Organic Chemistry III

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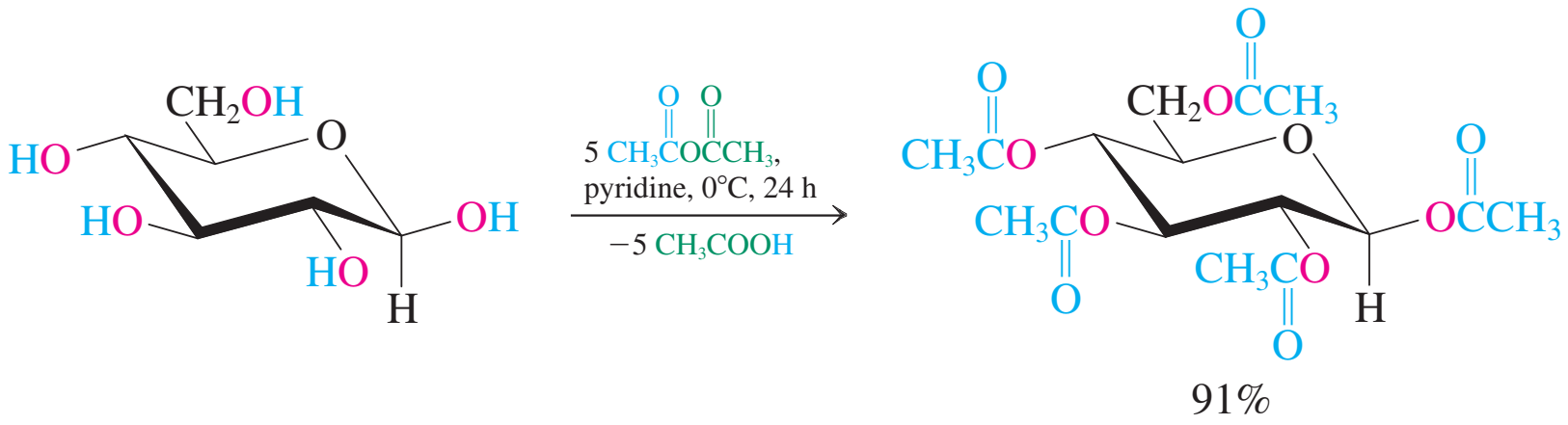
24-8 ESTER AND ETHER FORMATION: GLYCOSIDES

Because of their multiple hydroxy groups, sugars can be converted into alcohol derivatives.

Sugars can be esterified and methylated

Esters can be prepared from monosaccharides by standard techniques. Excess reagent will completely convert all hydroxy groups, including the hemiacetal function. For example, acetic anhydride transforms β-D-glucopyranose into the pentaacetate.

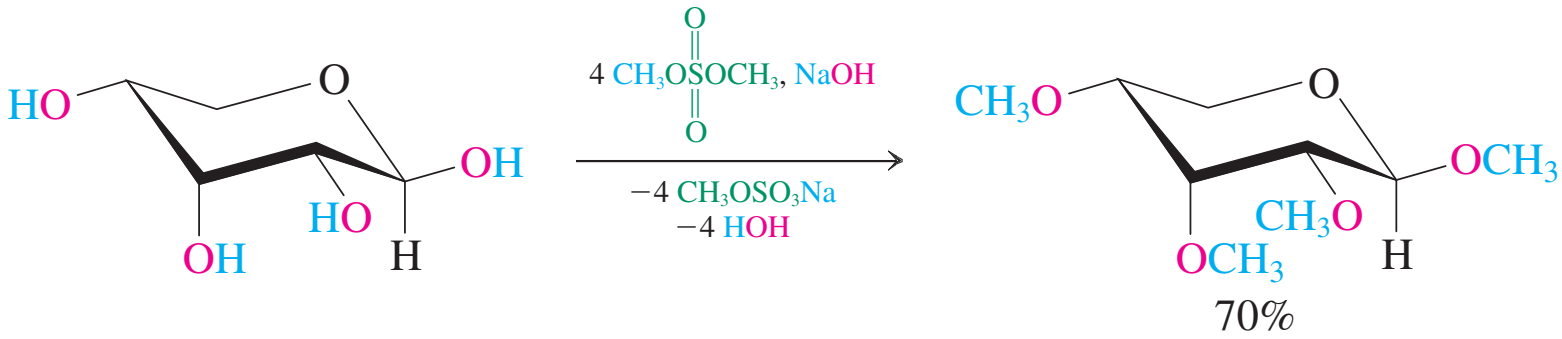
Complete Esterification of Glucose



β-D-Glucopyranose **β-D-Glucopyranose pentaacetate**

Williamson ether synthesis allows complete methylation.

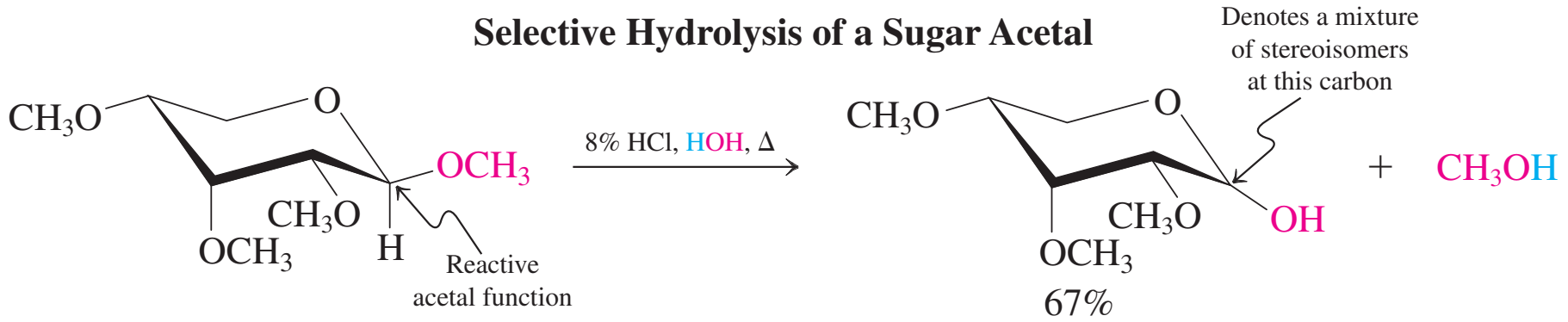
Complete Methylation of a Pyranose



β-D-Ribopyranose → **β-D-Ribopyranose tetramethyl ether**

The hemiacetal function at C1 is converted into an acetal group. The acetal function can be selectively hydrolyzed back to the hemiacetal.

Selective Hydrolysis of a Sugar Acetal

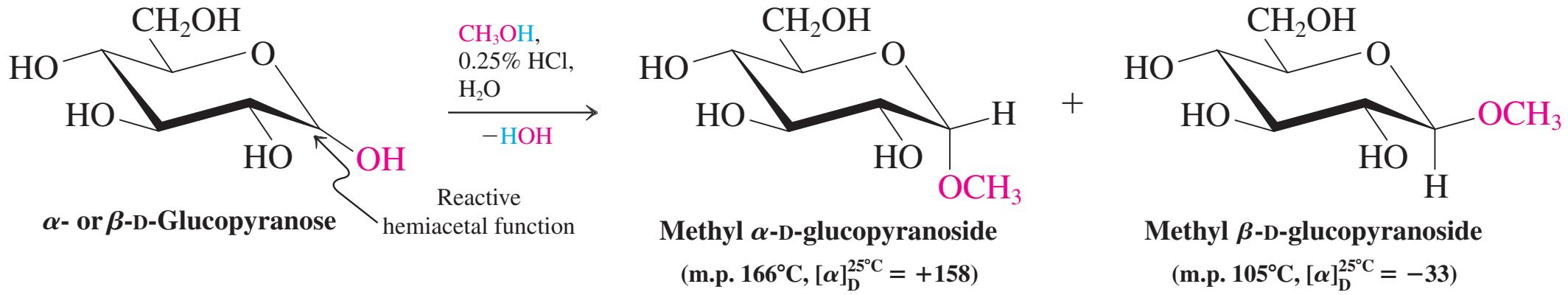


D-Ribopyranose trimethyl ether

(Mixture of α and β forms)

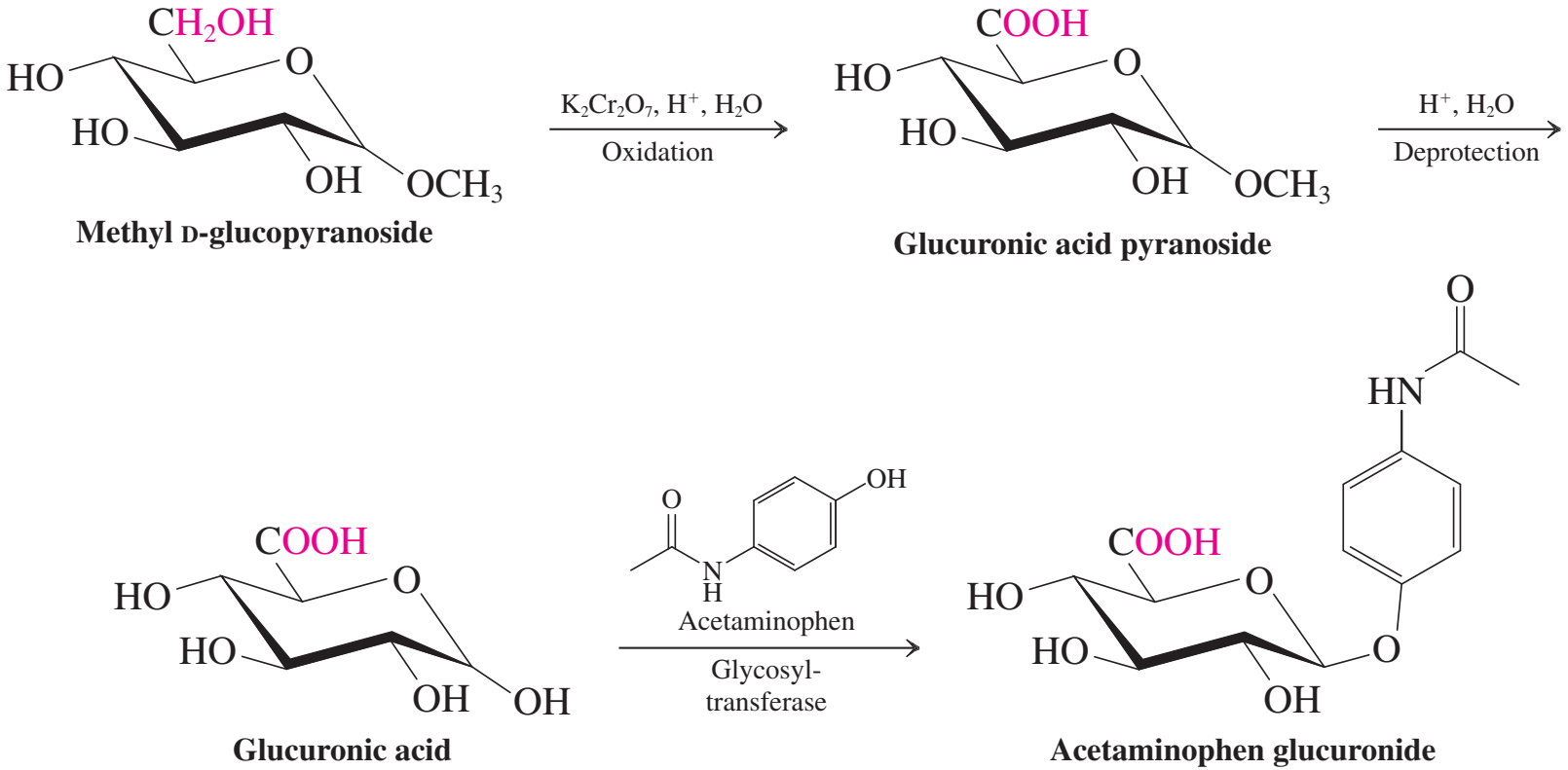
It is also possible to convert the hemiacetal unit of a sugar selectively into the acetal. For example, treatment of D-glucose with acidic methanol leads to the formation of the two methyl acetals. Sugar acetals are called **glycosides.** Thus, glucose forms **glucosides.**

Selective Preparation of a Glycoside (Sugar Acetal)



Because glycosides contain a blocked anomeric carbon atom, they do not show mutarotation in the absence of acid, they test negatively to Fehling's and Tollens's reagents (they are *non*reducing sugars), and they are unreactive toward reagents that attack carbonyl groups. Such protection can be useful in synthesis and in structural analysis.

