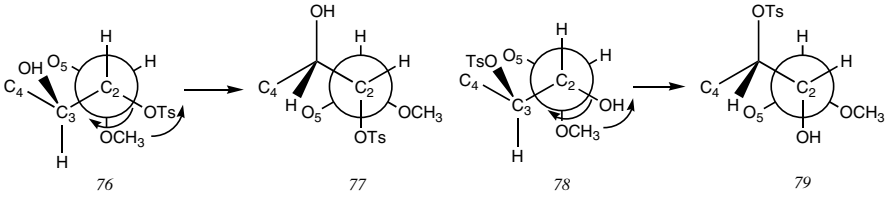


Fig. 8.28

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-toluenesulfonyl-D-hexopyranosides serve as convenient precursors of 2,3-epoxides. Thus α-D-glucopyranoside *80* gives with sodium methoxide exclusively the 2,3-*allo*-epoxide *81* [92], whereas the α-D-altropyranoside *82* gives 2,3-*manno*-epoxide *83* [93] (Fig. 8.29)

It has been suggested that these reactions proceed by initial base hydrolysis of the more reactive 2-*O*-sulfonate followed by ring epoxide closure [94]. This explanation is supported by the isolation of some methyl 4,6-*O*-benzylidene-3-*O*-*p*-toluenesulfonyl-α-D-gluco-pyranoside from ditosylate by a mild treatment

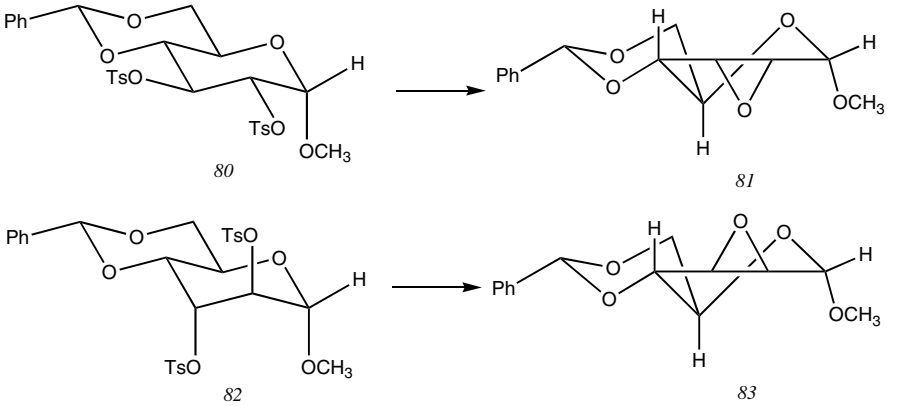


Fig. 8.29

with alkali [95]. This explanation is, however, not applicable to methyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside *84*, since the reaction with alkali gives the corresponding *talo*-epoxide *86* (Fig. 8.30), suggesting that the 3-*O*-*p*-toluenesulfonate was hydrolyzed by a base [96] rather than 2-*O*-tosylate. However, the α-anomer *86* gave the *gulo*-epoxide *88* together with small amount of *talo*-epoxide *88* [97].

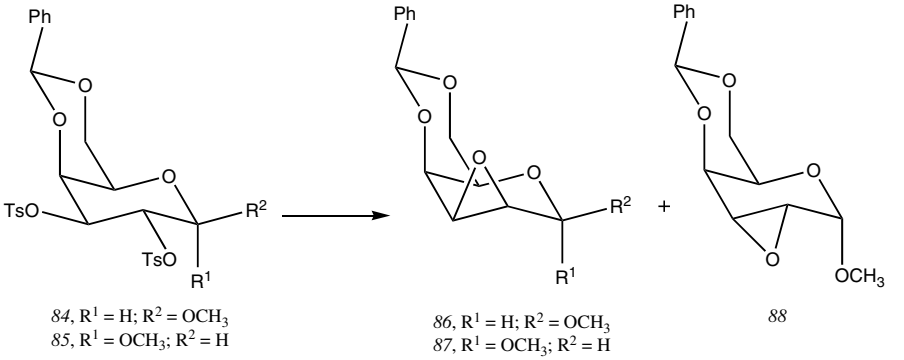


Fig. 8.30

It is interesting that 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *89* with alkali does not give the 5,6-epoxide *90* but the 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *91* [98] (Fig. 8.31).

The opening of epoxide rings is highly stereoselective, making thus epoxides very versatile and valuable synthetic intermediates in synthetic carbohydrate chemistry (for a general review of epoxides see [99]; for a review of the chemistry of sugar epoxides see [100]).

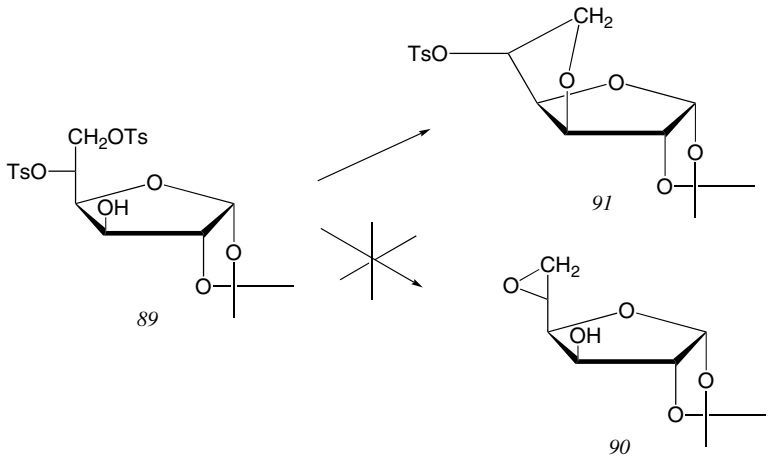


Fig. 8.31

The epoxide rings can be opened by many nucleophiles under both acidic and basic conditions as shown in Fig. 8.32, where N = HO^-, RO^-, NH_2, H^-, Cl^-, Br^-, N_3^-, RS^-, etc.

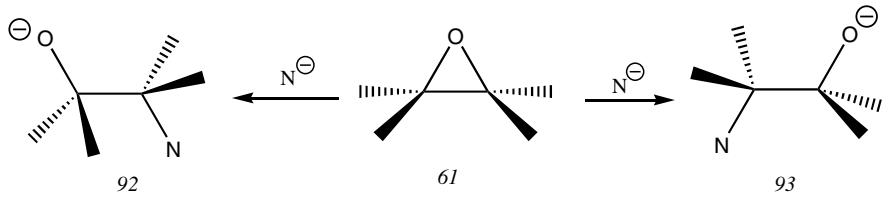


Fig. 8.32

The chiral epoxides, such as those found in carbohydrates, although able to theoretically give two products, in practice, one product is predominantly obtained depending on the site of the nucleophile attack (Fig. 8.32).

When the epoxide ring occupies the terminal position, the nucleophilic attack takes place almost exclusively at the terminal (primary) carbon (for steric reasons). Consequently the 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose *94* is a good intermediate for the synthesis of various six-substituted glucose derivatives *95* (Fig. 8.33).

All epoxide rings having both carbon atoms in their ring structures secondary (the epoxide ring is fused to a pyranoid ring), open with the inversion of configuration at the carbon attacked by a nucleophile, whereas the epoxides containing primary and secondary carbon atom in their structure are opened at the primary carbon and hence without inversion of the configuration of the chiral (secondary) carbon. When the epoxide ring is fused to a pyranoid ring with a rigid conformation,

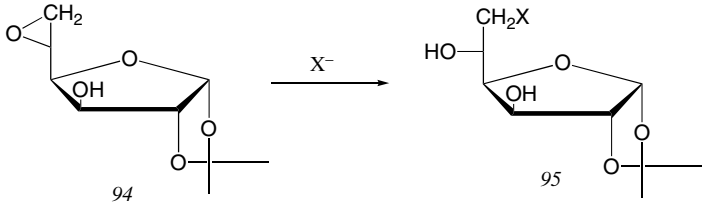


Fig. 8.33

as is the case in *trans*-fused 4,6-*O*-benzylidene-hexopyranosides, or the 1,6-anhydrohexopyranoses, the ring opening occurs with predominant formation of *trans*-diaxial products [101]. For example, 1,6:2,3-dianhydro-β-D-talopyranose *96* and 1,6:3,4-dianhydro-β-D-talopyranose *98* give 1,6-anhydro-2-substituted galactopyranose *98* and 1,6-anhydro-β-D-mannopyranose *99*, respectively, as predominant products [90] (Fig. 8.34).

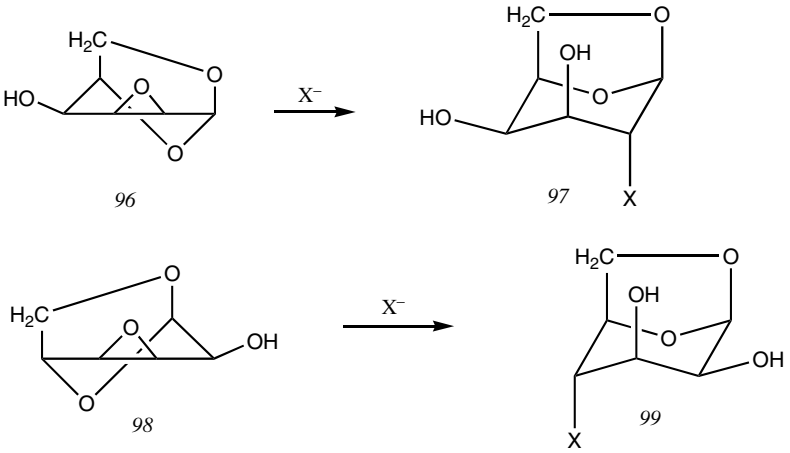


Fig. 8.34

The *trans*-diequatorial products are in both cases obtained in yields under 10%. Similarly, the epoxide rings of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside *100* and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside *102* are opened with nucleophiles again diaxially giving the corresponding C3- or C2-substituted altropyranoside derivatives, *101* or *103*, respectively (Fig. 8.35).

This approach has been used for the synthesis of a wide variety of carbohydrate derivatives. Thus, by using azide, hydrazine, ammonia, and primary or secondary amines as nucleophiles many aminosugars can be synthesized.

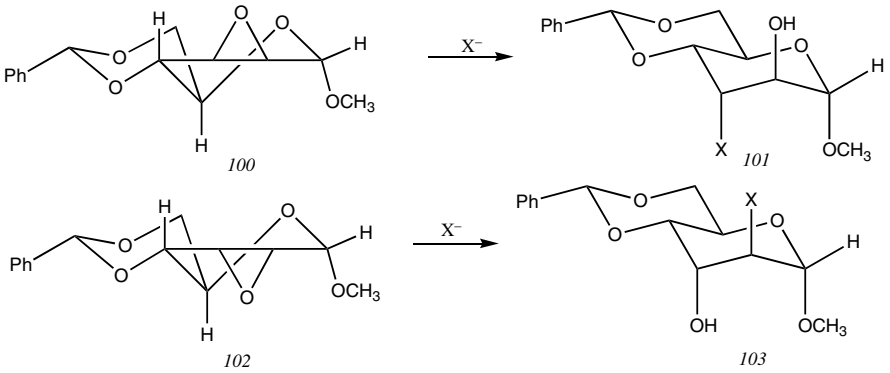


Fig. 8.35

Reduction of epoxides with lithium aluminum hydride affords deoxy-sugar derivatives in regioselective manner. However, the catalytic hydrogenation converts the epoxides to deoxy-sugars, but with much less regioselectivity.

Sodium hydrogen sulfide, sodium thiocarboxylates, sodium alkanethiolate, thiocyanates, etc., give thio-sugars.

Grignard reagents [102, 103] and magnesium halides [104] react with epoxides to give halogeno derivatives.

Diethylylmagnesium [105], sodium cyanide [106], and sodium salt of diethylmalonate [107] gave the corresponding branched-chain sugar (methyl 2-C-carbethoxymethyl-2-deoxy-α-D-altropyranoside).

The nucleophilic opening of 2,3- and 3,4-epoxides on flexible pyranoid rings has been extensively studied. Thus, for example, the epoxide ring of methyl 3,4-anhydro-β-D-galactopyranoside *105* has been opened with the following nucleophiles: H_2S [108], MeSH [109], $LiAlH_4$ [110], and CH_3O^- [111, 112], giving in all cases the 3-substituted D-gulo product (Fig. 8.36).

The methyl 3,4-anhydro-β-D-galactopyranoside can exist in two conformations: *104a* and *104b* (Fig. 8.36). The conformation *104a* is obviously more stable than conformation *104b* since *104b* is destabilized by a strong *syn*–diaxial interaction between the axial C1 methoxy group and the axial C5 hydroxymethyl group.

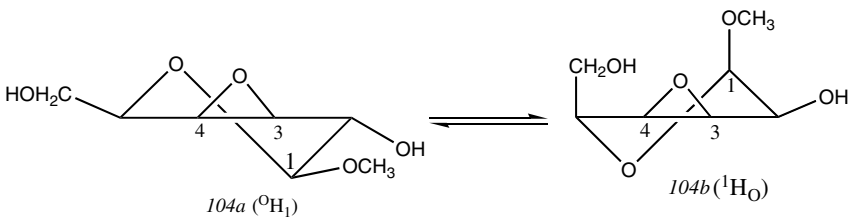


Fig. 8.36

Hence the methyl 3,4-anhydro-β-D-galactopyranoside will be attacked by a nucleophile at the C3 carbon giving the 3-substituted D-gulo product (Fig. 8.37).

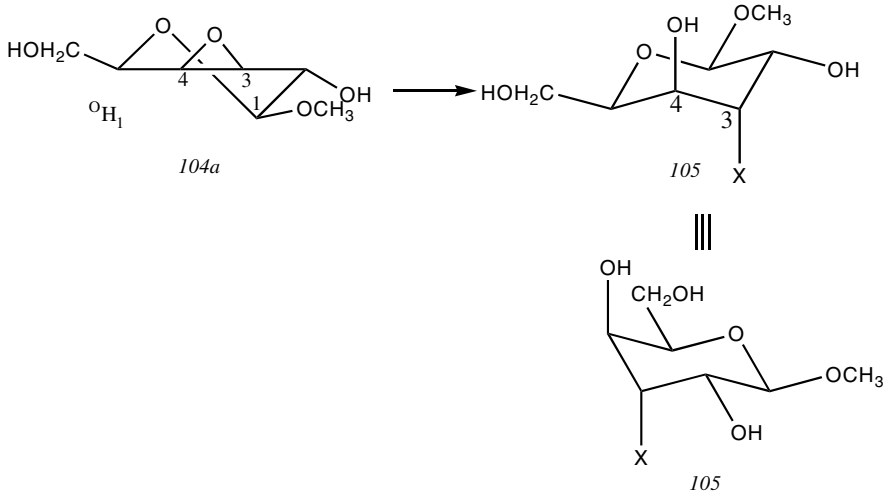


Fig. 8.37

Similarly, methyl 3,4-anhydro-β-L-ribopyranoside can also exist in two conformations: *106a* and *106b* (Fig. 8.38). The conformation *106a* is obviously more stable than the conformation *106b* because the former has fewer nonbonding steric interactions.

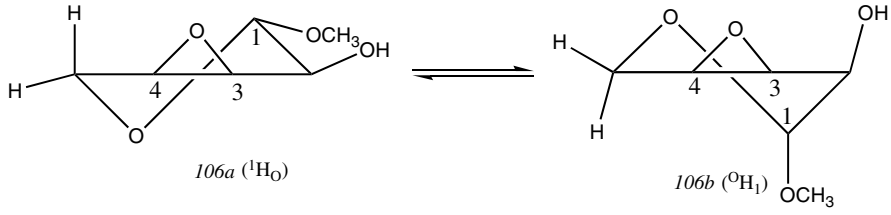
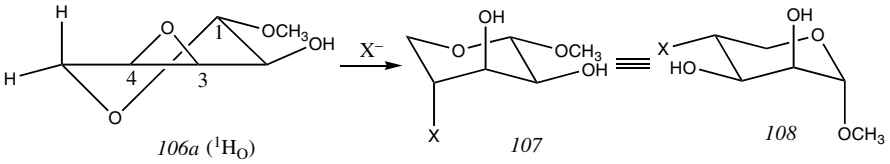


Fig. 8.38

Consequently, the reaction of methyl 3,4-anhydro-β-L-ribopyranoside *106* with hydrogen bromide [113] or various amines [108] opens the 3,4-epoxide ring exclusively at the C4 carbon atom, giving methyl 4-substituted-4-deoxy-α-D-lyxosides (Fig. 8.39).



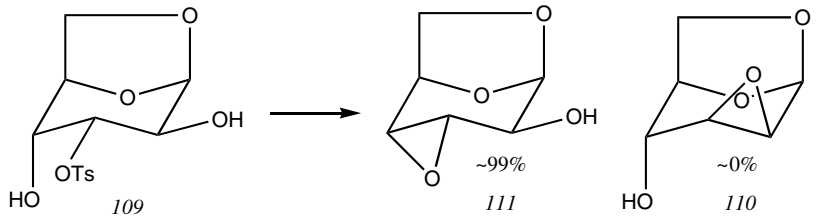
106a (^1H_O) *107* *108*

Fig. 8.39

Rearrangements of Anhydrosugars

Epoxide Migration

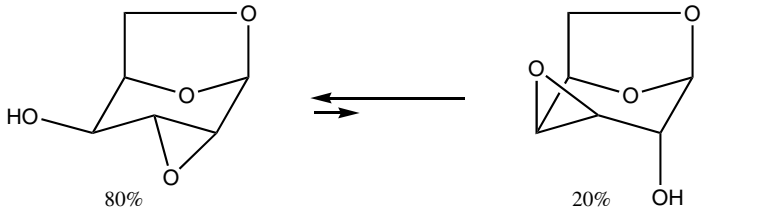
Treatment of 1,6-anhydro-3-*O*-*p*-toluenesulfonyl-β-D-altropyranose *109* with a base gave, instead of 1,6:2,3-dianhydro-β-D-mannopyranose *110*, the 1,6:3,4-dianhydro-β-D-altropyranose *111* (Fig. 8.40). Obviously, the C3 tosylate of *109* cannot be displaced by the C4 alkoxy anion because these two groups are *cis* oriented. So



109 *111* *110*

Fig. 8.40

the formation of *111* can only be explained by postulating the "migration of epoxide group," i.e., the first reaction product is *110* because the C2 hydroxyl and the C3 tosyl groups of *109* are *trans* oriented. The 2,3-manno derivative *110* rearranges



112, 1,6:2,3-di-anhydro-β-D-gulopyranose

113, 1,6:3,4-dianhydro-β-D-galactopyranose

Fig. 8.41

then to the more stable 3,4-altro derivative *111* having the C2 hydroxyl group equatorially oriented [114, 115]. An independent study has shown that the *altro* isomer preponderates in this equilibrium [116]. It has also been shown [117] that

in the equilibrium between 1,6:2,3-dianhydro-β-D-gulopyranose *112* and 1,6:3,4-dianhydro-β-D-galactopyranose *113*, the *gulo* isomer *112* (equatorial hydroxyl group) preponderates (Fig. 8.41).

The situation is obviously more complex with flexible oxirane derivatives, as was shown by comparison of equilibrium mixtures obtained after epoxide migration of different types of anhydro hexopyranoses [118–120], their 6-deoxy derivatives [121], and branched-chain hexoses [121, 122] (Fig. 8.42).

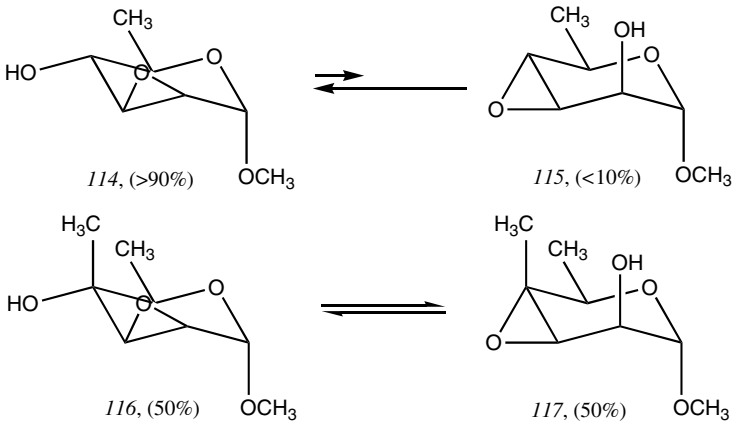


Fig. 8.42

Other Isomerizations of Epoxides

Treatment of methyl 2,3-anhydro-β-D-ribofuranoside (*118*) with 1 N sodium hydroxide at 100°C for 18 h gave methyl 3,5-anhydro-β-D-xylofuranoside *119* in 57% yield [123, 124] (Fig. 8.43).

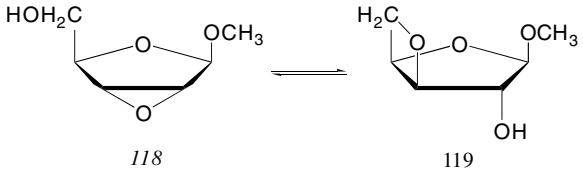


Fig. 8.43

However, treatment of methyl 2,3-anhydro-α-D-ribofuranoside *120* with sodium methoxide gave methyl 2-*O*-methyl-α-D-arabinofuranoside as the major product [123] (Fig. 8.44).

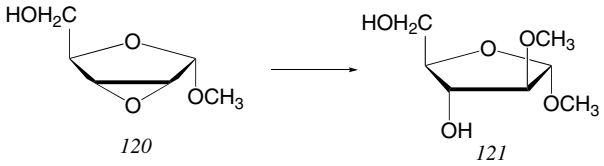


Fig. 8.44

Acid hydrolysis of methyl 2,3-anhydro-α-D-gulopyranoside *122* gave as the major product 3,6-anhydro-D-galactose *123* (Fig. 8.45).

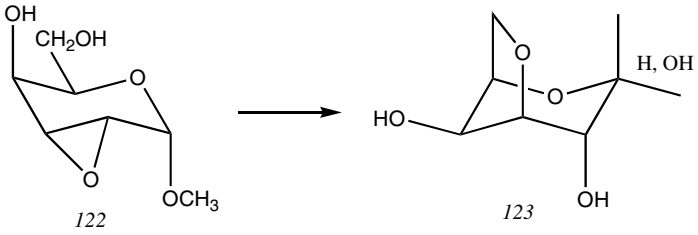


Fig. 8.45

The reaction may follow two courses: (A) the 2,3-anhydro ring is opened first giving initially the methyl 3,6-anhydro-α-D-galactopyranoside *124* and then the hydrolysis of glycosidic bond takes place, giving *123,* or (B) the glycosidic bond may be hydrolyzed first giving the 2,3-anhydro-D-gulose, which is subsequently converted to 3,6-anhydro-D-galactose *123* (Fig. 8.46).

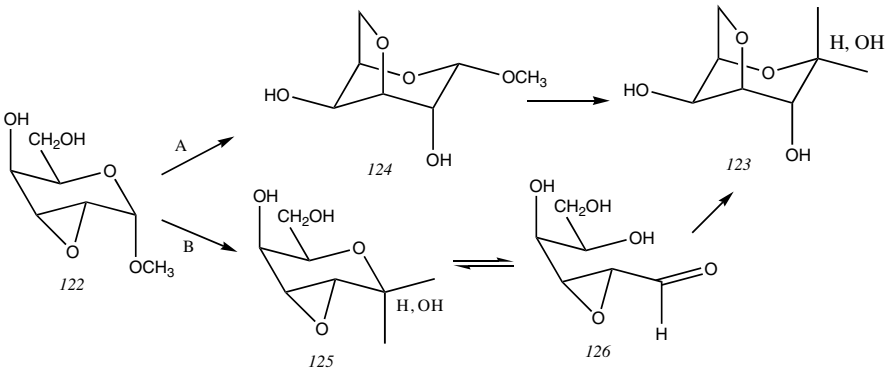


Fig. 8.46

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Chapter 9
Amino Sugars

Amino sugars are monosaccharides in which one or more hydroxyl groups of a sugar chain is replaced by an amino group. The amino group(s) can be free or derivatized (it is usually acylated, but it can be alkylated, too).

The amino sugars are widespread in nature. They are building blocks of many complex saccharides such as heparin, hyaluronate, and keratan sulfate (*N*-acetylglucosamine *1*), chondroitin 4- and 6-sulfate, and dermatan sulfate (*N*-acetylgalactosamine *2*). They are found in glycoconjugates of both vertebrates and invertebrates, such as glycosaminoglycans (vertebrates) and peptidoglycans (bacteria) (*N*-acetylglucosamine *1*), glycoproteins (sialic acid *3*, structure determined by Gottschalk [1]) as well as in many natural products such as antibiotics: *streptomycin* (2-deoxy-2-methylamino-L-glucopyranoside, *4*), *erythromycin* (*desosamine* – 3,4,6-trideoxy-3-dimethylamino-D- *xylo*-hexopyranose *5*, structure determined by Bolton et al. [2, 3]), *nystatin* (*mycosamine 6*, structure determined by Walters et al. [4, 5] and the stereochemistry by von Saltza et al. [6, 7]), neomycins [*neosamine B* or *paromose* – 2,6-diamino-2,6-dideoxy-L-idose, *7* from neomycin B, structure determined by Haskell et al. [8]], *neosamine* **C** – 2,6-diamino-2,6-dideoxy-D-glucose, *8* from neomycin C, *muramic acid*, *9* [9, 10] (Fig. 9.1).

Due to their biological importance, synthesis of amino sugars has attracted a great attention of carbohydrate chemists over the years. There are several strategies employed in the synthesis of amino sugars, as for example, the ammonolysis of sugar epoxides (oxiranes), direct displacement of alkyl or arylsulfonates, or halides by nitrogen nucleophiles, such as ammonia, hydrazine, or azide (in two latter cases followed by reduction), and reduction of oximes obtained from aldosuloses.

Ammonolysis of Oxiranes

The opening of an epoxide ring always takes place in such a way that the amino and the alcohol group in the product are *trans* oriented (Fürst–Plattner rule [11]) (Fig. 9.2).

The proportion of each isomer (*11* or *12*) will depend on the structure and preferred conformation of parent sugar epoxide (i.e., on steric interactions between

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_9,

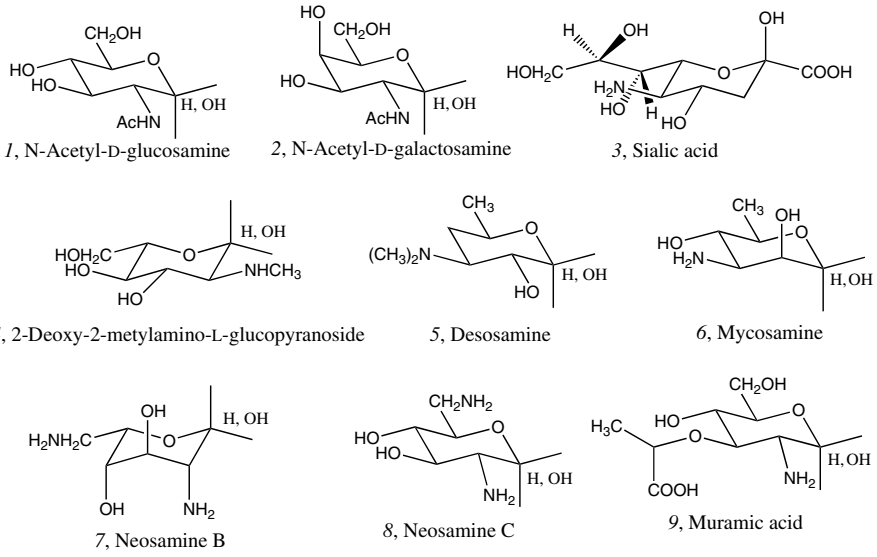


Fig. 9.1

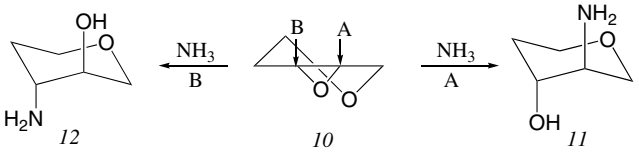


Fig. 9.2

the incoming ammonia and various substituents on a pyranoside ring) [12–15]. Thus, for example, the ammonolysis of methyl 2,3-anhydro-4,6-di-*O*-methyl-β-D-mannopyranoside *13* gives 90% of methyl 3-amino-3-deoxy-β-D-altropyranoside *15* and 10% of methyl 2-amino-2-deoxy-β-D-glucopyranoside *14* [16] (Fig. 9.3).

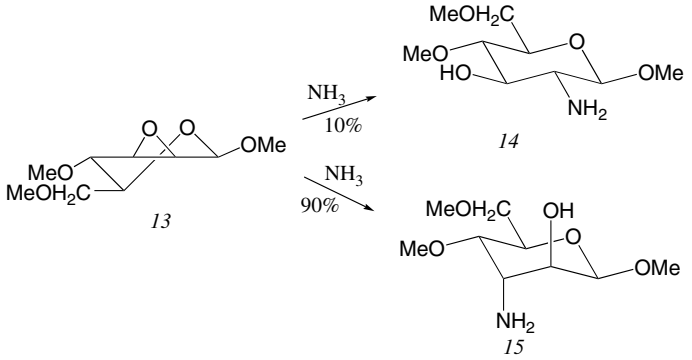
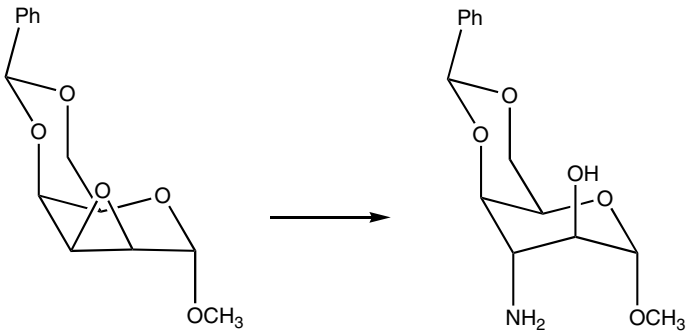


Fig. 9.3

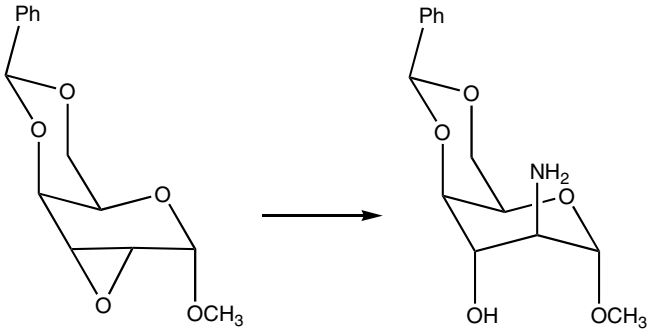
The ammonolysis of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-talopyranoside *16* gives methyl 3-amino-4,6-*O*-benzylidene-3-deoxy-α-D-idopyranoside *17* [17–19] as the predominant product (Fig. 9.4). The reason for this is that the epoxides undergo exclusively *trans*-diaxial opening. When chair–chair inversion is not possible, there is a chair–twist boat inversion which then allows a *trans*-diaxial opening leading to a chair which then undergoes a final chair interconversion to the more stable chair. This results then in *trans*-diequatorial products [13, 14].



16 *17*

Fig. 9.4

Ammonolysis of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-gulopyranoside *18* gives methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-idopyranoside *19* as the major product [18] (Fig. 9.5). Methylamine also attacks the C2 carbon giving the corresponding methylamino derivative.



18 *19*

Fig. 9.5

Ammonolysis of methyl 3,4-anhydro-6-deoxy-α-L-talopyranoside *20* gave exclusively methyl 3-amino-3-deoxy-α-L-idopyranoside *21* [20] (Fig. 9.6). Similar preference for the attack of a nucleophile to C3 carbon in methyl 3,4-anhydro-6-deoxy-α-L-talopyranoside *20* was previously reported by Charalambous and

Percival [21] during their study on the opening of the 3,4-epoxide ring of methyl 3-deoxy-α-L-talopyranoside *20* with sodium methoxide (diaxial opening). They isolated two products, methyl 6-deoxy-3-*O*-methyl-L-idose *23* and methyl 6-deoxy-4-

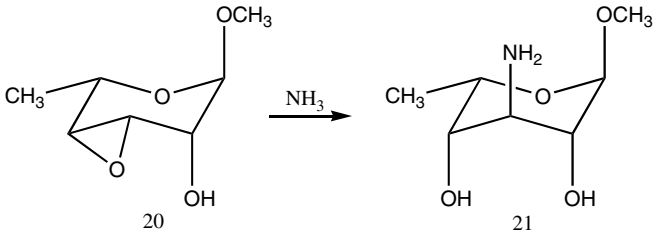


Fig. 9.6

O-methyl-L-mannose *24* in 2:1 ratio (Fig. 9.7). However, when they treated methyl 6-deoxy-3,4-anhydro-2-*O*-methyl-α-L-talopyranoside *22* with sodium methoxide under the same experimental conditions they obtained exclusively 6-deoxy-2,4-di-*O*-methyl-L-mannose *25*. The attack of methoxide anion took place exclusively at the C4 carbon (Fig. 9.7).

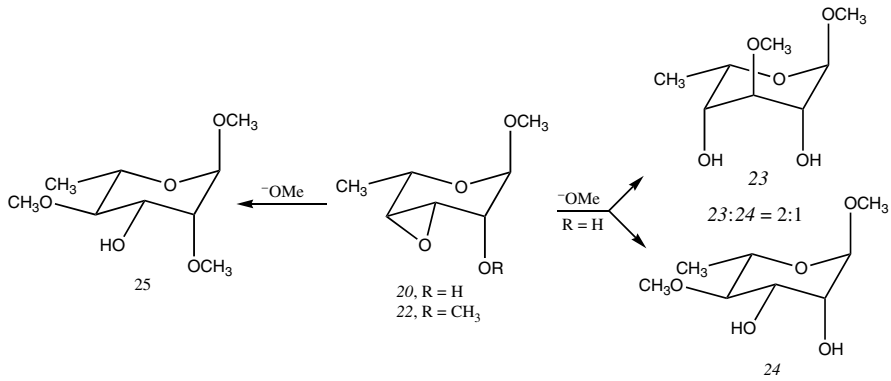
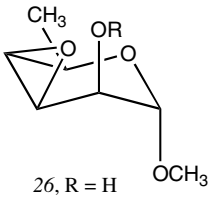


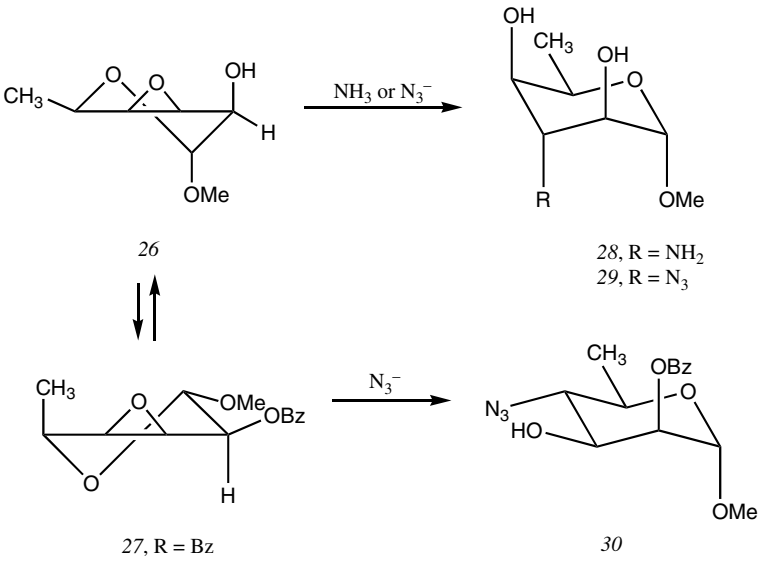
Fig. 9.7

Stevens et al. [22, 23] used these observations to prove the structure of perosamine (4-amino-4,6-dideoxy-D-mannose) and for its synthesis. Since, in the presence of a substituent at the O2 (methyl group), the attack of a nucleophile to 3,4-epoxide of *27* (Fig. 9.8) is directed away from the C3 carbon and to the C4 carbon it is reasonable to assume that the interference of the O2 substituent and the incoming nucleophile is steric in nature. If so then increase in the bulkiness of the O2 substituent should increase the overall regioselectivity. Thus instead of a methyl group as the O2 substituent Stevens et al. opted for the benzoyl group since benzoyl group is much larger than methyl group. However, since benzoate is easily removed by alkali, such as ammonia, the azide was selected as the nitrogen nucleophile.



26, R = H
27, R = Bz

Fig. 9.8



26

28, R = NH_2
29, R = N_3

27, R = Bz

30

Fig. 9.9

In full agreement with Percival et al. [21] findings, the attack of azide nucleophile to the 3,4-anhydro ring of *26* (Fig. 9.8) took place predominantly at the C3 carbon (C3:C4 attack ratio was 3:1) whereas the azide nucleophile attacked predominantly the C4 carbon of methyl 3,4-anhydro-2-*O*-benzoyl-6-deoxy-β-D-talopyranoside *27* (Fig. 9.9) giving methyl 4-azido-4,6-dideoxy-α-D-mannopyranoside *30* [22, 23] (C3:C4 attack ratio was 1:4). The lack of higher regioselectivity was explained by relative conformational flexibility of *26* and *27* and by the steric interaction in transition state (Fig. 9.9).

In case of terminal epoxides having in their epoxide ring structures a primary and a secondary carbon atom a nitrogen nucleophile will attack exclusively the primary carbon of this terminal epoxide.

For example, reaction of *31* with liquid ammonia gives the 6-amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-β-L-idofuranose *32* [24] (Fig. 9.10).

Sterically shielded 3-*O*-methanesulfonyl group does not react with ammonia under the reaction conditions.

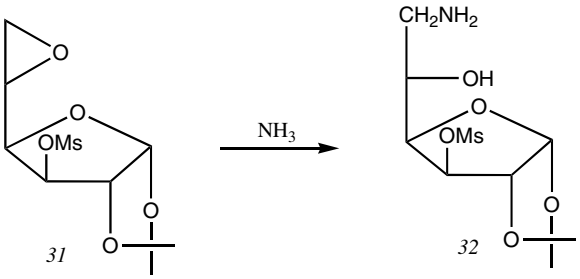


Fig. 9.10

Nucleophilic Displacement of Sulfonates (or Halides) with Nitrogen Nucleophiles

Halides (or sulfonic esters) at the primary carbon of a monosaccharide (the C6 in hexopyranoses and hexofuranoses or the C5 in pentofuranoses) can be directly displaced with ammonia to give 6-amino-6-deoxy or 5-amino-5-deoxy sugar. For example, methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-D-glucopyranoside *33* reacts with ammonia to give methyl 6-amino-6-deoxy-D-glucopyranoside *34* [25] (Fig. 9.11).

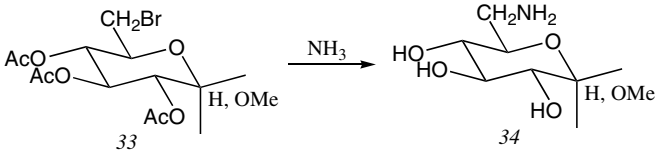


Fig. 9.11

Ammonolysis of 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-xylofuranose *35* gave 5-amino-5-deoxy-α-D-xylofuranose *36* [26, 27] (Fig. 9.12).

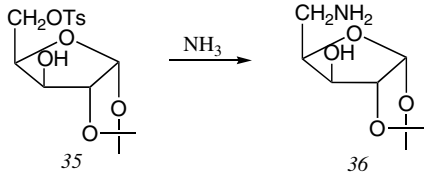


Fig. 9.12

The hydrazinolysis of *35* followed by reduction of the 5-hydrazo product also gave *36* [28].

The nucleophilic displacement of primary *p*-toluenesulfonates with azide, followed by reduction (or hydrogenation) of the obtained azido derivative to the amino group is probably the best method for obtaining the primary amino sugars [29, 30].

The direct nucleophilic displacement of sulfonic esters of secondary alcohols by ammonia is much more difficult than that of primary sulfonates. The ammonolysis of secondary sulfonates requires higher temperatures resulting, due to the harsher reaction conditions, in increased formation of side products and decreased yield of desired product. Much better results are obtained by displacing the secondary sulfonate with hydrazine, or even better with azide as nitrogen nucleophile. The resulting hydrazino or azido derivatives must then be reduced to the corresponding amino sugars.

In the absence of neighboring group participation, the nucleophilic displacement of secondary sulfonates is highly stereoselective and always takes place with the inversion of configuration at the reacting carbon. For example, 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose *37* reacts with ammonia [31, 32] to give 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose *38* or with hydrazine to give 3-deoxy-3-hydrazino-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose *39* [32, 33] (Fig. 9.13).

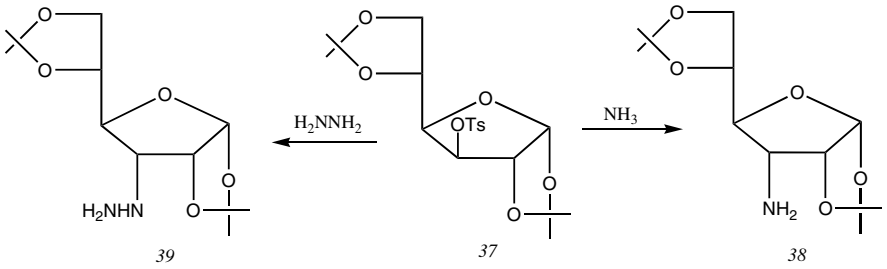
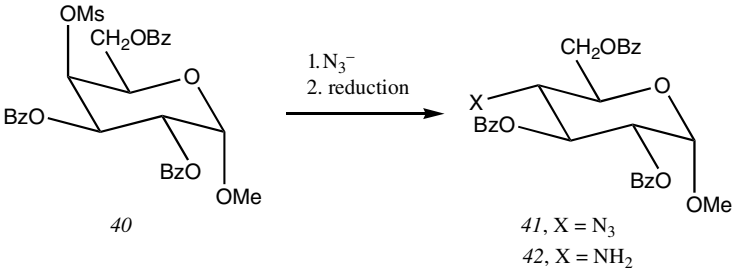


Fig. 9.13

It is interesting to note that 3-*p*-toluenesulfonate of *37* is highly resistant to direct displacement with charged nucleophiles such as acetate or benzoate; displacement with azide, however, does takes place, but only at high temperatures and in *N,N*-dimethylformamide [34] or hexamethylphosphoric triamide [35] which solvents are known to solvate well cations but not anions, thus not increasing the bulkiness of a negatively charged nucleophile via solvation.

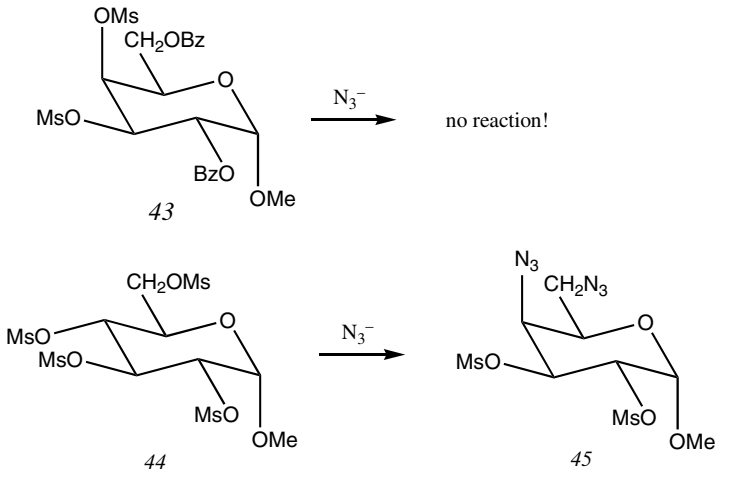
Nucleophilic displacement of alkyl or arylsulfonates by azide is generally the preferred method for introducing the amino group (after reduction of azide), because azide is a better nucleophile than ammonia or hydrazine and it is less basic resulting in fewer side reactions. For example, methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-galactopyranoside *41* was converted to methyl 4-amino-2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-glucopyranoside *42* [36] (Fig. 9.14).



40 *41*, X = N_3 *42*, X = NH_2

Fig. 9.14

Interestingly, methyl 2,6-di-*O*-benzoyl-3,4-di-*O*-methanesulfonyl-α, β-D-galactopyranoside *43* did not react with sodium azide after extended heating in hexamethylphosphoric triamide [37], whereas methyl 2,3,4,6-tetra-*O*-methanesulfonyl-α-D-glucopyranoside *44* gave methyl 4,6-diazido-4,6-dideoxy-2,3-di-*O*-methanesulfonyl-α-D-galactopyranoside *45* under less forcing conditions [38] (Fig. 9.15).



43 *44* *45*

Fig. 9.15

Reaction of 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methanesulfonyl-α-D-manno-pyranoside *46* (Fig. 9.16) proceeds by contraction of the pyranoside to furanoside ring via the participation of the ring oxygen, giving methyl 5-azido-5,6-dideoxy-2,3-*O*-isopropylidene-α-L-talofuranoside *47* as the only product [39].

Hydrazinolysis of *46* proceeds, however, primarily with the direct displacement [40] of the C4-sulfonate, giving, after hydrogenation, methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-L-talopyranoside *48*, together with small amounts of rearranged products *47*.

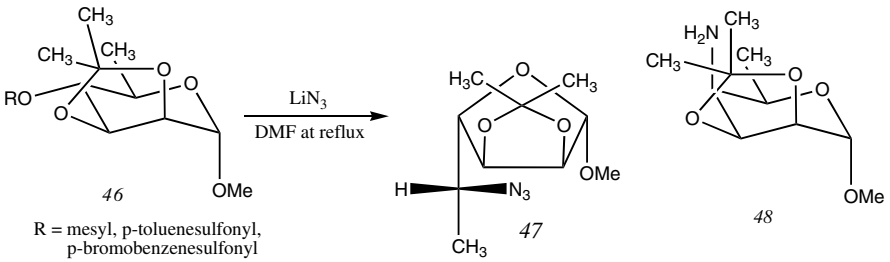


Fig. 9.16

2-Deoxy-2-amino sugars are biologically probably the most important amino sugars because they are the building blocks of many glycoconjugates (glycoproteins, glycolipids, glycosaminoglycans, peptidoglycans, etc.). Thus, for example, glycoproteins are proteins that are glycosylated at either L-serine or L-threonine (the O-linked oligosaccharides) (Fig. 9.17) or at the amido nitrogen of L-asparagine residue of a protein backbone (the N-linked oligosaccharides) (Fig. 9.18).

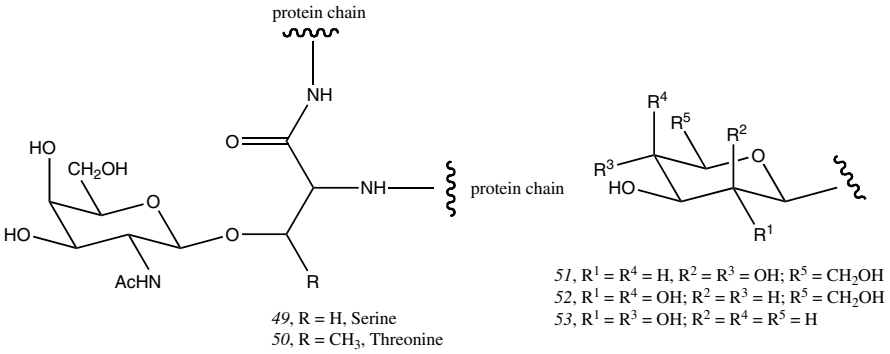
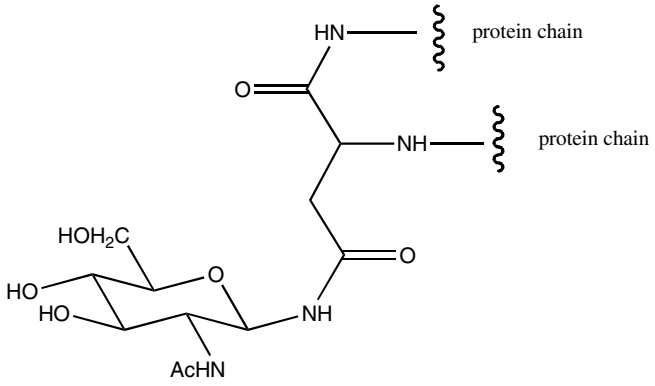


Fig. 9.17

The first monosaccharide that is glycosidically linked to an amino acid of a protein is, in both cases, a 2-deoxy-2-amino sugar: in glycoproteins having the O-linked oligosaccharide is the *N*-acetylgalactosamine; however, D-mannose *51*, D-galactose *52*, and D-xylose *53* residues are also found as the first carbohydrate glycosidically linked to the hydroxyl group of L-serine or L-threonine (Fig. 9.17). The first carbohydrate residue linked to L-asparagine (found in N-linked oligosaccharides) is always *N*-acetylglucosamine (Fig. 9.18).

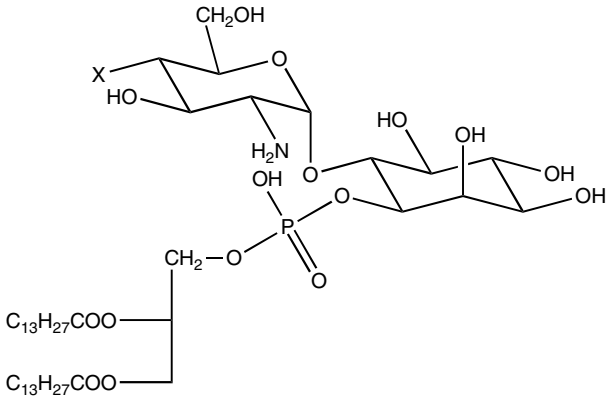
Glycosyl phosphatidylinositol (GPI)-linked proteins are not in a true sense of the word glycoproteins because the role of a carbohydrate moiety is not to modify the protein's physico-chemical properties and thus its biological activity, but to anchor the protein via phosphatidylinositol to the cell membrane. Typically, phosphatidylinositol is glycosylated with *N*-acetylglucosamine which is then deacetylated. To the obtained glucosamine are then added three mannose residues. In the next step,



54, L-Asparagine

Fig. 9.18

ethanolamine is added to the terminal mannose residue via a phosphate diester bond and to the amino group of ethanolamine a protein is linked with its carboxy terminal via an amide bond *55* (Fig. 9.19).



55, X = three mannose residues + phosphate + ethanol amine + protein

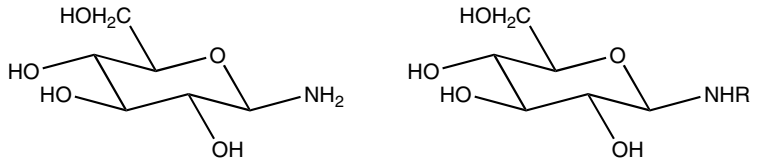
Fig. 9.19

This is perhaps the unique example of an amino sugar existing in nature with its amino group underivatized. The possible reason could be that the proximity of the phosphate proton to the glycosidic oxygen of D-glucosamine residue could represent a threat to the survival of the glycosidic bond of the amino sugar and phosphatidylinositol if the amino group is acetylated. Removal of the acetate from the *N*-acetamido group makes the glycosidic bond very stable and resistant to acid-catalyzed hydrolysis (vide supra). It is well established that essentially all eukaryotes add glycolipid anchor to certain proteins in order to express these pro-

teins at the cell surface and to regulate their presence in that location. GPI-anchored proteins are also present in trypanosomes, such as *Plasmodium falciparum* (malaria parasite).

Glycosylamines and N-Glycosides

Glycosylamines are generally defined as 1-amino-1-deoxy derivatives of monosaccharides *56* or *N*-alkylamino-1-deoxy or *N*-arylamino-1-deoxy derivatives of monosaccharides *57*, as shown in Fig. 9.20.



56 *57*

Fig. 9.20

The 1-amino sugars are discussed separately from the other amino sugars not only because they are chemically very different but also because the understanding of their chemistry has a direct bearing on the understanding of the chemical behavior of ribonucleic and deoxyribonucleic acids (RNA and DNA).

Cyclic forms of sugars with a free reducing group react with ammonia, alkyl-, and arylamines, esters of amino acids, and urea derivatives giving the corresponding glycosylamine derivatives. Amides normally do not react with reducing sugars because the amido nitrogen is insufficiently nucleophilic. However, aldoses do undergo acid-catalyzed condensation with urea and thiourea [41–46]. The great stability of *N*-glycosylureas and glycosylguanidines toward acid-catalyzed hydrolysis can be attributed to the involvement of the electron pair of the nitrogen atom at the C1 in the delocalization within the amide or guanidine group making this nitrogen unavailable for protonation. This may be the reason why in N-linked glycoproteins the oligosaccharide chain is attached to a protein via *N*-acetylglucosamine glycosidically linked to the amido nitrogen of asparagine residue of protein.

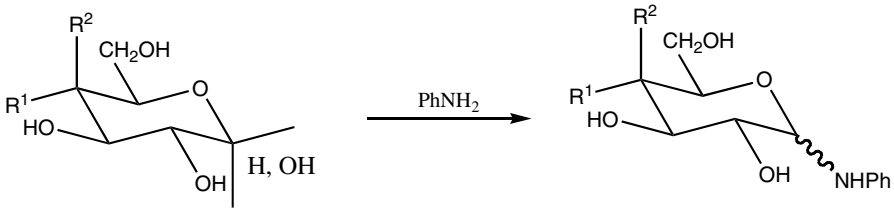
Glycosylamines are obtained by treating aldohexoses [47–50] or aldopentoses [50, 51] with cold concentrated solution of ammonia in alcohol. The product usually crystallizes when solution is kept for a prolonged time.

N-Alkylaldosamines are easily prepared by reacting aldoses with primary or secondary aliphatic amines [52–59].

Several *N*-alkyl D-glucosylamines were prepared by heating D-glucose with the corresponding amine in the presence of small amount of 0.5 N HCl [52].

N-Arylaldosamines have been known for a long time. Sorokin [60–63] synthesized *N*-phenyl D-glucosamine, D-galactosamine, and D-fructosylamine by heating aniline with free sugars at 130–135°C, or by heating the amine and the reducing

sugar in boiling methanol or ethanol, containing up to 10% of water. Also small amounts of acids have been used to catalyze the reaction. *N*-Phenylglucosamine and *N*-phenylgalactosamine were in this way obtained in good yields (Fig. 9.21).



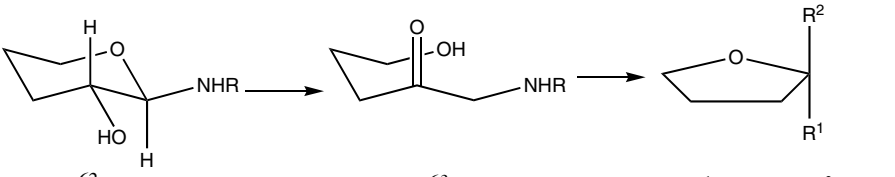
58, R^1 = OH; R^2 = H
59, R^1 = H; R^2 = OH

60, R^1 = OH; R^2 = H
61, R^1 = H; R^2 = OH

Fig. 9.21

A simple general method, suitable for large-scale preparations, was developed by Weygand [64]. It consists of dissolving the sugar in a minimum amount of hot water and heating the solution with an arylamine for a few minutes longer than required for achieving the complete miscibility; the product crystallizes on adding alcohol and cooling.

The preparation of *N*-alkylglycosamines is often complicated by subsequent and rapid *Amadori rearrangement* [65], whereby an N-substituted glycosylamine isomerizes to an N-substituted 1-amino-1-deoxy-ketose [66] (Fig. 9.22).



62 *63*

64, $R^1 = CH_2NH_2$; R^2 = OH
65, R^1 = OH; $R^2 = CH_2NH_2$

Fig. 9.22

The two mechanisms depicted in Fig. 9.23 were postulated by Kuhn et al. [67, 68] and Weygand [69] (Mechanism A) and Isbell and Frush [50] (Mechanism B).

These two reaction mechanisms proposed for this rearrangement (Fig. 9.23) differ in the site of protonation in the initial step. According to Weygand [69] (Mechanism A) the initial protonation of *N*-glycosylamine *66* takes place at the nitrogen atom *67*. Proton is then transferred to the ring oxygen causing the opening of the pyranoside ring with the simultaneous formation of immonium transition state intermediate *69* $\rightleftarrows$ *70* which collapses to enolamine *71*. Tautomerization to acyclic 1-substituted amino ketose *72* followed by cyclization gives 1-N-substituted ketosylamine *73* (Fig. 9.23).

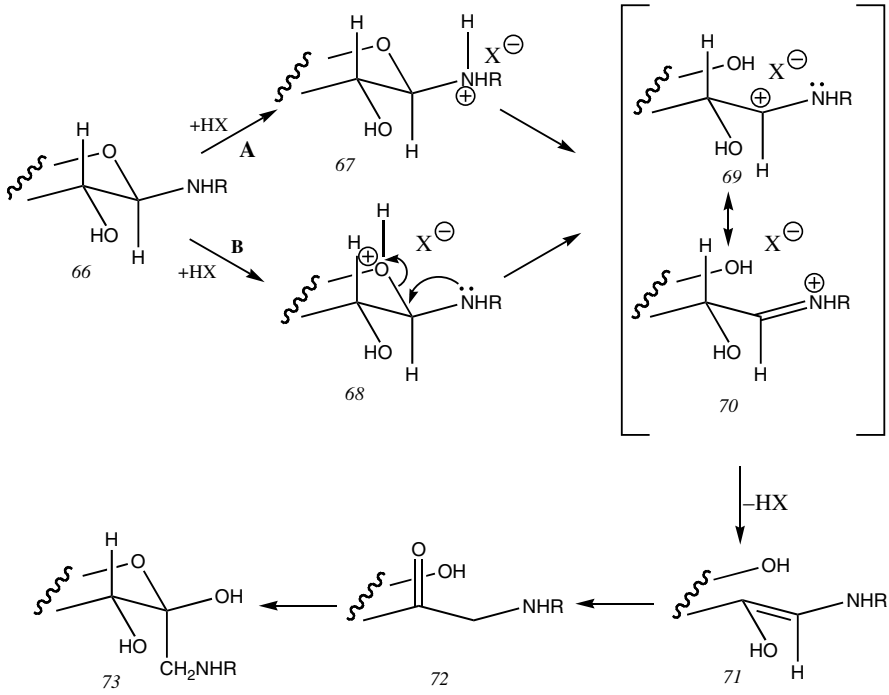


Fig. 9.23

Isbell and Frush [50] developed the currently accepted view [70] (Mechanism B) that postulates that the initial protonation takes place at the ring oxygen giving *68* which is probably more likely because of the analogy with the mechanism of mutarotation and hydrolysis of glycosylamines. The positively charged C1 carbon of immonium intermediate *69* withdraws the electrons from the C2 carbon weakening thus the C2–H bond so that it can be easily removed from the C2 by a base and gives "enolamine " *71*. This intermediate rearranges first to the amino-ketone *72* and then to the corresponding cyclic form *73*.

Ketosylamines undergo a rearrangement to 2-amino-2-deoxyaldoses. This rearrangement, termed *Heyns rearrangement*, can be in a way regarded as reverse Amadori rearrangement, because the 1-N-substituted ketose is converted into a 2-amino aldose. Since new asymmetric C2 carbon is produced, two epimeric rearrangement products are obtained (Fig. 9.24). Thus, for example, N-substituted D-fructosylamine *74*, obtained by reaction of D-fructose in liquid ammonia or in methanolic ammonia, rearranges stereoselectively to 2-amino-2-deoxy D-glycose by acid catalysis [71–73]. D-Fructose undergoes spontaneous rearrangement to 2-alkylamino-2-deoxy-D-glucose derivatives when reacted with cyclohexyl- and isopropyl amines [74], as well as with butylamine [75] in the cold.

The mechanism of Heyns rearrangement is similar to the mechanism of Amadori rearrangement, as shown in Fig. 9.25. The protonation of the ring oxygen of *77*,

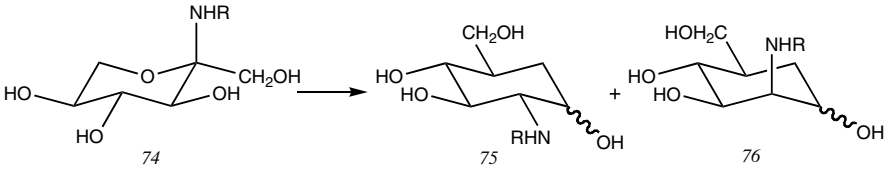


Fig. 9.24

followed by ring opening, gives immonium transition state intermediate (*78* ↔ *79*) that is by deprotonation of the hydroxymethyl group of *79* converted to "enolamine" *80*. The isomerization of "enolamine" *80* to 2-amino-aldehyde *81* followed by cyclization gives the 2-amino-2-deoxy aldopyranose *82* (Fig. 9.25).

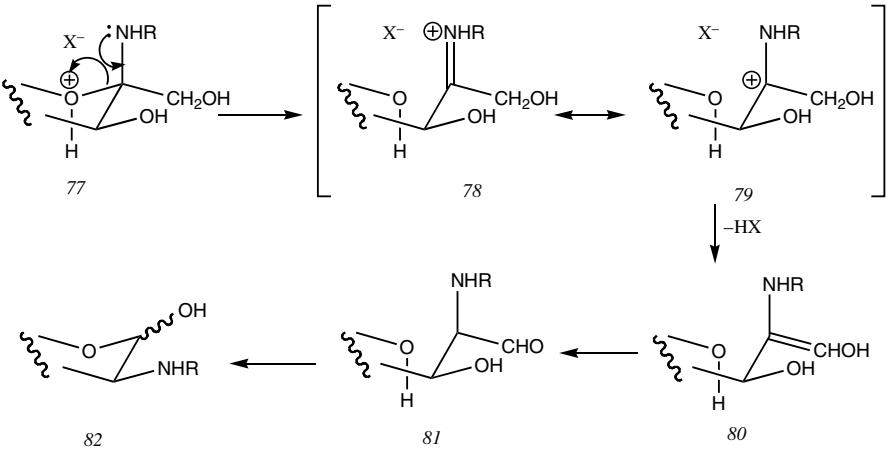


Fig. 9.25

Glycosylamines undergo simple mutarotation in solution. A kinetic study of the mutarotation of N-*p*-tolylglycosylamines in aqueous NaOH at pH 12.99 showed that the reaction is first order [76–78]. Isbell and Frush [50] proposed a mechanism for mutarotation assuming that the initial protonation takes place at the ring oxygen *83* that is followed by the ring cleavage and formation of open-chain immonium intermediate *87*. Rotation about the C1–C2 bond and the re-closure of the pyranoid ring results in the formation of the other anomer *88* (Fig. 9.26).

In aqueous solutions, the acid-catalyzed hydrolysis of all glycosylamines is preceded by a rapid anomerization to a mixture of about 10% α- and 90% β-form [76]. Although the anomerization must involve an acyclic intermediate, this form cannot be present in appreciable concentrations since the reaction shows good first-order kinetics and the rate constants are equal, regardless of whether starting from α- or the β-form. Thus when studying the acid-catalyzed hydrolysis of glycosamines it is always a rapidly interconverting mixture of isomers that is being studied [76].

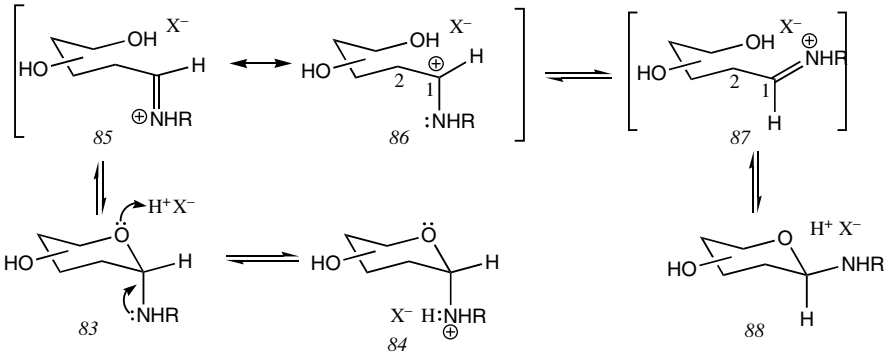


Fig. 9.26

The hydrolysis could be envisaged to proceed either via the formation of cyclic oxocarbenium ion *91*, as is the case in the acid-catalyzed hydrolysis of *O*-glycosides, or via the formation of acyclic immonium ion *85* (protonated Schiff base) (Fig. 9.27).

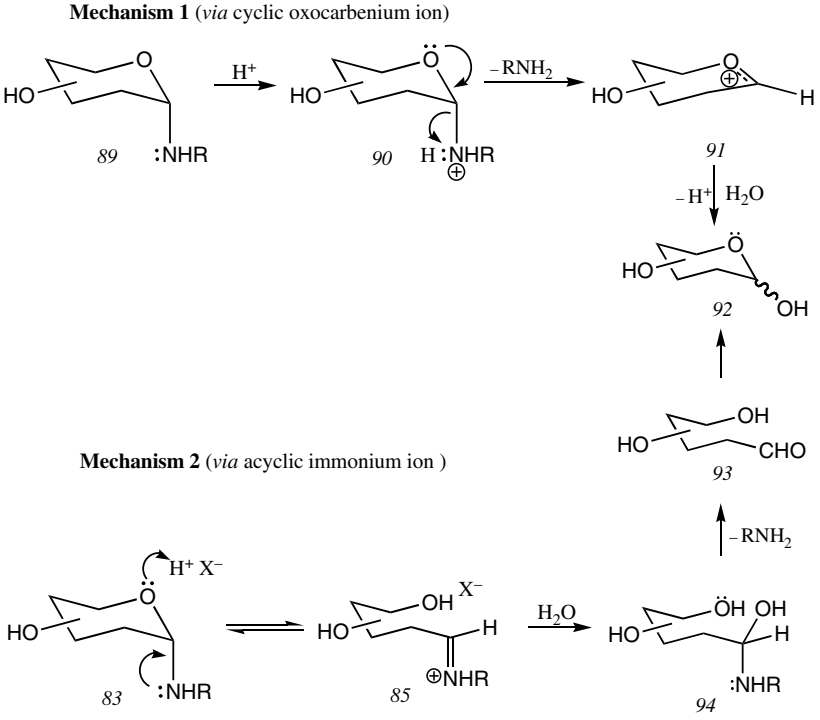


Fig. 9.27

The hydrolysis of the more easily hydrolyzed glycosylamines (for example, N-*p*-tolyl) was studied in buffers and was found to undergo general acid catalysis, excluding thus the Mechanism 1. However, it is consistent with Mechanism 2, since general acid catalysis mechanism in the hydrolysis of Schiff bases is well established [79, 80] and has also been shown to involve kinetically equivalent specific acid/general base catalysis [81]. The *N*-arylglycosylamines are far more resistant to hydrolysis than *N*-alkylglycosylamines, because the lone pair of electrons on nitrogen is more available to form the immonium cation in alkylamines than in arylamines where it is overlapping with the aromatic π-electrons of benzene ring.

A very important group of *N*-glycosides are nucleosides (or nucleotides) that are the building blocks of ribo- and deoxyribonucleic acids (DNA and RNA, respectively). These *N*-glycosides are chemically different from *N*-alkyl and *N*-arylglycosylamines because the glycosidic nitrogen as a part of a ring system is conjugated with a network of double bonds in pyrimidine or purine base. This electronic orbital overlap makes the *N*-glycosidic nitrogen atom of nucleosides less susceptible to protonation and thus makes nucleosides more stable to acid-catalyzed hydrolysis than *N*-alkyl and *N*-arylglycosylamines. In Figs. 9.29 and 9.31 the structures of most important nucleosides are given. As can be seen there are two classes

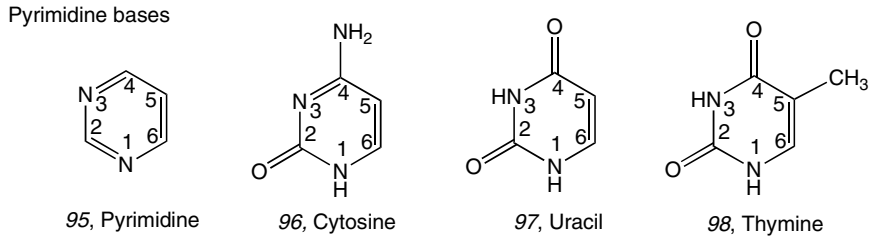


Fig. 9.28

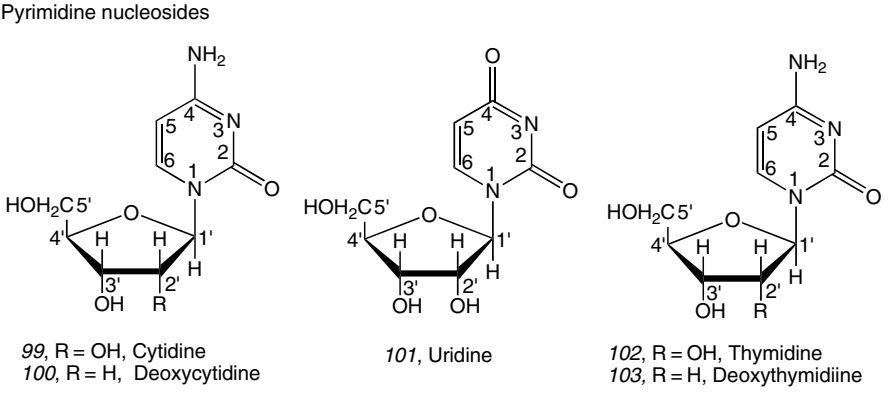


Fig. 9.29

of nucleosides: one having a pyrimidine derivative as the base (Figs. 9.28 and 9.29) and the other group of nucleosides having a purine derivative as the base (Figs. 9.30 and 9.31). In pyrimidine nucleosides the N1 nitrogen is glycosidically linked via β glycosidic bond to ribose or to 2-deoxy ribose molecule.

In purine nucleosides the N9 nitrogen is linked via a β-glycosidic bond to D-ribofuranose (in ribonucleic acids, RNA) or to 2-deoxy-D-ribofuranose (in deoxyribonucleic acids, DNA).

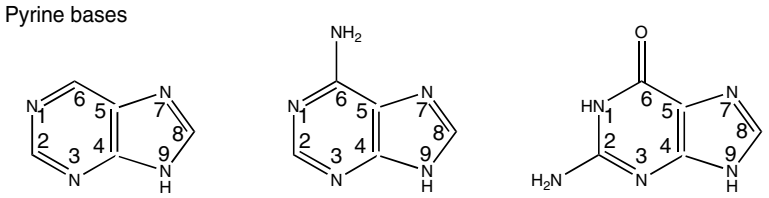


Fig. 9.30

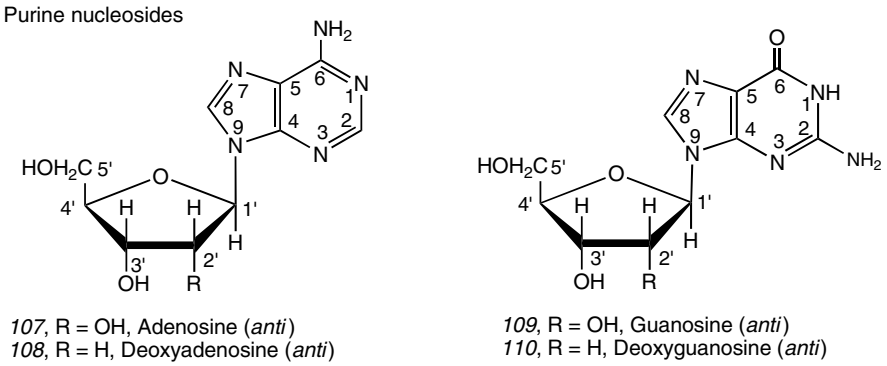


Fig. 9.31

Acid-Catalyzed Hydrolysis of Purine and Pyrimidine Nucleosides

Acid-catalyzed hydrolysis of purine and pyrimidine nucleosides has been extensively studied [82–96].

It was initially believed that the acid-catalyzed hydrolysis of nucleosides (and hence nucleotides) proceeds by a similar mechanism as the hydrolysis of alkyl- and arylglycosylamines, i.e., via an open-chain protonated Schiff base intermediate [82]. However, while in case of glycosylamines the sugar ring cleavage is aided by resonance stabilization of the open-chain form by the amine nitrogen forming an imine,

such stabilization is less likely with nucleosides because the aromatic nitrogens at N1 (pyrimidines) and N9 (purines) cannot donate their lone pair electrons due to conjugation with the aromatic ring π electrons. Consequently, with the overwhelming support of experimental data the consensus regarding the mechanism of acid-catalyzed hydrolysis of nucleosides has shifted toward direct C1′-N fission with the formation of oxocarbenium transition state.

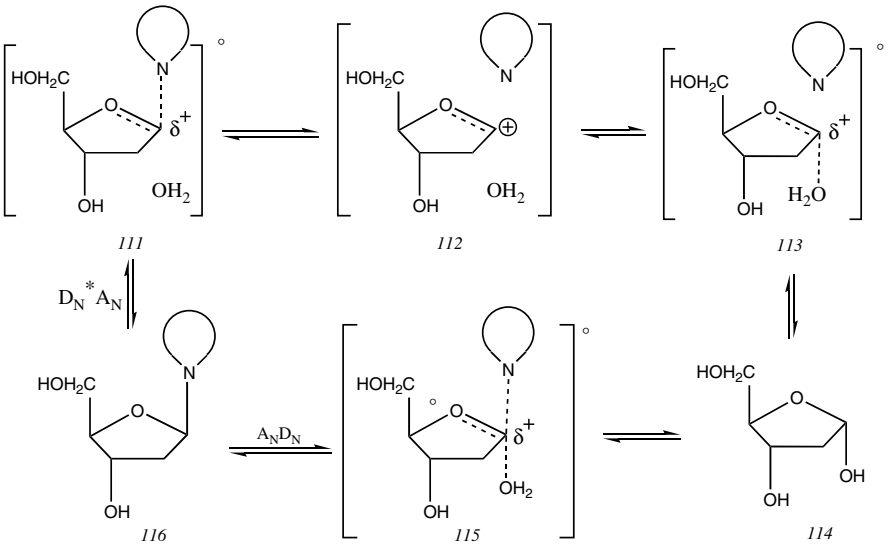


Fig. 9.32

Glycoside hydrolyses tread the borderline between the concerted and stepwise reactions and almost invariably proceed through either stepwise $D_N{}^*A_N$ (S_N1) reactions or highly dissociative A_N D_N (S_N2) mechanisms [82, 97–99] (Fig. 9.32). Thus, these reactions form either a discrete oxocarbenium ion intermediate or an oxocarbenium ion-like transition state (highly dissociative A_ND_N reactions are occasionally referred to as being "S_N1-like," which is incorrect). If both the nucleophile and the leaving group are in the reaction coordinate at the transition state, then the mechanism is A_ND_N (S_N2), no matter how dissociative is the transition state. Therefore, highly dissociative A_ND_N transition states should be perhaps referred to as "oxocarbenium ion-like" rather than "S_N1-like" where leaving group departure is far advanced over nucleophile approach, and positive charge accumulates on the sugar ring.

The ribofuranosyl oxocarbenium ion is expected to be more stable than glucopyranosyl oxocarbenium ion, based on higher reactivity of *O*-ribosides [82] and therefore more prone to proceed through $D_N{}^*A_N$ (S_N1) mechanism. However, acid-catalyzed hydrolysis of nucleosides can proceed by either of these two mechanisms: (AMP) [100] and (NAD^+) [101] proceed via A_ND_N mechanism, though hydrolysis of dAMP appears to be stepwise $D_N{}^*A_N$ [102].

The stability of the glycosyl linkage toward acid-catalyzed hydrolysis varies widely. It is dependent on both the nature of the base (and its substituents) and the nature of the sugar (and its substituents). 2-Deoxyribonucleosides are more labile than ribonucleosides; purine nucleosides are more reactive than pyrimidine substrates [103].

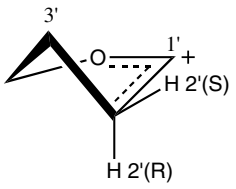
The stability of 2-deoxyribonucleosides toward acid-catalyzed hydrolysis decreases in the order uracil (or thymine) > cytosine > adenine > guanine nucleoside. Acylation of the heterocyclic base can have a marked effect on the rate of acid-catalyzed cleavage of the glycosyl linkage [104, 105], notwithstanding implications to the contrary [106]. Esterification of sugar hydroxyl groups affects the stability of the glycosyl bond as shown in case of 2′*O*-acetyldeoxyguanosines [107], thymidine phosphates [108, 109], and 2′-*O*-*p*-toluenesulfonyl adenosine [110], and by the remarkable stability of 2′,3′,5′-tri-*O*-(3,5-dinitrobenzoyl)-uridine [110].

DNA is <10-fold more stable to depurination than nucleosides, and the native DNA was 4-fold more stable than denatured DNA [111].

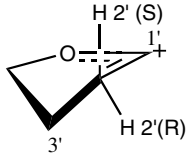
Depyrimidation is <20-fold slower than depurination in DNA [112]. It is also slower in DNA than in nucleosides and slower in native than denatured DNA by a factor of 2–6 [112].

Nonenzymatic mechanisms of purine and pyrimidine hydrolysis have been studied extensively [82–96].

Hyperconjugation between the 2′-hydrogen atoms of (deoxy)nucleosides and the cationic center at C1′ in oxocarbenium ion helps to stabilize the transition state. Hyperconjugation can be described as donation of electron density from the C2′–H2′ σ-bond(s) into the empty *p* orbital at C1′, forming the C2′–C1′ π-bond. Hyperconjugation in ribosyl oxocarbenium ions is conformation dependent because there is only one H2′. In deoxyribosyl oxocarbenium ions, both H2′ hydrogens can contribute, lessening thus the conformational dependence (Fig. 9.33).



115, 3'-endo-1

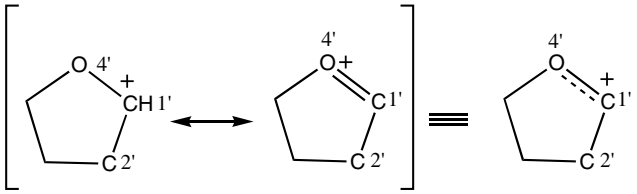


116, 3'-exo-1

Fig. 9.33

TS analyses have shown that all nonenzymatic *N*-glycoside hydrolyses and most enzymatic reactions form oxocarbenium ion-like TS in the 3′-*exo* conformation.

Forming an oxocarbenium ion requires rehybridization of the anomeric carbon (C1′) from sp^3 to sp^2. There is increased π-bonding between C1′ and O4′, the ring oxygen, and between the C1′ and C2′ to a lesser extent. Resonance forms imply a molecule that is somewhere between carbocation, *110a*, and an oxonium ion, *110b* (Fig. 9.34).



117a *117b* *117*

Fig. 9.34

The +1 charge on an oxocarbenium ion is centered at the anomeric carbon, C1′, but is delocalized around the furanoid ring. Although the ring oxygen is formally trivalent in the dominant oxonium resonance form, *117b*, quantum-mechanical calculations showed it still bears a negative charge in the oxocarbenium ion [97, 112].

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Chapter 10
Oxidation of Monosaccharides

Oxidation is a very important reaction in carbohydrate chemistry because it enables the synthesis of a great variety of monosaccharides and their derivatives from simple monosaccharides. As already mentioned in Chapter 5 the carbohydrates have three types of chemically distinct hydroxyl groups: (1) the primary hydroxyl groups which are always exocyclic and (2) two types of secondary hydroxyl groups: endo- and exocyclic hydroxyl groups.

The anomeric and the primary hydroxyl groups are the only two hydroxyl groups that can be selectively oxidized in the presence of unprotected other hydroxyl groups: the anomeric hydroxyl group probably due to electronic reasons (it is hemiacetal or lactol hydroxyl group and hence much more reactive than ordinary alcoholic hydroxyl group) and the primary hydroxyl group probably due to steric reasons.

Reactivity of all other secondary hydroxyl groups toward oxidation is practically indistinguishable and therefore the oxidation of a particular hydroxyl group in a monosaccharide requires regioselective protection of all other hydroxyl groups with protecting groups that are stable toward the used oxidation reagent.

Our discussion of oxidation of monosaccharides will be divided into two sections: (1) the selective oxidation of carbohydrates that involves the oxidation of primary and anomeric hydroxyl group and (2) the nonselective oxidation of any other secondary hydroxyl group.

We should, however, mention a third type of oxidation of carbohydrates which is accompanied by the C–C bond cleavage between the vicinal carbons bearing hydroxyl groups. This type of oxidation will be discussed at the end of this chapter.

Selective Oxidations of Monosaccharides

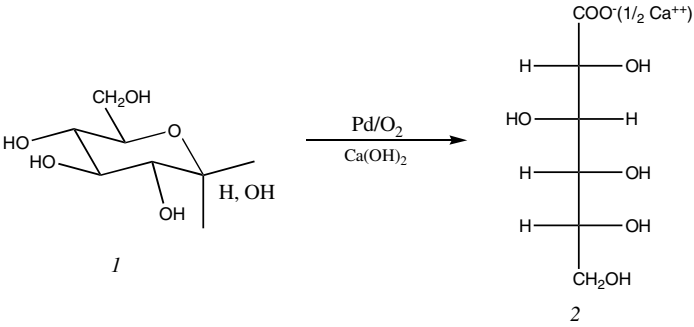
Catalytic Oxidation

Catalytic oxidation of carbohydrates has been extensively investigated by Heynes and coworkers and the subject has been thoroughly discussed [1–4]. The most effective catalyst is platinum black or platinum on carbon, and the oxidant is air that

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_10,

is passed through a vigorously stirred solution of a substrate. The solvent is usually water, but organic solvents have also been used. Yields vary from excellent to poor, but the high selectivity and the ease of isolation of the oxidation product make this method preparatively very useful. The catalytic oxidations can be carried out at room or elevated temperatures. Mechanistically, the catalytic oxidations are regarded as dehydrogenations [1, 4].

Aldoses are readily oxidized to aldonic acids. Oxidation of D-glucose at room temperature [5] or at elevated temperature [6] (55°C) in the presence of theoretical amount of alkali that is required to combine with the formed gluconic acid gives a nearly quantitative yield of gluconic acid. A palladium precipitated on calcium carbonate was used in both cases as the catalyst, and the gluconic acid was isolated as calcium salt (Fig. 10.1).



1 *2*

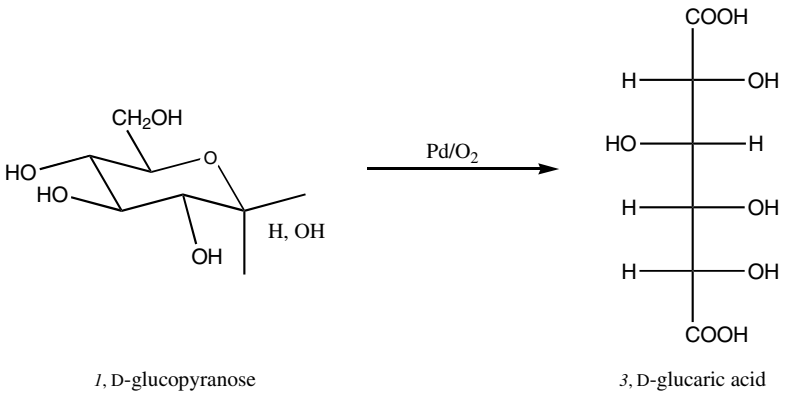
Fig. 10.1

No oxidation of primary hydroxyl group took place under these reaction conditions. This oxidation can also be performed with platinum on carbon as the catalyst and in the presence of 1 mol-equivalent of a base [7]. D-Galactose, D-mannose, D-xylose, and L-arabinose have all been converted to the corresponding aldonic acids [8] in this way. The pentoses are oxidized more rapidly than hexoses (usually in 45 min at room temperature as compared to several hours for hexoses).

If the oxidation of aldoses is performed at elevated temperatures (e.g., 50°C) with platinum-on-carbon as the catalyst, the primary C6 hydroxyl group will also be oxidized in addition to the anomeric hydroxyl group giving the corresponding glycaric acids. D-Glucose is in this way converted to D-glucaric acid *3* in 54% yield [9] (Fig. 10.2).

Hence, the anomeric carbon of free aldoses can be selectively oxidized at room temperature to carboxylic group giving aldonic acids or aldonolactones, whereas at higher temperatures, the C6 hydroxyl group is also oxidized giving aldaric acids.

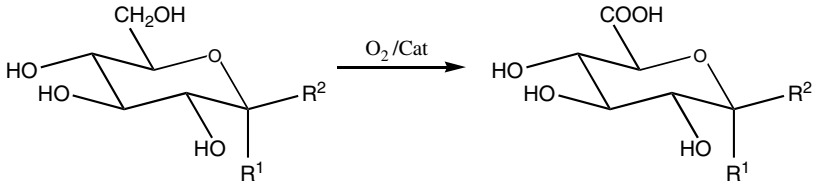
If the reactive anomeric hydroxyl group is suitably blocked, as is the case in alkyl or aryl glycosides, uronic acids can be readily obtained by catalytic oxidation of the primary C6 hydroxyl group of hexopyranoses using platinum as the catalyst. Thus, for example, methyl α-D-glucopyranoside *4* is catalytically oxidized in 87% yield to



1, D-glucopyranose *3*, D-glucaric acid

Fig. 10.2

methyl α-D-glucopyranosiduronic acid *6* [10]. D-Glucurono-6,3-lactone is obtained in only 16% yield since the acid hydrolysis of methyl glucosidic bond requires harsh conditions. The methyl β-D-glucopyranoside *5* gives on catalytic oxidation the corresponding glucuronic acid *7* in 68% yield. The oxygen is used as oxidizing agent, and Pt black, Pt/C, Pt/Al_2O_3, PtO_2 as the catalyst (Fig. 10.3).



4, R^1 = OMe; R^2 = H
5, R^1 = H; R^2 = OMe

6, R^1 = OMe; R^2 = H
7, R^1 = H; R^2 = OMe

Fig. 10.3

Bromine Oxidation

Bromine reacts with free aldoses (for example, *1*) in both acid and alkaline solutions, whereas iodine reacts only in alkaline solution. Since this oxidation is a two-electron transfer reaction, 1 mol of bromine is consumed per mole of aldose giving 1 mol of glyconolactone *8* and 2 mol of hydrobromic acid (Fig. 10.4).

The accumulation of hydrobromic acid during bromine oxidation greatly lowers the rate of reaction and inhibits further oxidation. To minimize this inhibiting effect of hydrobromic acid, the oxidation is conducted in the presence of calcium or barium carbonate or calcium benzoate [11, 12] as "solid bases." It is interesting to note that although other strong acids inhibit the rate of bromine oxidation too, the

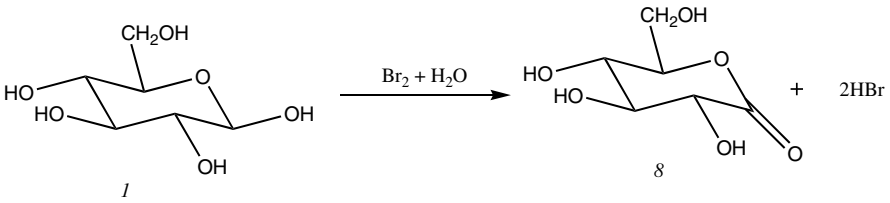


Fig. 10.4

inhibition is greatest with HBr and HCl [13]. It has been speculated that this effect may be due, in part, to complexation of 1 mol of hydrobromic acid with 1 mol of free bromine giving Br_3^-, which is ineffective as oxidant [14]. The yields of oxidation products are usually very high: D-gluconic acid *8* is obtained from D-glucose *1* in 96% yield, whereas D-xylonic acid is obtained in 90% yield from D-xylose in buffered solutions [14].

From a study of bromine oxidation of free aldoses in the presence of barium carbonate and bromides (pH about 5.4) Isbell and Pigman [15] have concluded that the active oxidant is free bromine, not hypobromous acid. Furthermore, it was found [16] that cyclic forms of a monosaccharide, not free aldehyde, are oxidized directly under these conditions. Thus pyranoses yield 1,5-lactones and furanoses, 1,4-lactones directly and in high yield.

The faster oxidation of β-anomers as opposed to α-anomers has been explained [17, 18] by using the known fact from conformational analysis that equatorial substituents are more reactive than axial ones (the hydroxyl group is in β-D-anomers equatorially oriented).

Barker et al. [17, 18] have found that the rates of bromine oxidation of α-D-anomers may be related to the rate of mutarotation into β-D-anomers so that the actual rate of oxidation of α-D-anomers is much lower. A straight line relationship was obtained for the observed rate of bromine oxidation and the rate of α- to β-mutarotation of studied sugars. Hence, the rate-determining step in the oxidation of the α-D-glucose is its anomerization into the β-D-anomer. It was found that the true rate of oxidation of α-D-glucose is about 1/250th that of the β-D-anomer.

Nonselective Oxidation of Secondary Hydroxyl Groups

Generally, the oxidation of a particular hydroxyl group in a monosaccharide requires blocking (protecting) with appropriate protective groups of all other hydroxyl groups that would also react under the used experimental conditions. Thus in nonselective oxidation of carbohydrates, a selective protection of all hydroxyl groups, except the one which is to be oxidized, has to be performed. The topic of selective protection of hydroxyl groups of glycofuranoses and glycopyranoses and their deprotection will be dealt with in a separate chapter.

Ruthenium Tetroxide (RuO_4) Oxidation

Ruthenium tetroxide was discovered by Claus [19] in 1860, but it took almost 100 years to realize that RuO_4 is rapidly reduced to RuO_2 by alcohol, acetaldehyde, and the like [20] and that it can be used as a very potent oxidant in neutral solution and at room temperature [21]. The most suitable solvent for RuO_4 oxidations is carbon tetrachloride wherein the RuO_4 dissolves with a dark red color. Alcohol-free chloroform and dichloromethane were also found to be satisfactory. Thus ruthenium tetroxide is stable in all these solvents. Ether, benzene, and pyridine are highly unsuitable as solvents because on contact with RuO_4 they either explode or catch fire [21].

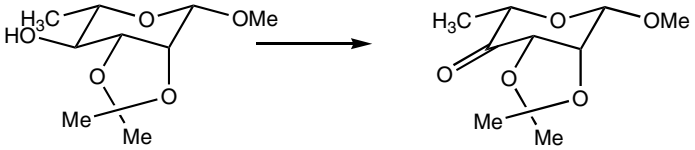
Beynon et al. [22] were the first to demonstrate the usefulness of RuO_4 for oxidation of secondary hydroxyl groups in carbohydrates. Using the equivalent amounts of carbon tetrachloride solution of ruthenium tetroxide they were able to oxidize a number of suitably protected methyl glycosides to corresponding glycopyranosiduloses. The oxidation was conducted at room temperature and it was usually completed within 1–4 h. The structures of monosaccharides that were oxidized and the structures of obtained corresponding "uloses" are given in Figs. 10.5 and 10.6. The yields of products obtained are given in Table 10.1.

The study of RuO_4 oxidation of partially protected methyl glycosides has shown not only that the glycosidic linkage is unaffected by the reagent but also that benzoate, benzylidene, and isopropylidene groups can all be safely used for selective protection of hydroxyl groups in monosaccharides which are to be oxidized.

Two procedures are generally employed for the RuO_4 oxidation of carbohydrates [23]:

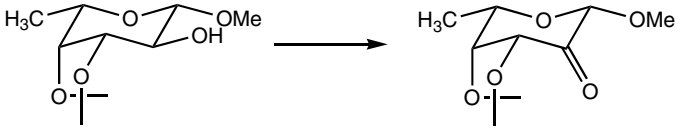
(a) Oxidation of protected monosaccharide with a slight molar excess of ruthenium tetroxide (both dissolved in carbon tetrachloride) (monophasic system); or (less satisfactorily)
(b) Oxidation of protected monosaccharide with catalytic quantity of ruthenium tetroxide [24] (substrate and RuO_4 dissolved in carbon tetrachloride) in the presence of aqueous solution of sodium metaperiodate (biphasic system). The reaction mixture is vigorously stirred so that the RuO_2 obtained after partial oxidation of the monosaccharide is reoxidized back to RuO_4 with sodium metaperiodate. The regenerated RuO_4 then redissolves in carbon tetrachloride (RuO_4 is much more soluble in carbon tetrachloride than in water) where it oxidizes another quantity of protected monosaccharide. This process is being repeated until all of the monosaccharide has been oxidized. Regenerated RuO_4 redissolves in CCl_4 and oxidizes there an additional amount of selectively protected carbohydrate. Sodium metaperiodate is reduced to sodium iodate in this reaction. This method requires vigorous stirring or shaking.