The selective oxidation of the terminal hydroxy function of glucose happens when protected at C1 as the methyl pyranoside. After deprotection, glucuronic acid forms and plays an important role in the metabolism of drugs and other foreign materials in the body, and the presence of the reactive hemiacetal unit and the water-solubilizing carboxy group are crucial for its function. A glycosyl transferase enzyme catalyzes displacement of the anomeric –OH by the targeted material (e.g. in acetaminophen). Such derivatization renders a drug highly water soluble to allow for rapid excretion through urination.



Methyl D-glucopyranoside

Glucuronic acid pyranoside

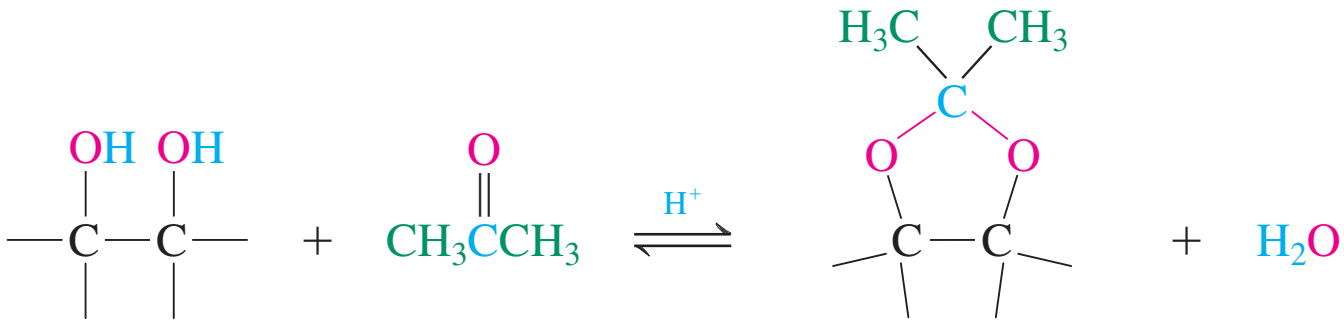
Glucuronic acid

Acetaminophen glucuronide

Neighboring hydroxy groups in sugars can be linked as cyclic ethers

The presence of neighboring pairs of hydroxy groups in the sugars allows for the formation of cyclic ether derivatives. For example, it is possible to synthesize five- or six-membered cyclic sugar acetals from the vicinal (and also from some β-diol) units by treating them with carbonyl compounds.

Cyclic Acetal Formation from Vicinal Diols



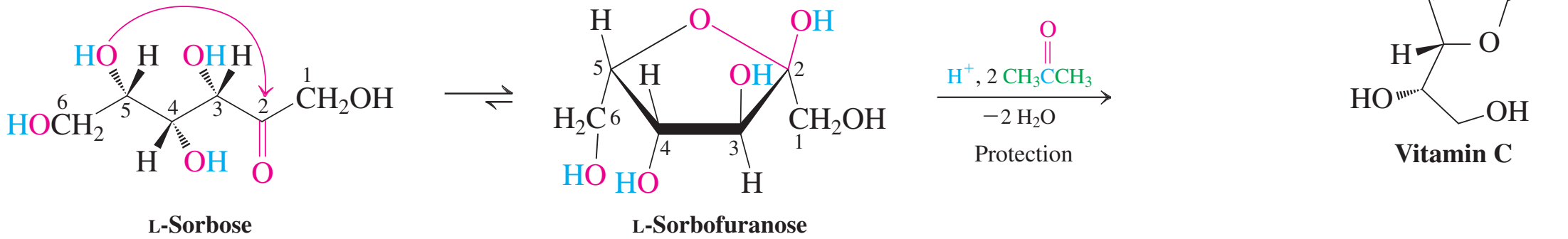
Acetone acetal

Such processes work best when the two OH groups are positioned cis to allow a relatively unstrained five- or six-membered ring to form. Cyclic acetal and ether formation is often employed to protect selected alcohol functions.

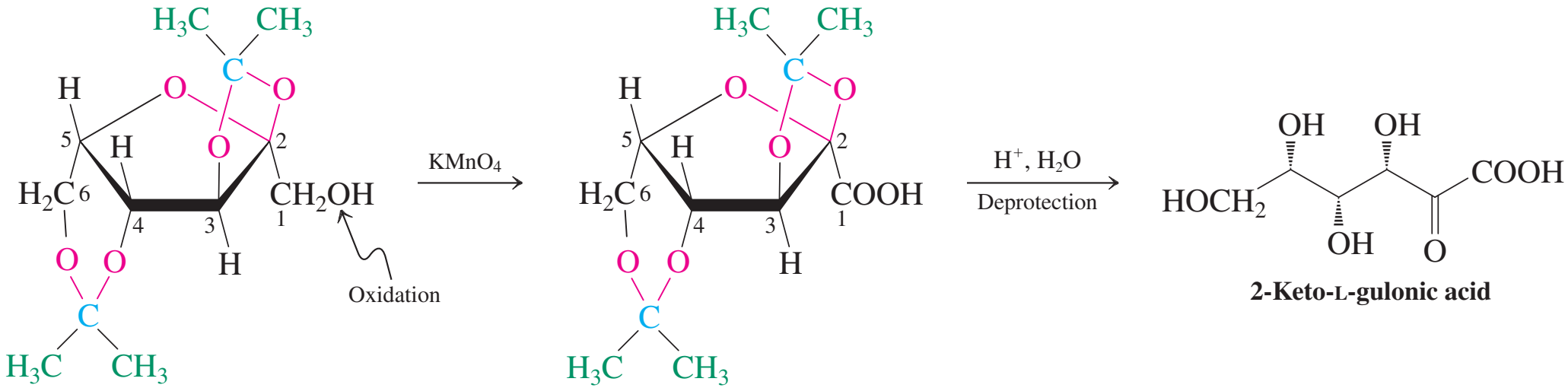
The remaining hydroxy moieties can then be converted into leaving groups, transformed by elimination, or oxidized to carbonyl compounds.

An important step in the commercial synthesis of vitamin C is the selective oxidation of the C1 hydroxy group of L-sorbose to the corresponding carboxylic acid (2-keto-L-gulonic acid). To accomplish this task, all other alcohol functions have to be protected in the form of two adjacent acetal units.

Acetalization of L-Sorbose



L-Sorbose **L-Sorbofuranose** **Vitamin C**



2-Keto-L-gulonic acid

24-9 STEP-BY-STEP BUILDUP AND DEGRADATION OF SUGARS

Larger sugars can be made from smaller ones and vice versa, by chain lengthening and chain shortening.

Cyanohydrin formation and reduction lengthens the chain

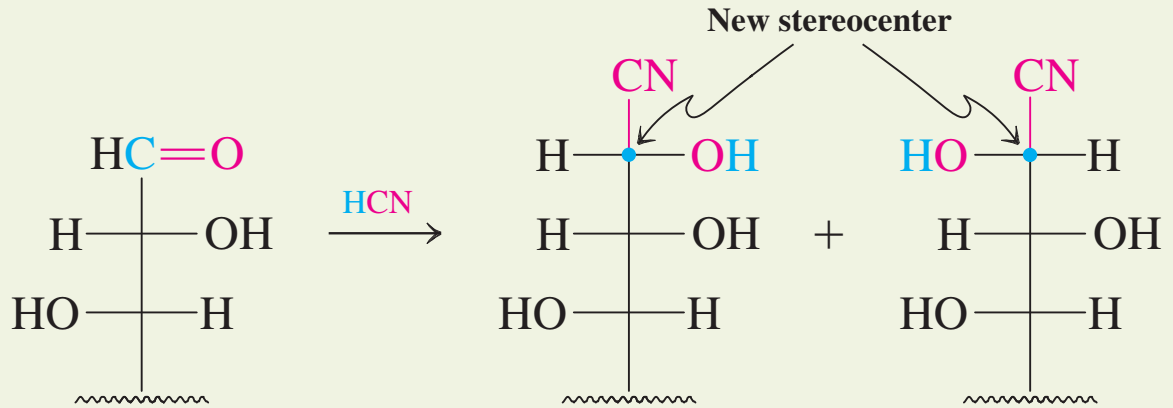
To lengthen the chain of a sugar, an aldose is first treated with HCN to give the corresponding cyanohydrin. Because this transformation forms a new stereocenter, two diastereomers (epimers) appear.

Separation of the diastereomers and partial reduction of the nitrile group by catalytic hydrogenation in aqueous acid gives the aldehyde groups of the chain-extended sugars.

In this hydrogenation, a modified palladium catalyst (similar to the Lindlar catalyst) allows selective reduction of the nitrile to the imine, which hydrolyzes under the reaction conditions.

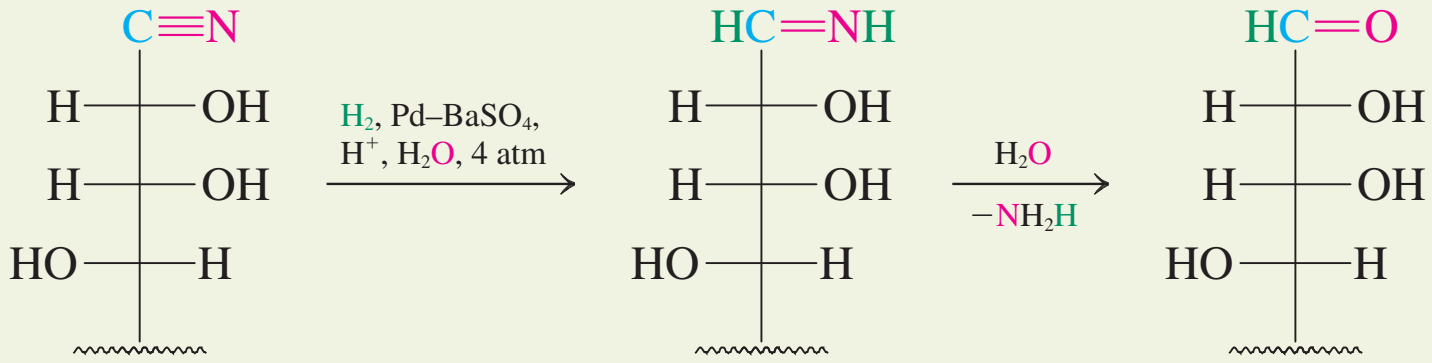
Sugar Chain Extension Through Cyanohydrins

Step 1. Cyanohydrin formation



Two new diastereomeric nitriles

Step 2. Reduction and hydrolysis (only one diastereomer is shown)



Imine **Extended sugar**

This chain-lengthening sequence is an improved and shortened version of what is known as the **Kiliani-Fischer synthesis** of chain-extended sugars. In the late 1800s, Kiliani demonstrated that addition of cyanide to an aldose gives the cyanohydrin, which, upon hydrolysis, is converted into the chain-extended aldonic acid.

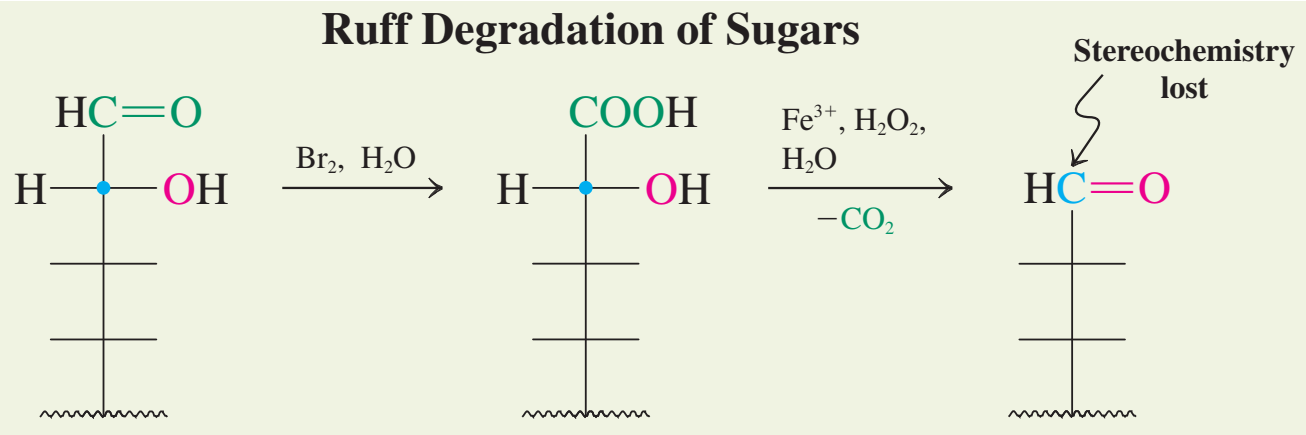
Fischer subsequently succeeded in converting this aldonic acid into an aldose by lactone formation followed by reduction (for Fischer's reduction method).

Ruff degradation shortens the chain

This procedure removes the carbonyl group of an aldose and converts the neighboring carbon into the aldehyde function of the new sugar.

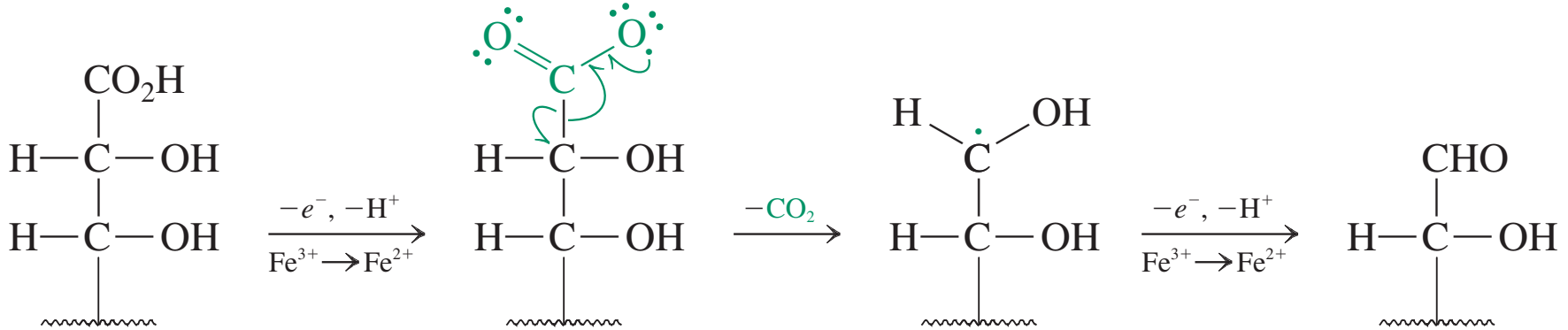
The **Ruff degradation** is an oxidative decarboxylation. The sugar is first oxidized to the aldonic acid by aqueous bromine. Exposure to hydrogen peroxide in the presence of ferric ion then leads to the loss of the carboxy group and oxidation of the new terminus to the aldehyde function of the lower aldose.

During this process, the stereochemistry of the hydroxy carbon next to the carbonyl is lost. Consequently, two epimeric aldoses at that center will give the same new sugar.



The oxidative decarboxylation takes place by means of two one-electron oxidations. The first gives a carboxy radical, which is unstable and rapidly loses CO_2. The resulting hydroxy-substituted radical is oxidized again to give the aldehyde.

Ruff degradation gives low yields because of the sensitivity of the products to the reaction conditions. Nevertheless, the procedure is useful in structural elucidations.



24-10 RELATIVE CONFIGURATIONS OF THE ALDOSES: AN EXERCISE IN STRUCTURE DETERMINATION

Imagine that we have been presented with 14 jars, each filled with one of the aldoses in Figure 24-1, each labeled with a name, but *no structural formula.* How would we establish the structure of each substance *without using spectroscopy?*

Fischer made one assumption that the dextrorotatory enantiomer of 2,3-dihydroxypropanal (glyceraldehyde) had the D (and not the L) configuration. This assumption was proved correct only after a special kind of X-ray analysis was developed in 1950.

We begin with chain extension of D-glyceraldehyde, obtaining a mixture of D-erythrose and D-threose.

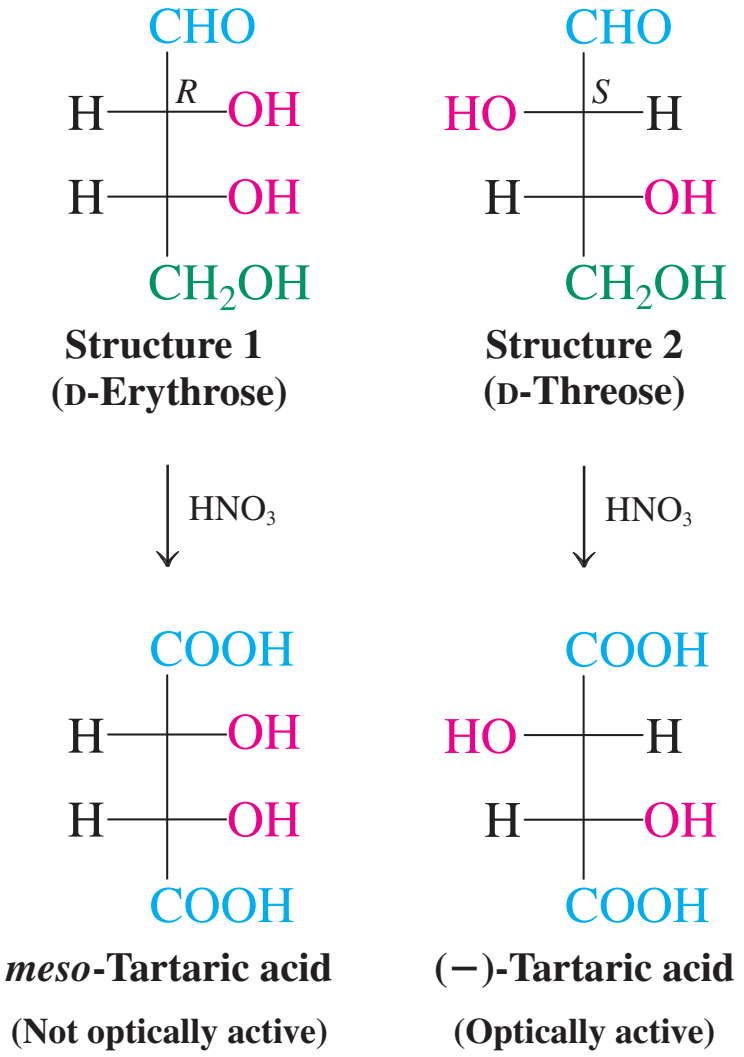
The structures of the aldotetroses and aldopentoses can be determined from the optical activity of the corresponding aldaric acids

Oxidation of D-erythrose with nitric acid gives *optically inactive meso*-tartaric acid, which tells us that D-erythrose must have structure 1, with both –OH groups on the *same side* in the Fischer representation.

In contrast, oxidation of D-threose forms an *optically active* acid. Thus, D-threose must have the opposite stereochemistry at C2 (structure 2).

Both must have the same (*R*) configuration at C3, the carbon derived from the C2 stereocenter of our starting material, D-glyceraldehyde.

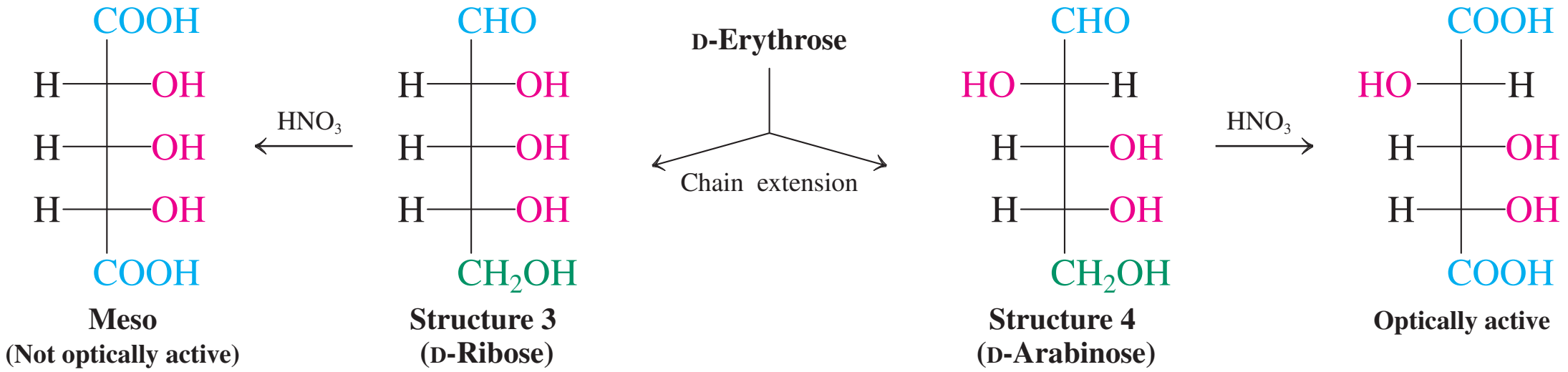
The difference is at C2: D-Erythrose is 2*R*; D-threose, 2*S*.