Although CrO_3–Py can oxidize a chemically resistant secondary hydroxyl group of a monosaccharide [25–27], the yields are generally better with RuO_4 as the oxidant [23]. For example, oxidation of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose *29* (Fig. 10.7) was not successful with CrO_3 in pyridine, acetone,



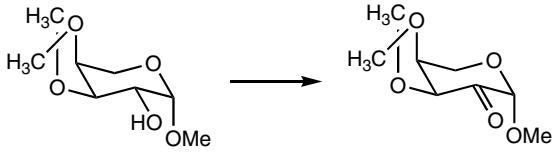
9, Metyl 6-deoxy-2, 3-isopropylidene-α-L-mannopyranoside

10, Metyl 6-deoxy-2, 3-isopropylidene-α-L-*lyxo*-4-hexulopyranoside



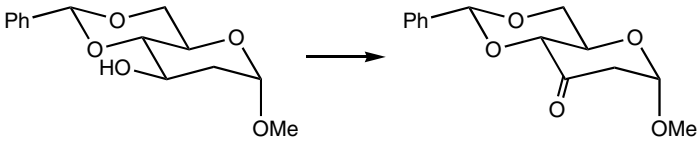
11, Methyl 6-deoxy-3, 4-O-isopropylidene-α-L-galactopyranoside

12, Methyl 6-deoxy-3, 4-O-isopropylidene-α-L-*lyxo*-hexulopyranoside



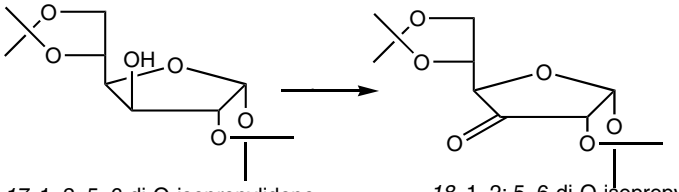
13, Methyl 3, 4-O-isopropylidene-β-L-arabinopyranoside

14, Methyl 3, 4-O-isopropylidene-β-L-*erythro*-pentulopyranoside



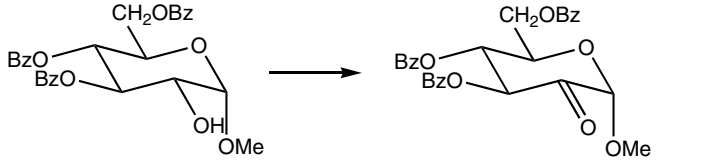
15, Methyl 4, 6-O-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside

16, Methyl 4, 6-O-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose



17, 1, 2: 5, 6-di-O-isopropylidene-α-D-glucopfuranose

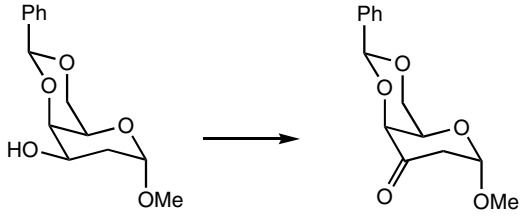
18, 1, 2: 5, 6-di-O-isopropylidene-α–D-*ribo*-hexopyranosid-3-ulose



19, Methyl 3, 4, 6,-tri-O-benzoyl-α-D-glucopyranoside

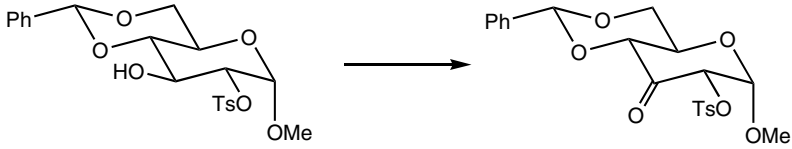
20, Methyl 3,4,6-tri-O-benzoyl-α-D-*arabino*-hexopyranosidulose

Fig. 10.5



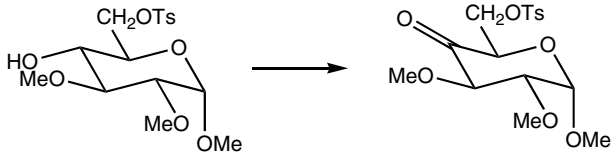
21, Methyl 4,6-O-benzylidene-2-deoxy- α-D-*lyxo*-hexopyranoside

22, Methyl 4,6-O-benzylidene-2-deoxy-α-D-*threo*-3-hexulopyranoside



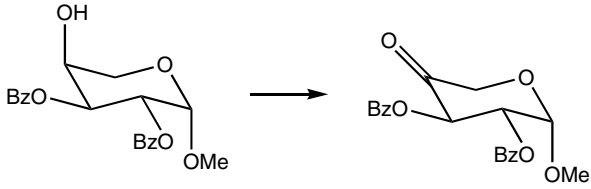
23, Methyl 4,6-O-benzylidene-2-O-p-toluenesulfonyl-α-glucopyranose

24,Methyl 4,6-O-benzylidene-2-O- p-toluene-sulfonyl-α-D-*ribo*-hexopyranosid-3-ulose



25, Methyl 2, 3-di-O-methyl-6-O-tosyl-α-D-glucopyranoside

26, Methyl 2, 3-di-O-methyl-6-O-tosyl-αD-*xylo*-hexopyranosid-4-ulose



27, Methyl-2, 3-di-O-benzoyl-β-L-arabinopyranoside

28, Methyl 2, 3-di-O-benzoyl-β-L-*threo*-pentopyranosid-4-ulose

Fig. 10.6

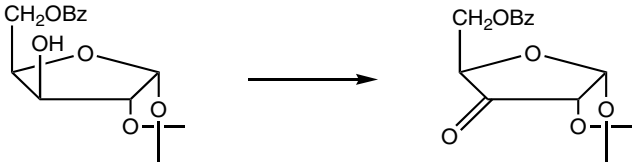
or acetic acid. It could also not be accomplished with aluminum isopropoxide, potassium permanganate, or lead tetraacetate in acetone. Chromium trioxide in *tert*-butyl alcohol did give some product, but in very low yield. The RuO_4, however, gave the corresponding 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentos-3-ulose *30* in 55% yield [28, 29].

It has been reported that prolonged treatment of some aldofuranose derivatives with excess of ruthenium tetroxide [28, 29] gives lactones by an oxygen insertion

Table 10.1 Ruthenium tetroxide oxidation of various partially protected monosaccharides

Monosaccharide	Oxidation product	Yield (%)
Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside *9*	Methyl 6-deoxy-2,3-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose *10*	
Methyl 6-deoxy-3,4-*O*-isopropylidene-α-L-galactopyranoside *11*	Methyl 6-deoxy-3,4-*O*-isopropylidene-α-L-*lyxo*-hexopyranosidulose *12*	70 (crude) 45 (pure)
Methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside *13*	Methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose *14*	80 (crude) 40 (pure)
Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside	Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose	47
1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *17*	1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose *18*	ca. 75
Methyl 3,4,6-tri-*O*-benzoyl-α-D-glucopyranoside *19*	Methyl 3,4,6-tri-*O*-benzoyl-α-D-*arabino*-hexopyranosidulose *20*	50
Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside *21*	Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-3-hexopyranosid-3-ulose *22*	47
Methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside *23*	Methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulfonyl-α-D-*ribo*-hexopyranosid-3-ulose	85
Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside *25*	Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-hexopyranosid-3-ulose	89
Methyl 2,3-di-*O*-methyl-6-*O*-tosyl-α-D-glucopyranoside *27*	Methyl 2,3-di-*O*-methyl-6-*O*-p-toluene-sulfonyl-α-D-*xylo*-hexopyranosid-4-ulose	83
Methyl 2,3-di-*O*-benzoyl-β-L-arabinopyranoside *29*	Methyl 2,3-di-*O*-benzoyl-β-L-*threo*-pentopyranosid-4-ulose	93

Note. The oxidation products of the first four monosaccharides were identical with the samples obtained when CrO_3–Py was used as the oxidant.



29, 5-O-Benzoyl-1,2-O-isopropylidene-α-D-xylofuranose

30, 5-O-Benzoyl-1,2-O-isopropylidene-α-D-*erythro*-pentos-3-ulose

Fig. 10.7

reaction into the initially formed glycosuloses. The problem of this over oxidation is minimized if instead of sodium metaperiodate and sodium bicarbonate, potassium metaperiodate and potassium carbonate that are sparingly soluble in water are used for the reoxidation of ruthenium dioxide to ruthenium tetroxide [30].

The improved procedure for oxidation of "isolated" secondary hydroxyl groups to ketones in partially protected sugar derivatives:

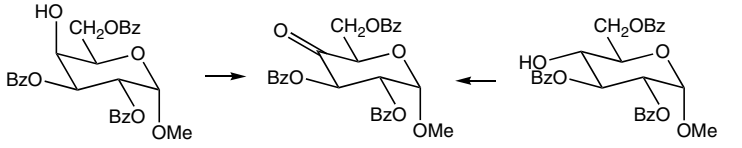
A partially protected carbohydrate is dissolved in enough ethanol-free chloroform to give an approximately 15% solution, and the equal volume of water is

added. For each mole of substrate, 0.24 mol of anhydrous potassium carbonate, 1.3 mol of potassium periodate, and a catalytic amount (ca. 0.05 mol) of ruthenium dioxide as dihydrate are then added. The reaction mixture is vigorously stirred and the progress of oxidation is followed by tlc. At the end of reaction, the isopropyl alcohol is added to the reaction mixture to reduce the residual ruthenium tetroxide. The ruthenium dioxide is removed by filtration of the suspension, and the two layers are separated. The aqueous layer is extracted with chloroform, and the combined extract and washings dried, and evaporated in vacuo to give the oxidized product.

A few examples of monosaccharides that are successfully oxidized by using the *improved* procedure and the yields of "uloses" obtained are listed in Table 10.1 and in Fig. 10.8. Both methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside *31* and 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside *33* (Fig. 10.8) were oxidized with RuO_4 (using the equivalent amount of oxidant) whereby pure, crystalline methyl 2,3,6-tri-*O*-benzoyl-α-D-*xylo*-hexopyranosid-4-ulose *32* was obtained in good yields (81% from *31* and 79% from *33*) [31] (Fig. 10.8).

The *p*-toluenesulfonyl group is stable toward the oxidant, as shown by oxidation of 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside to the corresponding 3-ulose (Fig. 10.8). However, after 20 h only about 15% of the corresponding 3-ulose was obtained in addition to almost 50% of starting material [31] (the oxidation was performed with an equivalent amount of RuO_4). Thus this oxidation procedure has no advantage over the Pfitzner–Moffatt method [32] (vide infra).

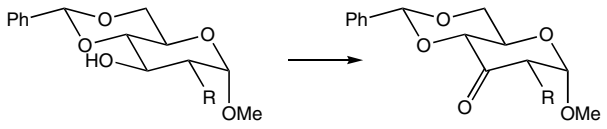
The RuO_4 was also used for the oxidation of acetamidoglucosides (Fig. 10.8). For example, using the catalytic amount of RuO_4 methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside yielded the corresponding 3-ulose in 58% yield, which is not as good as the oxidation of the same substrate by Pfitzner–Moffatt reagent [32] (vide infra).



31, methyl 2, 3, 6-tri-O-benzoyl-α–D-galactopyranoside

32, methyl 2 ,3, 6-O-tri-O-benzoyl-α-D-*xylo*-hexopyranosid-4-ulose

33, Methyl 2, 3, 6-tri-O-benzoyl-α-D-glucopyranoside



23, R = OTs, Methyl 4,6-O-Benzylidene-2-O-p-toluene-sulfonyl-α-D-glucopyranoside

34, R= AcNH, Methyl 2-acetamido-4,6-benzylidene-2-deoxy-2-α-D-glucopyranoside

24, R = OTs, Methyl 4,6-O-benzylidene-2-O-p-toluenesulfonyl-α-D-*arabino*-hexopyranosid-2-ulose

35, R = AcNH, Methyl 2-acetamido-4,6-O- benzylidene-2-deoxy-α-D-*arabino*-hexopyranosid-2-ulose

Fig. 10.8

Dimethyl Sulfoxide Oxidation

The structure of dimethyl sulfoxide (DMSO) is usually represented as a resonance hybrid of the following two resonance structures (Fig. 10.9).

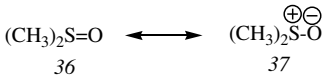


Fig. 10.9

Resonance structure *36* (Fig. 10.9) owes its existence to the ability of the *3d* orbital of sulfur to accommodate an additional electron pair, in this case the *p* electrons of oxygen [33]. Although there is still debate over which hybrid best represents the structure of DMSO, or sulfoxides in general, it seems certain that the sulfur–oxygen bond can be justly characterized as being *semipolar* [34]. The molecular structure of dimethyl sulfoxide from spectroscopic and gas electron diffraction data and the force field and ab initio calculations support earlier observations emphasizing the needlessness of the hypervalency concept for describing the bonding properties in DMSO because the S:O bond is ionic and thus the octet rule is not violated [35].

The oxidizing capacity of DMSO is directly dependent on its ability to act as a nucleophile. Its basicity is slightly greater than that of water [36], and its nucleophilicity has been estimated to exceed that of ethanol toward alkylsulfonate esters [37].

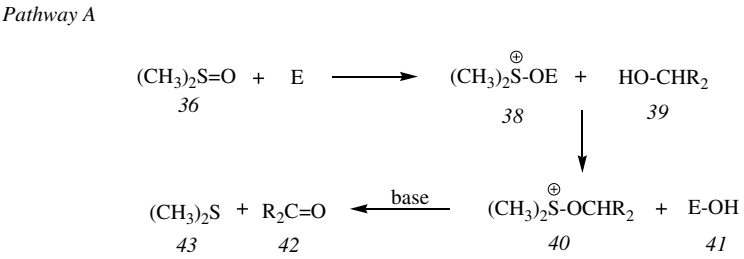


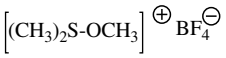
Fig. 10.10

E = electrophile.

There are two routes by which a substrate may be converted into dimethylalkoxysulfonium salt intermediate *40*; which route will be taken is determined by the structure of substrate. These two routes are illustrated in Figs. 10.10 and 10.12.

The first pathway (*Pathway A*) (Fig. 10.10) involves reaction of DMSO with an "activating" electrophilic species E forming intermediate *38*; the EO group is subsequently displaced by a substrate that is to be oxidized, usually a hydroxyl group. There is a strong indication that most of the DMSO oxidations involve the formation of the same *dimethylalkoxysulfonium salt intermediate 40* (Fig. 10.10) which

subsequently reacts with a base to give the carbonyl product *42* and dimethyl sulfide *43* [$(CH_3)_2S$ = DMS]. It has been demonstrated that dimethyl methoxysulfoxonium trifluoroborate *44* (Fig. 10.11) forms formaldehyde in the presence of a base [38, 39]. In the presence of sodium ethoxide and sodium isopropoxide it under-



44

Fig. 10.11

goes rapid alkoxide exchange, with inversion of configuration at the sulfur [40, 41] that is followed by subsequent formation of acetaldehyde and acetone, respectively [38, 39].

The oxidation of alkyl halides or sulfonates is thought to proceed via the same transition state intermediate dimethylalkoxysulfonium salt *40* which is, however, directly formed by bimolecular nucleophilic displacement of the leaving group X (X = Cl, Br, I, or a sulfonate) linked to the carbon that is to be oxidized by the oxygen of DMSO [42–45] (*Pathway B*) (Fig. 10.12).

Pathway B

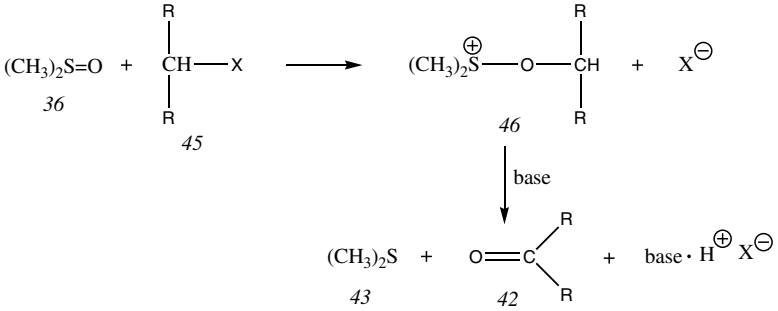


Fig. 10.12

Although not experimentally verified, the mechanism proposed above is generally accepted as the reaction mechanism. It should be, however, pointed out that it is quite possible that both bimolecular and unimolecular processes are operative depending on the substrate [46].

DMSO–DCC Method (Pfitzner–Moffatt Oxidation)

Pfitzner–Moffatt oxidation [47–49] involves addition of an alcohol substrate to a solution of DCC (dicyclohexyl carbodiimide) in DMSO containing phosphoric acid or pyridinium trifluoroacetate as a proton source resulting in nearly neutral reaction condition. This method is applicable for oxidation of both primary and secondary

hydroxyl groups of carbohydrates. Steric effects are not important except in highly hindered structures where the oxidation of less hindered hydroxyl group will be favored. Tosylates, tertiary alcohols, olefins, and amines are unaffected by the reaction condition.

The mechanism illustrated in Fig. 10.13 was proposed by Albright and Goldman [50]. It was later proved to be correct by using ^{18}O-labeled DMSO (all of ^{18}O-label ended up in *N,N′*-dicyclohexylurea) and by using deuterium-labeled carbon bearing hydroxyl group which is to be oxidized (deuterium-labeled DMSO was isolated from the reaction) [51].

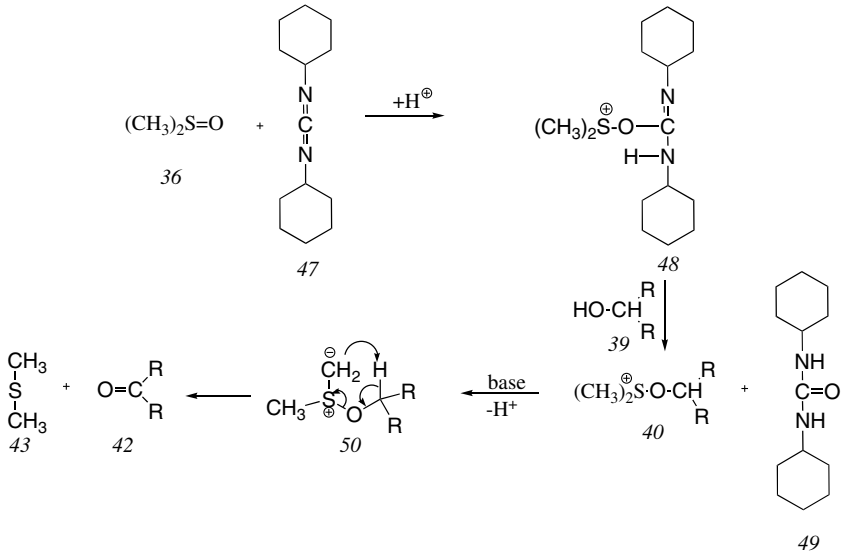
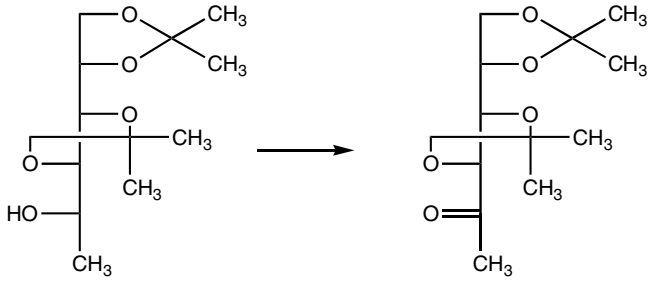


Fig. 10.13

Oxidation of 1,2:3,4-di-*O*-isopropylidene-L-rhamnitol (*51*, Fig. 10.14) with Pfitzner–Moffatt reagent (DMSO–DCC–anhydrous H_3PO_4) (25–30°C, 18 h) yields 1-deoxy-3,4:5,6-di-*O*-isopropylidene-L-fructose *52* in 49.5% yield. The oxidation of the same substrate with DMSO–P_2O_5 (25–30°C, 48 h) gave the same product in 34% yield [52].

Methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside *53* (Fig. 10.15) gave on oxidation with DMSO–DCC, in the presence of pyridine and trifluoroacetic acid (30°C, 18 h), methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose *54* in 71% yield whereas oxidation of *53* with DMSO–Ac_2O (30°C, 24 h) gave *54* in even better yield (81%) [52].

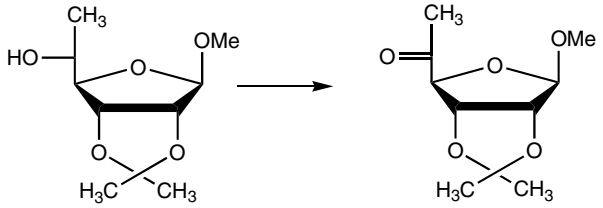
Oxidation of 3-*O*-benzyl-2,4-ethylidene-D-erythritol *55* with DMSO–DCC–pyridinium trifluoroacetate (room temperature, 20 h) gave 3-*O*-benzyl-2,4-*O*-ethylidene-aldehydo-D-erythrose *56* in 84.6% yield, whereas with DMSO–Ac_2O the same substrate could not be oxidized into the corresponding aldehyde *56* [53] (Fig. 10.16).



51, 1,2:3,4-di-O-isopropylidene-L-rhamnitol

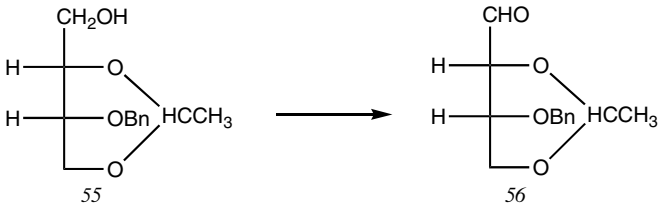
52, 1-deoxy-3,4:5,6-di-O-isopropylidene-L-fructose

Fig. 10.14



53 *54*

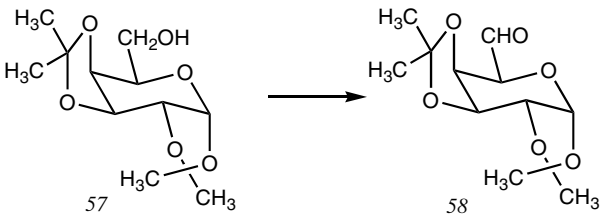
Fig. 10.15



55 *56*

Fig. 10.16

Oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *57* with DMSO–DCC–pyridinium phosphate in benzene (room temperature, 5 h) gave 1,2:3,4-di-



57 *58*

Fig. 10.17

O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose *58* in about 80% yield [54] (Fig. 10.17).

DMSO–Acetic Anhydride Method

In this method the DMSO is activated by acetic anhydride and is used for oxidation of primary and secondary hydroxyl groups to corresponding carbonyl groups and is essentially similar to the Pfitzner–Moffatt method [55].

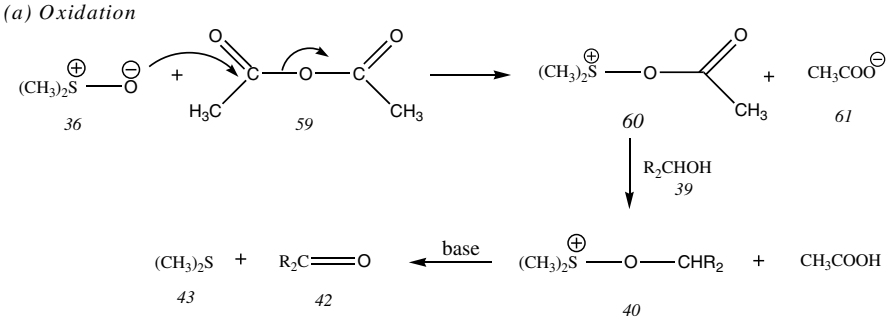


Fig. 10.18

The reaction of DMSO and organic acid anhydrides has been well studied [39, 56–58] and the intermediate *60* (Fig. 10.18), which results from nucleophilic attack of DMSO at one carbonyl carbon of acetic anhydride, may undergo two reactions: it can either react with an alkoxy group and form dimethylalkoxysulfonium salt *40* which is then transformed to carbonyl group by action of a base, or the acetate can be eliminated from *60* via an intramolecular hydrogen transfer *62* [59] giving sulfonium ylide *63* which on reaction with the hydroxyl group of a carbohydrate gives a side product methylthiomethyl ether *64* [55] (Fig. 10.19).

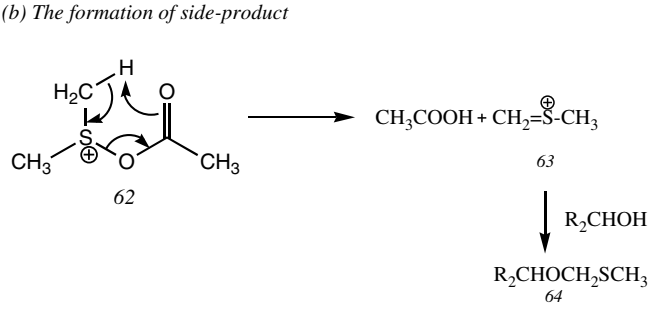


Fig. 10.19

Compared to Pfitzner–Moffatt method this method of oxidation, in general, gives lower yields of corresponding carbonyl compounds when unhindered primary and the secondary hydroxyl groups are oxidized. Methylthiomethyl ethers and acetates are also obtained as side products. The method appears to be superior to the DMSO–DCC oxidation of hindered hydroxyl groups.

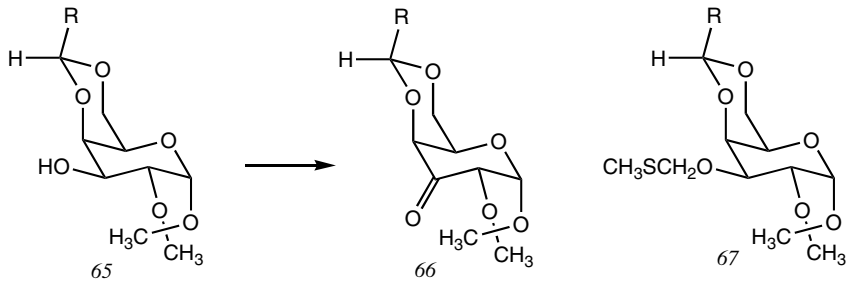
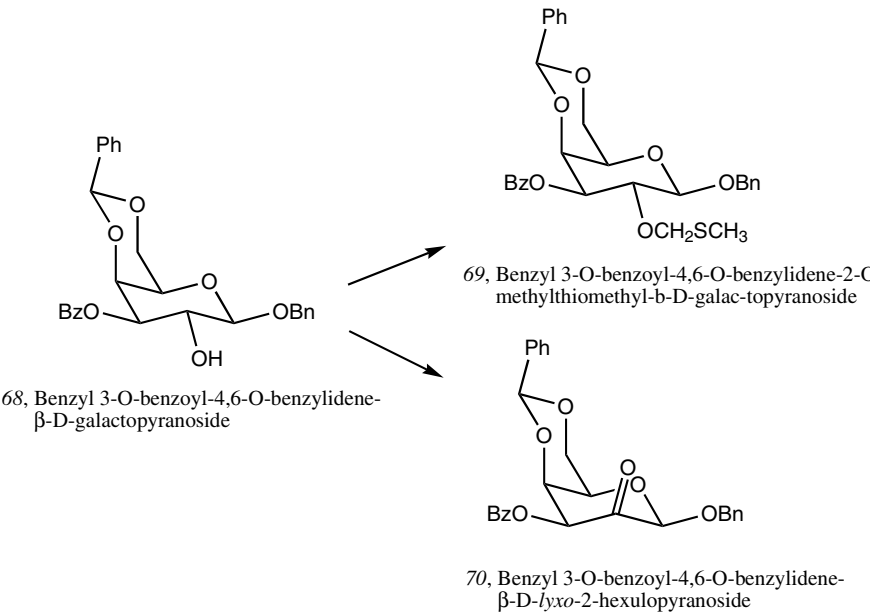


Fig. 10.20

Oxidation of 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-α-D-galactopyranose *65* (Fig. 10.20) with DMSO–Ac_2O (25°C, 36 h) gave in 44% yield 4,6-*O*-ethylidene-1,2-*O*-isopropylidene-α-D-*xylo*-hexopyranosid-3-ulose *66* together with the 3-*O*-methylthiomethyl ether *67* (19%); oxidation of *62* with DMSO–P_4O_{10} (65°C, 2 h) gave *66* in 63% yield [60, 61].



68, Benzyl 3-O-benzoyl-4,6-O-benzylidene-β-D-galactopyranoside

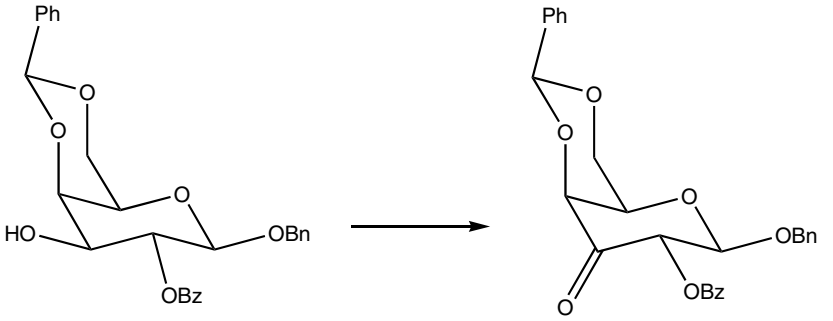
69, Benzyl 3-O-benzoyl-4,6-O-benzylidene-2-O-methylthiomethyl-b-D-galac-topyranoside

70, Benzyl 3-O-benzoyl-4,6-O-benzylidene-β-D-*lyxo*-2-hexulopyranoside

Fig. 10.21

The oxidation of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside *68* with DMSO–Ac_2O (25°C, 4 days) gave almost exclusively the 2-*O*-methylthiomethyl ether *69* (81% yield) (Fig. 10.21); the oxidation product 2-ulose *70* could be detected only in traces (tlc). However, oxidation of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside *68* with DMSO–P_4O_{10} (60°C, 15 h) gave benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*lyxo*-2-hexulopyranoside *70* in 73.5% [60, 61] (Fig. 10.21).

Oxidation of benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside *71* with DMSO–Ac_2O gave a complex mixture of products (tlc), but the oxidation with DMSO–P_4O_{10} (60–65°C, 14 h) gave benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*xylo*-hexo-pyranosid-3-ulose *72* in 62.5% yield [60, 61] (Fig. 10.22).

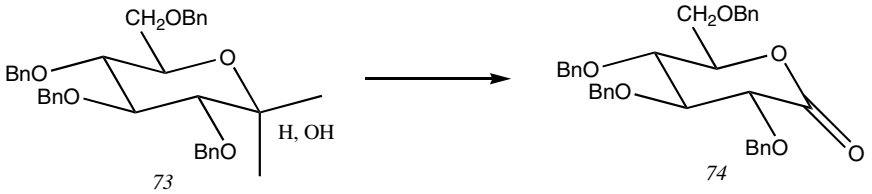


71, Benzyl 2-O-benzoyl-4,6-O-benzylidene-β-D-galactopyranoside

72, Benzyl 2-O-benzoyl-4,6-O-benzylidene-β-D-*xylo*-3-hexulopyranoside

Fig. 10.22

Oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose *73* with DMSO–Ac_2O (room temperature, overnight) gave 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone *74* in 84% yield [62] (Fig. 10.23).



73 *74*

Fig. 10.23

However, the oxidation of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose *75* with DMSO–P_4O_{10} at elevated temperature gave methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate *76* [63] (Fig. 10.24). It is highly probable that 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone was the initial product of oxidation which was converted to the corresponding methyl ester, via solvolysis with methanol during the work-up.

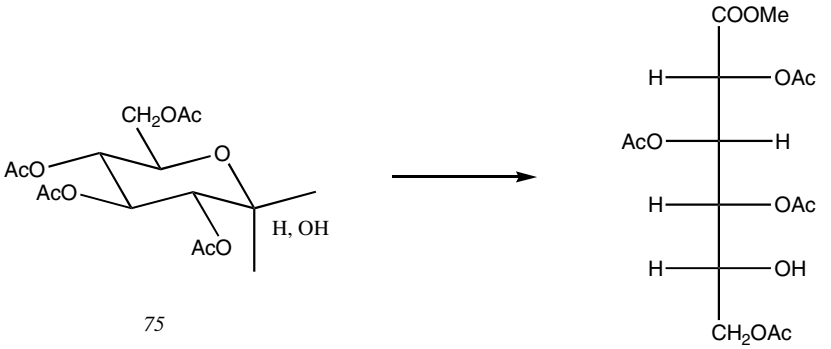


Fig. 10.24

Oxidation of 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose *77* with DMSO–Ac_2O (room temperature, 48 h) gave 1,2:5,6-di-*O*-isopropylidene-β-D-*erythro*-hexopyranos-2,3-diulose *78* in 70% yield [64] (Fig. 10.25).

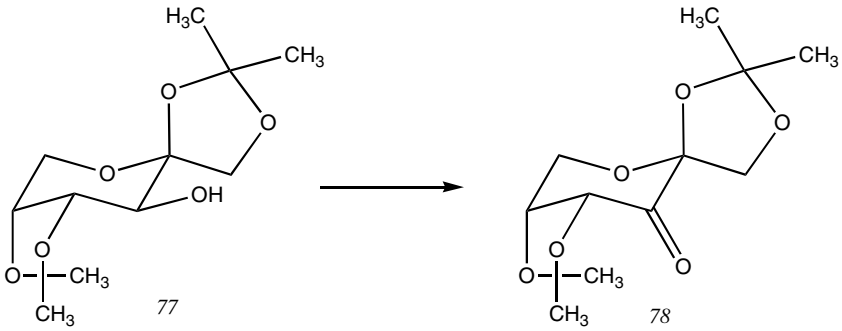


Fig. 10.25

Oxidation of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose *29* with DMSO–Ac_2O gave 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-3-pentosulofuranose *30* in only 31% yield [65] (Fig. 10.26).

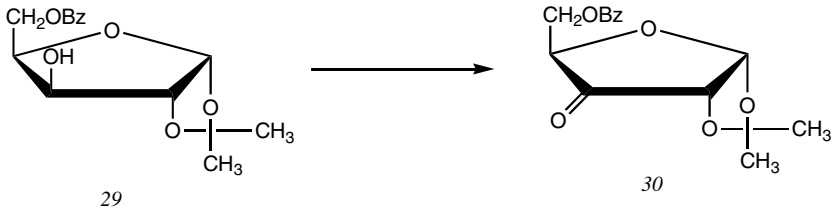


Fig. 10.26

The oxidation of 2,3,4,6-tetra-*O*-benzyl-*N,N*-dimethyl-D-gluconamide *79* with DMSO–Ac_2O (room temperature, overnight), gave 2,3,4,6-tetra-*O*-benzyl-*N,N*-

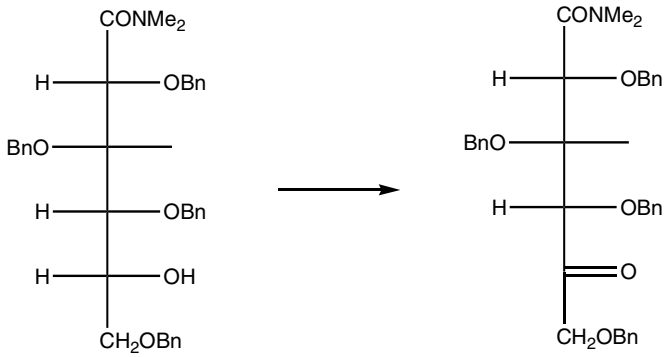


Fig. 10.27

dimethyl-D-*xylo*-5-hexulosonamide *80* (1,3,4,5-tetra-*O*-benzyl-*N,N*-dimethyl-L-sorburonamide) in almost 80% yield [66] (Fig. 10.27).

Oxidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-altropyranose *81* with DMSO–Ac_2O (room temperature, 24 h) gave 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-allono-1,5-lactone *82* in 93% yield as a single product (Fig. 10.28). It is inter-

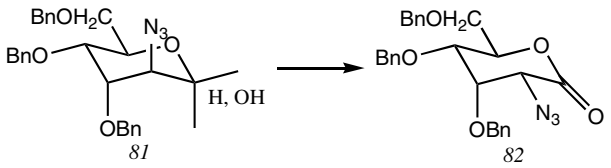


Fig. 10.28

esting that the epimerization of the C2 azido group during the oxidation reaction was almost quantitative. The oxidation of 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-allopyranose *83* with DMSO–Ac_2O (room temperature, 24 h) gave 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-allono-1,5-lactone *84* in 100% yield [67] (Fig. 10.29).

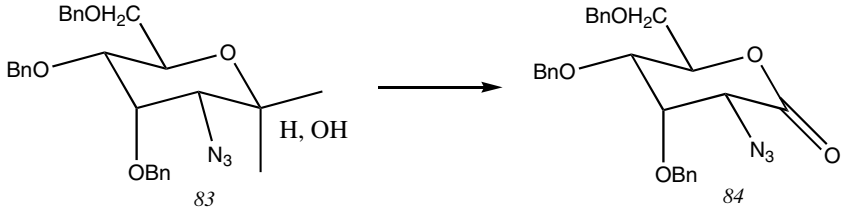
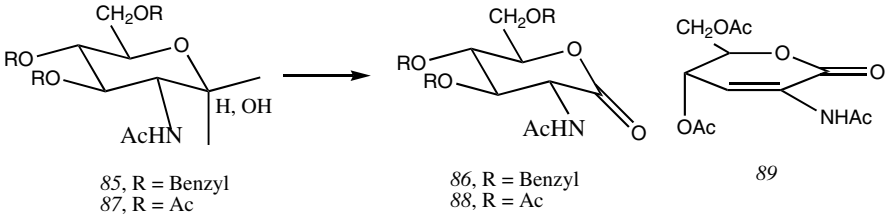


Fig. 10.29

Oxidation of 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose *85* with DMSO–Ac_2O (room temperature, overnight) gave the 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone *86* in 92% yield [68] (Fig. 10.30).



85, R = Benzyl
87, R = Ac

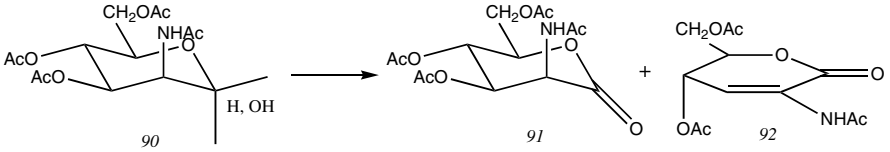
86, R = Benzyl
88, R = Ac

89

Fig. 10.30

However, the oxidation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose *87* with DMSO–Ac_2O (room temperature, overnight) gave 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucono-1,5-lactone *88* in only 15% yield. The major product, obtained in 50% yield, was the 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone *89* an oxidation-elimination product [68] (Fig. 10.30).

The oxidation of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-mannopyranose *90* with DMSO–Ac_2O (room temperature, overnight) gave, however, the expected 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-manno-1,5-lactone *91* as the major



90

91

92

Fig. 10.31

product (42%); the unsaturated 1,5-lactone *92* (the oxidation-elimination product) was obtained in only 16% yield [68] (Fig. 10.31).

The above experiments suggest that DMSO–Ac_2O oxidation of the C1-hydroxyl group to lactone is proceeding smoothly when hexopyranose is alkylated, but when it is acylated it undergoes significant oxidation elimination giving the unwanted unsaturated sugar lactones sometimes as the major product.

DMSO–Phosphorus Pentoxide

DMSO and phosphorus pentoxide have been used for a limited number of carbohydrate oxidations [32, 63]. No mechanistic details have been elaborated, but in light of previous mechanisms, phosphorus pentoxide (P_4O_{10}), which is an anhydride, probably acts as an electrophile (E group) to activate the DMSO, resulting in

oxidation via pathway A. This oxidation method like DMSO–Ac_2O is capable to oxidize some carbohydrates that are inert to Pfizner–Moffat oxidation [32, 63]. The formation of methylthiomethyl ether has also been reported to be the side product in this oxidation [69] as was previously observed in DMSO–Ac_2O oxidations.

Oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *17* with DMSO–P_2O_5 (50°C, 48 h) 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofurano-3-ulose *18* in 45% yield [52] (Fig. 10.5). When the oxidation was performed at room temperature for 24 h 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofurano-3-ulose *18* was obtained in 65% yield [63].

Oxidation of methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulfonyl-α-D-glucopyranoside *23* with DMSO–P_2O_5 gives methyl 4,6-*O*-benzylidene-2-*O*-*p*-toluenesulfonyl-α-D-*ribo*-hexopyranosod-3-ulose *24* (Fig. 10.6) in 49% yield [52], whereas oxidation of benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside *71* with DMSO–P_4O_{10} (in dimethylformamide solution) (60–65°C, 14 h) gives benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*xylo*-3-hexulopyranoside *72* in 62.5% yield [60, 61] (Fig. 10.22).

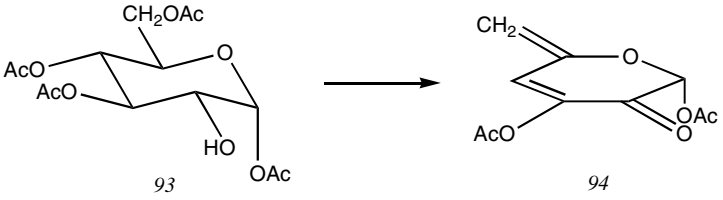
DMSO–Sulfurtrioxide Pyridine ("Parikh–Doering" Oxidation)

Primary and secondary alcohols can be oxidized to aldehydes and ketones with pyridinium–sulfurtrioxide–DMSO complex, in the presence of triethylamine [70, 71].

Methylthiomethyl ether derivative of a carbohydrate, which is often formed in significant quantities as by-product in DMSO–acetic anhydride oxidation, is formed in negligible amounts in "Parikh–Doering" oxidation and the yields of aldehydes or ketones compare favorably with those obtained in the DMSO–DCC method.

1,2:4,5-di-*O*-Isopropylidene-β-D-fructopyranose *77* was oxidized with DMSO-SO_3·Py-Et_3N to 1,2:5,6-di-*O*-isopropylidene-β-D-*erythro*-hexopyranos-2,3-diulose *78* (Fig. 10.25) in 65% yield [72]. Only a trace of methylthiomethyl ether was obtained.

Oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *57* with DMSO-SO_3Py.-Et_3N gave 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose *58* in 85% yield [72] (Fig. 10.17).

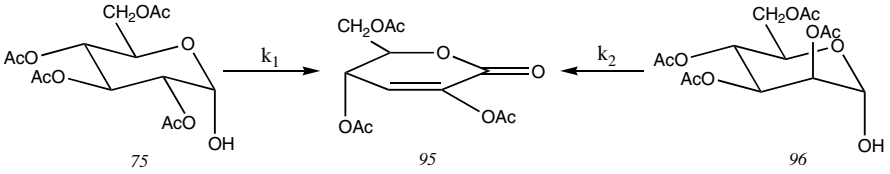


93 *94*

Fig. 10.32

Oxidation of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose *93* (Fig. 10.32) with DMSO-SO_3·Py-Et_3N gives the elimination product 3,5-diene-2-one *94* in 61% yield [72].

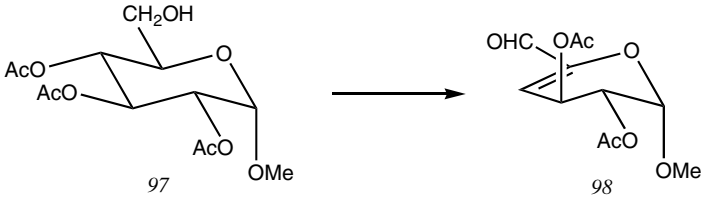
Oxidation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose *75* gives 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-en-2-ol-1,5-lactone *95* in 81% yield, whereas the oxidation of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranose *96* under the same reaction conditions also gives the oxidation-elimination lactone *95*, but the reaction was three times slower ($k_2 = 1/3\ k_1$) [72](Fig. 10.33).



75 *95* *96*

Fig. 10.33

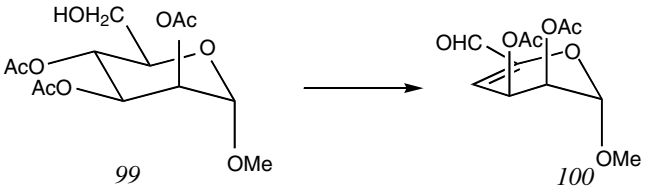
Oxidation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside *93* with DMSO-SO_3·Py-Et_3N gives methyl 2,3-di-*O*-acetyl-6-aldo-4-deoxy-β-L-*threo*-hex-4-enopyranoside *94* in (82% yield) [72] (Fig. 10.34).



97 *98*

Fig. 10.34

Oxidation of methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside *99* with DMSO-SO_3·Py-Et_3N (room temperature, 15 min) gave methyl 2,3-di-*O*-acetyl-6-aldo-4-deoxy-β-L-*erythro*-hex-4-enopyranoside *100* in 75% yield [72] (Fig. 10.35).



99 *100*

Fig. 10.35

Chromium Trioxide Oxidation

The mechanism of the chromic acid or its anhydride chromium trioxide oxidations has been very thoroughly investigated [73].

It has been postulated that the initial step in chromium trioxide oxidations is fast and reversible esterification of the hydroxyl group that is to be oxidized with chromium trioxide and the formation of a chromic acid ester. This is followed by a rate-determining deprotonation of the carbinol carbon. This deprotonation can be an

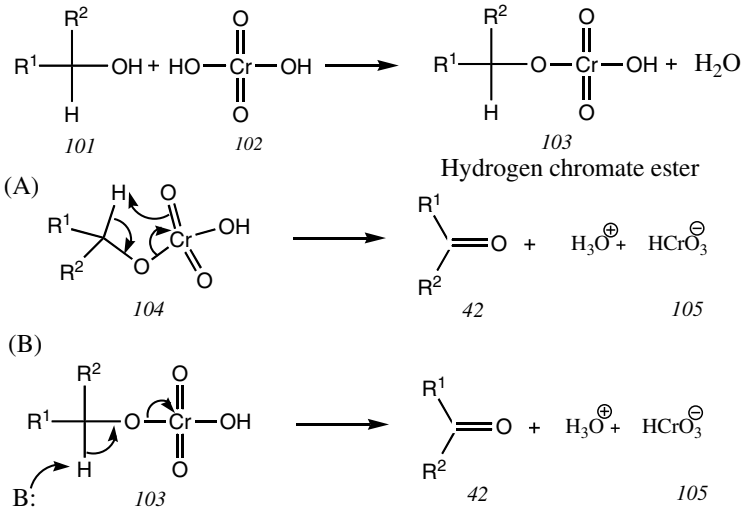


Fig. 10.36

intramolecular process involving the formation of a five-membered cyclic transition state *104* (A in Fig. 10.36) or it could be an *intermolecular* process with a water molecule acting as a general base, or pyridine molecule or any other anion serving as a base (B in Fig. 10.36). In any case, the electron pair of the carbinol carbanion formed by deprotonation of *103* is transferred to alcoholic oxygen that takes place simultaneously with the breaking of the oxygen–chromium bond and the transfer of the electron pair of the chromium oxygen bond to chromium (two-electron reduction of chromium) (Fig. 10.36).

Chromium Trioxide–Pyridine Oxidation

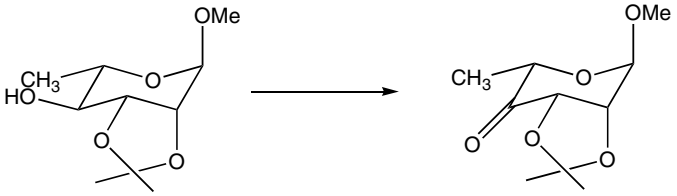
The chromium trioxide–pyridine complex [74–76] is a well-established reagent for the oxidation of primary and secondary alcohols to corresponding carbonyl derivatives in the steroid field. The oxidant was found to be also effective for the oxidation

of primary and secondary hydroxyl groups of suitably protected carbohydrates. This topic together with some other oxidants has been reviewed [77].

The oxidation is generally performed in dichloromethane [78] (12.5 g of the reagent dissolves in 100 mL of dichloromethane at room temperature) and the dichloromethane solution of the oxidant is prepared in situ [79]. Using 12:1 molar ratio of oxidant to substrate the primary alcohols of carbohydrates have been smoothly oxidized to aldehydes in 53–75% yield [80].

Sugar derivatives with sterically hindered endocyclic secondary hydroxyl groups, such as the 3-OH in 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *17*, could not be oxidized with CrO_3–pyridine complex to the corresponding 3-ulose *18* [25–27] (Fig. 10.5).

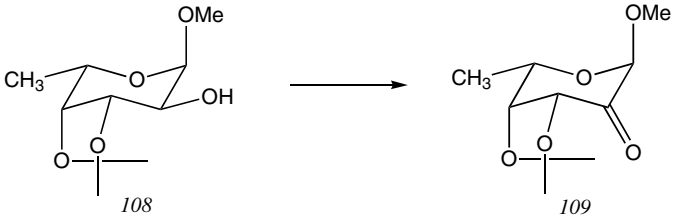
Oxidation of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside) *106* with CrO_3–pyridine complex in pyridine gives in ca. 50% yield (34% pure) methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose [81] *107* (Fig. 10.37).



106 *107*

Fig. 10.37

Oxidation of methyl 6-deoxy-3,4-*O*-isopropylidene-α-L-galactopyranoside (methyl 3,4-*O*-isopropylidene-α-L-fucopyranoside) *108* with CrO_3–pyridine complex in pyridine gives methyl 6-deoxy-3,4-*O*-isopropylidene-α-L-*lyxo*-hexopyranosidulose *109* in 36% yield [82] (Fig. 10.38).



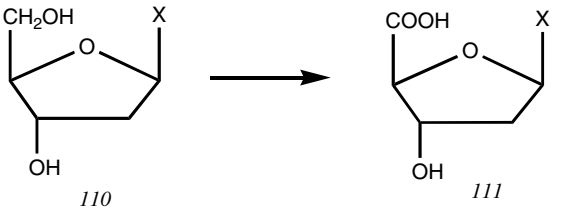
108 *109*

Fig. 10.38

Oxidation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside *15* with CrO_3–pyridine complex in pyridine gives methyl 4.6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *16* in 52% yield [83] (Fig. 10.5).

Oxidation of methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside *13* with CrO_3–pyridine in pyridine gave, after 20 h, 48% of methyl 3,4-*O*-isopropylidene-β-L-*erythro*-pentopyranosidulose [84] *14* (Fig. 10.5).

Treatment of 2′-deoxyribonucleosides *110* with CrO_3–pyridine gives the corresponding uronic acids *111* (Fig. 10.39). However, the free purine or pyrimidine bases are obtained in appreciable amount as the reaction side products [85] (Fig. 10.39). The formation of free purines or pyrimidines during these oxidations was probably due to the oxidation of the 3′-hydroxyl group to the carbonyl group, thus making the 2′-hydrogen atoms more acidic and prone to deprotonation by a base which results in a base-catalyzed elimination of the purine or pyrimidine (Fig. 10.39).



X = thymine, cytosine, adenine, guanine

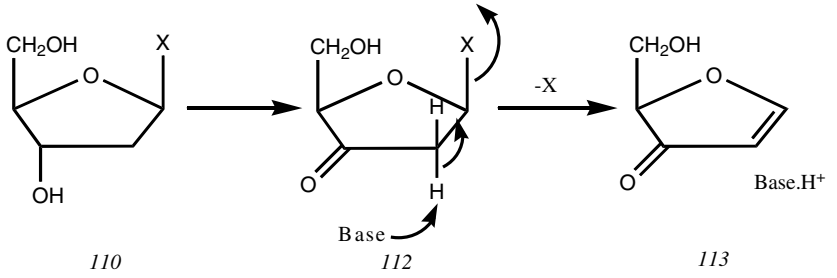


Fig. 10.39

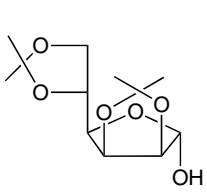
Garegg and Samuelson [86] studied the oxidation of carbohydrates with CrO_3–pyridine complex in dichloromethane in the presence of 1 mol of acetic anhydride per mole of oxidant. The oxidations were performed at room temperature with the excess of oxidant. The experiments with various molar ratios of reagent and hydroxyl compound demonstrated that the optimal results, with almost quantitative yields of oxidized product formed in 5–10 min, were obtained when a 4:1 ratio was used. The results are presented in Table 10.2 and some of the structures in Fig. 10.40

A strong dependence of yield upon the molar excess of used oxidant was observed for 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *58* only. With a molar ratio of 3:1 and 30-min reaction time, the yield of 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose was ca. 65%. A molar ratio

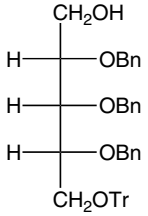
Table 10.2 Oxidation of various partially protected carbohydrates

Starting sugar	Product	Yield (%)
1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (*17*)	3-ulose	>90
Methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-glucopyranoside (*23*)	3-ulose	95
1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (*58*)	6-aldehyde	93
2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (*114*)	1,4-lactone	97
2,3,4-tri-*O*-benzyl-6-*O*-trityl-D-ribitol (*115*)	1-aldehyde	87

of 4:1 and a 5-min reaction time gave 93% yield. Variations in the reaction time indicated that the product is susceptible to further oxidation.



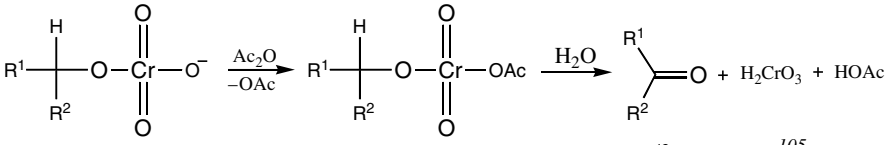
114, 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose



115, 2,3,4-tri-O-benzyl-6-O-trityl-D-ribitol

Fig. 10.40

A possible reason for the high yields obtained in the oxidation when 1 M equivalent of acetic anhydride per mole of chromium trioxide–pyridine complex is added in dichloromethane may be that the acetic anhydride facilitates the reduction of chromium (VI) from the intermediate ester as shown in Fig. 10.41. In this oxidation the acetic anhydride plays a role that is analogous to the role it plays in the methyl sulfoxide–acetic anhydride oxidation (vide supra).



103 *116* *42* *105*

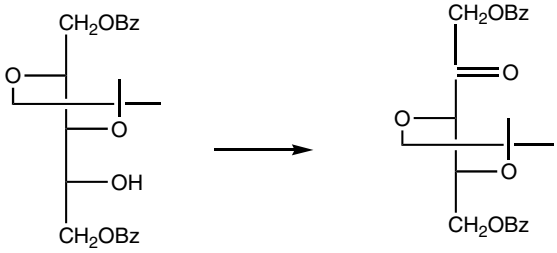
Fig. 10.41

The above speculation about the role of acetic anhydride in the oxidation of the primary or secondary hydroxyl groups to aldehydes or ketones (Fig. 10.41) is based on the generally accepted mechanism for the oxidation of alcohols to carbonyl derivatives with CrO_3 as proposed by Westheimer [87] (vide supra). As already stated, according to this mechanism a rapid and reversible formation of chromate ester is followed by rate-determining abstraction of proton from the carbinol carbon

atom. However, the initial step (esterification) may become rate-determining if the hydroxyl group which is to be oxidized is sterically highly hindered [88, 89].

Chromium Trioxide–Acetic Acid

The oxidation of 1,5-di-*O*-benzoyl-2,3-*O*-isopropylidene-D-arabinitol *117* with CrO_3–acetic acid in benzene gave 1,5-di-*O*-benzoyl-3,4-*O*-isopropylidene-D-xylulose *118* in 50% yield [90] (Fig. 10.42).



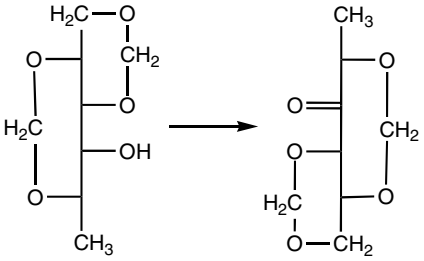
117, 1,5-di-O-benzoyl-2,3-O-isopropylidene-D-arabinitol

118, 1,5-di-O-benzoyl-3,4-O-isopropylidene-D-xylulose

Fig. 10.42

Similarly, the oxidation of 1,3:2,5-di-*O*-methylene-L-rhamnitol *119* gave 2,5:4,6-di-*O*-methylene-1-deoxy-L-*arabino*-3-hexylose *120* in 67% yield [91] (Fig. 10.43).

Stensio and Wachtmeister [92] observed that the oxidation with chromium trioxide–pyridine complex was faster when performed in acetic acid.

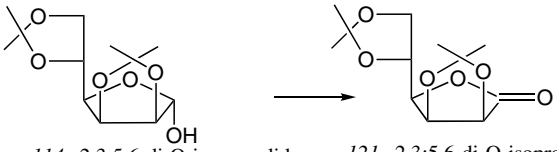


119 *120*

Fig. 10.43

Pyridinium Chlorochromate

Pyridinium chlorochromate (PCC) was found to be a useful reagent for oxidizing primary and secondary hydroxyl groups of partially protected carbohydrate

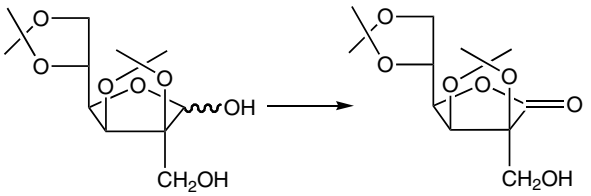


114, 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose *121*, 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose

Figure 10.44

Fig. 10.44

derivatives, and it has been used for the preparation of protected aldonolactones. PCC is an inexpensive commercially available reagent which is easy to handle. Oxidation of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose *114* gave 2,3:5,6-di-*O*-isopropylidene-α-D-mannofurano-1,4-lactone *121* in 84% yield [93] (Fig. 10.44).



122, 2,3:5,6-di-O-isopropylidene-2-C-hydroxymethyl-D-mannofuranose *123*, 2,3:5,6-di-O-isopropylidene-2-C-hydroxymethyl-D-mannofurano-1,4-lactone

Fig. 10.45

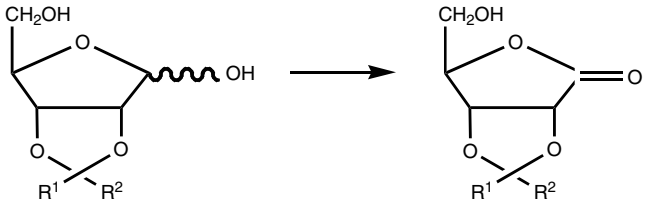
Oxidation of 2,3:5,6-di-*O*-isopropylidene-2-*C*-hydroxymethyl-D-mannofuranose *122* with PCC gave the corresponding lactone *123* in 71% yield [94] (Fig. 10.45).

Similarly, when 2,3-*O*-cyclohexylidene-D-ribose *124* is oxidized with PCC in dichloromethane the corresponding D-ribonolactones *125* is obtained without oxidation of the primary hydroxyl group [95] (Fig. 10.46). Pyridinium dichromate (PDC) gave the same result [95], while under the same reaction conditions the oxidation of 2,3-*O*-isopropylidene-D-ribose *126* with PCC gave a mixture of products.

In all procedures using chromium trioxide as oxidant the workups are tedious and almost always involve the chromatographic purification of product.

Pyridine chlorochromate is a good oxidant for a large-scale preparation of keto sugars [93] and its reactivity is increased when used together with a molecular sieve [96, 97].

Thus oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *17* with pyridine chlorochromate gave 40–45% [98] or 63% [93] of the corresponding 3-ulose *18* (Fig. 10.5). However, the yield can be increased to up to 96% by using pyridinium dichromate–acetic anhydride [99].



124, $R^1 = C_6H_{10}$; $R^2 = H$
2,3-O-cyclohexylidene-D-ribofuranose
126, $R^1 = R^2 = CH_3$
2,3-O-isopropylidene-D-ribofuranose

125, $R^1 = C_6H_{10}$; $R^2 = H$
2,3-O-cyclohexylidene-D-ribofuranolactone
127, $R^1 = R^2 = CH_3$
2,3-O-isopropylidene-D-ribofuranolactone

Fig. 10.46

Nicotine Dichromate

Nicotinium dichromate is another chromium (VI) oxidant that was reported to be useful in oxidations of partially protected carbohydrates [98, 100]. It was found that the rate of oxidation and the yield depend upon the solvent used. Thus the oxidation was very fast and yields were high when benzene was used as the solvent and 1:2 oxidant–pyridine mixture was used (see Table 10.3).

Table 10.3 Oxidation of Sugars with Nicotinium dichromate [100] (at 80°C; nicotine dichromate–pyridine molar ratio 1:2)

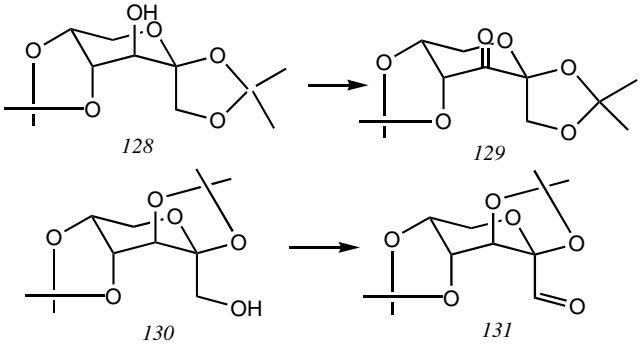
Carbohydrate	Ulose	Oxidant/sugar molar ratio	Time	Yield[a]
17	*18*	3:1	2.5 h	85(75)
58	*59*	2:1	20 min	90(75)
128	*129*	3:1	1 h	94(85)
130	*131*	3:1	30 min	92(81)

[a]The numbers in parenthesis indicate the yields of pure products (after distillation or crystallization).

The structures of compounds *128, 129, 130,* and *131* are given in Fig. 10.47.

Pyridinium Dichromate–Acetic Anhydride

Smooth and efficient oxidation of primary and secondary hydroxyl groups of partially protected carbohydrates in dichloromethane was achieved with pyridinium dichromate–acetic anhydride, whereby high yields of the corresponding uloses are obtained. Typically 0.6 M equivalent of pyridinium dichromate and 3.0 M equivalent of acetic anhydride are used. Even the unreactive hydroxyl group of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose *17* was oxidized efficiently (96% yield). In the following table the results of conducted studies [99] are given (Table 10.4).



128 *129* *130* *131*

Fig. 10.47

Table 10.4

Carbohydrate	Product	Yield (%)
23 (Fig. 10.6)	*24*	93
58 (Fig. 10.17)	*59*	71
17 (Fig. 10.5)	*18*	96

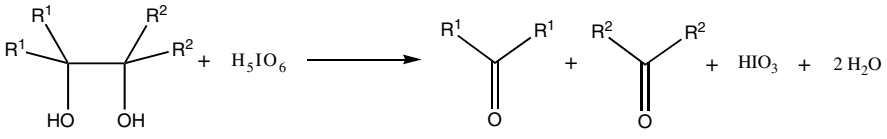
Oxidations were performed at 40°C (0.5–2.0 h) with 1.0 mmol of substrate. All yields refer to isolated product.

The use of pyridinium dichromate–acetic acid-molecular sieve system has also been described [101] for small-scale oxidation of sugars.

Oxidation of Carbohydrates with the Cleavage of Carbohydrate Chain

Periodate Oxidation

Periodic acid and its salts quantitatively cleave the carbon–carbon bond of 1,2-diols [102, 103] (Fig. 10.48).



132 *133* *134* *135*

Fig. 10.48

The periodate oxidations named "Malapradian oxidations" were quantitative and reasonably fast at room temperature. They can be carried out over a wide range of pH.

The method was soon extended to the cleavage of 1,2-hydroxycarbonyl *136* and 1,2-dicarbonyl compounds [102–104] *137* and then to the oxidation of 1,2-aminoalcohols [105] *138* (Fig. 10.49).

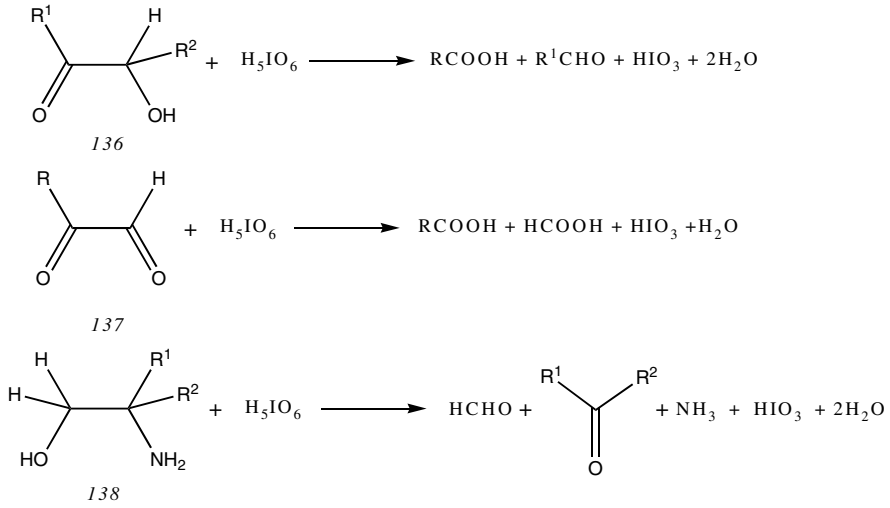


Fig. 10.49

These periodate oxidations are also chemoselective – e.g., the monofunctional alcohols, aldehydes, and ketones are either inert or react only very slowly with the reagent. However, periodate does oxidize some other organic functional groups, such as active methylene carbons, some phenols, and thiols.

Equilibrium between periodic acid and its various anions is set up rapidly; i.e., there is rapid oxygen exchange between various periodate ions and water. There is some uncertainty as to the state of periodate monoanion in water. Considering

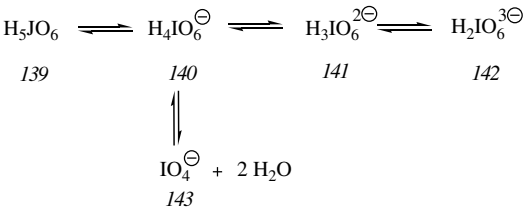


Fig. 10.50

only monomers, the main equilibria are thought [106, 107] to be as represented in Fig. 10.50. Criegee [108] observed that periodic acid, similar to lead tetraacetate,

oxidized *cis*-glycols more rapidly than *trans*-isomers and suggested that a logical interpretation for this observation is that *cis*-glycols might be forming a cyclic intermediate *145*, an ester of periodic acid (Fig. 10.51).

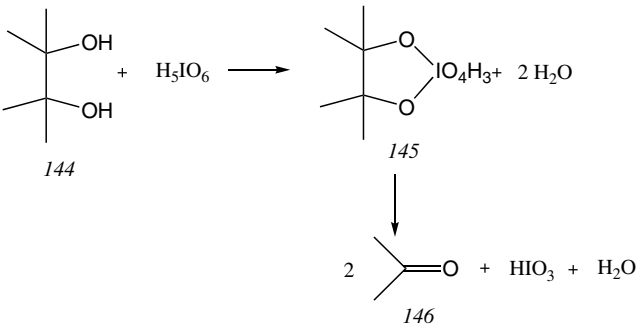


Fig. 10.51

The *cis* isomer of cyclohexane-1,2-diol was approximately 30 times more reactive than *trans* isomer, supporting thus the proposed hypothesis for the formation of cyclic diol–periodate complex [109].

The unreactivity of some 1,2-diols to periodate provided an additional strong support for the formation of a cyclic, rather than an open-chain, intermediate [110–112], because most of these unreactive 1,2-diols have geometries that prevent the formation of a cyclic periodate ester, as is the case in *trans*-decalin-9,10-diol *147* (Fig. 10.52). Although *trans*-cyclopentane-1,2-diol *148* is cleaved by periodate

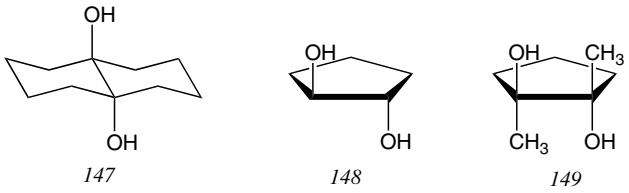


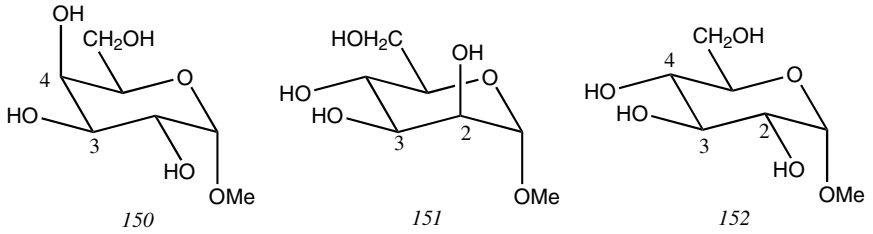
Fig. 10.52

[113, 114] the corresponding *trans*-1,2-dimethyl-cyclopentane-1,2-diol *149* is inert [115], since the formation of a cyclic intermediate would involve not only considerable distortion of the cyclopentane ring but also steric compression between nearby atoms and groups.

All these evidence suggests that a cyclic periodate ester is the key reaction intermediate, and Duke [116] showed that the kinetic form of oxidation of ethane diol by periodate could be interpreted in terms of such an intermediate *145* (Fig. 10.51), present in appreciable concentration, and decomposing slowly to product.

In full agreement with the postulate that a cyclic periodate ester is the intermediate in periodate oxidations of vicinal diols was the observation that aldohexopyranosides having *cis*-oriented hydroxyl groups in their pyranoside structures, such as the

3,4-hydroxyl groups in methyl α-D-galactopyranoside *150* or 2,3-hydroxyl groups in methyl α-D-mannopyranoside *151*, are oxidized faster than glycosides having their hydroxyl groups *trans*-oriented, as is the case in methyl α-D-glucopyranoside [117] *152* (Fig. 10.53).



150 *151* *152*

Fig. 10.53

The influence of the steric arrangements of the hydroxyl groups upon the rate of oxidation was also investigated [118–122]. Some rules for oxidation were suggested from a viewpoint of conformational analysis by Honeyman and Shaw [123, 124].

Oxidation of D-glucose was investigated in detail [125–129] (Fig. 10.54) and it was correctly concluded that the first bond cleaved was the bond between the C1 and C2 carbons, and then gradually the glycol linkages of the higher carbons are cleaved.

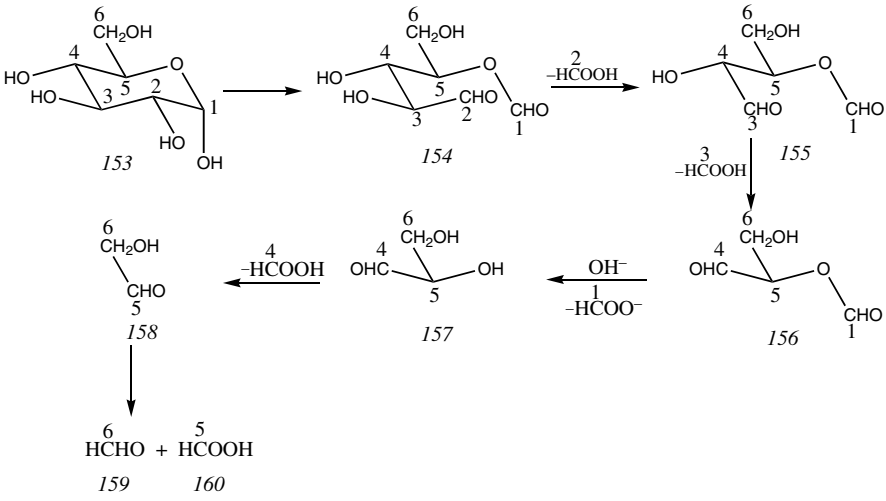
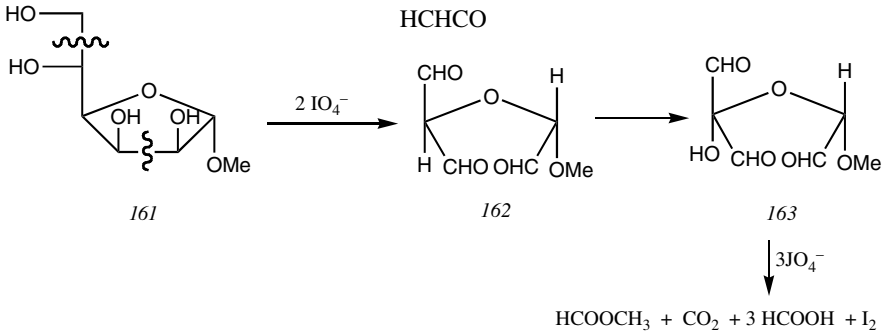


Fig. 10.54

For each 1,2-diol cleavage, there are two electrons lost from the respective carbons that are transferred to iodine of periodate reducing it to iodate, i.e., for each C–C bond cleavage 1 mol of periodate is consumed. Therefore, in the oxidation of D-glucose there will be 5 mol of periodate consumed, five formate molecules

released (one by hydrolysis of formate ester), and 1 mol of formaldehyde. So, the oxidation of diols having both hydroxyl groups secondary results in the formation of formic acid, whereas oxidation of diols in which one hydroxyl group is primary and the other secondary results in the formation of formaldehyde and formic acid. Thus, formaldehyde is liberated only at the end of oxidation.

In addition to C–C bond cleavage of the diols, the C–H bond of active methylene or methine group is also oxidized. This non-typical course of oxidation, named "overoxidation" [118, 119], sometimes accompanied with the formation of elemental iodine [117, 130, 131], is encountered in treatment of some derivatives which on oxidation yield malonaldehyde or its derivatives [118]. To such substances belong, besides some disaccharides such as cellobiose, maltose, and lactose [131–135], also some hexofuranosides (e.g. methyl α-D-mannofuranoside [136]) and some deoxy sugars [130, 137] (Fig. 10.55).



161 *162* *163*

Fig. 10.55

The overoxidation depends on pH, temperature, and concentration of both sugar and periodate [138]. Complications due to overoxidation are encountered with deoxy sugars [130, 139] as well as with some nitrogen [140–149] and sulfur-containing sugars [150–152] which yield sulfoxides or even sulfones by oxidation with periodate. Phosphate esters of sugars are also complicated [153].

Lead Tetraacetate Oxidation

Lead tetraacetate is employed in carbohydrate chemistry in a similar way as the periodic acid [154–157]; however, it is a stronger oxidant because it cleaves besides 1,2-glycols also α-ketoalcohols and α-diketones, as well as α-hydroxyacids, oxalic acid, and formic acid (Fig. 10.56).

The mechanism of oxidation of 1,2-diols by lead tetraacetate was proposed by Criegee [157] and is assumed to proceed via a five-membered ring cyclic intermediate [158, 159] (Fig. 10.57).

The proposed mechanism is supported by the following facts: (1) kinetics are second order (first order in each reactant); (2) addition of acetic acid retards the

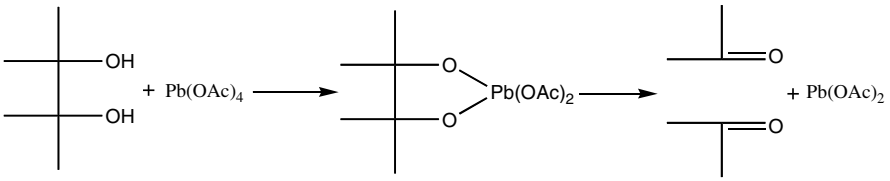


Fig. 10.56

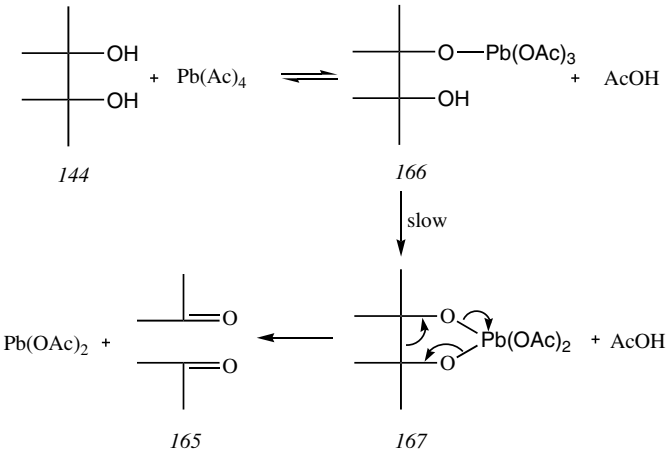


Fig. 10.57

reaction (drives the equilibrium to the left); and (3) *cis* glycols react much more rapidly than *trans* glycols [160].

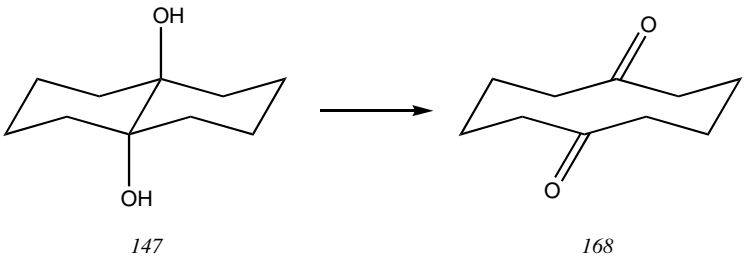
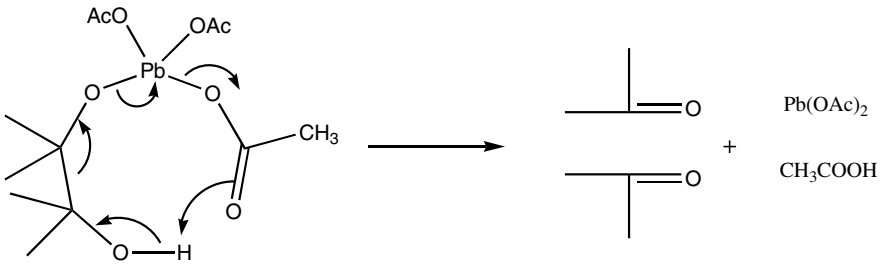


Fig. 10.58

Whereas the *trans*-decalin-9,10-diol *147* (Fig. 10.58) is inert to the oxidation with periodate, because of its inability to form the cyclic ester, it is cleaved by lead tetraacetate to cyclodecane-1,6-dione *168*, although other glycols that cannot form cyclic esters are not cleaved by either reagent [161].

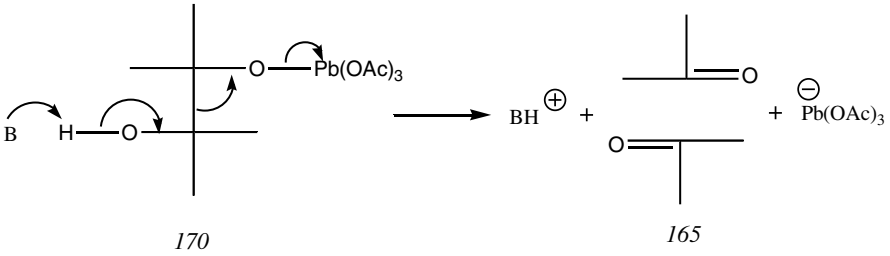
To explain the oxidation of *147* the following transition state has been proposed [160].



169 *165*

Fig. 10.59

The intermediate *169* (Fig. 10.59) might also break down with an intermolecular proton transfer to an external base [160] (*170* in Fig. 10.60), instead with an intramolecular transfer to acetate of intermediate *169,* shown in Fig. 10.59.



170 *165*

Fig. 10.60

By comparing the rates of oxidation of D-mannitol and D-glucitol (in 50% acetic acid), and D-galactitol in glacial acetic acid [162, 163] it was found that the configuration of alditol exerts little influence on the course of the reaction (Fig. 10.61).

If, however, the oxidation of hexitols was compared with the oxidation of lower alditols, the latter were found to be oxidized with greater difficulty [163, 164]. For example, in 50% acetic acid at 0°C, the percentage of the theoretical uptake of lead tetraacetate found [163] in 1-min reaction time was D-mannitol, 100; glycerol, 10; and ethylene glycol, 4. These results suggest that a *vic*-diol containing two secondary hydroxyl groups are oxidized more readily than the one containing a primary and a secondary hydroxyl group, in agreement with observations on simple aliphatic 1,2-diols [160] (Fig. 10.62).

From this it may be concluded that the oxidation occurs more rapidly toward the center of the hexitol chains than at the ends.

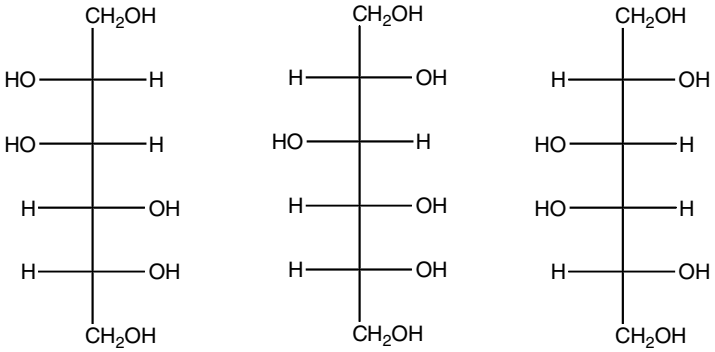


Fig. 10.61

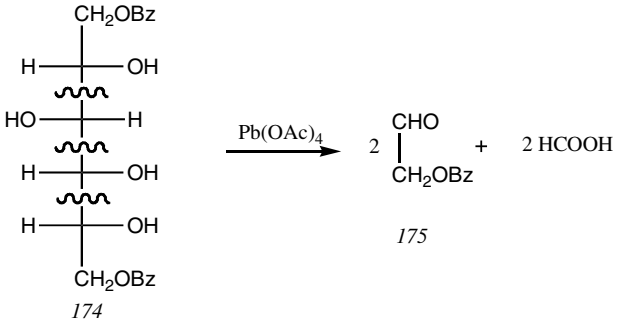


Fig. 10.62

The use of lead tetraacetate has been particularly well illustrated by Hockett and Fletcher [165] in a study of di- and tri-benzoates of D-glucitol and D-mannitol as shown in Fig. 10.63.

On dibenzoylation of D-glucitol 15 isomeric diesters are possible. However, one major product was isolated which on oxidation with lead tetraacetate gave no trace of formaldehyde, it consumed 3 moles of oxidant and produced 2 moles of formic acid. Since only primary hydroxyl groups can be converted to formaldehyde by oxidation with lead tetraacetate, the absence of formaldehyde suggests that the two primary hydroxyl groups of D-sorbitol (D-glucitol) must be the ones benzoylated. If so then the oxidation of four internal secondary hydroxyl groups will require 3 mol of lead tetraacetate (for cleavage of each C–C bond inside D-glucitol chain 1 mol of lead tetraacetate is needed) and 2 moles of formic acid *178* will be produced in addition to 2 moles of 2-*O*-benzoyl glycolaldehyde *177*. Since this was exactly what was experimentally found it was concluded that the structure of isolated D-glucitol dibenzoate is 1,6-di-*O*-benzoyl-D-glucitol [165].

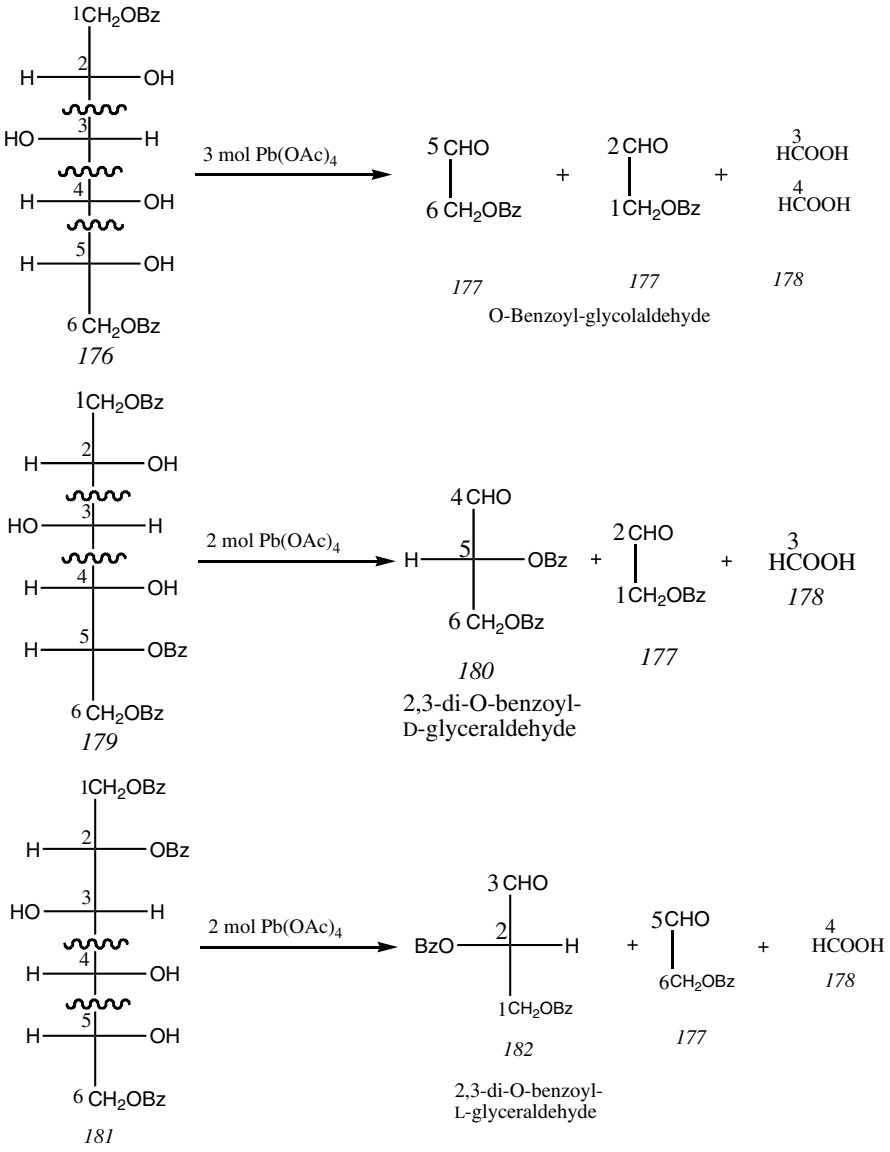


Fig. 10.63

A tribenzoyl derivative of D-sorbitol was obtained as a by-product in the preparation of 1,6-di-*O*-benzoyl-D-sorbitol (Fig. 10.63). The oxidation with lead tetraacetate of this D-sorbitol tribenzoate produced no formaldehyde, indicating that both primary hydroxyl groups must be benzoylated. The consumption of oxidant was 2 mol suggesting that two internal C–C bonds have been cleaved. The only two

possible structures that are supported by these observations are 1,2,6-tri-*O*-benzoyl-D-sorbitol and 1,5,6-tri-*O*-benzoyl-D-sorbitol. It is obvious that these two isomers cannot be distinguished by oxidation alone. However, since 1,5,6-tri-*O*-benzoyl-D-sorbitol produces 2,3-di-*O*-benzoyl-D-glyceraldehyde *180*, whereas the 1,2,6-tri-*O*-benzoyl-D-sorbitol produces the 2,3-di-*O*-benzoyl-L-glyceraldehyde *182*, by determining the configuration of the obtained 2,3-di-*O*-benzoyl-glyceraldehyde by optical rotation, it can be determined whether D-sorbitol tribenzoate was 1,2,6- or 1,5,6-.

A tribenzoyl D-mannitol derivative obtained (Fig. 10.64) as a by-product in preparation of 1,6-di-*O*-benzoyl-D-mannitol could be 1,2,6-tri-*O*-benzoyl-D-mannitol *184*, 1,5,6-tri-*O*-benzoyl-D-mannitol *185*, 1,3,6-tri-*O*-benzoyl-D-mannitol *186*, and 1,4,6-tri-*O*-benzoyl-D-mannitol *187*, under the presumption that the primary hydroxyl groups are the most reactive ones and will be benzoylated first. The oxidation with lead tetraacetate of this tribenzoyl D-mannitol gave 2,3-di-*O*-benzoyl-D-glyceraldehyde, 2-*O*-benzoyl ethanal, and 1 mol of formic acid. Two moles of oxidant are consumed, indicating the cleavage of two C–C bonds. This result is compatible only with the structures of 1,2,6-tri-*O*-benzoyl-D-mannitol *184* or 1,5,6-tri-*O*-benzoyl-D-mannitol *185*, because the lead tetraacetate oxidation of *186* or *187* would consume only 1 mol of oxidant, and both 1,3,6-tri-*O*-benzoyl-D-mannitol *186* and 1,4,6-tri-*O*-benzoyl-D-mannitol *187* would give 2-*O*-benzoyl ethanal and 2,4-di-*O*-benzoyl-D-erythrose as oxidation products. In the case of *186* the 2,4-di-*O*-benzoyl-D-erythrose will contain the carbon atoms 1–4 and 2-*O*-benzoyl ethanal the carbon atoms 5 and 6, whereas the erythrose obtained from *187* will contain the carbon atoms 3–6, whereas the 2-*O*-benzoyl ethanal will contain the carbon atoms 1 and 2. This is because the structures *186* and *187* are

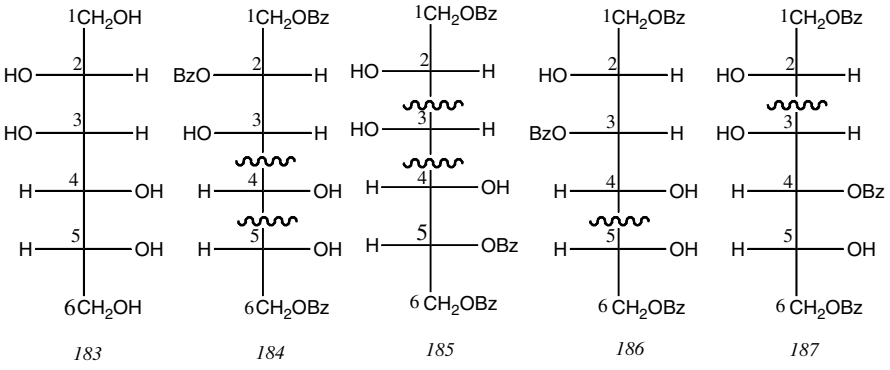


Fig. 10.64

identical (they are interconvertible via rotation in the plane of paper by 180°) (D-mannitol has a center of symmetry passing between the carbon atoms 3 and 4) (Fig. 10.65).

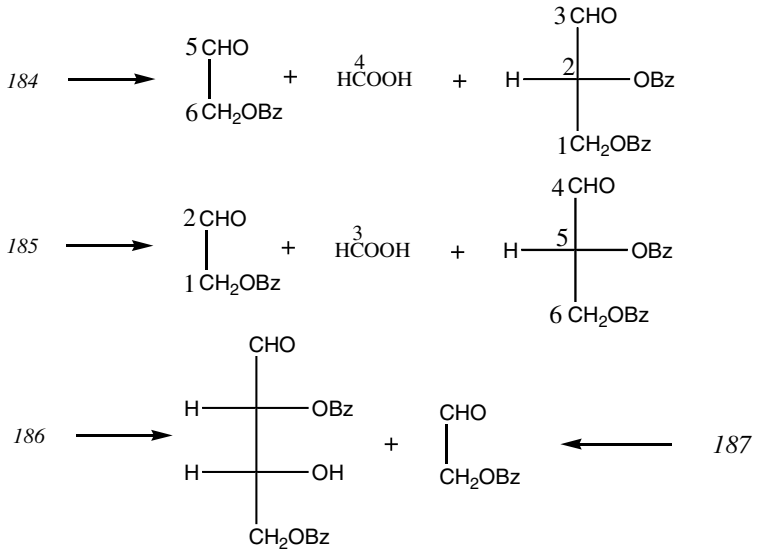


Fig. 10.65

Pentavalent Organobismuth Reagents

Five-valent bismuth reagents, especially triphenylbismuth carbonate, show remarkable functional group selectivity, permitting alcohol oxidation even in the presence of benzenethiol, indole, and pyrrole (Fig. 10.66).

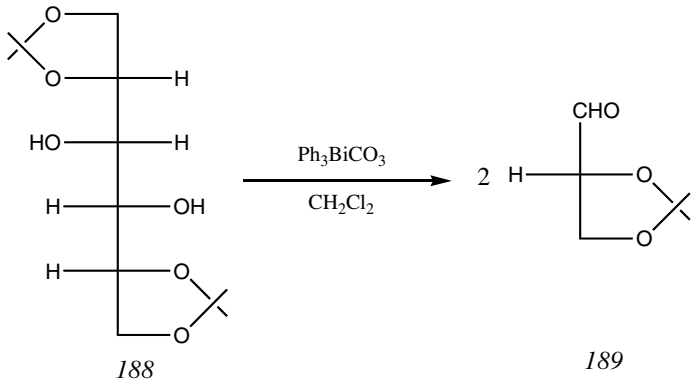


Fig. 10.66

Thus, for example, 1,2:5,6-di-*O*-isopropylidene-D-mannitol *188* is oxidized (40°C, 2 h) to 2,3-*O*-isopropylidene glyceraldehyde *189* in 89% yield [166].

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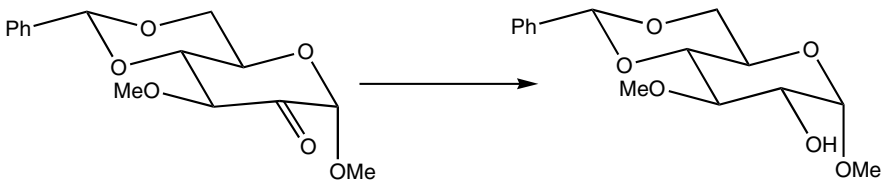
Chapter 11
Addition of Nucleophiles to Glycopyranosiduloses

Two distinct types of interactions control the stereochemistry of nucleophilic addition to glycopyranosiduloses. One is the classical nonbonded steric interaction and torsional strain between the incoming nucleophile and substituents on a pyranoside ring. These types of interactions are typical for all polysubstituted six-membered cyclic compounds. The second type of interaction is the electrostatic (dipolar) or electronic interaction between the incoming nucleophile and the glycosidic and/or the ring oxygen and is typical for carbohydrates. We will illustrate these by examining the stereochemistry of addition of various nucleophiles to the carbonyl carbon of glycopyranosid-2-, 3-, and 4-ulose of both α- and β-anomers.

The Addition of a Hydride Ion (Reduction)

Reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose *1* with $LiAlH_4$ in ether gives the corresponding D-gluco-derivative *2* as the only product [1] (Fig. 11.1).



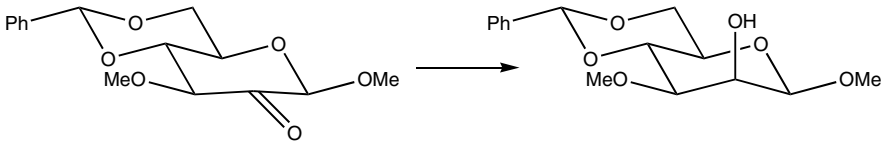
1 *2*

Fig. 11.1

However, reduction of the corresponding β-anomer *3* gives methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside *4* as the only product [1] (Fig. 11.2).