Chain extension of D-erythrose gives a mixture of two pentoses: D-ribose and D-arabinose. Their configurations at C3 and C4 must be the same as those of C2 and C3 in D-erythrose; they differ at C2, the new stereocenter created in the lengthening procedure.

Nitric acid oxidation of D-ribose gives an optically inactive (meso) acid; thus D-ribose has structure 3.

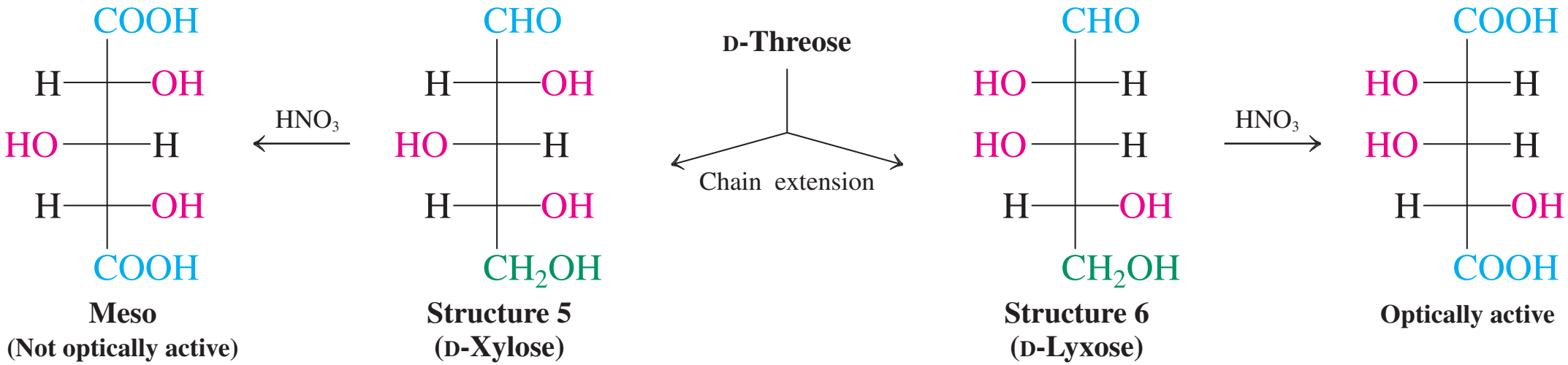
D-Arabinose oxidizes to an optically active acid; it must have structure 4.



Proceeding in the same way from D-threose, chain extension gives a mixture of D-xylose and D-lyxose.

The oxidation product of D-xylose is meso; therefore D-xylose has structure 5.

The optically active oxidation product of D-lyxose confirms its structure as 6.



Meso
(Not optically active)

Structure 5
(D-Xylose)

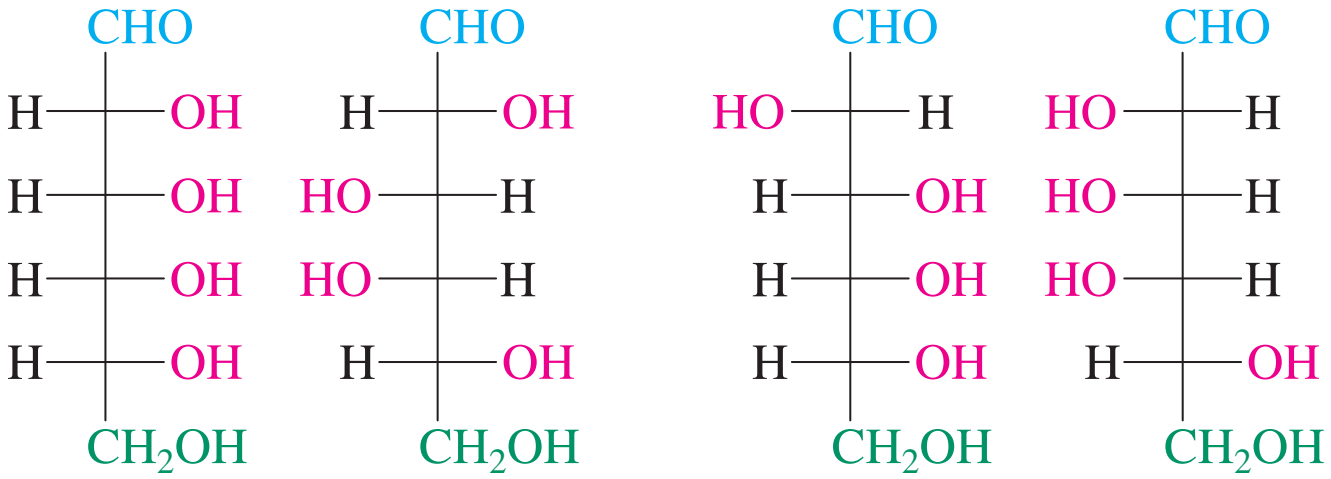
Structure 6
(D-Lyxose)

Optically active

Symmetry properties also define the structures of the aldohexoses

The four aldopentoses can extend the chain to give four pairs of aldohexoses, each pair distinguished from the others by the unique sequence of stereocenters at C3, C4, and C5. The members of each pair are epimers and differ only in their configuration at C2.

The structural assignment for the four sugars obtained from D-ribose and D-lyxose, accomplished by oxidation to the corresponding aldaric acids. Both D-allose and D-galactose give optically inactive oxidation products, in contrast with D-altrose and D-talose, which give optically active dicarboxylic acids.



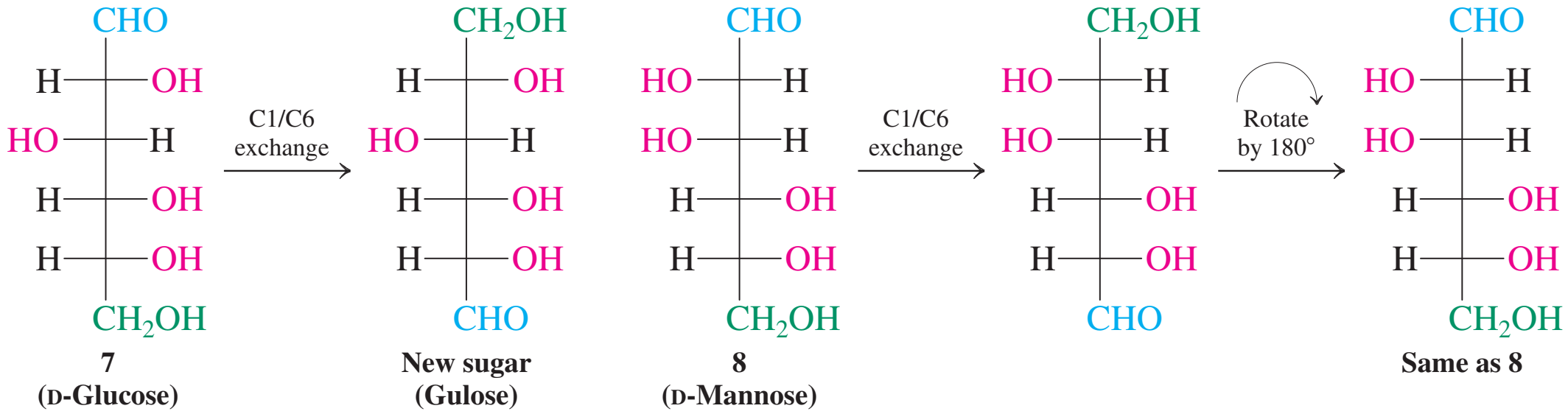
The structural assignments of the four remaining hexoses (with structures 7–10) cannot be based on the approach taken so far, because all give optically active diacids upon oxidation.

Fischer found that chain extension of D-arabinose gave a mixture of D-glucose and D-mannose, one of which must have structure 7 and the other structure 8.

He developed a procedure to *exchange* the functionalities at C1 and C6 of a hexose—converting C1 to a primary alcohol and C6 to an aldehyde.

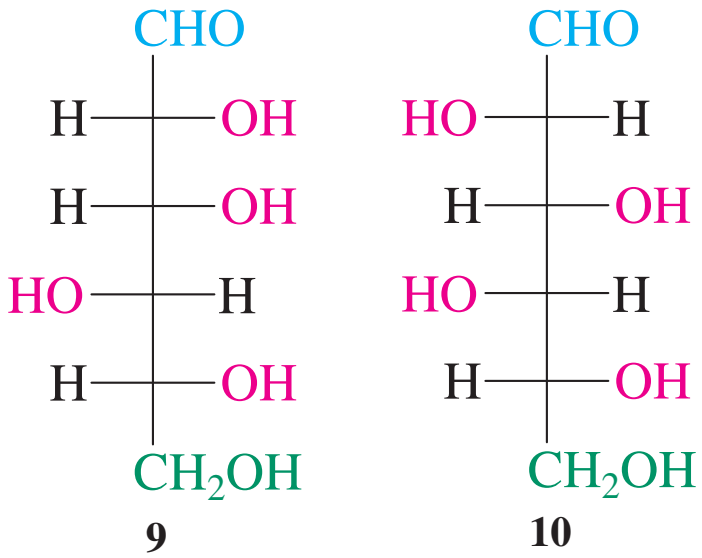
Starting with both D-glucose and D-mannose, he found that the result of C1/C6 exchange in glucose was a *new sugar,* which did not exist in nature and was given the name gulose.

On the other hand, exchange of C1 and C6 in mannose returned mannose, unchanged. If we perform a C1/C6 exchange in 8 and then rotate the resulting Fischer projection by 180^{o}, we realize that the initial and final structures are identical: The exchange procedure gives the *original sugar* back.



With the synthesis of gulose, one of the two remaining hexoses (the products of chain lengthening of D-xylose) was identified as structure 9.

By process of elimination, the other, D-idose, could be assigned structure 10.