A view has been adopted [2] that the transition-state geometry for the reaction of metal hydrides (and organometallic reagents) with carbonyl groups resembles the geometry of the starting ketone and that nonbonded steric interactions, torsional strain, and electrostatic interactions (dipole–dipole repulsions) are the controlling

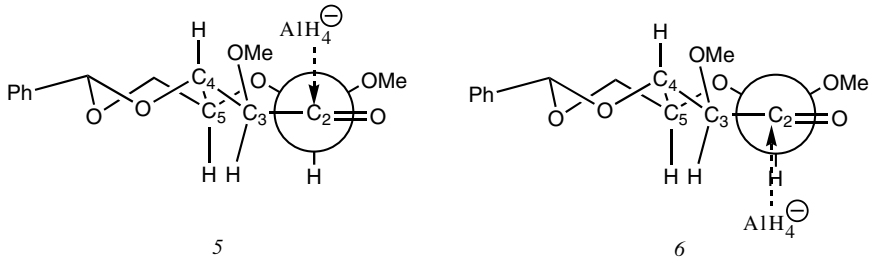
M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_11,



3 *4*

Fig. 11.2

factors in determining the direction of approach of an electronegative nucleophile to a carbonyl carbon. In the case of methyl D-*arabino*-hexopyranosid-2-ulose of the β-series, e.g., *3* (Fig. 11.2), the axial approach of metal hydride anion to the C2 carbonyl carbon, resulting in the formation of the transition state *5* (Fig. 11.3), requires that the negatively charged metal hydride ion approaches the C2 carbonyl carbon from a direction bisecting the C_1–O_1 and C_1–O_5 torsional angle. Since the



5 *6*

Fig. 11.3

C_1–O_1 and C_1–O_5 bonds are polarized and act as two equally oriented dipoles, with the resultant dipole bisecting this torsional angle, an approach which will appose a negatively charged ion between them should be energetically unfavorable owing to strong electrostatic interactions. An "equatorial" approach of the negatively charged metal hydride ion to the C2 carbonyl carbon of *3*, resulting in the formation of the transition state *6* (Fig. 11.3), will, however, not only be free from this electrostatic interaction, but the torsional strain and nonbonded steric interactions will be at a minimum as well.

In the transition state *7* (Fig. 11.4) which results from an "axial" approach of the negatively charged metal hydride ion to the C2 carbonyl carbon atom of methyl D-arabino-hexopyranosid-2-uloses of the α-series (*1* in Fig. 11.1), the electrostatic interactions of the type described for the transition state *5* are not present. Furthermore, there will be no torsional strain. The only interaction in *7* is one 1,3-*syn* axial steric interaction between the axially oriented C4 hydrogen atom and the incoming metal hydride anion. An "equatorial" approach of the negatively charged metal hydride ion to the C2 carbonyl carbon of *1* resulting in the formation of the transition state *8* (Fig. 11.4) should be, however, subject to a considerable torsional strain and dipolar interaction between the axially oriented C1 methoxy group and

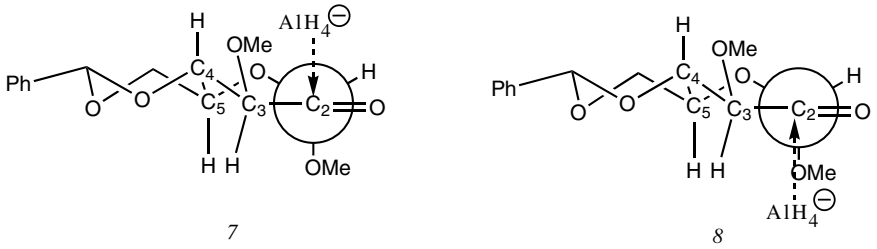


Fig. 11.4

the approaching metal hydride anion. Furthermore, in the transition state *8*, there will be two nonbonded steric interaction between the approaching metal hydride anion and the axially oriented hydrogens at the C3 and the C5 carbon.

Shaban and Jeanloz [3, 4] used this highly stereoselective reduction of β-D-*arabino*-hexopyranosid-2-uloses to β-D-mannopyranoside derivatives, to prepare a β-D-mannopyranosyl-containing oligosaccharide, from a properly protected β-D-glucopyranosyl-containing disaccharide having the C2 hydroxyl group free *9* which was oxidized to the corresponding β-D-*arabino*-hexopyranosyl-2-ulose containing disaccharide *10*. Stereoselective reduction of the hexosdiulose *10* with sodium borohydride gave then the protected β-D-mannopyranosyl-containing disaccharide *11* (Fig. 11.5).

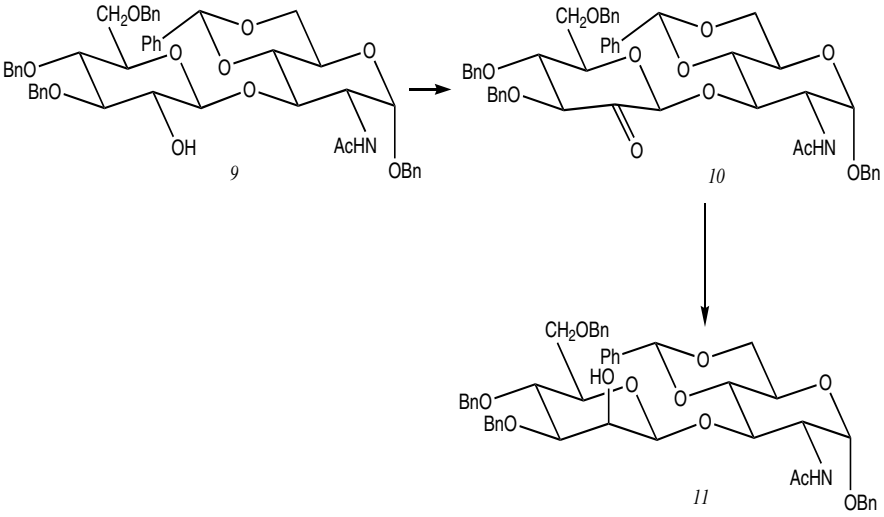
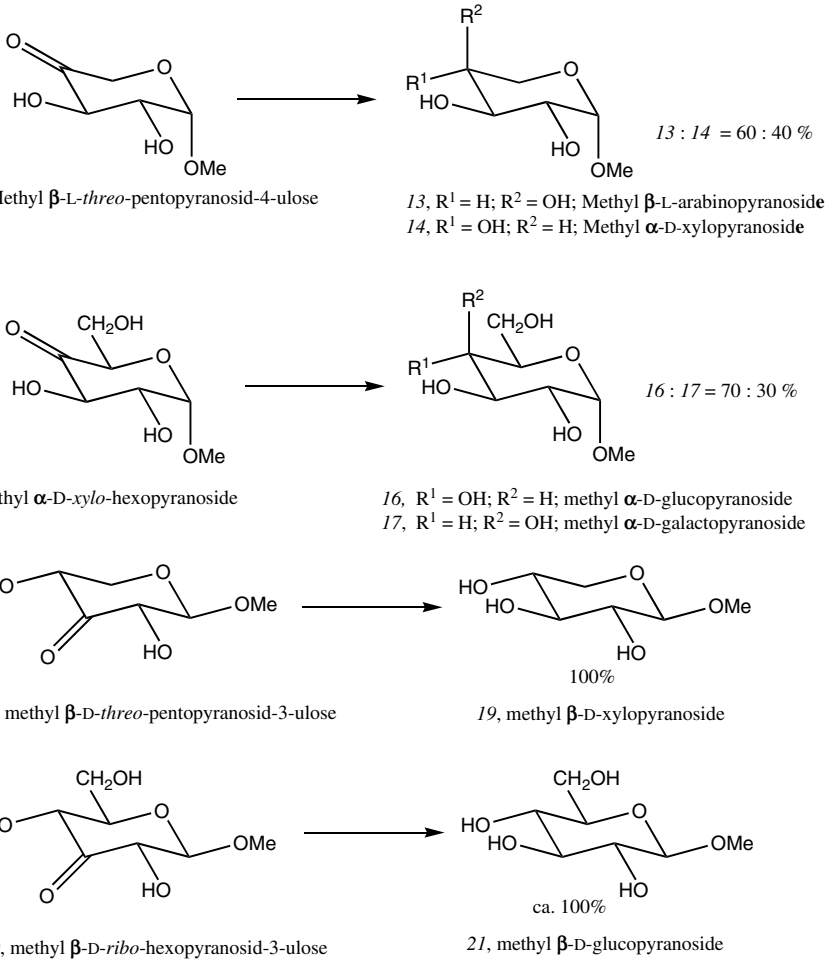


Fig. 11.5

During a study of the regioselective mono-oxidation of nonprotected or partially protected methyl glycopyranosides by bistributyltinoxide–bromine method, Tsuda et al. [5, 6] have identified the oxidation products by NMR spectroscopy

and by reducing them with $NaBH_4$ in methanol. By using glc or tlc, Tsuda et al. [5, 6] identified the reduction products and determined the ratio of products obtained in cases where more than one product was obtained by a reduction of given glycopyranosidulose.



12, Methyl β-L-*threo*-pentopyranosid-4-ulose

13, R^1 = H; R^2 = OH; Methyl β-L-arabinopyranoside
14, R^1 = OH; R^2 = H; Methyl α-D-xylopyranoside

15, methyl α-D-*xylo*-hexopyranoside

16, R^1 = OH; R^2 = H; methyl α-D-glucopyranoside
17, R^1 = H; R^2 = OH; methyl α-D-galactopyranoside

18, methyl β-D-*threo*-pentopyranosid-3-ulose

19, methyl β-D-xylopyranoside

20, methyl β-D-*ribo*-hexopyranosid-3-ulose

21, methyl β-D-glucopyranoside

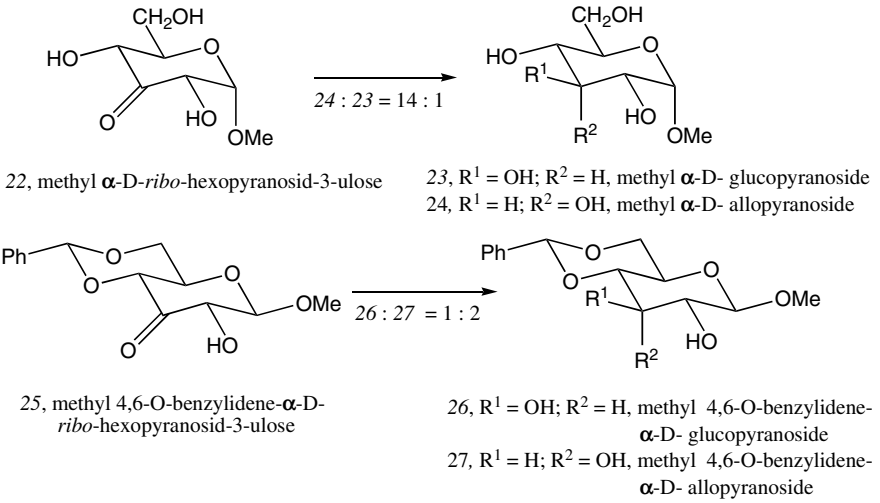
Fig. 11.6

Thus, reduction of methyl β-L-*threo*-pentopyranosid-4-ulose *12* (Fig. 11.6) gave methyl β-L-arabinopyranoside *13* and methyl α-D-xylopyranoside *14* in 60:40 ratio, whereas the reduction of methyl α-D-*xylo*-hexopyranosid-4-ulose *15* gave the mixture of methyl α-D-gluco- (*16*) and α-D-galactopyranoside (*17*) in 7:3 ratio [5].

The reason for the improved stereoselectivity in the reduction of *15* over that of *12* could be due to the presence of the C6 hydroxymethyl group and stiffening of the $^4C_1$ conformation of pyranoid ring.

The reduction of both methyl β-D-*threo*-pentopyranosid-3-ulose *18* and the methyl β-D-*ribo*-hexopyranosid-3-ulose *20* proceeded with almost 100% stereoselectivity to give methyl β-D-xylopyranoside *19* in the former and methyl β-D-glucopyranoside *21* in the latter case [5].

The reduction of methyl α-D-*ribo*-hexopyranosid-3-ulose *22* (Fig. 11.7) gives highly stereoselective methyl α-D-allopyranoside *24*, with very small amounts of methyl α-D-glucopyranoside *23* (*24*:*23* ratio is 14:1). However, the reduction of methyl 4,6-*O*-benzylidene-β-D-*ribo*-hexopyranosid-3-ulose *25* proceeds with a poor stereoselectivity giving methyl β-D-glucopyranoside *26* and methyl β-D-allopyranoside *27* in 1:2 ratio [5, 6]. The loss of stereoselectivity observed in the reduction of *25* as compared to the reduction of *22* is probably due to the absence of electrostatic interactions between the approaching complex hydride anion and the C1–OMe dipole.



22, methyl α-D-*ribo*-hexopyranosid-3-ulose

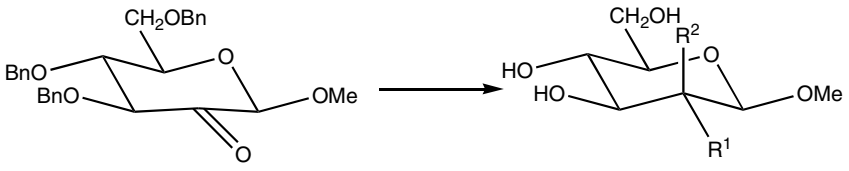
23, R^1 = OH; R^2 = H, methyl α-D- glucopyranoside
24, R^1 = H; R^2 = OH, methyl α-D- allopyranoside

25, methyl 4,6-O-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose

26, R^1 = OH; R^2 = H, methyl 4,6-O-benzylidene-α-D- glucopyranoside
27, R^1 = H; R^2 = OH, methyl 4,6-O-benzylidene-α-D- allopyranoside

Fig. 11.7

The catalytic reduction of methyl 3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosid-2-ulose *28* in presence of Adams catalyst (Pt) followed by



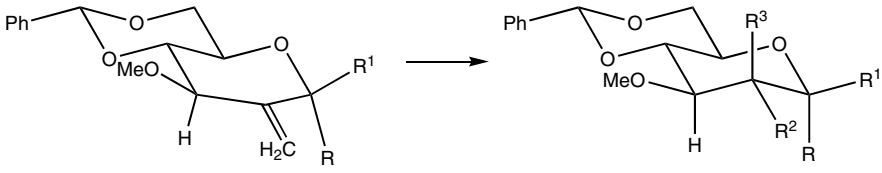
28

29, R^1 = H; R^2 = OH
30, R^1 = OH; R^2 = H

Fig. 11.8

another hydrogenation in presence of Pd–C (to remove the benzyl groups) gave in 84% yield [7] the 95:5 mixture of methyl β-D-mannopyranoside *29* and methyl β-D-glucopyranoside *30* (Fig. 11.8). It can be assumed that in this case steric interactions in the catalyst–carbonyl group transition state are the only factors that influence the stereochemical outcome of this reduction.

The comparison of the stereochemistry of catalytic hydrogenation of 2-carbonyl group of methyl α- and β-D-glycopyranosid-2-uloses and the stereochemistry of catalytic hydrogenation of 2-deoxy-2-*C*-methylene group of methyl α- and β-D-2-deoxy-2-*C*-methylene glycopyranosides (Fig. 11.9) provided interesting results. Similar to catalytic hydrogenation of the C2 carbonyl group of methyl



31, R = OMe; R^1 =H
32, R = H; R^1 = OMe

33, R = OMe; $R^1 = R^3 = H$; $R^2 = CH_3$
34, R = OMe; $R^1 = R^2 = H$; $R^3 = CH_3$
35, $R = R^2 = H$; R^1 = OMe; $R^3 = CH_3$

Fig. 11.9

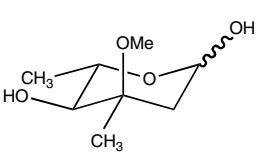
3,4,6-tri-*O*-benzyl-β-D-*arabino*-hexopyranosid-2-ulose *28* [7], and to sodium borohydride reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-*arabino*-hexopyranosid-2-ulose *3* where, in both cases, methyl 4,6-*O*-benzylidene-3-*O*-methyl-β-D-mannopyranoside *4* was obtained as the only product [1] (Fig. 11.2), the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-β-D-*arabino*-hexopyranoside [8] *32* (Fig. 11.9) gives, in quantitative yield, methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-β-D-mannopyranoside *35* as the only product. However, while reduction of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose *1* with $LiAlH_4$ gives the corresponding α-D-gluco-derivative *2* as the only product [1] (Fig. 11.1) the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside *31* gave a mixture of both C2 epimers, i.e., methyl 4,6-*O*-benzylidene-2-deoxy-2-C, 3-*O*-dimethyl-α-D-gluco- and α-D-mannopyranoside, *33* and *34* (Fig. 11.9), in the ratio ranging from 0.3 to 3.0, depending on the solvent and the nature of the catalyst.

The obtained results could be best explained by assuming that electronic interactions between the electronegative borohydride that approaches the electrophilic C2 carbonyl carbon and the electronegative anomeric methoxy group are responsible for the stereochemical outcome of the reduction of the C2 carbonyl carbon in both anomeric glycosides, whereas the stereochemical outcome of catalytic reductions of both 2-uloses and 2-deoxy-2-*C*-methylene derivatives are controlled solely by steric interactions.

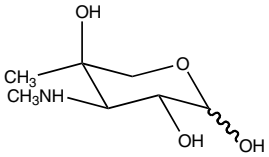
The Addition of Carbon Nucleophiles: Synthesis of Branched Chain Sugars

Until 1960 the branched chain sugars were classified as rare sugars [9, 10] but discovery of numerous branched chain sugars in various antibiotics as their glycosidic components has stimulated extensive research on their synthesis, chemistry, and biochemistry.

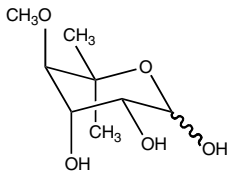
Group 1:*Methyl-branched-chain sugars.*



36, Cladinose

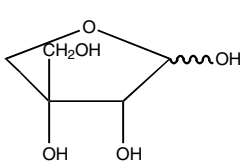


37, Garosamine

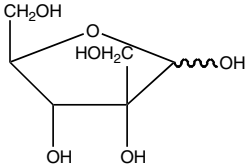


38, Noviose

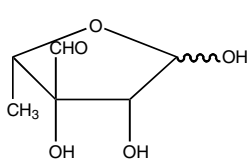
Group 2: *Hydroxymethyl and formyl branched-chain sugars*



39, Apiose

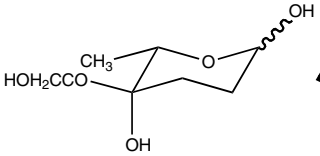


40, Hamamelose

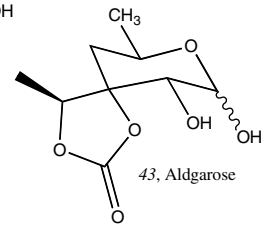


41, Streptose

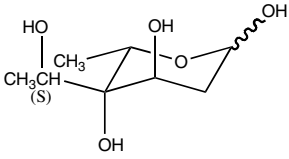
Group 3: *Two-carbon branched-chain sugars.*



42, Pillarose

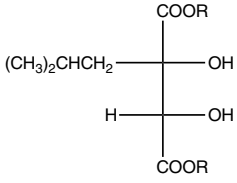


43, Aldgarose

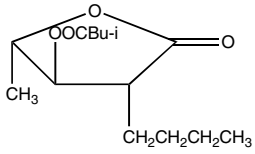


44, **γ**-Octose

Group 4: *Higher branched-chain sugars.*



45



46, Blastmycinone

Fig. 11.10

The branched chain sugars have been found as glycosidic components in many antibiotics isolated from microorganisms and higher plants. Two very informative reviews have been published dealing with this topic [11, 12].

Depending on the structure of the branching group, the branched chain sugars can be classified into several groups: (1) methyl branched chain sugars, (2) hydroxymethyl- or formyl branched chain sugars, (3) two-carbon branched chain sugars, and (4) higher branched chain sugars.

In Fig. 11.10 are given a few examples of these four groups of branched chain sugars. Cladinose (*36*) is the sugar component of erythromycin, garosamine (*37*) is found in the antibiotic gentamicin, noviose (*37*) is the component of antibiotic novobiocin, apiose (*39*) and hamamelose (*40*) are found in plants, and streptose (*41*) in the antibiotic streptomycin. Pillarose (*42*), aldgarose (*43*), and γ-octose (*44*) are found in antibiotics pillaromycin A, aldgamycin E, and quinocycline A, respectively. Finally, the higher branched chain sugar *45* (unnamed) and blastmycinone (*46*) are found in loroglossin (a constituent of orchids) and in the antibiotic blastmycin.

Most branched chain sugars found in Nature have a polar group attached to the branching carbon; most often this is a hydroxyl group or its methyl ether, but an amino or a nitro group is also found attached to the tertiary branching carbon.

The addition of carbon nucleophiles to glycosiduloses has been extensively used for the synthesis of branched chain sugars in which the branching carbon has a hydroxyl group attached to it (most of the sugars in Group 1). The carbon nucleophiles used were either organometallics (such as methyl Grignard reagents and methyllithium) or diazomethane; in the latter case an extra step was required, i.e., the opening of the spiro epoxide which is initially obtained as a result of the addition of diazomethane to a glycosidulose.

The addition of phosphorus ylides (phosphoranes) to glycosiduloses (Wittig reaction) giving the corresponding *C*-alkylidene derivatives was used for the synthesis of branched chain sugars without or with the hydroxyl group attached to branching carbon.

The opening of epoxide ring of a carbohydrate oxirane derivative with a carbon nucleophile is most often used for the synthesis of the branched chain sugars of Group 2.

The Addition of Organometals

The carbon nucleophiles used for the addition to a carbonyl carbon of a glycopyranosidulose are most often methyl Grignard reagent or methyllithium. The diastereofacial selectivity is controlled by several factors and will be discussed later.

The addition of a methyl nucleophile to a glycopyranosidulose gives a branched chain sugar in which the chiral-branching carbon is a tertiary alcohol (Fig. 11.11). In order to understand the mechanism of nucleophilic addition, the absolute configuration of the newly created branched carbon must be known. However, the absence of

hydrogen atom at the branching carbon introduces an additional complication since the ^{1}H NMR spectroscopy cannot be used for configurational assignment.

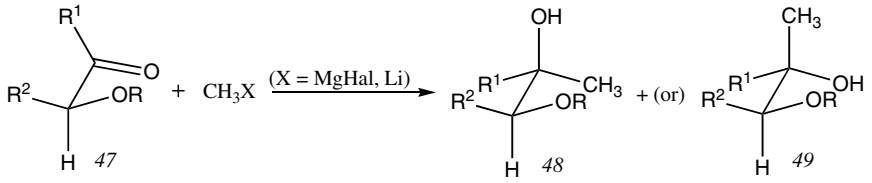
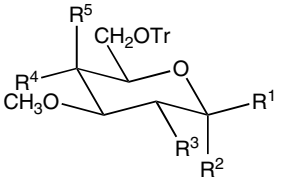


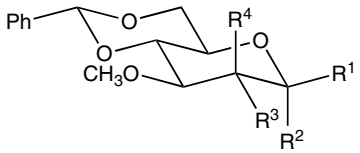
Fig. 11.11

If the R^1 has a higher priority than the CHR^2OR group according to Cahn–Ingold–Prelog convention [13], then the configuration of the branching carbon in *48* will be *S* and in *49 R*; if the R^1 has a lower priority than the CHR^2OR then the configuration of the branching carbon in *48* will be *R* and in *49 S*.

The determination of configuration of tertiary carbon in branched chain glycopyranosides was notoriously difficult, because a simple and reliable method was not available for a long time. Thus, for example, the configuration of a branching carbon has been determined from IR frequencies of the tertiary OH group [14], from chromatographic and electrophoretic mobilities in solvent systems with borate buffer [15, 16] or phenylboronic acid [14], from the kinetics of periodate oxidation [15], from the formation of cyclic carbonates [15] and bicyclic hemialdals [15, 16], and from degradation reactions [17–20]. In the case of nitroalkyl branched chain sugars or sugar alcohols, the configuration of branching carbon was deduced from ORD and CD spectra [21–24]. Finally, the configurations of tertiary alcoholic centers in branched chain sugars were also determined by NMR spectroscopy using lantanide shift reagents [25].



50, $R^1 = H$; $R^2 = R^3 = OMe$; $R^4 = CH_3$; $R^5 = OH$
51, $R^1 = H$; $R^2 = R^3 = OMe$; $R^4 = OH$; $R^5 = CH_3$
52, $R^1 = H$; $R^2 = OMe$; $R^3 = CH_3SO_3$; $R^4 = CH_3$; $R^5 = OH$
53, $R^1 = H$; $R^2 = OMe$; $R^3 = CH_3SO_3$; $R^4 = OH$; $R^5 = CH_3$
54, $R^1 = H$; $R^2 = OMe$; $R^3 = R^5 = OH$; $R^4 = CH_3$
55, $R^1 = H$; $R^2 = OMe$; $R^3 = R^4 = OH$; $R^5 = CH_3$
56, $R^1 = R^3 = OMe$; $R^2 = H$; $R^4 = CH_3$; $R^5 = OH$
57, $R^1 = R^3 = OMe$; $R^2 = H$; $R^4 = OH$; $R^5 = CH_3$



58, $R^1 = R^4 = H$; $R^2 = OCH_3$; $R^3 = CH_3$
59, $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = CH_3$
60, $R^1 = OCH_3$; $R^2 = R^3 = H$; $R^4 = CH_3$

Fig. 11.12

Table 11.1 C13 chemical shifts of equatorial and axial C4 methyl group in branched chain sugars

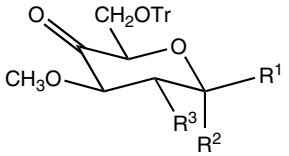
Branched chain sugar	C13 chemical shift (in ppm) of the C4 methyl group
Methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (*50*) (equatorial CH_3)	21.8
Methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (*51*) (axial CH_3)	15.6
Methyl 4-*C*-methyl-3-*O*-methyl-2-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (*52*) (equatorial CH_3)	21.7
Methyl 4-*C*-methyl-3-*O*-methyl-2-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (*53*) (axial CH_3)	15.3
Methyl 4-*C*-methyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside (*54*) (equatorial CH_3)	21.9
Methyl 4-*C*-methyl-3-*O*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside (*55*) (axial CH_3)	15.4
Methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-galactopyranoside (*56*) (equatorial CH_3)	21.3
Methyl 4-*C*-methyl-2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-glucopyranoside (*57*) (axial CH_3)	16.0
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-methyl-α-D-glucopyranoside (*58*)	12.4
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-methyl-α-D-mannopyranoside (*59*) (axial CH_3)	11.0
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*O*-methyl-β-D-mannopyranoside (*60*) (axial CH_3)	5.7

Using the observation made in the study on conformational equilibria of methyl cyclohexanes [26–28] that the carbon-13 chemical shift of an axial methyl group is ~6 ppm upfield relative to that of an equatorial methyl group, Miljkovic et al. [29] have unequivocally determined the configuration of the branching carbon atom in a number of branched chain sugars having methyl group as the branching chain (see Fig. 11.12 and Table 11.1).

The addition of methyllithium to methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose *61* and to methyl 3-*O*-methyl-2-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose *62* in ether at –80°C gave, in each case, only one isomer: methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside *51* (70%) (from *61*) and methyl 3-*O*-methyl-2-*O*-methanesulfonyl-4c-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside *55* (53%) (from *62*) (Fig. 11.12) [30].

The branched chain sugars *50–57* were obtained by the addition of methylmagnesium iodide or methyllithium to the methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α- and β-D-*xylo*-hexopyranosid-4-ulose *61* and *63* and methyl 3-*O*-methyl-2-*O*-methylsulfonyl-6-*O*-triphenylmethyl-α-D-*xylo*-hexopyranosid-4-ulose *62* in ether at –80°C (Fig. 11.13).

Reaction of oxo-sugars *61* and *62* with methylmagnesium iodide in ether at –80°C proceeded again stereospecifically, but the products obtained were the C4



61, $R^2 = R^3 = OCH_3$; $R^1 = H$
62, $R^2 = OCH_3$; $R^1 = H$; $R^3 = CH_3SO_3$
63, $R^1 = R^3 = OCH_3$; $R^2 = H$;

Fig. 11.13

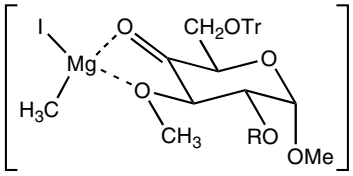
epimers of branched chain sugars *50* and *52*, i.e., *61* gave methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galactopyranoside *51* (94%) and *62* gave methyl 3-*O*-methyl-2-*O*-methanesulfonyl-4c-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside *53* (53%) [30] (Fig. 11.12).

The stereochemistry of the addition of Grignard reagent to the glycopyranosid-4-uloses *61* and *62* was found to be dependent on the reaction temperature [30], the solvent [31, 32], and the nature of the halogen atom [30].

Thus, treatment of an ethereal solution of *61* and/or *62* with methylmagnesium iodide at –80°C afforded *50* and/or *52* as the only isolable products. At reflux, both C4 epimers, *50* and *51* (from *61*) and *52* and *54* (from *62*) were obtained, but the isomers having the methyl group in equatorial orientation (*50, 52*, and *54*) predominated in ca. 6:1 ratio (the branched chain sugars *54* and *55* are the products of desulfonylation of branched chain sugars *52* and *53* under the given experimental conditions). The dependence of the stereochemistry of the addition reaction upon the nature of the solvent was demonstrated by refluxing a 10:1 ether–tetrahydrofuran solution of *62* with methylmagnesium chloride whereby a mixture of C4 epimers *52* and *53* was obtained in 1.3:1 ratio. The dependence of the stereochemistry of the addition reaction upon the nature of the halogen atom was demonstrated by reacting methylmagnesium iodide with *62* under the same experimental conditions whereby a mixture of C4 epimer *52* and *53* was now obtained in 2.3:1 ratio (the isomer *53* with the axial methyl group predominated) (Fig. 11.4).

The preferred equatorial addition of methyl group of methylmagnesium iodide to the C4 carbonyl group of *60* or *61* was explained [30] to be due to "chelation" of the magnesium atom of Grignard reagent with the C4 carbonyl oxygen and the C3 oxygen atom prior to the addition of methyl carbanion to the carbonyl carbon [32–34] as depicted in Fig. 11.14.

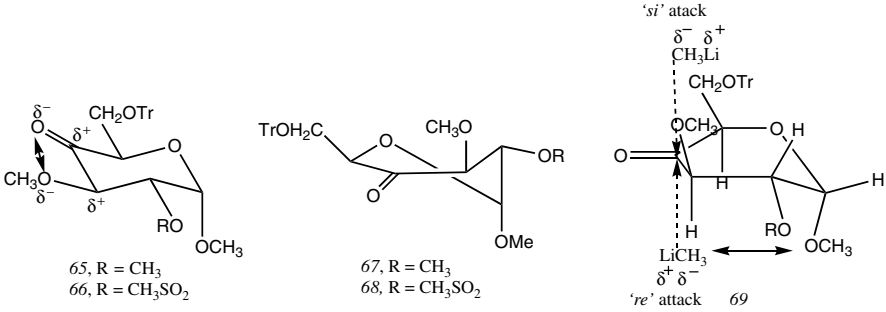
Thus the formation of a cyclic five-membered ring complex *64* will force the glycopyranosid-4-uloses *61* and *62* to adopt the $^4C_1$ conformation prior to the addition of methyl group to the C4 carbonyl carbon. The solvent dependence and to some extent the temperature dependence of stereochemistry of the addition of methyl group of Grignard reagent to the carbonyl carbon of *61* and *62* does support this view.



64, R = CH_3, CH_3SO_2

Fig. 11.14

The axial stereospecificity of methyllithium addition to the C4 carbonyl carbon of glycopyranosid-4-uloses *61* and *62* (ether and at –80°C) was rationalized as follows. Studies on conformational equilibrium of α-halocyclohexanones [35–39] have shown that conformations with the halogen atom axially oriented are strongly favored in solvents of low dielectric constant. This tendency of halogens to adopt the axial rather than equatorial orientation was attributed to the strong electrostatic



65, R = CH_3
66, R = CH_3SO_2

67, R = CH_3
68, R = CH_3SO_2

Fig. 11.15

repulsion of nearly coplanar and equally oriented C=O and C–halogen dipoles in conformations having the halogen atom equatorially oriented.

A similar situation can be expected to exist in case of glycopyranosid-4-uloses *61* and *62* since in the $^4C_1$ conformation the C3-methoxy group is equatorially oriented; however, due to an electrostatic repulsion of nearly coplanar and equally oriented C=O and C–OMe dipoles this conformation should be destabilized in solvents of low dielectric constant (e.g., ether). Consequently, oxo-sugars *61* and *62* will most likely adopt, in ether solution and at –80°C, either the half-chair conformation *67* or *68* (Fig. 11.15) or a conformation that is very close to the half-chair conformation *69*. The adoption of any such conformation prior to the reaction with methyllithium could then be responsible for the exclusive "*si*" attack of methyl carbanion to the C4 carbonyl carbon of *67* or *68,* since strong electrostatic and nonbonding steric interactions between the electronegative methyl group of methyllithium that approaches the C4 carbonyl carbon from the "*re*" direction and the axially oriented C1 methoxy group will completely impede the "*re*" addition of methyllithium (Fig. 11.15).

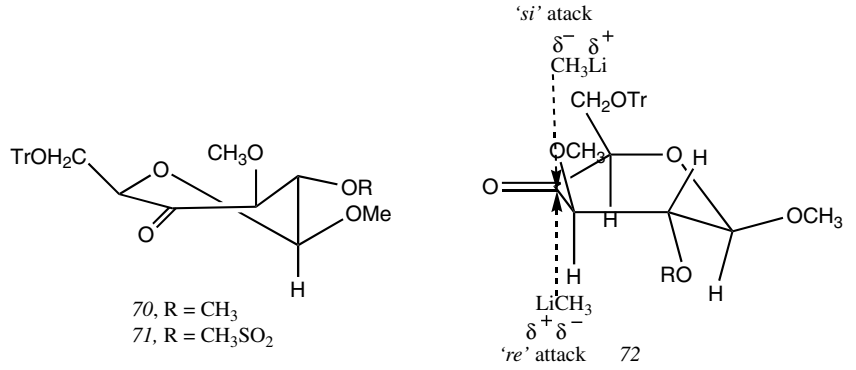


Fig. 11.16

This rationalization is supported by the observation that methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose *72* (Fig. 11.16), the β-anomer of *61*, where the "1,4-*synaxial*" stereoelectronic interactions between the approaching methyl carbanion and the electronegative anomeric methoxy group does not exist when the attack comes from the "*re*" face, gave with methyllithium, in an ethereal solution at –80°C, a mixture of both C4 epimers *50* and *51* (Fig. 11.12) in which the epimer having the methyl group equatorially oriented (*50*) predominated in 3:1 ratio.

It is interesting to note that 4-*tert*-butyl-cyclohexanone reacted with methylmagnesium iodide and methyllithium in ether at –80°C considerably slower, and the addition was not stereoselective giving in each case a mixture of both C1 epimers (*74* and *75*) [30] (Fig. 11.17). Thus, methylmagnesium iodide gave a mixture of C1 isomers in 1.7:1 ratio in which the epimer with the equatorial methyl group (*74*) predominated; methyllithium gave a mixture of epimers in 3.6:1 ratio in which the epimer *74* again predominated.

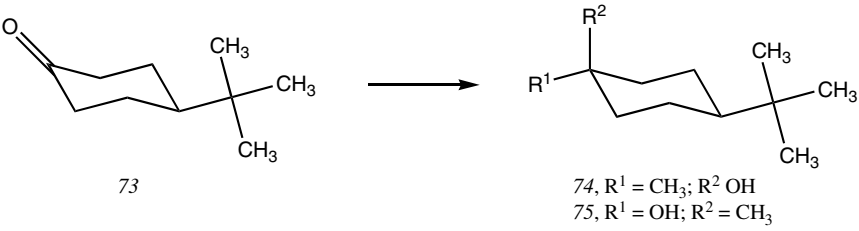


Fig. 11.17

It should be noted that in reactions with both Grignard reagent and methyllithium considerable amounts of starting material were isolated: 25 and 21%, respectively.

In agreement with these findings [30], Hanessian et al. [40] reported that the addition of methyllithium to the C4 carbonyl carbon of glycopyranosid-4-ulose *76*

gave, in quantitative yield, only the epimer *77* having the axially oriented methyl group at the C4 branching carbon (Fig. 11.18).

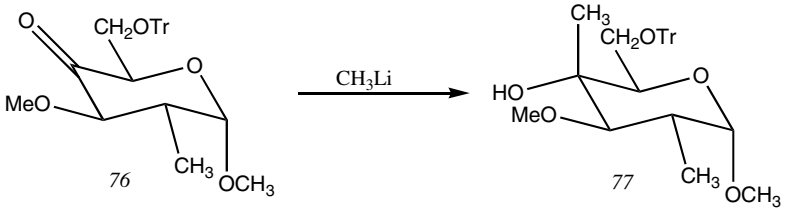


Fig. 11.18

To examine the generality of the above proposed hypothesis [30] Yoshimura et al. [41, 42] studied the stereoselectivity of addition of methyllithium and methylmagnesium iodide to a select number of hexopyranosiduloses (Figs. 11.19 and 11.20). The addition of methyllithium to methyl 6-deoxy-2,3-di-*O*-methyl-α-D-*xylo*-hexopyranosid-4-ulose *78* proceeded, as expected, highly stereoselectively giving the stereoisomer *80* as the only product (Fig. 11.19). In this study they also examined the addition of methylmagnesium iodide and methyllithium to a number of glycopyranosid-4-uloses [43] (Fig. 11.20), and the authors tried to explain the

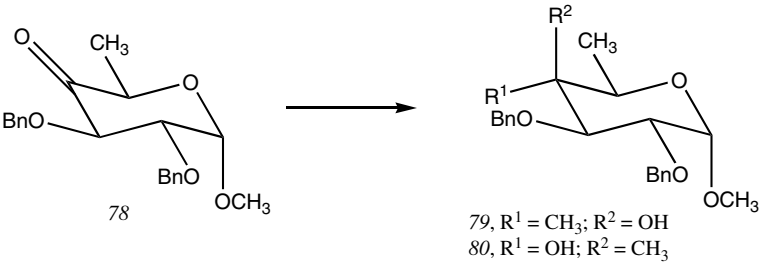
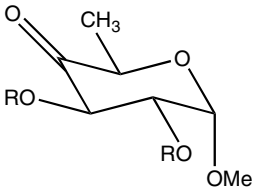


Fig. 11.19

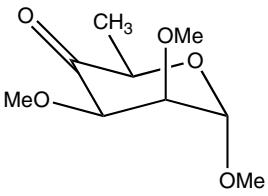
observed stereoselectivities using Miljkovic et al. hypothesis [30]. Depending on the substrate used, the observed stereoselectivities ranged from 100% to 2.3:1.

The conclusions drawn from the obtained results are, according to the opinion of this author, flawed since the glycopyranosid-4-uloses chosen for the study had, except for the substrate (*78*), either one (*81* and *82*) or two (*83*) axial substituents on the pyranoside ring or were the bicyclic systems having the 2,3-*O*-methylene acetal five-membered ring attached to the pyranoside ring of a glycopyranosid-4-ulose (compounds *84–86*), introducing thus not only the uncertainty regarding the conformation of a sugar which reacts with methyllithium or Grignard reagent but also additional stereoelectronic interactions between the attacking nucleophile and the substituent(s) on the pyranoside ring.

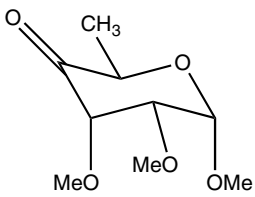
The addition of methylmagnesium iodide to methyl 4,6-*O*-benzylidene-2-*O*-benzoyl-α-D-*ribo*-hexopyranosid-3-ulose *87* in ether at room temperature gave after



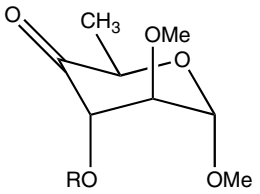
78, α-D-*xylo*, R = CH_3, Bn



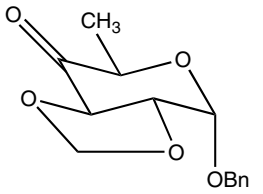
81, α-D-*lyxo*



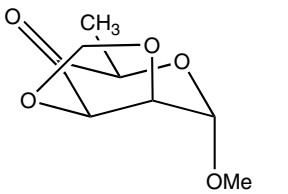
82, α-D-arabino



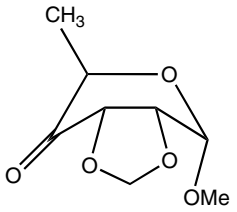
83, α-D-ribo, R = CH_3, Bn



84, 2,3-O-methylene-α-D-*xylo*



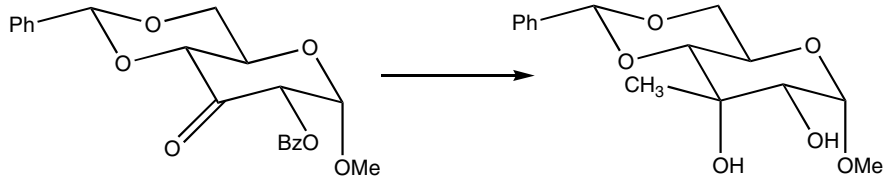
85, 2,3-O-methylene-α-D-*lyxo*



86, 2,3-O-methylene-α-D-*ribo*

Fig. 11.20

24 h the D-*talo*-derivative *88* in 40% yield (the benzoyl group was removed during the reaction) [44] (Fig. 11.21).

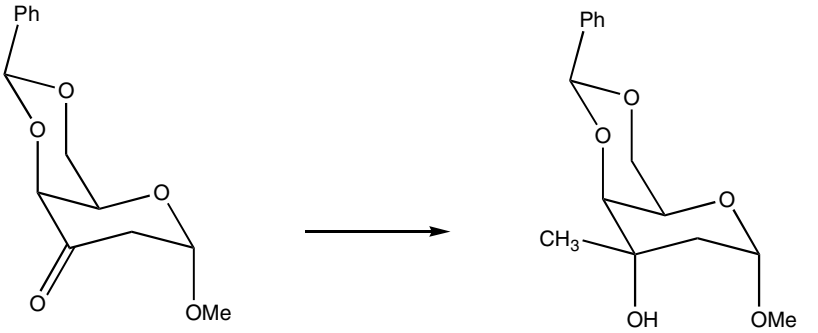


87 *88*

Fig. 11.21

Similarly, the addition of methylmagnesium iodide to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-hexopyranosid-3-ulose *89*, in ether and 0°C, gave methyl

4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*lyxo*-hexopyranoside *90* in 91% yield together with traces of the C3 epimer methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*xylo*-hexopyranoside [45] (Fig. 11.22).



89 90

Fig. 11.22

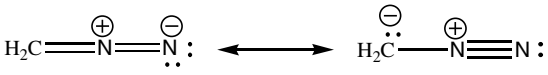
The configuration of the branching C3 carbon was determined by converting *90* into D-arcanose *91* and then comparing it with the natural L-arcanose *92* (Fig. 11.23).

91, D-arcanose *92*, L-arcanose

Fig. 11.23

Addition of Diazomethane

Diazomethane is a resonance hybrid of the following two canonical forms (Fig. 11.24):



93 *94*

Fig. 11.24

Consequently in all of its reactions diazomethane reacts as a nucleophile. Thus, it adds to the carbonyl carbon of an aldehyde or ketone giving the corresponding spiro epoxides (Fig. 11.25):

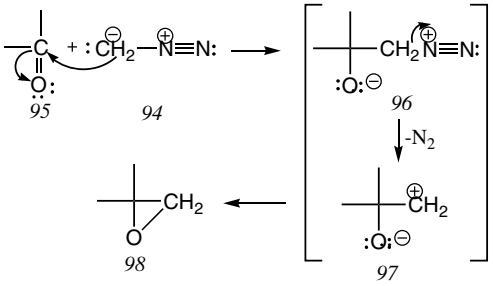


Fig. 11.25

It should be noted that intermediate *97* may undergo a *Sato rearrangement* resulting in insertion of a methylene carbon in the carbon skeleton of an aldehyde or ketone (for a review see [46]) (Fig. 11.26).

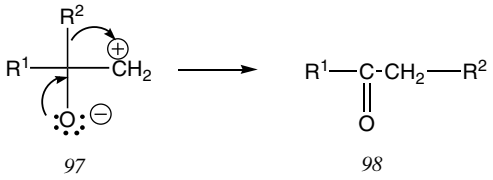


Fig. 11.26

The addition of diazomethane to methyl 4,6-*O*-benzylidene-3-*O*-methyl-α- and β-D-*arabino*-hexopyranosid-2-uloses (*1* and *3*, respectively) and methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*ribo*-hexopyranosid-2-ulose *99* [47] (Fig. 11.27) gave the following spiro epoxides: *1* gave a mixture of epimeric spiro epoxides *100* and *103*, *3* gave the spiro epoxide *101*, whereas *99* gave the spiro epoxide *102* as the predominant product (Fig. 8.27) (Table 11.2).

The stereochemical outcome of the addition of diazomethane to *1*, *3*, and *99* did not parallel the stereochemical outcome of the Grignard reagent addition to these glycosid-2-uloses. The authors proposed a highly speculative explanation for the observed stereoselectivity of diazomethane addition.

The addition of diazomethane to methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose *104* gave *107* in 73% yield. Methyl 4,6-*O*-benzylidene-2-*O*-methyl-β-D-*ribo*-hexopyranosid-3-ulose *105* gave diazomethane *108* and *109* (76.5 and 17.6% yield, respectively). The addition of diazomethane to methyl 4,6-*O*-benzylidene-2-*O*-methyl-α-D-*arabino*-hexopyranosid-3-ulose *106* (Fig. 11.28)

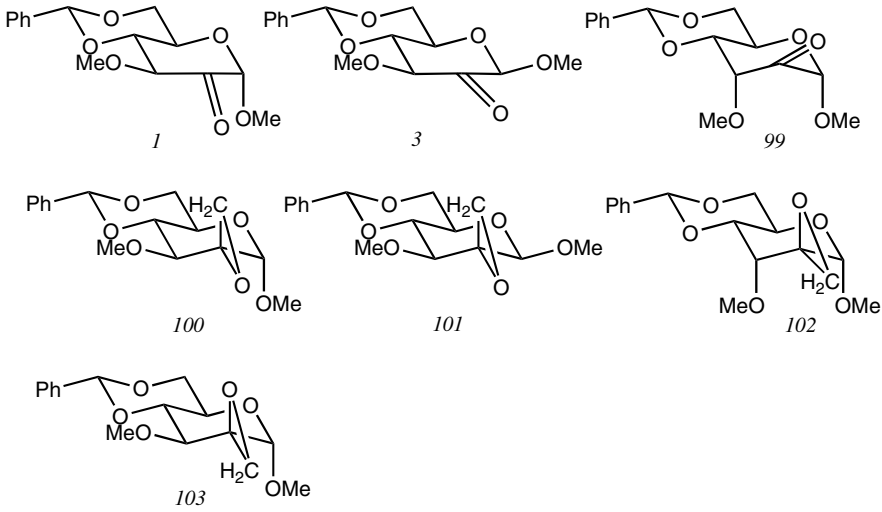


Fig. 11.27

Table 11.2 Yields of products and the direction of attack of carbon nucleophile of diazomethane to the carbonyl carbon of the methyl 4,6-*O*-benzylidene-α- and β- D-hexopyranosid-2-uloses

	Yields of products (%)	
Glycosid-2-ulose	Axial attack	Equatorial attack
α-D-*arabino*-, *1*	31.3 (*99*)	63.7 *(102)*
β-D-*arabino*-, *3*	92.5 (*100*)	–
α-D-*ribo*-, *99*	–	83.5 (*101*)

gave methyl 3,3'-anhydro-4,6-*O*-benzylidene-3-*C*-hydroxymethyl-2-*O*-methyl-α-D-altropyranoside *110* in 41% yield [48] together with a pyranoside ring expansion product.

The reduction of spiro epoxides with $LiAlH_4$ gives hydroxylated branched chain carbon with the methyl group as the branched chain, whereas the opening of spiro epoxides with a nucleophile (OH^-, NH_3, etc.) gives hydroxylated branched chain carbon with the functionalized methyl group, such as hydroxymethyl, aminomethyl, as the branched chains.

Synthesis of Branched Chain Sugars with Functionalized Branched Chain

The preparation of branched chain sugars with functionalized branched chain can be accomplished in two ways:

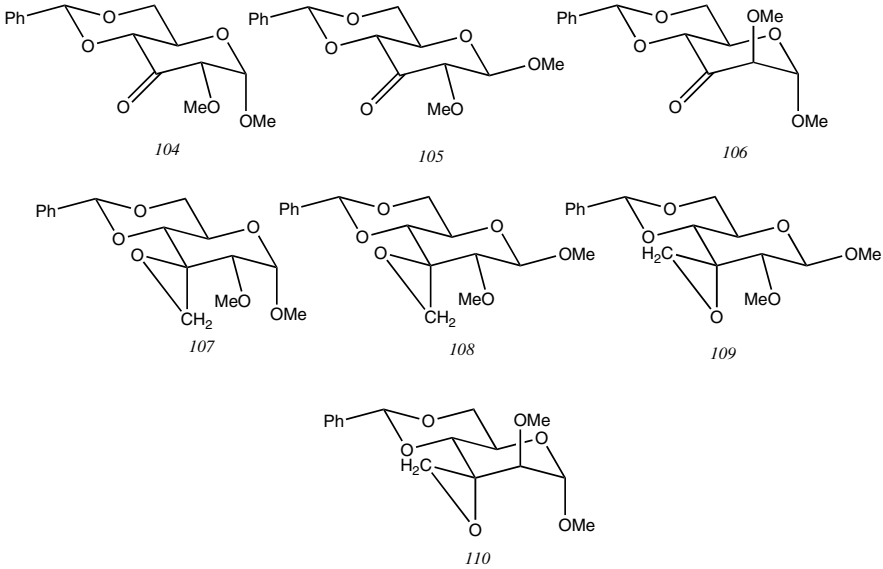


Fig. 11.28

(1) By opening of the spiro epoxide ring obtained by addition of diazomethane to the carbonyl carbon of a glycopyranosidulose with nucleophiles other than hydride ion
(2) By addition of a functionalized carbon nucleophile, such as (a) lithium 1,3-dithiane, (b) vinylmagnesium halide, (c) methoxyvinyllithium, (d) 1, 1-dimethoxy-2-lithio-2-propene.

2-Lithio-1,3-Dithiane as the Nucleophile

2-Lithio-1,3-dithiane [49, 50] *111* (Fig. 11.29) is a stable compound and as a nucleophile was used extensively for chain extension and chain branching in synthetic carbohydrate chemistry [51]. The products obtained by the addition of 2-lithio-1,3-dithiane to glycopyranosiduloses can be converted to methyl or to formyl branched chain sugars by opening the sugar oxirane rings by catalytic hydrogenation (methyl) and via mercuric oxide–boron trifluoride hydrolysis (formyl).

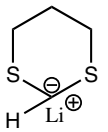


Fig. 11.29

Thus, the addition of lithium dithiane to methyl 4,6-*O*-benzylidene-2-deoxy-, 2-*O*-benzoyl, 2-acetamido, or 2-*O*-methyl-α-D-*ribo*-hexopyranosid-3-ulose gave the corresponding methyl-4,6-*O*-benzylidene-α-D-allopyranosides with dithianyl group equatorially oriented as the only product [44, 52] (see Fig. 11.30).

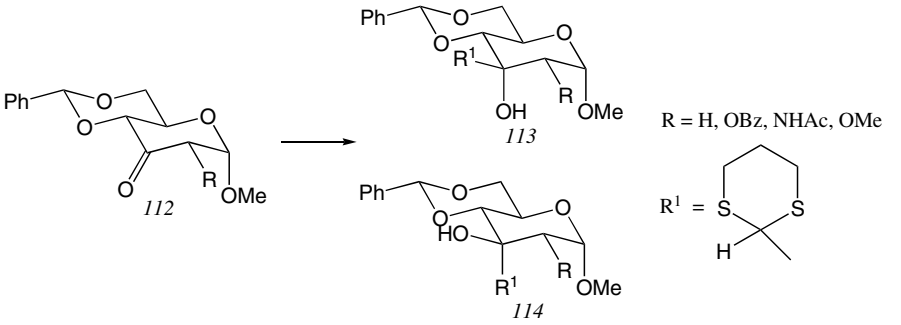


Fig. 11.30

The synthesis of branched chain sugar aldgarose *115* (Fig. 11.31) was accomplished by using dithiane carbanion as carbon nucleophile [53]. Thus the addition of 2-methyl-2-lithio-1,3-dithiane to 4,6-dideoxy-3-ulose *116* (Fig. 11.32) gave a mixture of two C3 dithiane epimers *117* and *118*, one existing in the $^4C_1$ and the other in the $^1C_4$ conformation, since in these conformations the bulkiest substituent (1,3-dithiane) is in the equatorial position. The low stereoselectivity (*117:118* = 3:2)

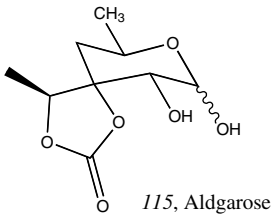


Fig. 11.31

is probably due to the fact that the anomeric methoxy group is equatorial (β) in *165*. Also, the pyranoside ring of 4-deoxy sugars may be, due to the absence of the C4 hydroxyl group, more flexible which may result in the loss of stereoselectivity. The conversion of *117* to D-aldgarose required first the conversion of dithiane group into the carbonyl group with $HgCl_2$/HgO in refluxing methanol followed by sodium borohydride reduction of the obtained acetyl group; two isomers in the branched chain *120* and *121* were obtained in 10:7.1 ratio with 85.3% overall yield. If the reduction was performed with lithium aluminum hydride in the presence of 1 mol-equivalent of *tert*-butanol the *120* and *121* were obtained in 10:4.3 ratio with overall yield of 50.3%. For the reduction in the presence of 2 mol-equivalents

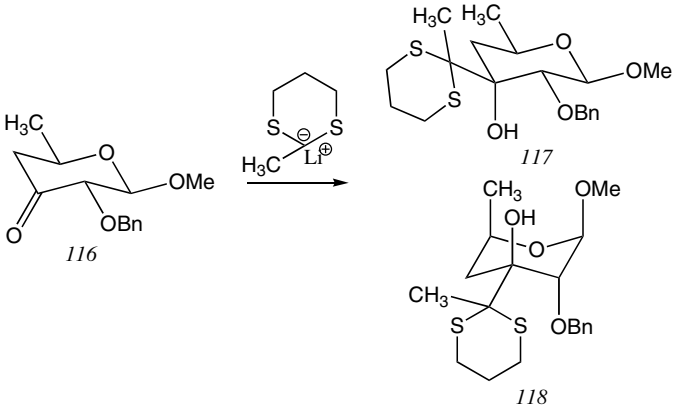


Fig. 11.32

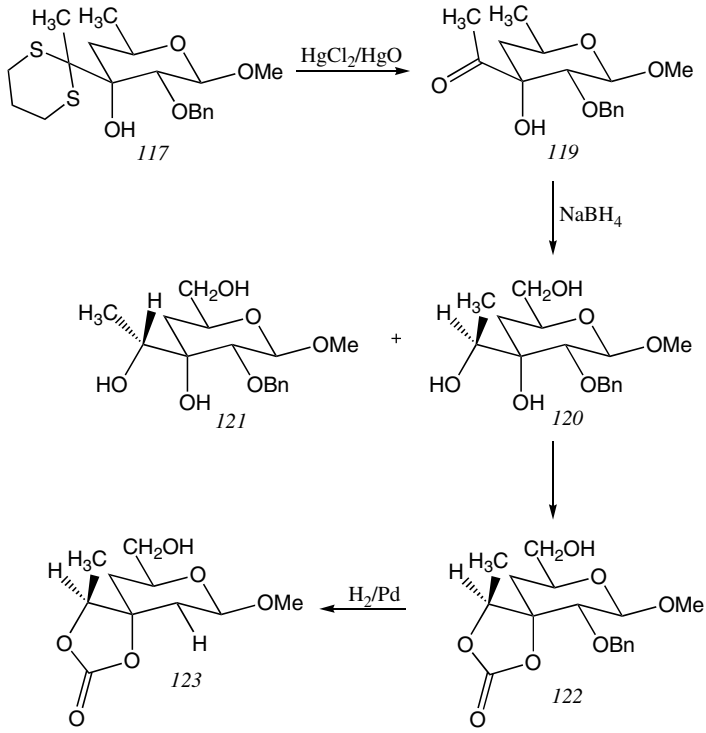


Fig. 11.33

of *tert*-butanol, *120* and *121* were obtained in 10:2.6 ratio in 61.8% overall yield (Fig. 11.33).

Vinyl Carbanion as the Nucleophile

Another method for introducing functionalized branching chain is the reaction of vinylmagnesium bromide with glycopyranosiduloses. Thus, methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-3-*C*-vinyl-α-D-allopyranoside *125* was obtained in 92% yield by addition of vinylmagnesium bromide to methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-*ribo*-hexopyranosid-3-ulose *124* (Fig. 11.34). The addition of vinylmagnesium bromide to methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-*arabino*-hexopyranosid-3-ulose *126* again resulted in the addition from the equatorial side giving in 54% yield methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-α-D-*altro*-pyranoside [54] *127,* in addition to some *allo*-branched chain sugar *125* which was formed probably by epimerization of the axially oriented C2 methyl group caused by the basic reaction conditions prior to the addition of the vinyl group.

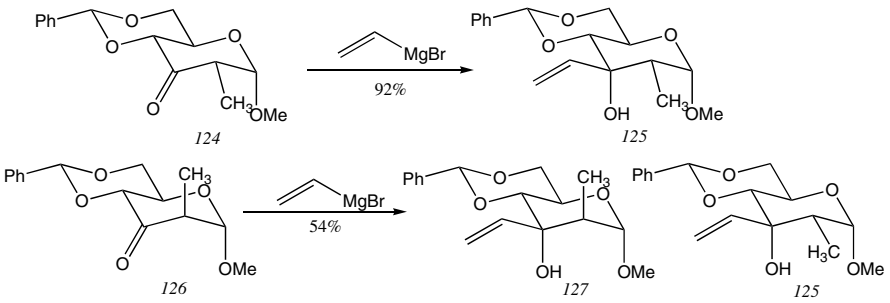


Fig. 11.34

Methoxyvinyl Lithium and 1,1-Dimethoxy-2-Lithio-2-Propene

Some other two-carbon carbanions used for the introduction of more complex branching chains are methoxyvinyl lithium *128* (introduction of acetyl group and 2-hydroxyacetyl branched chain [55, 56]) and 1,1-dimethoxy-2-lithio-2-propene *129* [57] (Fig. 11.35) which was used in the synthesis of pillarose *130* [58] (Fig. 11.35).

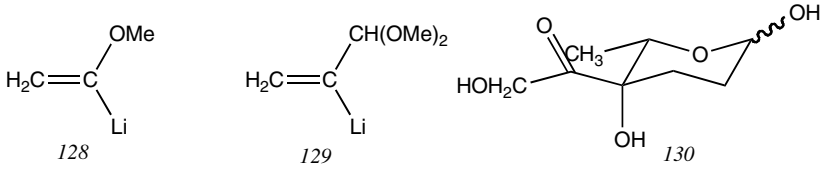


Fig. 11.35

In Fig. 11.36 is shown the addition of methoxyvinyl lithium to the methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose *131*. The addition was stereoselective, and the product *133* was obtained in 41% overall yield [58].

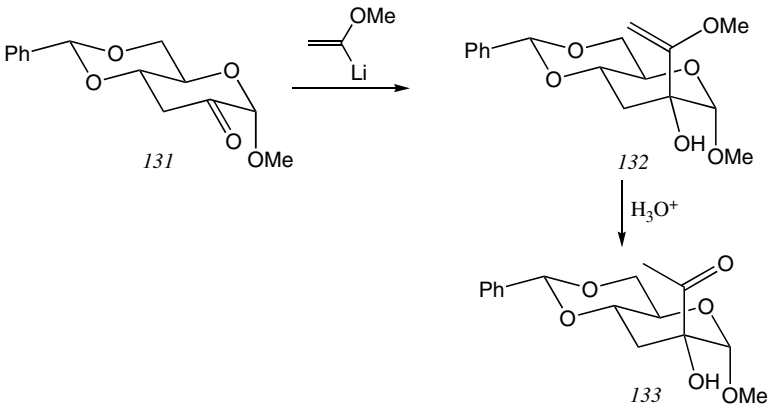


Fig. 11.36

1,1-Dimethoxy-2-lithio-2-propene *129* (Fig. 11.35) was used for the synthesis of *C*-methylene branched chain sugar intermediates [57, 59] needed for the synthesis of hamamelose G (*134*), a naturally occurring branched chain pentose (Fig. 11.37).

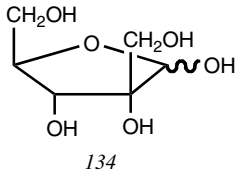


Fig. 11.37

The first step of the synthesis of hamamelose G, i.e., the addition of 1,1-dimethoxy-2-lithio-2-propene *129* to 2,3-*O*-isopropylidene-D-glyceraldehyde *135*, is depicted in Fig. 11.38.

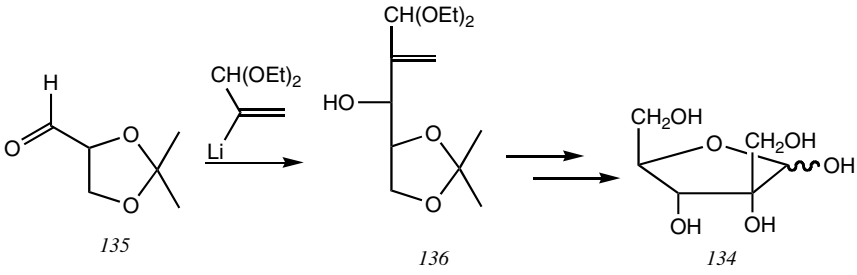


Fig. 11.38

Reformatsky Reaction

An interesting approach for the synthesis of functionalized branched chain sugars is the Reformatsky reaction [60–63]. Reformatsky reagent obtained from ethyl bromoacetate and zinc, in refluxing tetrahydrofuran, adds highly stereoselectively

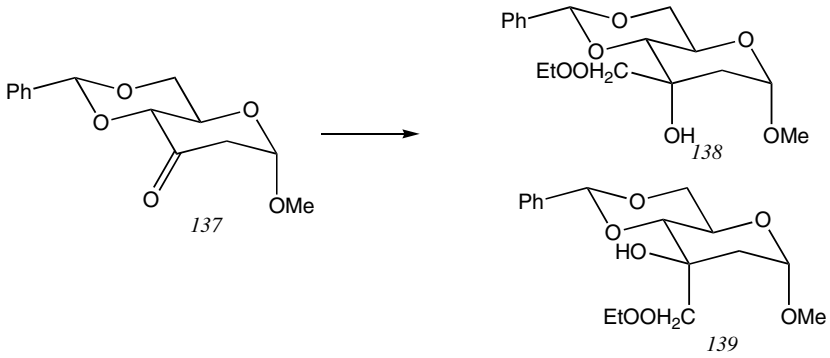


Fig. 11.39

to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *137* giving in 86% overall yield the branched chain sugars *138* and *139* in 94:6 ratio [64] (Fig. 11.39). The configuration of C3 branching carbon was established by using methyl 4,6-*O*-benzylidene-2-deoxy-2,2-dideutero-α-D-*erythro*-hexopyranosid-3-ulose *140* for the Reformatsky reaction and by converting the obtained branched chain sugar to (*S*)-(–)-(1,1-^{2}H)-citric acid *142*, the absolute configuration of which is known (Fig. 11.40).

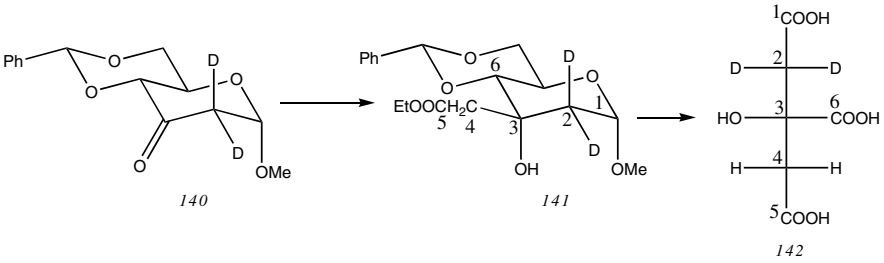


Fig. 11.40

Ethyl bromoacetate adds, at –78°C, to methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose *143* or to methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *145* in the presence of zinc and laminated silver-graphite highly stereoselectively from the *re*-face to give *144* or *146*, respectively (in both products the branched chain is equatorially oriented) [65] (Fig. 11.41). The firm proof for the configuration of branching carbons was not provided.

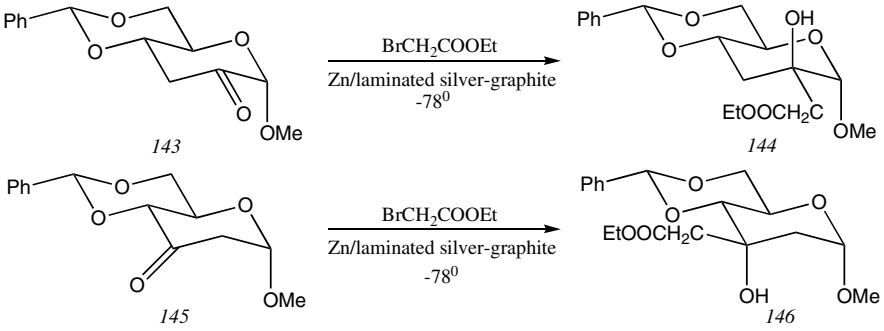


Fig. 11.41

2-Bromomethyl-acrylic acid ethyl ester *147* adds to methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose *143* in the presence of zinc, under usual conditions [66], giving, in 64% overall yield, a mixture of C2 epimers *148* and *149* in 54:10 ratio (Fig. 11.42).

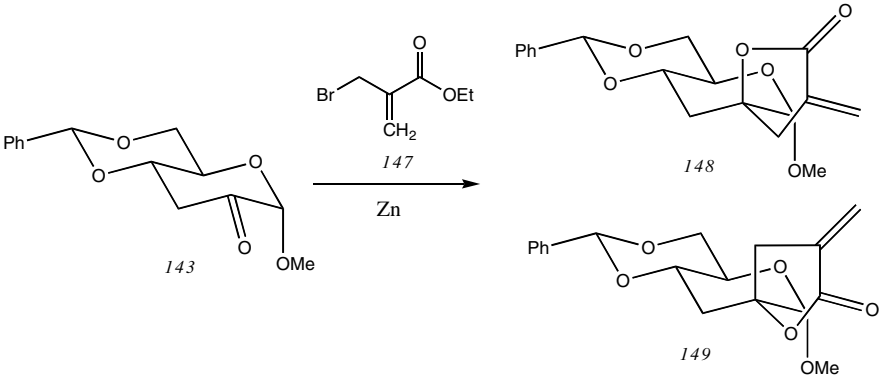
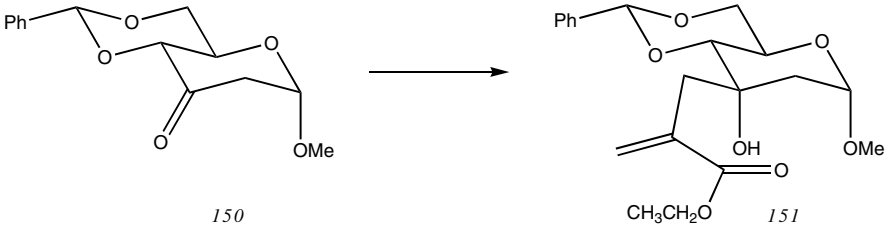


Fig. 11.42

The stereochemistry of addition of carbon nucleophiles to hexopyranosid-2-uloses in Figs. 11.41 and 11.42 seems to be less selective as compared to the stereochemistry of addition of other nucleophiles to the C2 carbonyl carbon of methyl α-D-hexopyranosid-2-uloses in which case the addition was observed to be taking place exclusively from the *si*-face due to the stereochemical control of the anomeric methoxy group (vide supra).

The addition of ethyl 2-bromomethyl-acrylate *147*, at –78°C, to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *150* in the presence of laminar zinc/silver-graphite [67] gave, in 92% yield, the adduct *151* as the only product (the addition took place, as expected, from the *re*-face) (Fig. 11.43).



150 *151*

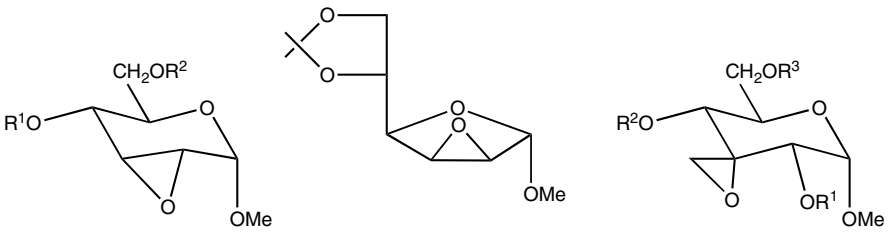
Fig. 11.43

Unlike the adducts obtained in the addition of 2-bromomethyl-acrylate *147* to methyl hexopyranosid-2-ulose derivative *143,* the adduct *151* could not be converted to the spiro α-methylene-γ-lactone.

The authors claimed that the stereochemistry of branching carbons in *148*, *149*, and *151* were established by comparison of these products with the previously described products of similar Reformatsky reactions [65]. However, the references cited did not support these claims, and consequently the stereochemistry of branching carbons must be considered unknown.

Opening of Oxiranes with Nucleophiles

There are two types of oxiranes that were used for the synthesis of branched chain sugars: endocyclic oxiranes and spiro oxiranes. Endocyclic oxiranes consist of an epoxide ring on either the pyranose or the furanose ring (*152* and *153*) and spiro oxiranes (*154*) are obtained by the addition of diazomethane on hexo- or pentopyranosidulose or by epoxidation of *n*-deoxy-*n*-*C*-methylene sugar derivatives (Fig. 11.44).



152 *153* *154*

Fig. 11.44

The opening of an oxirane ring must always take place in the *trans*-diaxial fashion. Thus, for example, the endocyclic oxirane *155* opens with the exclusive formation of *156,* as depicted in Fig. 11.45; product *157* is not formed. This puts certain limitations on the use of this method for the synthesis of branched chain sugars,

because first the branching chain will always be axially oriented and second the position of the branching carbon is predetermined by the configuration of the oxirane ring (in this case it can only be the C2 carbon).

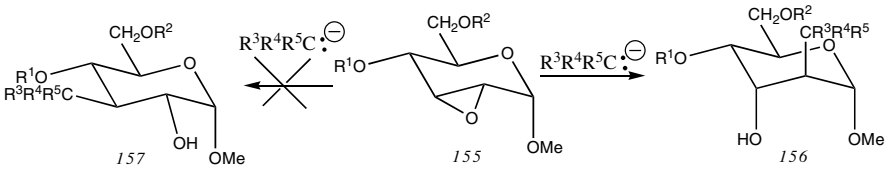


Fig. 11.45

Thus, the diaxial opening of the oxirane ring of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-L-mannopyranoside *158* and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside *160* (Fig. 11.46) with ethylmagnesium chloride gave 3-deoxy-3-*C*-ethyl- and 2-deoxy-2-*C*-ethyl derivatives *159* and *161*, respectively [68, 69].

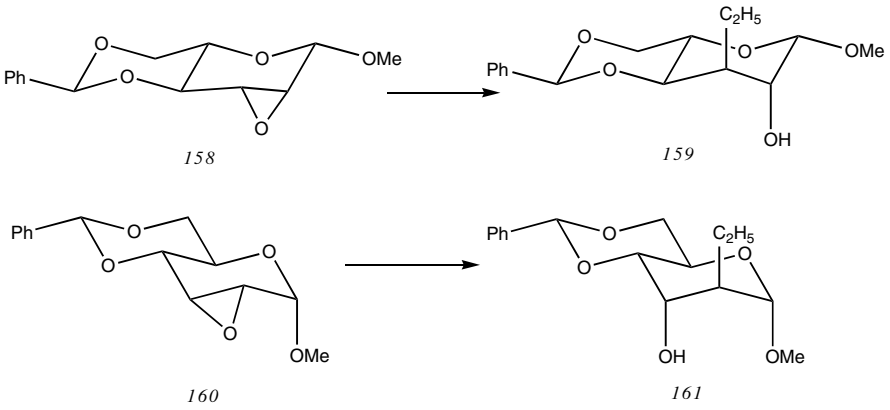
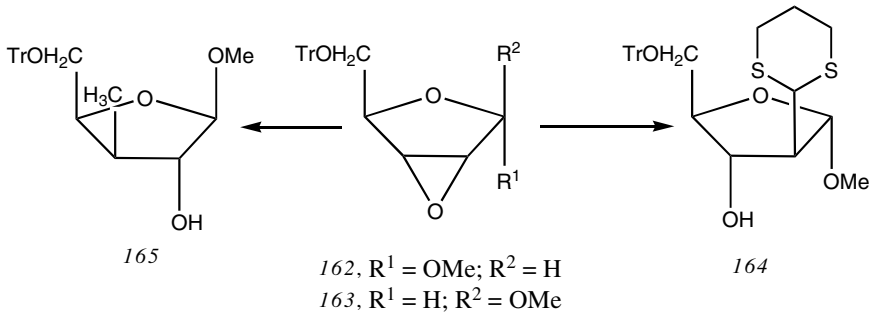


Fig. 11.46

The methyl 2,3-anhydro-5-*O*-trityl-α-D-ribofuranoside *162* reacts with the 2-lithio-1,3-dithiane regioselectively to give the 2-*C*-dithianyl derivative *164*, whereas the methyl 2,3-anhydro-5-*O*-trityl-β-D-ribofuranoside *163* reacts with methylmagnesium chloride also regioselectively to give 3-deoxy-3-*C*-methyl derivative *165* (Fig. 11.47). In this case the regioselectivity of oxirane ring opening seems to be controlled by the anomeric configuration.

Ethyl disodiomalonate [70, 71], hydrogen cyanide–triethylaluminum [72], dimethylmagnesium [73], and lithium dimethylcuprate [40, 74] are other carbon nucleophiles used for opening of the oxirane ring.



165

162, R^1 = OMe; R^2 = H
163, R^1 = H; R^2 = OMe

164

Fig. 11.47

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Chapter 12
Chemistry of the Glycosidic Bond

Introduction

Because of the importance and the role the carbohydrates play in living organisms, the formation and hydrolysis of glycosidic bond are probably the two most important reactions in carbohydrate chemistry. Just as the amino acids are the building blocks for the synthesis of peptides and proteins in living organisms, the monosaccharides are the building blocks for the synthesis of oligosaccharides, polysaccharides, and glycoconjugates (glycoproteins, glycosaminoglycans, glycolipids, and proteoglycans to name a few). The synthesis of oligo- and polysaccharides as well as glycoconjugates requires the formation of glycosidic bonds, i.e., the formation of a chemical bond between the C1 carbon of a monosaccharide and any hydroxyl oxygen of another monosaccharide or a hydroxyl oxygen of any molecule that bears hydroxyl group, such as a hydroxyamino acid (serine, threonine), a lipid (sphingosine), and phosphatidyl inositol. The glycosidic bond can also be formed between the anomeric C1 carbon of a monosaccharide and the amido nitrogen of asparagine (as, for example, in N-linked glycoproteins) or the nitrogen of a purine or a pyrimidine base (as, for example, in ribo- and deoxyribonucleosides).

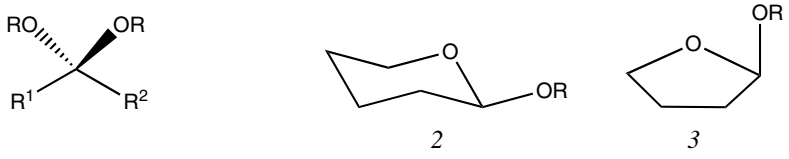
The formation of glycosidic bonds takes place during the biosynthesis of various oligo- and polysaccharides or glycoconjugates whereas the hydrolysis of glycosidic bonds occurs during the processing of biosynthetic intermediates in the biosynthesis of complex saccharides or during metabolism of complex saccharides and glycoconjugates in cells.

Unlike the synthesis of peptides and proteins from amino acids, where the only issues that a synthetic chemist has to deal with are the selection of a reagent for the peptide bond formation, the selection of proper protection groups for relatively simple side chains of amino acids, and the prevention of possible racemization of amino acids during synthesis, the synthesis of oligo- and polysaccharides represents a much greater challenge to a synthetic chemist because the monosaccharides are structurally much more complex molecules than amino acids. First, they contain several hydroxyl groups (or sometimes other functional groups, such as acetamido and carboxyl) that, for the oligosaccharide or polysaccharide synthesis, require multiple regioselective protection that is often difficult to accomplish because it is

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_12,

difficult to distinguish them chemically. Second, there are two types of glycosidic bond that a monosaccharide can form, α- or β-glycosidic bond, so that the stereoselectivity in the glycoside bond formation is a very important issue for the synthesis of oligo- and polysaccharides. Third, one should not forget that monosaccharides exist in two ring structures, furanoses and pyranoses, and that in some instances this issue must be addressed too. Finally, the selection of protection groups in an oligosaccharide synthesis is a very important and often difficult problem, because they have to be not only regioselective but also removable under mild conditions so that the newly formed glycosidic bond will not be hydrolyzed on their removal. In peptide or protein synthesis this problem does not exist because the peptide bonds are chemically very resistant. Since the nature of the C2 substituent most often determines the stereochemistry of the newly formed glycosidic bond, much attention has been given to the protection of the C2 hydroxyl group.

Chemically the glycosidic bond is an acetal bond and generally has the same chemical properties. However, whereas in acetals or ketals formed by condensing an aldehyde or ketone with an alcohol both alkoxy groups are identical (the acetal carbon is achiral since it has a plane of symmetry) (*1* in Fig. 12.1), the glycosides are mixed acetals having as one alkoxy group the C5 or the C4 hydroxyl group of a parent monosaccharide in its pyranoid or furanoid form (*2* or *3*, respectively, in Fig. 12.1) and the other alkoxy group is an alcohol, another monosaccharide, hydroxyamino acid, lipid, etc. Consequently the anomeric carbon in glycosides is chiral (Fig. 12.1).



1, R = alkyl; R^1 and R^2 are H, alkyl, aryl, or carbon atoms of the same molecule

2 and *3,* R = alkyl, aryl, monosaccharide, amino acid, lipid, etc.

Fig. 12.1

Glycoside Synthesis

The first synthesis of an *O*-glycoside (to distinguish the glycosides from the more recently synthesized *C*-glycosides, which are not really glycosides, but rather C2 alkyl tetrahydrofuran or tetrahydropyran derivatives) was carried out by Michael [1–3] by reacting the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride *4* with potassium phenoxide (Fig. 12.2):

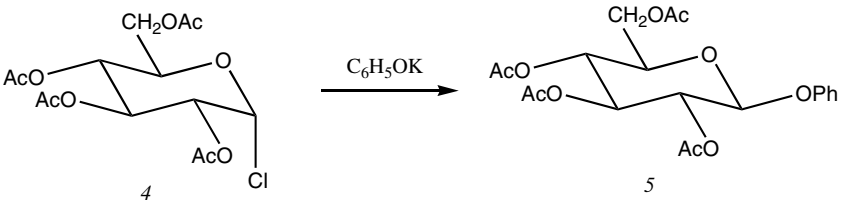


Fig. 12.2

Fischer Glycosidation

In 1893 E. Fischer [4, 5] developed a synthesis of glycosides of lower alcohols by refluxing a monosaccharide (for example, D-glucose) with an alcohol in the presence of an anhydrous mineral acid (for example, HCl). If the concentration of mineral acid is several percent, α- and β-glycopyranosides are obtained (Fig. 12.3). However, if the concentration of mineral acid (HCl) is low (for example, 0.7%) and if the reaction is conducted at room temperature, the reaction of D-glucose with anhydrous methanol affords a mixture of methyl α- and β-D-glucofuranosides in good yield (Fig. 12.4).

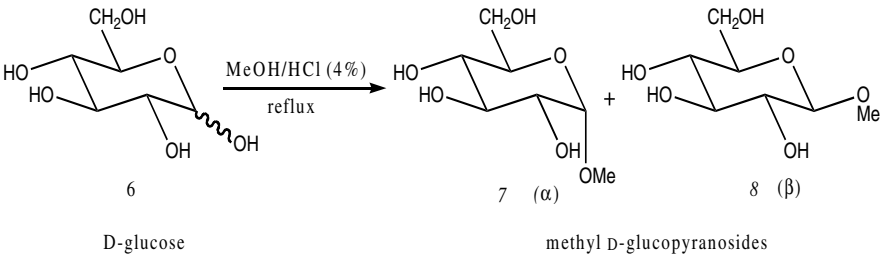


Fig. 12.3

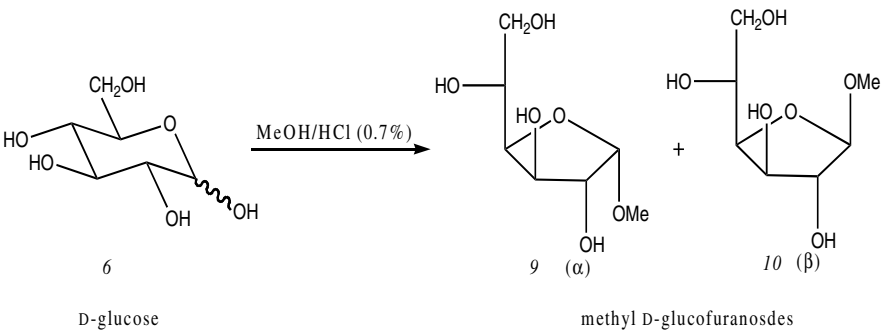


Fig. 12.4

The above results suggest that the furanoid forms of D-glucose must be much more reactive toward glycosidation and that the obtained glucofuranosides are therefore kinetic products. Raising temperature and increasing the concentration of HCl converts the less stable methyl furanosides to more stable methyl α- and β-D-glucopyranosides suggesting that the latter are thermodynamic products. Thus, methyl glucopyranosides are most likely formed by both isomerization of methyl furanosides and direct glycosidation of glucopyranose (see Fig. 12.5).

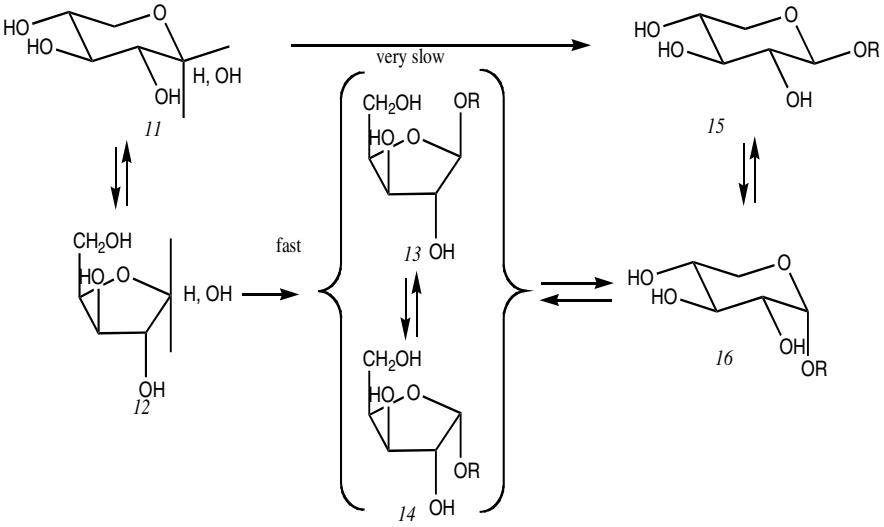


Fig. 12.5

The mechanism of Fischer glycosidation was studied in detail by using D-xylose [6, 7]. It has been shown that the formation of equilibrium mixture of glycosides (*15* and *16*) (Fig. 12.5) proceeds in four reaction steps that greatly differ in their rates of equilibrium formation (Figs. 12.5 and 12.6). In the first step, the free xylose, which is an equilibrium mixture of α- and β-D-xylopyranoses *11* and α- and β-D-xylofuranoses *12*, is converted into a mixture of α- and β-D-xylofuranosides (*13* and *14*) that, in the second step, undergoes an acid-catalyzed anomerization until an equilibrium mixture of α- and β-xylofuranosides is obtained. In the third step, the furanoside to pyranoside ring isomerization takes place, and finally in the fourth step, anomerization of α- and β-D-xylopyranosides takes place until the final equilibrium mixture of obtained pyranosides is formed (*15* and *16*) (Fig. 12.5). So the end result of these intramolecular isomerizations is the formation of an equilibrium mixture of all four methyl xylosides *13*, *14*, *15*, and *16*. It is important to note that the first two steps are considerably faster than the last two steps.

A possible reaction mechanism for the Fischer synthesis of glycosides is shown in Figs. 12.6, 12.7, and 12.8. The proposed mechanism suggests that D-xylopyranose does not undergo direct glycosidation. Instead it is first converted to xylofuranose (*11*→*17*) (Fig. 12.6) which then undergoes glycosidation. That is probably not

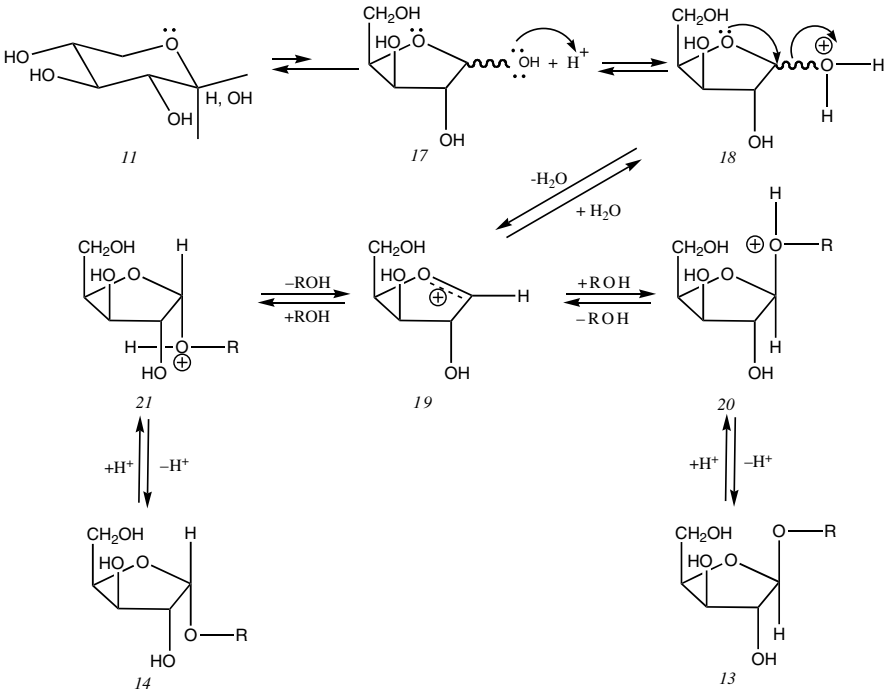


Fig. 12.6

completely true, because the pyranose does, although much slowly, undergo glycosidation reaction on its own. It is assumed that protonation of glycosidic oxygen of glycofuranoses leads to the formation of oxocarbenium ion *19* which then adds an alcohol to the C1 carbon from either side of the molecule resulting in the formation of α- and β-D-xylofuranosides *13* and *14*.

The alcoholic solution of D-xylose consists predominantly of a mixture of α- and β-D-xylopyranoses *11* and a mixture of α- and β-D-xylofuranoses *12* (in Fig. 12.5). Since direct glycosidation of xylopyranoses is a very slow process and glycosidation of xylofuranoses is a fast process, the xylofuranoses will be removed from equilibrium mixture by the glycosidation resulting in the conversion of an additional amount of xylopyranoses to xylofuranoses and this process will continue until all of glycopyranose has been converted to a mixture of xylofuranose glycosides (Fig. 12.6).

The proposed reaction mechanism is in agreement with the observation that short reaction times, or small amounts of acid catalyst in the glycosylation reaction, favor the formation of furanosides as the predominant products, while higher concentrations of acid catalyst or by allowing the reaction to reach equilibrium, the predominant products are pyranosides.

The obtained mixture of α- and β-D-xylofuranosides *22* and *23* then undergoes ring isomerization via the acyclic oxocarbenium transition state *24* (Fig. 12.7). For

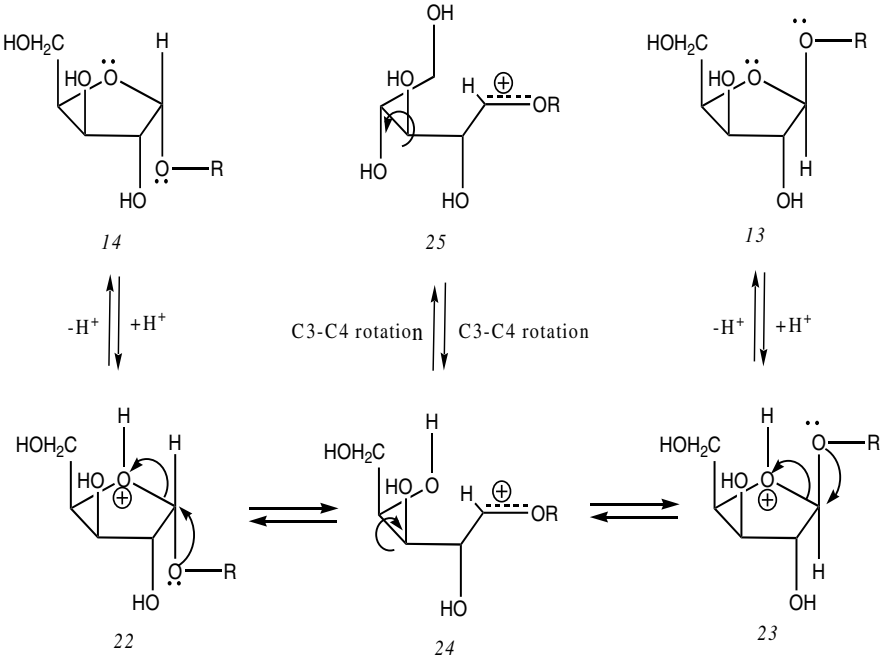


Fig. 12.7

this, the protonation of the ring oxygen must first take place followed by the C1–O4 bond rupture resulting in the formation of the acyclic oxocarbenium intermediate *24*. The rotation about the C3-C4 bond prior to the ring closure (the reverse reaction of ring rupture) brings the C5 hydroxyl group in position to attack the oxocarbenium ion and thus close the pyranoside ring *25* (Fig. 12.8). The anomerization of α- and β-D-xylopyranosides takes place again via cyclic oxocarbenium ion transition state (Fig. 12.8) [8]. It should be noted that the anomerization of α- and β-D-xylopyranoses can also take place via the acyclic oxocarbenium ion *25.*

Although acyclic acetals are feasible intermediates in the glycosidation of sugars, Bishop and Cooper [6, 7] did not find evidence for their presence in equilibrium mixture. However, by using radiochemical techniques, two groups of researchers have reported the presence of acyclic acetals in the glycosidation reaction mixtures. Heard and Barker [9] observed the presence of acyclic dimethyl acetal in the product mixture obtained by methanolysis of D-arabinose, and Ferrier and Hatton [10] reported the presence of acyclic dimethyl acetal in the glycosidation reaction mixture of D-xylose and D-glucose.

While still useful for the preparation of methyl glycosides, Fischer method is not at all suited for the much more complicated synthesis of oligosaccharides or for the glycosylation of other natural products (proteins, lipids, etc.).

Since Fischer synthesis often gives a complex mixture of anomeric and ring isomers it is not considered to be the preparative method of choice for the syntheses of glycosides. For example, the equilibrium mixture obtained by acid-catalyzed

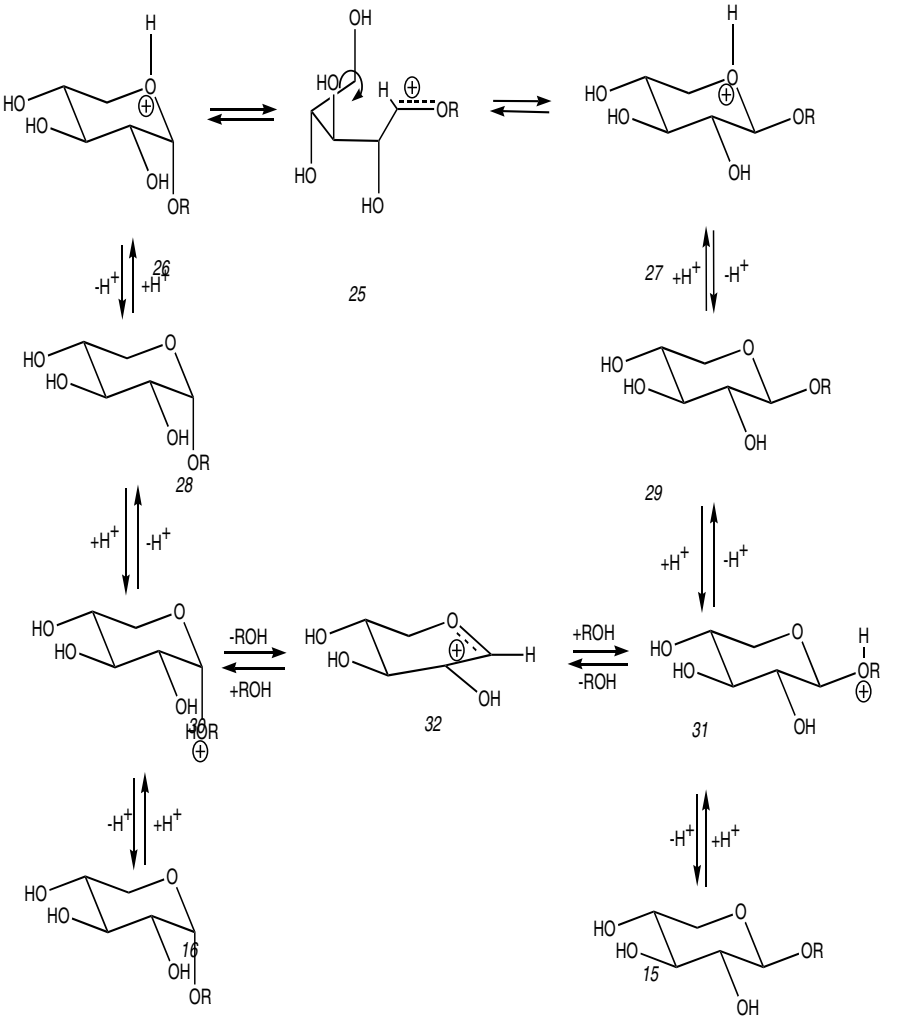


Fig. 12.8

methanolysis of D-galactose consists of methyl α-D-galactofuranoside 6.2%, methyl β-D-galactofuranoside 16.3%, methyl α-D-galactopyranoside 57.8%, and methyl β-D-galactopyranoside 19.7% [11]. Usually, the preparative application of Fischer synthesis is based on two approaches. According to one approach the Fischer reaction is terminated at a kinetically controlled stage to prepare furanosides. Thus, for example, methyl α-D-arabinofuranoside can be prepared in good yield in this way [12]. Another approach is to allow the reaction mixture to reach equilibrium and then isolate the predominant isomer. Which isomer will predominate depends on the sugar. In some cases the predominant isomer is formed in great excess, as

is for example the case with methyl α-D-mannopyranoside [11] which is, at equilibrium, 94% and sometimes the desirable product crystallizes directly from equilibrium mixture, allowing thus its easy isolation, as is the case with benzyl β-L-arabinopyranoside [13] that is isolated with 75% yield.