24-11 COMPLEX SUGARS IN NATURE: DISACCHARIDES

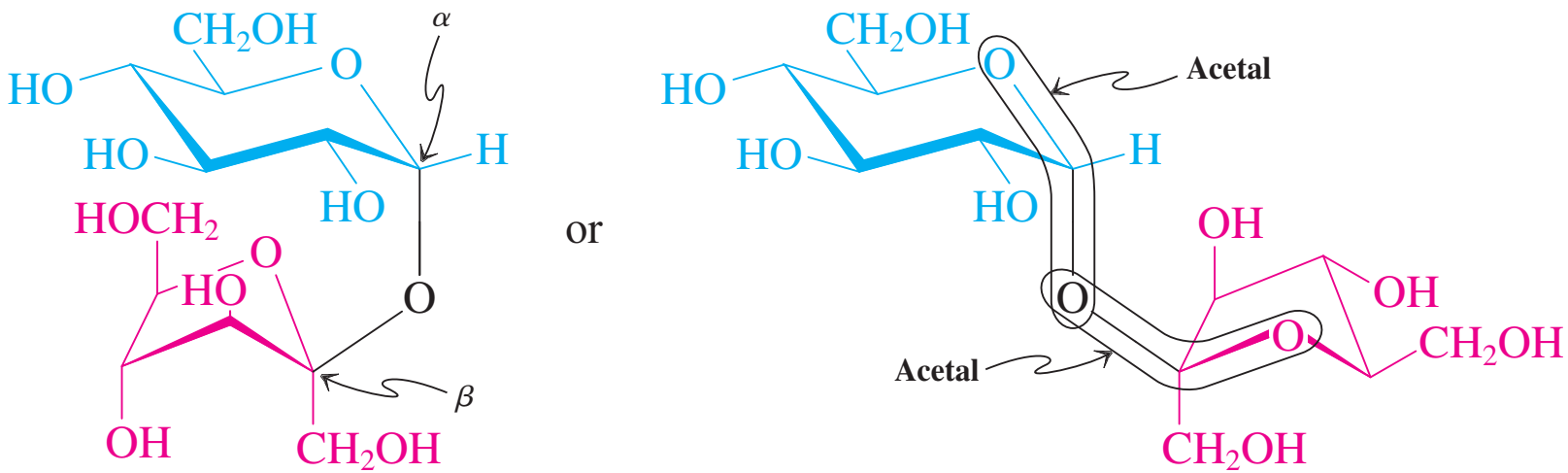
Sucrose, ordinary table sugar, is one of the few natural chemicals consumed in unmodified form (water and NaCl are examples of others). Its average yearly consumption in the United States is about 77 pounds per person.

Sugar is isolated from sugar cane and sugar beets, in which it is particularly abundant (about 14–20% by weight), although it is present in many plants in smaller concentrations. World production is about 168 million tons a year.

Sucrose is a disaccharide derived from glucose and fructose

The structure of sucrose can be deduced from its chemical behavior. Acidic hydrolysis splits it into glucose and fructose.

It is a nonreducing sugar. It does not form an osazone. It does not undergo mutarotation. These findings suggest that the component monosaccharide units are linked by an acetal bridge connecting the two anomeric carbons; in this way, the two cyclic hemiacetal functions block each other.



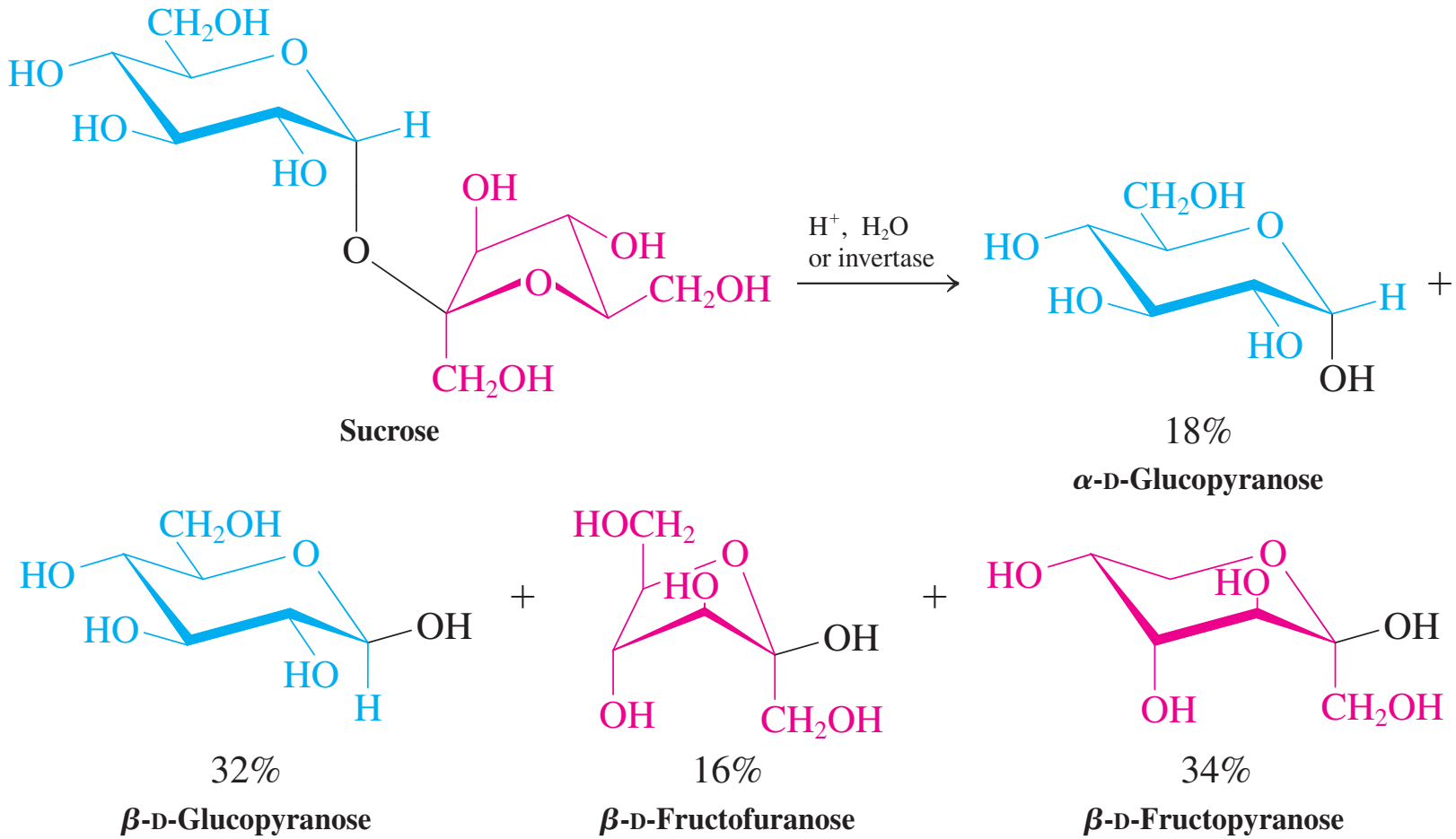
Sucrose, a β-D-fructofuranosyl-α-D-glucopyranoside

Sucrose has a specific rotation of +66.5. Treatment with aqueous acid decreases the rotation until it reaches a value of -20. The phenomenon, known as the **inversion of sucrose,** is related to mutarotation of monosaccharides.

It includes three separate reactions: **(I)** hydrolysis of the disaccharide to the component monosaccharides α-D-glucopyranose and β-D-fructofuranose; **(II)** mutarotation of α-D-glucopyranose to the equilibrium mixture with the β form; and **(III)** mutarotation of β-D-fructofuranose to the slightly more stable β-D-fructopyranose.

Because the value for the specific rotation of fructose (-92) is more negative than the value for glucose (+52.7), the resulting mixture, sometimes called **invert sugar,** has a net negative rotation, *inverted* from that of the original sucrose solution.

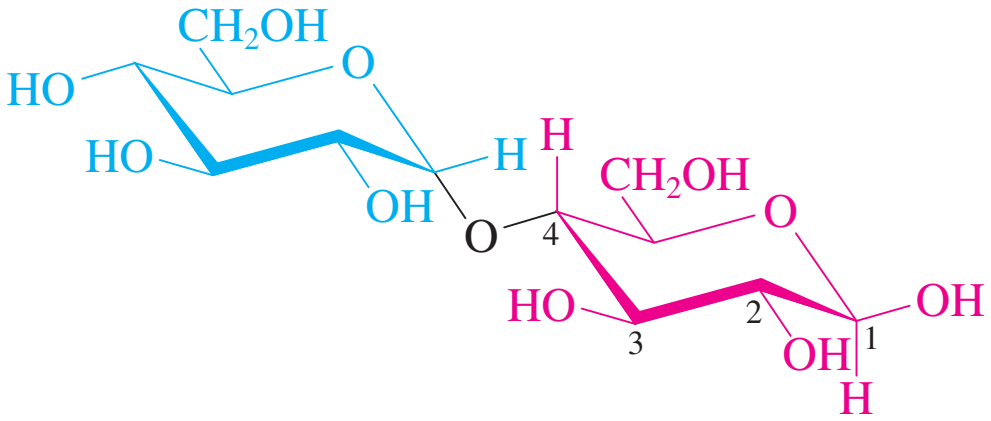
Inversion of Sucrose



Maltose (malt sugar) is a dimer of glucose in which the hemiacetal oxygen of one glucose molecule (in the α anomeric form) is bound to C4 of the second. It is also obtained in 80% yield by enzymatic (amylase) degradation of starch.

In this arrangement, one glucose retains its unprotected hemiacetal unit with its distinctive chemistry. Maltose is a reducing sugar; it forms osazones, and it undergoes mutarotation.

Maltose is hydrolyzed to two molecules of glucose by aqueous acid or by the enzyme maltase. It is about one-third as sweet as sucrose.

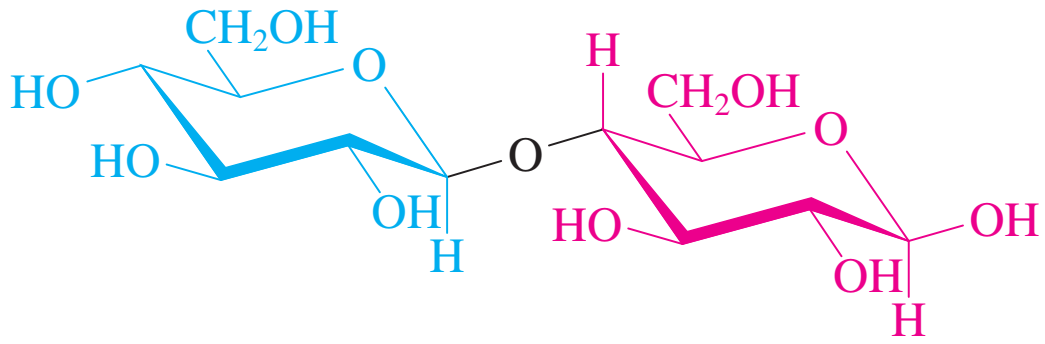


β-Maltose, an α-D-glucopyranosyl-β-D-glucopyranose

Cellobiose is obtained by the hydrolysis of cellulose. Its chemical properties are almost identical with those of maltose, which differs only in the stereochemistry at the acetal linkage—β instead of α.

Aqueous acid cleaves cellobiose into two glucose molecules just as efficiently as it hydrolyzes maltose.

However, enzymatic hydrolysis requires a different enzyme, β-glucosidase, which specifically attacks only the β-acetal bridge. In contrast, maltase is specific for α-acetal units of the type found in maltose.

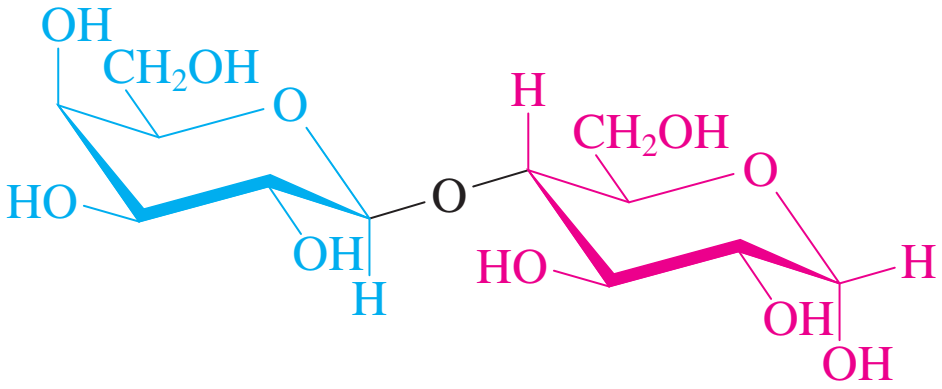


β-Cellobiose, a β-D-glucopyranosyl-β-D-glucopyranose

After sucrose, the most abundant natural disaccharide is **lactose** (milk sugar). It is found in human and most animal milk (about 5% solution). Its structure is made up of galactose and glucose units. Crystallization from water furnishes only the α anomer.

Lactose contains an unprotected hemiacetal unit and is therefore a reducing sugar that undergoes mutarotation. The first step of its degradation in the body is hydrolysis of the glycosidic bond by the enzyme lactase to give galactose and glucose.

Lack of this enzyme causes lactose intolerance, a condition that is associated with abdominal cramps and diarrhea after the consumption of milk and other dairy products.



Crystalline α-lactose, a β-D-galactopyranosyl-α-D-glucopyranose

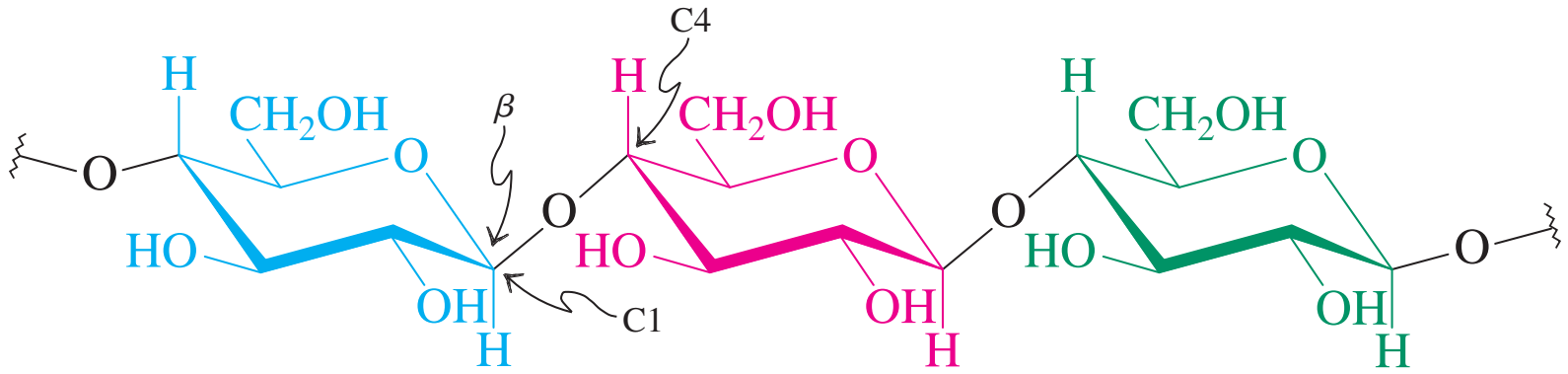
24-12 POLYSACCHARIDES AND OTHER SUGARS IN NATURE

Polysaccharides are the polymers of monosaccharides. Their possible structural diversity exceeds that of alkene polymers, particularly in variations of chain length and branching.

The three most abundant natural polysaccharides— cellulose, starch, and glycogen—are derived from the same monomer: glucose.

Cellulose and starch are glucose polymers

Cellulose is a poly-β-glucopyranoside linked at C4, containing about 3000 monomeric units and having a molecular weight of about 500,000. It is largely linear.



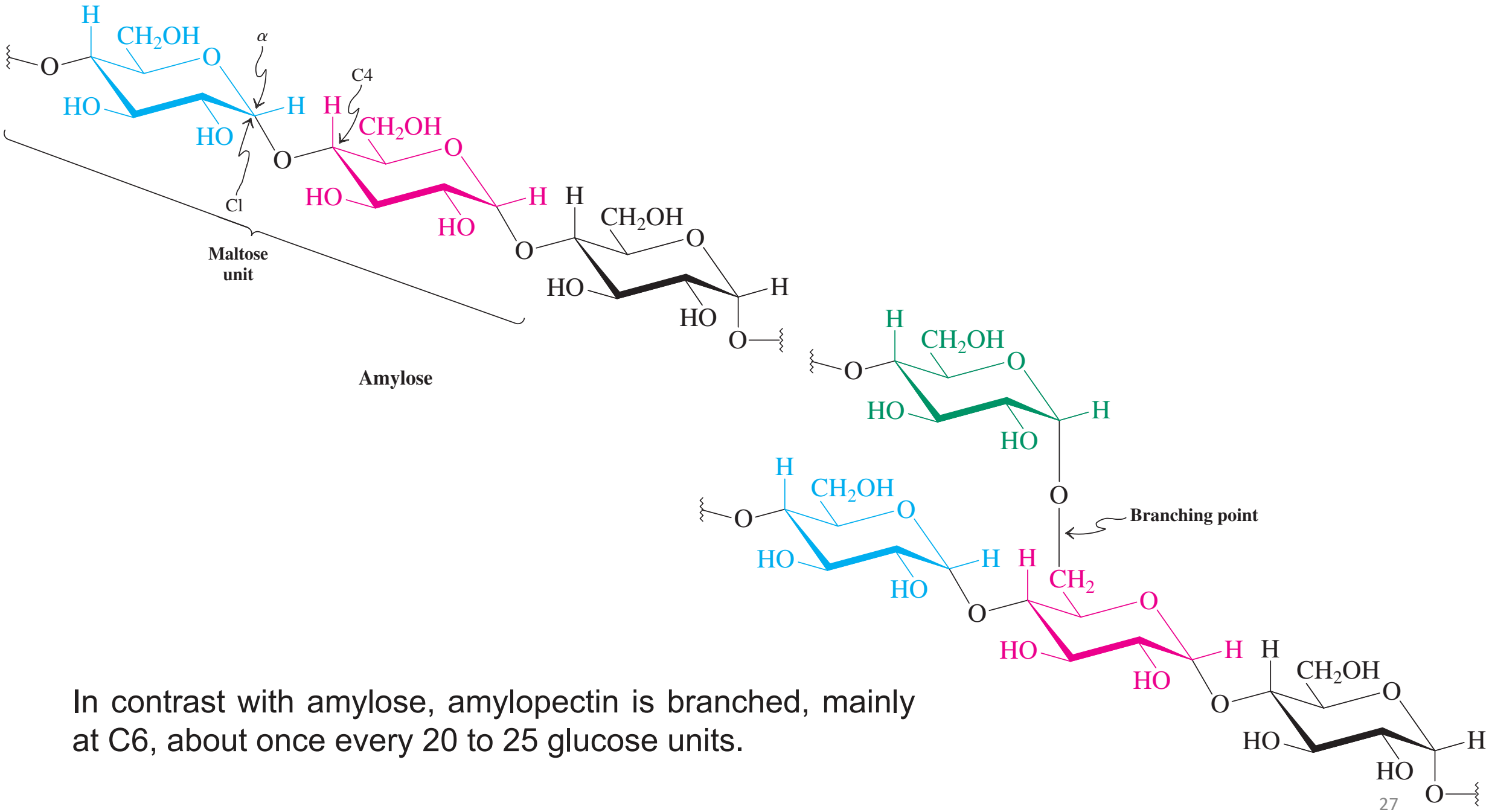
Cellulose

Individual strands of cellulose tend to align with one another and are connected by multiple hydrogen bonds. The development of so many hydrogen bonds is responsible for the highly rigid structure of cellulose and its use as the cell-wall material. Cellulose is abundant in trees and other plants. Cotton fiber is almost pure cellulose, as is filter paper. Wood and straw contain about 50% of the polysaccharide.

Like cellulose, **starch** is a polyglucose, but its subunits are connected by α-acetal linkages. It functions as a food reserve in plants and (like cellulose) is readily cleaved by aqueous acid into glucose. Major sources of starch are corn, potatoes, wheat, and rice.

Hot water swells granular starch and allows the separation of the two major components: **amylose** (~20%) and **amylopectin** (~80%). Both are soluble in hot water, but amylose is less soluble in cold water.

Amylose contains a few hundred glucose units per molecule (molecular weight, 150,000–600,000). Its structure is different from that of cellulose, even though both polymers are unbranched. The difference in the stereochemistry at the anomeric carbons leads to the strong tendency of amylose to form a helical polymer arrangement.



In contrast with amylose, amylopectin is branched, mainly at C6, about once every 20 to 25 glucose units.

Glycogen is a source of energy

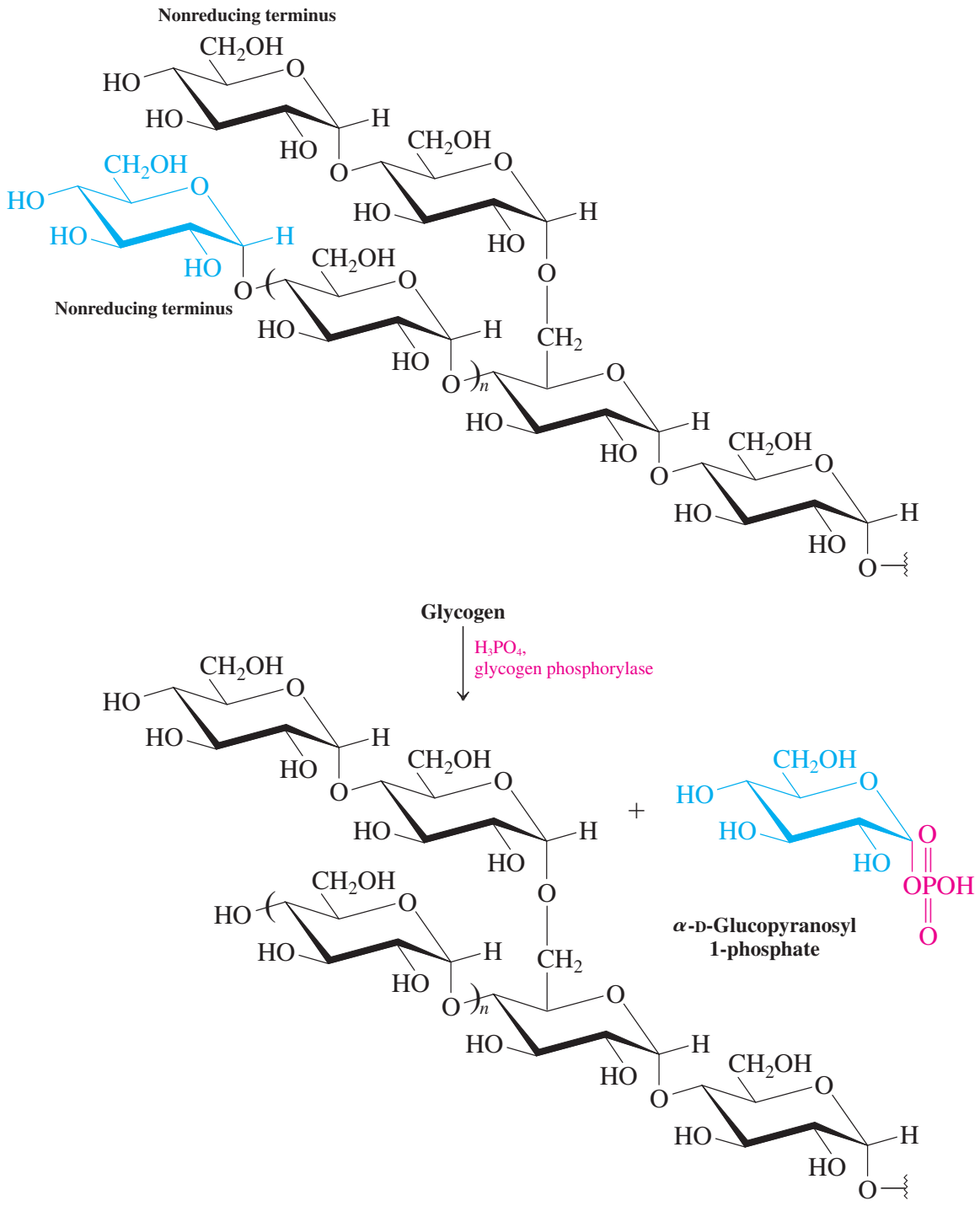
Another polysaccharide similar to amylopectin but with greater branching (1 per 10 glucose units) and of much larger size (as much as 100 million molecular weight) is **glycogen.**