Königs –Knorr Synthesis

In 1901 Königs and Knorr [14] developed a new method for the synthesis of glycosides which was immediately recognized as the more general and useful preparative method than Fischer method and which is still used today (modified or unmodified). The Königs–Knorr method consists of reacting a fully acetylated glycosyl halide *33* with an alcohol or with a hydroxyl group of another sugar (dissolved in a dry inert solvent) in the presence of silver carbonate or silver oxide as promoter and acid acceptor [14] (Fig. 12.9).

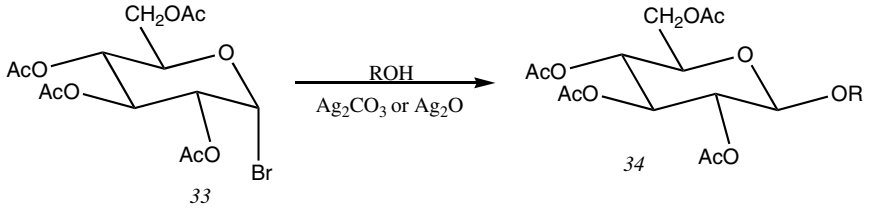


Fig. 12.9

O-Acylglycosyl halides (excluding fluorides) react with alcohols also directly (in the absence of silver carbonate or silver oxide) to yield glycosides. Thus, a variety of *O*-benzoylglycosyl halides react directly with methanol to give 1,2-*trans*-*O*-benzoylglycosides. For example, tri-*O*-benzoyl-β-D-ribopyranosyl bromide *35*, in anhydrous methanol, gave methyl tri-*O*-benzoyl-β-D-ribopyranoside *36* with 88% yield [15] (Fig. 12.10).

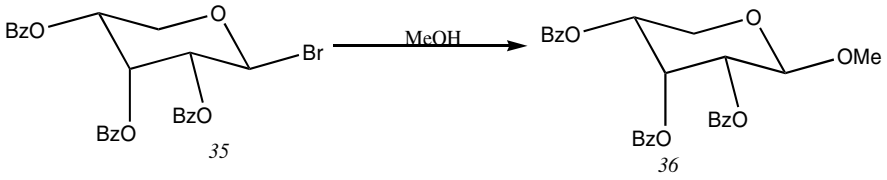


Fig. 12.10

Similarly, methyl tetra-*O*-benzoyl-β-D-glucopyranoside *38* was obtained with 90% yield from tetra-*O*-benzoyl-α-D-glucopyranosyl bromide *37* [16] (Fig. 12.11).

It has been shown that glycosyl halides having the C2 acyl substituent *trans*-oriented relative to the C1 halogen are much more reactive than their corresponding *cis*-isomers (see Table 12.1).

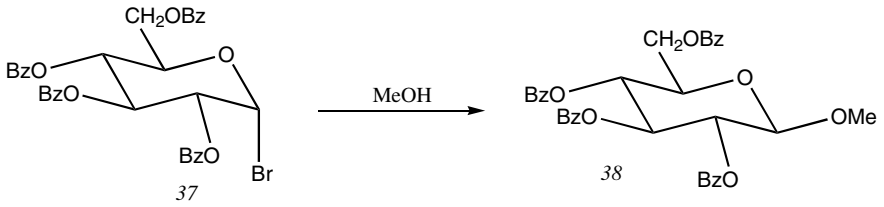


Fig. 12.11

Table 12.1 Reaction of tri-*O*-benzoyl-D-pentopyranosyl halides with 1:9 dioxane:methanol at 20°C

Tribenzoate of	$k \times 10^4$ (min., $\log_{10}$)
1,2-*cis*-α-D-Ribosyl bromide	40
1,2-*trans*-β-D-Ribosyl bromide	760
1,2-*cis*-α-D-Ribosyl chloride	0.62
1,2-*trans*-β-D-Ribosyl chloride	53

The mechanism of Königs–Knorr reaction has been extensively studied for many years. The obtained results are often contradictory and many aspects of the reaction mechanism are still unclear [17].

The addition of hydroxyl ions does not increase the rate of solvolysis of *O*-acetylglycopyranosyl halides in methanol and in aqueous acetone, but the addition of water does increase the rate, thus supporting the proposed unimolecular carbonium ion mechanism [18]. The glycopyranosyl halides that bear an acyloxy group at the C2 carbon, which is *cis* to 1-halide, usually react with the inversion of anomeric configuration, whereas the glycopyranosyl halides having the C2 acyloxy group *trans* to 1-halides react with the retention of anomeric configuration. This stereochemical outcome has been explained by neighboring group participation of the C2 acyloxy group in the transition state by formation of an 1,2-cyclic carboxonium cation *41*, thus, on one side, stabilizing the transition state and, on the other side, forcing the nucleophile to approach the C1 carbon from the 1,2-*trans* direction (Fig. 12.12). The stability of the intermediary carboxonium cation has a profound influence upon the rate and the course of reaction. The formation of transition state requires flattening of the pyranoid ring and the adoption of a conformation that resembles the half-chair conformation with the C2, C1, O5, and C5 atoms lying in one plane (*40* and *41* in Fig. 12.12). It has been suggested that a large equatorial substituent at the C5 carbon hinders the formation of transition state [19] *41* and this argument was used to explain the greater rate of methanolysis of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide *42* than that of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide *43* (Fig. 12.13).

The slower rate of methanolysis of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide *44* (Fig. 12.13) than that of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide *43* has been ascribed to Pitzer strain between the C2 and the C3 acetoxy groups that increases during the formation of transition state.

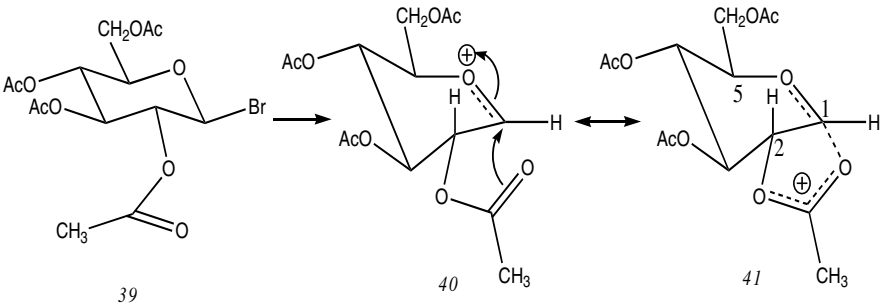


Fig. 12.12

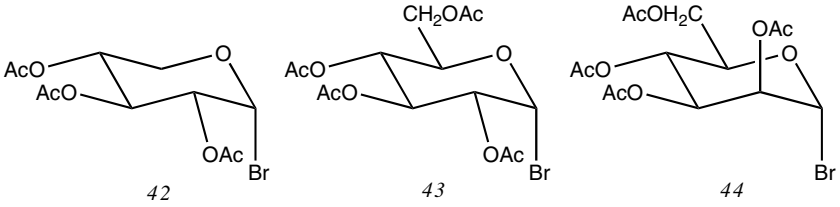


Fig. 12.13

The stereochemical consequence of stabilization of the oxocarbenium ion via neighboring group participation of the C2 acyl group in 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide *39* has been the exclusive formation of β-D-glucoside.

When, however, the nucleophilicity of carbonyl group of the C2 acetoxy group is decreased by substituting the three hydrogen atoms of methyl group with chlorine [20], as is the case in 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D-glucopyranosyl chloride *45*, the methanolysis of *45* in pyridine, containing silver nitrate as promoter, gives methyl 3,4,6-tri-*O*-acetyl-2-*O*-trichloroacetyl-α-D-glucopyranoside *46* (Fig. 12.14).

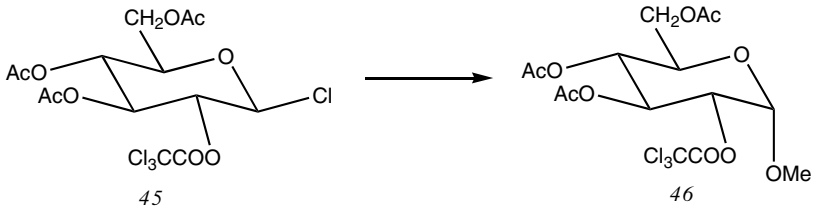


Fig. 12.14

The three chlorine atoms have removed the nucleophilicity of the carbonyl oxygen by electron-withdrawing inductive effect of these chlorine atoms and thus prevented the formation of cyclic carboxonium ion [21, 22].

Hence, in order to accomplish the synthesis of 1,2-*cis* glycosides by Königs–Knorr reaction, the protection group at the C2 carbon must be a nonparticipating group.

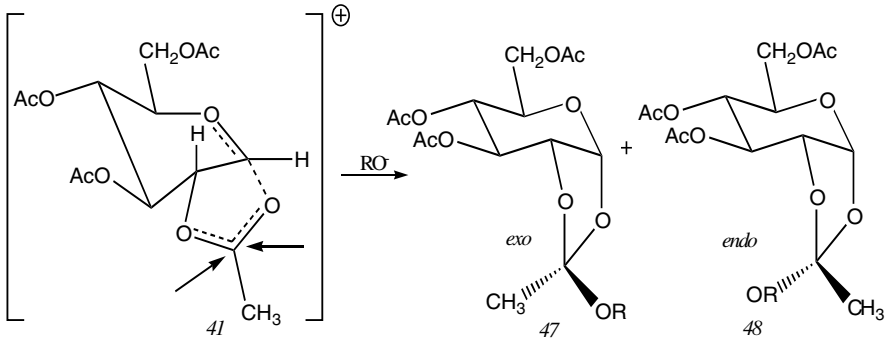


Fig. 12.15

The attack of a nucleophile on oxocarbonium ion *41* does not always have to take place at the C1 carbon; it can also attack the carbonyl carbon of the C2 acetate giving rise to one or both diastereomeric *orthoesters 47* and *48* (Fig. 12.15). The orthoester formation is often a side reaction of the Königs–Knorr reaction. By slightly changing the experimental conditions, the formation of orthoesters can be made to be the major pathway of Königs–Knorr reaction.

For example, the reaction of tri-*O*-acetyl-2-*O*-acyl-α-D-glucopyranosyl halides with a variety of alcohols in 2,4,6-trimethylpyridine containing tetraalkyl ammonium halide gives 1,2-orthoesters in high yield [23]. In each case the alkoxy group in dioxolan ring was shown (by NMR) to be in the *exo*-configuration *47* (*trans* to the pyranose ring) (Fig. 12.15). The use of 1,2-orthoesters as active intermediates for the synthesis of glycosides was developed by Kochetkov and his co-workers and will be discussed later.

Numerous modifications and improvements of Königs–Knorr reaction have been reported. For example, the use of anhydrous calcium sulfate and small amounts of iodine proved to be very useful and most often improved the yield [24, 25]. In order to avoid the need for a drying agent (drierite) for removal of water formed during Königs–Knorr reaction, silver salts of hydroxycarboxylic acids have been suggested as both promoters and acid acceptors [26–29]. The Königs–Knorr reaction was found to be strongly dependent on the solvent.

To overcome the difficulties that arise from the heterogeneity of reaction mixture that is typically associated with Königs–Knorr reaction (the catalyst and the acid acceptor are usually insoluble in the solvents used), silver salts with nonnucleophilic anion that are soluble in organic solvent were used in combination with silver carbonate or oxide. In fact silversalt in solution, for example silver perchlorate, serves as a homogenous catalyst whereas silver carbonate or oxide added to

the reaction mixture serves as acid acceptor during which step the soluble catalyst is regenerated (Fig. 12.16).

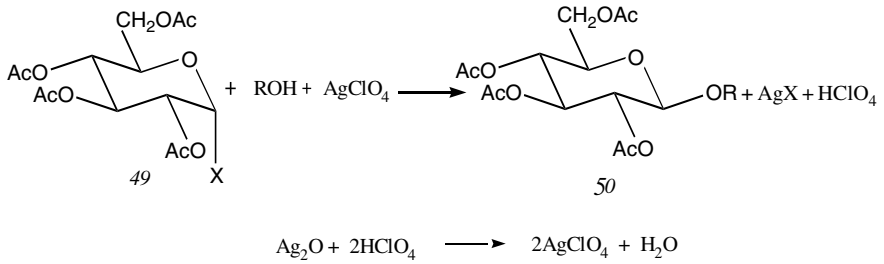


Fig. 12.16

The Königs–Knorr reaction is usually faster in the presence of soluble catalysts. Various soluble silver salts were used, e.g., tetrafluoroborate, hexafluorophosphate, trifluoromethanesulfonate (triflate), or *p*-toluenesulfonate (tosylate). The yields obtained with these catalysts are almost quantitative but the stereochemical outcome was strongly dependent on reaction conditions and the structure of protecting groups in the glycosyl halide [30–32].

A solution of silver triflate catalyst in methylene chloride in combination with 1,1,3,3-tetramethylurea as a soluble acid acceptor has been shown to be an effective system for glycosidation [33, 34]. The reaction was performed under strictly anhydrous conditions in dark for 4 h. The disaccharide *53* was obtained with 47% yield. In three other experiments the respective disaccharides were obtained with yields ranging from 72 to 86% (Fig. 12.17).

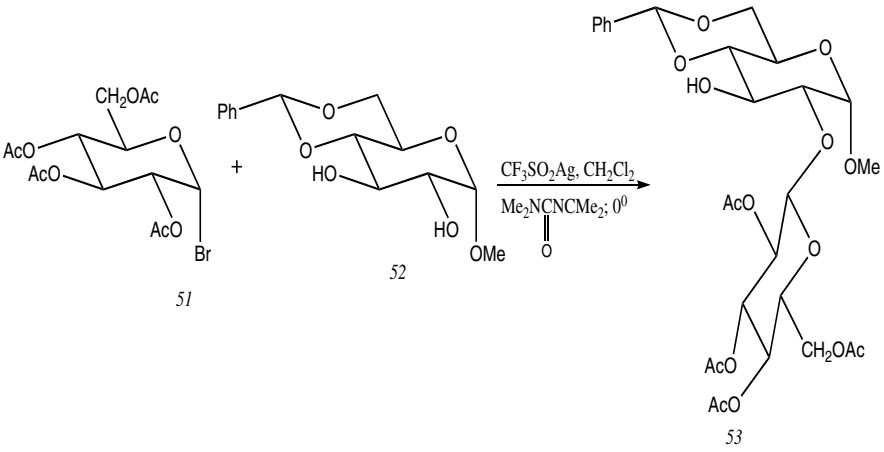


Fig. 12.17

Helferich and Wedemeyer [35] found that mercuric cyanide in nitromethane as solvent is both the catalyst and acid acceptor in the Königs–Knorr reaction and results in significantly improved yields of glycosides.

Alkyl β-D-glucopyranoside tetra-acetates were obtained in high yield by the use of a mixture of mercuric bromide as the catalyst and yellow mercuric oxide as the acid acceptor [36]. Another modification for the synthesis of α-D-glucosides and α-D-galactosides uses a mixture of mercuric bromide and mercuric cyanide [37].

Finally, by using mercuric acetate or ferric chloride some α-D-glycosides could be synthesized in spite of the presence of a participating group at the C2 carbon [38, 39].

Synthesis of Acylated Glycosyl Chlorides and Bromides

It is now appropriate to briefly discuss the synthesis of glycosyl halides (chlorides and bromides).

Acylated glycosyl halides can be prepared by the action of hydrogen bromide (or chloride), titanium tetrachloride, or aluminum trichloride on a peracylated sugar.

Colley [40] and Königs and Knorr [14] prepared glycosyl halides from unsubstituted sugars and acyl chloride or bromide, whereby tetra-*O*-acetyl-glycosyl halides were obtained directly.

Fischer and Armstrong [41] prepared the chloride and bromide, in almost quantitative yield, by treating the β-D-glucopyranose pentaacetate with the liquid hydrogen halide (hydrogen chloride or hydrogen bromide).

A decade later, Fischer [42] developed a more convenient method for the synthesis of glycopyranosyl halides, by treating either anomer of a peracetylated sugar with the acetic acid solution of hydrogen halide instead of liquid hydrogen halide. The reaction is effected at low temperature and can be very fast [43].

The acylated glycosyl halides can be prepared from corresponding methyl glycosides by reaction with an acetic acid solution of hydrogen halide (HCl or HBr). This method is particularly useful for the synthesis of acylated glycofuranosyl halides [44].

Acetylated glycosyl chlorides can be prepared under relatively mild conditions by reacting the corresponding peracetylated sugar with titanium tetrachloride [45]. It has been reported that the anomeric configuration of C1 acetate can have a profound effect upon the reactivity of peracetylated sugar with $TiCl_4$. Thus, for example, while penta-*O*-acetyl-α-D-glucopyranose is stable toward titanium tetrachloride, at 40°C, the β-anomer reacts extremely rapidly giving the tetra-*O*-acetyl-β-D-glycopyranosyl chloride, which then slowly anomerizes to the α-D-anomer.

Aluminum chloride–phosphorus pentachloride [46, 47] and zinc chloride–thionyl chloride [48] are also convenient methods for the preparation of glycosyl chlorides.

The stability of acylated glycosyl halides depends on the configuration and inductive and neighboring group effects. Thus, both anomers of benzoylated D-ribopyranosyl chlorides [49] and D-arabinofuranosyl bromides [50] are known to be considerably stable. There is, however, a large difference in stability between

the anomeric acetylated D-glycopyranosyl halides, the β-form being highly unstable and the α-form being stable. Consequently the β-anomer readily anomerizes to α-form.

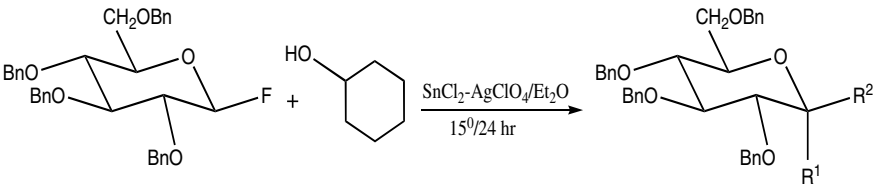
The preparation of unstable tetra-*O*-acetyl-β-D-aldopyranosyl chloride can be effected by treating the tetra-*O*-acetyl-α-D-glycopyranosyl bromide with "active" silver chloride [51] or by tetraethylammonium chloride in acetonitrile [52].

The reactivity of glycosyl halides depends, first, on their configurational relationship (*cis* or *trans*) with regard to the C2 substituent and, second, on whether the substituent at the C2 carbon is capable of becoming involved in the neighboring group participation or not.

Glycosyl Fluorides in Glycosylation

Glycosyl fluorides have now been widely and effectively used for O-glycosidation reaction, because of their much higher thermal and chemical stability as compared to the low stability of other glycosyl halides, such as glycosyl chlorides and bromides. Thus, for example, the glycosyl fluorides can be purified by distillation and even by column chromatography on silica gel. There are several good reviews on glycosyl fluorides as glycosyl donors [53–55].

The use of glycosyl fluorides as glycosyl donors was first developed by Mukaiyama et al. [56]. Thus 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride *54* was reacted with cyclohexanol *55* in ether, at –15°C, in the presence of 4 Å molecular sieves (to maintain the anhydrous conditions) and silver perchlorate–stannous chloride as fluorophilic activators. A mixture of anomeric cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α- and β-D-glucopyranosides (*56* and *57*, respectively) was obtained with 88% yield in which the α-anomer (*60*) predominated in almost 5:1 ratio (83:17) (Fig. 12.18).



54 *55* *56*, $R^1 = C_6H_{11}O$; $R^2 = H$
57, $R^1 = H$; $R^2 = C_6H_{11}O$

Fig. 12.18

Many activators for the O-glycosidation using glycosyl fluorides were developed over the years. For example, stannous chloride–trityl perchlorate catalyst was used for coupling 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride *58* with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside *59* whereby an anomeric mixture *60* was obtained with 95% yield, with the α-anomer strongly predominating (the α/β ratio was 22:3) [57] (Fig. 12.19).

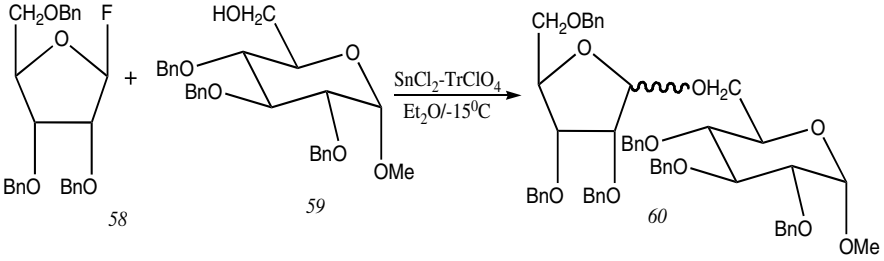


Fig. 12.19

Trimethylsilyl triflate [58] (TMSOTf) has been shown to be a very good catalyst for glycosidation of glycosyl fluorides (glycosyl donors) with trimethylsilyl ethers as glycosyl acceptors. The stereoselectivity of this glycosidation was found to be highly dependent on solvent, as illustrated in Fig. 12.20. Thus the reaction of 2,3,4-tri-*O*-benzyl-β-D-glycopyranosyl fluoride *54* and trimethylsilyl cyclohexyl ether *61* using TMSOTf as the catalyst, in acetonitrile, gave, after 2 h at 0°C, a mixture of cyclohexyl 2,3,4,6-tetra-*O*-benzyl-α- and β-D-glucopyranosides *62* and *63* with 92% yield, in which the β-anomer strongly predominated (α/β ratio was 1:6). If the glycosidation is performed in ether an anomeric mixture of cyclohexyl 2,3,4,6-

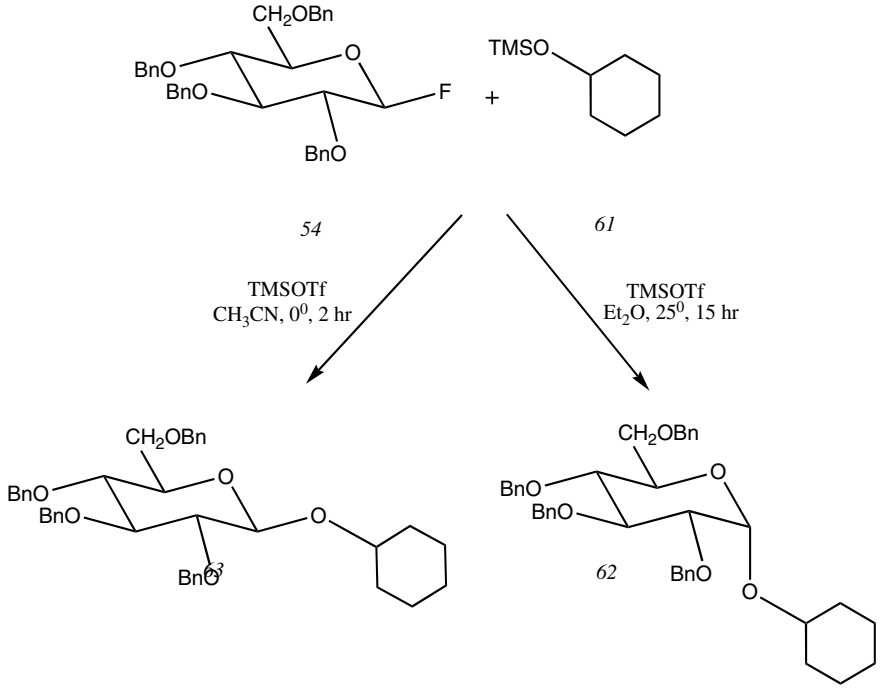
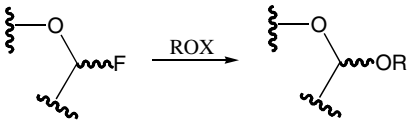


Fig. 12.20

Table 12.2 O-Glycosidation of glycosyl fluorides



Activator	X	Reference
$SnCl_2$–$AgClO_4$	H	[59, 60]
BF_3–Et_2O	H	[61–64]
Cp_2MCl_2–AgOTf (M = Zr or Hf)	H	[65–68]
Cp_2ZrCl_2–$AgBF_4$	H	[69]
$CpHfCl_2$–AgOTf	H	[69–71]
$Bu_2Sn(ClO_4)_2$	H	[72]
Me_2GaCl	H	[73]
Tf_2O	H	[74, 75]
$LiClO_4$	H	[76–78]
$Yb(OTf)_3$	H	[79]
$La(ClO_4)_3{\cdot}nH_2O$ (cat.)	TMS	[80]
$La(ClO_4)_3{\cdot}nH_2O$–$Sn(OTf)_2$	H	[81]
$TrB(C_6F_5)_4$ (cat.)	H	[82]

tetra-*O*-benzyl-α- and β-D-glucopyranoside is obtained (after 15 h at 25°C) with 81% yield, in which the α-anomer predominated (the α/β ratio was 6:1).

This procedure is operationally simple and is usable for large-scale preparations. Disaccharides are also obtainable by this method. The products do not undergo anomerization under the reaction conditions and, therefore, the observed stereochemical outcome is the result of kinetic control. The corresponding glycopyranosyl chlorides were inert to the tetrafluorosilane-promoted condensation under comparable conditions.

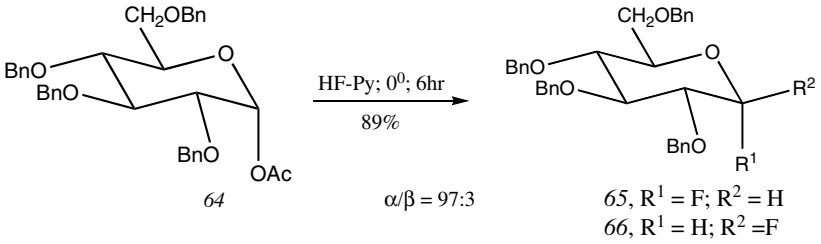
In Table 12.2 are listed many useful fluorophilic activators developed over the years for coupling of glycosyl fluorides with glycosyl acceptors that can be trifluorosilyl ethers or other compounds having a free hydroxyl group (for example, alcohol, sugar, hydroxyamino acid). For each promoter cited in Table 12.2 the corresponding reference is given.

Synthesis of Glycosyl Fluorides

We will now briefly describe methods for the synthesis of glycosyl fluorides (for a review see [83]).

Hydrogen fluoride–pyridine mixture (50–70%) [84] [pyridinium poly(hydrogen fluoride)(HF–Py)] converts both 1-hydroxy and 1-*O*-acetylated sugars to the corresponding glycosyl fluorides. Thus, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose *64* gave on treatment with HF–Py, with 89% yield, a mixture of

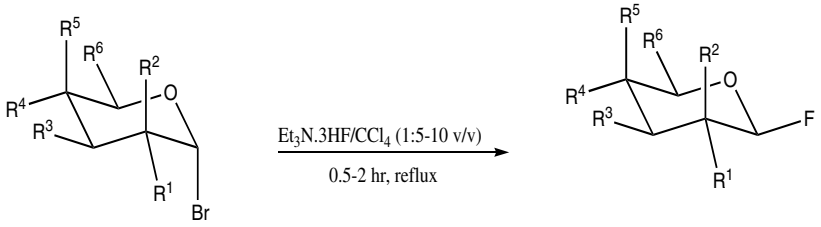
2,3,4,6-tetra-*O*-benzyl-α- and β-D-glycopyranosyl fluoride (*65* and *66*, respectively) with very high α-selectivity (α/β = 97:3) (Fig. 12.21).



64 α/β = 97:3 *65*, R^1 = F; R^2 = H; *66*, R^1 = H; R^2 = F

Fig. 12.21

A weaker acidic HF system, Et_3N–3HF, is suitable for preparation of kinetically favored β-glycosyl fluorides [85]. Thus, the glycopyranosyl fluorides of D-xylose *73*, L-arabinose *74*, D-glucose *75*, D-mannose *76*, and L-rhamnose derivatives as well as of galacturonic acid esters *77* and *78* were prepared from corresponding bromides (*67–72*) by bromine–fluorine exchange using this reagent (Fig. 12.22).



67, $R^1 = R^3 = R^4$ = OAc; $R^2 = R^5 = R^6$ = H
68, $R^1 = R^3 = R^5$ = OAc; $R^2 = R^4 = R^6$ = H
69, $R^1 = R^3 = R^4$ = OMe; $R^2 = R^5$ = H; $R^6 = CH_2OMe$
70, $R^2 = R^3 = R^4$ = OBz; $R^1 = R^5$ = H; $R^6 = CH_2OBz$
71, $R^1 = R^3 = R^5$ = OAc; $R^1 = R^4$ = H; R^6 = COOMe
72, $R^1 = R^3 = R^5$ = OAc; $R^1 = R^4$ = H; R^6 = COOBn
73, $R^1 = R^3 = R^4$ = OAc; $R^2 = R^5 = R^6$ = H
74, $R^1 = R^3 = R^5$ = OAc; $R^2 = R^4 = R^6$ = H
75, $R^1 = R^3 = R^4$ = OMe; $R^2 = R^5$ = H; $R^6 = CH_2OMe$
76, $R^2 = R^3 = R^4$ = OBz; $R^1 = R^5$ = H; $R^6 = CH_2OBz$
77, $R^1 = R^3 = R^5$ = OAc; $R^1 = R^4$ = H; R^6 = COOMe
78, $R^1 = R^3 = R^5$ = OAc; $R^1 = R^4$ = H; R^6 = COOBn

Fig. 12.22

Diethylaminosulfur trifluoride (DAST) [86, 87] was introduced into carbohydrate chemistry as fluorinating agents by Sharma and Korytnyk [88]. DAST reacts with a hydroxyl group giving an unstable and strongly electron-withdrawing group, C-OSF_2NEt_2, with liberation of HF; the attack of a fluoride ion (derived from HF) then forms the C–F bond (Fig. 12.23).

The first application of DAST for the replacement of anomeric hydroxyl group with fluorine was reported in 1985 [89, 90]. Since then it was widely accepted as a good procedure for the synthesis of glycosyl fluorides. For example, treatment of 2,3,5-tri-*O*-benzyl-D-ribofuranose *82* with DAST in THF gave a mixture of anomeric fluorides *83* with 94% overall yield in which the β-anomer predominated (β/α ratio = 9.9). However, if CH_2Cl_2 was used as the solvent, the β/α ratio was 2.0 [91] (Fig. 12.24).

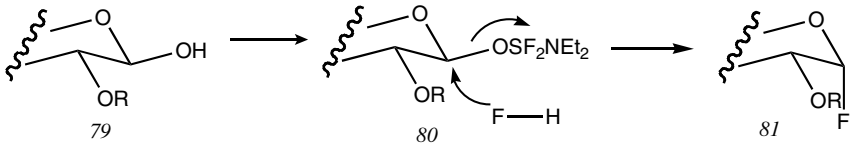


Fig. 12.23

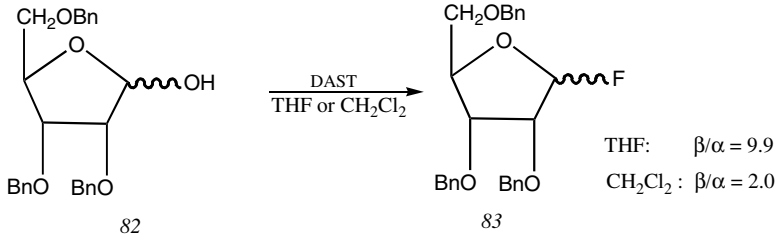


Fig. 12.24

Treatment of methyl 4,5,7-tri-*O*-benzyl-3-*O*-*t*-butyldimethylsilyl-α-D-gluco-hept-2-ulopyranosonate *84* with DAST gave a diastereomeric mixture of fluorides *85* and *86* with 94% overall yield [92] (the anomeric ratio was 3:1, but the assignment of anomeric configurations was not made) (Fig. 12.25).

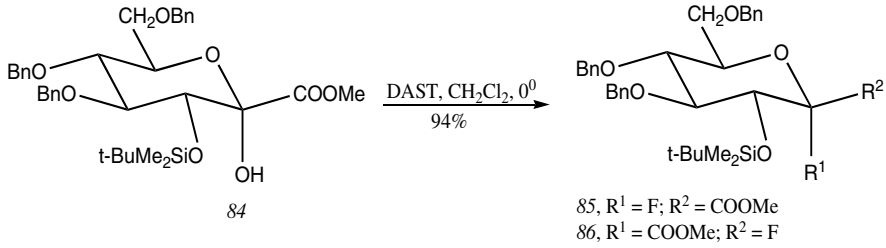


Fig. 12.25

The conversion of thioglycosides into glycosyl fluorides requires the NBS (*N*-bromosuccinimide) as sulfur activator and it is an important reaction in the synthesis of oligosaccharides. Treatment of phenyl 4-*O*-acetyl-1,6-dideoxy-2,3-di-*O*-methyl-1-thio-α- and β-D-allopyranoside *87* with DAST and NBS [61], in methylene chloride at –15°C, gave 4-*O*-acetyl-6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyl fluoride *88* with 79% yield (Fig. 12.26).

Orthoester Method of Glycosidation

It has already been mentioned that the attack of a nucleophile on oxocarbonium ion *41* (Fig. 12.27) obtained as a result of neighboring group participation of the

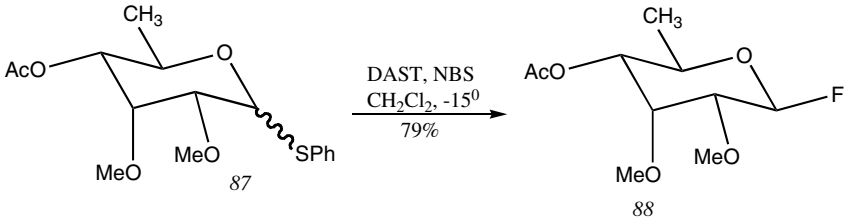


Fig. 12.26

C2 acetoxy group in the solvolysis of glycosyl halides does not always have to take place at the C1 carbon. A nucleophile can also attack the carbonyl carbon of the C2 acetate giving one or both diastereomeric orthoesters *47* and *48*. Hence the orthoesters formation is closely related to the Königs–Knorr reaction, because by a slight change in experimental conditions the formation of orthoesters can be made to become the major pathway of Königs–Knorr reaction.

The orthoesters synthesis and Königs–Knorr reaction have the same starting materials: an acylated glycosyl halide, an alcohol, and a halogen-binding promoter. Kochetkov [93–96] has played a leading role in the mechanistic study and in the development of application of orthoester method for the synthesis of oligosaccharides [95, 97–99]. The orthoester method produces stereoselectively 1,2-*trans*-glycosides and it is generally applicable to the synthesis of both pyranosides and furanosides of pentoses and hexoses.

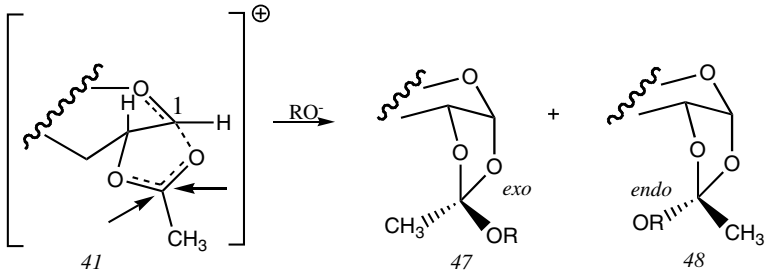


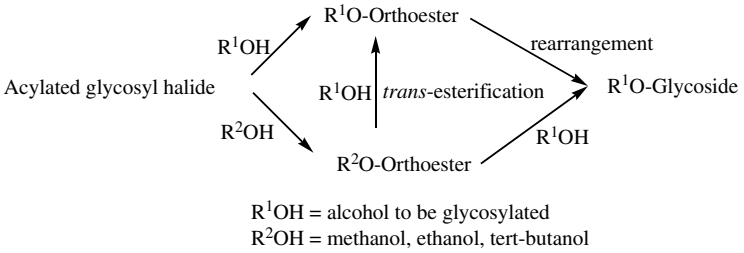
Fig. 12.27

Glycosylation of primary alcohols usually gives higher yields than that of secondary ones, although secondary alcohols are also successfully glycosylated.

The orthoester glycosylation consists typically of reacting methyl or ethyl orthoacetates (or orthobenzoates) of sugars with alcohols in nitromethane solution in the presence of catalytic amounts of mercury (II) bromide. *t*-Butyl orthoacetates of sugars in chlorobenzene with 2,6-lutidinium perchlorate catalyst give better yields [93, 100].

The synthesis of glycosidic bond using orthoester method starts by conversion of an acylated glycosyl halide into methyl, ethyl, or *tert*-butyl orthoester, which is then reacted with the alcohol that is to be glycosylated. Alternatively, the orthoester

of the alcohol that is to be glycosylated may be directly prepared [95, 101–103] and then rearranged into the corresponding glycoside [95, 104] (Scheme 12.1).



Scheme 12.1

Orthobenzoates of acylated sugars show significantly higher glycosylating activity in comparison with orthoacetates [94, 105].

In nonpolar solvents and in the presence of mercury(II) bromide as catalyst (the use of hard acid catalysts, such as sulfonic acids, or some other catalysts will be discussed later) an orthoester and a new alcohol react with the formation of new orthoester. In nitromethane solution reaction is catalyzed by mercury(II) bromide, and the direction of reaction depends on the amount of catalyst. Thus, in the presence of 1 mmol of mercury(II) bromide (per mol of orthoester) the preferred direction of reaction of orthoester with another alcohol is the formation of a new orthoester; however, in the presence of 20–100 mmol of catalyst the reaction proceeds in the direction of glycosidation with another alcohol and stereoselectively gives rise to 1,2-*trans*-glycosides. In most studied cases the composition of reaction mixture was carefully examined and the 1,2-*cis* isomers were not detected.

The mechanism of glycosylation via orthoesters proposed by using D-glucopyranose orthoester as the substrate [106, 107] is depicted in Fig. 12.28.

The attack of an electrophilic catalyst E ($HgCl_2$, for example) on one of the two oxygen atoms of an orthoester *89* (the exocyclic alkoxy oxygen or the C2 endocyclic oxygen, but never the endocyclic C1 oxygen) gives rise to the intermediate oxonium ions *90* or *93*, which are converted to the corresponding cyclic *91* or acyclic *94* acyloxonium ions, respectively. It was shown by ab initio calculations that the *90* → *91* or *93* → *94* conversion proceeds practically without an activation barrier [108]. The acyloxonium ions *91* and *94* are regarded as the only transition states that determine the product formation.

The cyclic oxocarbonium ion *91* can react with an alcohol in two ways. First, an alcohol (R^1OH or R^2OH) can attack the carbonyl carbon of *91* giving the same orthoester if the attacking alcohol is R^1OH, or a new orthoester if the attacking alcohol is the one to be glycosylated (R^2OH) (*91* → *95*) (Fig. 12.29). This step is fast. Second, the relatively slow irreversible reaction can take place if an alcohol (R^1OH or R^2OH) attacks the anomeric carbon of oxocarbonium ion *91*, which gives rise to a stereoselective formation of 1,2-*trans*-glycoside (*91* → *96)* (Fig. 12.29).

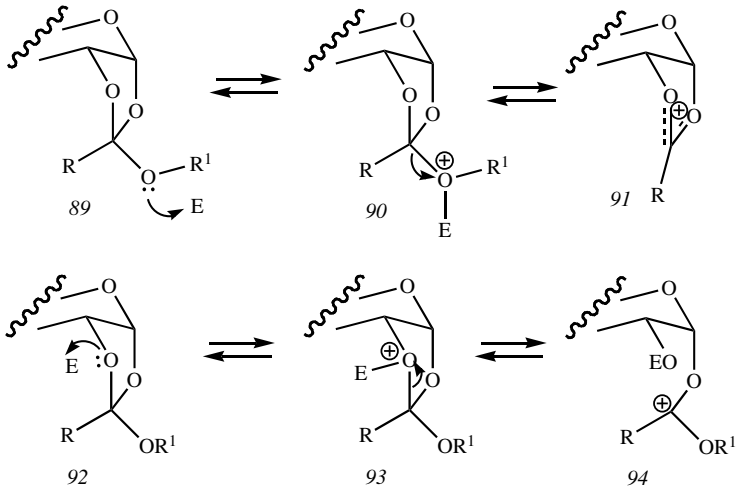


Fig. 12.28

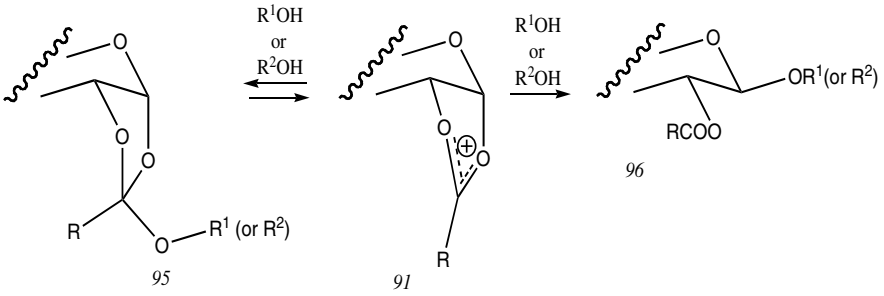


Fig. 12.29

Bochkov et al. [106] consider the attack of an alcohol on the anomeric carbon with the simultaneous breaking of the C1–O1 bond to be the rate-determining step in the glycosidation via orthoester method.

Based on experimental data the following mechanism has been proposed for the isomerization of orthoester catalyzed by mercury(II) bromide in nitromethane [107] and is depicted in Fig. 12.30. The attack of mercury(II) bromide (E in Fig. 12.28) on exocyclic oxygen of an orthoester is followed by dissociation of the complex to give an intimate ion pair *99*. The alkoxy mercury(II) bromide complex being negatively charged has relatively high nucleophilicity (certainly higher than the corresponding alcohol). The attack of this nucleophile on the C1 carbon will then result in *trans*-glycosidation (*99* → *100*) whereas the attack on the carbonyl carbon of the oxocarbonium ion will result in regeneration of orthoester (*98* → *97*) (Fig. 12.30).

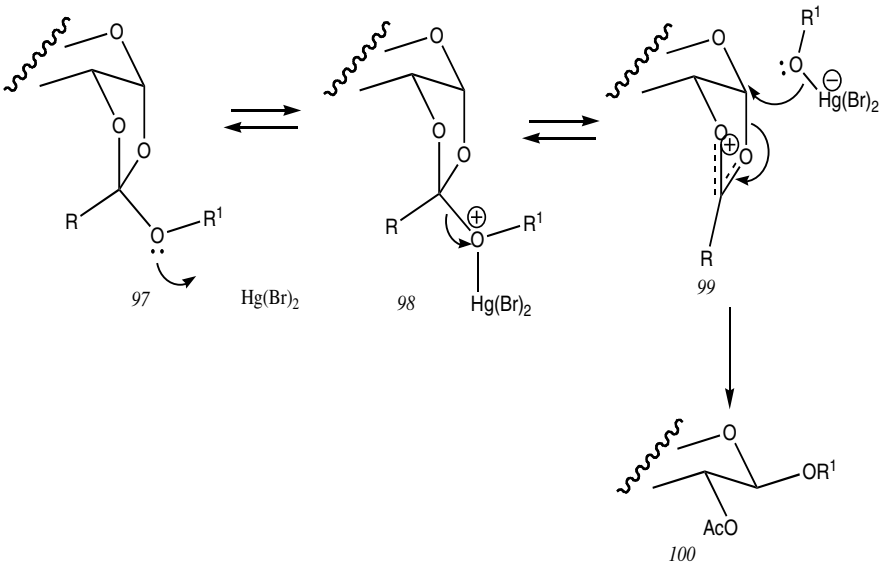


Fig. 12.30

The fate of acyclic acyloxonium ion *102* (Fig. 12.31) depends on the nature of used catalyst. When mercury(II) bromide is used as the catalyst, the initial product is the zwitter-ion *102* (Fig. 12.31), which is, due to intramolecular charge compensation, relatively unreactive.

Since this intimate ion pair is unable to dissociate, the only reaction that can take place is dissociation of the catalyst (mercuric bromide) from the oxygen–mercury complex *102* and regeneration of orthoester *95* (Fig. 12.31).

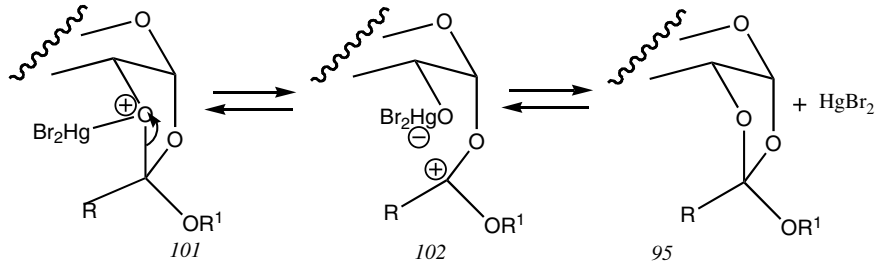


Fig. 12.31

The picture changes dramatically when the reaction is catalyzed by hard acids, such as *p*-toluenesulfonic acid (TsOH), 2,4,6-trinitrobenzenesulfonic acid $(O_2N)_3PhSO_3H$, or even picric acid $(O_2N)_3PhOH$ [95]. The 3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl-orthoester *103* and 3,4,6-tri-*O*-methyl-α-D-glucopyranosyl orthoester *104* were used as model compounds for the study of acid-catalyzed

glycosidation mechanism via orthoesters (Fig. 12.32). The composition of reaction mixtures was quantitatively analyzed for the presence of α- and β-glycosides *105*→*112* and cyclohexyl acetate by GLC. The conditions for the isomerization of orthoester *103* to β-glycoside *106* were optimized with regard to proton donor, counter ion (anion), solvent, and temperature.

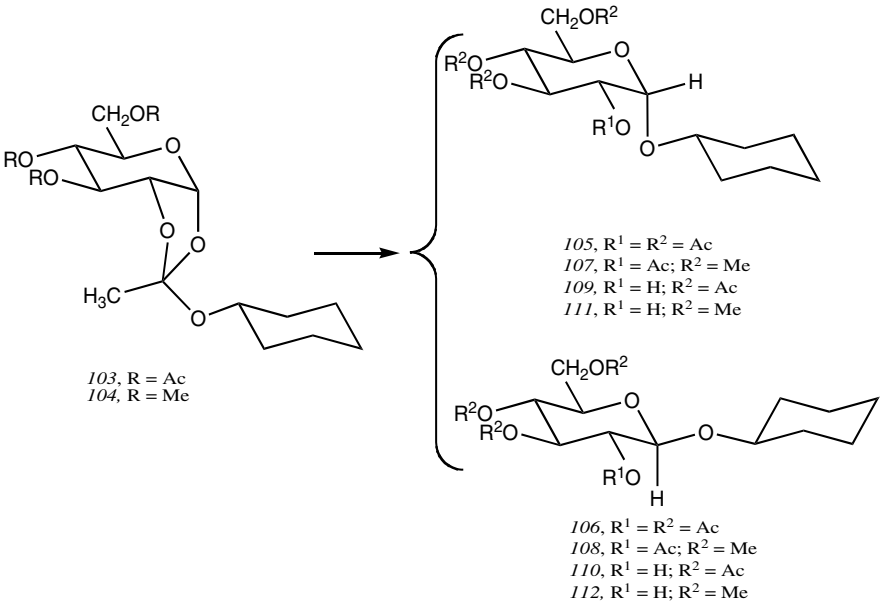


Fig. 12.32

The influence of the nature of the proton donor upon the isomerization of *103*→*106* was studied in the presence of a large excess of tetra-*n*-butylammonium perchlorate with respect to acid (the orthoester *103* is stable toward this salt). From the above-mentioned hard acids [TsOH, $(NO_2)_3PhSO_3H$, $(NO_2)_3PhOH$] the best yield of isomerization product *106* was obtained with picric acid; both sulfonic acids gave unsatisfactory results. Pyridinium perchlorates as catalysts fall into two distinct groups: (1) the spatially hindered 2,6-lutidine and 2,4,6-collidine perchlorates gave equally satisfactory results; (2) the unhindered pyridinium perchlorate produced substantially lower yields probably due to N-glycosylation that is not possible with 2,6-lutidine and 2,4,6-collidine perchlorates due to steric hindrance of ortho methyl groups. Further, study of isomerization of *104*→*108* in the presence of variety of anions has shown that the composition of products is strongly influenced by the nature of anion. The nature of solvent has relatively small effect upon the composition of reaction mixtures. Nevertheless the best solvent for the isomerization seems to be chlorobenzene. Finally, temperature has no effect upon the composition of reaction mixture.

Under the condition studied, the proton-catalyzed isomerization of *103*→*106* and *104*→*108* (reaction 1) is accompanied by formation of deacetylated glycosides

(*110* and *112*) (reaction 2) and by formation of cyclohexyl acetate and nonglycosidic products (reaction 3).

The isomerizations *103*→*106* and *104*→*108* take place stereoselectively giving 1,2-*trans*-glycosides (reaction 1). The C2 deacetylated glycosides are formed from both cyclohexyl 3,4,6-tri-*O*-acetyl- and 3,4,6-tri-*O*-methyl-α-D-glycosyl 1,2-orthoesters (Fig. 12.33). However, whereas the 1,2-*cis* glycoside *109* is formed practically stereoselectively from *103*, *104* gives under the same experimental conditions a mixture of *111* and *112*, in which *112* slightly predominates, indicating the participation of the C3 acetoxy group in the reaction. The X-ray structural analysis of ethyl homolog of the orthoester *103* has shown [109] that the pyranose ring of this compound in crystalline state exists in the twist conformation in which the C3 ace-

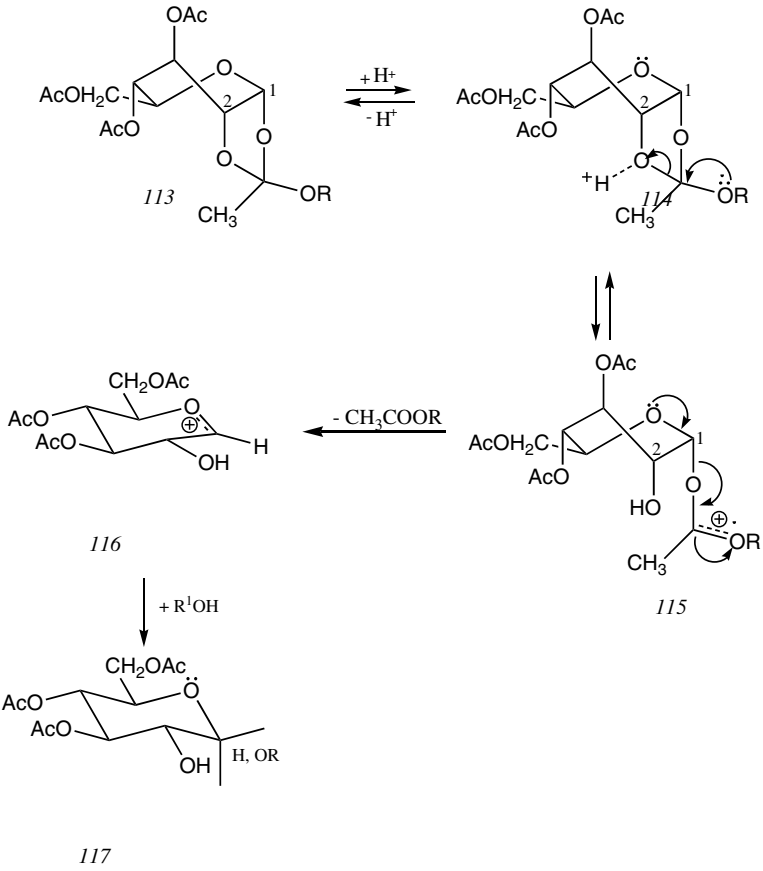


Fig. 12.33

toxy group is axially oriented and thus it is suitable for attack on the C1 whereas the CH_2OAc is oriented pseudo-equatorially, thus lending support to the hypothesis of participation of the C3 acetoxy group in stereoselective formation of glycosides.

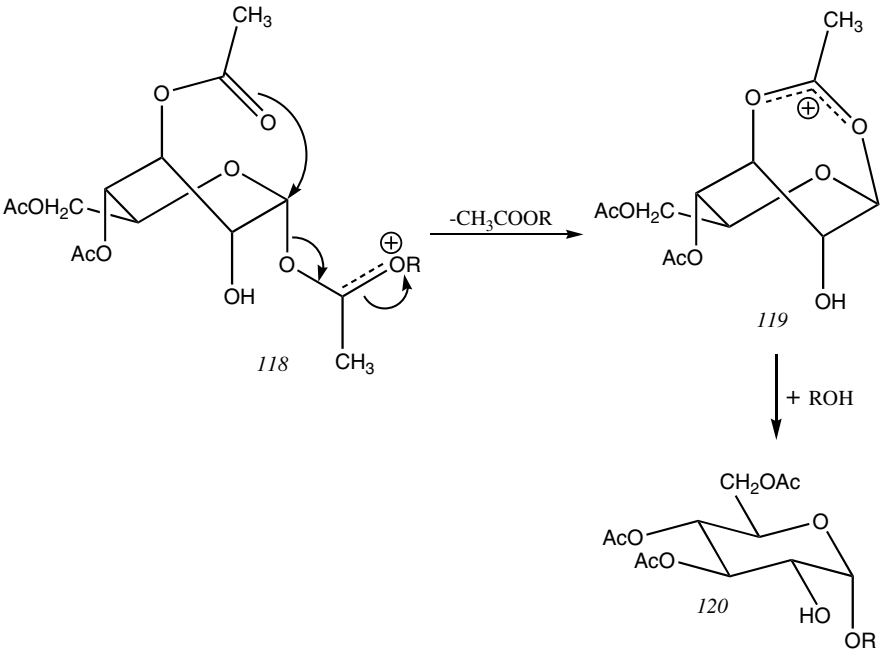


Fig. 12.34

Theoretically there are three oxygen atoms in the orthoester group that can be protonated: one is the exocyclic oxygen, and the other two are the endocyclic C1 and the C2 oxygens. However, from ab initio calculations of bicyclic alkyl orthoacetates [110] the C1 oxygen atom is the least basic of all oxygen atoms of an orthoester group and thus the least likely to be protonated. Since the exocyclic and the endocyclic C2 oxygen atoms are the preferred sites for protonation these two reactions will be discussed first.

The proton attack at the C2 oxygen atom of orthoester *113* could lead to the formation of the acyclic acyloxonium ion *115* (Fig. 12.33) that can undergo cleavage of the C1 alkyl acetate without or with the participation of the C3 acetoxy group. In the first case, the cyclic oxocarbenium ion will be formed which can react with an alcohol to give a mixture of anomeric glycosides (Fig. 12.33). In the second case the axially oriented C3 acetoxy group can expel the C1 alkyl acetate (via neighboring group participation) whereby a six-membered ring cyclic acetoxonium transition state intermediate *119* will be formed. The attack of an alcohol on this intermediate will take place exclusively from the α-side, giving thus stereoselectively the α-anomer as the only product (Fig. 12.34).

The protonation of the exocyclic oxygen of orthoester *113* followed by elimination of alcohol will result in the formation of 1,2-cyclic acetoxonium ion *122*, which can be attacked by an alcohol (the same one that was part of the orthoester, or another alcohol) either at the carbonyl carbon of the acetyl group or at the C1

carbon. In the first case, the same or the isomeric orthoester will be obtained (if the attacking alcohol is the one that was part of the orthoester), or another orthoester will be obtained (if the attacking alcohol is different from the one that was part of the orthoester). In the second case, if the attack takes place at the C1 carbon, the corresponding β-glycoside *123* will be obtained in which the aglycon can be either the alcohol that was part of the orthoester or the new one (Fig. 12.35).

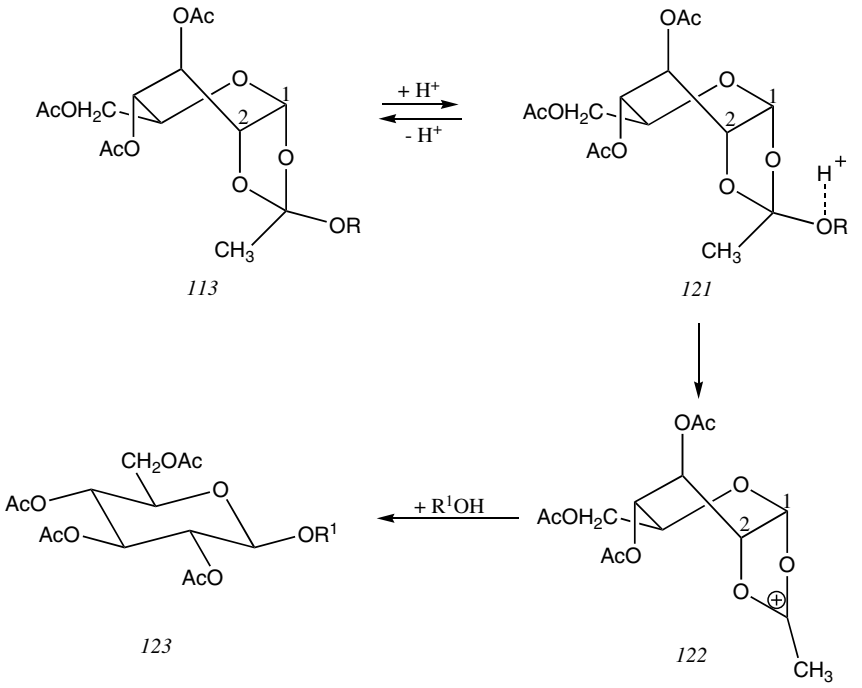


Fig. 12.35

The bicyclic orthoesters of sugars can be prepared by condensation of 1,2-*trans*-acylglycosyl halides with alcohols [111–114] in the presence of neutralizing agents. The reaction proceeds with participation of neighboring acyloxy group via orthoester cation, which reacts with alcohols to give orthoesters (Fig. 12.36) and can take place only when neutralization of liberated hydrogen halide acid is fast and efficient. Such compounds are silver oxide [111] or sterically hindered tertiary amines [112–114].

The orthoesters of sugars can also be prepared from 1,2-*cis*-glycosyl halides by condensation with alcohols in nitromethane as solvent and in the presence of 2,4,6-collidine as the base [23, 115], or in ethyl acetate as the solvent and in the presence of lead carbonate as the base [116]. In the last case the formation of orthoesters proceeds with the participation of solvent molecules (Fig. 12.37).

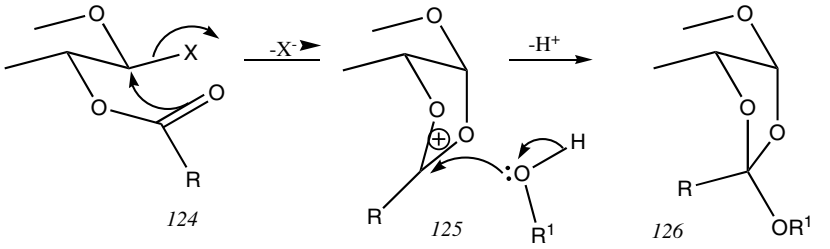


Fig. 12.36

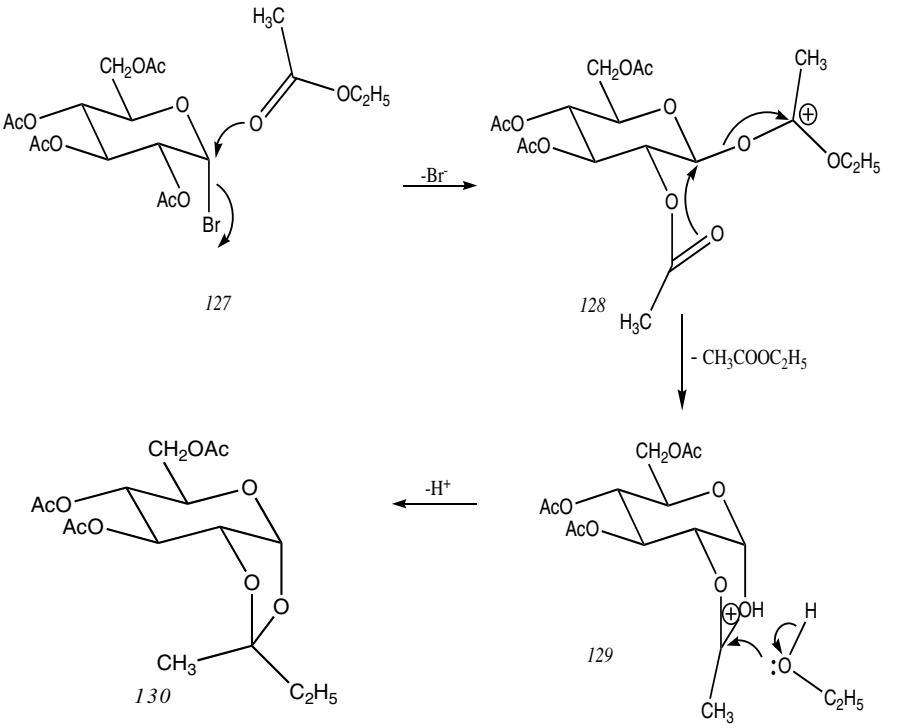


Fig. 12.37

Trichloroacetimidate Method of Glycosidation

Electron-deficient nitriles, such as trichloro- or trifluoroacetonitriles *131* (Fig. 12.38), are known to undergo direct and reversible base-catalyzed addition of alcohols giving *O*-alkyltrichloroacetimidates *132*. A detailed study of the addition of trichloroacetonitrile to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoses *133* (Fig. 12.39) has shown [117–122] that the addition of equatorial 1-oxide anion is a very rapid and reversible reaction and gives the β-trichloroacetimidate *134* as the predominant

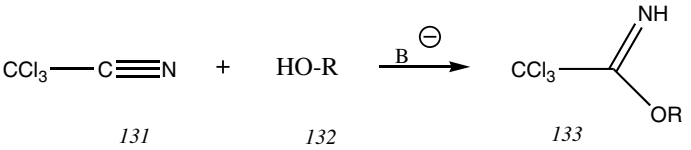


Fig. 12.38

or even the exclusive product. However, this product then undergoes slow, base-catalyzed anomerization (via the reverse reaction, anomerization of the 1-oxide anion, and renewed trichloroacetonitrile addition) to the α-trichloroacetimidate *135* with the electron-withdrawing 1-substituent in the axial configuration, which is, due to anomeric effect, thermodynamically a more stable anomer. Thus, depending on the base used [K_2CO_3, $CsCO_3$, and NaH or 1,8-diazabicyclo [5,4,0] undec-7-ene (DBU)] both anomeric trichloroacetimidates may be isolated in pure form and in high yield using kinetic or thermodynamic reaction control. Both anomers are thermally stable. In Table 12.3 are given several examples of synthesis of anomeric trichloroacetimidates of D-glucose.

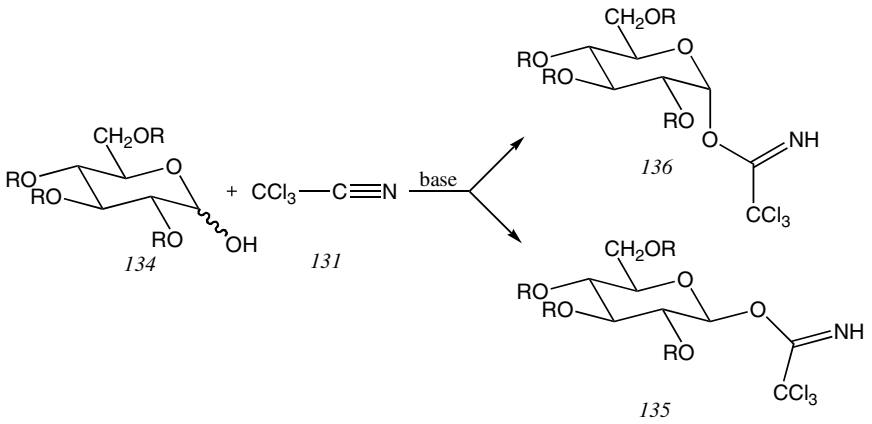


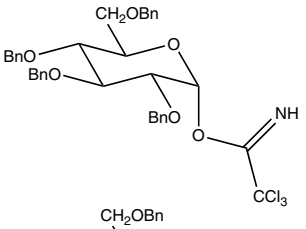
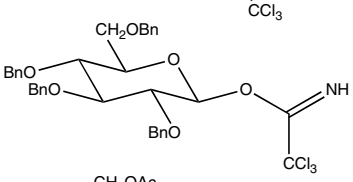
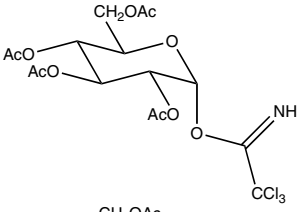
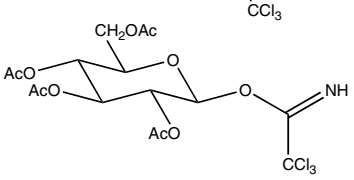
Fig. 12.39

The reaction of glycosyl acceptors (alcohols or sugars having one unprotected hydroxyl group) with *O*-glycosyl trichloroacetimidate donor requires the presence of an acid catalyst [117–120]. Boron trifluoride etherate ($BF_3 \cdot Et_2O$) at –40°C to room temperature (in dichloromethane or dichloromethane–*n*-hexane as solvents) or trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) at –80°C to room temperature (in ether or acetonitrile as solvents) proved to be very suitable acid catalysts [128, 129].

It has been shown [117, 118, 130, 131] that the solvents have an important and sometimes even dramatic influence upon the glycosidation with *O*-trichloroacetimidate glycosyl donors.

The *O*-trichloroacetimidate method for the glycoside synthesis can be illustrated with the reaction of per-*O*-acetylated α-D-glucosyl trichloroacetimidate *137* with

Table 12.3 Synthesis of trichloroacetimidates of D-glucose

Sugar	Reaction conditions	α/β ratio	yield, %	Ref.
	CH_2Cl_2, NaH, CCl_3CN room temperature	1 : 0	78	123, 124
	CH_2Cl_2, K_2CO_3, CCl_3CN room temperature	0 : 1	90	125-127
	CH_2Cl_2, K_2CO_3, CCl_3CN 48 hr, room temperature	1 : 0	98	124
	CH_2Cl_2, K_2CO_3, CCl_3CN 2 hr, room temperature	0 : 1	78	125

tetraacetyl D-glucose *138* at 0°C in the presence of boron trifluoride etherate as the catalyst whereby β,β-linked trehalose *139* is obtained in good yield (58%) (Fig. 12.40).

The glycosyl trichloroacetimidate *140* (Fig. 12.41) reacts readily at room temperature with Brønsted acids to give in high yields the corresponding glycosyl derivatives of anions of Brønsted acids *143* (Fig. 12.41).

The mechanism of this reaction is very simple. Protonation takes place at the imido-nitrogen activating the trichloroacetimidate group and making it thus a good leaving group which can easily be substituted with practically any nucleophile, as shown in Fig. 12.42.

The β-anomers that are initially formed from glycosyl-α-D-trichloroacetimidates, in the presence of strong acids, are converted, via anomerization, to thermodynamically more stable α-anomers (due to anomeric effect).

Carboxylic acids, being too weak to catalyze the anomerization, give β-*O*-acyl derivatives.

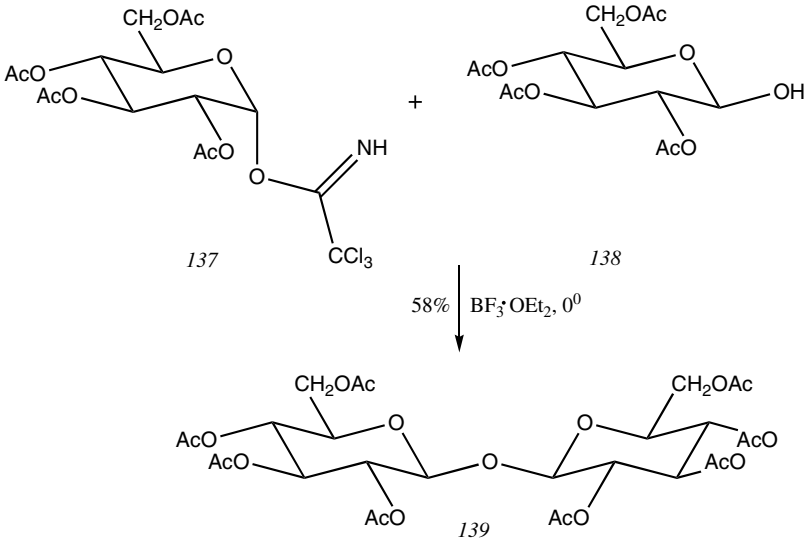


Fig. 12.40

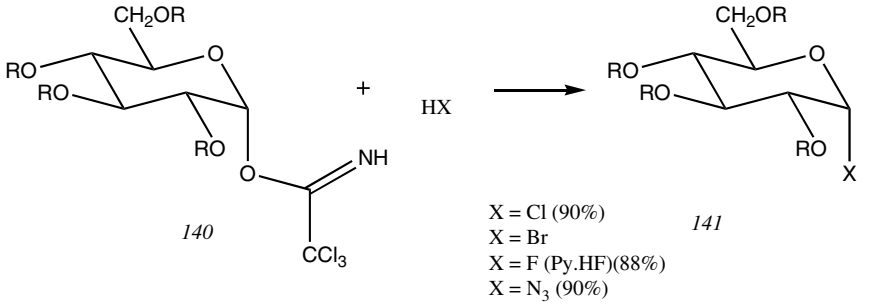


Fig. 12.41

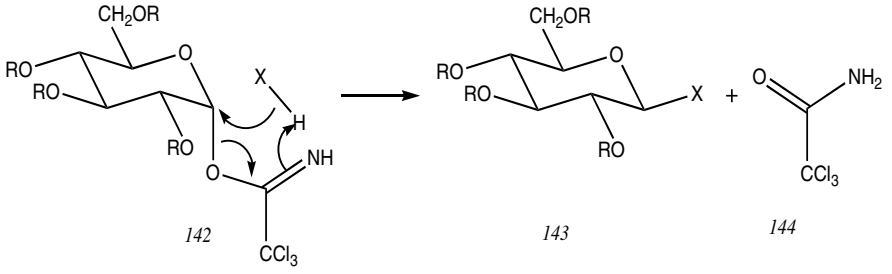
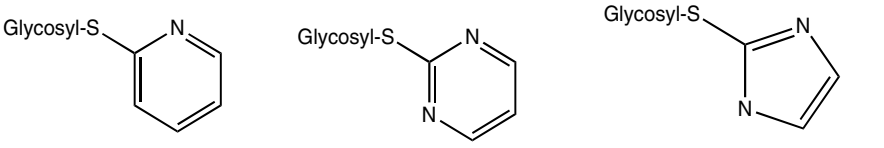


Fig. 12.42

For the reaction of alcohols (or other monosaccharides) with *O*-glycosyl trichloroacetimidates the Brønsted acids are not suitable. Hence, Lewis acid catalysts, such as boron trifluoride etherate ($BF_3 \cdot Et_2O$), at –40°C to room temperature in dichloromethane or dichloromethane–*n*-hexane as solvents, or trimethylsilyltriflate at –80°C to room temperature in ether or acetonitrile, respectively, are used in these instances.

Glycoside Synthesis via Remote Activation

In 1981, 2 years after R. B. Woodward′s death, his group published three papers on total stereoselective synthesis of erythromycin [132–134] and in the last communication they described successful glycosidation of the C3 and C5 hydroxyl groups of erythronilide A with cladinose (α-linkage) and desosamine (β-linkage), respectively, using as glycosyl donors 2-thiopyridinyl or 2-thiopyrimidinyl glycosides (Fig. 12.43). In 1980, Hanessian published a paper [135] on a fast and efficient formation of glycosides by "remote activation" using in addition, to 2-thiopyridinyl and 2-thiopyrimidinyl glycosides, the 2-thioimidazolinyl glycosides (Fig. 12.43). It

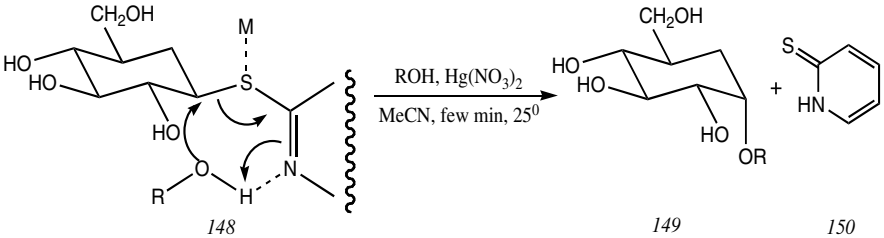


Pyridinyl-2-thioglycoside *145* Pyrimidinyl-2-thio glycoside *146* Imidazolinyl-2-thio glycoside *147*

Fig. 12.43

is very difficult to say who discovered this method particularly since it is known that Woodward was pretty slow in publishing his work.

The remote activation method consists in the activation of glycosyl acceptor (an alcohol or any hydroxyl-containing substrate) by increasing the nucleophilicity of an alcohol′s oxygen or of glycosyl acceptor oxygen by hydrogen bond between the alcohol′s hydrogen atom and the 2-thiopyridinyl, 2-thiopyrimidinyl, or 2-thioimidazolinyl nitrogen (Fig. 12.44). The reaction requires heavy metal catalyst,



148 *149* *150*

Fig. 12.44

such as silver nitrate, or preferably mercury(II) nitrate to activate the sulfur atom of thioglycoside glycosyl donor making it thus a better leaving group. In Table 12.4 are given the yields and the α/β ratio of glucopyranosides with various alcohols and a disaccharide [135].

Table 12.4 Formation of some alkyl D-glucopyranosides and a disaccharide

Glycoside receptor	Yield (%)	α/β ratio
Methanol	95	70:30
Ethanol	85	68:32
2-Propanol	77	62:38
2,2-Dimethyl-1-propanol	47	51:49
Cyclohexanol	75	51:49
1,2:3,4-di-*O*-Isopropylidene-α-D-galactopyranose	35	55:45

n-Pentenyl Glycosides as Glycosyl Donors

n-Pentenyl glycosides (NPGs) are a special type of chemically stable glycosyl donors, in which the *n*-pentenyl group can be chemospecifically activated to provide a good leaving group, generating thus a glycosyl donor that is ready for coupling to a glycosyl acceptor [136]. The concept of this method is illustrated in Figs. 12.45 and 12.46.

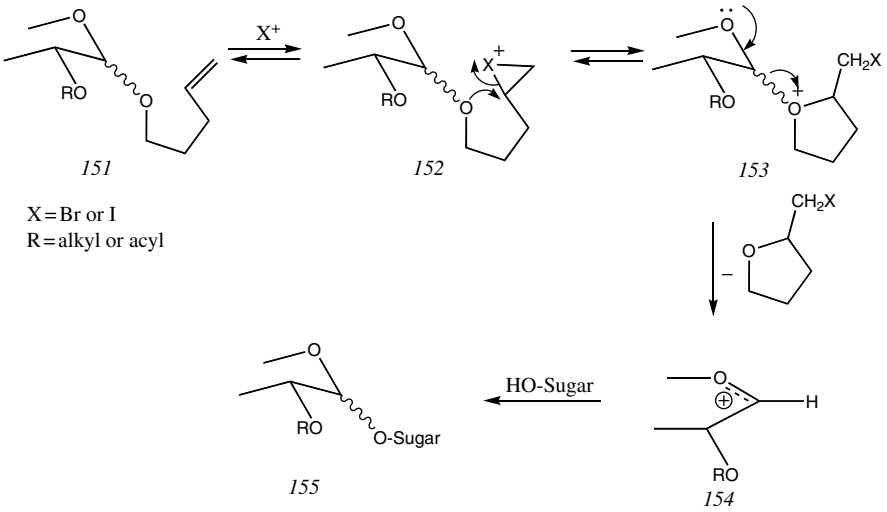


Fig. 12.45

There is a difference in reactivity toward electrophiles between the C2 alkylated and the C2 acylated *n*-pentenyl glycosides due to the influence of the C2 substituent upon the nucleophilicity of the glycosidic oxygen. Reaction of a glycosyl donor with an electrophile produces a positively charged intermediate (*153* in Fig. 12.45), the formation of which is less favorable when there is a C2 electron-withdrawing group,

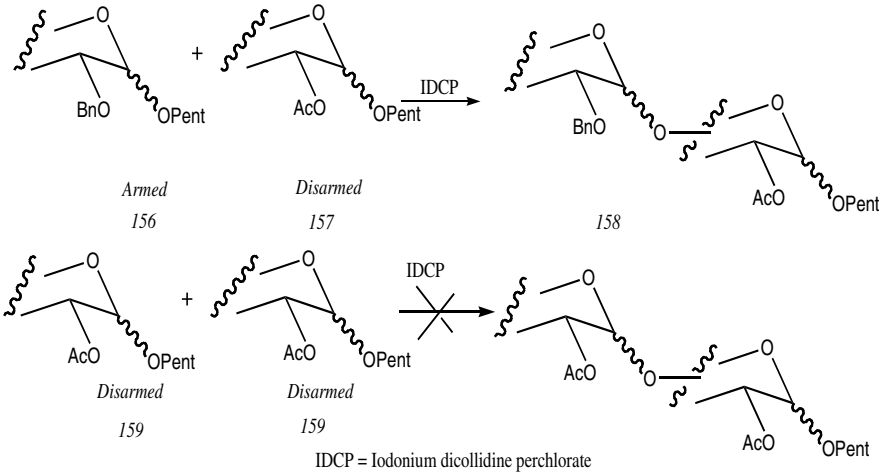


Fig. 12.46

such as an acyl group(acetyl, benzoyl, etc.). These glycosyl donors are termed *disarmed* glycosyl donors. On the other side, glycosyl donors that have an electron-donating substituent at the C2 carbon and thus favor the reaction with an electrophile that produces a positively charged intermediate are called *armed* glycosyl donors. Since the armed glycosyl donors react faster with electrophiles than the disarmed ones, in solution containing both disarmed and armed glycosyl donor molecules having one free hydroxyl group, the reaction with an electrophile will result in cross-coupling, and not self-coupling, i.e., an armed glycosyl donor will react with the disarmed one and not with an armed one, as well as a disarmed glycosyl donor will not react with a disarmed one [136], as illustrated in Fig. 12.46. The promoters for the activation of *n*-pentenyl group [137, 138] are iodonium dicollidine perchlorate (IDCP) and *N*-iodosuccinimide/triethylsilyl triflate (NIS/Et_3SiOTf). The mechanism of glycoside bond formation using *n*-pentenyl glycosides and IDCP is illustrated in Fig. 12.45. The electrophilic iodonium ion addition to the double bond of pentenyl moiety produces the cyclic iodonium ion *152*. Nucleophilic attack by the glycosidic oxygen results in an intermediate oxonium ion *153* that dissociates into a cyclic oxocarbenium ion *154* and an iodomethyltetrahydrofuran derivative. When the C2 hydroxyl group is protected with an electron-withdrawing ester substituent (disarmed glycoside) the glycosidic oxygen has a low nucleophilicity that will result in slow formation of *153*. On the other hand, protection of the C2 hydroxyl group with an electron-donating ether substituent (*armed glycoside*) increases the nucleophilicity and hence the substrate reacts considerably faster.

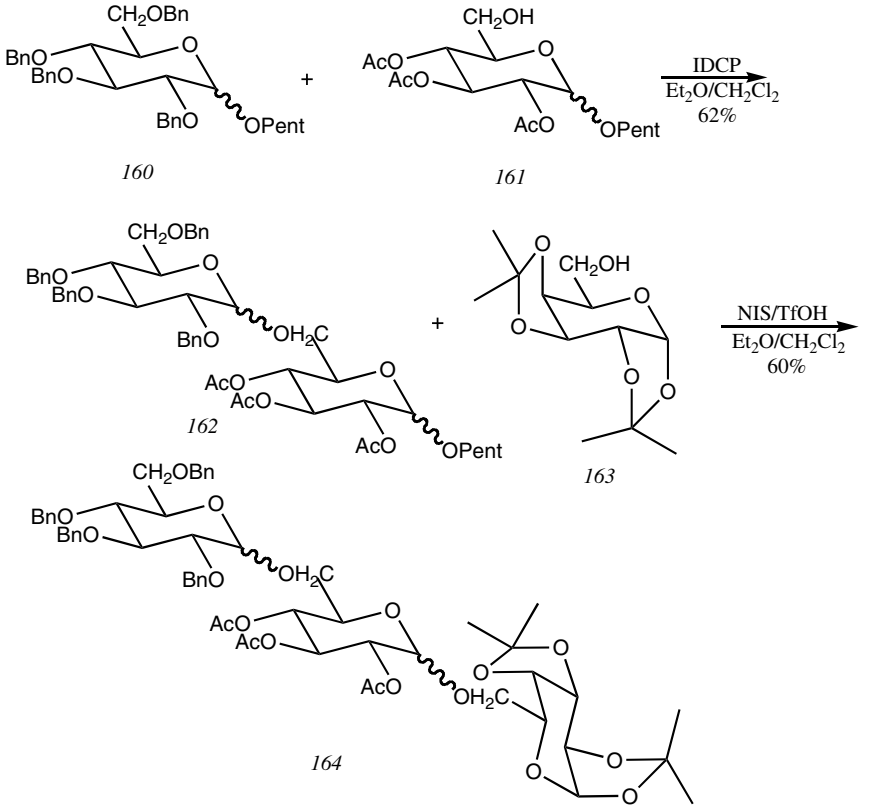


Fig. 12.47

Since the chemoselectivity relies on the fact that electron-donating C2 ether activates (*arms*) and an electron-withdrawing C2 ester deactivates (*disarms*) the anomeric carbon, coupling of an armed donor with a disarmed acceptor, in the presence of an activator, such as iodonium dicollidine perchlorate (IDCP), results in glycosidation, giving an anomeric mixture. The disarmed disaccharide could be further glycosylated with another acceptor, using the more powerful activator, *N*-iodosuccinimide/triflic acid (NIS/TfOH), giving a trisaccharide as shown in Fig. 12.47.

For reviews of this method see [139–142]. The *n*-pentenyl method of glycosidation was used successfully for the synthesis of many oligosaccharides (linear or branched) that are even fairly large (for example, nonasaccharide portion of high mannose glycoprotein is synthesized in this way [143]).

n-Pentenyl glycosides can be prepared by standard procedures that are used for the preparation of alkyl glycosides. Thus Fischer glycosidation *165*→*167* can be used for the preparation of *n*-pentenyl gluco-, manno-, and fucopyranoside (Fig. 12.48).

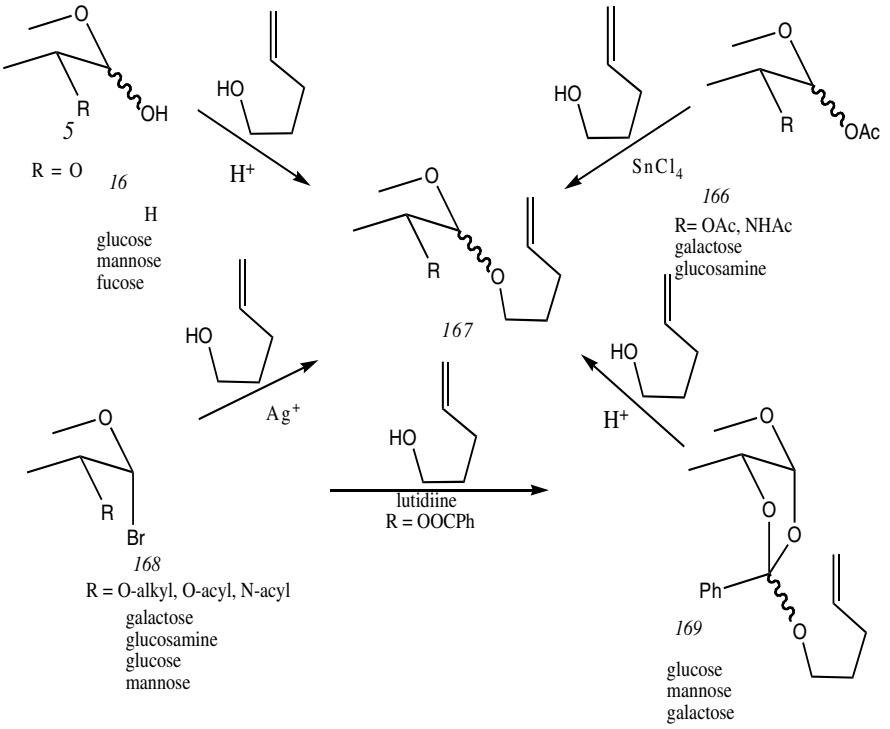


Fig. 12.48

The reaction is performed in the presence of an acid catalyst and gives a mixture of anomers; the α/β ratio for glucose is 2:1, whereas mannose gives almost exclusively α-anomer. The Fischer glycosidation with *n*-pentenol (*165→167*) gives poor yields with galactose and glucosamine. In these instances, the corresponding NPGs can be prepared using Königs–Knorr method (*168→167*) or glycosyl acetate method (*166→167)* (Fig. 12.48). The orthoesters *169* obtained by reacting perbenzoylated glycopyranosyl bromides with *n*-pentenol in the presence of lutidine (Fig. 12.48) can also serve as precursors for NPGs (*169→167*) (Fig. 12.47) or could be used directly for coupling with the glycosyl acceptors.

The promoters used for activating the NPGs for direct coupling are IDCP (intermediate potency) [144], NIS/Et_3SiTf [137], and even triflic acid (TfOH).

Glycals as Glycosyl Donors

The two components entering into a glycosylation reaction are differentiated according to which component contributes the anomeric carbon of the resultant glycoside. So the component that contributes the anomeric carbon is described as the glycosyl donor, and the other component is described as glycosyl acceptor. The donor

reacts with glycosyl acceptor to give a glycoside. In most glycosylation reactions the acceptor is a nucleophile that supplies the oxygen of the resultant glycoside by replacing the leaving group at the anomeric carbon of the electrophilic glycosyl donor. However, with development of novel glycosylation procedures [117, 118, 145–147] the terms "glycosyl donor" and "glycosyl acceptor" should be decoupled from terms "nucleophile" and "electrophile."

Utilizing glycals as glycosyl donors in disaccharide synthesis by haloniumcatalyzed coupling (iodoglycosylation) to suitably protected acceptors had been pioneered by Lemieux [148, 149] and Thiem [150–155] (Fig. 12.49). It has been shown by Thiem (vide supra) that these reactions have a high tendency for *trans*-diaxial addition thus providing an important route for the synthesis of α-linked disaccharides having an axial C2-iodo group on the nonreducing end. However, since displacement of the C2 I^+ iodine in such systems with a nucleophile is difficult

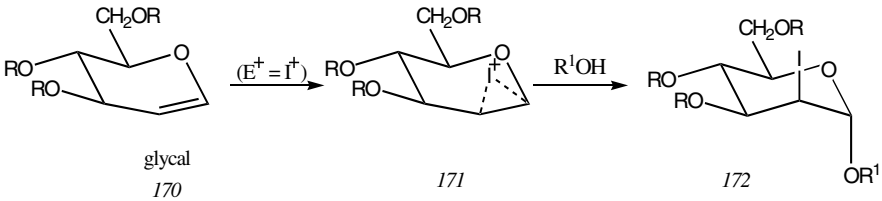


Fig. 12.49

[156] the Lemieux–Thiem method has thus far found its most useful application in the synthesis of 2-deoxyglycosides [150–155, 157].

Iodoglycosylation is carried out with glycal serving as a glycosyl donor. The glycal linkage is attacked by an "I^+ equivalent" reagent, such as *N*-iodosuccinimide or *sym*-collidine iodonium perchlorate, and the intermediate obtained (*171*) is attacked by a nonglycal acceptor *173* that is also present in the solution; the anomeric carbon of glycosyl acceptor has to be appropriately protected. The stereochemistry of glycosylation is controlled by *trans*-diaxial addition and the α-linked disaccharide is obtained (Fig. 12.50).

Coupling of a glycal donor with a nonglycal acceptor using iodoglycosylation approach can be used only for the synthesis of disaccharides but not for the synthesis of higher oligosaccharides. However, glycals could be used as building blocks for the synthesis of oligosaccharides higher than disaccharides if the armed–disarmed concept of Fraser-Reid could be utilized, namely if the nature of the C3 substituent does influence the rate of formation of cyclic transition state iodonium intermediate *171* (Fig. 12.51), namely if the positively charged iodonium transition state intermediate *171* is destabilized when the C3 hydroxyl group is substituted with an electron-withdrawing group, such as an acyl group (disarmed glycal), or stabilized when the C3 hydroxyl group is substituted with an electron-donating group, such as an alkyl group (armed glycal) as illustrated in Fig. 12.52.

The realization of this concept was achieved by Friesen and Danishefsky [158, 159]. Thus, the 3,4,6-tri-*O*-benzyl-glycal *177* was coupled with 3,6-di-*O*-benzoyl-

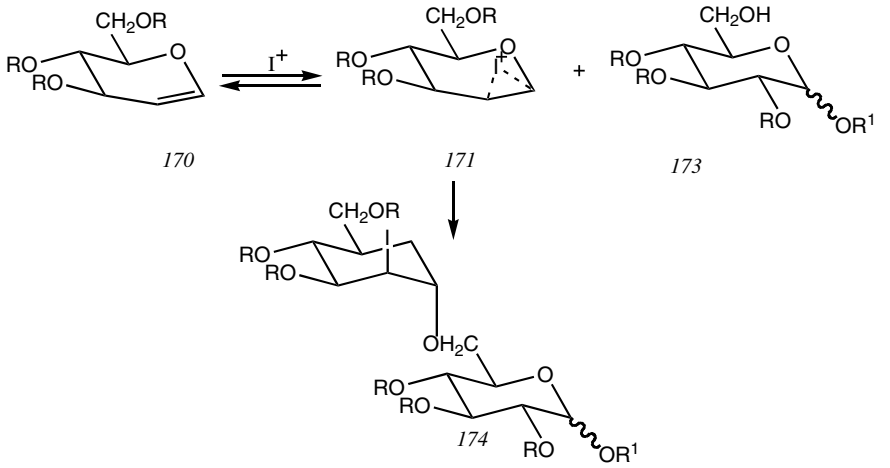


Fig. 12.50

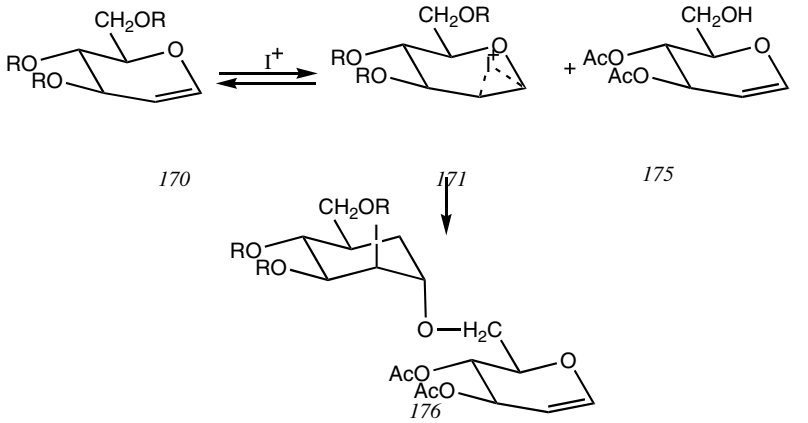


Fig. 12.51

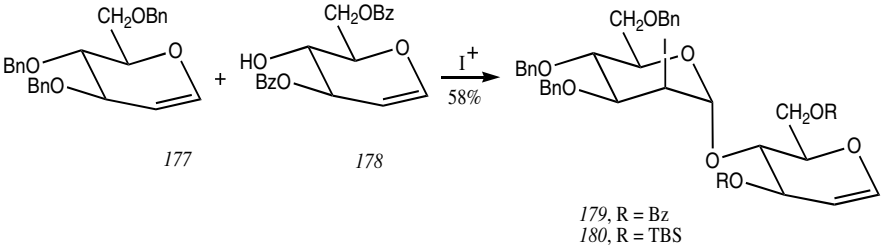


Fig. 12.52

glycal *178* to the corresponding disaccharide *179* with 58% yield (Fig. 12.52). The disaccharide *179* could be on one hand directly coupled to a nonglycal acceptor in the presence of I^+ with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *182*, showing that glycals bearing acyl-protecting groups are competent glycosyl donors in iodoglycal portion of disaccharide iodoglycosylation reactions with nonglycal acceptors (Fig. 12.53). On the other hand, the *179* must be armed by replacing the 3- and 6-benzoyl substituents with *tert*-butyl-dimethylsilyl (TBS) groups and the modified disaccharide *183* then reacted with a glycal acceptor *178* in the presence of I^+ (Fig. 12.54).