This compound is of considerable biological importance because it is one of the major energy-storage polysaccharides in humans and animals and because it provides an immediate source of glucose between meals and during (strenuous) physical activity.

It is accumulated in the liver and in rested skeletal muscle in relatively large amounts.

A special enzyme, glycogen phosphorylase, first breaks glycogen down to give a derivative of glucose, α-D-glucopyranosyl 1-phosphate. This transformation takes place at one of the nonreducing terminal sugar groups of the glycogen molecule and proceeds step by step—one glucose molecule at a time.

Because glycogen is so highly branched, there are many such end groups at which the enzyme can “nibble” away.

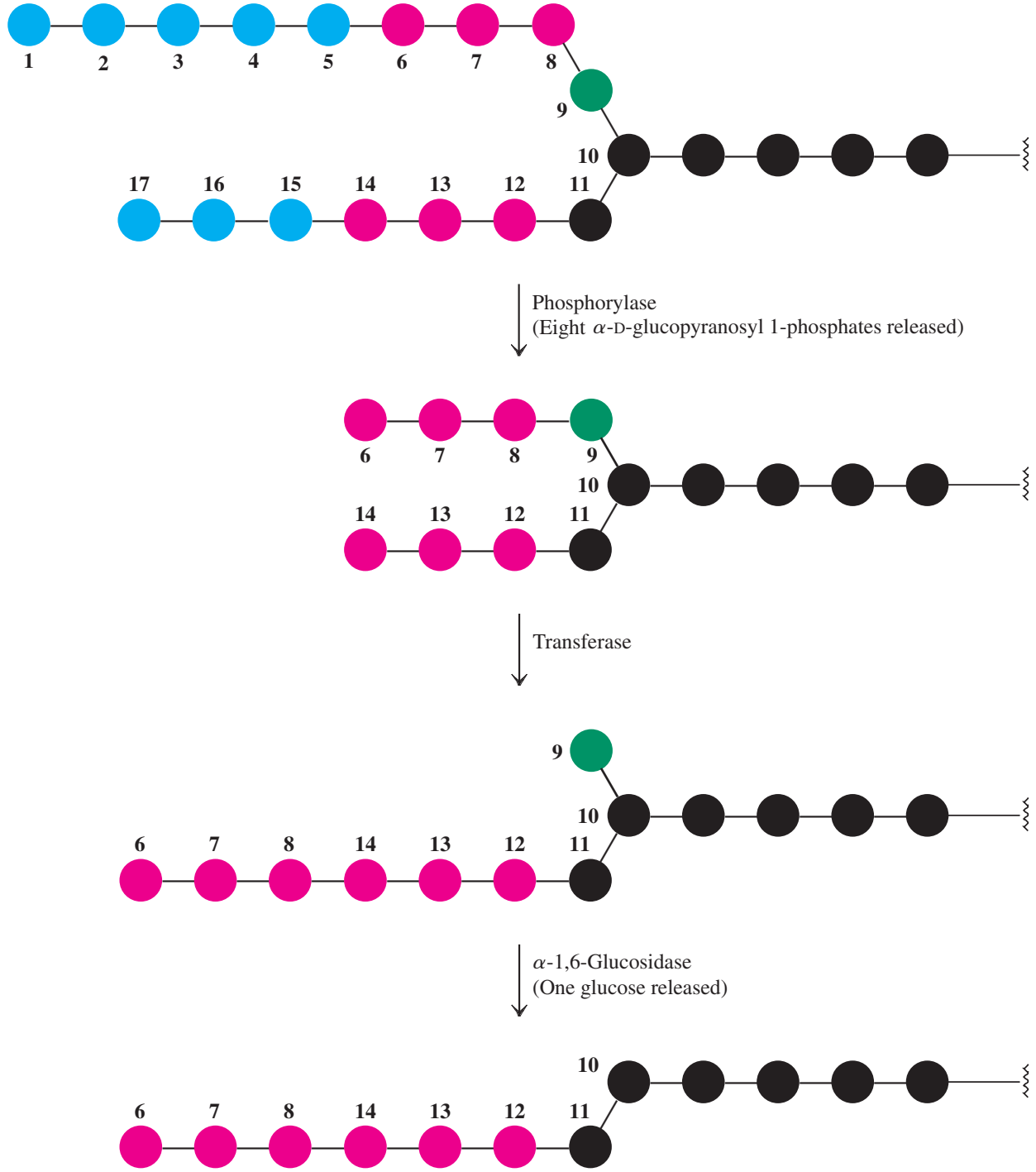

Nonreducing terminus
Nonreducing terminus
Glycogen
H_3PO_4,
glycogen phosphorylase
α-D-Glucopyranosyl
1-phosphate

Phosphorylase cannot break α-1,6-glycosidic bonds. As soon as it gets close to such a branching point, it stops.

At this stage, a different enzyme comes into play, transferase, which can shift blocks of three terminal glucosyl residues from one branch to another. One glucose substituent remains at the branching point.

Now a third enzyme is required to remove this last obstacle to obtaining a new straight chain. This enzyme is specific for the kind of bond at which cleavage is needed; it is α-1,6-glucosidase, also known as the de-branching enzyme.

When this enzyme has completed its task, phosphorylase can continue degrading the glucose chain until it reaches another branch, and so forth.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Phosphorylase
(Eight α-D-glucopyranosyl 1-phosphates released)
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7
8
9
10
11
12
13
14
Transferase
9
10
11
12
13
14
6
7
8
α-1,6-Glucosidase
(One glucose released)
10
11
12
13
14
6
7
8

Cell-surface carbohydrates mediate cell-recognition processes

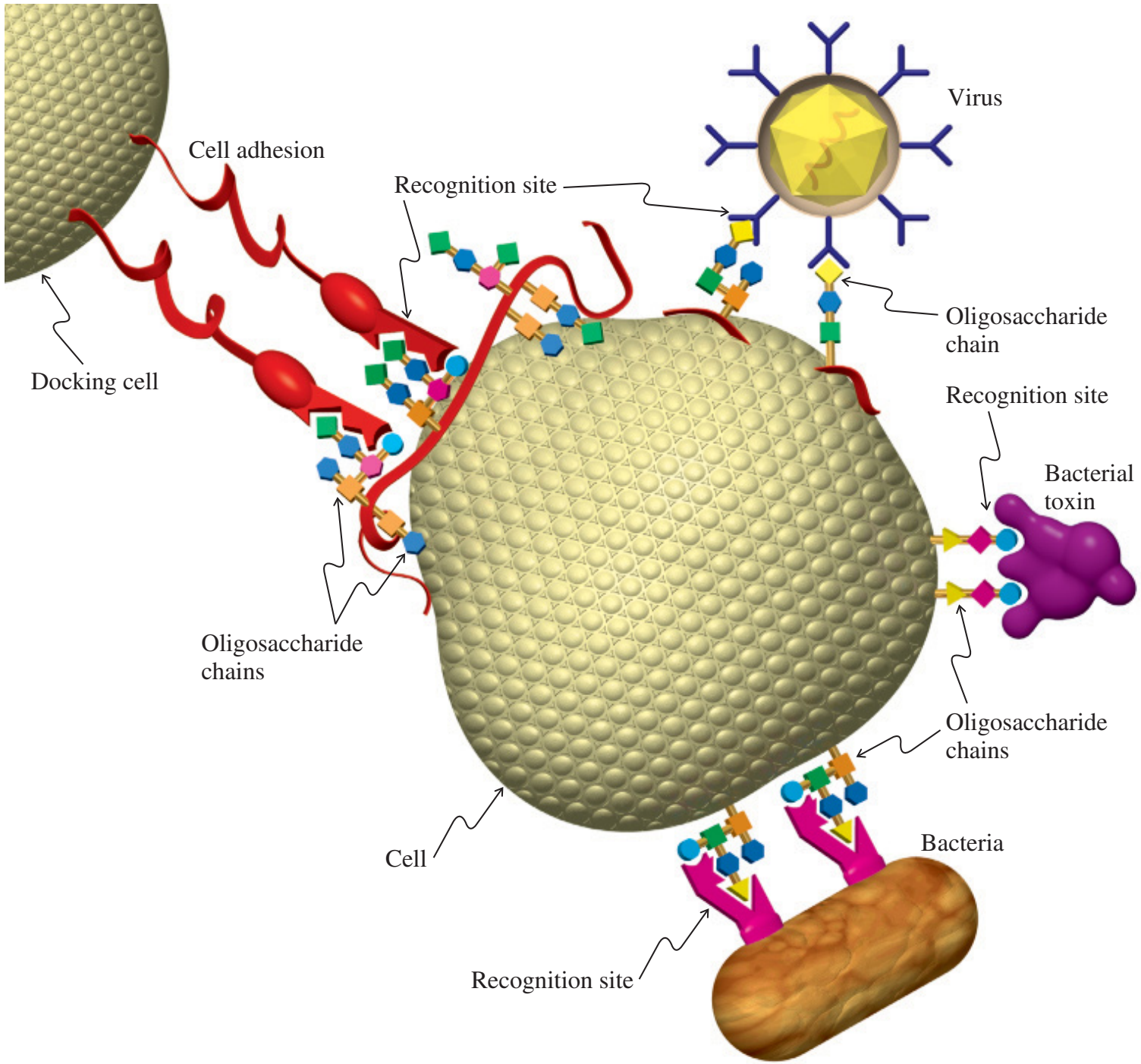
For multicellular organisms to function, each of the great variety of cells must be able to recognize and interact specifically with other cells and with various chemical species.

These specific interactions are described as **cell-recognition** processes.