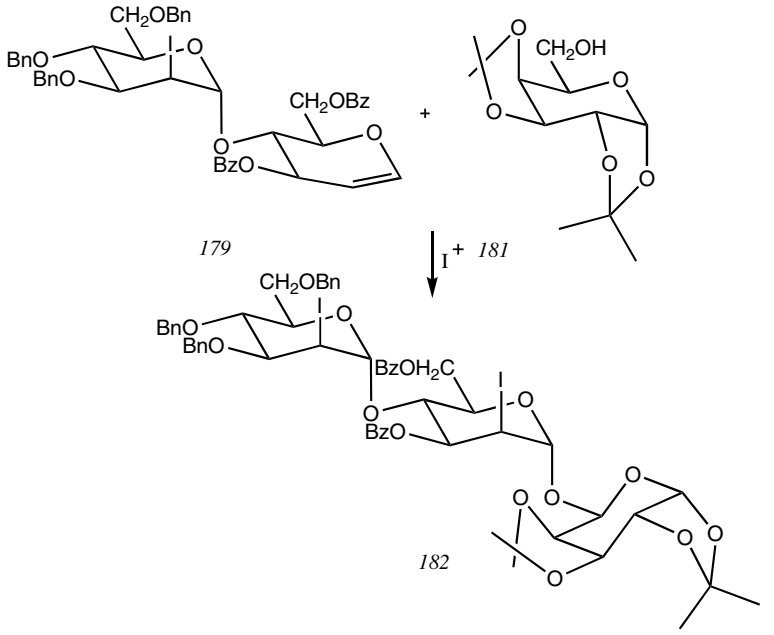


Fig. 12.53

In addition to in situ electrophilic activation of 1,2-double bond of a glycal by "I^+" (*N*-iodosuccinimide or *sym*-collidine iodonium perchlorate) that gives a non-isolable glycosyl donor intermediate *171* (Figs. 12.50 and 12.51) a glycal can be first converted into an isolable or identifiable glycosyl donor (for example, 1,2-anhydro sugar *185*) and then the obtained stable intermediate *185* used as actual glycosyl donor. In this approach, a glycal is only the precursor to a structurally defined glycosyl donor (*185* and *187*) (Figs. 12.55 and 12.56).

At the beginning of their investigation, Danishefsky et al. encountered two serious impediments to a broad applicability of 1,2-anhydrosugars as glycosyl donors for the synthesis of oligosaccharides. First was the actual synthesis of sugar 1,2-oxirane derivatives, and the second was the previous reports that various glycosyl acceptors add nonstereoselectively to sugar 1,2-oxiranes used as glycosyl donors.

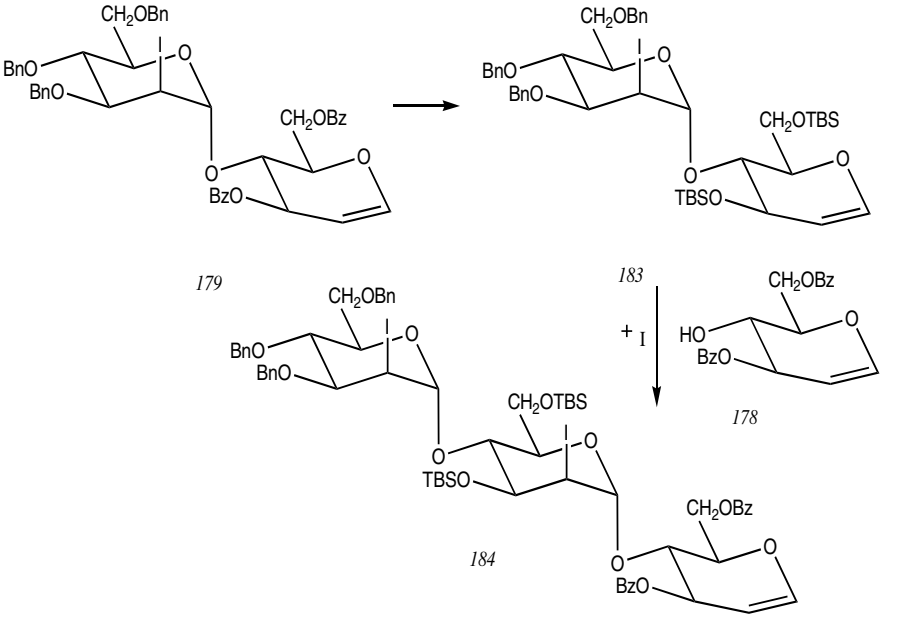


Fig. 12.54

An additional difficulty was the possibility of neighboring group participation of acyl-protecting groups in the ring opening of 1,2-epoxide.

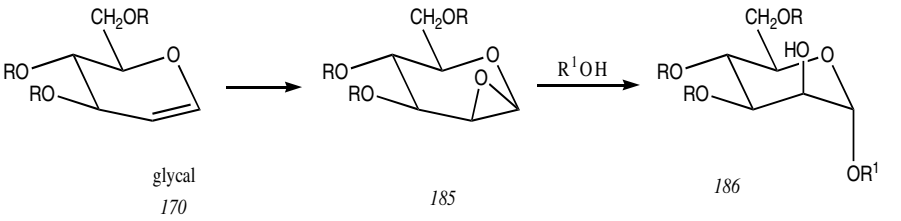


Fig. 12.55

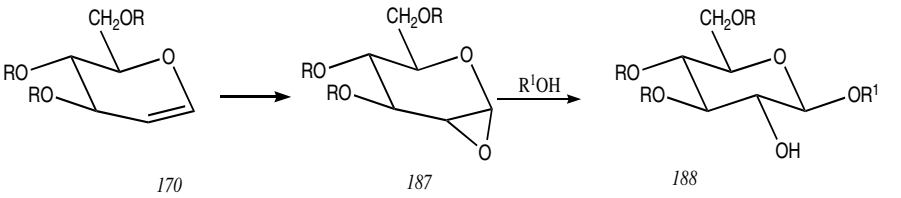
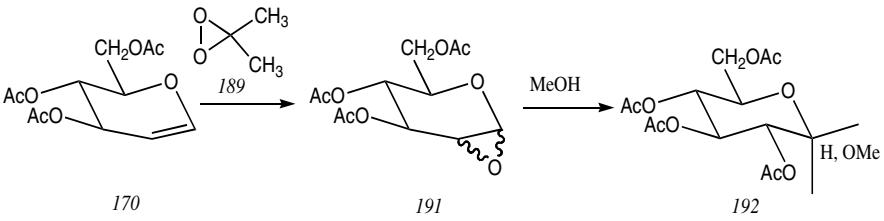


Fig. 12.56

The synthesis of sugar 1,2-oxiranes was accomplished by reacting a variety of glycals with 2,2-dimethyldioxirane [160] (DMDO) *189* in methylene chloride/acetone at 0°C [161]. The stereoselectivity of epoxidation depended upon the nature of substituents in the glycal ring. If the substituents were benzyl or *tert*-butyldimethylsilyl group (nonparticipating groups) the reaction gave highly stereoselectively the α-epoxides (*170* → *187*) (Fig. 12.56).

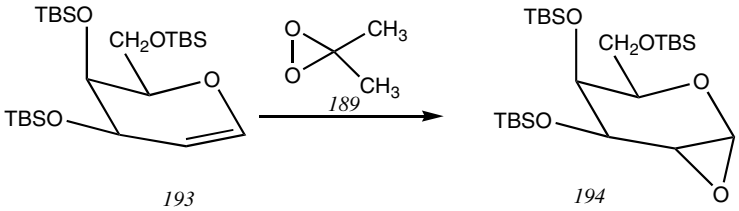
Solvolysis of *187* with neat methanol gave methyl β-D-glycoside *190*. However, the epoxidation of peracetylated glucal *170* gave a mixture of epoxides *191* which on solvolysis in methanol gave a mixture of methyl glycosides *192* (Fig. 12.57).



170 *191* *192*

Fig. 12.57

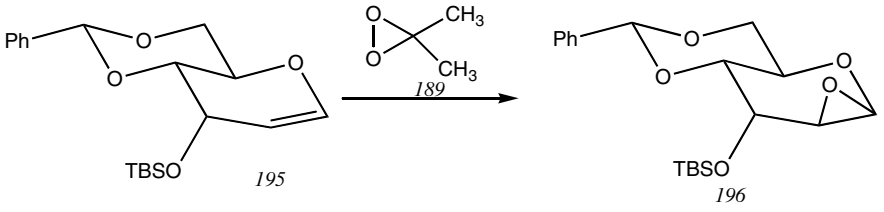
3,4,6-Tri-*O*-*tert*-butyldimethylsilyl-D-galactal *193* stereoselectively gave the α-oxirane *194* (Fig. 12.58).



193 *194*

Fig. 12.58

The glycal *195* bearing the axial C3 TBSO group undergoes selective epoxidation from its β-face, giving *196* as almost the only product (Fig. 12.59). On the other hand, gulal derivative *197* having large substituents on both faces of the double bond gave the 1:1 mixture of epoxides *198* (Fig. 12.60).



195 *196*

Fig. 12.59

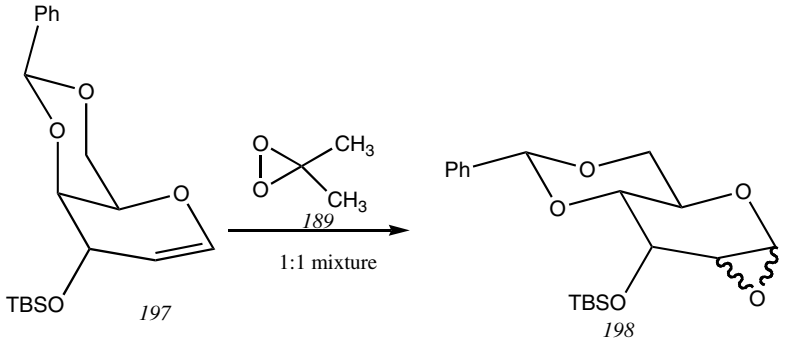


Fig. 12.60

Glycosylation of acceptors more complex than methanol and present in ca. stoichiometric amount was slow and required the presence of promoters. There is no universal promoter, but with ordinary alcohol acceptors (including the hydroxyl groups of another sugar), the most widely used promoter is anhydrous zinc chloride. In some special applications stannyl derivatives generated in situ gave the best results (for example, the synthesis of gangliosides). Using this approach it was possible to glycosylate cholesterol in a relatively good yield (Fig. 12.61).

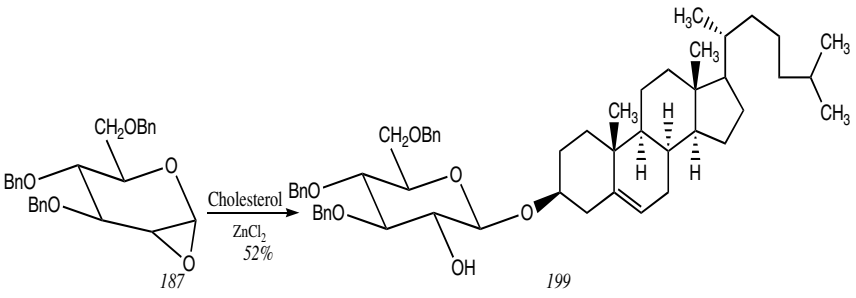


Fig. 12.61

Using 1,2-epoxy sugars as glycosyl donors Danishefsky et al. were able to synthesize many complex oligosaccharides, such as Lewis determinants, blood group determinants, and tumor antigens [162].

Thioglycosides as Glycoside Donors

It has been reported that 1-thioaldofuranosides undergo hydrolysis in aqueous solution in the presence of mercury(II) salts [163], and that acetylated aldose diethyl dithioacetals are converted into dimethyl acetals in methanol under similar conditions [164]. Further, ethyl 1-thio-α- and β-D-glucopyranosides, on treatment with bromine and silver carbonate in methanol, gave methyl β- and α-D-glucopyranosides, respectively, in high yield apparently by a way of bromosulfonium ion intermediate [165].

In 1973 Ferrier reported [166] that phenyl 1-thio-D-glucopyranosides in the presence of mercury(II) acetate are readily solvolyzed to give alkyl D-glucopyranosides with inverted anomeric configurations. Thus methanolysis of the β- and α-anomers afforded the methyl α- and β-D-glycosides with 74 and 87% yield, respectively. Furthermore, using the same procedure, they synthesized ethyl α-D-glucopyranoside with 67% yield, isopropyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside with 55% yield, cholesteryl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside with 78% yield, etc.

This pioneering study attracted widespread attention for 1-thioglycosides as glycosyl donors because 1-thioglycosides are stable compounds that are readily available, the 1-sulfur atom could be activated with a wide range of electrophilic activators, and the glycosylation reaction seems to proceed with a high anomeric stereoselectivity (Fig. 12.62).

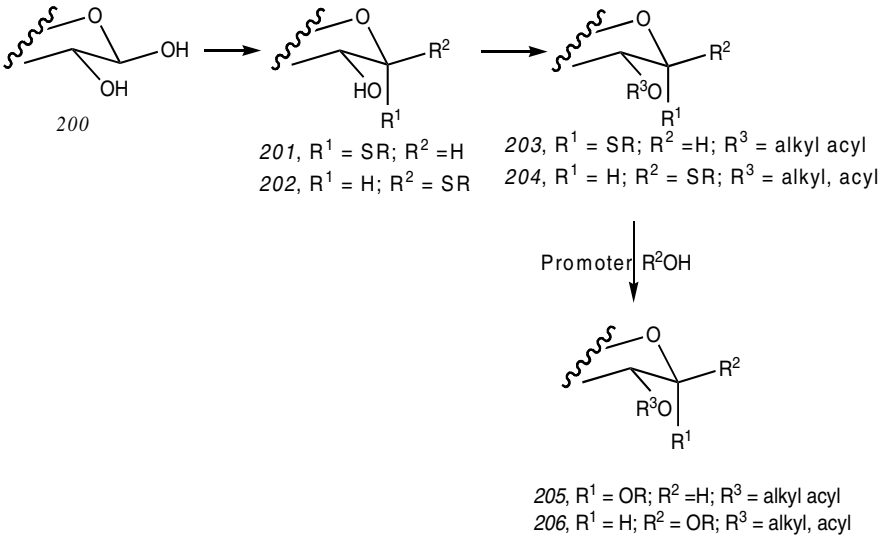


Fig. 12.62

The sulfur atom in 1-thioglycosides is a “soft” nucleophile and is able to react selectively with “soft” electrophiles such as heavy (transition) metal cations, halogens, alkylating and acylating agents. This fact made 1-thioglycosides very versatile glycosyl donors in the synthesis of oligosaccharides. Additionally, the hydroxyl groups of carbohydrates are “hard” nucleophiles, which can be functionalized with “hard” reagents, without affecting the anomeric alkyl (aryl) thio group after the introduction of alkyl (aryl) thioglycoside group.

The mechanism of glycosylation using alkyl (aryl) thioglycosides is very simple. A soft electrophile activates thioglycoside by producing intermediate alkyl (aryl) sulfonium ions *208* or *212*, that dissociate leaving oxocarbenium ion *209* or *213* as actual glycosylating species that then react with an alcohol or the hydroxyl group of another molecule that can be an appropriately protected sugar giving the glycoside or a disaccharide. If the C2 carbon is protected with a nonparticipating substituent (e.g., benzyl) a mixture of anomers is obtained (*210*), whereas if the C2 substituent is a participating one (e.g., acetate) the glycoside obtained is 1,2-*trans* (β) (*214*) (Fig. 12.63).

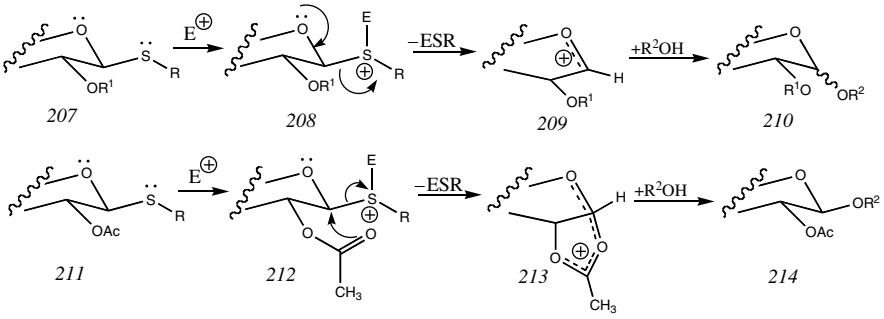


Fig. 12.63

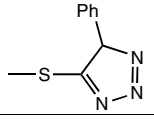
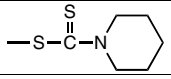
Following these initial observations, a number of different promoters were proposed for the construction of glycosidic bonds, such as copper(II) triflate [167], mercury(II) benzoate [168], mercury(II) nitrate [135], palladium(II) perchlorate [134, 169], *N*-bromosuccinimide [170], phenyl mercury(II) triflate [171], and mercury(II) chloride [166, 172]. However, None of these promoters gave consistently high yields needed for the synthesis of oligosaccharides.

An interest in developing new promoters was sparked by Lönn′s report that methyl triflate is an excellent thiophilic promoter for producing oxocarbenium cations from 1-thioglycosides that readily react with glycosyl acceptors (alcohols or appropriately protected sugars) to give glycosides or di- or oligosaccharides [173–176].

Unfortunately, methyl triflate had two serious disadvantages: first, it is very toxic, and second, in case of slow reacting glycosyl donors it methylates any free hydroxyl group giving thus methyl ethers in addition to glycosides. For these reasons an

extensive search for new promoters has been undertaken. Most of the new promoters use not only alkyl and aryl thioglycosides as glycosyl donors, but also isothiocyanates, as well as *S*-pyridyl and 1-phenyl-1*H*-tetrazol-5-yl-thioglycosides and glycosyl 1-piperidinecarbodithioates. The list of these promoters is given in Table 12.5.

Table 12.5 Glycosyl donors and acceptors

Activator	Thioglycoside	Reference
MeOTf - methyl triflate	–SMe, –SEt, –SPh	173-176
DMTST - dimethyl(methylthio) sulfonium triflate	–SMe, –SEt, –SPh	177
$NOBF_4$ - nitrosyl tetrafluoroborate	–SMe	178
MeSOTf, MeSBr - thiomethyltriflate, Bromothiomethane	–SMe, –SEt, –SPh	179
$TrClO_4$ - trityl perchlorate	–SCN, (ROTr acceptor)	180
PhSeOTf - Selenophenyl triflate	–SMe	181
MeI - methyl iodide	–SPy	182
NIS-TfOH - N-iodosuccinimide -Triflic acid	–SMe, –SEt, –SPh	183
IDCP - iodonium dicollidine perchlorate and IDCTf - iodonium dicollidine triflate	–SEt	138
AgOTf - silver triflate		184
TBPA - tris (4-bromophenyl) ammoniumyl hexachloroantimonate	–SEt, –SPh	185
DMTST, AgOTf, $SnCl_4$, $FeCl_3$		186, 187

In Fig. 12.64 are given the structures of some of the promoters cited in Table 12.5.

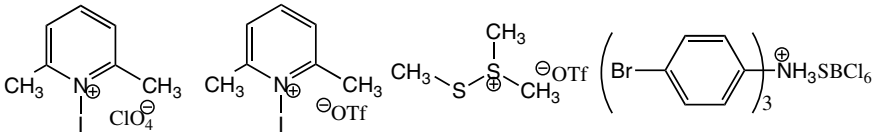


Fig. 12.64

The stereoselectivity of glycosidation depends upon the nature of the C2 substituent. If the C2 substituent in a glycosyl donor, such as *O*-acetyl and *O*-benzoyl group, is capable of stabilizing the oxocarbenium cation, generated by a promoter, via neighboring group participation, 1,2-*trans*-glycosides are obtained with excellent stereoselectivity [177]. If, however, the C2 substituent in a glycosyl donor, such

as *O*-benzyl group, is incapable of stabilizing the oxocarbenium cation via neighboring group participation, a mixture of α- and β-glycosides is obtained; the composition of the anomeric mixture is reported to be solvent dependent. Thus, for example, the proportion of 1,2-*cis* glycoside is increased if diethyl ether is used as the solvent; it was suggested that the solvent directly participates in stabilizing the intermediate oxocarbenium cation [176]. On the other hand, in acetonitrile as the solvent and with a nonparticipating C2 substituent in the glycosyl donor, 1,2-*trans*-glycosides are obtained again as a result of solvent participation [188].

The "armed–disarmed" concept developed for glycosylations with 4-pentenyl glycosides as glycosyl donors and acceptors [144] has been successfully applied for the synthesis ofoligosaccharides using thioglycosides as glycosyl donors and acceptors. If the glycosyl donor is activated ("armed") by having an electron-donating group at the C2 carbon of a glycosyl donor (*219*) and an electron-withdrawing group at the C2 carbon of a glycosyl acceptor (*220*), the chemoselective activation of the glycosyl donor is possible resulting in a synthesis of an oligosaccharide (*221*) [184] as shown in Figs. 12.65 and 12.66 [189].

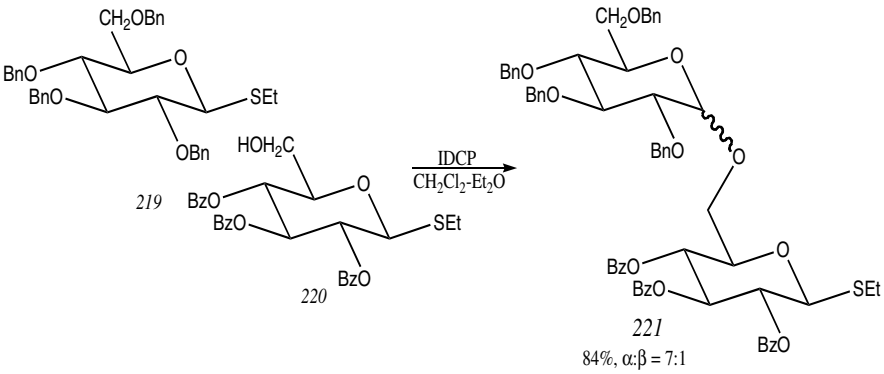


Fig. 12.65

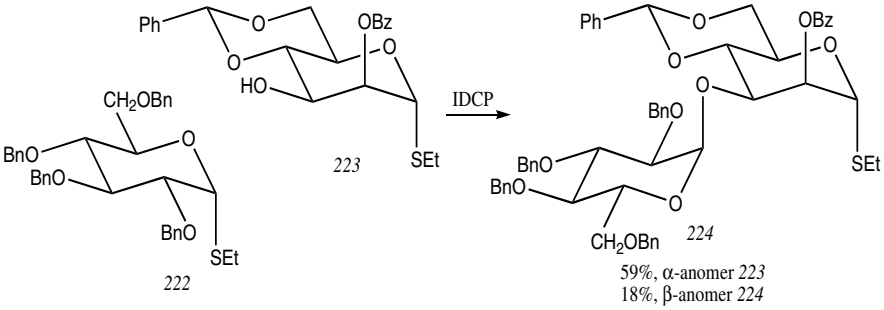


Fig. 12.66

Thioglycosides as glycosyl donors have been used in the syntheses of a large number of oligosaccharides. Thus, for example, they have been used in synthesis of ganglioside GM_2 [190], I-active ganglioside analog [191], etc. A selection of references dealing with the use of thioglycosides as glycosyl donors can be found in the review article by Garegg [192].

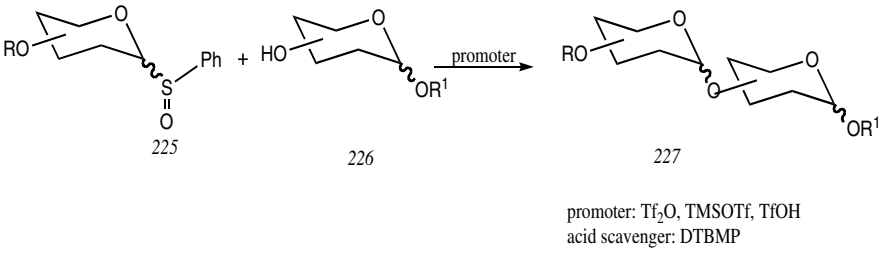
Synthesis of Thioglycosides

A great variety of methods exist [193, 194] for the preparation of alkyl and aryl 1-thioglycosides. Thus they can be prepared

1. by reacting acylated aldoses with a thiol in the presence of Lewis acids [193–202]
2. by reacting acylated glycosyl halides with thiolate anion [203–211]
3. by reacting glycosyl halides with thiourea derivatives [211]
4. by partial hydrolysis of dithioacetals [193, 212]
5. by reacting 1-thioaldose derivatives with aryldiazonium salts [193, 213]
6. by decomposition of glycosyl xanthates [193, 214–216]
7. by reacting glycosyl thiocyanates with Grignard reagent [193, 217]
8. by radical addition of 1-thiols to alkenes [218]
9. using acetylated glycosyl piperidine carbodithioates [187]

Glycosyl Sulfoxides as Glycosyl Donors

The oxidation of thioglycosides to sulfinyl glycosides provided a new and powerful group of glycosyl donors – glycosyl sulfoxides (*225*) [219]. Glycosyl sulfoxides react with glycosyl acceptors in the presence of a promoter, to give di-, tri-, or oligosaccharides. The promoters for these sulfinyl glycosides are triflic anhydride (Tf_2O) or trimethylsilyl triflates instoichiometric amount, or triflic acid in catalytic amount. The reaction is always carried out in the presence of an acid scavenger (2,6-di-*tert*-butyl-4-methyl-pyridine – DTBMP) (Fig. 12.67).



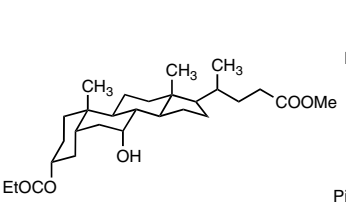
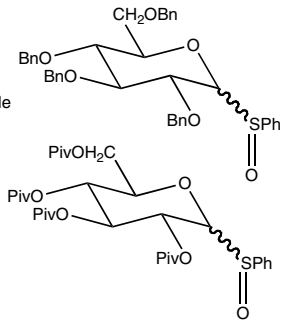
225 *226* *227*

promoter: Tf_2O, TMSOTf, TfOH
acid scavenger: DTBMP

Fig. 12.67

Using this method, Kahne was able to glycosylate very unreactive hydroxyl group at the C7 carbon of a deoxycholic acid derivative [219]. The yields seem to depend on the nature of the solvent; better yields are obtained in nonpolar solvents. The stereoselectivity of glycosylation depended upon the nature of the C2 substituent. Thus glycosylation with the glycosyl sulfoxide having at the C2 carbon a participating substituent gave exclusively β-glycoside; however, glycosyl sulfoxides having at the C2 carbon a nonparticipating substituent gave a mixture of α- and β-anomers. The composition of the mixture depended again upon the solvent (Table 12.6).

Table 12.6

Glycosyl acceptor	Glycosyl donor	Solvent	α/β ratio (yield)
		toluene	27:1 (86%)
		CH_2Cl_2	1:3 (80%)
		acetonitrile	1:8 (50%)
		CH_2Cl_2	all β (83%)

The glycosylation with glycosyl sulfoxides is highly efficient with rather unreactive glycosyl acceptors, it has a potential for chemoselective glycosylation, and it is applicable to the synthesis of oligosaccharides on solid supports.

One advantage of the sulfoxide method is its flexibility and wide scope. Lewis blood group antigens, namely Lewis a, Lewis b, and Lewis x (Le^a, Le^b, and Le^x), were synthesized using sulfoxides methodology [220].

Solid-Phase Synthesis of Oligosaccharides

There are two main advantages for using solid support for the synthesis of oligosaccharides over the synthesis in solution: first, there is no need for chromatographic purification of intermediates, and second, glycosyl acceptor can be used in excess raising thus the yield of reaction; the excess of glycosyl acceptor can be, after the coupling, washed out. While the automated solid-support syntheses of peptides and oligonucleotides are well-established methods for quite some time the development of solid-support oligosaccharide synthesis took much longer time.

The reasons for this is that in the oligosaccharide synthesis there are two major impediments: first, there is a requirement for the stereospecific formation of a glycosidic bond that links two monosaccharide units (α- or β-), and the second one

is that the selection of protecting groups for the monosaccharide units that are to be coupled in oligosaccharide synthesis is much more complex than in peptide or oligonucleotide synthesis.

The first question that has to be addressed is how the first monosaccharide should be linked to a polymer: via the anomeric carbon or by attaching the polymer to one of the hydroxyl groups on a monosaccharide. Thus, the first monosaccharide linked to the polymer may act either as the glycosyl acceptor or as the glycosyl donor. We will illustrate both of these approaches.

In the first example [221] the polymer *228* is attached to the C6 carbon of glycal *229* giving *230*. The epoxidation, reaction of oxirane with ethane thiol, and acylation with pivaloyl chloride gave ethyl 3,4-di-*O*-benzoyl-2-*O*-pivaloyl-1-thio-β-D-glucopyranoside *231*. The reaction of *231* with 3,6-di-*O*-benzyl-D-glycal *232* in the presence of methyl triflate (Fig. 12.68) gives disaccharide *233*. Repetition of epoxidation, opening of epoxide with ethane thiol, and acylation with pivaloyl chloride, as well as coupling with glycal *232* two more times, gave a tetrasaccharide *237*.

In the second example we will describe the solid-phase synthesis of a heptasaccharide phytoalexin elicitor (HPE) [221].

Polystyrene *238* was functionalized to phenolic polystyrene *239* [222] (although only *p*-substituted polystyrene is shown, it is estimated that phenolic polystyrene contains both *p*- and *m*-hydroxyphenyl rings. The functionalization was performed to the extent 0.25–1.0 mmol/g) (Fig. 12.69).

The *o*-nitrobenzyl alcohol *242* was used for its ease of attachment to and cleavage from sugar. This aglycon was synthesized in the following way. The commercially available 5-hydroxy-2-nitrobenzaldehyde *240* (Fig. 12.70) was first reacted with 1,3-diiodopropane in the presence of Cs_2CO_3 in DMF and the obtained aldehyde *241* was reduced with $NaBH_4$ to afford iodobenzyl alcohol *242* with 92% overall yield (Fig. 12.70).

Glycosidation of *242* with phenyl 2-*O*-benzoyl-3,4-di-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside *243* in the presence of dimethylthiomethylsulfonium triflate (DMTST) proceeded with 95% yield to afford exclusively β-glucoside *244*. This glycoside was then attached to phenolic polystyrene *239* by using Cs_2CO_3 in DMF at 25°C to afford the conjugate *245* (Fig. 12.70) with > 90% yield (Fig. 12.70).

Cleavage of the carbohydrate fragment from the resin was effected by irradiation of *245* (Fig. 12.70) in THF at 25°C to afford the monosaccharide with 95% yield.

The building blocks for the synthesis of HPE are shown in Fig. 12.71. After several reiterative steps heptasaccharide HPE *256* (Fig. 12.72) was obtained with 20% overall yield. Figure 12.72 shows the detailed synthesis of only tetrasaccharide *254* because the remaining steps are the repetition of previous steps. In the first step, the polymer-linked sugar derivative having the C6 hydroxyl group free (*249*) was glycosylated with phenylthioglycoside *247* in the presence of dimethylthiomethylsulfonium triflate (DMTST) giving *250* with >96% yield. Removal of the fluorenylmethoxycarbonyl (Fmoc) protective group with Et_3N in CH_2Cl_2 at 25°C and glycosylation of the obtained *251* with *248* in the presence of

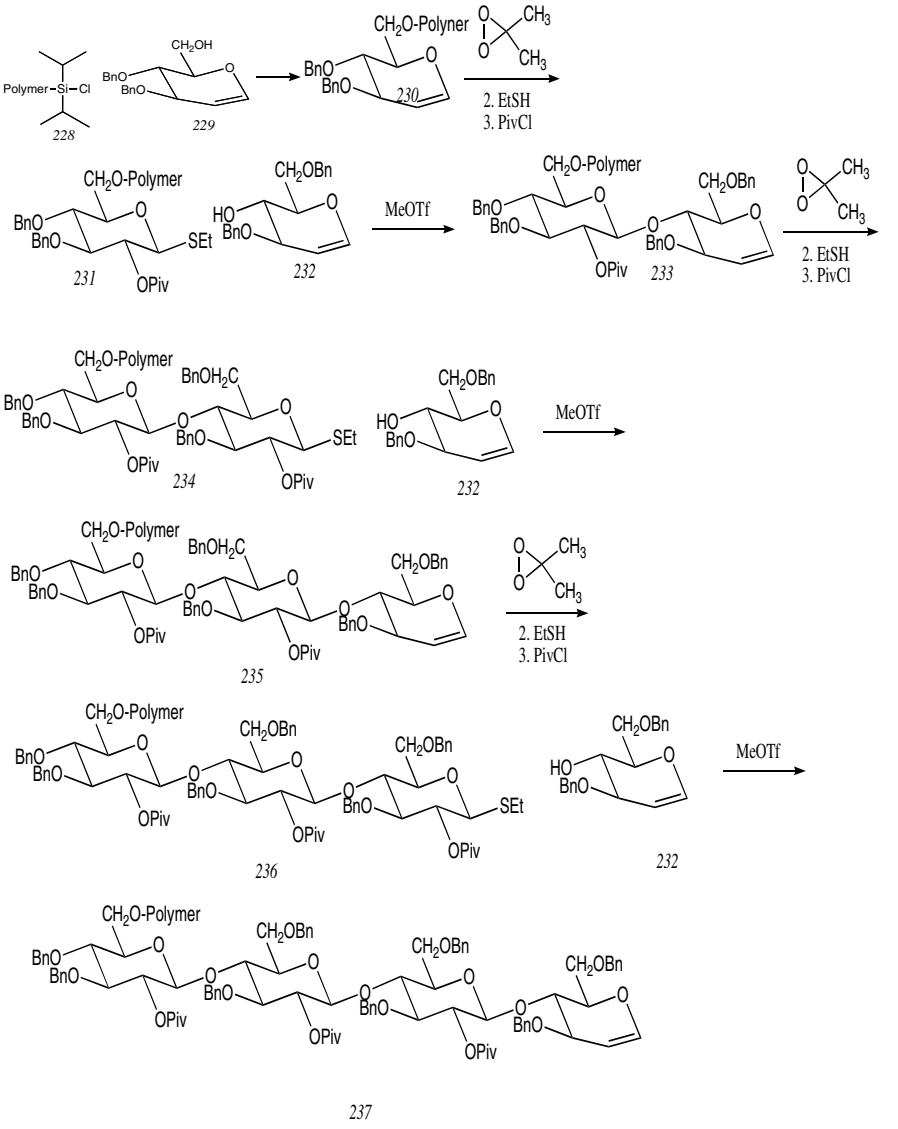


Fig. 12.68

DMTST gave *252*. Removal of *tert*-butyldiphenylsilyl (TBDPS) group from *252* and glycosylation of the obtained *253* with *246* in the presence of DMTST gave tetrasaccharide *254* which was then converted into *255* by desilylation. Repeating these steps three more times, fully blocked heptasaccharide linked to the polymer was synthesized. Photolytic cleavage of heptasaccharide from the resin followed by

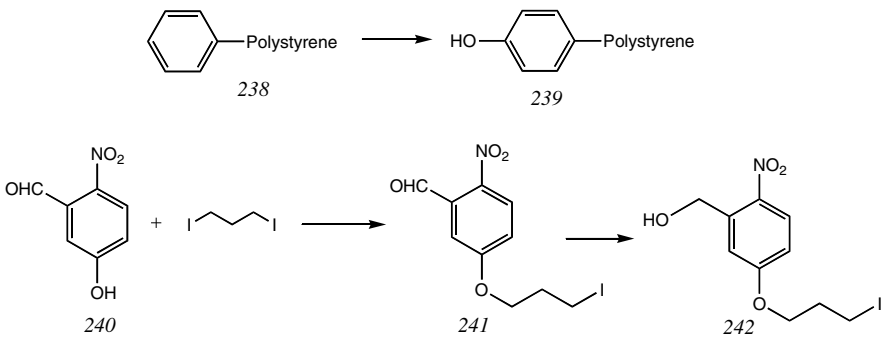


Fig. 12.69

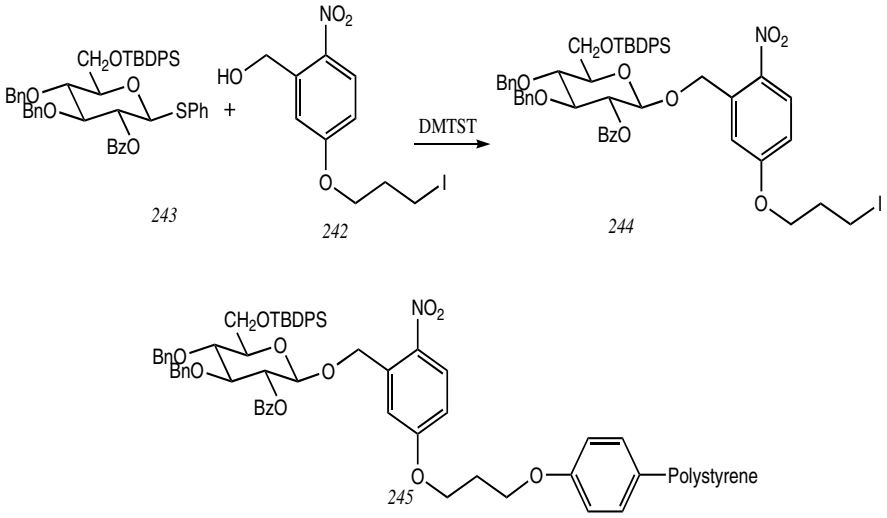


Fig. 12.70

acetylation of the anomeric hydroxyl group of monosaccharide at the reducing end gave a mixture of α- and β-anomers of fully blocked heptasaccharide HPE. Hydrogenolysis and treatment with NaOH in MeOH gave HPE *256* with 20% overall yield.

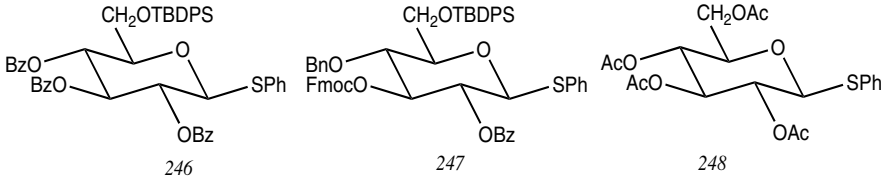


Fig. 12.71

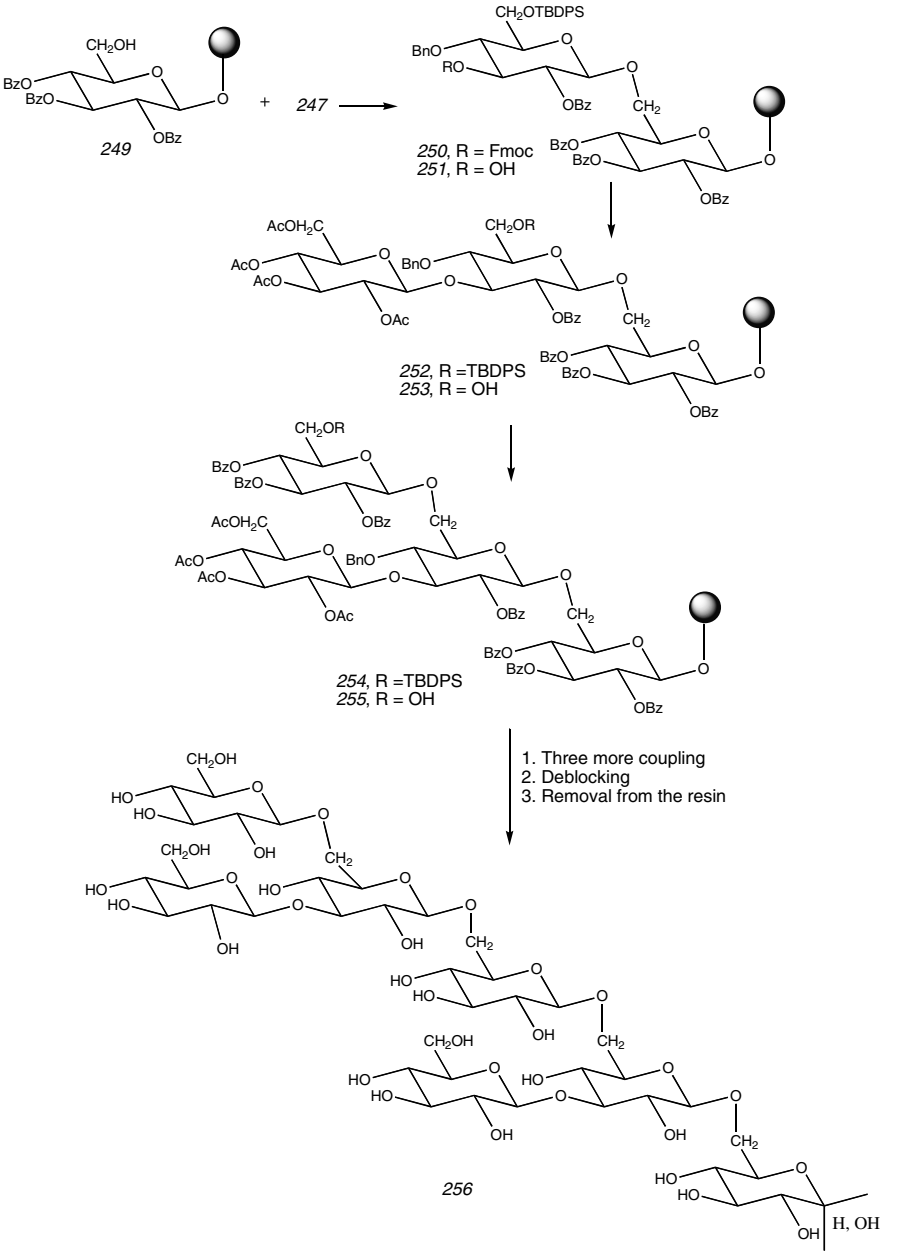

249
247
250, R = Fmoc
251, R = OH
252, R =TBDPS
253, R = OH
254, R =TBDPS
255, R = OH
1. Three more coupling
2. Deblocking
3. Removal from the resin
256
H, OH

Fig. 12.72

Automated Oligosaccharide Synthesis

There is a good review article published on development of an automated oligosaccharide synthesizer by Seeberger et al. [223] and we will not discuss this topic here.

Cleavage of Glycosidic Bonds

Acid-Catalyzed Hydrolysis of Glycosides

The acid-catalyzed hydrolysis of glycosides is theoretically a reverse process of acid-catalyzed glycosidation. However, since the acid-catalyzed hydrolysis always involves a single sugar moiety, such as α- or β-anomer of a pento- or hexofuranoside or an α- or β-anomer of a pento- or hexopyranoside, whereas the acid-catalyzed glycosylation always involves a mixture of several isomeric forms of a sugar at equilibrium, such as α- and β-anomers as well as the ring isomers (the furanoid and the pyranoid forms), these two processes obviously cannot be expected to proceed via identical reaction mechanism and the same transition states. This statement is, however, not entirely true since in the acid-catalyzed glycosidation a small proportion of sugar pyranoside present in the equilibrium undergoes direct glycosidation, and only this process will be the reverse process of acid-catalyzed hydrolysis. Several good reviews have been published on this subject [224–226].

As we have already seen, the glycosides are mixed acetals wherein the aldehydo C1 carbon is on one hand linked via exocyclic oxygen atom to an alkyl, aryl, or any other molecule and, on the other hand, is linked via the endocyclic oxygen atom to the C5 (pyranosides) or the C4 (furanosides) carbon of a sugar. The initial step of an acid-catalyzed hydrolysis of a glycoside, as well as of any acetal or ketal, is the fast and reversible protonation of one of these two acetal oxygens (Fig. 12.73).

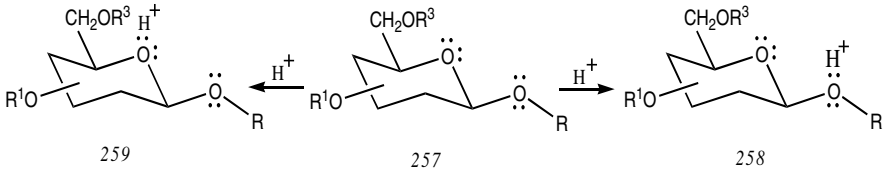


Fig. 12.73

Depending on the site of protonation two reaction mechanisms could be envisioned. If the glycosidic oxygen is protonated giving *261* (Fig. 12.74) the following step could be the unimolecular elimination of an alcohol with the assistance of the axially oriented nonbonding electron pair of the ring oxygen and the formation of the corresponding oxocarbenium ion *262*. In the presence of water in the reaction mixture (which is always the case in hydrolysis reactions) water molecules, and not alcohol molecules, will add to the positively charged carbon of oxocarbenium ion *262* giving first the hydrolyzed monosaccharide protonated at the anomeric hydroxyl

group *263* which will, after deprotonation, give the hydrolyzed sugar *264*. Since in oxocarbenium ion *262* the C5, O5, C1, and C2 atoms all lie in one plane (the sugar molecule must assume the half-chair conformation due to the double bond character of the C1–O5 bond), the water molecules can add from either face of the oxocarbenium ion and hence a mixture of α- and β-glycopyranoses will be obtained (Fig. 12.74).

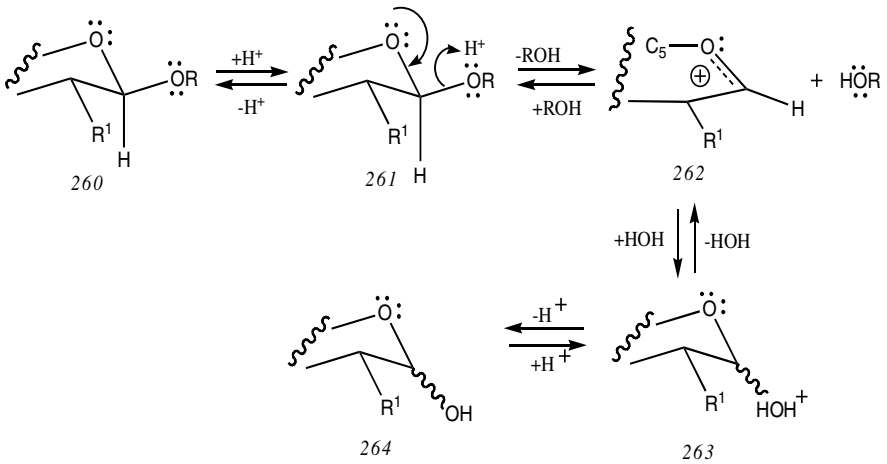


Fig. 12.74

If the ring oxygen (O5 in pyranosides, or O4 in furanosides) is protonated *265* (Fig. 12.75) the C1–O5 bond will be broken and an acyclic oxocarbenium ion *266* will be formed (this time by the participation of one nonbonded electron pair of glycosidic oxygen) (Fig. 12.75). The addition of a water molecule to *266* will form the hemiacetal *267* that is protonated at the anomeric hydroxy oxygen. This intermediate will be in equilibrium with the hemiacetal protonated at the methoxy oxygen (*268*). Now, the elimination of alcohol from *268* will result in formation of protonated aldehydo sugar *269* that by cyclization and deprotonation gives the hydrolyzed sugar *264*.

There is, however, a third possible mechanism that can be envisioned for the hydrolysis of glycosides and that is the nucleophilic (S_N2) displacement of the protonated methoxy group with water as the nucleophile, as shown in Fig. 12.76.

In order to elucidate the reaction mechanism of glycoside hydrolysis we must first fully understand the relationship between the rate of hydrolysis and steric and electronic factors present in both glycon and aglycon of a sugar glycoside. The rates of hydrolysis of many glycosides have been measured and found to be influenced by many factors such as the type of a sugar, the ring size of a sugar, the anomeric configuration of glycosidic bond, the nature of substituents on a sugar ring, the conformation of a sugar, and the size and polarity of an aglycon.

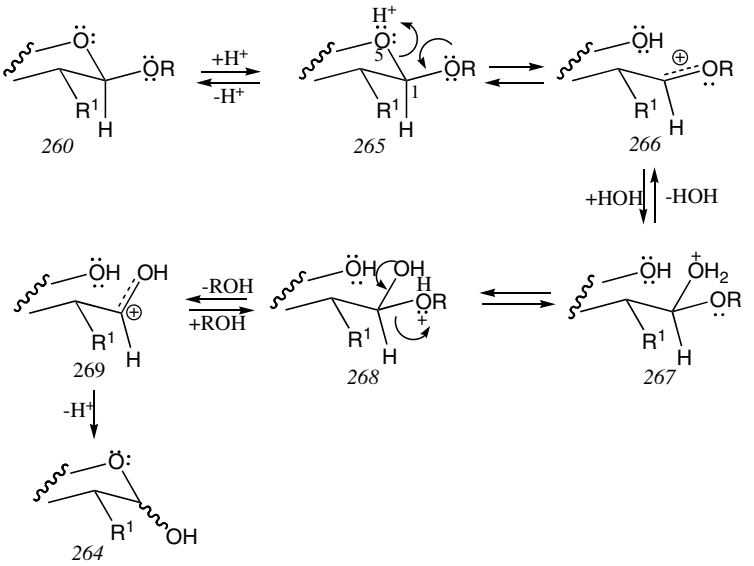


Fig. 12.75

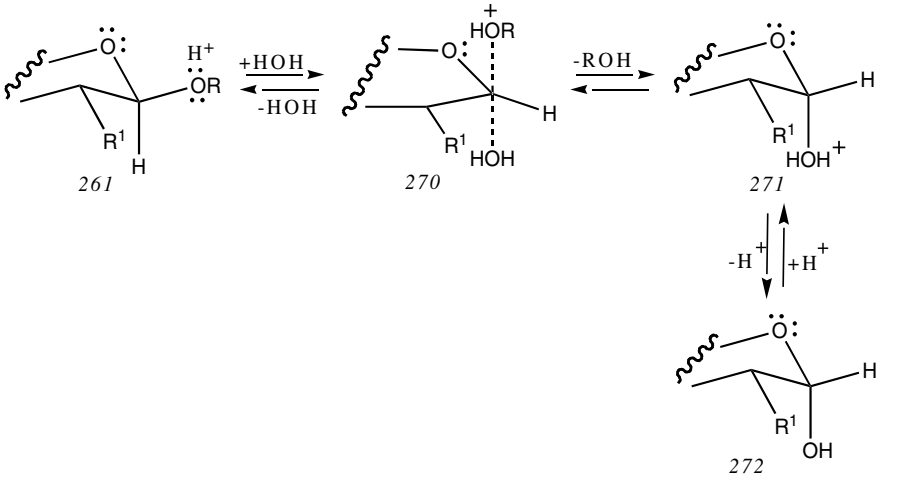


Fig. 12.76

The observations that glycofuranosides are generally hydrolyzed much faster than glycopyranosides (ca. 50–200) [227, 228] (it should be remembered that furanosides are also formed much faster than pyranosides, vide supra) and that kinetic parameters for the acid-catalyzed hydrolysis of glycofuranosides and glycopyranosides are very different (the entropies of activation for the acid-catalyzed

hydrolysis of all glycofuranosides are negative, whereas they are positive for the glycopyranosides) suggest that they are probably hydrolyzed by different mechanisms and therefore we will discuss them separately.

The Acid-Catalyzed Hydrolysis of Glycopyranosides

The glycopyranosides with equatorially oriented aglycon are hydrolyzed roughly twice faster than glycopyranosides having the aglycon axially oriented and this ratio seems to be dependent neither on the structure of glycon nor on the nature of aglycon. In Table 12.7 are given the relative rates of acid-catalyzed hydrolysis of select group of methyl aldopyranosides.

Table 12.7 Relative rates of acid-catalyzed hydrolysis of methyl α- and β-aldopyranosides[19] in 0.01–0.5 M HCl or H_2SO_4 at 58–100°

Methyl D-glycopyranoside	Relative rates	α:β ratio	Orientation of 1-OMe group
α-D-Gluco-	1.0 [229]	1:1.9	Axial
β-D-Gluco	1.9 [229]		Equatorial
α-D-Galacto-	2.4 [229]	1:2.4	Axial
β-D-Galacto-	5.7 [229]		Equatorial
α-D-Manno-	5.2 [229]	1:1.8	Axial
β-D-Manno-	9.2 [229]		Equatorial
α-D-Xylo-	4.5 [229]	1:2.0	Axial
β-D-Xylo-	9.1 [229]		Equatorial
α-L-Arabino-	13.1 [229]	1.5:1	Equatorial
β-L-Arabino-	9.0 [229]		Axial
α-L-Rhamno-	8.3 [229]	1:2.3	Axial
β-L-Rhamno-	19.0 [229]		Equatorial
α-D-Glucopyranosiduronic acid	0.47 [230]	1:1.3	Axial
β-D-Glucopyranosiduronic acid	0.62 [230]		Equatorial
2-Deoxy-α-D-gluco-	2090 [231]	1:2.5	Axial
2-Deoxy-β-D-gluco-	5125 [231]		Equatorial
2,3,4,6-Tetra-*O*-methyl-α-D-gluco-	0.16 [232]	1:2.5	Axial
2,3,4,6-Tetra-*O*-methyl-β-D-gluco-	0.40 [232]		Equatorial

The removal of the hydroxyl group at either the C2 or the C6 carbon accelerates the acid-catalyzed hydrolysis. Whereas the rate acceleration of acid-catalyzed hydrolysis is enormous for the C2 deoxy glycopyranosides (ca. 2–5 $\times$ 10^3 times) the rate acceleration for the C6 deoxy glycopyranosides is much smaller (only ca. 8 times).

The acid-catalyzed hydrolysis of pentopyranosides is generally faster than that of hexopyranosides (4.5–9.0 times) but slower than acid-catalyzed hydrolysis of 6-deoxy-hexopyranosides.

The introduction of an electron-withdrawing group at the C6 carbon reduces the rate of acid-catalyzed hydrolysis (the acid-catalyzed hydrolysis of methyl glycoside of D-glucuronic acid is ca. 2 times slower).

In Table 12.8 are given the rate coefficients and kinetic parameters for the hydrolysis of select glycosides in 2.0 N HCl extrapolated to 60°C. The concentration of HCl for the hydrolysis of methyl 2-deoxy-α- and β-D-glucopyranoside was 0.1 N.

Table 12.8 Rate coefficients and kinetic parameters for the hydrolysis of select glycopyranosides [231]

Pyranoside	$10^5\ k\ (s^{-1})$	E (kcal/mol)	$\Delta S^{\neq}$ at 60°C (cal/deg mol)
Me α-D-gluco-	0.708	34.1 ± 1.0	+ 14.8
Me β-D-gluco-	1.26	34.3 ± 0.4	+ 16.5
Me α-D-galacto-	3.55	34.0 ± 0.3	+ 17.7
Me β-D-galacto-	5.13	32.3 ± 0.6	+ 13.3
Me α-D-manno-	2.09	31.9 ± 0.4	+ 10.4
Me α-D-xylo-	2.69	33.5 ± 0.9	+ 15.7
Me β-D-xylo-	5.89	33.6 ± 0.9	+ 17.5
Me 6-deoxy-α-D-galacto-	20.0	33.9 ± 0.6	+ 20.8

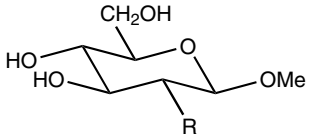
In order to elucidate the mechanism of acid-catalyzed hydrolysis of glycopyranosides a detailed knowledge is needed of the breakdown of conjugate acid obtained after protonation of one of the two acetal oxygens, i.e., the molecularity of the rate-determining step, which is the C1–O1 or the C1–O5 bond cleavage depending on whether the glycosidic or the ring oxygen is protonated. The experimental results suggest that the hydrolysis of glycopyranosides proceeds by an A-1 (acid-catalyzed unimolecular) mechanism (Ingold terminology [233]).

The first-order rate velocity coefficients (k_1) were found to be constant for the hydrolysis of D-glucopyranosides in perchloric acid solutions in concentrations ranging from 0.465 to 3.782 M [234]. Plots of $\log k_1$ against the Hammett acidity function, H_0, and against the pH were found to be almost linear in the first and not linear in the second instance, suggesting that analogous to the acid-catalyzed hydrolysis of acetals [235], the hydrolysis of glycopyranosides proceeds by an A-1, and not an A-2, mechanism. However, since the solvent is in large excess over the reactants, both A-1 and A-2 will follow a first-order rate law and consequently other criteria must be used to unequivocally determine the molecularity of the reaction.

The effect of a substituent on the rate of hydrolysis of a glycosidic bond is strongly dependent on its electronegativity and its size. The nature of substituent at the C2 and the C6 carbons of a pyranoside seems to have the most profound effect. Thus, for example, removal of hydroxy group from the C2 carbon dramatically increases the rate of hydrolysis of glycosidic bond. Thus, methyl 2-deoxy-β-D-arabino-hexopyranoside (*273* in Fig. 12.77) is hydrolyzed ca. 2500 times faster

than the parent sugar, methyl β-D-glucopyranoside *274*, whereas replacement of the C2 hydroxyl group with a more electronegative group such as chlorine (*275* in Fig. 12.77) reduces the rate of hydrolysis by a factor of 35 [236] compared to the

Fig. 12.77



273, R = H, methyl 2-deoxy-β-D-*arabino*-hexopyranoside
274, R = OH, methyl β-D-glucopyranoside
275, R = Cl, methyl 2-chloro-2-deoxy-β-D-glucopyranoside
276, R = NH_2, methyl 2-amino-2-deoxy-β-D-glucopyranoside

parent sugar (see Table 12.9). The replacement of the C2 hydroxy group with amino group, which under the reaction conditions becomes positively charged, reduces dramatically the rate of hydrolysis of glycosidic bond (see Table 12.9). From these kinetic studies it can be concluded that the more electron-attracting group attached to the C2 carbon, slower the hydrolysis of glycosidic bond, supporting thus the hypothesis that the hydrolysis of glycopyranosides proceeds via oxocarbenium ion and that its formation is the rate-determining step.

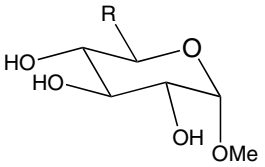
Table 12.9 Rates of hydrolysis in molar acid concentration at 72.9°C for the series of methyl 2-(X-substituted) glucopyranosides for various X substituents [237]

X	Anomer	Acid concentration	*t* (°C)	Rate of hydrolysis *k* (s^{-1})	Reference
–H	α	0.10 N HCl	49.7	2.4×10^{-2}	[238]
	β	0.10 N HCl	49.7	3.5×10^{-2}	[238]
–OH	α	2.0 N HCl	71.7	2.5×10^{-5}	[239]
	β	2.0 N HCl	71.1	5.0×10^{-5}	[239]
$–NHOCCH_3$	α	pH 0.75	78.2	5.1×10^{-6}	[237]
$–NHOCCH_3$	β	1.0 HCl	78.2	4.6×10^{3}	[237]
–Cl	β	2.0 N HCl	60	3.56×10^{-7}	[236]
$–NH_3^+$	β	1.0 N HCl	100	7.6×10^{-8}	[240, 241]

The influence of C5 substituent on the rate of glycoside hydrolysis was studied by comparing the rate of hydrolysis of methyl α-D-xylopyranoside *277* (Fig. 12.78) with that of methyl 6-deoxy-α-D-glucopyranoside *278*, methyl α-D-glucopyranoside *279* (the C5 substituent is hydroxymethyl group), methyl 6-*O*-methyl-α-D-glucopyranoside *280* (the C5 substituent is methoxymethyl group), methyl α-D-glucopyranosiduronic acid *281* (the C5 substituent is the carboxyl group), methyl 6-chloro-6-deoxy-α-D-glucopyranoside *282* (the C5 substituent is chloromethyl group), methyl 6-deoxy-6-iodo-α-D-glucopyranoside *283* (the C5

substituent is the iodomethyl group), and 6-amino-6-deoxy-α-D-glucopyranoside *284* (the C5 substituent is the aminomethyl group) (Fig. 12.78).

Fig. 12.78



277, R = H, methyl α-D-xylopyranoside
278, R = CH_3, methyl 6-deoxy-α-D-glucopyranoside
279, R = CH_2OH, methyl α-D-glucopyranoside
280, R = CH_2OCH_3, 6-O-methyl-α-D-glucopyranoside
281, R = COOH, methyl α-D-glucopyranosiduronic acid
282, R = CH_2Cl, methyl 6-chloro-6-deoxy-α-D-glucopyranoside
283, R = CH_2I, methyl 6-deoxy-6-iodo-α-D-glucopyranoside
284, R = CH_2NH_2, methyl 6-amino-6-deoxy-α-D-glucopyranoside

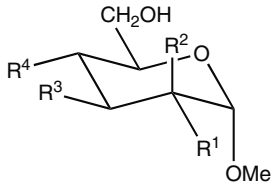
The hydrolysis of alkyl glucuronopyranosides in moderately concentrated acids has been found to proceed at a lower rate than the corresponding parent glycosides. This was attributed to the inductive effect of the electron-attracting carboxyl group (Table 12.10). Support for this explanation comes from the observation that methyl 6-amino-6-deoxy-α-D-glycopyranoside is hydrolyzed more slowly than methyl α-D-glycopyranosiduronide. As one can see methyl group at C5 does not introduce any significant change of rate coefficient; the C5 hydroxymethyl group, methoxymethyl group, and carboxyl group introduce fivefold decrease in rate coefficient; chloromethyl and iodomethyl introduce another sixfold decrease in reaction rate; and finally, 6-aminomethyl introduces another twofold decrease in reaction rate. Therefore, H ≈ CH_3 > CH_2OH ≈ CH_2OMe ≈ COOH > CH_2Cl ≈ CH_2I > CH_2NH_2 [242].

Table 12.10 Rate coefficients for the hydrolysis in 0.5 M sulfuric acid of methyl α-D-xylopyranosides and its homologs with different substituents at C5 [231, 242]

	$k \times 10^{-6}$ (s^{-1})		
R	60°C	70°C	80°C
H	3.06	13.9	57.9
CH_3	3.22	14.4	61.8
CH_2OH	0.637	2.85	12.6
CH_2OMe	0.449	1.90	8.52
COOH	0.572	1.93	7.41
CH_2Cl	0.092	0.441	1.92
CH_2I	0.099	0.445	1.82
CH_2NH_2	0.065	0.284	1.04

There is practically no difference in the rate of hydrolysis when there is no C5 substituent or if the C5 substituent is methyl group.

The removal of a hydroxyl group from various carbon atoms of a glycopyranoside has very different effect upon the rate of glycoside hydrolysis. In general, all mono-deoxy glycopyranosides are hydrolyzed faster than parent sugars, but 2-deoxy glycopyranosidesare hydrolyzed much faster than any other deoxy sugar. Thus, for



285, $R^1 = R^2 = H$; $R^3 = R^4 = OH$ methyl 2-deoxy-α-D-*arabino*-hexopyranoside
286, $R^1 = R^4 = OH$; $R^2 = R^3 = H$; methyl 3-deoxy-α-D-*ribo*-hexopyuranoside
287, $R^1 = R^3 = H$; $R^2 = R^4 = OH$; methyl 3-deoxy-α-D-*arabino*-hexopyranoside
288, $R^1 = R^3 = OH$; $R^2 = R^4 = H$; methyl 4-deoxy-α-D-*xylo*-hexopyranoside

Fig. 12.79

example, methyl 2-deoxy-α-D-arabino-hexopyranoside *285* is hydrolyzed over 2000 times faster than its parent sugar methyl α-D-glucopyranoside; methyl 3-deoxy-α-D-ribo-hexopyranoside *286* and methyl 3-deoxy-α-D-arabino-hexopyranoside *287* are hydrolyzed only 5 and 7 times faster, respectively, whereas methyl 4-deoxy-α-D-xylo-hexopyranoside *288* is hydrolyzed 40 times faster (Fig. 12.79) (Table 12.11).

Table 12.11 Relative rates of hydrolysis k/k_0 * of methyl deoxy-α-D-pyranosides relative to that of the parent sugar (see Fig. 12.75) (k_0 is the rate constant for the hydrolysis of parent glycoside under the same conditions)

Sugar	k/k_0	Conditions	Reference
2-Deoxy-(*285*)	2090	2.0 N HCl, 58°C	[231]
3-Deoxy-(*286*)	20	2.0 N HCl, 58°C	[231]
	7	1 N H_2SO_4, 100°C	[243]
3-Deoxy-(*287*)	5	1 N H_2SO_4, 100°C	[243]
4-Deoxy-(*288*)	40	2 N H_2SO_4, 58°C	[231]

Alkylation of hydroxyl group of a glycopyranoside, in general, reduces somewhat the rate of hydrolysis of the respective glycopyranoside. Although not very significant, the methylation of the C6 hydroxyl group has the largest influence on the rate of hydrolysis of glycosidic bond (the 6-*O*-methyl ether is hydrolyzed at almost half the rate of that of unsubstituted parent sugar ($k/k_0 = 0.6$); monomethyl ethers at the C2, C3, and C4 carbons of methyl β-D-glucopyranoside are hydrolyzed at 0.86, 0.99, and 0.83 of the rate of unsubstituted methyl-β-D-glucopyranoside) (Table 12.12).

Table 12.12 Rates of hydrolysis in 0.5 M sulfuric acid, at 70°C of monomethyl ethers of methyl-β-D-glucopyranoside [244]

Sugar	$k \times 10^{-6}$ (s^{-1})			E (kcal/mol)	$\Delta S^{\neq}$ at 60°C (cal/deg mol)
	60°C	70°C	80°C		
2-*O*-Methyl	1.19	5.22	20.8	33.4	+ 12.9
3-*O*-Methyl	1.27	5.66	23.8	34.0	+ 41.9
4-*O*-Methyl	1.15	4.97	21.2	33.8	+ 41.1
6-*O*-Methyl	0.84	3.88	16.1	34.9	+ 16.8
Unsubstituted	1.38	–	–		

Methylation of all hydroxyl groups of a hexopyranoside has a much greater effect on the rate of glycoside hydrolysis. Thus, methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside is hydrolyzed more than 6 times slower than the unsubstituted sugar, whereas the β-anomer is hydrolyzed only 3 times slower. Methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside is hydrolyzed ca. 2.5 times slower than its parent sugar, whereas methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside is hydrolyzed almost 6 times slower than the parent sugar. In general, tetramethylated glycopyranosides are hydrolyzed significantly slower than monomethyl ethers (Table 12.13).

Table 12.13 Rates of hydrolysis in 0.01 N HCl at 95–100° of tetra-*O*-methyl ethers of α- and β-D-hexopyranosides [245]

Sugar	$k \times 10^5$ min^{-1} ($k \times 10^5$ s^{-1})
Methyl α-D-glucopyranoside	25 (0.42)
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside	4 (0.067)
Methyl β-D-glucopyranoside	30 (0.5)
Methyl 2,3,4,6-tetra-*O*-methyl-β-D-glucopyranoside	10 (0.17)
Methyl α-D-mannopyranoside	10 (0.17)
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-mannopyranoside	4 (0.067)
Methyl α-D-galactopyranoside	23 (0.38)
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside	4 (0.067)

All kinetic studies thus far have strongly supported the hypothesis that hydrolysis of glycopyranosides proceeds via formation of a positively charged oxocarbenium ion and that the cleavage of C1—O1 bond is the rate-determining step in the acid-catalyzed hydrolysis, whereas the reversible protonation of one of the two acetal

oxygens and the nucleophilic attack of water molecule on the oxocarbenium ion transition state intermediate are very fast processes.

The study of the rate of hydrolysis of various glycopyranoside derivatives has clearly shown that it is most sensitive to the change of electronegativity at the C2 and C5 carbons since the C2 carbon is vicinal to the C1 carbon and the C5 carbon is vicinal to the O5 ring oxygen atom, the chief players in the formation of the oxocarbenium ion. Thus, the C2 electron-attracting substituent directly inhibits the formation of a positive charge on the C1 carbon, via inductive effect (positively charged C2 carbon will prevent the formation of a positively charged C1 carbon). The C5 electron-attracting substituent reduces the rate of hydrolysis, again via inductive effect. If the hydrolysis proceeds via a cyclic oxocarbenium ion transition state the C5 electron-attracting substituent will reduce the ability of the ring (O5) oxygen to donate its nonbonding electron pair needed to stabilize the carbonium ion intermediate formed after the cleavage of the C1—O1 bond. If the acid-catalyzed hydrolysis of a glycopyranoside proceeds via the C1—O5 bond cleavage, the C5 electron-attracting substituent will lower the basicity of the ring oxygen and thus its ability to be protonated that will reduce the concentration of the reactive conjugate acid that is transformed to the acyclic oxocarbenium ion transition state.

Feather and Harris published in 1965 a paper [19] suggesting that the conversion of a $^4C_1$ or $^1C_4$ glycopyranoside conformation into the ^4H (half-chair) conformation with the C5—O5—C1—C2 atoms lying in one plane (this is presumably the conformation of oxocarbenium ion in the transition state) requires rotation about the C2—C3 and the C5—C4 bonds. Thus they proposed that there is a correlation between the ease of rotations about these bonds and the rate of hydrolysis of glycosidic bonds. The conversion of a chair conformation ($^4C_1$ or $^1C_4$) of a glycopyranoside into a half-chair (^4H or ^1H) conformation requires the counter-clockwise rotation about the C1–O5 bond (if looked along the C1–O5 bond from the direction of the C1 carbon). This rotation is accompanied by a counter-clockwise rotation about the C2—C3 bond if looked along the C2—C3 bond and from the direction of the C2 carbon in which case the substituents at the C2 and C3 carbons assume a new conformation increasing or decreasing the distance between them. Thus the rates of hydrolysis are expected to be influenced by the configurations of the C2 and C3 carbons on a pyranoside ring (Fig. 12.80). Thus counter-clockwise rotation about C2—C3 bond (if looked along the C2—C3 bond and from the direction of the C2 carbon) predicts that the acid-catalyzed hydrolysis of methyl α-D-mannopyranoside should be slower than the hydrolysis of methyl α-D-glucopyranoside since the conversion of their $^4C_1$ conformations to the respective half-chair conformation shall bring the R^2 and R^3 substituents into closer proximity, increasing thus the Pitzer strain. However, the rate coefficients of acid-catalyzed hydrolysis of methyl α-D-manno- and methyl α-D-glucopyranoside (2.0 N HCl, 60°C, Table 10.4) are 2.09×10^{-5} and 0.78×10^{-5}, respectively, i.e., methyl α-D-mannopyranoside is hydrolyzed ca. 2.7 times more rapidly than methyl α-D-glucopyranoside [219], indicating that the stereoelectronic effects are more important than Pitzer strain in the acid-catalyzed hydrolysis of methyl α-D-mannopyranoside (for example, the participation of the axial C2 oxygen in stabilization of the oxocarbenium ion).

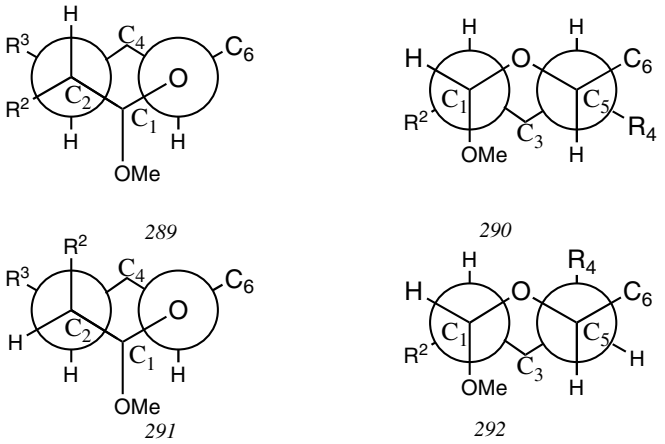


Fig. 12.80

The counter-clockwise rotation about the C5—C4 bond (if looked along the C5—C4 bond from the direction of the C5 carbon) predicts that the acid-catalyzed hydrolysis of methyl α-D-galactopyranoside should be slower than that of methyl α-D-glucopyranoside. This is, however, again contrary to experimental findings. The acid-catalyzed hydrolysis (2.0 N HCl, 60°C, Table 12.14) of methyl α-D-galactopyranoside is found to be ca. 6.6 times faster than that of methyl α-D-glucopyranoside (5.13×10^{-5} and 0.78×10^{-5}) (Table 12.8) [219]. Furthermore, there is no correlation between the size of the C5 substituent and the rate of the acid-catalyzed hydrolysis of a glycopyranoside. Thus, for example, there is very little difference in the rate of acid-catalyzed hydrolysis of methyl α-D-xylopyranoside and methyl 6-deoxy-α-D-glucopyranoside (3.06×10^{-6} and 3.22×10^{-6}, respectively) (Table 12.10) although the difference in the size of C5 substituents is very large (hydrogen vs. methyl group). Also the rates of acid-catalyzed hydrolysis of methyl 6-chloro-6-deoxy- and 6-deoxy-6-iodo-α-D-glucopyranoside are very similar (0.092×10^{-6} and 0.099×10^{-6}, respectively) in spite of the very large difference in size of the C5 substituent ($-CH_2Cl$ vs. $-CH_2I$) (Fig. 12.80).

The above experimental results are in full agreement with the conclusions that can be drawn from studying molecular models. Namely, the conversion of a chair conformation of a hexopyranoside to the corresponding half-chair conformation requires counter-clockwise rotation about the C1—O5 bond and about the C2—C3 bond, but not about the C5—C4 bond. The slight increase in Pitzer strain that results from these rotations in the course of conversion of a chair to a half-chair conformation of oxocarbenium ion transition state is not sufficient to significantly influence the rate of acid-catalyzed hydrolysis of a glycopyranoside.

On the other side, the electronegativity of the C2 or the C5 substituent has a profound influence on the rate of acid-catalyzed hydrolysis of glycopyranosides as is shown in Tables 12.6–12.8.

Acid-Catalyzed Hydrolysis of Glycofuranosides

Unlike numerous kinetic and mechanistic studies of acid-catalyzed hydrolysis of glycopyranosides [228, 231, 234, 238, 245–251] that led to the conclusion that glycopyranosides are hydrolyzed via an A-1 mechanism [the molecularity of the reaction, the entropy of activation (positive $\Delta S^{\neq}$), dissociation of methanol and the formation of oxocarbenium ion transition state intermediate] (Fig. 12.81), the acid-catalyzed hydrolysis of glycofuranosides has been much less studied [227, 231, 252–255].

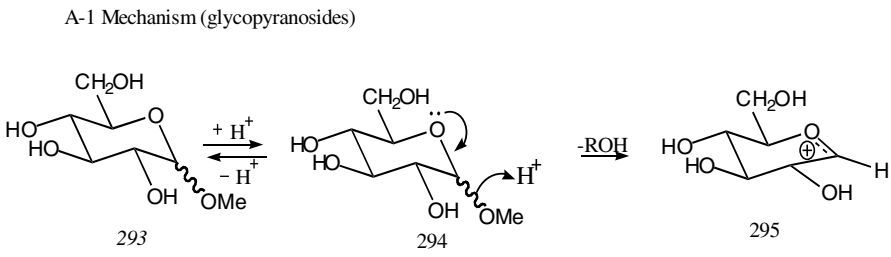


Fig. 12.81

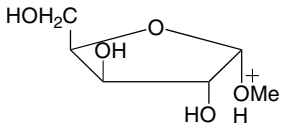
Although there have been a number of kinetic studies of the acid-catalyzed hydrolysis of sucrose (containing a ketofuranoside) [256–259] and of methyl and benzyl fructofuranoside [260], the first systematic kinetic and mechanistic study of acid-catalyzed hydrolysis of glycofuranosides was reported by Capon and Thacker [261] (see Table 12.14).

Table 12.14 The rate coefficients and kinetic parameters for the hydrolysis of select methyl furanosides in 1 M perchloric acid [261]

Methyl furanoside	t (°C)	$10^5\ k$ (s^{-1})	E_a (kcal/mol ± 1)	$\Delta S^{\neq}$ (e.u. ± 2)
α-D-Xylo-	25.03	39.5	20.2	–8.3
	35.04	120		
β-D-Xylo-	25.01	26.3	20.3	–8.9
	35.04	79.4		
β-L-Arabino-	24.92	4.46	23.1	–2.8
	35.12	16.2		
α-D-Galacto-	25.03	3.35	21	–9.4
	34.91	10.8		
β-D-Galacto-	25.02	0.405	22.8	–8.7
	35.12	1.43		
α-D-Gluco-	24.92	59.7	19.2	–11.0
	35.12	175		
β-D-Gluco-	25.00	21.0	20.5	–9.0
	34.00	64.3		

As can be seen from Table 12.14, the entropies of activation for the hydrolysis of all glycofuranosides studied are negative. This is in strong contrast with the positive values obtained with pyranosides [231, 234, 238, 250, 251] suggesting that glycofuranosides and glycopyranosides react by different mechanism.

The solvent deuterium isotope effect for the hydrolysis of methyl α-D-xylofuranoside in 1 M hydrochloric acid at 25°C, $k_{D2O}/k_{H2O} = 2.5$, indicates that the first step in the hydrolysis is a rapid and reversible proton transfer with formation of a conjugate acid which can theoretically be either *296* or *297* (Fig. 12.82).



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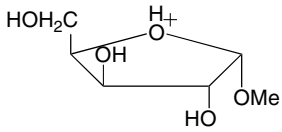


297

Fig. 12.82

After this initial protonation, two possible mechanisms can be postulated for the hydrolysis of glycofuranosides that are compatible with the negative entropy of activation: one that proceeds via a cyclic (protonation of the glycosidic oxygen) and the other that proceeds via an acyclic transition state intermediate (protonation of the ring oxygen).

In the first case, the large difference in entropy of activation between the acid-catalyzed hydrolysis of glycopyranosides and glycofuranosides as well as the negative sign is explained by postulating that glycofuranosides are hydrolyzed via an A-2 mechanism [231]. It is namely envisioned that the hydrolysis takes place via the protonation of glycosidic oxygen but without formation of a cyclic oxocarbenium ion transition state intermediate in the next step, as shown in the Fig. 12.83. Instead the protonated methoxy group undergoes nucleophilic displacement with a water molecule, i.e., the transition state of hydrolysis resembles the transition state of an S_N2 displacement. The A-2 mechanism is supported by the Bunnett *w* values (+1.0 to +2.4) falling in the range considered to indicate a mechanism in which water acts as a nucleophile.

An alternative explanation, however, has been proposed for the observed negative entropies of activation in the acid-catalyzed hydrolysis of glycofuranosides [261]. According to this explanation after protonation of the ring oxygen of a furanoside *303* the C1–O4 bond ruptures with the formation of acyclic oxocarbenium ion *305* in the transition state, indicating that the conjugate acid obtained by protonation of a glycofuranoside that leads to the hydrolysis of glycosidic bond is *303* and not *304* (Fig. 12.84).

The formation of the acyclic oxocarbenium ion *305* is supported by the results obtained from the study of acid-catalyzed hydrolysis of a number of 1,3-dioxolanes where it has been shown that the entropies of activation are also negative [262–265] although it is obvious that the hydrolysis must proceed with the ring opening. An

A-2 Mechanism (glycofuranosides)

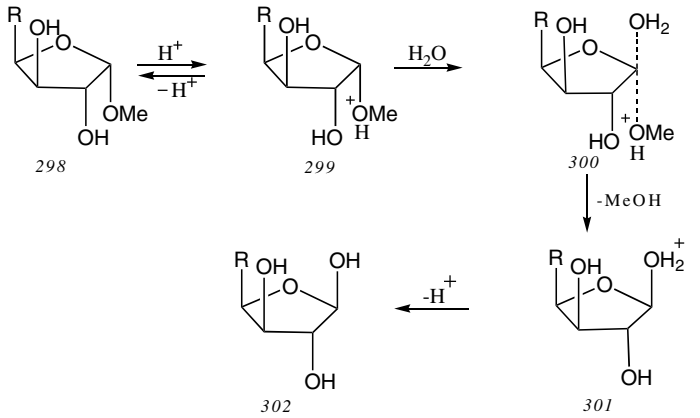


Fig. 12.83

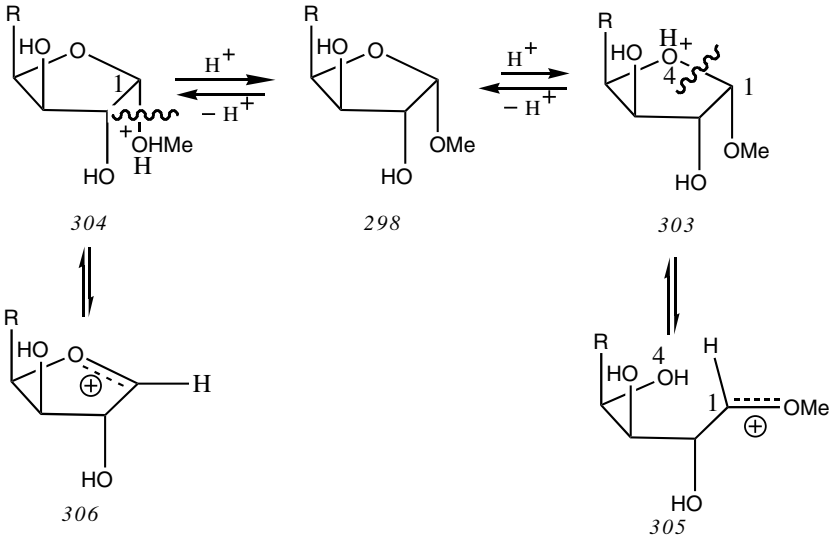


Fig. 12.84

explanation suggested by Capon and Thacker [261] is that the initial rupture of the C–O bond of the conjugate acid *308* is reversible, since the resulting hydroxyl group of *309* is part of the same molecule as the oxocarbenium ion. The reaction could be then written as described in Fig. 12.85.

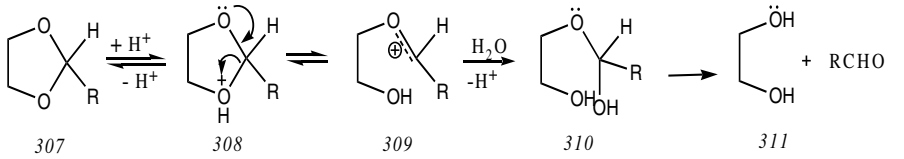
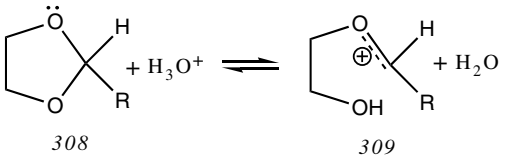


Fig. 12.85

The observed rate constant for the above reaction would then be given by $k_{obs} = k_2 K$, where K is the equilibrium constant (Fig. 12.86):

Fig. 12.86



The observed entropy of activation would then be $\Delta S^{\pm} = \Delta S^{\circ} + \Delta S_2^{\neq}$, where ΔS° is the standard entropy change for the above equilibrium. This would presumably have a positive value. The value of $\Delta S_2^{\neq}$ would be, however, strongly negative since it is the entropy of activation for a bimolecular reaction between the oxocarbenium ion *305* and the water molecule to give an oxonium ion *312* (Fig. 12.87). The overall value for $\Delta S^{\pm}$ could therefore be negative.

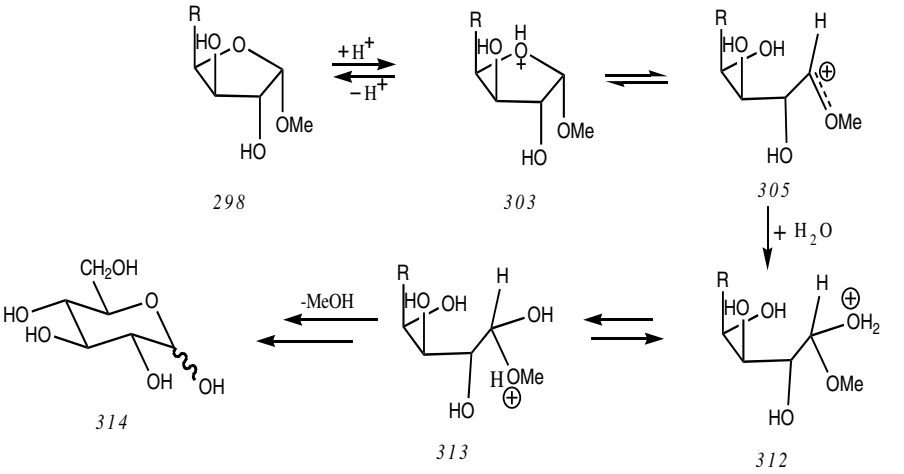
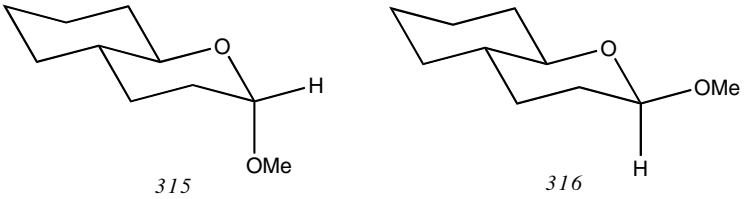


Fig. 12.87

Some Recent Developments Regarding the Mechanism of Glycoside Hydrolysis

In 1980 van Eikeren [266] undertook a study of acid-catalyzed hydrolysis of conformationally rigid methyl acetals *315* and *316* (Fig. 12.88) arguing that the rates of anomer hydrolysis may be affected by the conformation of a glycoside.

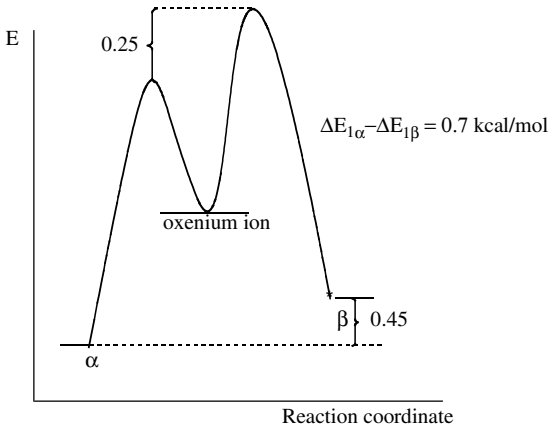


315 *316*

Fig. 12.88

From the composition of equilibrium mixture obtained after acid-catalyzed equilibration of *315* and *316* (68±1% of axial *315* and 32±1% of equatorial *316* anomer) it was calculated that the axial α-anomer *315α* is more stable than β-anomer *316β* by 0.45 kcal/mol which was in full agreement with the concept of anomeric effect. On the other hand, in contrast to the results for alkyl glycosides a comparison of the second-order rate constants showed that the axial anomer hydrolyses 1.51±0.22 times faster than the equatorial anomer indicating that the TS energy of the transition state in the hydrolysis of *315* is lower by 0.25 kcal/mol than the TS energy of the transition state in the hydrolysis of *316.* Thus the difference in energy between the TS of *315α* and *316β* is 0.7 kcal/mol (Fig. 12.89).

Fig. 12.89



The acid-catalyzed hydrolyses of the axial and equatorial anomers *315* and *316* were studied in aqueous HCl–acetone solvent mixtures maintained at constant temperature in water bath. The dependence of k_{obs} on acid concentration and

temperature was measured because the conclusions are justified only if the anomers show similar variations in rate with changes in the catalyzing acid and temperature.

Table 12.15 Activation parameters[a] for the hydrolysis of *315* and *316*

$[H^+]$[b] (M)	$\Delta H^{\neq 0}_{Ax}$ (kcal/mol)	$\Delta H^{\neq 0}_{Eq}$ (kcal/mol)	$\Delta S^{\neq 0}_{Ax}$ (cal/mol K)	$\Delta S^{\neq 0}_{Eq}$ (cal/mol K)
7.5×10^{-3}	+25.7	+24.6	+17	+13
2.5×10^{-2}	+26.1	+24.6	+21	+16

[a]Calculated from the slope and intercept of $\ln k_2$ vs. (temperature)$^{-1}$; temperature range 20–55^{0}C. Ax = axial and Eq = equatorial.
[b]Aqueous HCl–acetone mixtures (1/1 v/v)

The examination of the activation parameters for the hydrolysis of *315* and *316* (Table 12.15) shows that both anomers exhibit positive enthalpies and entropies of activation as would be expected for dissociative mechanism. The observation that the axial anomer exhibits a larger positive enthalpy and entropy of activation than the equatorial anomer suggests that the rate-determining transition state of the axial anomer involves more extensive C—O bond cleavage.

Thus, van Eikeren [266] concludes that the axial and equatorial anomers *315* and *316* must hydrolyze via different transition states and that the difference in their hydrolysis rates may be explained by postulating an early transition state for the equatorial anomer with little C—O bond breakage and a late transition state for the axial anomer with more extensive C—O bond breakage.

In order to shed some new light on the mechanism of acid-catalyzed hydrolysis of α- and β-D-glucopyranosides Deslongchamps et al. [267] carried out molecular modeling study of the various endocyclic and exocyclic cleavage pathways of tetrahydropyranyl acetals *317α* and *317β* (R = H in Fig. 12.90) during acid-catalyzed hydrolysis and then compared the reached theoretical conclusions with the experimental results obtained by using the conformationally rigid bicyclic tetrahydropyranyl acetals *315* and *316* [R = $(CH_2)_4$ in Fig. 12.90]. The reason for selecting the bicyclic conformationally rigid tetrahydropyranyl acetals for their experimental study was again to limit the effect of conformational change of a tetrahydropyranyl acetal upon the rate of its acid-catalyzed hydrolysis (see Eikeren [266]).

Deslongchamps et al. [267] have calculated the energies of the four possible transition structures *318α, 318β, 319α, 319β* and two intermediates *320* and *321* in the hydrolysis of the glycoside models *317α* and *317β* (Fig. 12.90).

For the hydrolysis of acetal *317α* → *322*, both the exocyclic (via *318α*) and the endocyclic (via *319α*) C—O bond cleavages take place via a chair-like transition state structure conformation with stereoelectronic assistance of one electron lone pair that is antiperiplanar to the leaving group. Molecular modeling indicates that the free energy of transition structure *318α* for the exocyclic mechanism is 1.72 kcal/mol lower than that of the endocyclic mechanism (*319α*). In addition, an entropy effect also favors the exocyclic mechanism (formation of two molecules: the

oxocarbenium ion *320* and methanol). It can therefore be expected that the transition structure for the exocyclic cleavage process for α-D-glycopyranosides will be highly favored which is in agreement with published results [268–272].

For the hydrolysis of *317β* →*322,* calculations indicate that the transition structure *318β* for the exocyclic C—O bond cleavage takes place via a sofa conformation with an endocyclic oxygen lone pair periplanar to the C—O bond (*syn* or *anti*) to be cleaved [273, 274].

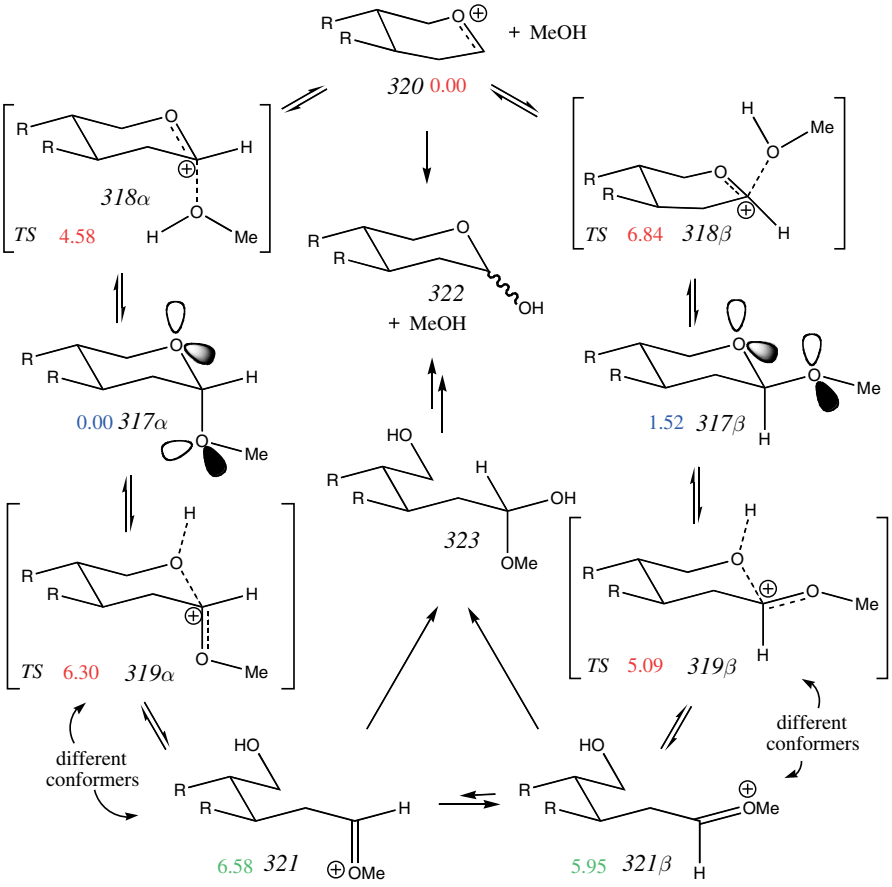


Fig. 12.90 [a]Numbers in red are relative energies (kcal/mol) of charged species 317, 320, 319, 321α, and 321β; numbers in blue are relative energies of acetals 317α and 317β, R = H (calculations), R = (CH2)4 (experimental). Numbers in green are for cations 321α and 321β in extended conformations (no interaction between cation and alcohol).

For the endocyclic C—O bond cleavage, calculations show that the transition structure geometry *319β* remains close to the chair ground-state conformation. This is the result of the participation of the exocyclic oxygen lone pair antiperiplanar to the leaving group. The enthalpy difference between the two transition state

structures *318β* and *319β* is 1.75 kcal/mol, now favoring the endocyclic C—O bond cleavage. On the other hand, entropy disfavors the opening of a ring over the exocyclic C—O bond cleavage, which leads to the formation of two molecules. Since the enthalpy favors *317β→319β* process and the entropy the *317β→318β*, both processes are likely to take place concurrently which is in accord with published experimental observations [275].

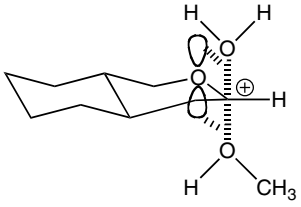
The results of calculations are in full agreement with the fact that the relative rate of hydrolysis of the α-anomer in a conformationally rigid model is faster than that of the β-anomer (rate ratio 3/2) [267, 276]. The transition structure *318α*for the exocyclic C—O bond cleavage has a lower energy (4.58 kcal/mol) than the β-anomer, *318β* (6.84 kcal/mol); it has also slightly lower energy than the other competing endocyclic C—O bond cleavage of the β-isomer (*319β*, 5.09 kcal/mol). The calculations show also that there is a small energy difference (0.63 kcal/mol) between the conformers *321β* and *321α* of the corresponding oxocarbenium ion *321*. The relative energy difference of these ions increased in the corresponding transition structures *319β* and *319α*, respectively (1.21 kcal/mol favoring *319β*). During the endocyclic hydrolysis of *317β*, the hydroxy-oxocarbenium ion *321β* could undergo a rotation and recyclize via conformer *321α*, to give the more stable anomer *317α*. However, experimental results show that the isomerization of the β-anomer into the α-anomer does not take place concurrently with hydrolysis [277]. This suggests that either the exocyclic cleavage via *318β* is much more favored entropically than the endocyclic cleavage via *319β* or the recyclization barrier is too high.

The experimental and theoretical studies of acid-catalyzed hydrolysis of various conformationally rigid acetal models [266–268] such as *315* and *316* (Fig. 12.89) have shown that it takes place via late transition state.

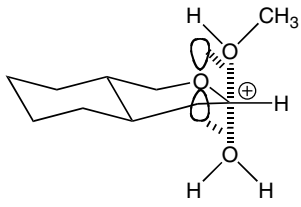
From this study Deslongchamps et al. [267] concluded that the α-glycosides undergo hydrolysis in their ground-state chair-like conformation via an exocyclic C—O bond cleavage while following the principle of kinetic stereoelectronic control (proper orbital alignment). β-Glycosides can be, however, hydrolyzed either by an exocyclic C—O bond cleavage via distorted twist-boat or sofa conformation or by an endocyclic C—O bond cleavage in the ground-state chair-like conformation. While van Eikeren [266] suggested an early transition state for the cleavage of equatorial anomer with little C-O bond breakage and a late transition state for the cleavage of axial anomer with more extensive C-O bond breakage, Deslongchamps et al. [267] *suggested that both cleavages take place via late transition states and with stereoelectronic control* whereby the cleavage of equatorial anomer takes place somewhat earlier. The exocyclic cleavage is favored by entropy and the endocyclic cleavage might be disfavored because the resulting hydroxy-oxocarbenium ion (like *321β*) might undergo a fast cyclization to give back the β-glycoside rather than undergoing a reaction with water to produce the hydrolysis product. On that basis, the hydrolysis of β-glycosides can take place via both the exocyclic and endocyclic pathways [278], the choice depending on the specific structure of the substrate and on the reaction conditions (acid-catalyzed or enzymatic [279]).

In hydrolyses that are carried out in water or in solvents containing water, it is now generally accepted [280] that an oxocarbenium ion is too reactive to have a real life time in the presence of a nucleophile such as water [281, 282].

Consequently a glycopyranosidic bond cleavage very likely proceeds via a transient [283] *oxocarbenium-like transition state*, with an sp^2-hybridized geometry at both the C1 and O5 atoms, allowing thus a considerable double bond character between the O5 and the C1 atoms and forcing the C5, O5, C1, and C2 atoms to assume a coplanar conformation. Hence this process does not involve a discrete carbocation in a first-order reaction, but is borderline S_N1–S_N2 reaction. In other words, the C1–OMe bond breaking is taking place simultaneously with the C1–OH_2 bond making (S_N2-like) (Fig. 12.91).



324, α-D-glycopyranoside TS (S_N2)



325, β-D-glycopyranoside TS (S_N2)

Fig. 12.91

In late transition state, both α- and β-D-glycopyranosides have essentially the same oxocarbenium ion with a CH_3OH group at a long distance ($\geq$ 1.80 Å). In this way, the CH_3OH in α- or β-transition state will have small steric interactions with the oxocarbenium ion. As a result, it is not surprising that ΔE between TSα and TSβ is only about 0.7 kcal/mol (see Fig. 12.91).

The above rationalization is confirmed experimentally by the addition of methanol in mild acid on enol ether *326* (Fig. 12.92). Under these kinetically controlled conditions a mixture of *317α* and *317β* was obtained in the ratio 76:24. This ratio corresponds to the energy difference of 0.70 kcal/mol for the transition state favoring the formation of *317α* which is in complete agreement with the AM1 [267] and 6.31G [268] calculations. This value is in agreement with that found by van Eikeren [266]. In addition, these calculations also show that the transition states are definitely late transition states and resemble the geometry of the oxocarbenium ion.

The primary ^{13}C [284, 285] and secondary α-deuterium [286] isotope effects were consistent with this S_N2-type itinerary. The conformation of oxocarbenium ion requires the coplanarity of the C5, O5, C1, and C2 atoms of pyranosidic ring and there are four possible conformations of transition state structure in which the C5, O5, C1, and C2 will be coplanar (Fig. 12.93): (1) the $^4H_3$, (2) the $^3H_4$, (3) $B_{2,5}$, and (4) the $^{2,5}B$ conformer. The route from reactant via transition state TS into the product is called the substitution pathway.

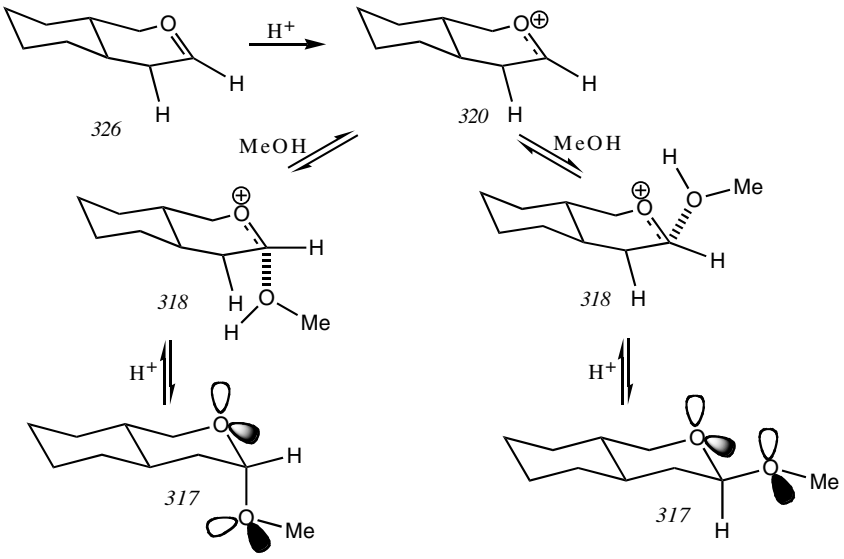


Fig. 12.92

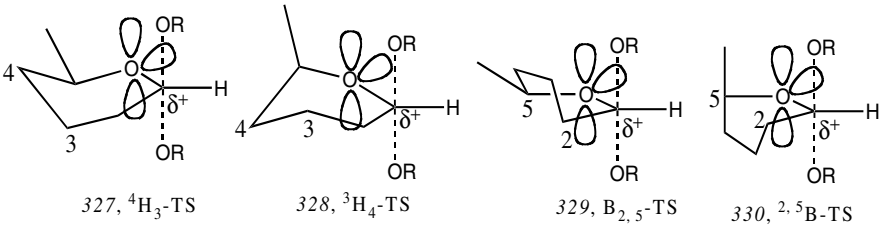


Fig. 12.93

By examining these TS geometries, Nerinckx et al. [280] have recently suggested explanation as to why there is such small difference in energy between these transition states and also as to why the rates of acid-catalyzed hydrolysis of α- and β-D-glycopyranosides are so close.

According to Antiperiplanar Lone Pair Hypothesis (ALPH) pathway the substitution of β-equatorial glycopyranosides is preceded by a conformational change from ground-state chair to a skew conformation in which the leaving group is in the axial orientation and in antiperiplanar orientation with regard to the *trans* lone electron pair of the ring oxygen. This sp^3 lone electron pair will hybridize at the TS into $2p_z$ orbital and thus allow the formation of the partial double bond toward the anomeric carbon [268, 270, 287]. The reaction then proceeds through an ALPH-compliant β-skew→$^4H_3$–TS→α-$^4C_1$ pathway (Fig. 12.94).

In the case of α-axial D-glycopyranosidic bond substitutions, the leaving group already has an ALPH-compliant orientation when the carbohydrate ring is in

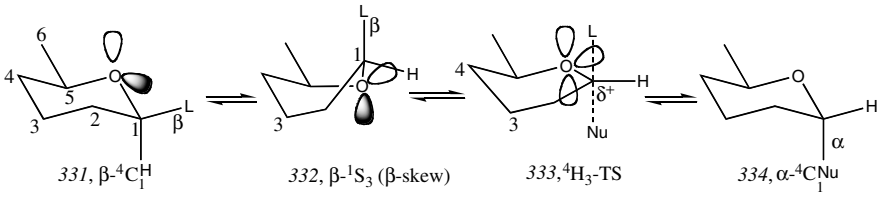


Fig. 12.94

the ground-state chair conformation. Thus the α-glycosides must hydrolyze via their ground-state conformation, as explicitly stated by Deslongchamps [268] (Fig. 12.95).

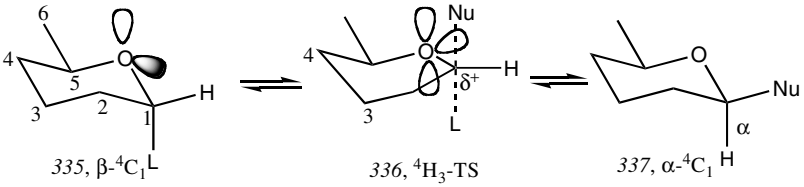


Fig. 12.95

Thus the energies of transition state intermediates for the hydrolysis of α- and β-D-glycopyranosides *338* and *339* must be very close, as shown in Fig. 12.96.

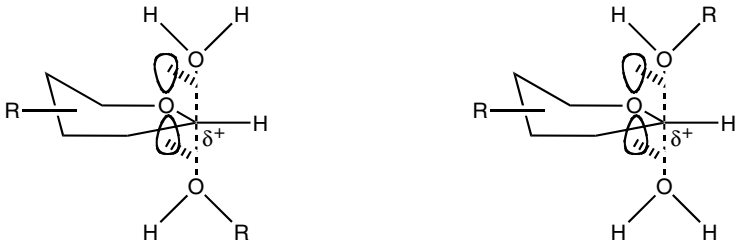


Fig. 12.96

It was established that both transition states are late and have essentially the same oxocarbenium ion in which the MeOH is at a long distance from the C1 carbon (≥1.80 A). What happens is while the MeOH is leaving, the H_2O is entering (S_N2-like reaction). But one should realize that TS energy is lowered by the fact that at TS, there is a *p*-orbital on O5 which assists this S_N2 reaction. Thus the anomeric effect still plays the same key role. In that case, the competing TS resemble *338* and *339* (Fig. 12.96) which again should have similar energy.

Acetolysis of Glycosides

The cleavage of a glycosidic bond by acetolysis is an alternative method to hydrolysis. Although both methods are acid catalyzed and presumably in case of glycopyranosides involve the formation of a cyclic oxocarbenium transition state they also have their differences. Thus, for example, the most important difference is that the hydrolysis is always performed in either aqueous solutions or in a solvent containing water, whereas the acetolysis is performed in nonaqueous solvents, typically acetic anhydride. In the case of acid-catalyzed hydrolysis the activation of glycosidic bond is effected by protonation of one of the two acetal oxygens (glycosidic or the ring oxygen), whereas in acetolysis the attacking species is not (H^+) but most likely the acetylium ion (Ac^+) [288–291]. Acetolysis can also be catalyzed by Lewis acids, such as ferric chloride ($FeCl_3$) [292, 293].

A review on acetolysis has been published by Guthrie and McCarthy [294].

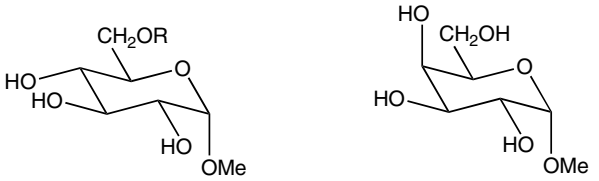
The study of the mechanism of acid-catalyzed hydrolysis of glycosidic bonds failed to answer two very important questions: (1)Why are the β-anomers of D-glycopyranosides (having the glycosidic oxygen equatorially oriented) hydrolyzed ca. 2–3 times more rapidly than α-anomers (having the glycosidic oxygen oriented axially) irrespective of the glycopyranoside structure? (2) Why the configurations of hydroxyl groups of the pyranoid ring (e.g., D-gluco-, D-galacto-) have no or very little influence upon the rates of hydrolysis of their glycosidic bonds? The postulated mechanism also contradicts the importance of relative basicities of ring and glycosidic oxygen in a glycopyranoside upon the rate of hydrolysis of the corresponding glycoside, and thus challenges the well-documented concept of anomeric effect. The one explanation for this "anomaly" could be that perhaps the electronic effects that do exist in all glycopyranoside structures are significantly "neutralized" in aqueous solution or in solvents containing water, due to hydrogen bonding between the sugar polar groups (hydroxyl groups and ring oxygen) and water molecules. This assumption is supported by the fact that the magnitude of anomeric effect is solvent dependent [295–299]. Another possible explanation could be that the energies of transition states for the hydrolysis of both anomers are close but the ground-state energies are different due to the anomeric effect whereby the α-anomer is more stable than the β-anomer. Since both transition states are late the β-anomer should reach the transition state easier and thus sooner than α-anomer, because its ground-state energy is higher than the ground-state energy of the α-anomer (the α-anomer being more stable will reach the transition state slightly later than the β-anomer).

The observed behavior of glycosidic bonds toward acid-catalyzed hydrolysis is contrary to what one would expect from the existence of anomeric effect and ALPH. Namely, it is known that due to the anomeric effect the axially oriented oxygen should have a higher basicity than the equatorial one, due to the mixing of axially oriented nonbonding electron pair of the ring oxygen with the antibonding orbital of the C1–O1 bond. Consequently, the concentration of conjugate acid resulting from protonation of the glycosidic oxygen should be higher in solutions of glycopyranosides having the glycosidic oxygen axially oriented (α-D-anomers) than in solution of glycopyranosides having the glycosidic oxygen equatorially

oriented (β-D-anomers). As a result, α-D-glycopyranosides should be hydrolyzed more rapidly than β-D-glycopyranosides, which is opposite to what is observed.

The mechanism of acid-catalyzed cleavage of glycosidic bonds could perhaps be better understood by studying the mechanism of acetolysis since it is performed in the absence of water (most often in acetic anhydride) and thus the electronic effects that exist in each glycopyranoside structure will not be "neutralized" by solvent and their influence upon the reactivity of glycosidic bond could be hopefully evaluated.

Dasgupta et al. [293] have studied the acetolysis of methyl α-D-glucopyranoside *340*, methyl 6-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside *341,* and methyl α-D-galactopyranoside *342*in acetic anhydride at 60°C using ferric chloride as cat-

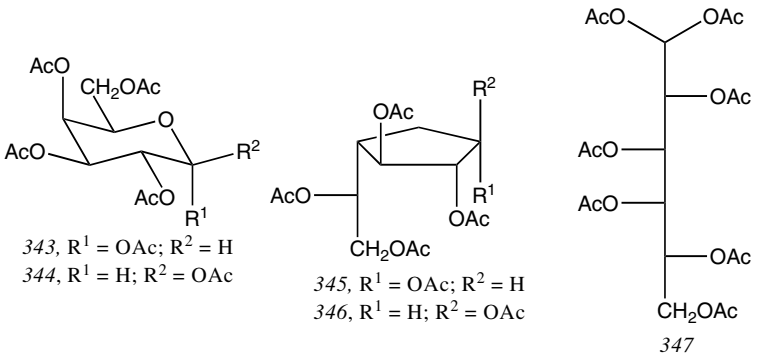


340, R = H
341, R = Ts

342

Fig. 12.97

alyst (Fig. 12.97). Methyl α-D-glucopyranoside *340* gave only two products, α- and β-penta-*O*-acetyl-D-glycopyranoses, whereas the acetolysis of methyl α-D-galactopyranoside *342* gave, under the same reaction conditions, five products of which the two major products were α- and β-penta-*O*-acetyl-D-galactopyranoses (*343* and *344*), the next two products were α- and β-D-galacto-furanose pentaacetates (*345* and *346*), and the last product was the acyclic hepta-*O*-acetyl-aldehydo-D-galactose (*347*) (Fig. 12.98). Furthermore, they observed that the acetolysis of methyl 6-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside *341* was, under the same reaction conditions, ca. 4 times slower than the acetolysis of *340*. The authors suggested two reaction mechanisms: one proceeding via formation of a cyclic oxocarbenium



343, R^1 = OAc; R^2 = H
344, R^1 = H; R^2 = OAc

345, R^1 = OAc; R^2 = H
346, R^1 = H; R^2 = OAc

347

Fig. 12.98

ion (the initial attack of the acetylium ion taking place at the glycosidic oxygen) and the other via the formation of an acyclic oxocarbenium ion (the initial attack of the acetylium ion taking place at the Ring oxygen). Both of these pathways are actually unsubstantiated.

With a slightly modified experimental procedure McPhail et al. [300] repeated the study of Dasgupta et al. [293] on the acetolysis of methyl α- and β-D-glucopyranosides. The discussion of reaction mechanism of acetolysis based on their experiments is described below.

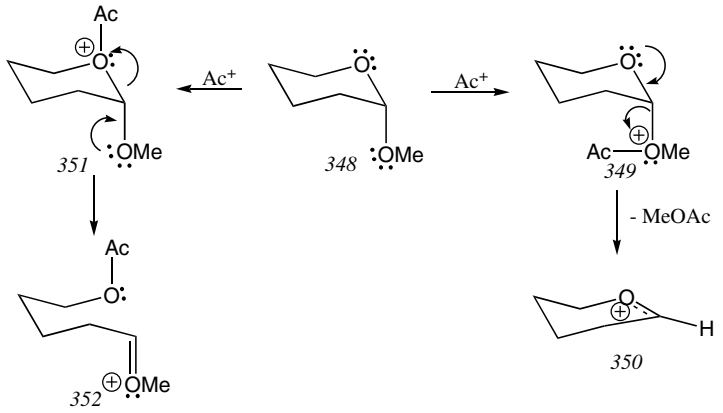
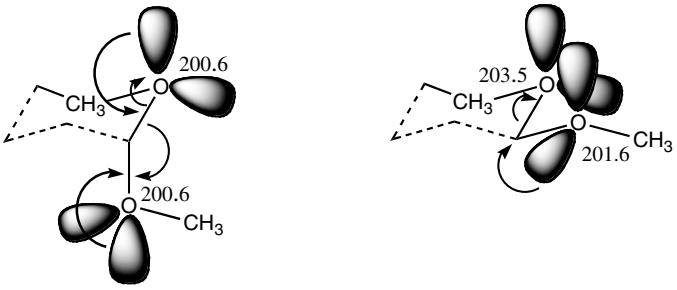


Fig. 12.99

The site of anomeric activation in glycoside cleavage has been a subject of long-standing controversy [301–306]. Early experiments were supporting the view that the activation occurs at the glycosidic oxygen (*352*), leading to the formation of cyclic oxocarbenium ion *350*, rather than at the ring oxygen (*351*) giving the acyclic counterpart *352* (Fig. 12.99).

The question of activation site is directly related to the question of relative basicities of glycosidic and ring oxygens, which is, in turn, related to anomeric effect [307, 310]. MO rationalization of anomeric effect invokes the donation of axially oriented nonbonding pair of ring oxygen to the antibonding orbital of the C1—O1 bond ($n \Leftrightarrow \sigma*$ donation) (antiperiplanar orientation of these two entities) making thus the glycosidic oxygen more basic than the ring oxygen and hence the preferred site for the attack of an electrophile (Ac^+) [308]. An ab initio study of dimethoxymethane has provided support for this postulate by determining the proton affinities for oxygens in a *gauche* and in an *anti* orientation of methyl group and one oxygen, as shown in Fig. 12.101. As indicated by broken lines, these rotamers correspond to axial and equatorial glycosides, respectively, and as observed by Lemieux [309] the $n\sigma*$ donations in *353* are in competition. Accordingly, Praly and Lemieux [310] found that for β-D-glycosides (*354*) (Fig. 12.100) the *exo*-anomeric effect was stronger than in α-D-glycosides. In view of these differences in oxygen basicities, a β-D-glycoside might be expected to be activated on the ring oxygen and react via

formation of an acyclic oxocarbenium ion *352*, whereas an α-D-glycoside would be expected to be activated at both oxygens (glycosidic and the ring oxygen) and consequently react by formation of either a cyclic *350* or an acyclic oxocarbenium ion *352* (Fig. 12.99).

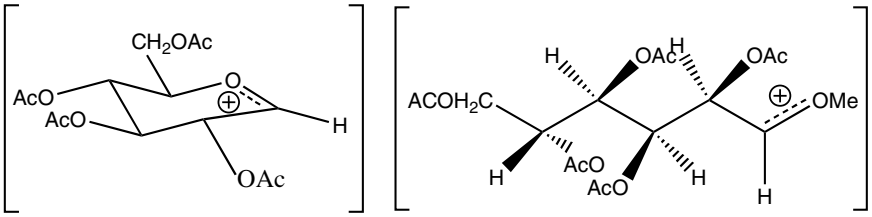


353 *354*

arrows indicate nσ* interactions

numbers represent calculated proton affinities (in kcal mol^{-1})

Fig. 12.100



355 *356*

Fig. 12.101

Their conclusion is that α- and β-D-glucopyranosides react through different mechanisms. From the fact that the ratio of the α- and β-D-glucopyranosyl acetates is 4:1 in both cases, they concluded that the cyclic oxocarbenium ion is produced from both anomers which is trapped by acetate anion. The acyclic oxocarbenium ion is responsible for the formation of both acyclic heptaacetate and the penta-*O*-acetyl furanose derivatives (Fig. 12.101).

In their study of acetolysis of methyl α-D-glucopyranoside using modified acetolysis medium (acetic anhydride, ferric chloride, and a small amount of concentrated sulfuric acid) McPhail et al. [300] found (by using gas chromatography and ^{1}NMR spectroscopy) that peracetylated α- and β-D-glucopyranoses were obtained with 73 and 18% yield, the mixture of α- and β-D-glucofuranose pentaacetates was obtained with 8% yield, and the acyclic D-glucose heptaacetate was obtained only in traces. For the β-D-glucopyranoside the same four products were obtained but in different

amounts: peracetylated α- and β-D-glucopyranoses were obtained with 19 and 5% yield, the mixture of α- and β-D-glucofuranose pentaacetates with 48% yield, and the acyclic D-glucose heptaacetate with 23% yield.

From this they concluded that contrary to what might be expected on the sole consideration of oxygen basicities, it is the β- and not the α-anomer that gives rise to both cyclic and acyclic oxocarbenium ions and that therefore there are factors other than basicities of two acetal oxygens in glycosides that determine the course of glycosidic bond cleavage.

The major objection to this study is the choice of methyl α- and β-D-glucopyranosides as substrates because the acetylation is faster than acetolysis and hence their model compounds were actually the peracetylated methyl α- and β-D-glucopyranosides. The presence of acetate at the C2 carbon will enormously complicate the acetolysis reaction pathway since the acetate is known to be an excellent participating group capable of altering the reaction pathway of activated glycosides as shown in Fig. 12.102. Thus, the formation of both cyclic and acyclic oxocarbenium ions by the activation of β-glycoside via the attack of acetylium ion on either the ring or the glycosidic oxygen will most likely be assisted by the C2 equatorial acetate via neighboring group participation. *Trans*-diaxial orientation of acetylium-activated ring oxygen and the carbonyl oxygen of C2 acetate would favor the opening of the pyranoside ring with the formation of *361* over the displacement of acetylium-activated equatorially oriented glycosidic oxygen by the C2 acetate (*357*→*358*). Therefore it can be expected that the β-glucopyranoside would prefer a pathway that would involve the formation of acyclic oxocarbenium ion transition state.

In the case of α-D-glucopyranoside the displacement of acetylium-activated ring oxygen or the acetylium-activated glycosidic oxygen by C2 acetate via neighboring group participation is not possible due to stereochemical reasons. So the only role of the C2 acetate in the acetolysis of α-D-glucopyranosides would be the stabilization of cyclic oxocarbenium ion.

The results reported in this study are consistent with this interpretation: the predominant products of acetolysis of methyl α-D-glucopyranoside is 4:1 mixture of penta-*O*-acetyl-α- and β-D-glucopyranoses (91%) with only 8% of penta-*O*-acetyl-D-glucofuranose and traces of acyclic heptaacetate. The acetolysis of methyl β-D-glucopyranoside gave a 4:1 mixture of only 24% of penta-*O*-acetyl-α- and β-D-glucopyranoses, whereas 48 and 23% of penta-*O*-acetyl-D-glucofuranose and the acyclic heptaacetate were obtained, respectively. The 4:1 ratio of penta-*O*-acetyl-α- and β-D-glucopyranoses obtained by acetolysis of both methyl α- and β-D-glycopyranosides is due to the anomerization of the reaction mixture after the acetolysis since the authors modified the $FeCl_3$–Ac_2O original reagent of Dasgupta [293] by adding a small amount of sulfuric acid to speed up the reaction.

In 1983 Miljkovic et al. [311, 312] studied the acetolysis of permethylated methyl α- and β-D-gluco-(*362* and *363*, respectively), methyl α- and β-D-galacto-(*364* and *365*, respectively), and methyl α- and β-D-mannopyranosides (*366* and *367*, respectively) (Fig. 12.103) in acetanhydride solution at 75°C containing

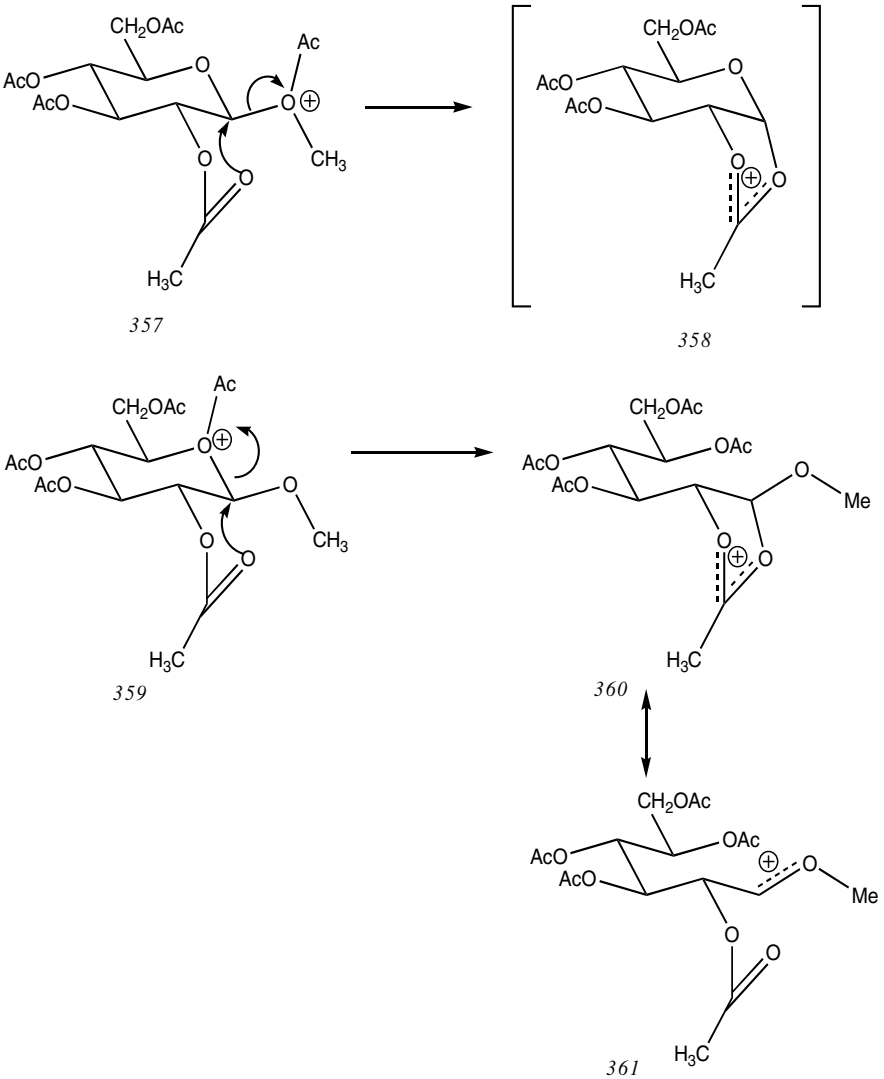
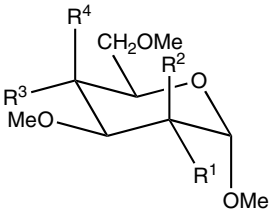
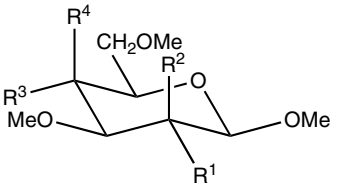


Fig. 12.102

3.33% of methanesulfonic acid. Since the C2 substituent in these glycopyranosides was a nonparticipating methoxy group the acetolyses of permethylated methyl glycopyranosides of glucose, galactose, and mannose were very clean reactions, giving, in addition to starting material, a mixture of α- and β-1-acetates as the only products. In all kinetic measurements the progress of acetolysis was monitored by a change of relative concentration of starting material, using HPLC and C18 column. The kinetic data are presented in Table 12.16.



362, $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
364, $R^1 = R^4 = OMe$; $R^2 = R^3 = H$
366, $R^1 = R^4 = H$; $R^2 = R^3 = OMe$



363, $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
365, $R^1 = R^4 = OMe$; $R^2 = R^3 = H$
367, $R^1 = R^4 = H$; $R^2 = R^3 = OMe$

Fig. 12.103

Table 12.16 Kinetic data for acetolysis of permethylated methyl glycopyranosides of D-glycose, D-galactose, and D-mannose (*362–367*) with acetic anhydride–methanesulfonic acid (30:1 v/v) at 75°C

Sugar	$10^3\ k_1$ (s^{-1})	$10^3 \times$ standard deviation	α/β ratio of 1-acetates
α-D-Gluco	1.87	0.0734	3.17
β-D-Gluco	0.12	0.00462	3.36
α-D-Galacto	37.10	1.43	2.97
β-D-Galacto	0.84	0.0709	3.22
α-D-Manno	1.08	0.0456	Only α-acetate
β-D-Manno	3.06	0.0631	Only α-acetate

From Table 12.16 it can be seen that the α-anomers of permethylated methyl D-gluco- and D-galactopyranosides are acetolyzed considerably faster than the corresponding β-anomers (15.58 and 44.17 times, respectively) which is in contradiction to the results obtained for acid-catalyzed hydrolysis of these two compounds where the β-anomer is hydrolyzed ca 1.9 times more rapidly than the α-anomer. The second observation is that permethylated methyl α- and β-D-galactopyranosides *364* and *365* are acetolyzed much faster than permethylated methyl α- and β-D-glucopyranosides *362* and *363* (α-gal/α-glc ≈ 20, and β-gal/β-glc ≈ 7). The permethylated methyl β-D-mannopyranoside *367* is, however, acetolyzed 2.83 times faster than the α-anomer *366* (Fig. 12.103).

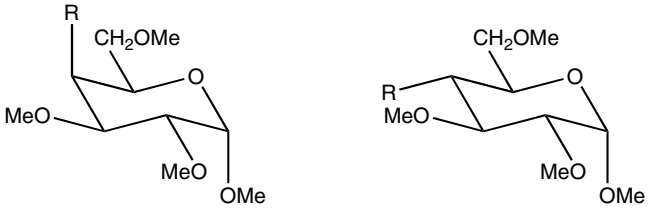
It is reasonable to assume that stereoelectronic interactions that are characteristic for a given alkyl- or aryl glycopyranoside structure must play an important role in determining the overall chemical behavior of its glycosidic bond. In protic and polar solvents (e.g., water) these electronic interactions must be neutralized by intermolecular interactions with solvent dipoles (solvation), whereas in aprotic solvents particularly those having relatively low dielectric constant (e.g., acetic anhydride $\varepsilon = 20.7$, as opposed to water $\varepsilon = 84.2$) the intramolecular electronic interactions must be fully operative and could be expected to influence the chemical behavior of

the anomeric carbon of a glycopyranoside. The basicity of the glycosidic oxygen, which is directly related to the anomeric effect, in nonpolar solvents with low dielectric constant can be expected to be higher than in polar protic solvents [312–314] and consequently the difference in relative basicities between the ring and glycosidic oxygens could be expected to be considerably larger. Thus the attack of acetylium cation could be expected to occur at the glycosidic rather than at the ring oxygen of a glycopyranoside. This activation will then be followed by formation of the oxocarbenium ion that will, in the presence of acetate anion, give a mixture of α- and β-1-acetates. Due to the presence of methanesulfonic acid in acetolyzing solution, the anomerization of 1-acetates will take place until the equilibrium is reached (α:β ratio ≈ 3:1, except for the mannose). This rationale is supported by findings that an acetic anhydride solution of D-glucose pentaacetate contains, after equilibration with sulfuric acid, approximately 87% of the α- and 13% of the β-anomer (α:β ratio ≈ 6.7), whereas in aqueous solution of D-glucose there is 36% of α- and 64% of β-anomer (β:α ratio ≈ 1.78). It is clear that the magnitude of anomeric effect that favors the α-anomer in the anomeric mixture is decreased in water.

The observed higher acetolysis rate of permethylated methyl β-D-mannopyranoside as compared to the α-anomer (β:α ratio 2.83) may seem to contradict the above explanation. However, there may be other reasons for such a behavior. First, it could be the much higher ground-state energy of the β-anomer as compared to α-anomer due to unfavorable electrostatic interactions of the axially oriented C2 methoxy group with the C—OMe and C1—O5 dipoles (Δ2 effect) and due to unfavorable torsional strain between the ring, glycosidic, and C2 oxygens. Second, the n^* orbital mixing in permethylated methyl-α-D-mannopyranoside could be expected to be less favored because this orbital mixing forces the flattening of the pyranoside ring and that will, in the case of mannopyranoside, result in increased torsional strain between the C2 and the C3 methoxy groups.

In order to understand why permethylated methyl α- and β-D-galactopyranosides acetolyzed 20 and 7 times more rapidly than the corresponding D-gluco derivatives, the rates of acetolysis of methyl 4-*O*-methyl- (*364*), 4-*O*-acetyl- (*368*) and 4-deoxy-4-acetamido-2,3,6-tri-*O*-methyl-α-D-galacto- (*370*), and the corresponding α-D-glucopyranosides (*362*, *369*, *371*) were compared (Fig. 12.104) and the results are given in Table 12.17 [311].

The data in Table 12.17 suggest that for 4-X-derivatives of methyl 4-X-2,3,6-tri-*O*-methyl-α-D-galactopyranoside the greater electronegativity of the C4 substituent the faster the rate of acetolysis. Thus 4-*O*-methyl derivatives acetolyze ca. 10 times faster than 4-*O*-acetyl derivative and the 4-*O*-acetyl derivatives acetolyze ca. 5 times faster than 1-acetamido derivative. When C4 substituent is equatorial, as is the case in D-glucopyranoside series, the influence of the change in electronegativity of the C4 substituent on acetolysis rates is much smaller. Thus the 4-*O*-methyl derivative acetolyzes only 2.9 and 3.3 times faster than 4-*O*-acetyl- and 4-*O*-acetamido derivatives, respectively. In the D-gluco series, the dependence of acetolysis rates upon the electronegativity of the C4 substituent can only be explained as a "through-bond" electronic interaction (inductive effect) with the ring oxygen, which is apparently rather small. However, in the D-galactoseries, the very large influence of the



364, R = OCH_3
368, R = OAc
370, R = NHAC

362, R = OCH_3
369, R = OAc
371, R = NHAc

Fig. 12.104

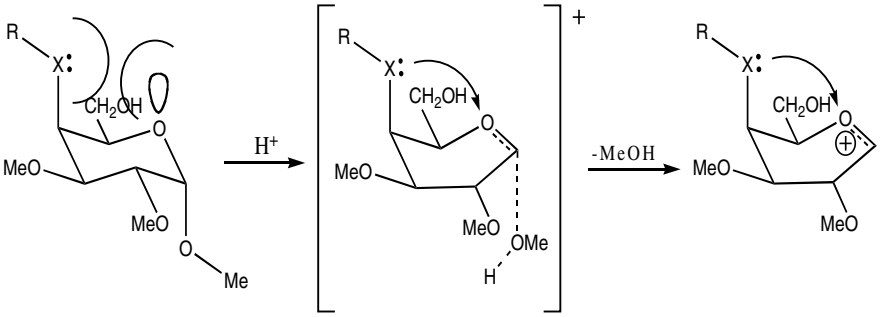
Table 12.17 Kinetic data for the acetolysis of methyl 4-*O*-methyl, 4-*O*-acetyl-, and 4-acetamido-4-deoxy derivatives of methyl 2,3,6-tri-*O*-methyl-α-D-galacto- (*362*, *368*, and *370*, respectively) and α-D-glucopyranosides (*362*, *369*, *371*, respectively)

Sugar	10^3 k (s^{-1})
Methyl	22.18
2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside (*364*)	25.79
Methyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-	2.44
galactopyranoside (*368*)	2.39
Methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-	0.44
galactopyranoside (*370*)	0.50
Methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (*362*)	1.67
	1.63
Methyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-	0.63
glucopyranoside (*369*)	0.61
Methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-	0.56
glucopyranoside (*371*)	0.47

electronegativity of the axially oriented C4 substituent on the acetolysis rate cannot be ascribed to this small through-bond interaction. The only possible explanation for the unusually large kinetic effect observed in the D-galacto series is a strong through-space electron donation of the axially oriented electronegative substituent at C4 into the oxocarbenium ion under formation. This effect, which is destabilizing in the neutral galactopyranoside due to electrostatic repulsion, becomes very stabilizing as the oxocarbenium ion appears (Fig. 12.105).

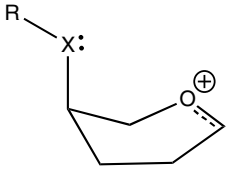
The ab initio calculations at the 6–31G* level of theory fully supported the above conclusions [312].

Calculations were conducted on model oxocarbenium ions corresponding to D-gluco- and D-galacto series (*375–380*) (Fig. 12.106) and olefin analogs (*381–386*) stereochemically identical to oxocarbenium models of these two series. Finally, the 4-substituted 2-alkoxy-tetrahydropyrans (*387–392*) were used to calculate difference in ground-stateenergies of 4-axially substituted and 4-equatorially substituted tetrahydropyrans. When considering only the low-energy conformers of acetals

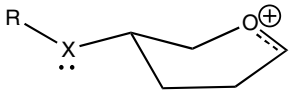


372, Pyranoside GS *373*, TS *374*, Oxocarbeniium ioin

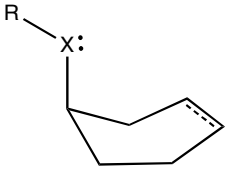
Fig. 12.105



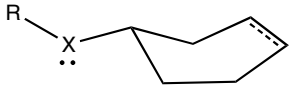
375, X = O; R = Me
377, X = O; R = Ac
379, X = NH; R = Ac



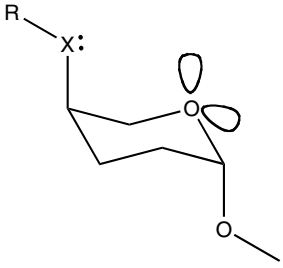
376, X = O; R = Me
378, X = O; R = Ac
380, X = NH; R = Ac



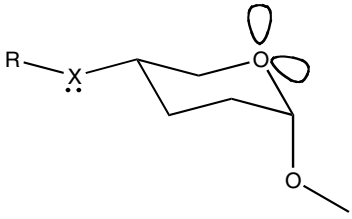
381, X = O; R = Me
383, X = O; R = Ac
385, X = NH; R = Ac



382, X = O; R = Me
384, X = O; R = Ac
386, X = NH; R = Ac



387, X = O; R = Me
389, X = O; R = Ac
391, X = NH; R = Ac



388, X = O; R = Me
390, X = O; R = Ac
392, X = NH; R = Ac

Fig. 12.106

387–392, it was found that the compound in which the C4 methoxy group is equatorially oriented (*388*) is 0.88 kcal/mol more stable than the compound *387* having the C4 methoxy group axial. This trend is reversed for the C4 acetamido derivatives: axial isomer *391* is now more stable, by 0.55 kcal/mol, than the equatorial isomer *392*. The C4 acetates fall between these two extremes since the axial and equatorial acetates (*389* and *390,* respectively) are almost equally stable. These observations are in complete agreement with the idea of repulsion between an electron-rich C4 axial substituent and the axially oriented sp^3-hybridized lone pair of electrons on the ring oxygen. In the case of acetamido acetal there exists an electronic attraction between the axially oriented sp^3-hybridized lone pair of electrons on the ring oxygen and the axially oriented C4 acetamido nitrogen since the axial isomer is preferred. The most likely reason for this is that the nitrogen atom has a partial positive charge due to donation of its nonbonding pair of electrons to the carbonyl oxygen of the acetamido group through delocalization involving carbonyl carbon and carbonyl oxygen. While the electronic interactions are rather small in neutral acetals, they are much more significant in corresponding oxocarbenium ions which are both geometrically and energetically very similar to the acetolysis transition structures. Thus, the oxocarbenium ion having the C4 methoxy group axially oriented (*375*) was found to be 4.06 kcal/mol more stable than the oxocarbenium ion with the C4 methoxy group equatorially oriented (*376*). The same electronic interaction can be seen in the oxocarbenium ion having the C4 acetoxy group axially oriented (*377*); however, it is somewhat smaller: the axial isomer is now favored by 2.89 kcal/mol over the equatorial isomer (*378*). In the case of acetamido derivatives, this interaction seems to no longer exist. Thus the oxocarbenium ion having the C4 acetamido group axially or equatorially oriented (*379* and *380*, respectively) has very similar energies: the axial isomer, however, is again favored, but only by 0.20 kcal/mol. It is interesting that while the nitrogen atom is sp^2 hybridized in all acetamido compounds (*380*, *385*, *386*, *391*, *392*) as expected, in the two rotamers of the oxocarbenium ion *381* around the C4-X bond in which the C4 acetamido group is axially oriented the nitrogen atom exhibits a high degree of sp^3 hybridization and the nitrogen lone pair of electrons points toward the oxocarbenium ion.

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Chapter 13
Synthesis of Polychiral Natural Products from Carbohydrates

Macrolide Antibiotics: Erythronolides A and B

Stereoselective synthesis of polychiral natural products is the most challenging problem for a synthetic organic chemist. The stereoselective synthesis of macrolide antibiotics represents one such difficult problem. They consist of macrocyclic lactone rings with many hydroxylated and methylated chiral carbons. In addition to that the macrocyclic lactones (macrolides) are usually glycosylated with amino sugars.

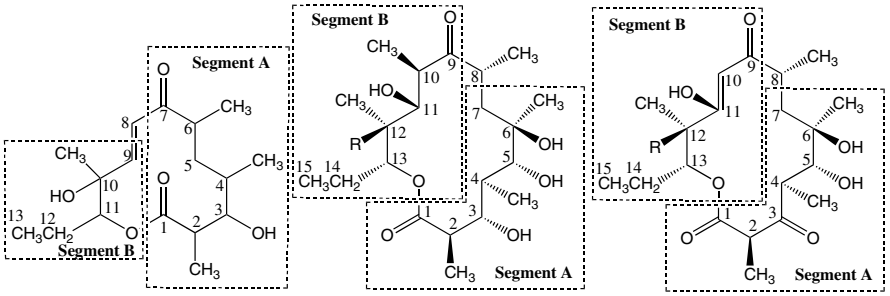
The striking resemblance of macrocyclic ring structure of macrolide antibiotics to "giant" branched chain sugars [3] inspired Woodward to describe magnamycin (carbomycin) as a *giant sugar* having at the same time the properties of a long-chain aliphatic acid. A realization that some 12- and 14-membered macrocyclic lactone rings can be dissected into two carbohydrate-like structural fragments prompted Miljkovic et al. [4–8] in 1972 to investigate the possibility of using carbohydrates for stereoselective synthesis of these stereochemically highly complex natural products because the chemical transformations of sugar molecules were known to often proceed highly stereoselectively.

Dissection of the macrocyclic lactone rings of methymycin, erythromycins A and B, picromycin, and narbomycin, as depicted in Fig. 13.1, afforded for methymycin one seven-carbon atom fragment (C1–C7) (Segment A) and one five-carbon atom fragment (C9–C13) (segment B) and for erythromycins A and B, picromycin, and Narbomycin two seven-carbon atom fragments (C1–C7) (Segment A) and (C9–C15) (Segment B) [7, 8].

Consequently, the construction of carbon skeleton of macrolides *1–5* (Fig. 13.1) from corresponding fragments would require that the C8 carbon atom be introduced either immediately before or during the coupling of the two fragments into the open-chain precursor of a given macrolide aglycone. An important advantage of dissecting the macrocyclic lactone rings as depicted in Fig. 14.1 is that it produces structurally similar fragments. This becomes particularly evident if Segments A and B of methynolide, erythronolides A and B, picronolide, and narbonolide are represented in the form of carbohydrate pyranoside-like structures (Figs. 13.2 and 13.3).

There are a couple of review articles dealing with this subject [1, 2].

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_13,



1, Methynolide

2, R = OH, Erythronolide A
3, R = H, Erythronolide B

4, R = OH, Picronolide
5, R = H, Narbonolide

Fig. 13.1

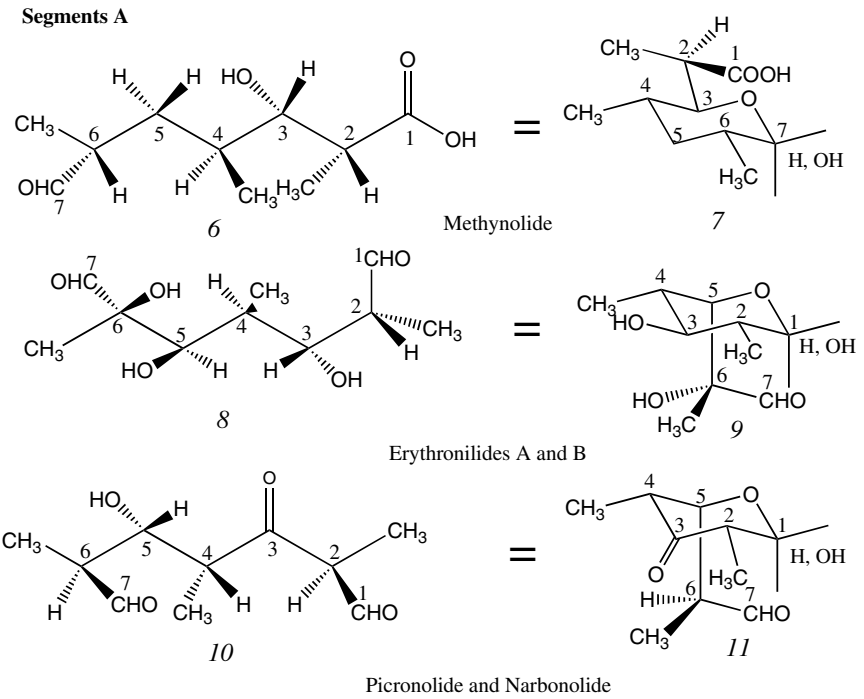


Fig. 13.2

Segment A of all five macrolide aglycones (*7*, *9*, and *11* in Fig. 13.2) has two structurally identical carbon atoms: the C2 and the C4 carbons in *9* and *11* and the C4 and the C6 carbons in *7*. All these carbon atoms have their methyl groups equatorially oriented when represented in the $^4C_1$ conformation of a pyranoside-like structure. The C3 carbon atom in *9* and *11* is oxygenated, whereas in *7* it is not linked

to oxygen. Finally, the side chain in *9* and *11*, consisting of C6 and the C7 carbon atoms of macrolide aglycones *2–5*, is axially oriented and is in *cis* configuration with respect to the C4 methyl group; however, in *7*, the side chain consisting of C1 and the C2 carbon atoms of methynolide is equatorially oriented and is in *trans* configuration with respect to the C4 methyl group.

Segment B of all five macrolide aglycones *12–21* (Fig. 13.3) has as common structural features the same side chain (ethyl group) and one configurationally identical carbon atom: the C13 carbon in *14–21* and the C11 carbon in *12* or *13*. Further, the C12 carbon in *16* and *20*, the C10 carbon in *13*, as well as the C12 carbon in *17* and *21* are structurally identical. It is important to note that the axially oriented C10

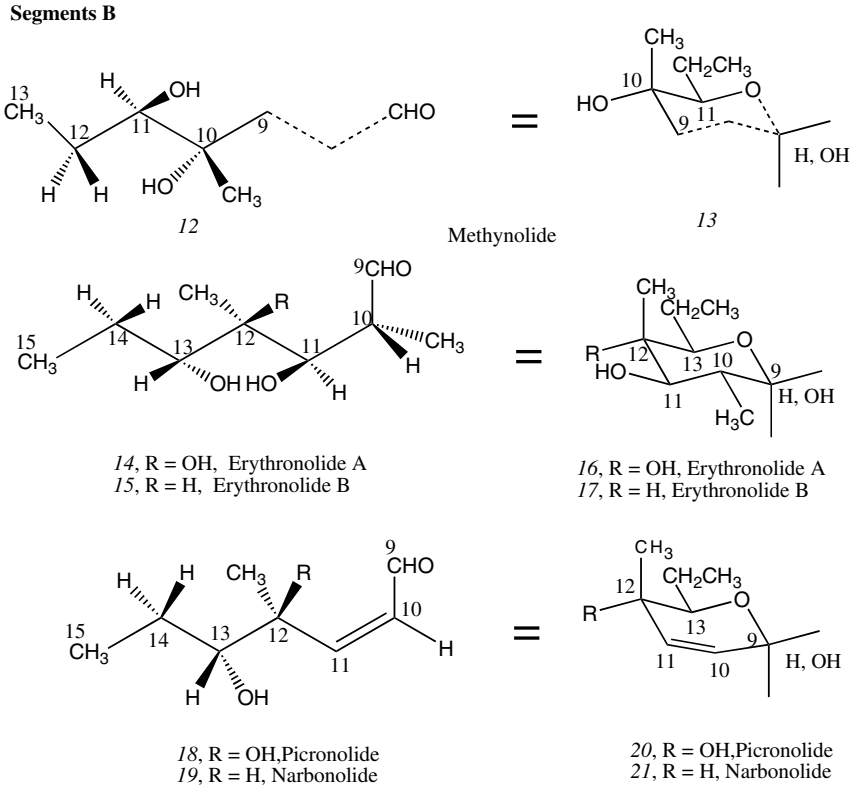


Fig. 13.3

methyl group in *13* and the C12 methyl group in *16–21* are in the *cis* configuration with respect to the equatorially oriented C11 ethyl group in *13* or with the C13 ethyl group in *16–21*.

If one compares the structure of D-glucopyranose with structures of segments A and B of erythronolides A and B, represented as glycopyranosides (synthons *9*

and *16*, respectively), it becomes apparent that the stereoselective conversion of D-glucose into synthons *9* and *16* requires the following transformations:

(1) The conversion of the C5 hydroxymethyl group of a D-glucopyranoside derivative to the C5 ethyl group, i.e., the synthesis of the 6-deoxy-6-*C*-methyl homolog of D-glucopyranoside. This represents the synthesis of the side chain (ethyl group) of synthon *16*, which will later become the C14 and the C15 carbons of erythronolides A and B.
(2) Introduction of an axial methyl group at the C4 carbon atom of a D-glucopyranoside derivative whereby a branched chain sugar will be obtained in which the C4 quaternary carbon has the (*S*) configuration (this represents the synthesis of the C12 carbon of erythronolide A).
(3) Replacement of the equatorially oriented C2 hydroxyl group of a D-glucopyranoside derivative with an equatorially oriented methyl group [synthesis of the C2 and the C10 carbon atoms of erythronolide A, both having the (*R*) configuration].
(4) Inversion of the configuration of the C5 carbon of a D-glucopyranoside derivative, resulting in the formation of the corresponding L-idopyranoside derivative (synthesis of the C4 carbon of erythronolide A).
(5) Replacement of the equatorial C4 hydroxyl group of a D-glucopyranoside derivative, with an axial methyl group, resulting in a 4-deoxy-4-*C*-methyl branched chain sugar (synthesis of the C4 carbon of erythronolide B).
(6) The stereoselective addition of an alkyl group to the exocyclic C6 carbonyl carbon of 7-deoxy-L-*ido*-heptopyranoside-6-ulose derivative, resulting in a chiral C6 tertiary alcohol with a (*R*) configuration (synthesis of the C6 carbon of erythronolide A).

Except for the replacement of the primary C6 hydroxyl group with a methyl group, all other chemical transformations of D-glucopyranoside derivatives required finding a way to efficiently control the stereochemistry of reactions 2–6.

At the time Miljkovic et al. started this investigation in 1972, the configurational determination of quaternary carbon of branched chain sugars and the stereoselective synthesis of quaternary C12 carbon of erythronolide A (having the C4 methyl group in synthon *16* axially oriented) seemed to be two problems that have to be dealt with first.

Configurational determination of a quaternary carbon of branched chain sugars posed, at the time of these pioneering studies, a serious problem, since there was no single physico-chemical method available by which one could make a quick, reliable, and unequivocal assignment of the configuration of the quaternary branching carbon. In search for such a method, published studies on conformational equilibrium of methylcyclohexane by C13 NMR spectroscopy turned out to be very helpful [9–11]. In these publications it was reported that the C13 chemical shift of an axial methyl group is shifted by ca. 6 ppm toward the higher magnetic field, as compared to the C13 chemical shift of an equatorial methyl group. This observation prompted Miljkovic et al. [5] to investigate whether the C13 chemical shifts of axial

and equatorial methyl groups linked to a quaternary carbon atom of branched chain sugars could be used for configurational assignments. The study which followed established that it can and that the axial methyl group linked to the quaternary carbon is shifted by ca. 6.4 ppm upfield for the α-anomers and by ca. 5.2 ppm for the β-anomers relative to an equatorial methyl group.

Simultaneously with the C13 NMR studies, a study was undertaken on the addition of methyl lithium and methyl magnesium bromide to the C4 carbon of an appropriately protected D-glucopyranosid-4-ulose derivative. From previous studies it was known that the additions of Grignard reagents and organolithium compounds to the carbonyl group in carbohydrates were highly stereoselective [12] and that in certain cases branched chain sugars epimeric at the branching carbon [13, 14] were obtained, and in other instances branched chain sugars with the same configuration at the branching carbon [15]were obtained. It was, however, not known what, if anything, controls the stereochemistry of these additions and consequently it was concluded that the addition of Grignard reagents and/or alkyl- or aryllithium to oxo-sugars cannot be reliably predicted [16].

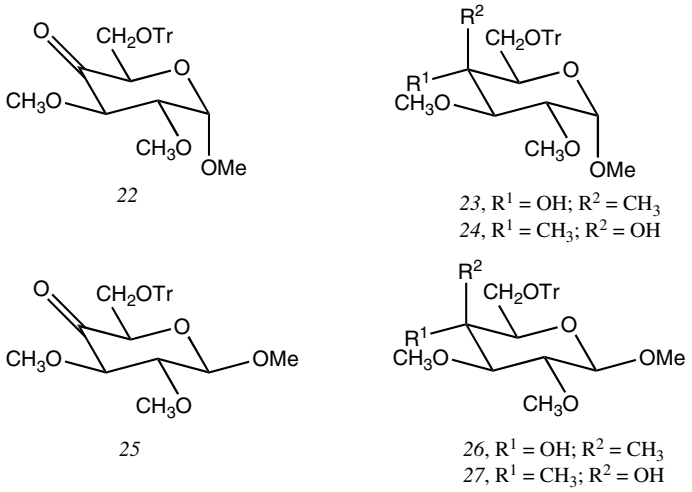
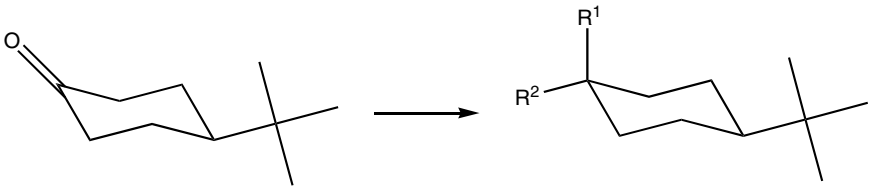


Fig. 13.4

As part of an effort to stereoselectively synthesize the C12 carbon of erythronolide A Miljkovic et al. [4] undertook a study of the addition of methyl lithium and methyl magnesium halides to methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-α- and β-D-*xylo*-hexo-pyranosid-4-ulose *22* and *25*, respectively, in ether at –80°C (Fig. 13.4) and found that the reaction of *22* with methyl lithium (LiBr-free) afforded methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-glucopyranoside *23* as the only product in 70% yield. The reaction of *22* with methylmagnesium iodide proceeded again stereospecifically giving exclusively methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-α-D-galacto-pyranoside *24* (the C4 epimer of *22*) in 94% yield (Fig. 13.4).

Contrary to the above results, methylmagnesium iodide and methyl lithium added nonstereoselectively and at a considerably slower rate to 4-*tert*-butylcyclohexanone *28* in ether and at –80°C, yielding in each case a mixture of both C1 epimers: *cis*-4-*tert*-butyl-1-methyl-cyclohexan-*r*-ol *29* and *trans*-4-*tert*-butyl-1-methyl-cyclohexan-*l*-ol *30* (Fig. 13.5). The isomer with equatorial methyl group was the preponderant product in both reactions.



28

29, $R^1 = OH$; $R^2 = CH_3$
30, $R^1 = CH_3$; $R^2 = OH$

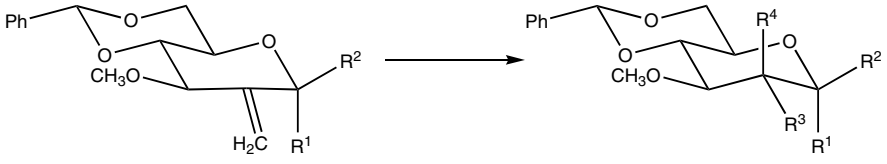
Fig. 13.5

The stereochemistry of the addition of Grignard reagent to the methyl α-D-*xylo*-hexo-pyranosid-4-ulose *22* was shown to depend on the reaction temperature, solvent [17, 18], and the nature of the halogen atom. Thus, treating an ethereal solution of *22* at reflux gave a mixture of both C4 epimers *23* and *24* in which the isomer with the methyl group equatorially oriented predominated in the 6:1 ratio. The dependence of stereochemistry of the addition of Grignard reagent upon the nature of the halogen atom and of the solvent was demonstrated in the following way: refluxing a 10:1 ether–tetrahydrofuran solution of *22* with methylmagnesium chloride gave a 1:1 mixture of C4 epimers *23* and *24*, whereas methylmagnesium iodide under the same reaction conditions gave a mixture of C4 epimers *23* and *24*, in which the axial isomer predominated in 2.3:1 ratio.

Dependence of the stereochemistry of addition of methyl lithium upon the anomeric configuration was discovered after the observation that the addition of methyl lithium to the methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose *25* in ether at –80°C proceeded with considerable loss of stereoselectivity giving both C4 epimers, *26* and *27*, respectively, in ca. 3:1 ratio, with the axial epimer being the predominant product. However, the addition of Grignard reagent was unaffected by the anomeric configuration because the methylmagnesium iodide added to methyl 2,3-di-*O*-methyl-6-*O*-triphenylmethyl-β-D-*xylo*-hexopyranosid-4-ulose *25* in ether at –80°C again stereoselectively gave methyl 2,3-di-*O*-methyl-4-*C*-methyl-6-*O*-triphenylmethyl-β-D-galactopyranoside *27* as the only product.

The observed dependence of the stereochemistry of addition of methyl lithium to methyl 2,3-di-*O*-methyl-α- or β-D-*xylo*-hexopyranosid-4-ulose *22* and *25* upon the anomeric configuration and the lack of dependence of the stereochemistry of addition of methylmagnesium iodide upon *22* and *25* are discussed in Chapter 11.

The high stereoselectivity observed in the reduction of C2 keto group of methyl α- and β-D-*arabino*-hexopyranosid-2-ulose with sodium borohydride [19] and its dependence upon the anomeric configuration prompted a study of catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α- and β-D-*arabino*-hexopyranoside *31* and *32* (Fig. 13.6) in order to determine if the stereochemistry of catalytic hydrogenation is perhaps also controlled by the anomeric configuration [6].



31, $R^1 = OCH_3$; $R_2 = H$
32, $R^1 = H$; $R^2 = OCH_3$

33, $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = CH_3$
34, $R^1 = OCH_3$; $R^2 = R^3 = H$; $R^4 = CH_3$
35, $R^1 = OCH_3$; $R^2 = R^4 = H$; $R^3 = CH_3$

Fig. 13.6

Unfortunately it has been found that whereas the catalytic hydrogenation of β-anomer proceeded highly stereoselectively (methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-β-D-*arabino*-hexopyranoside gave 2-deoxy-2-*C*-methyl-β-D-mannopyranoside *33* as the only product in 84% yield), the stereoselectivity of hydrogenation of the α-anomer *31* was not high and depended on the nature of the catalyst and the solvent used. Raney nickel catalyst and nonpolar solvents favored the isomer with the equatorial C2 methyl group (*35*) (*35*:*34* ratio was 2.9:1), whereas platinum and polar solvents favored the formation of the axial C2 methyl group (*34*) (*35*:*34* ratio 1:3.1).

With these key steps solved, the segments A and B of erythronolide A have been synthesized [7, 8] (Figs. 13.7 and 13.8).

A couple of years after Miljkovic et al. published their first studies on the synthesis of erythronolide A from D-glucose, Hanessian et al. [20–22] approached the synthesis of erythronolide A in an essentially identical way, dissecting the erythronolide 14-membered lactone ring in exactly the same way and synthesizing the segments A and B in a very similar manner. For that reason we will not attempt to describe their efforts.

In 1981, Kochetkov et al. reported the synthesis of the C1–C6 segment [23] of a number of 14-membered macrolide antibiotics and the synthesis of the C9–C13 segments [24] of erythronolides A and B and oleandonolide. In 1984 they revised the synthesis of the C9–C13 segment of erythronolide A [25] and finally in 1989, they published the full paper on stereoselective synthesis of erythronolides A and B from 1,6-anhydro-β-D-glucopyranose (levoglucosan) [26].

The synthetic strategy employed by Kochetkov's group is based on retrosynthetic considerations and envisaged the assembly of the erythronolides A and B skeleton

Synthesis of the segment B of Erythronolide A

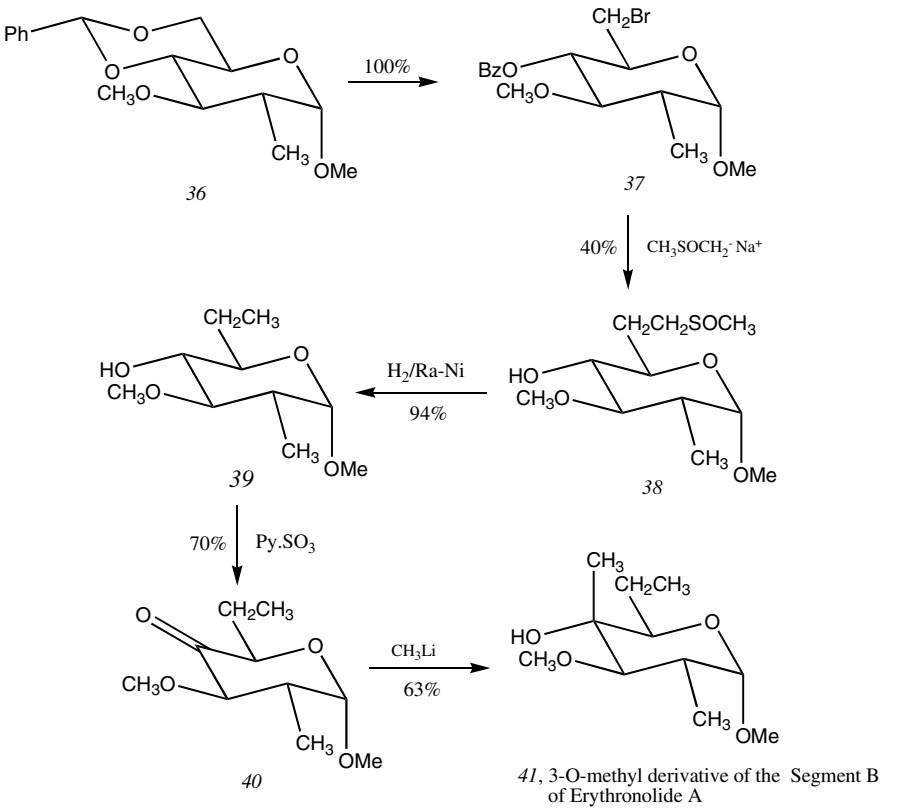


Fig. 13.7

in the C9–C13 + C7–C8 = C7–C13; C7–C13 + C1–C6 = C1–C13 sequence. The structures of C1–C6 and C9–C13 segments are shown in Fig. 13.9.

Bicyclic derivatives *59, 60,* and 61 were synthesized from 1,6-anhydro-β-D-glucopyranose (levoglucosan) *62* [25, 26, 27, 28].

Synthesis of the C1–C6 segment of erythronolides A and B is shown in Fig. 13.10. The mercaptolysis of *59* with 1,2-ethanedithiol in dichloromethane in the presence of borontrifluoro etherate at room temperature gave ethylene dithioacetal that was not isolated, but the reaction solution was cooled to –40°C and pyridine and acetic anhydride were added and the solution was kept for 2 h at –10°C. The acetate was again not isolated but the crude reaction mixture was treated with 1:1 mixture of acetone/2,2-dimethoxy propane in the presence of *p*-toluenesulfonic acid monohydrate giving *63* in 56.6% overall yield. Dethioacetalation of *63* with mercury (II) chloride–calcium carbonate mixture in acetonitrile–water gave the corresponding aldehyde *64* in 77% yield. Reaction of *64* with methylenetriphenylphosphorane

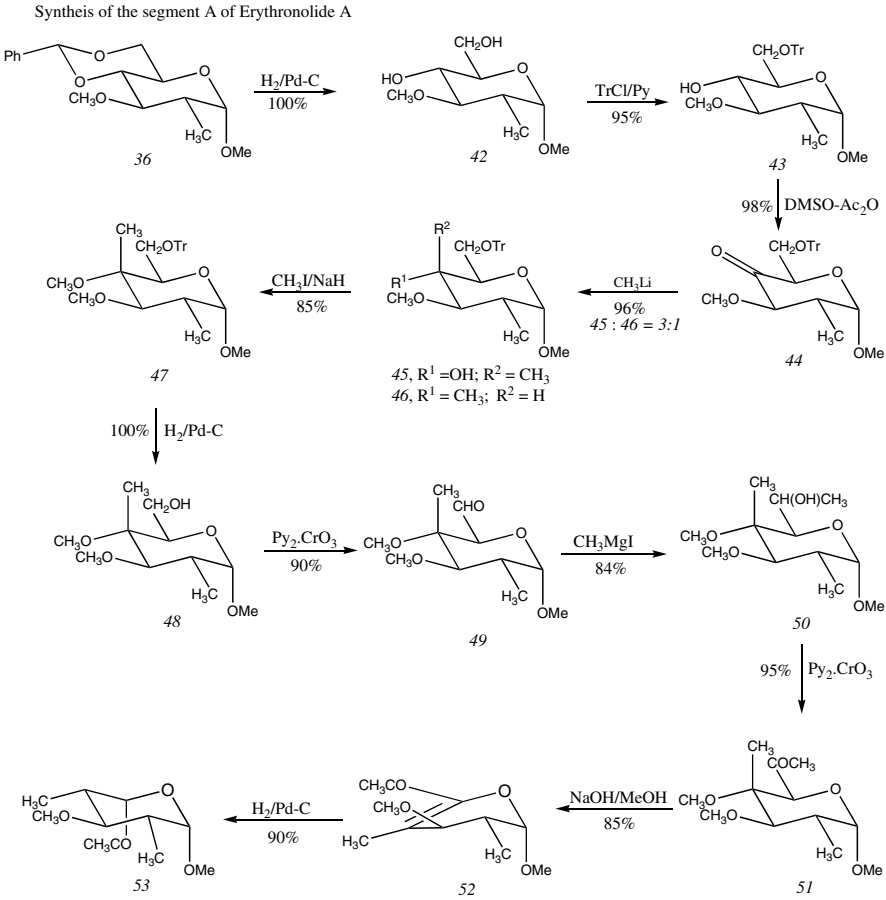


Fig. 13.8

gave a mixture of 6-*O*-acetyl *65* and 6-*O*-deacetylated olefin *66* which was treated with sodium methoxide in methanol to give *66* in 77.6% yield. Swern oxidation [29] of alcohol *66* followed by the addition of methylmagnesium chloride to the resulting C6 aldehyde and subsequent oxidation of the intermediate C6 hydroxyl group again by using the Swern procedure [loc. cit.] gave methyl ketone *67*. Mild alkaline isomerization of *67* at the C5 proceeded in almost quantitative yield giving the thermodynamically more stable ketone *58* in which the C3 and the C5 hydroxyl groups are in the *cis* orientation.

Starting material for the synthesis of aldehyde *68*, which is the C9–C15 segment of erythronolide B, was the bicyclic derivative *61* (Figs. 13.9 and 13.12) which has been previously synthesized [28] from *62* (Fig. 13.11).

Synthesis of the segment B of erythronolide B is shown in Fig. 13.12. Mercaptolysis of *61* and subsequent acetonation gave a dioxolan derivative *70* in 64% yield;

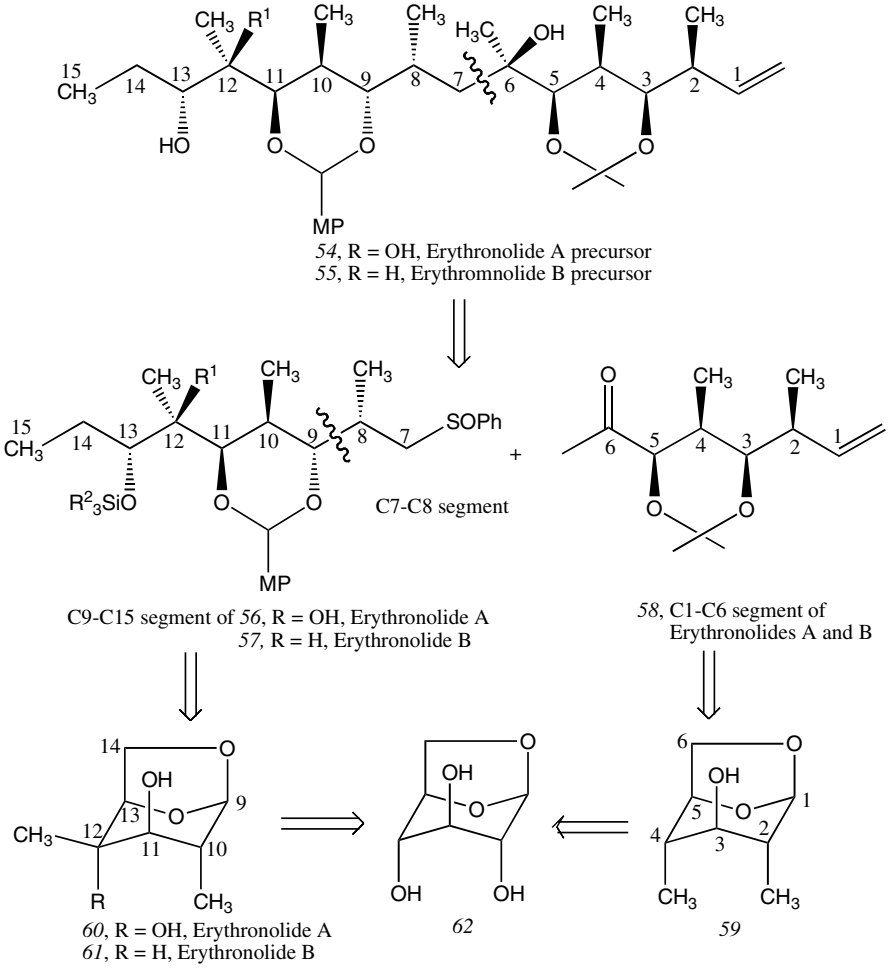


Fig. 13.9

the free C11 hydroxyl group in *70* was then protected as *p*-methoxybenzyl (PMB) ether yielding *71*. Mild acid hydrolysis of *71* gave the C13, C14 diol *72* that was converted [30] to hydroxy derivative *73*, by selective tosylation of the primary C14 hydroxyl group of *72*, the formation of the α-oxide, and opening of the latter with CH_3MgCl in the presence of a copper (I) salt. Since all of the above intermediates are extremely labile the reactions were performed as quickly as possible and without isolation of individual compounds. The protection of C13 hydroxyl group of *73* was accomplished by treating *73* with *tert*-butyldiphenylsilyl chloride, and the resulting thioacetal *74* was treated with mercuric (II) chloride–cadmium carbonate yielding the C9–C15 segment of erythronolide B (*75*).

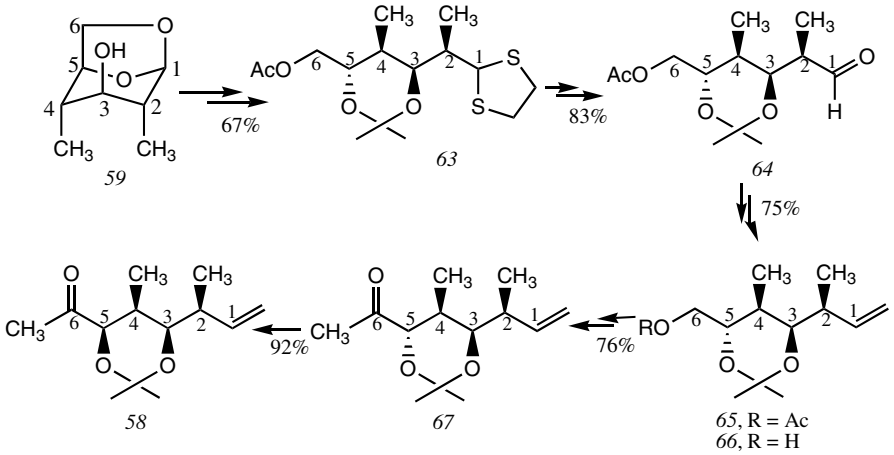


Fig. 13.10

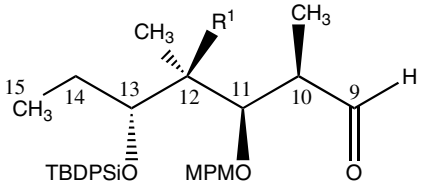


Fig. 13.11

The C9–C15 segment of erythronolide A *82* was prepared from the olefin 76 which was via stereoselective hydroxylation of the C4 methylene group with OsO_4-*N*-oxide-*N*-methyl-morpholine [31] converted to 60 (Fig. 13.13). The opening of the 1,6-anhydro ring of the di-*O*-benzyl derivative *77* by methanolysis (20% HCl/CH_3OH), whereby a mixture of methyl α- and β-D-glycopyranosides was obtained in ca. 3:1 ratio in 78% yield, was followed by oxidation of the primary hydroxyl group with $DMSO/COCl_2/Et_3N$ in dichloromethane [29] giving in 83% yield the corresponding C14 aldehyde *79*, which with methylenetriphenylphosphorane gave the corresponding olefin *80* (80%). The C14–C15 double bond was then reduced into the ethyl group by $LiAlH_4$–$CoCl_2$ (80%) [32] giving *81*. Debenzylation of *81* by hydrogenation with Raney nickel in ethanol followed by transglycosylation of *82* with allyl alcohol in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) gave a mixture of anomeric allyl glycosides *83*. Selective acetylation with acetic anhydride and pyridine gave the C11 monoacetyl derivative *84* in quantitative yield. Conversion of the monoacetate *84* to methoxymethyl (MOM) ether *85* followed by deacetylation proceeded also in quantitative yield to

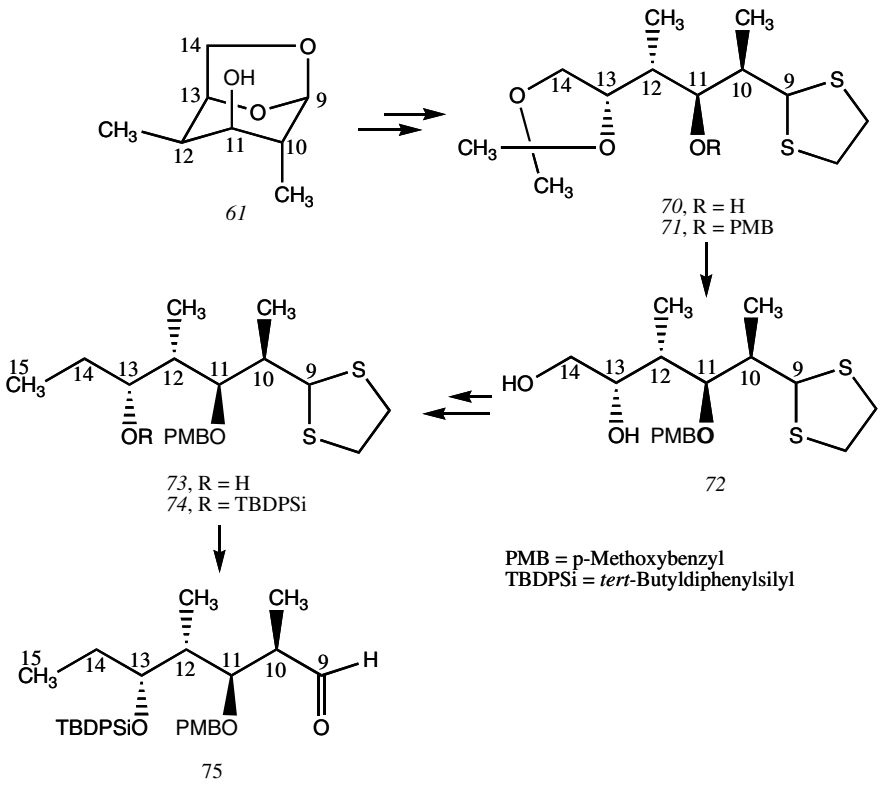


Fig. 13.12

give C11 alcohol *86*. Alkylation of *86* with *p*-methoxybenzyl chloride (PMB chloride) gave the corresponding C11 PMB–ether *87*. The selectively protected allyl glycoside *87* was converted by the known method [33] to the free monosaccharides *88*, which was reduced with $NaBH_4$ in aqueous ethanol to give, in quantitative yield, the *89*. The selective monobenzoylation of the primary hydroxyl group gave the C9 benzoate *90*. Mild acid hydrolysis removed the MOM protection group from the C12 hydroxyl group of benzoate *90* giving diol *91*. Silylation of the C12 and C13 hydroxyl groups with *tert*-butyldimethylsilyl triflate (TBSOTf) gave the bis TBS–ether *92* which was then debenzoylated giving the C9 primary alcohol *93*. Swern oxidation [29] of *93* gave the aldehyde *94* representing the C9-C15 segment of erythronolide A.

Next step in the synthesis of erythronolides A and B was the stereoselective addition of the two-carbon fragment, that will be the C7–C8 carbon segment of erythronolides A and B, to the C9–C15 segments of erythronolides A and B *94* and *75*, to give the C7–C15 segment that will be coupled with the C1–C6 segment to give the seco-acids of erythronolides A and B. This step of synthesis is particularly challenging since it involves creation of two chiral carbons, C8 and C9, in the acyclic

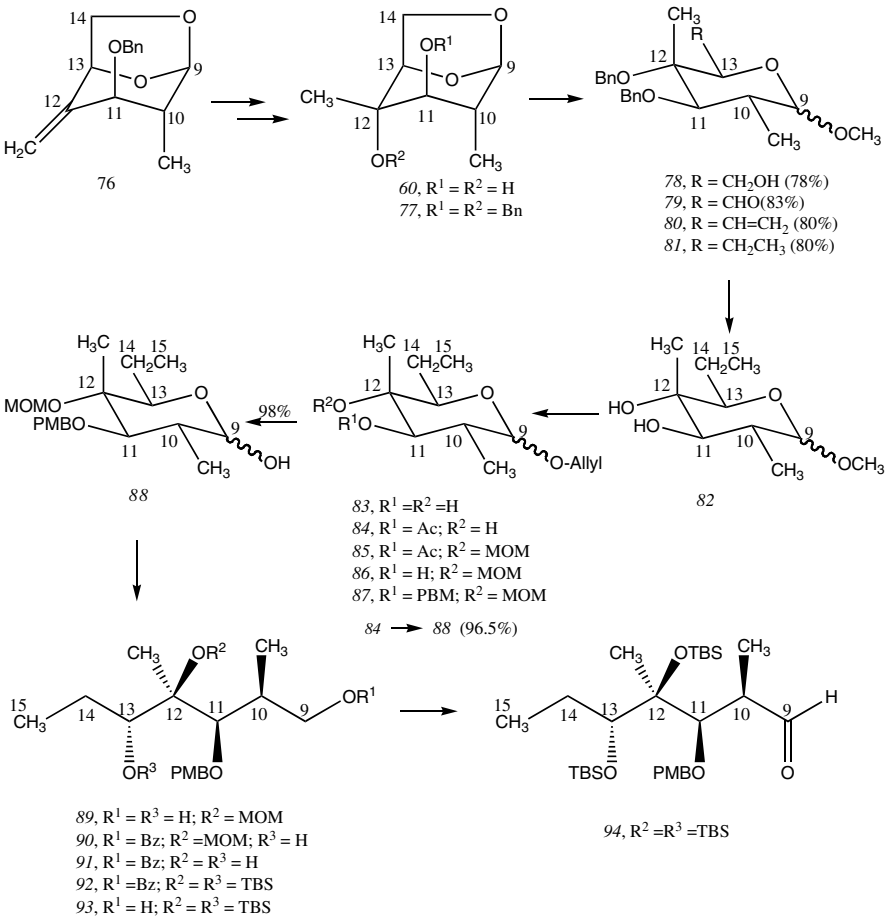


Fig. 13.13

substrates, eliminating thus the convenience of the stereocontrol of chemical transformations in pyranoside six-membered ring which was so useful in the synthesis of *94* and *75*.

Syn-selective aldol condensation of ethyl trityl ketone with aldehydes *76* and *95* gave the desired (8,9-*syn*-9,10-*anti*)-aldol *95* and *96* as the sole products (Fig. 13.14). Treatment of aldol *95* or *96* with DDQ in dichloromethane solution in the presence of molecular sieves (3 Å) [34] gave in 82–85% yield 9,11-*O*-*p*-methoxybenzylidene derivatives *97* or *98* as a single isomer at the methine carbon.

Reductive cleavage of the trityl ketones *97* or *98* with $LiBHEt_2$ [35] gave alcohols *99* and *100*, which were with Ph_2S_2–Bu_3P [36] readily converted to phenyl sulfides *101* and *102*. Oxidation of *101* and *102* with MCPBA (*m*-chloro-*p*-methylbenzoic

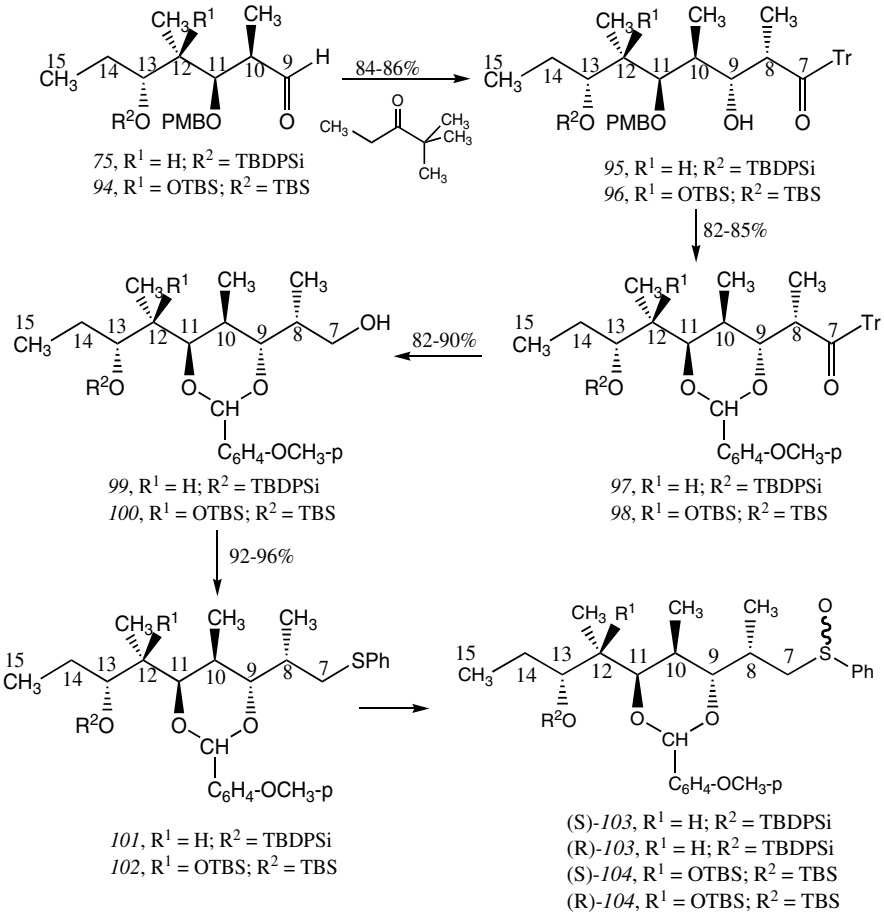


Fig. 13.14

acid) gave a mixture of epimeric sulfoxides: the (*S*)-epimers *103* and *104* and the (*R*)-epimers *103* and *104*, which can be easily separated by chromatography. Thus the C7–C15 segments of erythronolides A and B have been synthesized. The configuration at the sulfur atom has been determined on the basis of specific rotation of individual compounds [37].

The oxidation of phenyl sulfides *101* and *102* gave the (*S*)-isomer as the predominant product (65%) and the (*R*)-isomer as the minor product (33%). As it turned out, the (*S*)-isomer did not couple with the C1–C6 segment, whereas the (*R*)-isomer did give a mixture of two products in 7:1 ratio.

Since all attempts to change the selectivity of oxidation of sulfide *101* in favor of the desired (*R*)-isomer *103* failed, a smooth and convenient method of isomerization of sulfoxide (*S*)-isomer *103* was developed. Thus treatment of (*S*)-*103* with TFA (trifluoroacetic acid) in tetrahydrofuran-2,4,6-collidine at –78°C for 20 min followed

by addition of water gave a mixture of (*R*)-*103* and (*S*)-*103* isomers in 77:23% ratio.

In this way, oxidation, separation, and isomerization of the (*S*)-isomer of the sulfide *101* was converted in high overall yield to (*R*)-sulfoxide *103*. The reaction of (*R*)-*103* with ketone *58* gave two products with high selectivity. The main coupling product *107* was obtained in 88% yield. By similar treatment the isomeric sulfoxides (*R*)-*104* and (*S*)-*104* were separated and (*S*)-sulfoxide was isomerized into mixture of (*R*)- and (*S*)-*105* in 75:22% ratio (Fig. 13.15).

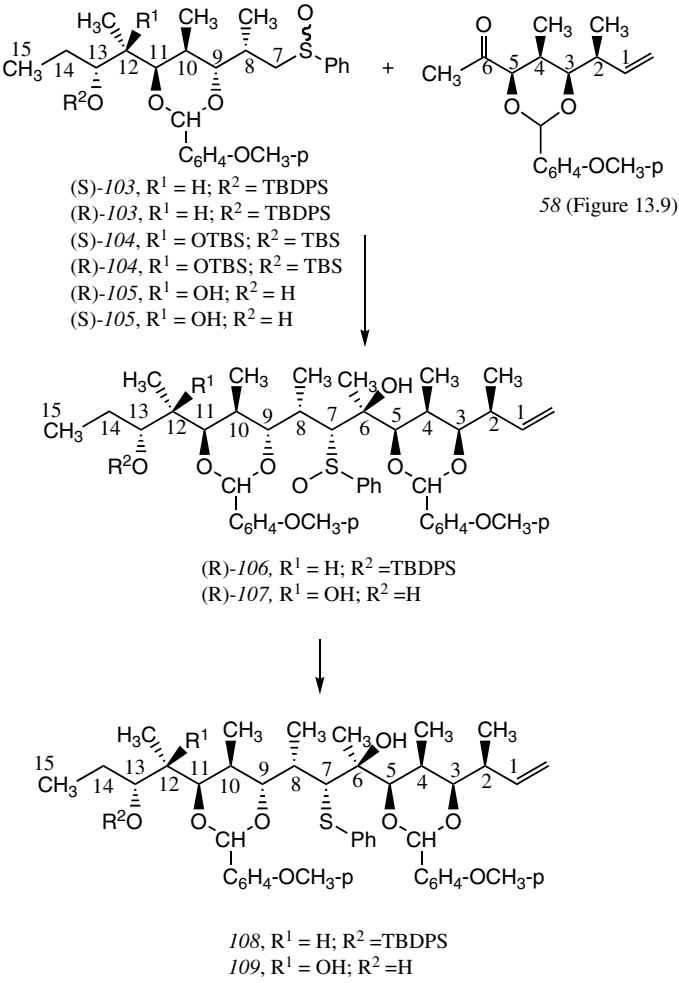


Fig. 13.15

The sulfoxide (*R*)-*104* was coupled to methyl ketone *58* in dry tetrahydrofuran at –60°C in the presence of lithium diisopropylamide (LDA). The coupling product

(*R*)-*106* was obtained, after chromatography, in 41% yield. The sulfoxide group in the coupling product (*R*)-*106* was immediately reduced with NaI/$Na_2S_2O_3$ in acetone since the sulfoxide is extremely labile. In this way the sulfide *108* was obtained in 84% yield.

An attempt to couple the anion of (*R*)-*104* sulfoxide (the C7–C15 segment of erythronolide A) with the methyl ketone *58* (the C1–C6 segment of erythronolides A and B) under the same reaction conditions failed. The conformational analysis of the (*R*)-*104* by using molecular space-filling models led to the conclusion that the absence of reaction may be due to the steric overcrowding caused on the one hand by the C8 methyl group and on the other hand by the 12-*O*-TBS group. Therefore, the (*R*)-*104* sulfoxide was desilylated with $(n\text{-Bu})_4NF{\cdot}3H_2O$, and the desilylated product (*R*)-*105* reacted with the methyl ketone *58* giving the adduct *107* in 45% yield. Since the reaction product was a complicated mixture containing unreacted sulfoxide *105*, excess methyl ketone *58*, and traces of two more products, the pure compound *107* was obtained in only 23% yield. The low yield was explained by instability of *107*. Deoxygenation [38] of *107* gave the corresponding sulfide *109*, which was desulfurated to *111* (Fig. 13.16), the precursor of the (9*S*)-dihydroerythronolide A seco-acid *113*. The olefin *111* was finally converted to the (9*S*)-dihydroerythronolide A seco-acid *113* by ozonization and oxidation with *m*-chloroperbenzoic acid (Fig. 13.16).

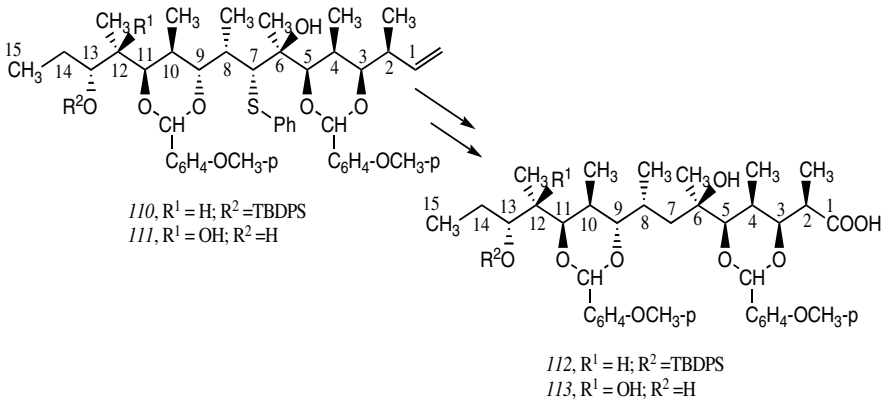
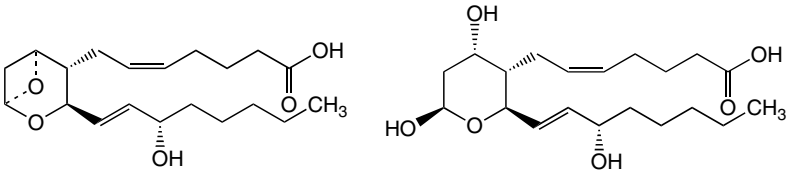


Fig. 13.16

Thromboxane B_2

Thromboxanes are members of the family of lipids known as eicosanoids. The two major thromboxanes are thromboxane A_2 (*114*) and thromboxane B_2 (*115*) (Fig. 13.17).

There are two reports dealing with stereoselective synthesis of thromboxane B_2 from D-glucose, one by Corey et al. [39] and the other by Hanessian et al. [40, 41]. Corey's approach [39] is shown in Fig. 13.18.

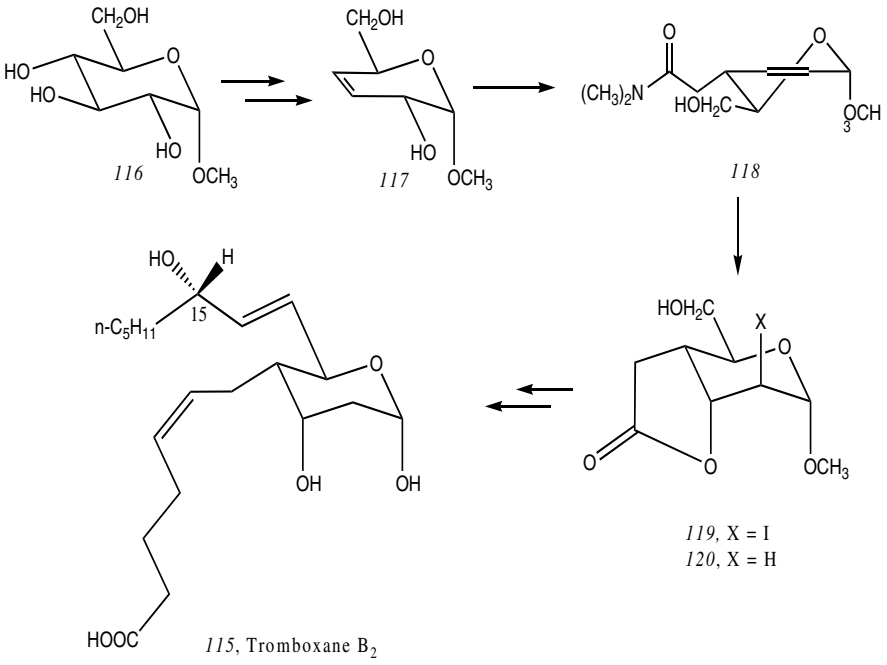


114, Tromboxane A_2

115, Tromboxane B_2

Fig. 13.17

The key intermediate in the thromboxane B_2 synthesis, the lactone *120*, was stereoselectively synthesized from D-glucose. Two key intermediates in this synthesis were the 3,4-unsaturated sugar *117,* obtained from D-glucose in three steps, and the stereospecific conversion of allylic alcohol *117* to the dimethylamide *118* by Claisen rearrangement [42, 43] in >75% yield. Treatment of *118* with iodine in tetrahydrofuran at 0°C afforded *119* in ca. 80% yield, which with tributyltin hydride [44] afforded, in quantitative yield, the hydroxy lactone *120* which was converted by standard methodology [44] to thromboxane B_2 *115* and its C15 epimer.



116 *117* *118*

119, X = I
120, X = H

115, Tromboxane B_2

Fig. 13.18

Hanessian [40, 41] used D-glucose to make methyl 4,6-*O*-benzylidine-3-*O*-benzoyl-2-deoxy-α-D-*ribo*-hexopyranoside *121* which was the actual starting material for the synthesis of thromboxane B_2 (Fig. 13.19). Debenzylidenation of *121*, blocking of the primary hydroxyl group with *t*-butyldiphenylsilyl chloride, followed by oxidation with DMSO in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and pyridinium trifluoroacetate afforded the C4 ulose *122* in 75% overall yield. Reaction of *122* with dimethyl (methoxycarbonyl) methylphosphonate in the presence of *tert*-butoxide gave a 1:1 mixture of *E*- and *Z*-isomers of methyl 3-*O*-benzoyl-6-*O*-*tert*-butyldiphenylsilyl)-2,4-dideoxy-*erythro*-hexopyranoside *123* and *124*. Hydrogenation of the *123* and *124* mixture with 20% palladium hydroxide on charcoal gave methyl 3-*O*-benzoyl-6-*O*-*tert*-butyldiphenyl–2,4-dideoxy-4-*C*-[(methoxycarbonyl) methyl]-α-D-*ribo*-hexopyranoside *125* in 70% yield. Although the authors do not discuss this, it is reasonable to assume that the catalytic hydrogenation gave the epimeric mixture of C4 methoxycarbonyl derivatives, since the next step which is lactonization, by treating the *125* first with potassium carbonate for 60 h at room temperature and then with Rexyn 102 (H^+), gave lactone *126* in only 51% yield. For the rest of the synthesis of thromboxane B_2 which is the synthesis of two side-chains the reader is referred to the cited reference since for their synthesis carbohydrates were not used.

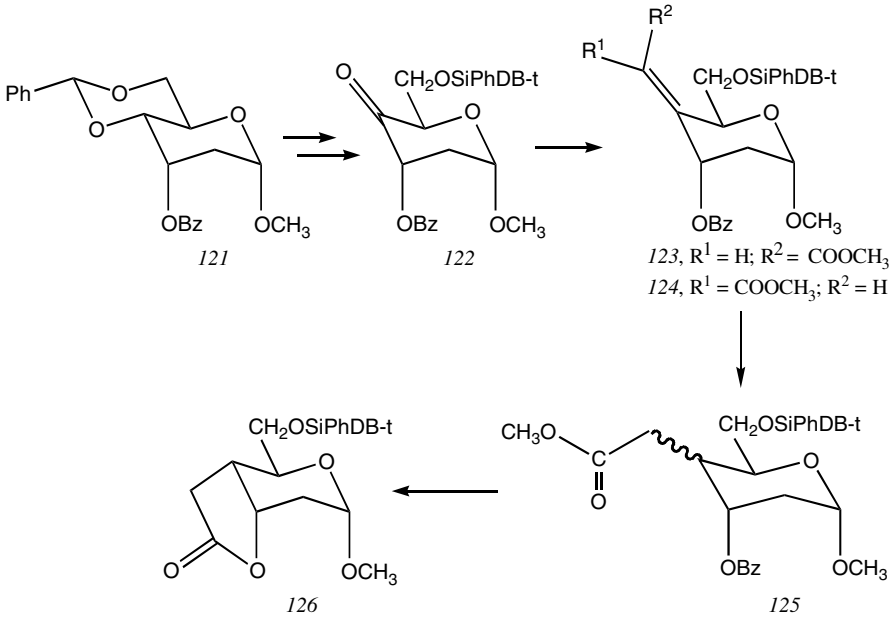
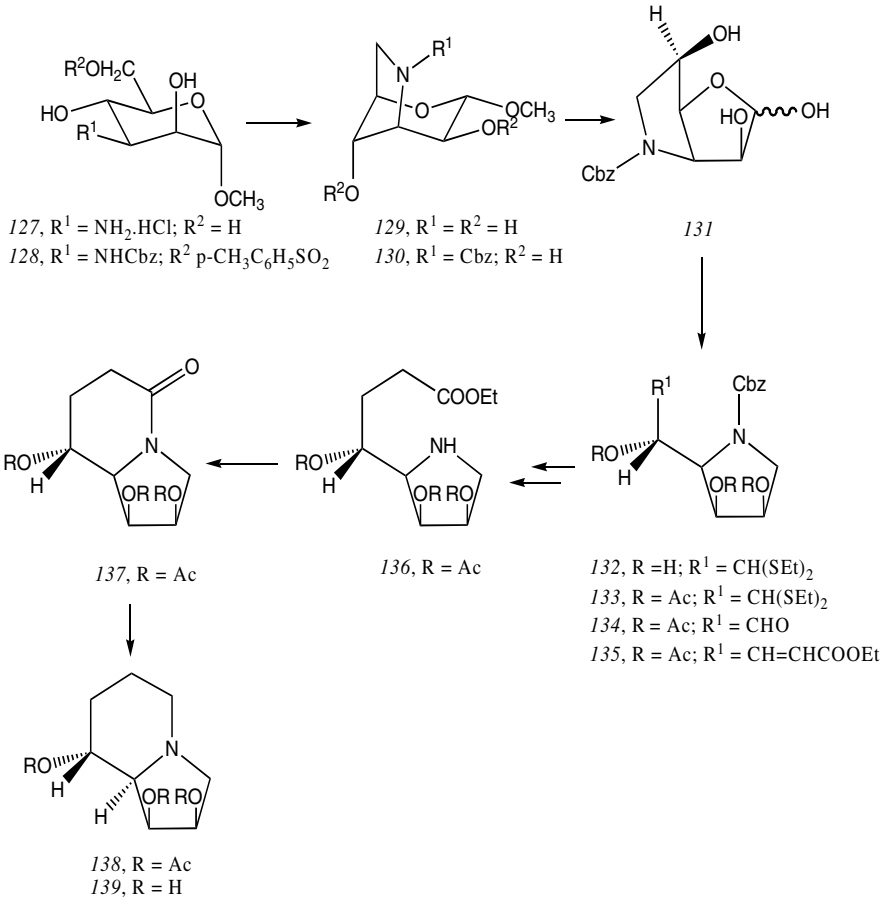


Fig. 13.19

Swainsonine

Swainsonine *139* (Fig. 13.20) is a very potent and specific α-mannosidase inhibitor and disrupts the processing of glycoproteins. This alkaloid has been originally isolated from the legume *Swainsona canescens* [45] but it has also been shown to be present in plants and other micro-organisms [46–49].

There are two syntheses of Swainsonine from carbohydrates published: one from 3-amino-3-deoxy-D-mannose derivative and the other from D-mannose. Synthesis of Swainsonine from 3-amino-3-deoxy-D-mannopyranose [50] was the first synthesis from a carbohydrate and starts from methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride *127* and is shown in Fig. 13.20.



127, $R^1 = NH_2.HCl$; $R^2 = H$
128, $R^1 = NHCbz$; R^2 p-$CH_3C_6H_5SO_2$

129, $R^1 = R^2 = H$
130, $R^1 = Cbz$; $R^2 = H$

131

132, R =H; $R^1 = CH(SEt)_2$
133, R = Ac; $R^1 = CH(SEt)_2$
134, R = Ac; $R^1 = CHO$
135, R = Ac; $R^1 = CH{=}CHCOOEt$

136, R = Ac

137, R = Ac

138, R = Ac
139, R = H

Fig. 13.20

N-Benzyloxycarbonylation of methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride *127* (obtained from D-glucose in 20–25% yield [51]) and selective tosylation gave the 6-*O*-*p*-toluenesulfonate *128* in 82% overall yield. Removal of carbobenzoxy group by catalytic hydrogenation followed by refluxing of the obtained free amine in ethanol containing sodium acetate gave the 3,6-epimine *129* in >52% overall yield (from *127*). *N*-Benzyloxycarbonylation of *129* followed by acid hydrolysis of *130* afforded the free 3,6-dideoxy-3,6-iminohexofuranose *131* in 52% yield.

The 3,6-iminohexose *131* was reacted with ethanethiol in the presence of hydrochloric acid to give the diethyl dithioacetal *132* in 74% yield. Acetylation of *132* followed by dethioacetalation of *133* with mercury (II) chloride–cadmium carbonate gave the *aldehydo*-hexose *134*. Reaction of *134* with ethoxycarbonylmethylenetriphenylphosphorane gave an olefin *135* that on hydrogenation with palladium on charcoal as the catalyst hydrogenated not only the double bond but also removed the carbobenzoxy group, giving initially the free amine *136* which reacted with ethoxycarbonyl group to give a 1:1 mixture of two products, one of which was the desired cyclic lactam *137*.

Reduction of the cyclic lactam *137* with borane·dimethylsulfide complex gave a mixture of two products, one of which was tri-*O*-acetylswainsonine *138*, which on deacetylation was converted to swainsonine *139*. This was the first reported total synthesis of swainsonine which was achieved in an overall yield of 2.7% from *127*.

The synthesis from D-mannose derivative *140* [52] is shown in Fig. 13.21. Benzyl α-D-mannopyranoside *140* was treated with *tert*-butyldiphenylsilyl chloride in the presence of imidazole and the product was acetonated with 9:1 acetone/2,2-dimethoxypropane in the presence of a trace of camphor sulfonic acid to give *141* in 86% yield. The oxidation of the C4 hydroxyl group of *141* with pyridinium chlorochromate (PCC) yielded a ketone which was reduced by sodium borohydride to give benzyl 6-*tert*-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-D-talopyranoside *142* in 88% overall yield. Esterification of *142* with trifluoromethanesulfonic anhydride/pyridine gave the D-talotriflate ester *143* which on treatment with sodium azide in *N,N*-dimethylformamide at room temperature gave the C4 azidomannose derivative *144* (second inversion of configuration at the C4 carbon) in 67% yield. Removal of the *tert*-butyldiphenylsilyl protection group with fluoride ion followed by oxidation of the C6 primary hydroxyl group with pyridinium chlorochromate gave an unstable aldehyde which was immediately reacted with formylmethylene triphenylphosphorane to give the azidoaldehyde *145*. Hydrogenation of azidoenal *145* in the presence of 10% palladium on charcoal in methanol led to the formation of the secondary amine *146*. Removal of the anomeric benzyl group in *146* is accomplished by hydrogenation in acetic acid using palladium black as the catalyst until all the secondary amine is consumed. This hydrogenation causes the hydrogenolysis of the benzyl group to form a lactol which is in equilibrium with an open-chain aminoaldehyde which undergoes reductive amination to form the isopropylidene swainsonine *147*. Finally, the isopropylidene group was removed with trifluoroacetic acid–D_2O giving swainsonine *139*.

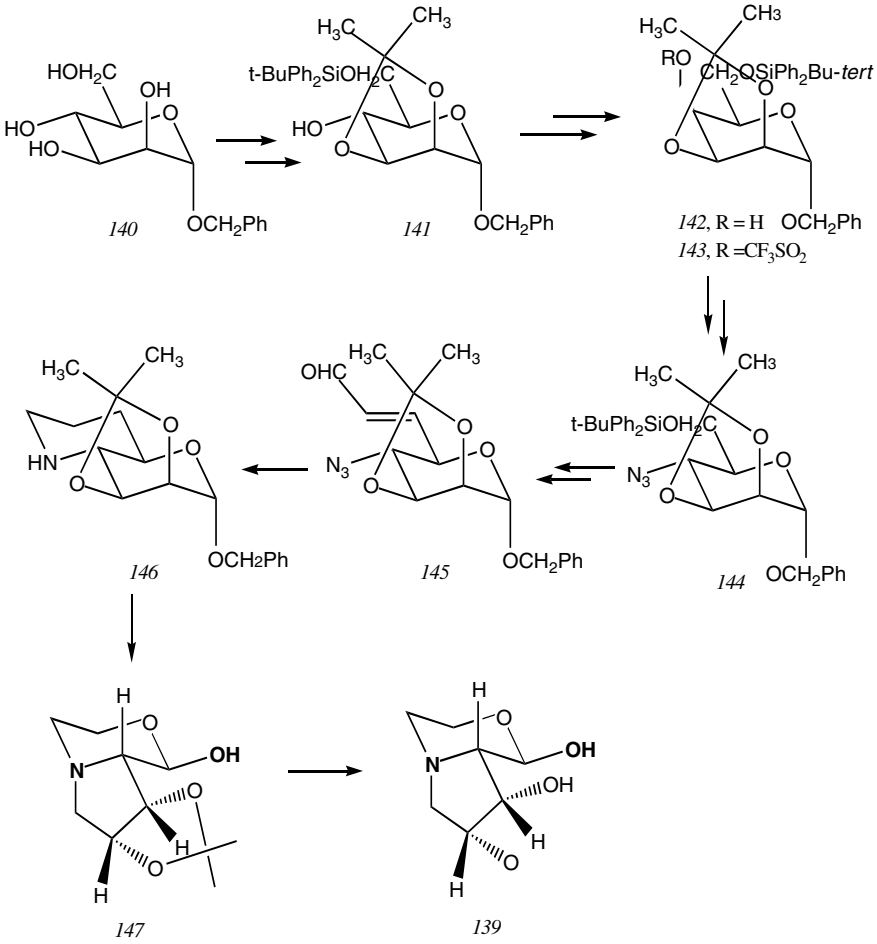


Fig. 13.21

Biotin

Biotin, also known as vitamin H or B7, is important in the catalysis of essential metabolic reactions. It is used in cell growth, the synthesis of fatty acids, and metabolism of fats and amino acids in gluconeogenesis. It also plays a role in the citric acid cycle and is helpful in maintaining a steady blood sugar level.

There are two stereoselective synthesis of biotin from carbohydrates reported in the literature. The first one uses D-mannose as the starting material [53] and the second one the 1,6-anhydro-β-D-glucose [54]. Use of the conformationally rigid 1,6-anhydro-β-D-glucose *62* was essential for the successful, stereoselective synthesis of biotin. The synthetic scheme is shown in Fig. 13.22.

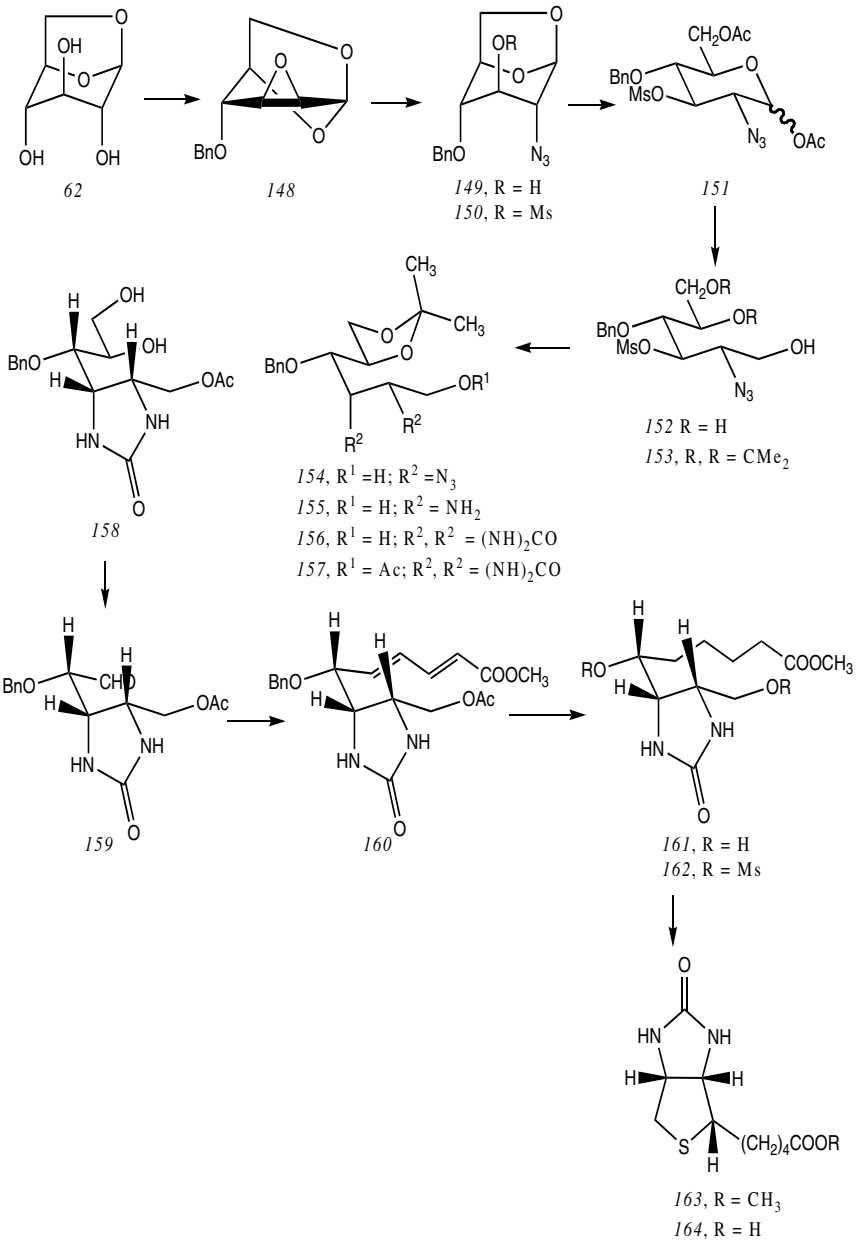

62
148
149, R = H
150, R = Ms
151
152 R = H
153, R, R = CMe2
154, R1 =H; R2 =N3
155, R1 = H; R2 = NH2
156, R1 = H; R2, R2 = (NH)2CO
157, R1 = Ac; R2, R2 = (NH)2CO
158
159
160
161, R = H
162, R = Ms
163, R = CH3
164, R = H

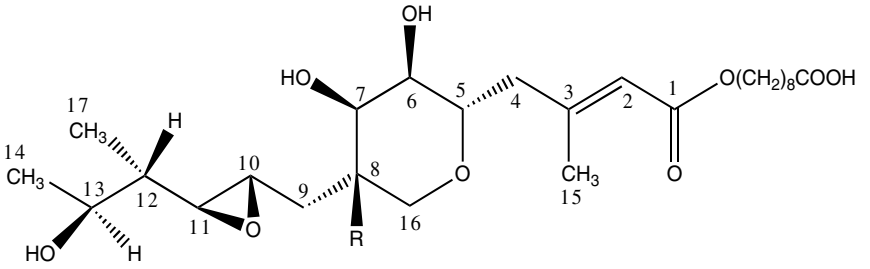
Fig. 13.22

Opening of the oxirane ring of 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose *148* with sodium azide and ammonium chloride in 4:1 2-methoxyethanol–water for 22 h at 120°C gave, in 85% yield, 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-glucopyranose *149*. Esterification of the C3 hydroxyl group with methanesulfonyl anhydride in pyridine gave the corresponding C3 mesylate *150*. The acetolysis of *150* with acetic anhydride–4% BF_3 etherate for 3 h at room temperature gave, in 95% yield, an anomeric mixture of diacetates *151* in the α:β ratio 8:3. Solvolysis of *151* with 1% HCl in methanol for 16 h at room temperature followed by reduction with $NaBH_4$ in the presence of boric acid in ethanol at 0–5°C gave the triol *152*. Treatment of the triol *152* with 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate for 15 h at room temperature gave the 5,6-isopropylidene derivative *153*. The C3 azido group was introduced by treating the *153* with sodium azide in DMF. The selective hydrogenation [55] of the diazide *154* in the presence of benzyl group was effected by using Lindlar catalyst in ethanol whereby the diamine *155* was obtained in quantitative yield. Reaction of *155* with phosgene ($COCl_2$) in carbon tetrachloride and aqueous Na_2CO_3 at 0–5°C gave ureide *156*. Acetylation of *156* with acetic anhydride–pyridine followed by deisopropylidenation of monoacetate *157* in 80% aqueous acetic acid for 3.5 h at 70°C gave 5,6-diol *158*. $NaIO_4$ oxidation of *158* in 50% aqueous ethanol for 1 h at room temperature gave aldehyde *159* and subsequent reaction of *159* with [3-(carbomethoxy)-2-propen-1-ylidene]triphenylphosphorane [53, 56] in dichloromethane at room temperature gave unsaturated ester *160*. Hydrogenation of *160* using 10% Pd–C in methanol and subsequent deacetylation by CH_3ONa in methanol gave diol ester *161*. Methanesulfonylation of *161* with 15 equivalents of methanesulfonyl chloride in pyridine-dichloroethane for 15 h at –10°C gave dimesylate *162*, which was treated without purification with large excess of Na_2S in *N,N*-dimethylformamide for 3 h at 100°C to give the biotin methyl ester *163*, which was hydrolyzed to (+)-biotin *164*.

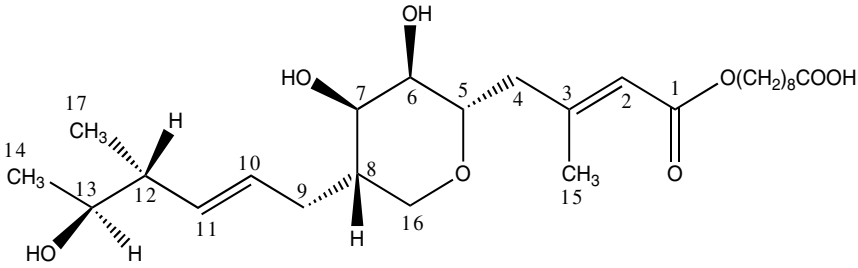
Pseudomonic Acid C

Pseudomonic acids are a small group of antibiotics of unique structure. Three representatives of this family are Pseudomonic acid A (*165*), Pseudomonic acid B (*166*), and Pseudomonic acid C (*167*) (Fig. 13.23). They are produced by the strain *Pseudomonas fluorescens* [57–59].

The synthesis of (+)-methyl pseudomonate C from D-xylose [60] *169* is shown in Figs. 13.24 and 13.25. The D-xylopyranose *169* was converted into cyanide *171* as previously described [61] by acetylation of *168*, conversion of the tetraacetate *169* into tri-*O*-acetyl-α-D-xylopyranosyl chloride *170*, and by displacing the obtained chloride with potassium cyanide. The base-catalyzed hydrolysis of 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl cyanide *171* followed by esterification of the obtained carboxylic acid with methanol in the presence of HCl (70%) gave the corresponding



165, R = H, Pseudomonic acid A
166, R = OH, Pseudomonic acid B



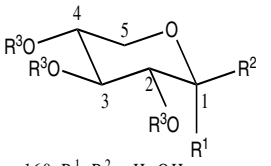
167, Pseudomonic acid C

Fig. 13.23

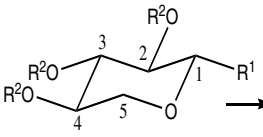
methyl ester *172*. By reduction of *172* with lithium aluminum hydride the methoxycarbonyl group was converted to hydroxymethyl group and the reaction of *173* with PhCH $(OCH_3)_2$ in the presence of *p*-toluenesulfonic acid gave the benzylidene acetal *174* (85%). Tosylation of *174* with *p*-toluenesulfonyl chloride in pyridine (70%) and the treatment of the 3,4-di-tosyl derivative *175* with sodium methoxide in chloroform at room temperature gave in quantitative yield the 3,4-epoxide *176* which represented the precursor of the central ring structure of pseudomonic acid C.

The basic assumption in this synthetic approach was that the rigid tricyclic epoxide *176* will undergo a regiospecific oxirane ring opening with a suitable allylic anion at the C4 carbon. Hence the synthesis of the left side chain of pseudomonic acid C is undertaken starting from D-glucose and is described in Scheme 2 of Fig. 13.24. D-Glucose *177* is converted to methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside *178* as described elsewhere [62]. The inversion of the configuration at the C2 carbon of *178* was effected by oxidation of *178* with DCCI–DMSO–TFA–pyridine at room temperature, and then by reduction of the corresponding 2-ulose with lithium aluminum hydride in ether at 0°C whereby methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-allopyranoside *179* was obtained in 95% yield. The C2 hydroxyl group was then blocked with *tert*-butyldimethylsilyl protection group by reacting *179* with *tert*-butyldimethylsilyl chloride in

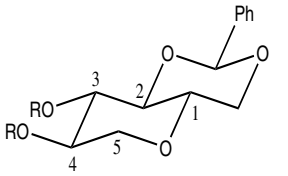
Scheme 1



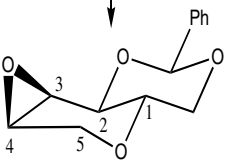
168, R^1, R^2 = H, OH
169, R^1, R^2 = H, OAc; R^3 = Ac
170, R^1 = Cl; R^2 = H; R^3 = Ac



171, R^1 = CN; R^2 = Ac
172, R^1 = $COOCH_3$; R^2 = H
173, R^1 = CH_2OH; R^2 = H



174, R = H
175, R = Ts



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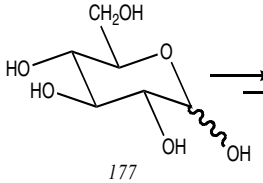
Scheme 2



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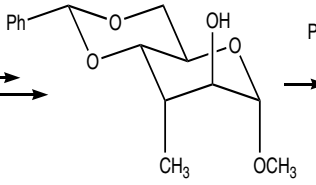

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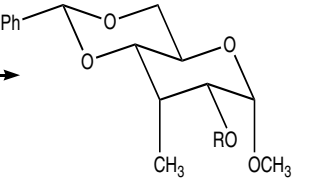
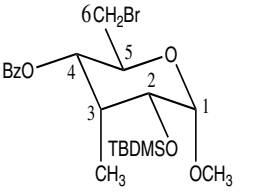


179, R = H
180, R = TBDMS



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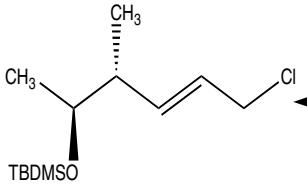

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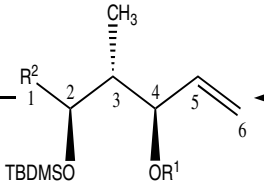
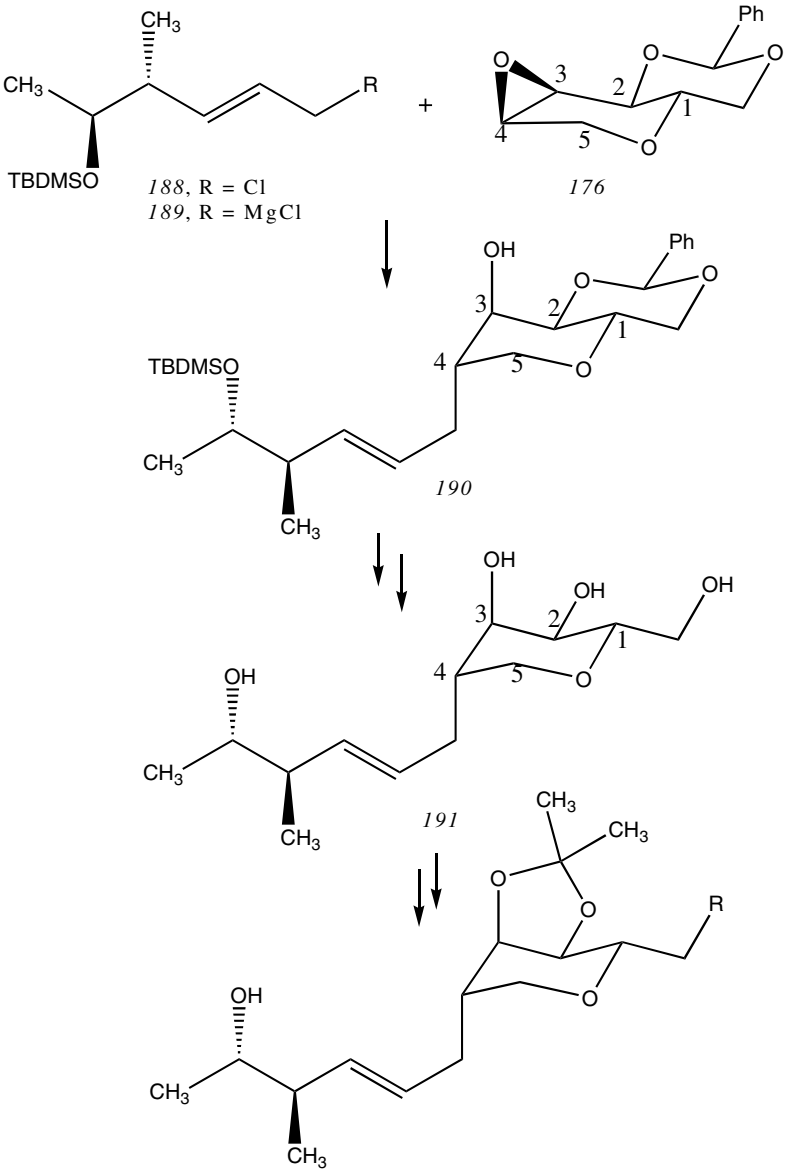


182, R^1 = Bz; R^2 = CHO
183, R^1 = Bz; R^2 = CH_2OH
184, R^1 = Bz; R^2 = CH_2OTs
185, R^1 = Bz; R^2 = I
186, R^1 =Bz; R^2 = CH_3
187, R^1 = H; R^2 = CH_3

Fig. 13.24



188, R = Cl
189, R = MgCl

176

190

191

192, R = OH
193, R = OTs
194, R = CN
195, R = $COCH_3$

Fig. 13.25

N,N-dimethylformamide in the presence of imidazole giving *180* in 83% yield. Debenzylidenation of *180* with *N*-bromosuccinimide in CCl_4 at 80°C in the presence of barium carbonate to neutralize the released HBr gave methyl 4-*O*-benzoyl-6-bromo-3,6-dideoxy-2-*tert*-butyldimethylsilyl-3-*C*-methyl-α-D-allopyranoside *181* in 75% yield. Reductive β-elimination of bromide *181* with activated zinc [63, 64] [acid-washed zinc (100 equivalents) in 9:1 propanol–water at 80°C for 30 min] gave *182*. This was the key reaction in this synthesis.

The copper-catalyzed (CuI) oxirane ring opening [65] of *176* with Grignard reagent *189* (Fig. 13.25) which was made from *188* (two equivalents, THF, –30°C, 10 min) afforded the expected product *190* in 43% yield. The important aspect of this reaction is that it involves the "nonrearranged" allylic Grignard reagent and gives the E double bond. These two features were critical but not obvious (for discussion of these features, see [66–69]).

Selective tosylation of *191* followed by isopropylidenation gave *193* which on treatment with potassium cyanide produced *194*. The ketone *195* was obtained from cyanide in 84% yield by treatment of the cyanide *194* with trimethylaluminum in the presence of $Ni(acac)_2$ [70] followed by acid-catalyzed hydrolysis (Fig. 13.25).

The epoxidation of the double bond of *195* with MCPBA in dichloromethane at room temperature gave a 2:3 mixture of epimeric epoxides *196* and *197*, one of which was identical with the natural product (Fig. 13.26).

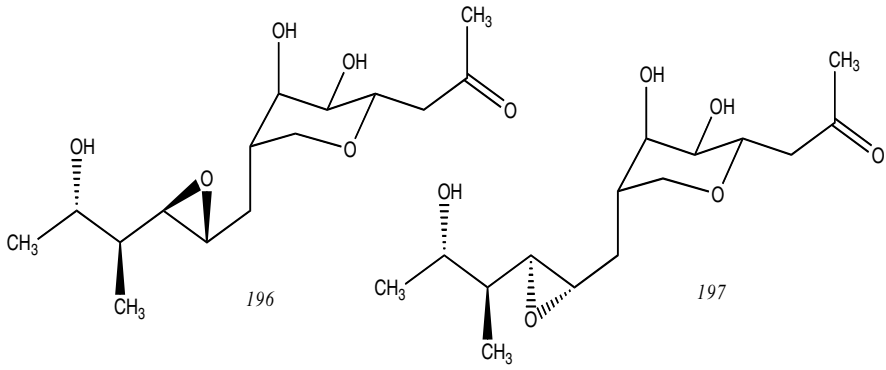


Fig. 13.26

Elongation of the right side chain was essentially performed as already described [71, 72].

A different approach for the synthesis of pseudomonic acid C was taken by Keck et al. [73]. The adopted strategy was to synthesize the pseudomonic acid C from three fragments: the lower left appendage *198*, the central tetrahydropyran segment *199*, and the upper right appendage. Stereochemically there were many challenges: the synthesis of the C2–C3 and the C10–C11 double bonds (pseudomonic acid C numbering) with E-stereochemistry and the stereoselective C1 and C4 alkylation (lyxose numbering). The stereochemistry of the C2 and the C3 hydroxyl groups (lyxose numbering) is identical with the C6 and the C7 hydroxyl groups of

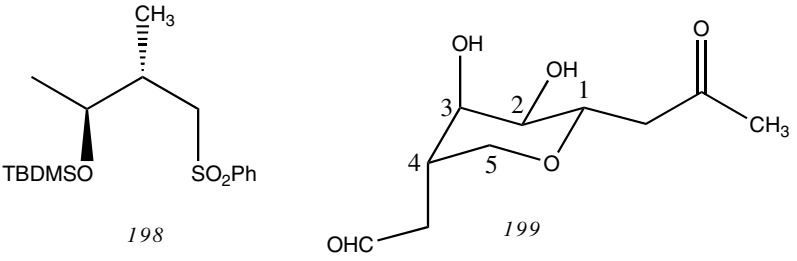


Fig. 13.27

pseudomonic acid A. The key to the strategy adopted was the recognition of the structure *199* (Fig. 13.27) as that of a highly modified L-lyxose *200* (Fig. 13.28). The authors assumed that the incorporation of a latent acetaldehyde at C4 (lyxose numbering) could be accomplished by free radical allylation with allyltri-*N*-butylstannane [74] and the incorporation of a latent acetone moiety at C1 (lyxose numbering) could be similarly accomplished with either allyl- or methallyl-tri-*n*-butylstannane.

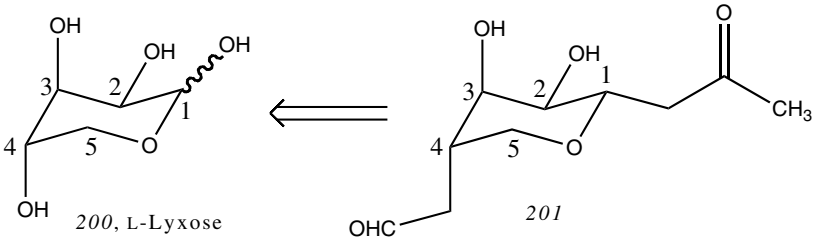


Fig. 13.28

The first task was to differentiate the C2 and C3 hydroxyl groups from C1 and C4 hydroxyl group of L-lyxose *200* and then to differentiate the C1 and the C4 hydroxyl groups from each other. Furthermore, it was desirable to make the β face of the molecule sterically as crowded as possible so that the free radical C-C bond formation at the C4 carbon takes place from the α face. Differentiation of the C2 and the C3 hydroxyl groups from the C4 hydroxyl group could very well be accomplished by acetonation because the former are in *cis* orientation, whereas the C3 and the C4 hydroxyl groups are *trans* oriented (diaxial). However, it was well known that the free lyxose preferentially forms 1,2-acetonide from its furanoside form [75]. Therefore, the anomeric hydroxyl group of L-lyxose had to be blocked first. That was accomplished by reacting L-lyxose *200* with benzyl alcohol (benzyl alcohol was used as the solvent and reagent and *p*-toluenesulfonic acid was used as the catalyst). The anomeric mixture of benzyl glycosides *201* was then treated with dimethoxypropane and *p*-toluenesulfonic acid in acetone giving the desired acetonide *202* in 85% overall yield from L-lyxose (Fig. 13.29).

The introduction of allyl residue (the latent acetaldehyde) at the C4 carbon was accomplished by using free radical methodology reported earlier [74], namely the C4 hydroxyl group was first converted to the phenyl thionocarbonate *203* by treating *202* with methyl lithium and phenyl chlorothionocarbonate in anhydrous ether at –80°C (90% yield). This was then subjected to photolysis, in toluene solution, with 450-W Hanovia lamp ($\lambda > 300$ nm) in the presence of allyl-tri-*n*-butylstannane for 65 h at 23°C, whereby the desired C4-allyl adduct *204* was obtained in 80% yield. Stereochemical control of this free radical reaction was the result of approach of allyl-tri-*n*-butylstannane to the less hindered α face of a C4 free radical derived from *203*, leading to the desired α allyl derivative *204* (the β face of the molecule was inaccessible due to the bulky 2,3-isopropylidene group). The C4-allyl derivative *204* was converted to the C4 acetaldehydo compound *205* by treating the *204* with OsO_4 and $NaIO_4$. The acetaldehyde was then reduced with sodium borohydride in ethanol to primary alcohol *206*, which was with methanesulfonyl chloride in pyridine converted to the mesylate *207*. Treatment of *207* first with sodium thiophenoxide (PhSNa) in *N,N*-dimethylformamide and then the oxidation of the phenylthio derivative *208* with peracetic acid in dichloromethane and buffered with $NaHCO_3$ gave the desired phenyl sulfone *209* (Fig. 13.29).

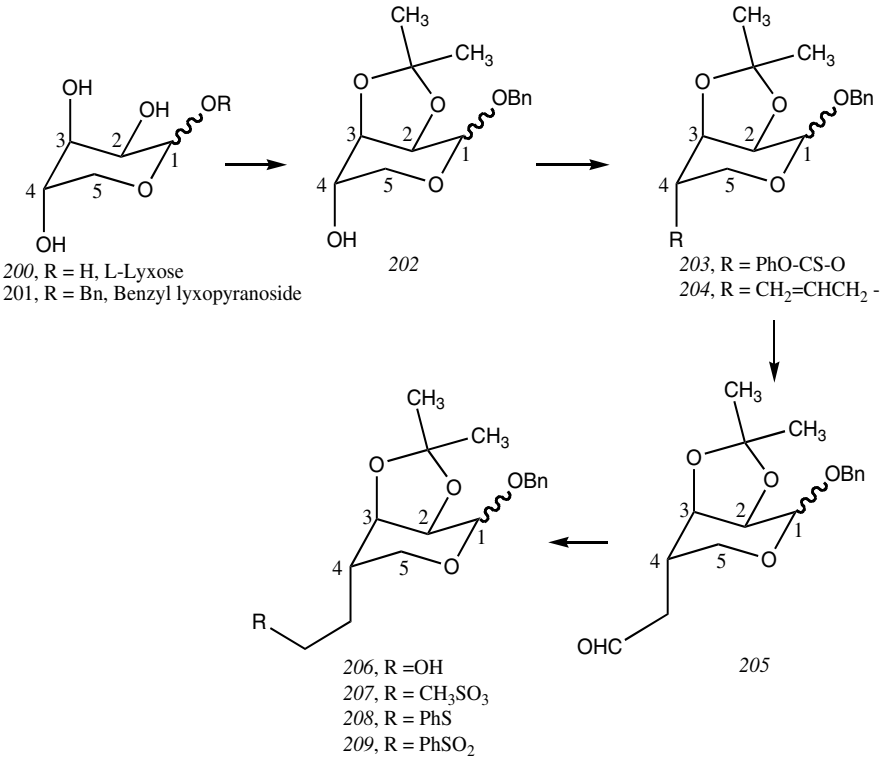


Fig. 13.29

The synthesis of the lower left appendage was accomplished from commercially available (*S*)–(+)-ethyl-3-hydroxybutanoate *210* as shown in Fig. 13.30 (the numbering is pseudomonic acid C numbering). The methylation of dianion obtained by treating *211* with lithium diisopropylamide and methyl iodide according to the gen-

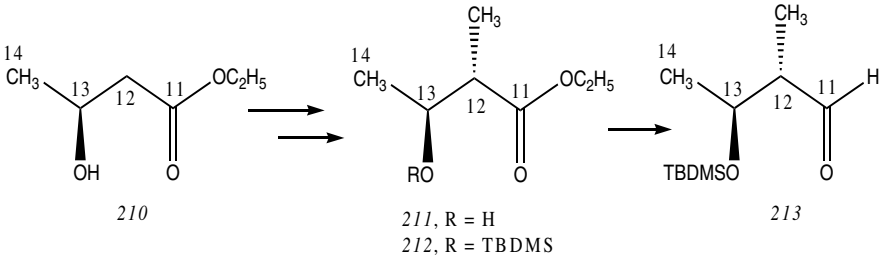


Fig. 13.30

eral protocol by Frater [76, 77] gave stereoselectively the C12 methyl derivative *211*. After blocking the C13 hydroxyl group of *211* with *tert*-butyldimethylsilyl group, the ester group of *212* was reduced with diisobutylaluminum hydride in toluene to aldehyde *213* in 87% yield.

The condensation of phenyl sulfone *209* (Fig. 13.29) with the aldehyde *213* (Fig. 13.30) proceeded smoothly to afford *214* (Fig. 13.31). The C12 hydroxyl group was activated by mesylation and the obtained *215* was subjected to reductive elimination which resulted in *trans* C11–C12 double bond formation and simultaneous debenzylation giving *216* (Fig. 13.31).

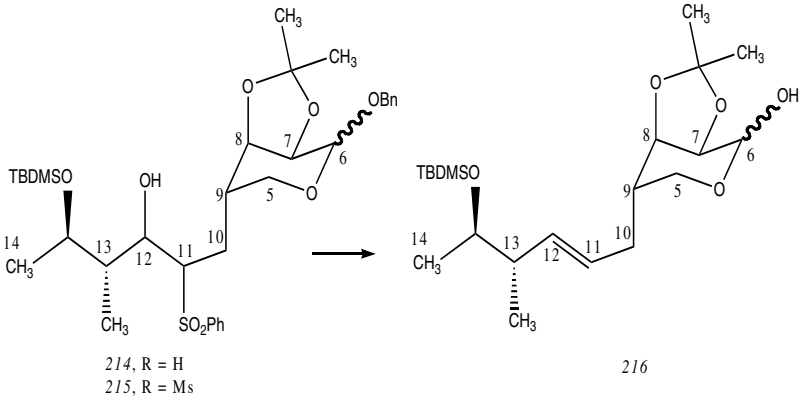


Fig. 13.31

The upper right appendage was then introduced by using Wittig reaction with stabilized ylide $(Ph)_3P{=}CHCOCH_3$ which was shown with free furanoses to produce *C*-glycoside in high yields [71, 78]. Thus methyl ketone *217* was obtained (Fig. 13.32).

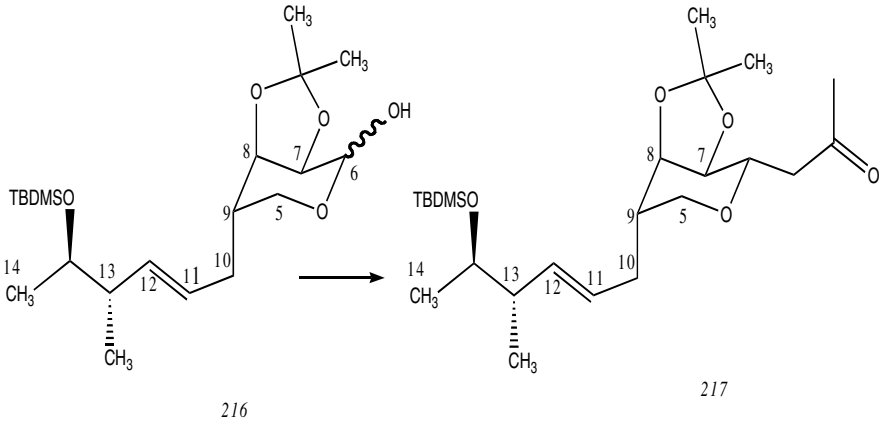


Fig. 13.32

Horner–Wadsworth–Emmons reaction of *217* with (methyldimethylphosphono) acetate *218* [79–83] gave in 75% yield *219* in which the C2, C3 double bond had *E* configuration. Deacetonation of *219* with 85% acetic acid in tetrahydrofuran (THF) gave finally, in 93% yield, the methyl ester of pseudomonic acid *220* (Fig. 13.33).

A much more convergent strategy for the synthesis of (+)-pseudomonic acid C was published by the same authors [84] in 1989. The approach is outlined in Fig. 13.34 and is based on the assumption that a suitably functionalized allyl fragment *221,* with X = SPh, SOPh, or SO_2Ph, should couple via an addition–fragmentation mechanism with a carbon-centered radical derived from iodide *222*.

Preparation of iodide *222* started from the known benzyl 2,3-*O*-isopropylidene-L-lyxopyranoside *202* (mixture of anomers) [73]. Mesylation of *202* with methanesulfonyl chloride in pyridine at room temperature gave the corresponding 4-mesylate *225* that on treatment with 1:1 1 N HCl/THF gave diol *226* in 87% overall yield from *202*. Epoxide formation to yield *227* was accomplished in 96% yield by treating *226* with potassium *tert*-butoxide in THF at room temperature for 30 min. Reaction of *227* with 2.0 N HI in acetone at reflux followed by isopropylidenation of the resulting 4-iodo-2,3-diol *228* with dimethoxy 2-propane and *p*-toluenesulfonic acid in acetone gave the desired iodide *222* in 85% overall yield from the epoxide *227* (Fig. 13.35).

Synthesis of sulfone *232* is shown in Fig. 13.36. It starts from the readily available ester *229* which was homologated to allyl alcohol *230* in one-pot operation (65% yield) via reduction and in situ Horner–Wadsworth–Emmons reaction according to the Takacs protocol [85], followed by the addition of 2.1 equivalents of $(i\text{-Bu})_2AlH$ and workup. The conversion of allyl alcohol *230* to sulfone *231* was initiated by [2, 3] sigmatropic rearrangement of the derived sulfenate (1.0 equivalent of *n*-BuLi, THF, 0°C; PhSCl) via the general procedure of Evans [86] followed by oxidation with oxone [87] to give the desired sulfone *232* as ca. 2:1 mixture of epimers (the configurations of epimeric sulfones were not assigned but they are separable).

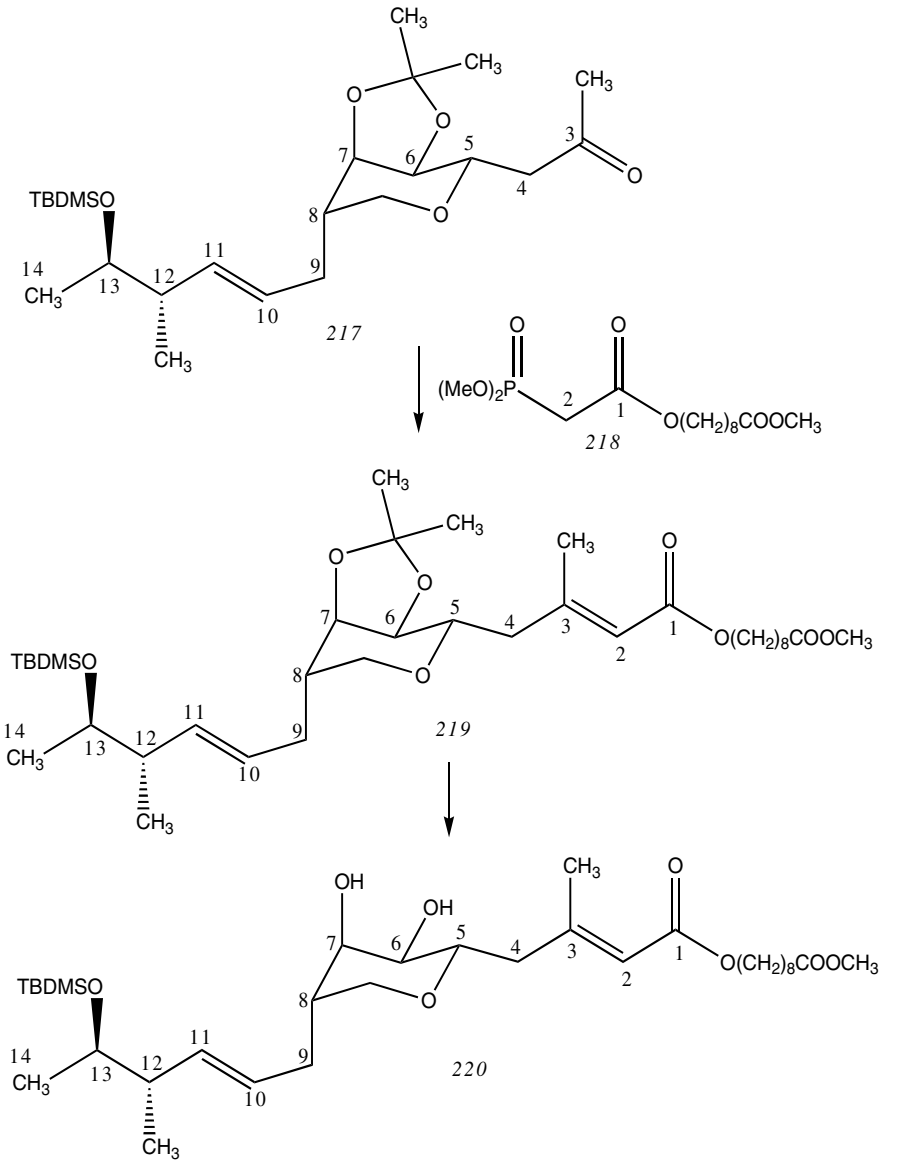


Fig. 13.33

The coupling of *232* and *222* was accomplished in 74% yield by slow addition (syringe pump) of a THF solution of sulfone *232* and hexabutylditin to an irradiated (450-W Hanovia lamp using Pyrex filter) THF solution of iodide *222* and hexabutylditin under argon atmosphere. The addition of the upper right appendage was accomplished as previously described [73].

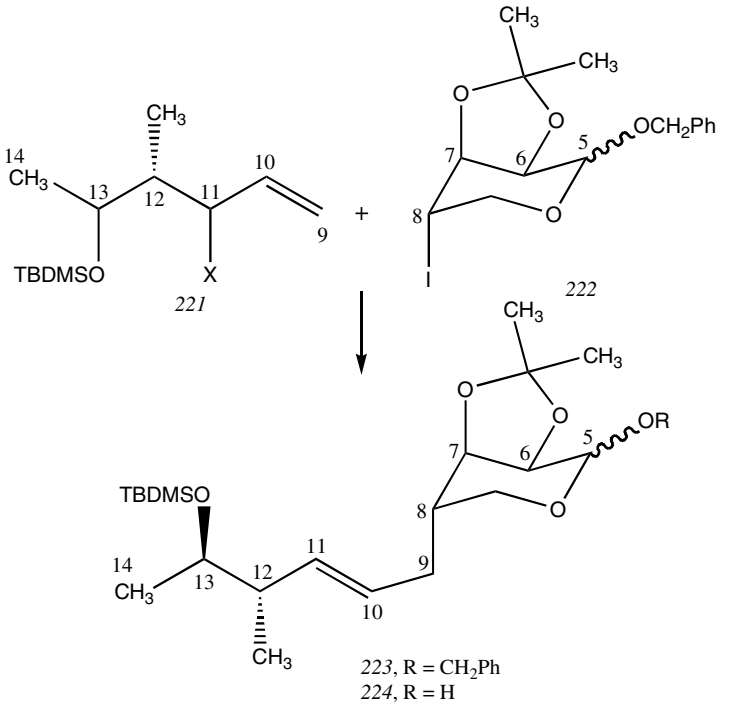


Fig. 13.34

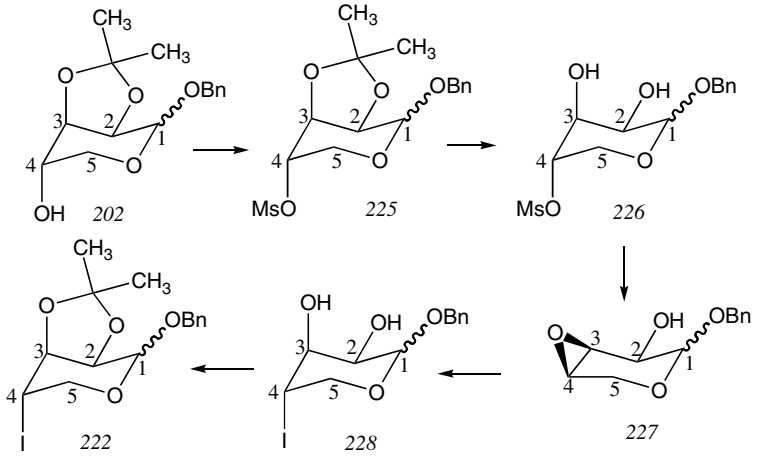


Fig. 13.35

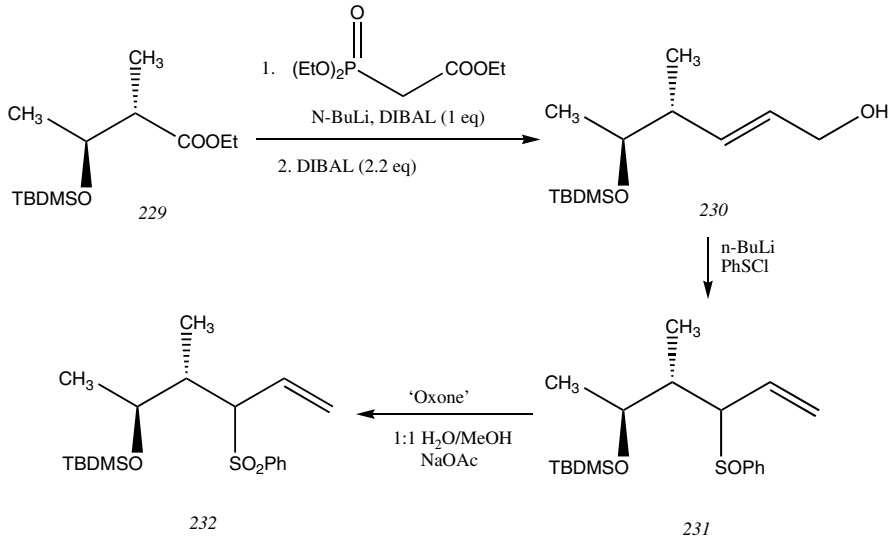
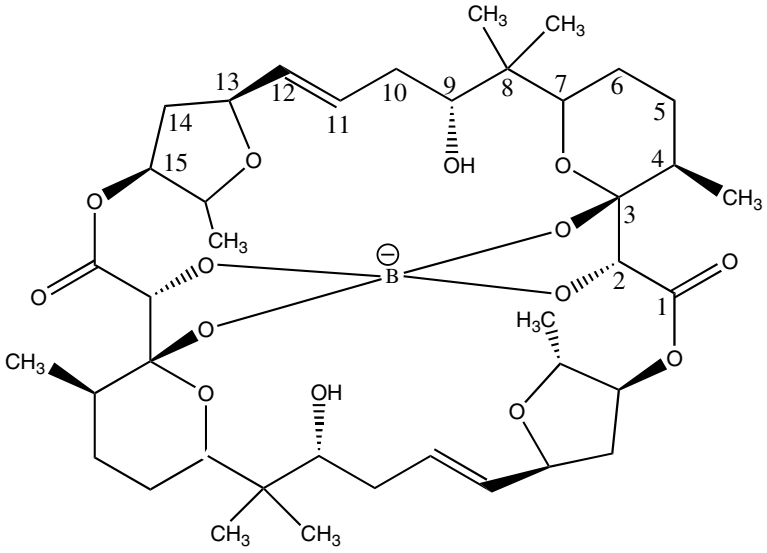


Fig. 13.36

Aplasmomycin

Aplasmomycin *233* (Fig. 13.37) is a boron-containing antibiotic from a marine-derived strain *Streptomyces griseus* that exhibits activity against gram-positive



233

Fig. 13.37

bacteria and Plasmodia [88]. It belongs to the family of borate-bridged antibiotics of which the boromycin was the first known member [89]. Aplasmomycin has C_2 symmetry indicating that it is composed of two identical subunits.

Corey et al. [90, 91] approached the synthesis of aplasmomycin by constructing the precursors corresponding to the C3–C10 fragment *235* starting from (+)-pulegone and the C11–C17 fragment *234* starting from D-mannose shown in Fig. 13.38.

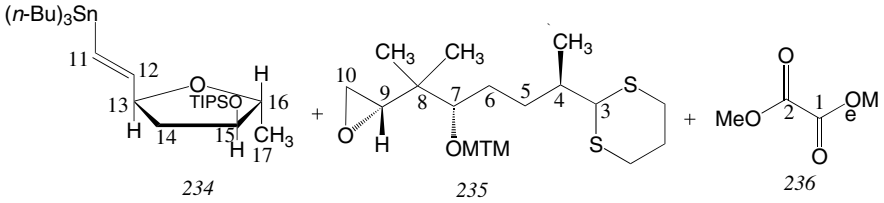


Fig. 13.38

We will describe the synthesis of fragment *234* since this is the part of the synthesis of aplasmomycin where carbohydrate is used as a chiral synthon. We will not describe the synthesis of fragment *235* since it is made from (+)-pulegone and the carbon atoms C1 and C2 are made from dimethyloxalate *236*. We will, however, describe the coupling of fragments *234, 235*, and *236* into C1–C17 fragment of aplasmomycin as well as the coupling of the obtained two identical fragments into macrocyclic lactone aplasmomycin (Fig. 13.39).

The synthesis of the C11–C16 fragment *234* started from 2,3:5,6-di-*O*-isopropylidene-D-mannose *237* which can be easily prepared from D-mannose with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid in acetone. Reaction of *237* with methyllithium in ether at –40°C for 1 h and then at 0°C for 6 h proceeded stereospecifically to give 99% yield of the diol *238*. The *238* was converted to tetrahydrofuran derivative *239* via tosylation in pyridine of the methyl carbinol *238*. The selective hydrolysis of the 5,6-*O*-isopropylidene group was accomplished in 90% yield at 60% conversion with (30:2:1 methanol–water–12 N HCl) at 4°C for 24 h to give the 5,6-diol *240*. Oxidation of 5,6-diol *240* with equimolar amounts of $NaIO_4$ and sodium bicarbonate in aqueous solution at 0°C gave the C5 aldehyde *241* which with bromotrichloromethane and tris (dimethylamino) phosphine at –50°C for 2 h, at –10°C for 1 h, at 5°C for 0.5 h was converted to dichloroolefin *242* in 75% yield. Reaction of *242* with *n*-butyllithium in THF at –78°C for 1.5 h afforded acetylene *243* in 99% yield. The 2,3-*O*-isopropylidene group was cleaved with 10:1 methanol–4 N HCl at 23°C for 24 h giving the 2,3-diol *244* in 92% yield. Selective silylation of the C2 hydroxyl group was accomplished with triisopropylsilyl chloride in the presence of 4-(dimethylamino)pyridine in dichloromethane at 0°C for 18 h. The C3 hydroxyl group of the C2 TIPS ether *245* was then converted to the triflate ester *246* by treating *245* with trifluoromethanesulfonic anhydride in presence of pyridine in dichloromethane solution at –10°C for 5 h (85% yield). Displacement of triflate by iodide using tetra-*n*-butylammonium iodide in benzene at

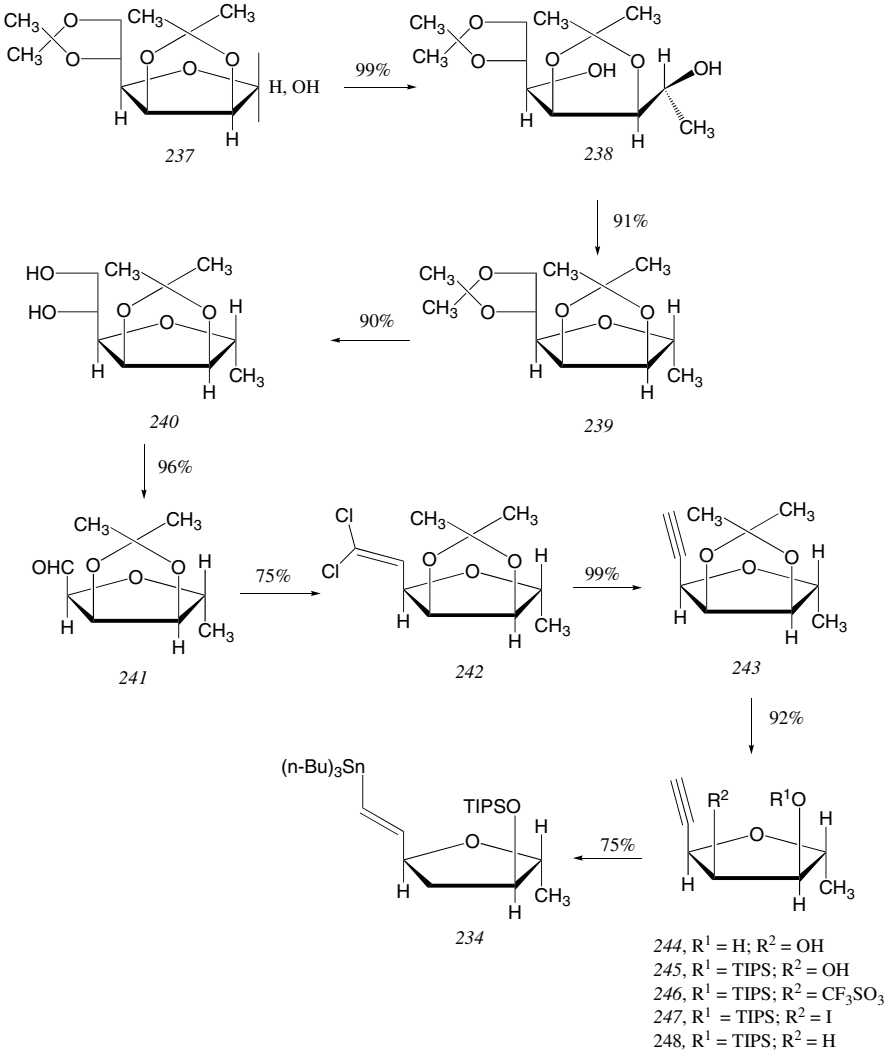


Fig. 13.39

reflux for 2 h gave 3-deoxy-3-iodo derivative *247* in 94% yield, which with sodium borohydride and tri-*n*-butyltin chloride in ethanol under sunlamp irradiation gave 3-deoxy derivative *248* in 85% yield. Heating of *248* with tri-*n*-butyltin hydride and azobis(isobutyronitrile) at 90°C for 3 h gave the *trans*-vinylstannane *234* in 75% yield (Fig. 13.40).

The coupling of the vinylstannane fragment *234* with the epoxide *235* (prepared from (+)-pulegone) to form *250* corresponding to the C3–C17 segment of aplasmomycin was carried out as follows (Fig. 13.41). Reaction of *234* with

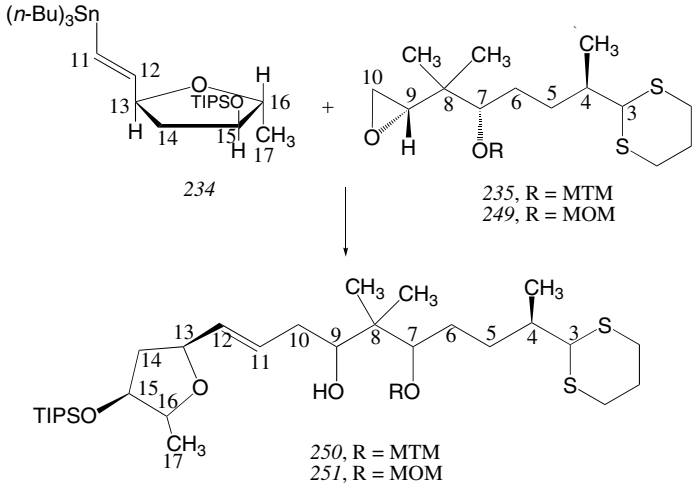


Fig. 13.40

n-butyllithium in THF at –78°C for 1 h and –50°C for 1.5 h produced the lithium reagent corresponding to *234* which was sequentially treated with cuprous cyanide at –78°C for 1 h and the epoxide *235* (at –35°C for 2 h, –25°C for 24 h, and –15°C for 24 h) to give the coupling product *250* in 75% yield. In strictly analogous way the epoxide MOM ether *249* was coupled to *234* to give *251* as the product. The intermediates *250* and *251* that correspond to the C3–C17 segment of the two identical C1–C17 molecular subunits were finally coupled to aplasmomycin using two different synthetic routes.

The MTM ether *250* was converted to C7, C9 bisilylated derivative *252* in 85% overall yield by the following sequence: silylation of the C9 hydroxyl group with *tert*-butyldimethyl-silyl triflate-2,6-lutidine [92], followed by the cleavage of MTM ether using silver nitrate-2,6-lutidine in 4:1 THF–water at room temperature for 2 h [93] and silylation of the C7 hydroxyl group with *tert*-butyldimethylsilyl triflate-2,6-lutidine, as described above for the C9 hydroxyl group (Fig. 13.40). Metalation of the dithiane *254* was accomplished using *n*-butyllithium

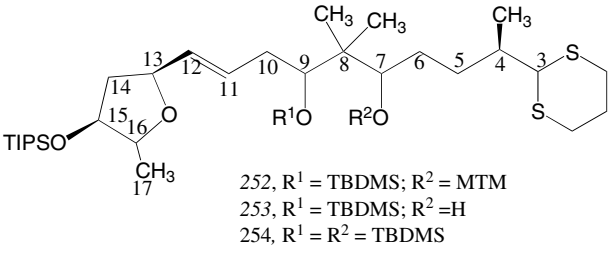


Fig. 13.41

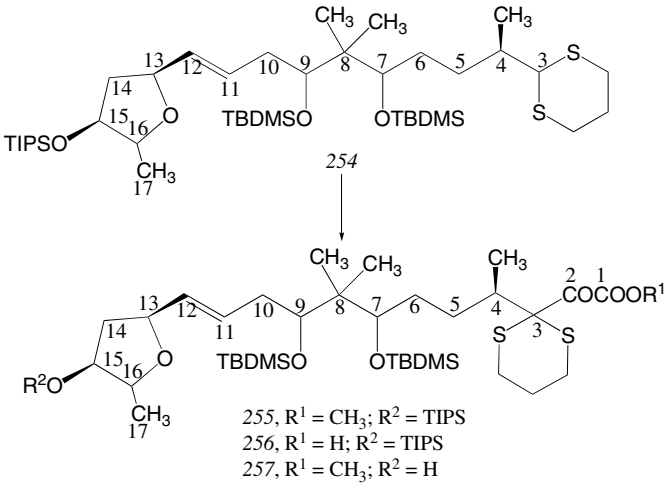


Fig. 13.42

and tetramethylenediamine in THF at –30°C for 2 h to give lithium reagent which was cooled to –78°C, treated with hexamethylphosphorictriamide (HMPA), and then reacted with dimethyl oxalate in THF at –78°C for 30 min, –50°C (30 min), –30°C (30 min), and 0°C (15 min), whereby a ketoester *255* was obtained in 96% yield (Fig. 13.41). Conversion of ketoester *255* to the corresponding keto acid *256* is accomplished in quantitative yield by heating *255* with lithium iodide and 2,6-lutidine in dimethylformamide at 75°C for 18 h. The transformation of *256* to hydroxy ketoester *257* in 97% yield was accomplished by treating *256* with tetra-*n*-butylammonium fluoride in THF at room temperature for 30 min (Fig. 13.42). Reaction of *256* with *257* in the presence of *N,N*-bis[2-oxo3-oxazolinodyl]

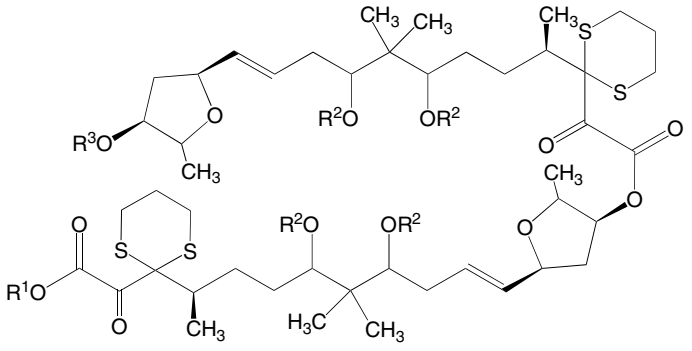
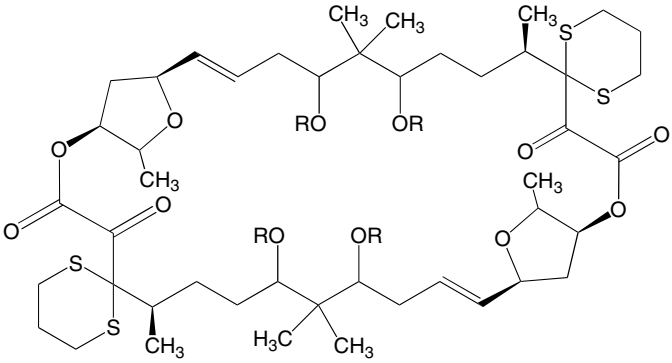
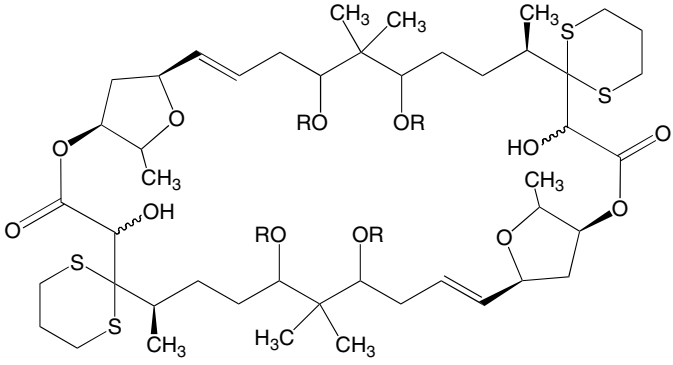


Fig. 13.43



261, R = TBDMS

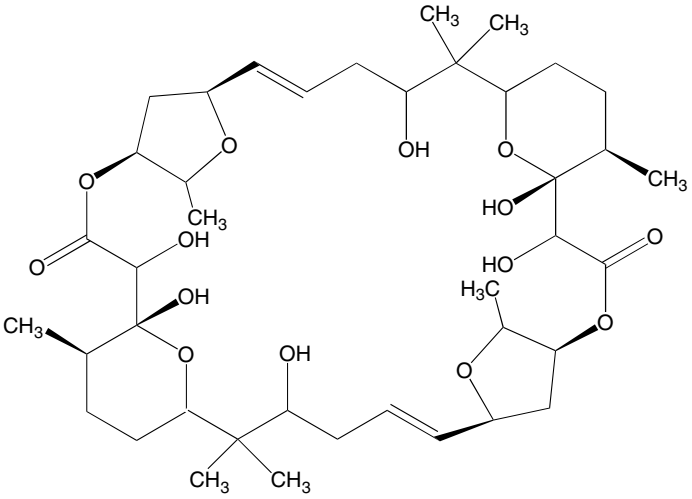


262

262, R = TBDMS
263, R = H

Fig. 13.44

phosphorodiamidic chloride (BOP chloride) [94] and triethylamine in dichloromethane at room temperature for 2 h gave the ester *258* in 98% yield (Fig. 13.43). Cyclization of *258* to the macrocycle *261* was accomplished in the following way. Methyl ester cleavage of *258* was effected in 96% yield with lithium iodide-2,6-lutidine in DMF affording the acid *259*, as previously described; the triisopropylsilyl group of *259* was cleaved in 96% yield with tetra-*n*-butylammonium fluoride in THF at room temperature giving the hydroxy acid *260* and the lactonization of the resulting hydroxy acid *260* in the presence of BOP chloride, as previously described, gave *261* in 71% yield. Reduction of two α-keto groups with sodium borohydride in ethanol at –20°C gave the epimeric mixture of diols *262* in 88% yield. Desilylation of *262* with 7:3 acetonitrile–48% HCl at –10°C for 20 min and at room temperature



264

Fig. 13.45

for 2 h gave tetrol *263* in 95% yield. Finally, two dithioacetal groups were removed by treating 263 with mercuric chloride–calcium carbonate in 4:1 acetonitrile–water at room temperature for 9 h giving in 94% yield the "deboro" aplasmomycin *264,* obtained as a mixture of diastereomers differing in configuration at the carbon atom α to the lactone carbonyls (Figs. 13.44 and 13.45).

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Chapter 14
Carbohydrate-Based Antibiotics

Antibiotics are most often defined as bacterial or fungal products that inhibit the growth of other microorganisms. There is a broader definition proposed [1] that defines antibiotics as chemical compounds derived from or produced by living organisms which are capable, in small concentration, to inhibit the life processes of microorganisms. This definition, however, does not include a vast number of chemically modified (semisynthetic) and synthetic antibiotics. Antibiotics are isolated from bacteria, yeast, molds, algae, and lichens, as well as from higher plants.

There are many antibiotics isolated from microorganisms and even many more chemically modified natural antibiotics (so-called semisynthetic antibiotics) that have been made in order to increase their activity, improve their selectivity, and decrease their side effects. Chemically, antibiotics belong to many classes of organic compounds, but here we are only interested in antibiotics that are carbohydrate related, i.e., in antibiotics that contain carbohydrates as a part of their structure.

There are generally three types of antibiotics that are carbohydrate related. First group consists of antibiotics in which the carbohydrates are glycosidically linked to cyclitols or aminocyclitols (aminoglycoside antibiotics), such as streptomycin, kanamycin, amikacin. Second group of antibiotics consists of oligosaccharides in which the individual monosaccharides are linked both glycosidically and also with one or more orthoester linkages (orthosomycins). Finally, carbohydrates may be glycosidically linked to noncarbohydrate part of an antibiotic, as is the case in macrolide antibiotics erythromycins, nystatin, etc., and many other classes of carbohydrate-related antibiotics.

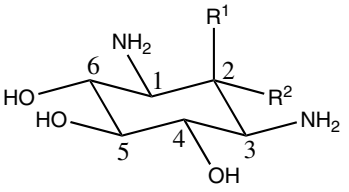
Aminoglycoside Antibiotics

Aminoglycoside antibiotics represent a group of carbohydrate-based antibiotics that consist of an aminocyclitol such as streptamine (*1*), 2-deoxy-streptamine (*2*), epistreptamine (the C2 epimer of streptamine) (*3*), streptidine (*4*), or 2-deoxy-streptidine (*5*) to which various amino sugars are glycosidically linked (Fig. 14.1). For example, streptomycin, kanamycin, neomycin, amikacin, gentamicin,

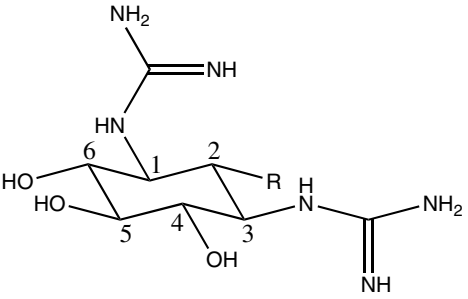
M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_14,

tobramycin, netilmicin are some of the members of this family of antibiotics. There are two good reviews on aminoglycoside antibiotics [2, 3].

Streptomycin and dihydrostreptomycin are effective against tuberculosis; neomycins are used locally for skin infections and orally for bacterial enterocolitis; paromomycins are used orally against amoebic dysentery and bacterial enterocolitis; kanamycins are highly effective against *Proteus* infections; gentamicin, sisomicin, netilmicin, tobramycin, and dibekacin are indispensable for treatment of severe *Pseudomonas* infections; amikacin is valuable for severe infections caused by gram-negative microorganisms resistant to tobramycin, dibekacin, sisomicin, netilmicin, gentamicin, and kanamycin, as well as spectinomycin which is active against penicillin-resistant gonorrhea.



1, R^1 = H; R^2 = OH, Streptamine
2, R^1 = R^2 = H , 2-Deoxystreptamine
3, R^1 = OH; R^2 = H, Epistreptamine



4, R = OH, Streptidine
5, R = H, 2-Deoxystreptidine

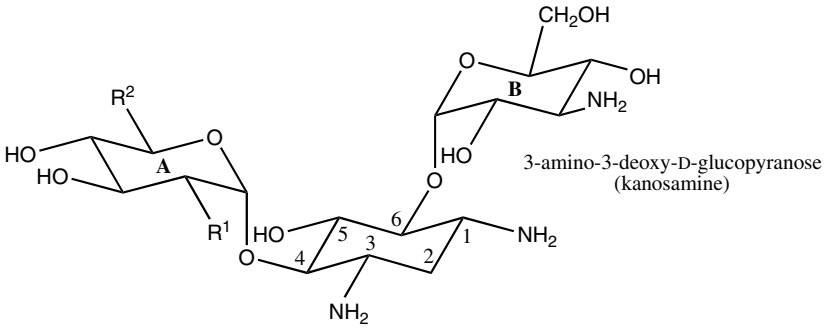
Fig. 14.1

It is interesting to note that aminoglycoside antibiotics are predominantly bactericidal (not bacteriostatic).

Kanamycin

Kanamycin was isolated from fermentation broth of *Streptomyces kanamyceticus* [4] by absorption on Amberlite IRC-50 and elution with 1 N HCl. It has been shown to be the mixture of three components: kanamycin A, kanamycin B, and kanamycin C.

From a study of products of acid hydrolysis of kanamycin A, Cron et al. [5] proposed the structure of kanamycin A to be a trisaccharide-like molecule consisting of two amino sugar moieties glycosidically linked to 2-deoxystreptamine. One hexosamine unit was determined to be 6-amino-6-deoxy-D-glucopyranose [6], and the other hexosamine, named kanosamine, was determined to be 3-amino-3-deoxy-D-glucopyranose [7] and proposal was made that the two hexosamine residues were attached to 2-deoxystreptamine at the C4 and C6 hydroxyl groups. Independent studies on the structure of kanamycin A were conducted by Ogawa et al. [8], and



2-Deoxystreptamine
6, $R^1 = OH$; $R^2 = CH_2NH_2$, Kanamyciin A
7, $R^1 = NH_2$; $R^2 = CH_2NH_2$, Kanamycin B
8, $R^1 = NH_2$; $R^2 = CH_2OH$, Kanamycin C

Fig. 14.2

the absolute structure of kanamycin A was determined by Umezawa et al. [9]. The crystal structure of kanamycin A was determined by Koyama et al. [10] and is shown in the Fig. 14.2 (structure *6*). The absolute sequence of the C4–C6 substitution was first determined by Hitchens and Rinehart [11] from their studies on neomycin.

The structure of kanamycin B (*7*) was determined by Ito et al. [12] and the structure of kanamycin C (*8*) by Murase [13].

The structural difference of kanamycins A, B, and C is in the structure of the amino sugar **A** that is α-glycosidically linked to the C4 hydroxyl group of streptamine. In kanamycin A (*6*), this sugar is 6-amino-6-deoxy-D-glucopyranose ($R^1 = OH$, $R^2 = CH_2NH_2$); in kanamycin B (*7*), it is 2, 6-diamino-2,6-dideoxy-D-glucopyranose ($R^1 = NH_2$; $R^2 = CH_2NH_2$); and in kanamycin C (*8*), it is 2-amino-2-deoxy-D-glucopyranose ($R^1 = NH_2$; $R^2 = CH_2OH$) (Fig. 12.2).

Umezawa et al. have reported the first total synthesis of both kanamycin B [14, 15] and kanamycin C [16, 17].

Kanamycin shows inhibitory activity against a wide range of gram-positive and gram-negative bacteria. It has been found to be a particularly valuable chemotherapeutic agent for the treatment of serious gram-negative infections and streptomycin-resistant tuberculosis. The ototoxicity and nephrotoxicity, which are typical side effects of aminoglycoside antibiotics, are much less associated with kanamycin. The mechanism of action of kanamycin, as well as of all other aminoglycoside antibiotics, is the inhibition of protein synthesis at the prokaryotic ribosomal level.

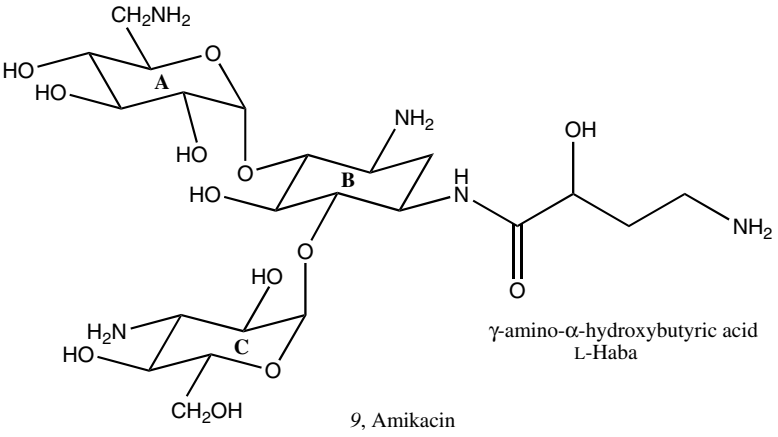
After the first observation of Umezawa et al. [18] that the inactivation of kanamycin by kanamycin-resistant organism is due to O-phosphorylation of kanamycin, it was established that the major inactivation mechanisms of aminoglycoside-resistant organisms are N-acetylation [19–24], O-phosphorylation [25–30], and O-adenylylation [31–33].

One approach to prevent inactivation of aminoglycoside antibiotics was to either remove the functional group that is target for inactivating enzymes or to modify the aminoglycoside antibiotic in such a way to inhibit the inactivating enzyme either at the binding site or at the active site toward the aminoglycoside molecule. Using the first approach, Umezawa et al. [34–36] have synthesized the 3′-deoxykanamycin A and 3′,4′-diedoxykanamycin B, since it has been shown that the 3′-hydroxyl group of aminoglycoside antibiotics is an important target site of phosphorylating enzymes. The modified aminoglycoside antibiotics have shown to be active against kanamycin resistant *Escherichia coli* and *Pseudomonas* species. The product of the second approach is semisynthetic antibiotic amikacin.

Amikacin

Amikacin is a semisynthetic derivative of kanamycin A. It has higher activity against clinical isolates of *Enterobacter* species, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* than gentamicin sulfate, kanamycin sulfate, or tobramycin, and no major toxicity has been observed with normal doses.

Amikacin is kanamycin A that has the C3 amino group of 2-deoxystreptamine (ring B) acylated by L-haba (L-4-amino-2-hydroxybutyric acid) as shown in Fig. 14.3.



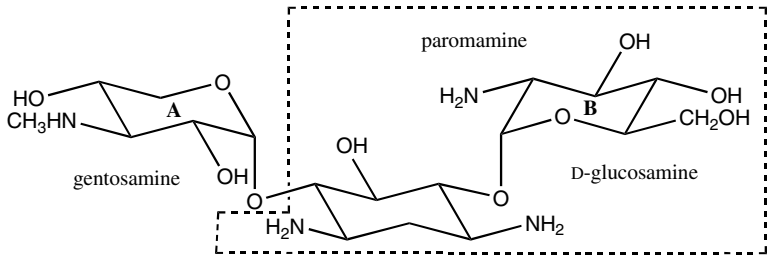
9, Amikacin

Fig. 14.3

The synthesis of amikacin was accomplished by Kawaguchi et al. [37].

Gentamicins

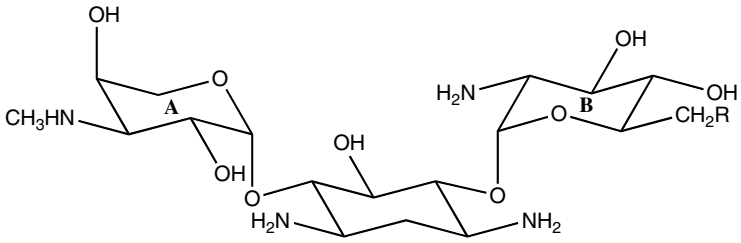
Weinstein et al. [38] have isolated gentamicins, an antibiotic complex produced by *Micromonospora purpurea* and *M. echinospora* or variants thereof. Gentamicins A, A_1, A_2, A_3, A_4; gentamicins B and B_1; and gentamicins C, C_1, C_2, C_{2b} have been identified in this complex mixture. The structure of gentamicin A (Fig. 14.4) has been elucidated by Maehr and Schaffner [39, 40].



10, Gentamicin A

Fig. 14.4

The structures of gentamicins A_1, A_3, A_4 [41] and of gentamicin A_2 [42] are shown in Figs. 14.4 and 14.5.



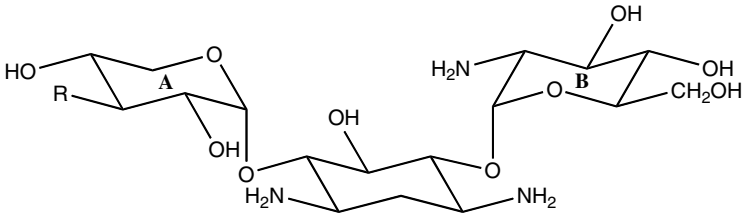
11, R = OH, Gentamicin A_1
12, R = NH_2, Gentamicin A_3

Fig. 14.5

As can be seen from Figs. 14.4–14.6, the structural variations are on both sugar residues.

Gentamicin B (*15* in Fig. 14.7) together with small amounts of gentamicin B_1 (*16*) is produced by a variety *Micromonospora,* and it shows a broad spectrum of activity [43].

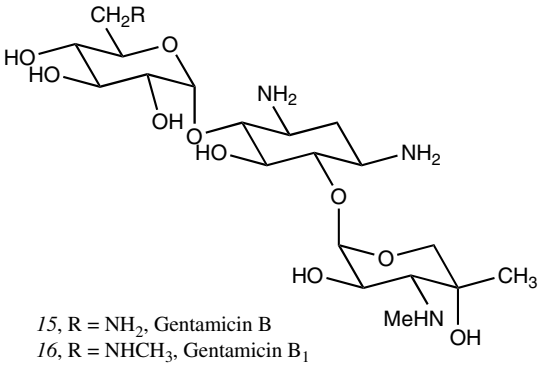
Gentamicin C is an aminoglycoside antibiotic that represents a mixture of several closely related and structurally similar compounds of which the most important are Gentamicins C_1 ($R^1 = R^2 = CH_3$), C_{1a} ($R^1 = R^2 = H$), C_2 ($R_1 = CH_3$, $R^2 = H$),



13, R = OH, Gentamicin A_2

14, R = $\begin{matrix} CH_3 \\ \diagdown N \text{—} \\ \diagup \\ HCO \end{matrix}$, Gentamicin A_4

Fig. 14.6



15, R = NH_2, Gentamicin B
16, R = $NHCH_3$, Gentamicin B_1

Fig. 14.7

and C_{2b} ($R^1 = H$, $R^2 = CH_3$). Gentamicin C is the broad-spectrum antibiotic and is the most extensively used aminoglycoside antibiotic. The structures of gentamicins C antibiotic have been elucidated by Cooper et al. [44] and are represented in Fig. 14.8.

The synthesis of racemic purpurosamine B (Fig. 14.8) was reported by Chmielewski et al. [45].

Tobramycin (Nebramycin)

Tobramycin (*21* in Fig. 14.9) is a broad-spectrum antibiotic produced by a number of *Streptomyces* species. It is more active than gentamicin against *Pseudomonas aeruginosa* but less active against other gram-negative bacteria. Both the nephrotoxicity and ototoxicity in guinea pigs are less than those of gentamicin but generally greater than for kanamycin. An important feature is the high activity against strains

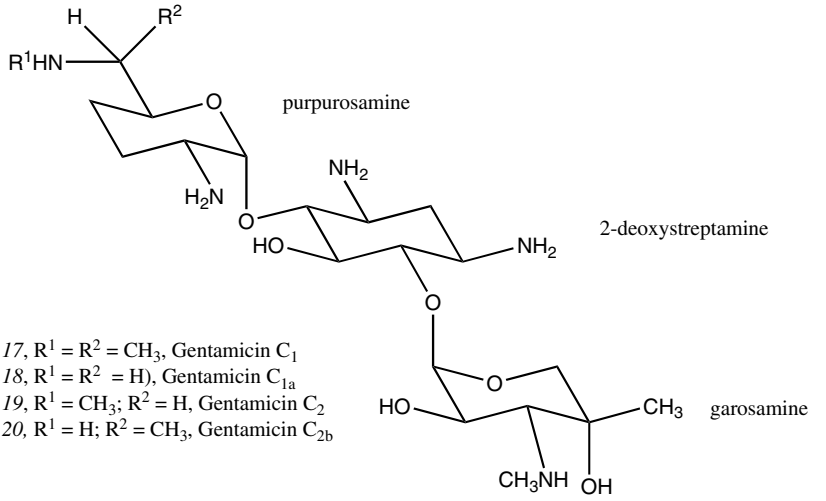


Fig. 14.8

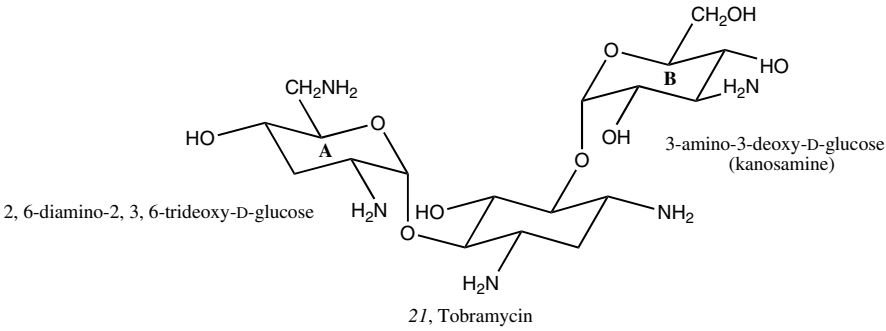


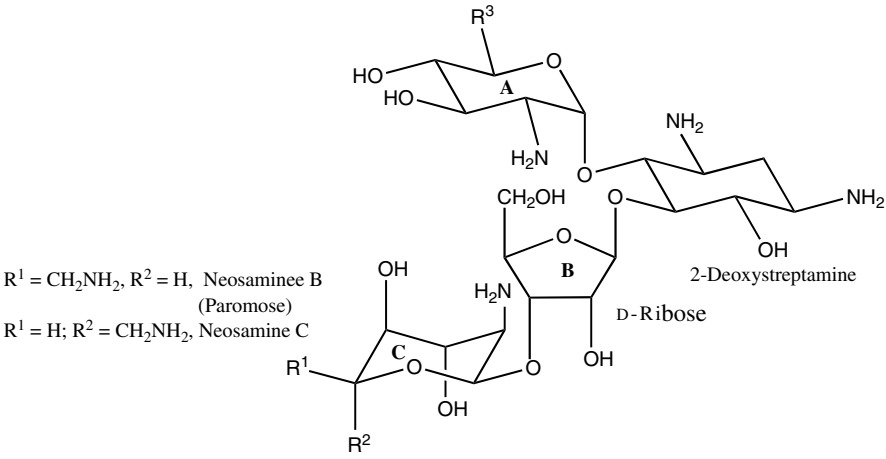
Fig. 14.9

of *Pseudomonas* that are resistant to gentamicin. It has been also shown to be active in vitro against *Enterobacter*, *E.coli*, *Klebsiella*, and *S. aureus*.

The structure of tobramycin was determined by Koch and Rhoades [46] and is shown in the Fig. 14.9. As can be seen, it is very similar to the structure of kanamycin B except that the amino sugar A has no C3 hydroxyl group. Synthesis of tobramycin was accomplished by two groups: Takagi et al. [47] and Tanabe et al. [48].

Neomycin B (Actilin, Enterfram, Framecetin, Soframycin)

Neomycin B is obtained from cultures of *Streptomyces fradiae* and subsequently from other *Streptomyces* species such as *Streptomyces coeruleoprunus*. Neomycin is active against gram-positive and gram-negative bacteria, mycobacteria, and actinomycetes. It is active against streptomycin-resistant bacteria, including tuberculosis organisms. It was discovered by Waksman and Lechevalier [49], and the structure of neomycins B and C (Fig. 14.10) was determined by Rinehart et al. [50–53]. The absolute configuration of neomycin C was determined by Hitchens and Rinehart [11]. Total synthesis of neomycin C was reported by Umezawa et al. [54, 55] and of neomycin B by Usui and Umezawa [56, 57].



22, $R^1 = CH_2NH_2$, $R^2 = H$, $R^3 = CH_2NH_2$, Neomycin B
23, $R^1 = H$; $R^2 = CH_2NH_2$, $R^3 = CH_2NH_2$, Neomycin C
24, $R^1 = CH_2NH_2$; $R^2 = H$; $R^3 = CH_2OH$, Paromomyciin I
25, $R^1 = H$; $R^2 = CH_2NH_2$; $R^3 = CH_2OH$, Paromomycin II

Fig. 14.10

Paromomycin

Paromomycins I and II (Fig. 14.10) are closely related to neomycins B and C. The only difference between them is in the structure of amino sugar A. In neomycins B and C, the R^3 substituent of amino sugar A is aminomethyl group (CH_2NH_2), whereas in paromomycins I and II it is the hydroxymethyl group (CH_2OH).

Paromomycin (catenulin, hydroxymycin, moenomycin A) has been isolated from cultures of *Streptomyces rimosus* [58], *Streptomyces catenulae* [59], and *Streptomyces chrestomyceticus* [60, 61]. Structure of paromomycin was determined by Haskell et al. [11, 62–65].

Butirosins A and B

Butirosins A and B were produced by *Bacillus circulans*. The structures of both butirosins differ in the structure of pentose (in butirosin A the pentose is D-arabinose, and in butirosin B, it is D-ribose). The structures of both butirosins have been determined by Woo et al. [66–68] from mass spectra and are shown in Fig. 14.11.

Butirosin B was synthesized by Ikeda et al. [69] and by Akita et al. [70].

It is active against a number of gram-positive and gram-negative organisms, particularly *Pseudomonas aeruginosa*.

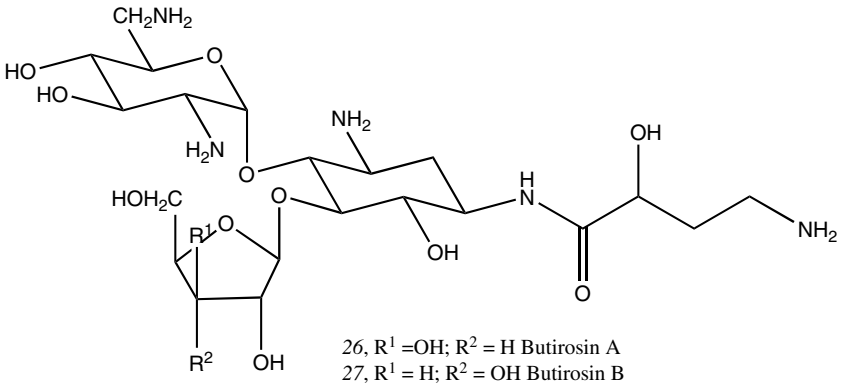


Fig. 14.11

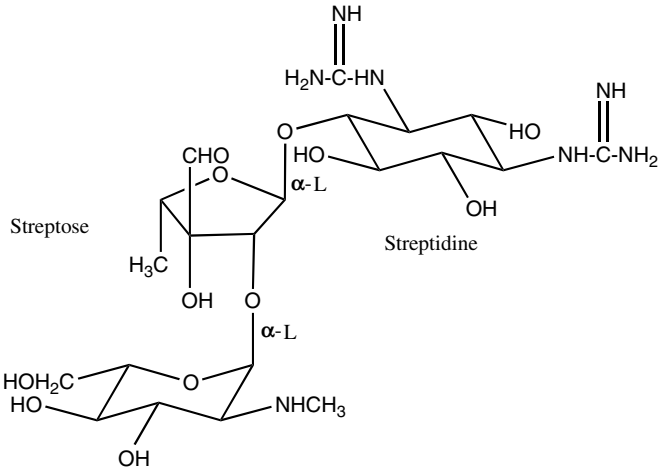
Streptomycin A

It is one of the two aminoglycosidic antibiotics isolated from cultures of *Streptomyces griseus* [71]. The antibiotic is normally used as the trihydrochloride and is freely soluble in water. It is active against a range of gram-positive and gram-negative bacteria and mycobacteria, particularly against *Mycobacterium tuberculosis*. Structure was determined by Kuehl et al. [72]. It was found that two sugar components are not individually glycosidically linked to streptidine, as is the case in other aminoglycoside antibiotics, but that they are linked as disaccharide streptobiosamine to the C4 carbon atom of streptidine (Figs. 14.12 and 14.13)

The 2-deoxy-2-methylamino-L-glucose was synthesized by Wolfrom and Thompson [73], and streptose was synthesized by Dyer et al. [74]. The total synthesis of streptomycin was accomplished by Umezawa et al. [75].

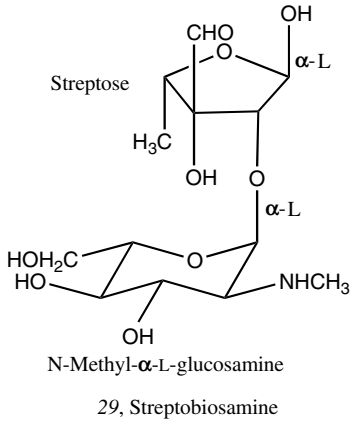
Orthosomycins

Orthosomycins (also known as oligosaccharide antibiotics) are a family of carbohydrate-based antibiotics which are characterized by the presence of one or



28, Streptomycin

Fig. 14.12

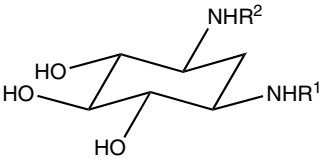


29, Streptobiosamine

Fig. 14.13

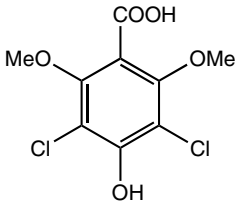
more orthoester linkages in their oligosaccharide structure. These antibiotics include Destomycin-**A** [76–78] (*32*), Destomycin-**B** [78, 79] (*33*) and Destomycin-**C** [80, 81] (*34*), Flambamycin [76–80] (*36*), *Everninomycins*: **B** [81] (*37*), **C** [82] (*38*), **D** [83] (*39*), and *Hygromycin* **B** [87] (35).

This group of antibiotics can be conveniently subdivided into two distinct subgroups based on additional structural features, namely (a) those which contain an aminocyclitol residue (*30*) (Fig. 14.14) (for example destomycins and hygromycin B) (Fig. 14.15) and (b) those which are esters of dichlorisoeverninic



R^1 = H, or Me; R^2 = H, or Me

30



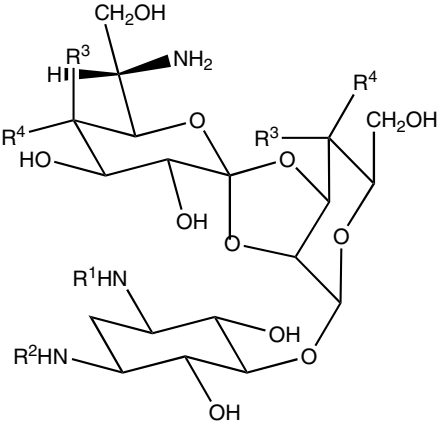
31

Fig. 14.14

acid (*31*) (Fig. 14.14) [for example flambamycin (Fig. 14.16) and everninomicins (Fig. 14.17)].

Destomycin A

Destomycin family of antibiotics consists of destomycin A, B, and C (Fig. 14.15). Destomycin A is the major component isolated from the culture broth of *Streptomyces rimofaciens*. Destomycins are aminoglycoside antibiotics with two sugar units and one 2-deoxy-*N*,*N*-dimethyl-streptidine molecule. In destomycins A and C and in hygromycin B (Fig. 14.15), the amino sugar is a heptose, 6-amino-6-deoxy-L-glycero-D-galacto-heptopyranose. In destomycin B, the amino sugar is 6-amino-6-deoxy-L-glycero-D-glucopyranose. The other sugar component in destomycins A



32, Destomycin A, $R^1 = R^4 = H$; $R^2 = CH_3$; $R^3 = OH$
33, Destomycin B, $R^1 = R^2 = CH_3$; $R^3 = H$; $R^4 = OH$
34, Destomycin C, $R^1 = R^2 = CH_3$; $R^3 = OH$; $R^4 = H$
35, Hygromycin B, $R^1 = CH_3$; $R^2 = R^4 = H$; $R^3 = OH$

Fig. 14.15

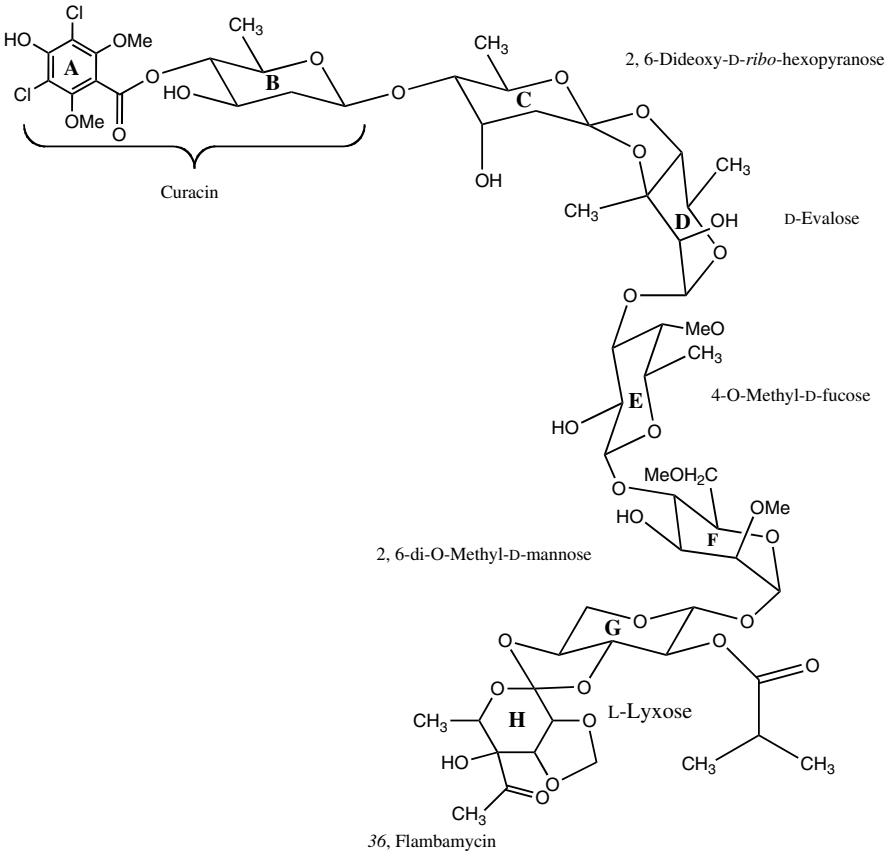
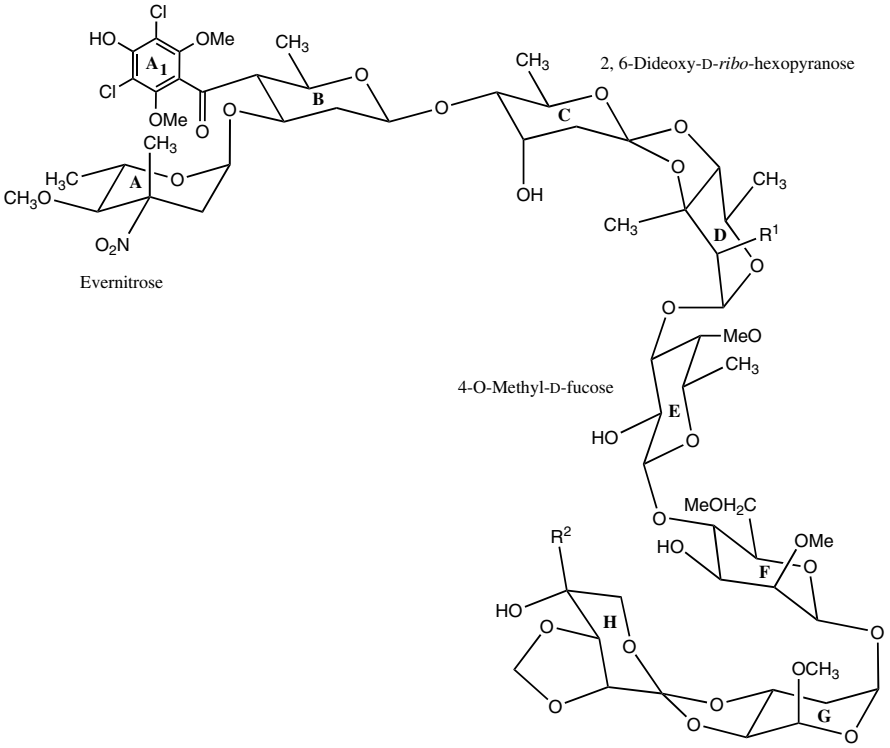


Fig. 14.16

and C is D-mannose, and in destomycin B and hygromycin B, it is D-talose. In all four antibiotics, the heptose and hexose are linked via an orthoester linkage between the C1 of heptose and the C2 and the C3 hydroxyl groups of hexose.

Destomycin family of antibiotics is produced by *S. rimofaciens* and was isolated by Kondo et al. [76]. Structures of destomycins A and B were elucidated by Kondo et al. [77–79] and of destomycin C by Shimura et al. [80]. Synthesis of destomycin C was reported by Tamura et al. [81]. It shows anthelmintic activity in poultry.

Hygromycin B is produced by *Streptomyces hygroscopicus*. It was isolated by Mann and Bromer [82], and the structure was determined by Neuss et al. [83]. Hygromycin A does not belong to the family of orthosomycins, although it is produced by the same microorganism as is the hygromycin B and bears the same name and therefore we will not discuss it.



37, Everninomicin-B, $R^1 = OH$; $R^2 = CH(OCH_3)CH_3$
38, Everninomicin-C, $R^1 = R^2 = H$
39, Everninomicin-D, $R^1 = H$; $R^2 = CH(OCH_3)CH_3$

Fig. 14.17

Flambamycin

The antibiotic flambamycin is produced also by *S. hygroscopicus*, and it was isolated in 1974 by Ninet et al. [84]. The structure of flambamycin was elucidated by Ollis et al. [85–92]. The structure was elucidated on the basis of degradation such as acid hydrolysis, methanolysis, and determination of the structure of degradation products. At first Ollis et al. proposed the incorrect structure for flambamycin [89], but 3 years later they proposed the correct structure [90]. In 1979 Ollis et al. reported the results of their studies on the ^{13}C NMR spectra of flambamycin and its derivatives [91] and on mass spectral studies of flambamycin and its degradation products [92].

Zagar and Scharf reported the synthesis of the terminal A–B–C disaccharide fragment of flambamycin, curamycin, and avilamycin [93].

Everninomicin

The structures of everninomicins B [94, 95], C [96], and D [97] were elucidated by classical degradation studies which included acidic hydrolysis, acidic methanolysis, and permethylation studies. Structural and stereochemical assignments proposed for flambamycin, everninomicins, and all degradation products were based on extensive studies by IR, UV, ^{1}H and ^{13}C NMR spectroscopy, as well as by low- and high-resolution mass spectrometry. In some cases, circular dichroism and X-ray crystallography were used for identification of fragments.

Everninomicin D (*39*, Fig. 14.17) is the major component present in the mixture of everninomicins produced by cultures of *Micromonospora carbonacea*. It is highly active in vitro against a variety of gram-positive bacteria, including penicillin-resistant strains, but inactive against gram-negative organisms, e.g., *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Salmonella schotmulleri*. Stereocontrolled synthesis of the everninomycin A_1B(A)C ring framework was reported by Nicolaou et al. [98] and the total synthesis of everninomycin was reported by Helen J. Mitchell [99].

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Chapter 15
Higher-Carbon Monosaccharides

Introduction

Higher-carbon sugars are defined as sugars having more than six carbon atoms in their carbon chain. Thus monosaccharides containing seven or more consecutive carbon atoms belong to this class of monosaccharides, e.g., heptoses, octoses, nonoses, decoses. There are many reviews written on this topic [1–10].

Higher-carbon sugars have been found in Nature, and they often have very important biological functions, as is the case with sialic acids (e.g., *N*-acetyl-neuraminic acid, NANA, *1*) [11–13] (Fig. 15.1).

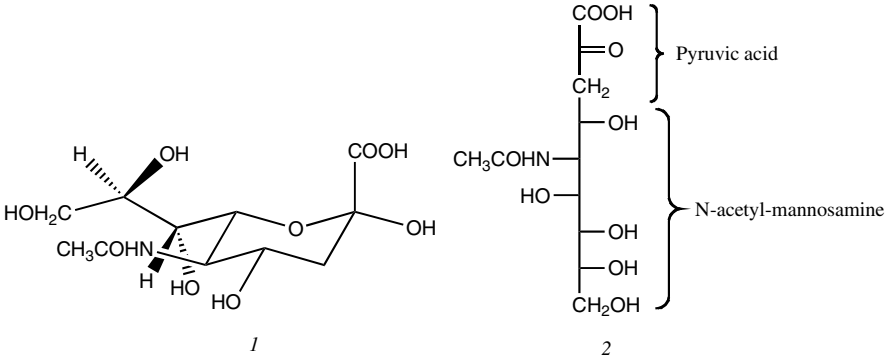


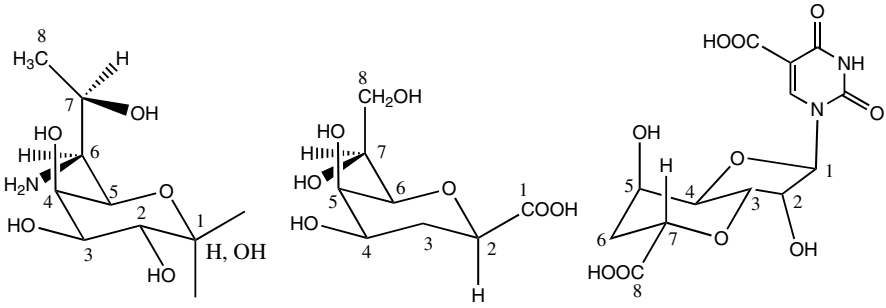
Fig. 15.1

The *N*-acetyl-neuraminic acid (*N*-acetyl-5-amino-3,5-dideoxy-D-glycero-D-galacto-*non*-2-*ulosonic* acid) in Fig. 15.1, shown in the α-D-pyranose form, plays a variety of very important roles in living organisms. One of the most obvious roles is providing the negative charge to glycoproteins on cell membranes, thus influencing the behavior of cells (for example, it has been calculated that $>10^7$ NANA residues are bound to the surface of a single human eryhtrocyte). The importance of this electronegative shield is severalfold. For example, in some cell types, membrane sialic acids prevent aggregation due to electrostatic repulsion in blood platelets, erythrocytes, and carcinoma cells, whereas in others, for example in chick, embryonic

M. Miljković, *Carbohydrates*, DOI 10.1007/978-0-387-92265-2_15,

muscle cells, aggregation is facilitated, most probably by Ca^{2+} bridges. The repulsive, electrostatic forces of sialic acids contribute also to the rigidity of the cell surface. Sialic acid residues are important Ca^{2+}-binding sites in the muscle cells. Antirecognition effect of sialic acids, i.e., the protection of survival of various serum glycoproteins in blood stream that have their terminal galactosyl residues sialylated, is one of the most fascinating functions of sialic acids. Finally, but not lastly, sialic acids linked to various gangliosides serve often as receptors for various toxins, such as diphtheria, tetanus, cholera, botulism.

Lincosamine [14] (6-amino-6,8-dideoxy-D-galacto-*octose*) (*3*) (Fig. 15.2) is a component of a therapeutically important antibiotic lyncomycin. Another octose, KDO (*4*) (3-deoxy-D-*manno*-2-octulosonic acid) (Fig. 15.2) is a sugar component of lipopolysaccharides and capsular polysaccharides, which occur in the cell surface of gram-negative bacteria, and is an important bridging link in their membrane structure. Octosyl acids [15, 16] are a class of nucleoside antibiotics consisting of a C_8 monosaccharide attached to a pyrimidine base (Fig. 15.2). They are unusual eight-carbon bicyclic monosaccharides which are N-glycosydically



3, Lincosamine *4*, KDO *5*, Octosyl acid A

Fig. 15.2

linked to novel pyrimidine bases [15]. Some octosyl acids are powerful phosphodiesterase inhibitors [17, 18]. Hikosamine (4-amino-4-deoxy-D-glycero-D-galacto-D-gluco-*undecose*) *6* (Fig. 15.3) is a higher-sugar component of antibiotic hikizimycin which is active against *Helminthosporium* and numerous other species of plant-pathogenic fungi.

A number of heptoses, heptitols, and heptulose have been found in Nature, for example, bacterial cell wall polysaccharides contain D- and L-glycero-D-*manno*-heptopyranose *7* and *8*, respectively (Fig. 15.4) and 6-deoxy-D-manno- and D-altro-heptopyranose *9* and *10*, respectively (Fig. 15.5).

Unusual C_9 branched chain higher-carbon sugar-like structures have been found to be a part of complex lipids of thermoacidophilic bacteria, for example calditol *11* [19–21] (Fig. 15.6).

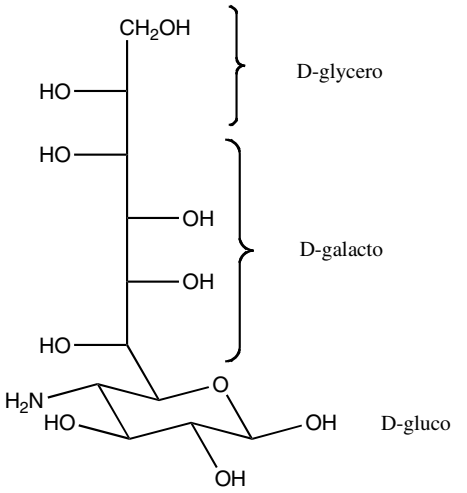


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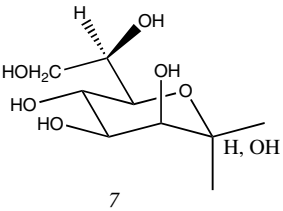
Fig. 15.3



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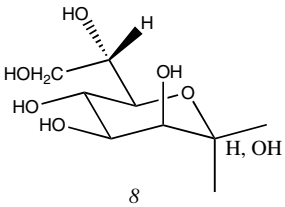

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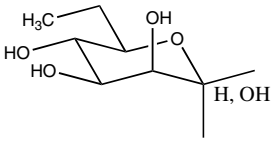
Fig. 15.4



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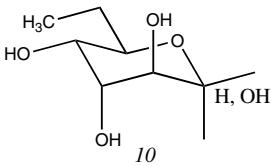

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Fig. 15.5

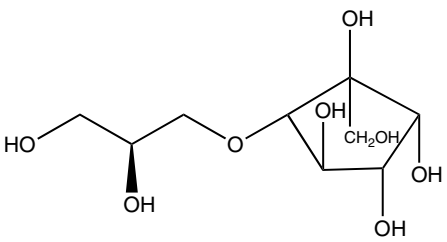

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Fig. 15.6

Synthesis of Higher-Carbon Sugars

Since the late 1970s, synthesis of higher-carbon sugars attracted a great interest of a number of organic synthetic chemists. A reason for this rise of synthetic activities in this field was assessing dependence of biological function and activity of the higher-carbon sugars upon their structural modifications. This is the same reason why there has been the synthesis of all 'natural products with biological activity generating such a wide interest in synthetic chemist community for so many years.

There are many approaches for the synthesis of higher-sugars, of which we are going to discuss only a few:

1. Extension of carbohydrate skeleton via Wittig olefination reaction and stereoselective hydroxylation of the generated olefinic bond
2. Aldol condensation and related approaches
3. De novo synthesis.

Wittig Olefination

In the Wittig reaction, an aldehyde or a ketone is treated with a phosphorous ylide (also called phosphorane) to give an olefin [22–24] (Fig. 15.7).

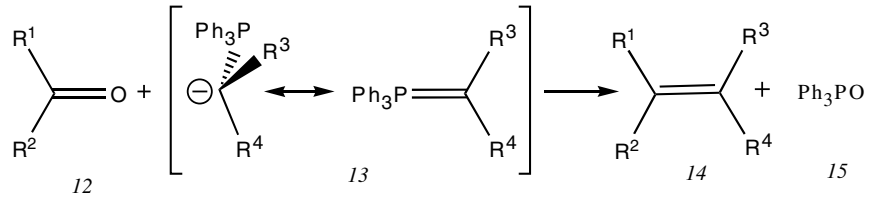


Fig. 15.7

As a first example of this approach, let us describe the total synthesis of (+)-α-homonojirimycin [25]*29* (Fig. 15.8), a naturally occurring azaheptose which is a powerful α-glucosidase inhibitor, isolated from leaves of *Omphalea diandra*.

The starting material for the synthesis of homonojirimycin *29* was the chiral allyl alcohol *16*, which was obtained from ethyl D-tartrate as described by Iida et al. [26] and Aoyagi et al. [27]. The allylic alcohol *16* was converted to *syn*-epoxide by the Sharpless asymmetric epoxidation [28]. Regio- and stereoselective epoxide ring opening was effected by using diethylaluminum amide [29] at 0°C, giving the aminoalcohol *18* as a single stereoisomer with 70% yield (Fig. 15.8). The amino group of *18* was selectively protected with benzyl chloroformate (aq. Na_2CO_3, CH_2Cl_2) with 98% yield. The two hydroxyl groups of the obtained carbamate *19* were methoxymethylated and the *tert*-butyldimethylsilyl group of the obtained *20* was removed with an overall yield of 86%. Swern oxidation of the primary hydroxyl group of *21* gave aldehyde *22* with 98% yield, which was transformed into the

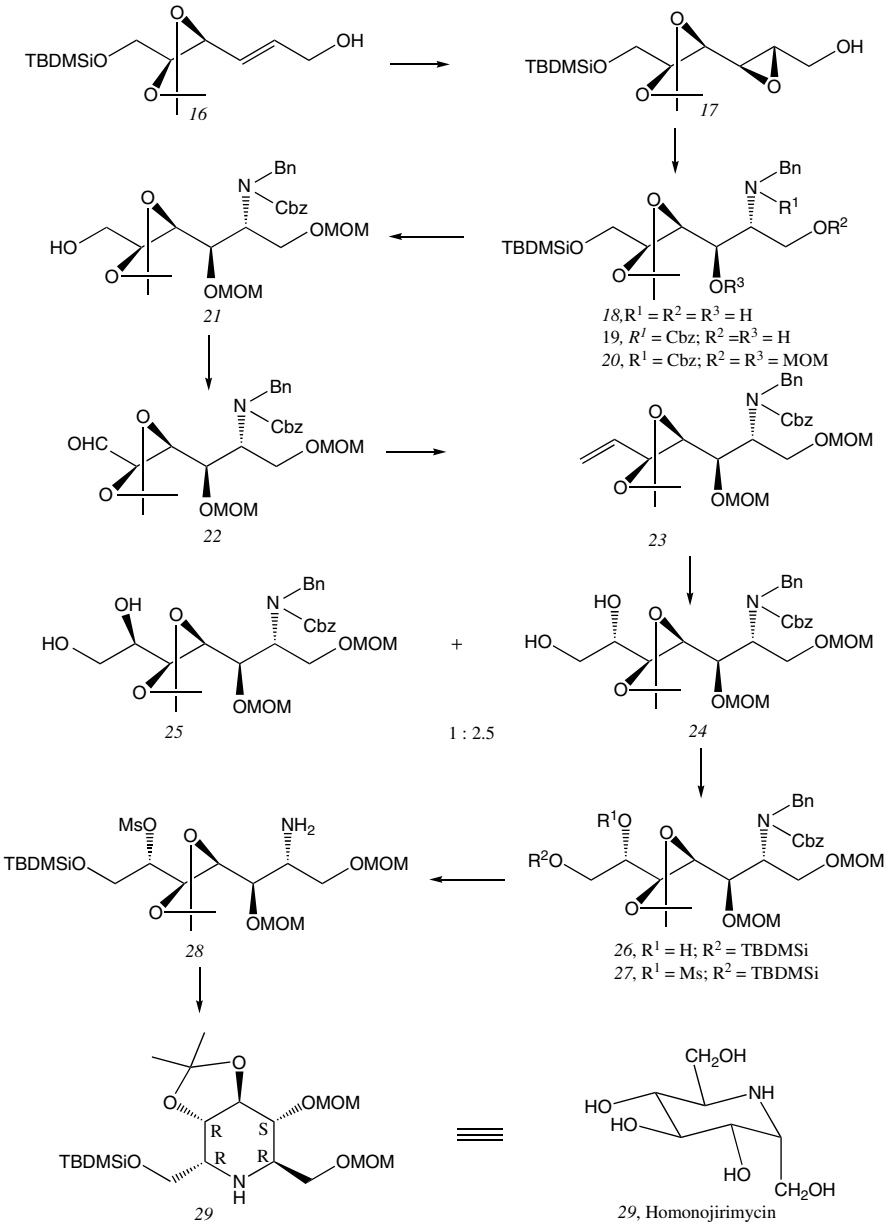


Fig. 15.8

alkene *23* by the Wittig reaction with 84% yield. Hydroxylation of *23* with catalytic amount of osmium tetroxide in the presence of 2 equivalent of *N*-methylmorpholine oxide in aqueous acetone gave the mixture of diols *24* and *25* in which the desired

anti-stereoisomer *24* predominated in the ratio 2.5:1(total yield 90%). The diol *24* was converted via regioselective silylation with *tert*-butyldimethylsilyl chloride to the TBDMSi ether *26* which was then mesylated into the corresponding mesylate *27*. The simultaneous removal of the carbobenzoxy and benzyl groups was effected by catalytic hydrogenation over palladium hydroxide in methanol. Finally the intramolecular displacement of the mesyl group with the amino group was effected by the heating of the methanolic solution of *28* to which some triethyl amine was added, whereby the protected (+)-homonojirimycin *29* was obtained at 81%.

α-Amino acids bearing a sugar moiety attached by a carbon–carbon bond represent unique substructures in many biologically active molecules [4]. Pyranosidic arrangements are rare and are found, for example, in the antibiotics amipurimycin [30] and miharamycin [31].

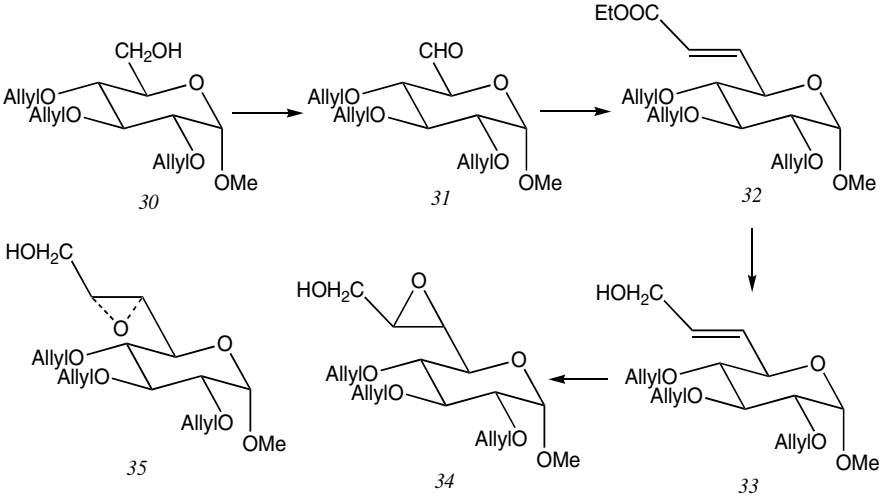


Fig. 15.9

Bessodes et al. [32] have reported chiral synthesis of biologically important terminal α-amino-acyl glycosides. Methyl 2,3,4-tri-*O*-allyl-α-D-glucopyranoside *30* which was used as a starting material for this synthesis was obtained in three steps from methyl α-D-glucopyranoside by selective tritylation of the C6 hydroxyl group, allylation of the remaining free hydroxyl groups, and detritylation by formic acid. Oxidation of *30* with DMSO-oxalyl chloride to 6-aldehydo derivative *31* followed by reaction with ethyl triphenylphosphoranylidene acetate gave the *E*-olefin *32*, with 88% yield. Reduction of the ester group of *32* with DIBAL gave *E*-2,3,4,tri-*O*-allyl-6,7-dideoxy-α-D-*gluco*-oct-6-enopyranoside *33* with 95% yield.

The titanium-catalyzed epoxidation of *33* in the presence of diisopropyl D-tartrate (DIPT) [28] gave epoxide *34*, with 93% yield, as the only product. If the same reaction was performed in the presence of diisopropyl L-tartrate, an inseparable mixture of epoxides *34* and *35* was obtained with 93% yield, in which the ratio

of the desired epoxide *34* to the undesired epoxide *35* was 1:4. The regioselective 6,7-epoxide ring opening was effected by treating the mixture of epoxides *34* and *35* with titanium diisopropoxide diazide [33], and the obtained regio- and diastereoisomers *36*, *37*, *38*, and *39* (Fig. 15.10) were separated by column chromatography. The regioselectivity in the epoxide ring opening of *34* and *35* was estimated to be ca. 80%. The reduction of azide *38* with $LiAlH_4$ followed by acetylation of *36* with

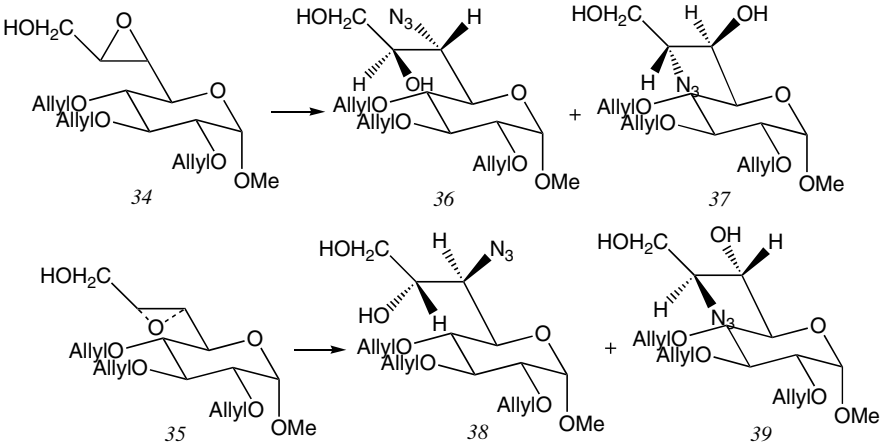


Fig. 15.10

acetic anhydride in methanol gave the 6-acetamido derivative *40* which was then oxidized with periodic acid and potassium dichromate to aminoacyl sugar *42* (Figs. 15.9 and 15.11).

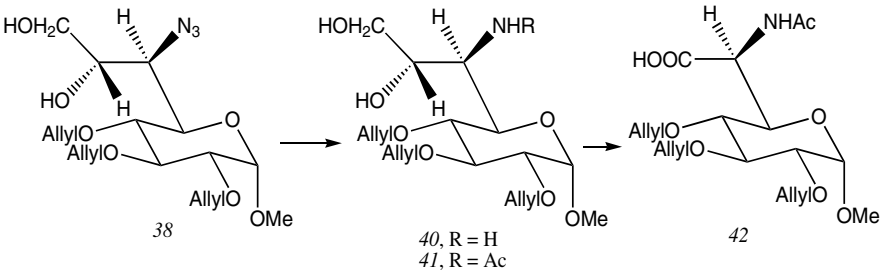


Fig. 15.11

In a series of papers, Brimacombe et al. [34–41] have approached the synthesis of higher-carbon sugars using Wittig olefination (Fig. 15.12) of 1,2: 3,4-di-*O*-isopropylidene-6-*aldehydo*-α-D-galactopyranose *43* followed by catalytic osmylation [42] of obtained unsaturated sugars *44* or *46* either according to Kishi empirical rule [43] or via Sharpless epoxidation with diisopropyl L-(+)-tartrate [28, 44, 45].

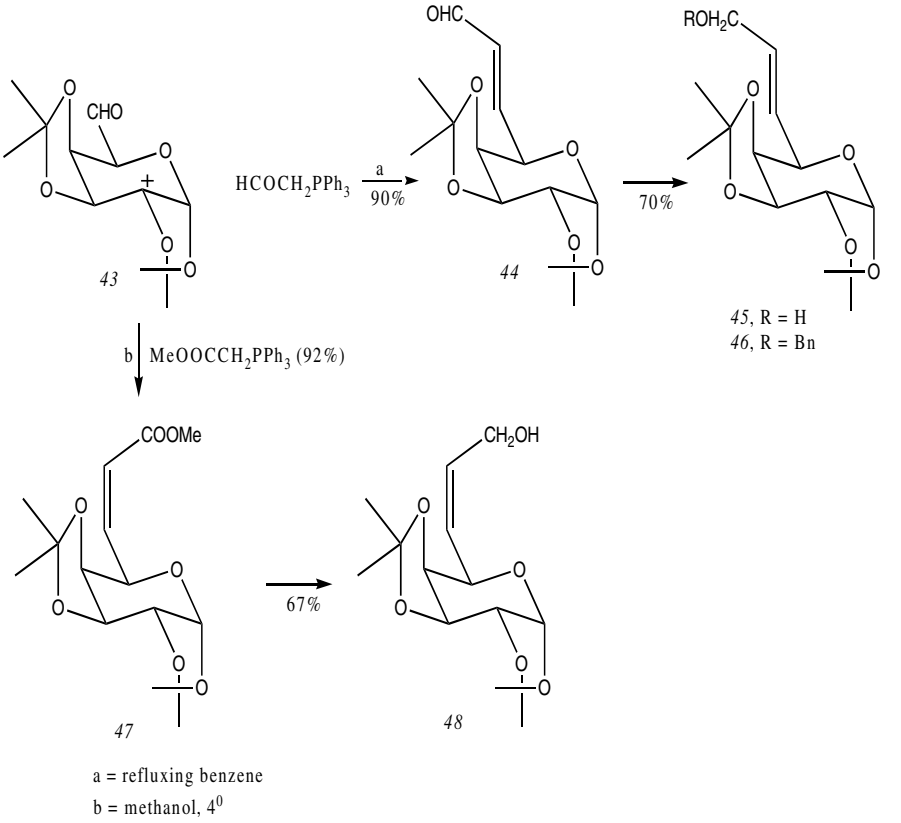


Fig. 15.12

Catalytic osmylation [42] of *E*-octenopyranose *45* gave a mixture of 1,2:3,4-di-*O*-isopropylidene-β-L-*threo*-D-*galacto*-octopyranose *49* and α-D-*threo*-D-*galacto* isomer *50* in the ratio 7:1. Catalytic osmylation of the benzylated derivative *46* was less stereoselective, giving a mixture of *49* and *50* (after removal of benzyl group) in the ratio 3:1 (Fig. 15.13). It should be noted that, for the reason of clarity, only the side chain comprising of carbon atoms C6, C7, and C8 was shown in Fig. 15.13.

Catalytic osmylation of *Z*-octenopyranose *47* produced a mixture containing 1,2:3,4-di-*O*-isopropylidene-β-L-*erythro*-D-*galacto*-octopyranose *51* and 1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose *49* in the ratio 1:7 (Fig. 15.14).

Titanium-catalyzed asymmetric epoxidation [28, 44, 45] of the *E*-octenopyranose *46* with di isopropyl L-(+)-tartrate ((+)-DIPT) at –23°C readily gave a single 6,7-oxirane *57* (6,7-anhydro-1,2:3,4-di-*O*-isopropylidene-β-L-threo-D-galacto-octopyranose) with 66% yield. By contrast, titanium-catalyzed epoxidation of the

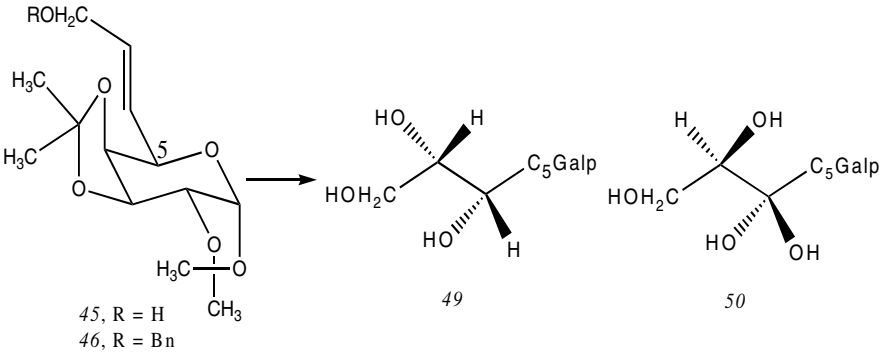


Fig. 15.13

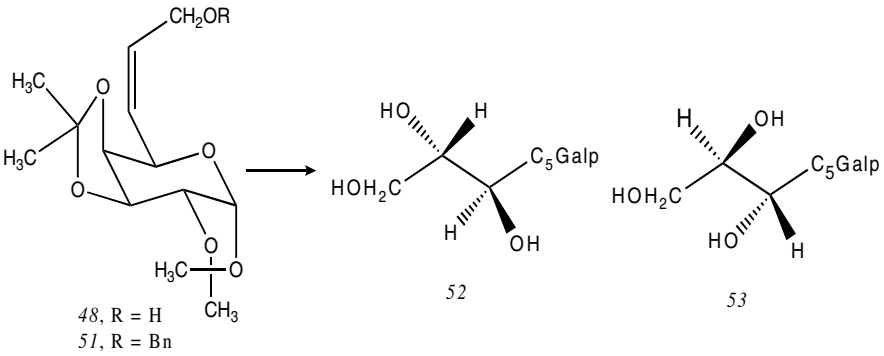


Fig. 15.14

E-octenopyranose *45* with diisopropyl D-(–)-tartrate ((–)-DIPT) at –23°C was incomplete after 8 days and gave a mixture of epoxides *54* and *56* in which the epoxide *56* slightly predominated (Fig. 15.15). Treatment of a solution of epoxide *54* in 1,4-dioxane–water with sodium hydroxide gave finally 1,2:3,4-di-*O*-isopropylidene-α-D-*threo*-D-*galacto*-octopyranose *53* with 64% yield.

It is likely that the 7,8-epoxide *58* is the intermediate in this reaction because of the possibility for the neighboring group participation of the C8 hydroxyl group as shown in Fig. 15.16.

Brimacombe et al. [38, 41] have used the same approach to make decitols and decoses. Acetonation of the C6 and C7 hydroxyl groups, oxidation of the C8 hydroxyl group to aldehyde, another Wittig reaction, and Sharpless epoxidation of the obtained olefin followed by treatment with sodium hydroxide produced the corresponding decitols and/or a decose again as the mixture of isomers.

Secrist and Barnes [46] synthesized methyl peracetyl α-hikosaminide, the undecose portion of the nucleoside antibiotic hikizimycin, by allowing the unstabilized five-carbon carbohydrate phosphorane to react with a six-carbon

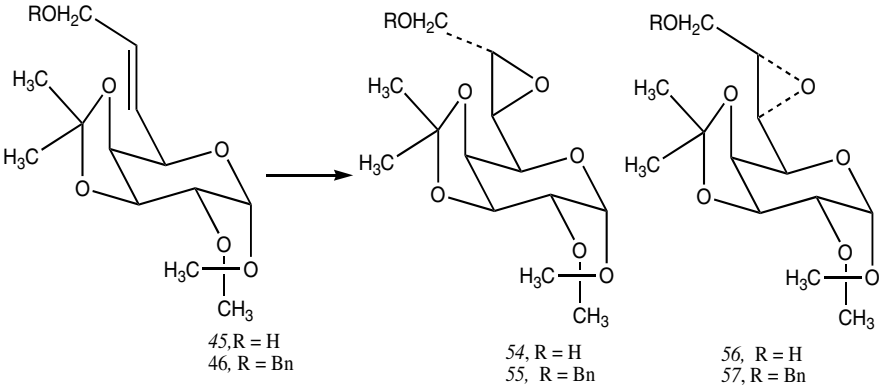


Fig. 15.15

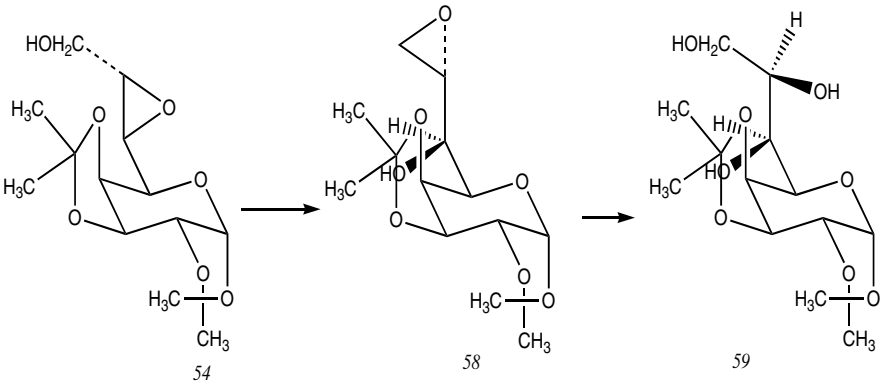


Fig. 15.16

carbohydrate 6-aldehyde. Thus, the reaction of 2,3:4,5-di-*O*-cyclohexyliden-1-deoxy-1-triphenylphosphonio-D-arabinitol iodide *60* (obtained with 67% yield from 2,3:4,5-di-*O*-cyclohexylidene-D-arabinitol) with methyl 4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-*dialdo*-glucopyranoside *61* gave exclusively the corresponding *Z*-olefin *62* with 50% yield (no *E*-olefin was present). The C4 azide was then reduced with $LiAlH_4$ to the amino group, and the obtained amino sugar *63* was irradiated in the presence of diphenyl disulfide, whereby a 3:2 mixture of the *E*- and *Z*-olefins was obtained, which was separated by chromatography. This was needed because the *E*-olefin was the right substrate for catalytic hydroxylation. After the amino group was acetylated with acetic anhydride, the olefin *64* was treated with osmium tetroxide and *N*-methylmorpholine in 5:1 THF water to produce one isomer of diol *65* (Fig. 15.17).

Miljkovic and Habash-Marino [47] also approached the synthesis of higher-carbon sugars as precursors for polyhydroxylated macrocyclic lactones by using

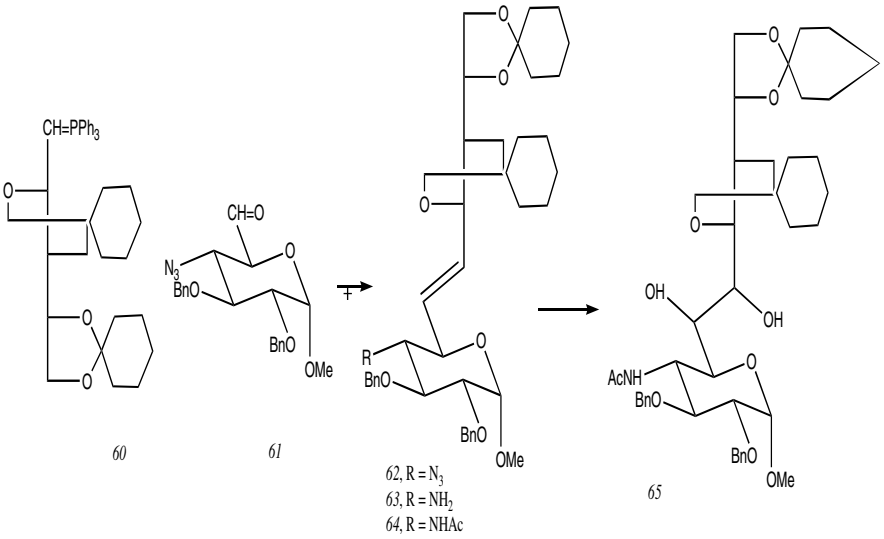


Fig. 15.17

the Wittig reaction. However, glycopyranosyl triphenylphosphorane was used for coupling with an aldehydo sugar. Thus, 6-deoxy-6-iodo-2,3,4-tri-*O*-methyl-α-D-glucopyranoside was reacted with triphenyl phosphine, whereby the corresponding triphenylphosphonium salt *66* was obtained with a yield of 99% (Fig. 15.18). Reaction of *66* in the presence of *n*-butyl lithium at –60°C with 2,3,4-tri-*O*-methyl-

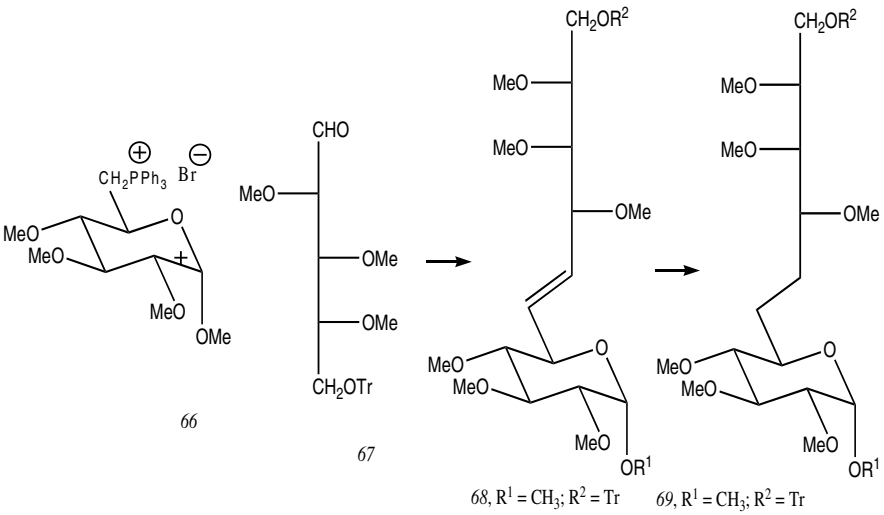


Fig. 15.18

6-*O*-trityl-*aldehydo*-D-arabinose *67* gave, with 57% yield, methyl *E*-6, 7-diedoxy-2,3,4,8,9,10-hexa-*O*-methyl-11-*O*-trityl-D-*arabino*-α-D-*gluco*-undec-6-enopyrano side *68* (the corresponding *Z*-isomer was not detected). Catalytic hydrogenation of *68* gave methyl 6,7-dideoxy-2,3,4,8,9, 0-hexa-*O*-methyl-D-*arabino*-D-*gluco*-undecanoside *69* which was converted in several steps to 6,7-dideoxy-2, 3,4,5,8,9,10-hepta-*O*-methyl-D-*arabino*-D-*gluco*-undecanoic acid *71* which was then lactonized [48] to macrocyclic lactone *72* by "double activation" method [49–53] (Fig. 15.19).

The 6,7-olefinic bond could also be hydroxylated via catalytic osmylation or Sharpless epoxidation, if undecanoses were desired, but Miljkovic et al. wanted to explore the possibility of converting higher-carbon sugars into macrocyclic polyhydroxylated lactones.

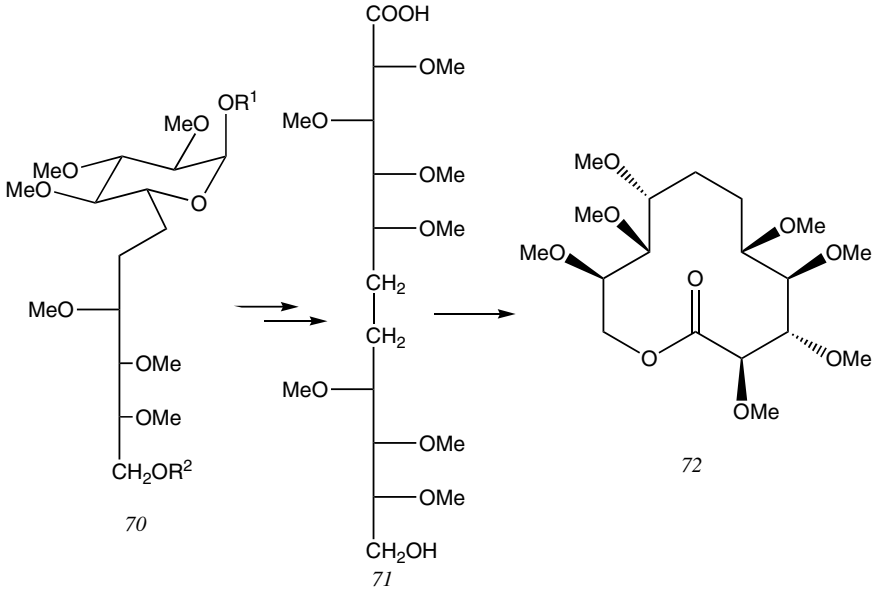


Fig. 15.19

Aldol Condensation

Vasella et al. [54] developed a method for chain elongation of uloses by the base-catalyzed addition of 1-deoxy-1-nitro-aldoses to aldehydes followed by subsequent solvolytic displacement of the nitro group by a hydroxy group. Thus, for example, the addition of 1-deoxy-2,3:5,6-di-*O*-isopropylidene-1-nitro-α-D-mannofuranose *73* to 6-aldo-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose *74* in the presence of tetrabutylammonium fluoride gave, with 78% yield, the corresponding 7-nitro derivative *75* as single product. Acetylation of the C6 hydroxyl group of *75*

followed by treatment of the C6 acetate *76* with $NaHCO_3$ in formamide at 100°C gave the corresponding hemiacetal *77* with 69% yield as the mixture of two anomers in 3:1 ratio (Fig. 15.20).

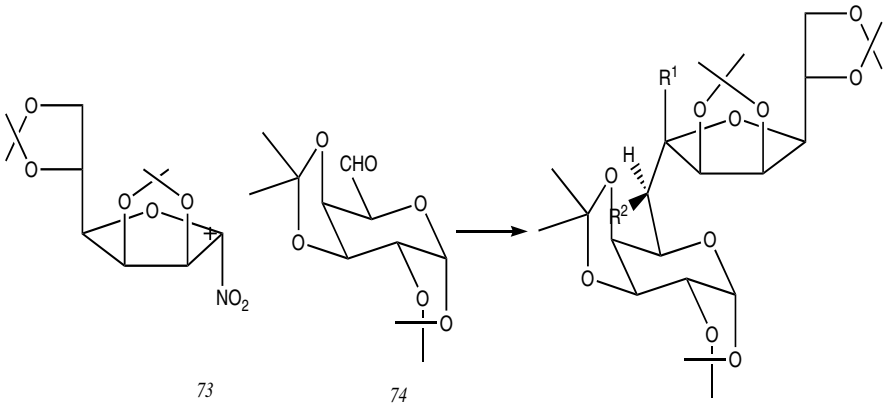


Fig. 15.20

Chapleur reported [55] that lithium enolate *79* of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *78* obtained by treating *78* with *n*-butyl lithium at –30°C reacts with electrophiles to give the C2 alkylated derivatives *80–83* with 40–50% yield, as shown in Fig. 15.21.

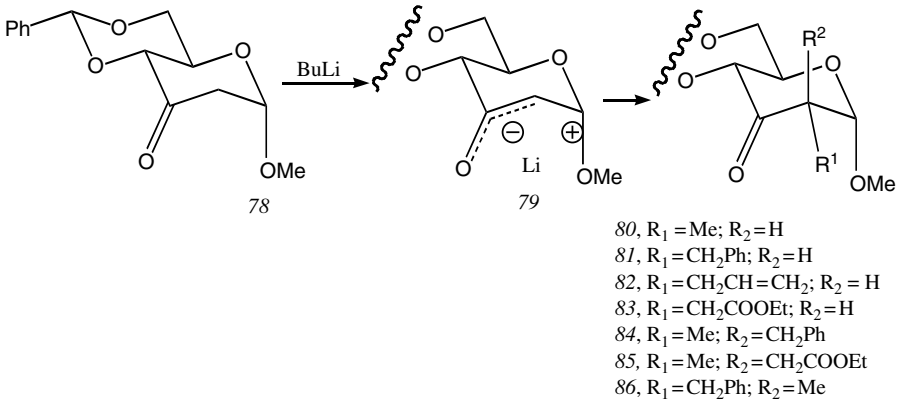


Fig. 15.21

Alkylation of C2 alkyl derivatives *80* with benzyl bromide or ethyl bromoacetate and *81* with methyl iodide gave the C2 dialkyl derivatives *84*, *85*, and *86* in which the second alkyl group is axially oriented. This implies that the preferred side for

the electrophilic attack is the β-face and that the monoalkyl derivatives *80* and *81* with the C2 alkyl groups equatorially oriented are the results of epimerization of the initially formed axial derivatives. The "axial" alkylation of enolate is due to stereoelectronic control. Namely, the orbital overlap producing a pyranose ring in the chair conformation can only take place via an axial attack on enolate (steric control is due to the axially oriented α-methoxy group). Another important observation made in these studies was that the C1 methoxy group is remarkably resistant to β-elimination.

These findings prompted Fraser-Reid et al. [56–59] to use the principle of double stereodifferentiation [60, 61] to synthesize the higher-carbon sugars using aldol condensation of chiral aldehyde and chiral ketone.

Thus they reacted the enolate of 2-deoxy-3-oxo-pyranoside *87* with a number of sugar aldehydes and found that the aldol addition takes place exclusively from β-face due to the α-anomeric configuration of *87* and that the stereochemistry of the newly created chiral carbon is entirely controlled by the aldehydo sugar (α- or α, β-chelation) (Figs. 15.22 and 15.23).

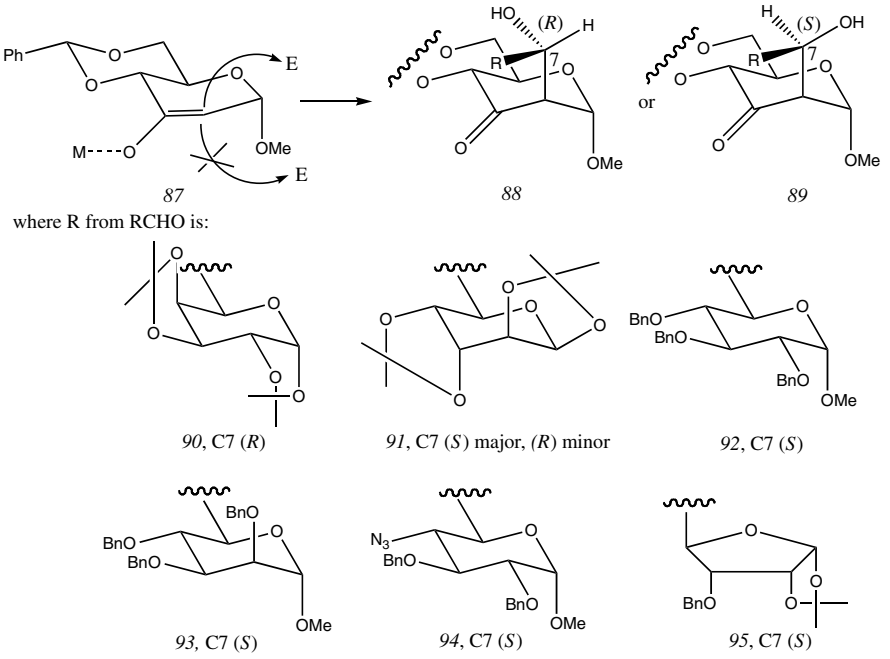


Fig. 15.22

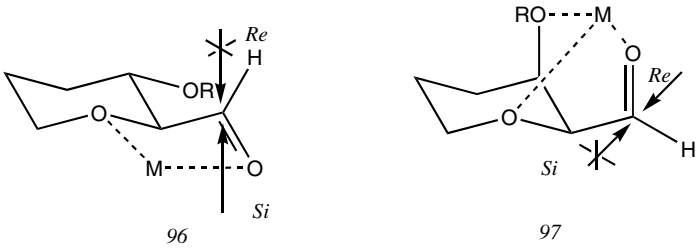


Fig. 15.23

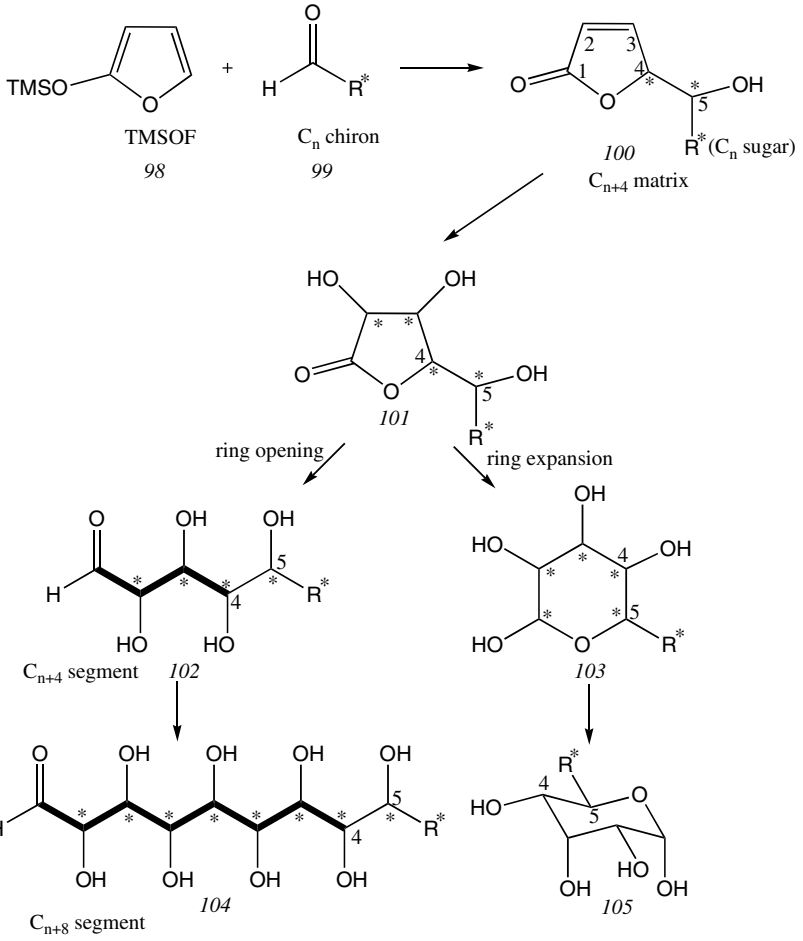


Fig. 15.24

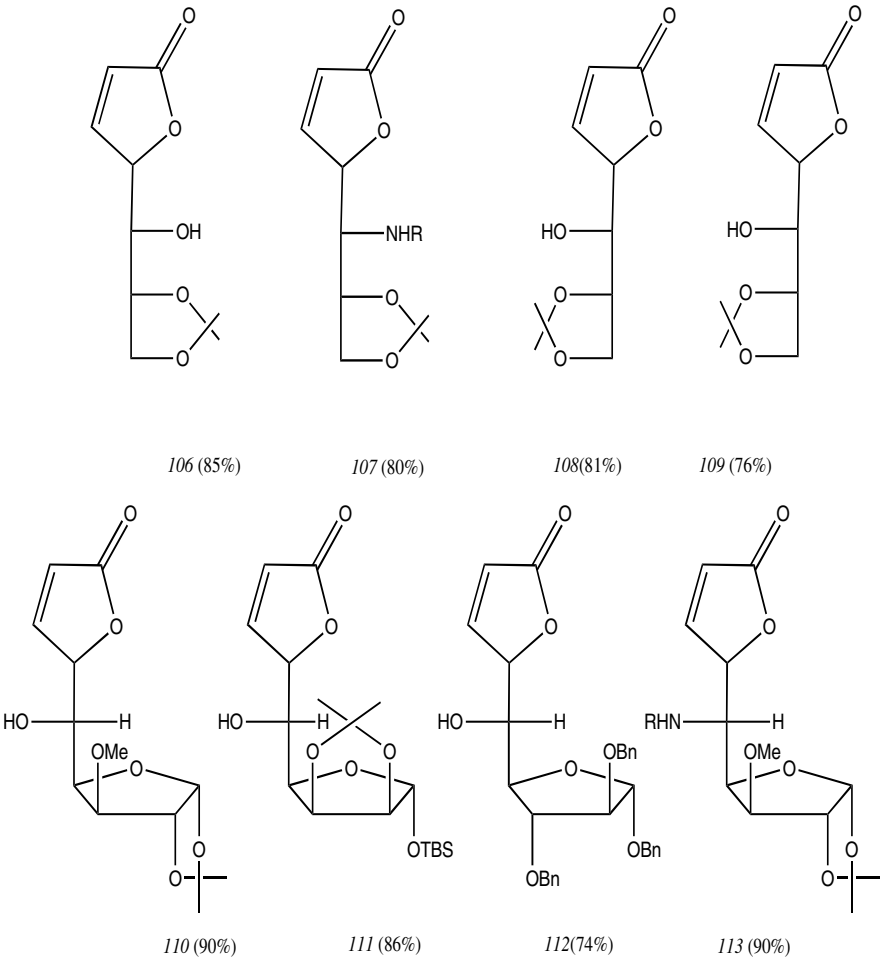


Fig. 15.25

The selectivities observed in products imply that each of the aldehydes controls the stereochemistry independently from the ketone. This facial stereoselectivity seems to be dependent upon the alkoxy substitution at the α- and/or β-carbons of the aldehyde, if Cram cyclic model is assumed with α-chelation, as in *96,* or α, β-chelation, as in *97* [62]. The results with aldehydes *89* and *90* are consistent with the α-, β-chelation shown in *96.* The literature suggests [63] that aldol reaction of *78* with *91–94*, to give *anti*-Cram products only, can be rationalized by the α-chelation pattern depicted in *95* (Fig. 15.21).

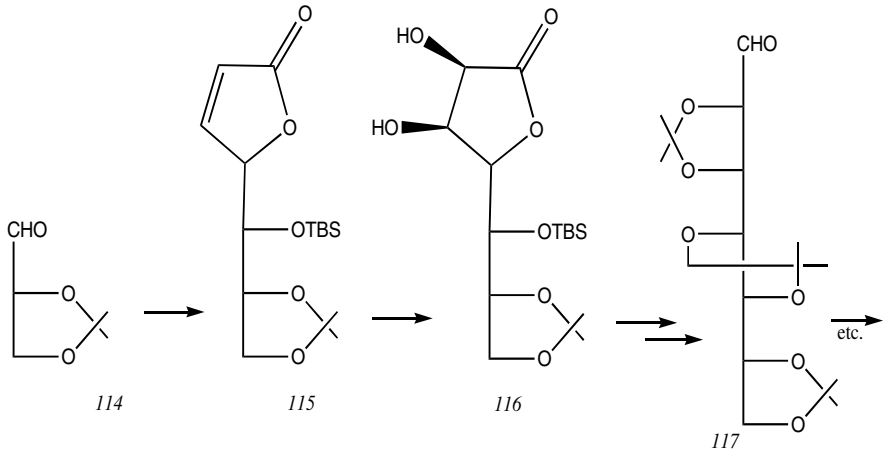


Fig. 15.26

The Butenolide Approach

Jefford pointed out [64–67] that commercially available 2-(trimethylsiloxy)-furan (TMSOF) *98* can be an attractive synthon for the assembly of butenolides. Aldol-type condensation of TMSOF with certain carbonyl compounds, depending on the reaction conditions and catalysts, results in the formation of *erythro* and/or *threo* butenolides in high yield, as is shown in Fig. 15.24.

The stereospecific 4,5-*threo*-5,6-*erythro* (*syn*, *anti*) butenolide matrices such asthe C_{n+4} matrix *100* were made by treating an aldehydo sugar precursor in dichloromethane with TMSOF at –80°C in the presence of BF_3 etherate. In this way many butenolide matrices were prepared [68–71](Fig. 15.25).

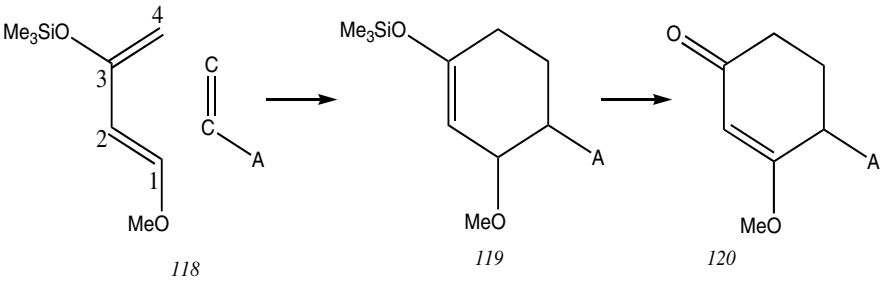
Figure 15.26 depicts the carbohydrate chain elongation by four carbon atoms, using the butenolide approach.

Total Synthesis of Higher-Carbon Monosaccharides

This approach developed by Danishefsky et al. [2–8] consists of a Diels–Alder reaction and reiterative cyclocondensation.

In classical Diels–Alder reaction, a dienophile consists of two carbon atoms connected by either a double or a triple bond. Danishefsky has developed the synthesis of a new class of highly activated and functionalized siloxydienes [72] (Fig. 15.27) that have been found to be very valuable reagents. They are prepared from the corresponding α, β-unsaturated ketones. The electron donating effects of the 1- and 3-oxygens are synergistic, thus serving to endow such dienes with a high degree of reactivity and apparently total regioselectivity as opposed to electron-withdrawing

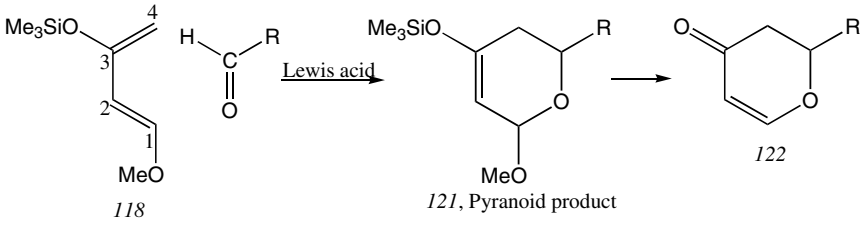
dienophiles. Moreover, the functionality endowed by such dienes, their corresponding cycloadducts, can be very nicely exploited in the synthesis of polyfunctional target systems. Figure 15.27 shows all-carbon Diels–Alder reaction with siloxydienes, where A (activating group) is CO, CN, or NO_2.



118 *119* *120*

Fig. 15.27

Danishefsky et al. have shown [73] that the cyclocondensation of dienes with aldehydes can be accomplished in the presence of Lewis acids. They have also shown [74, 75] that under appropriate catalysis, a large number of syloxydienes react with virtually any aldehyde. Figure 15.28 shows Lewis acid-catalyzed cyclocondensation of diene *118* with an aldehyde giving the corresponding dihydropyranone *122*.



118 *121*, Pyranoid product *122*

Fig. 15.28

Using heavily oxygenated dienes (e.g., *123* in Fig. 15.29) in cyclocondensations with aldehydes was instrumental in obtaining various types of sugars, such as galactosyl types of sugars [74](Fig. 15.29). A methodology was developed to introduce the oxygen function subsequent to cyclocondensation by oxidation with manganese (III) acetate [76]. In this way, glucose-like stereochemistry is generated at C4.

The reduction of the C3 keto group in *123* or *124* was accomplished with sodium borohydride–Ce (III) chloride (Luche reagent) [77] which is known to give equatorial alcohols. In this way, a very rapid and highly stereoselective routes to the glucal and galactal family of monosaccharide was developed.

The CC double bond of the galactal and glucal precursors can be functionalized either equatorially or axially at C2 with high stereoselectivity. Thus, for example, if the meta-chloroperbenzoic acid (MCPBA) reacts with the glucal-type system that

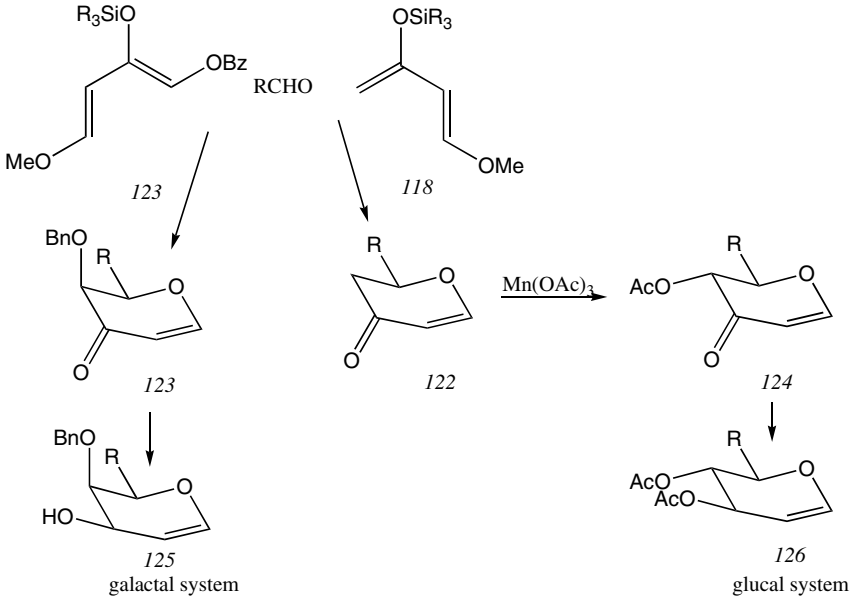


Fig. 15.29

has unprotected C3 hydroxyl group, β-hydroxyl group at C2 will be introduced, giving mannose-like configuration. However, if MCPBA reacts with the glucal-type system that has protected C3 hydroxyl group, α-hydroxyl group at C2 will be introduced giving glucose-like configuration (Fig. 15.30). Similarly, the galactal-type system will give under the same reaction conditions either the talose-like structure or the galactose-like configuration (Fig. 15.30).

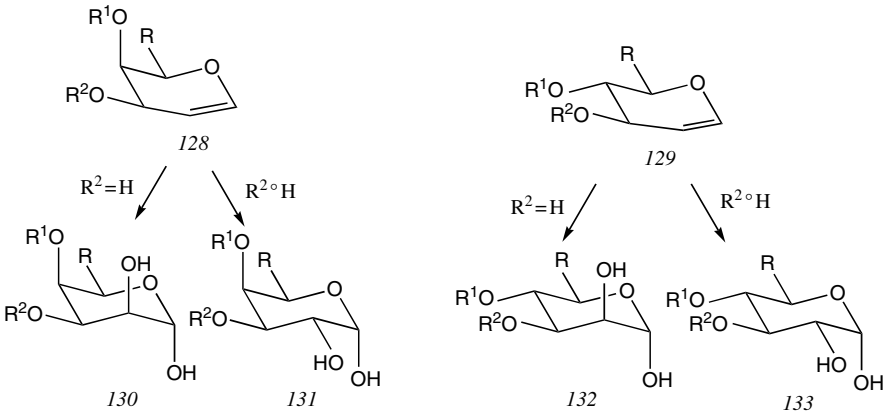


Fig. 15.30

Synthesis of higher-carbon sugars was approached by reiterative cyclocondensation principle, depicted in Fig. 15.31.

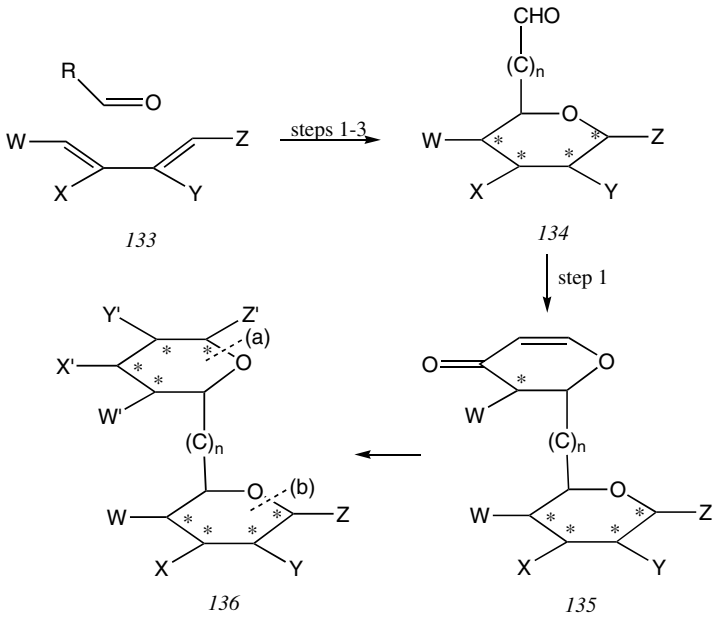


Fig. 15.31

Cyclocondensation of an aldehyde with diene *133* under Lewis acid catalysis leads to pyranoid structure *134* which is then manipulated as described above to achieve the appropriate stereochemistry of chiral carbon atoms. In the following stage of synthesis, a new aldehyde will be made on the side chain of the obtained pyranoid structure (compound *134*). Another cyclocondensation of this aldehyde with diene *133* gives compound *135* which after functionalizing of the ring carbon atoms with appropriate stereochemistry, as described above, can be converted to a higher-carbon sugar *136*.

This reiterative cyclocondensation strategy was applied to the total synthesis of octosyl acid A [78], peracetyltunicamynyluracil [79], and peracetyl-β-methylhikozamide [80].

The total synthesis of octosyl acid A is shown in Fig. 15.32. The "ribose aldehyde" *137* was used as starting material. Although also available by total synthesis [80] for this synthesis, it was prepared from D-ribose.

Cyclocondesation of aldehyde *137* with the diene *118* (Fig. 15.27) in the presence of a Lewis acid catalyst gave, with very high stereoselectivity, the bis-saccharide *138* [81], with 85% yield. Thus, the ribose ring fully controls the chirality at the C5′ carbon in the newly formed pyranone. The stereogenic center at the C7′ was formed by Luche reduction ($NaBH_4$–$CeCl_3$ in methanol, vide supra) of *138*. The obtained alcohol *139* was converted into *p*-methoxybenzyl (PMB) ether *140*. The

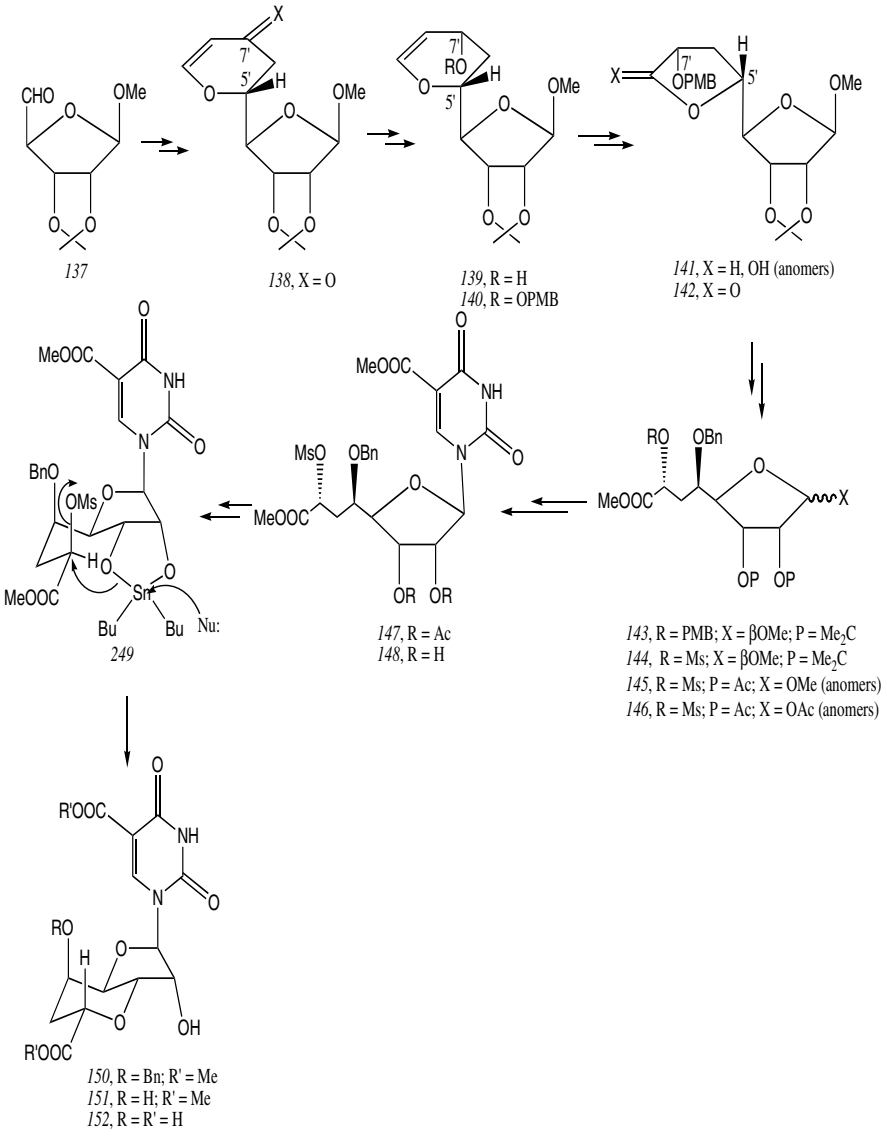


Fig. 15.32

compound *140* was then subjected to degradation with osmium tetroxide (catalytic) and sodium metaperiodate. After cleavage of the resulting formate (K_2CO_3–ethanol, room temperature), lactol anomers *141* were obtained with 93% yield. Oxidation of *141* with Ag_2CO_3–celite–xylene (reflux) afforded lactone *142*. After suitable functional group adjustments (several steps), the pyrimidine base was installed and mesyl-substituted cyclic stannane *249* was made. Fortunately, the otherwise

difficult ring closure of the 3-hydroxyl group of the ribose with the C7 carbon of the side chain proved to be possible via the tin derivative [78].

N-Acetylneuraminic acid was subject of great attention of many chemists and biochemists over the years due to its extraordinary biological importance. The first synthesis of *N*-acetylneuraminic acid was reported by Cornforth et al. [82, 83] by condensation of *N*-acetylglucosamine with oxaloacetic acid at pH 11 with the yield of 2%. Since the *N*-acetylneuraminic acid is composed of *N*-acetylmannosamine and pyruvic acid residues, the fact that it is obtained from *N*-acetylglucosamine suggests that epimerization of *N*-acetylglucosamine↔*N*-acetylmannosamine takes place in strongly alkaline solutions. In 1962 Carroll and Cornforth [84] repeated the synthesis of *N*-acetylneuraminic acid, but this time from *N*-acetylmannosamine and sodium oxaloacetate at pH 10. This time they obtained the *N*-acetylneuraminic acid in the 9 and 10% yield.

Kuhn and Baschang [85] have considerably increased the yield of *N*-acetylneuraminic acid when 2-*N*-acetyl-2-deoxy-4, 6-*O*-benzylidene-D-mannosamine is condensed with the potassium salt of di-tert-butyl-oxalacetate instead of sodium oxaloacetate. The initially obtained lactone is converted to *N*-acetylneuraminic acid with 34% yield by heating the lactone on water bath (Fig. 15.33).

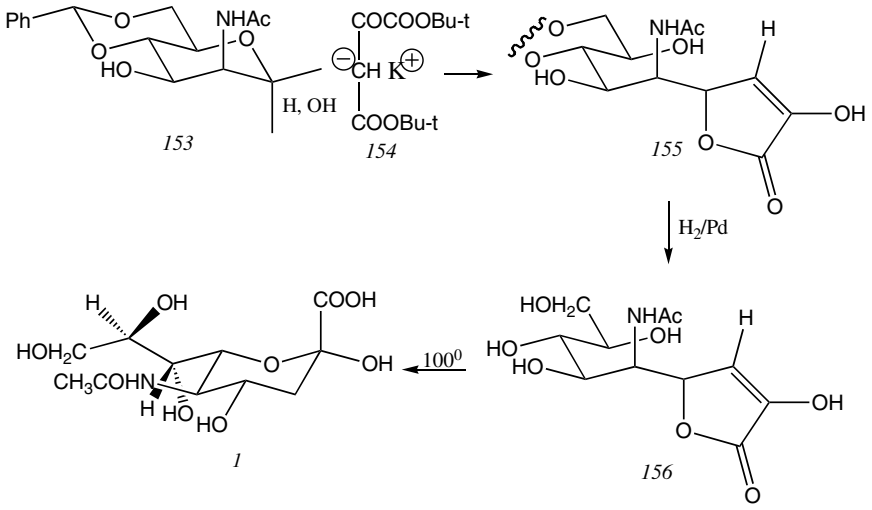


Fig. 15.33

Similar yield of *N*-acetylneuraminic acid was obtained by using *N*-acetylmannosamine instead of the corresponding 4,6-*O*-benzylidene derivative.

A very elegant total synthesis of *N*-acetylneuraminic acid was described by Danishefsky et al. [86]. The same group [87] described earlier a similar version of the total synthesis of *N*-acetylneuraminic acid.

The (*S*)-selenoaldehyde *159* used as dienophil in cyclocondensation with an appropriate diene was prepared from (*R*)-methyl lactate *157* in three steps: the mesylation of (*R*)-methyl lactate, displacement of mesyl group by $PhSe^-$ to (*S*)-seleno ester *158*, and the reduction with DIBAL of the ester group to the (*S*)-seleno aldehyde *159* (Fig. 15.34).

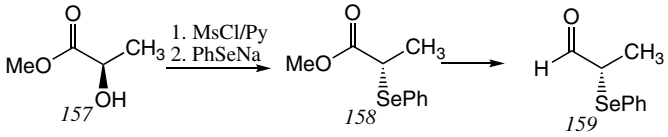


Fig. 15.34

The furyl diene needed for cyclocondensation with (*S*)-seleno aldehyde *159* was prepared from the mixture of geometrical isomers of furyl enone *160* by methylation with diazomethane (Fig. 15.35). The mixture of two geometrical isomers obtained by methylation was separated by chromatography on silica gel. The enone *161* led to pure *E*-diene *163*, while enone *162* led to the pure *Z*-diene *164* (Fig. 15.35). Of

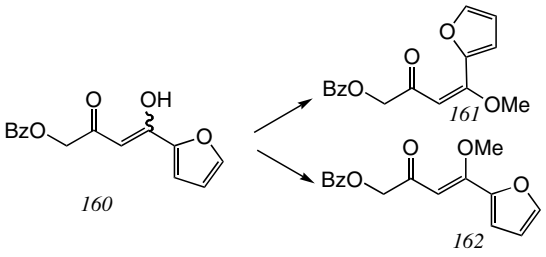


Fig. 15.35

the two dienes *163* and *164*, only diene *164* undergoes cyclocondensation with the (*S*)-selenoaldehyde *159* (Fig. 15.36) in methylene chloride at –78°C and in the presence of a Lewis catalyst ($BF_3.OEt_2$) giving the 5:1 mixture of *cis 165* and *trans*

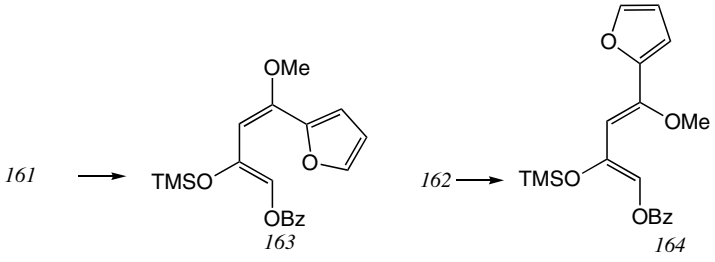


Fig. 15.36

166 dihydropyrones (Fig. 15.37). Optical purities in the range of 95% of *165* were realized when an aqueous workup for isolation of *158(S)* was avoided. Apparently aqueous treatment led to partial racemization of this labile selenoaldehyde.

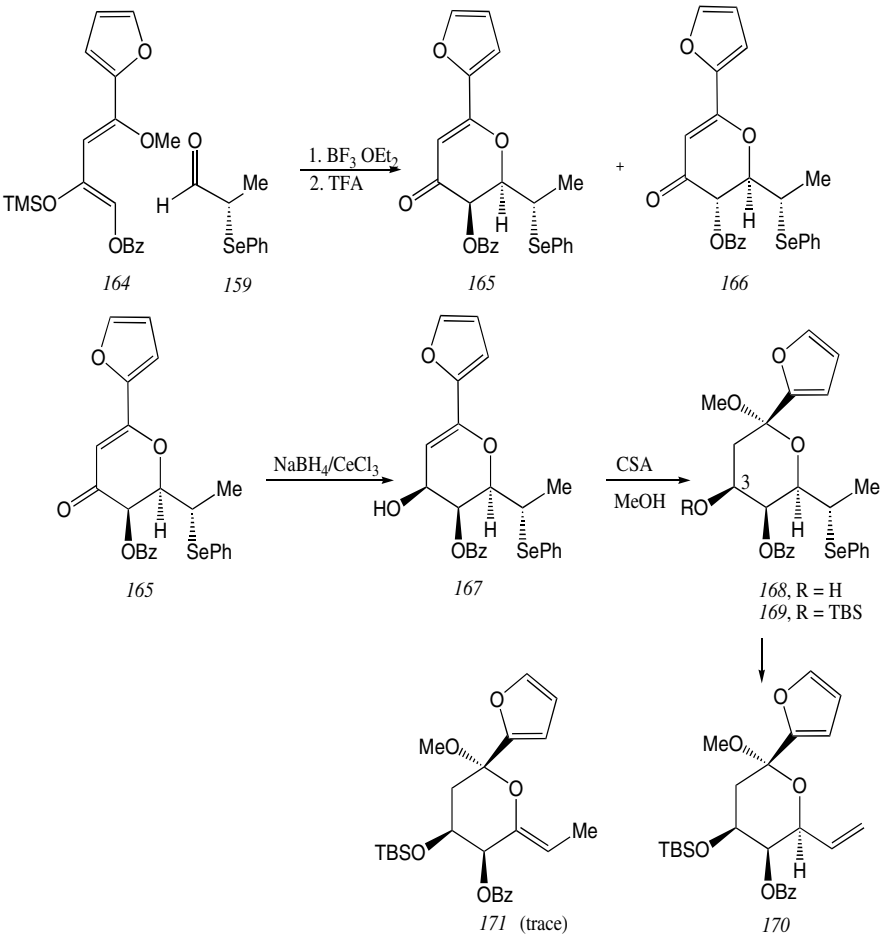


Fig. 15.37

Reduction of keto group of *165* with sodium borohydride in the presence of cerium (III) chloride [88] afforded the equatorial alcohol *167*. Addition of methanol to the double bond was accomplished in the presence of camphorsulfonic acid (CSA) giving axial glycoside *168*. After blocking the C3 hydroxyl group with TBS (*tert*-butyldimethylsilyl group), the phenylseleno group was removed from *169* by oxidative elimination using hydrogen peroxide giving almost exclusively the olefin *170* in 81% yield (olefin *171* was also present but only in traces). Osmium tetroxide

hydroxylation of *170* (Fig. 15.37) gave diol *172* which was then cleaved with lead tetraacetate giving the aldehyde *173*. Condensation of *173* with Still phosphonate [89] gave, with 80% yield, the *Z*-enoate *174* (with less than 5% of *E*-isomer). The hydroxylation of *174* with OsO_4 proceeded with a high stereoselectivity (ca. 20:1) to give the desired product *175* with 90% yield, which was then perbenzoylated to *176*.

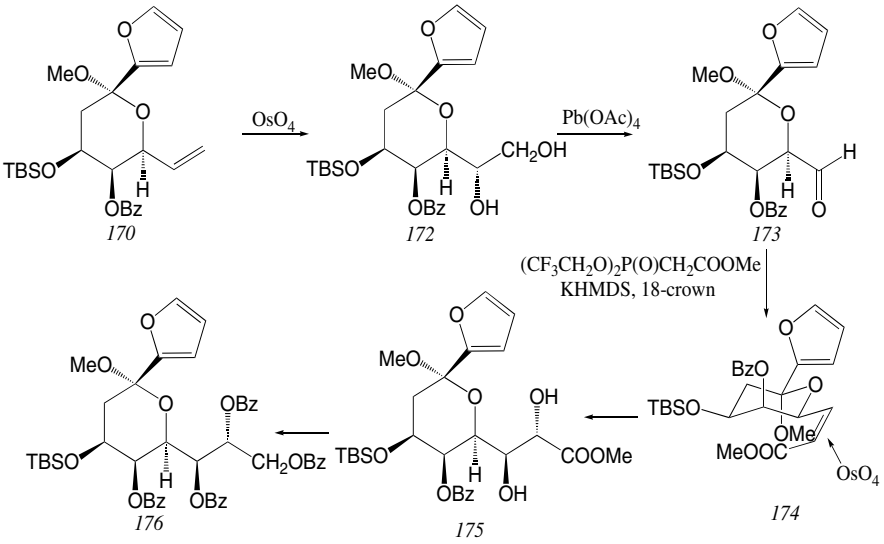


Fig. 15.38

At this point, the furan ring was oxidized with ruthenium tetroxide in the presence of excess of sodium bicarbonate as a buffer [90] (Fig. 15.38). The reaction was complete after 1 min giving the corresponding carboxylic acid that was esterified with diazo-methane to *177* (Fig. 15.39). The TBS protecting group was now removed with HF in methanol. The major product (60%) was the expected 4-hydroxy compound *178*. The other 30% was compound *179* that was obtained from *178* by benzoyl group migration. Reaction of *178* with potassium carbonate induced again benzoyl migration to produce additional amounts of *179*.

The conversion of *179* to the corresponding triflate *180* and displacement of triflate with azide using tetra-*n*-butylammonium azide gave the corresponding azide *181* with 86% yield. Reductive acetylation was accomplished in two steps: the azide group was first reduced with hydrogen in the presence of Lindlar catalyst to the amino group and the obtained amine *182* was acetylated with acetic anhydride to give *183*. Debenzoylation and hydrolysis of the methyl ester finally gave *N*-acetylneuraminic acid *1* (Fig. 15.39).

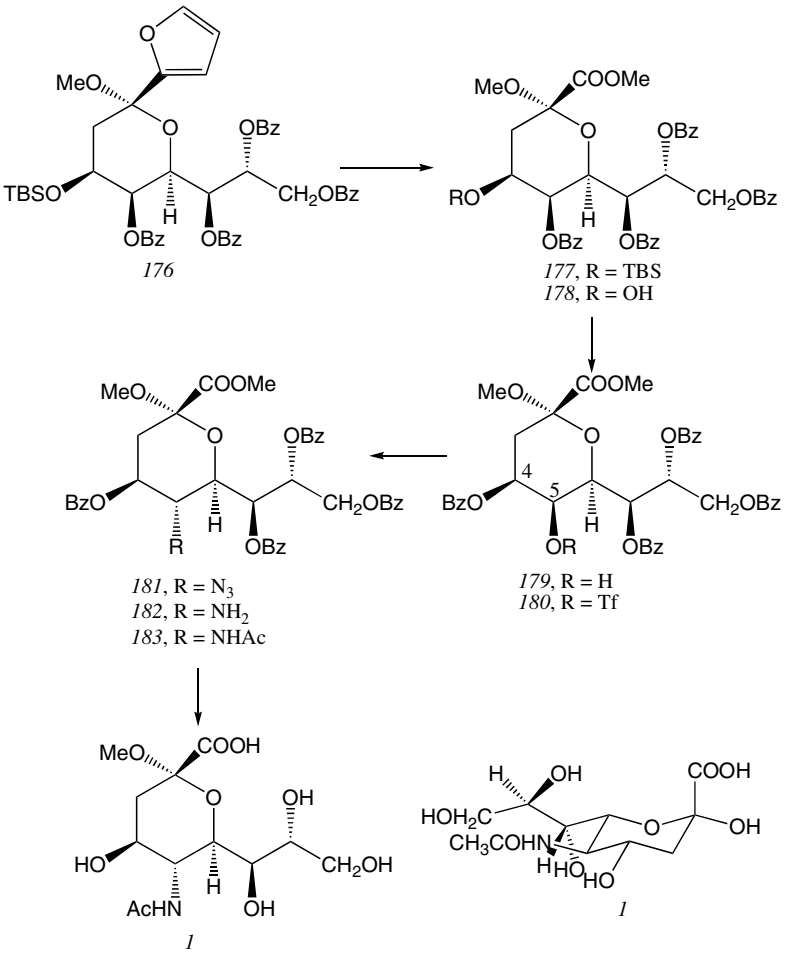


Fig. 15.39

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