Cell recognition usually involves noncovalent binding, commonly by means of hydrogen bonds, with molecules on the exterior surface of the cell. After binding takes place, movement of extracellular material into the interior of the cell may occur.

Cell recognition is central to virtually every cell function. Examples of recognition in cell–cell interactions include the response of the immune system to invasion by “foreign” cells, infection of cells by bacteria or viruses, and fertilization of ova by sperm.

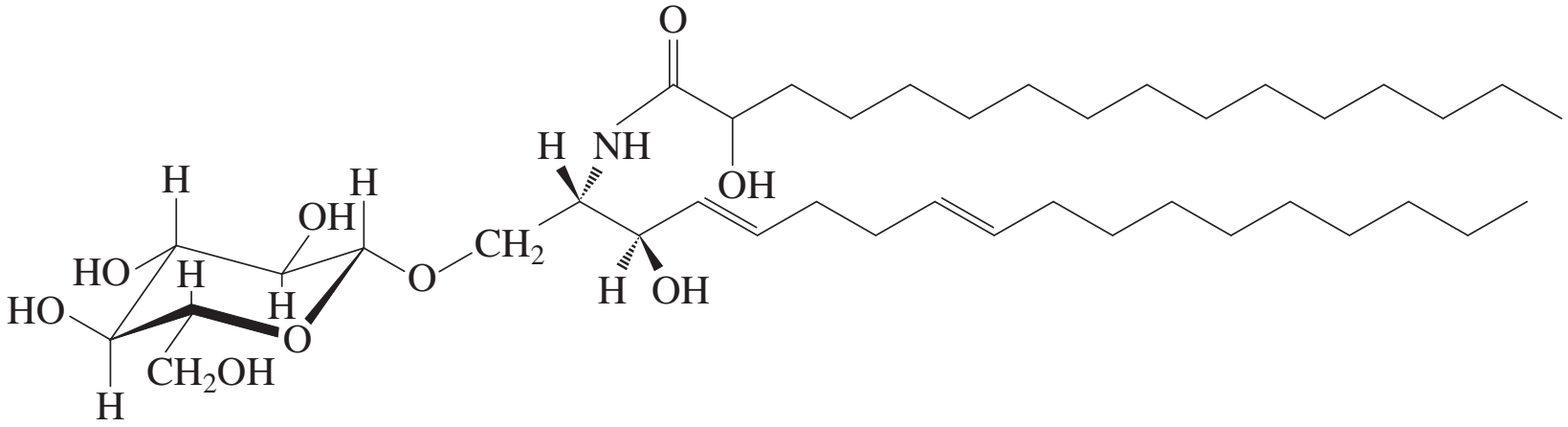
Certain bacteria, such as cholera and pertussis (“whooping cough”), do not invade cells directly, but the toxins they produce bind to cell surfaces and are subsequently “escorted” inside.


Virus
Cell adhesion
Recognition site
Docking cell
Oligosaccharide chain
Recognition site
Bacterial toxin
Oligosaccharide chains
Oligosaccharide chains
Cell
Bacteria
Recognition site

These recognition processes are based on carbohydrates that are present on cell surfaces. The carbohydrates are linked either to lipids (**glycolipids**) or to proteins (**glycoproteins**) that are embedded in the cell wall.

Glucosyl cerebroside is the simplest of the glycolipids and a polar carbohydrate “head” that resides on the cell surface, attached to two virtually nonpolar “tails” that embed in the cell membrane. Differences in carbohydrate composition at the “head” give rise to the different functions that these species display.

For example, cholera toxin binds specifically to a glycolipid called GM1 penta-saccharide. This substance is found naturally at the surface of the cells of the intestine that are responsible for water absorption. The result is disruption of this function and severe diarrhea.



Glucosyl cerebroside

The human blood groups—O, A, B, and AB—are each characterized by different oligosaccharides on the red blood cell surface. When an incompatible blood type is introduced by transfusion, the body's immune system produces antibodies that bind to the oligosaccharides on the surfaces of the foreign red cells, causing them to clump together. The result is widespread clogging of blood vessels and death.

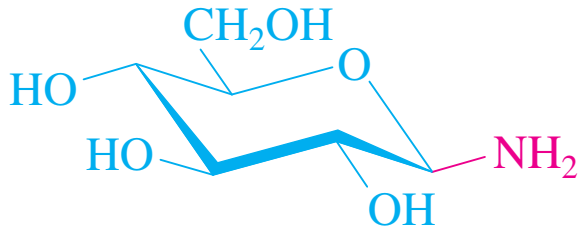
Type O cells are "coated" with a hexasaccharide whose structure is common to all four blood groups; therefore, type O cells are not recognized as "foreign" by any recipient, regardless of blood type. In type A and type B blood cells, two different additional saccharides are linked to the type O hexasaccharide. It is this "seventh" saccharide that triggers the immune response. Therefore, persons of types A and B cannot donate to each other, and neither can donate to someone of type O. By contrast, type AB cells contain both the type A and type B saccharides, and therefore individuals with type AB blood can receive transfusions from any donor without risk of immune system reaction.

Some scientists speculate that the presence of different blood groups (and the associated antibodies) may play a role in inhibiting viral infection: Viruses transmitted between persons with different blood groups might have a greater likelihood of being recognized as "foreign" and destroyed by the recipient's immune system.

Modified sugars may contain nitrogen

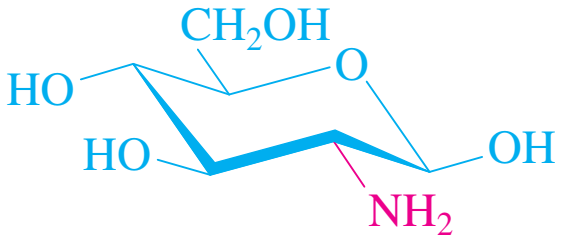
Many of the naturally occurring sugars have a modified structure or are attached to some other organic molecule.

In one large class of sugars, at least one of the hydroxy groups has been replaced by an amine function. They are called **glycosylamines** when the nitrogen is attached to the anomeric carbon and **amino deoxy sugars** when it is located elsewhere.



β-D-Glucopyranosylamine

(A glycosylamine)



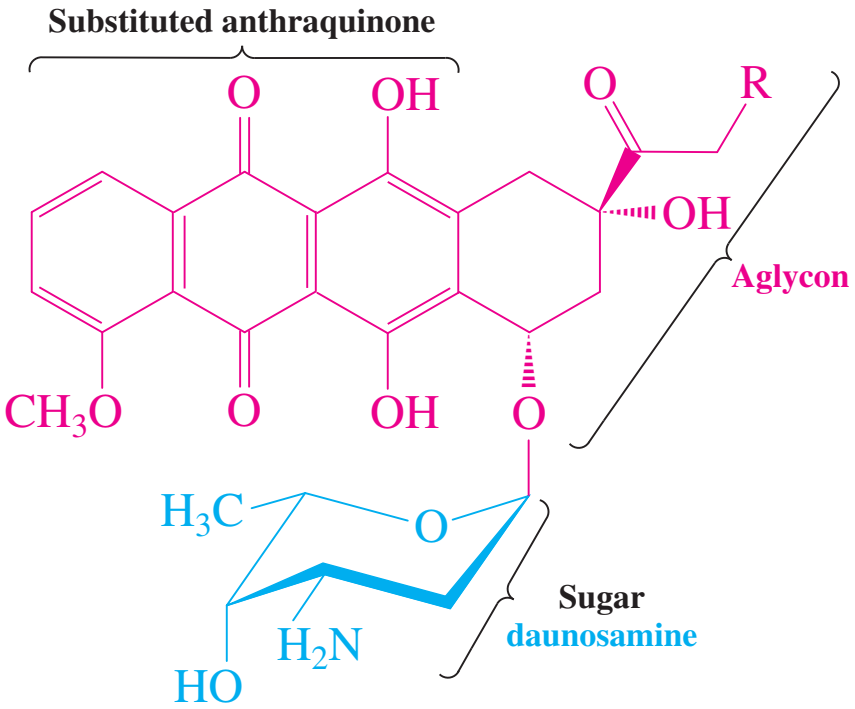
2-Amino-2-deoxy-D-glucopyranose

(An amino deoxy sugar)

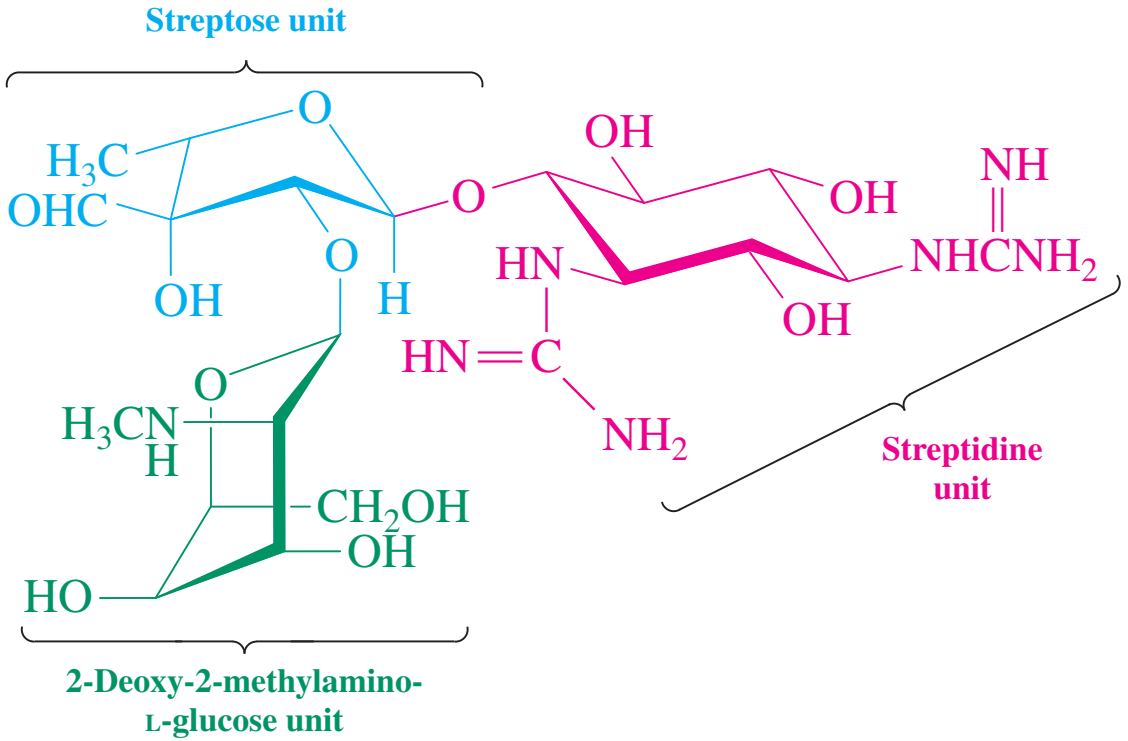
When a sugar is attached by its anomeric carbon to the hydroxy group of another complex residue, it is called a **glycosyl group.** The remainder of the molecule (or the product after removal of the sugar by hydrolysis) is called the **aglycon.**

An example is adriamycin, a member of the anthracycline family of antibiotics. Adriamycin and its deoxy analog daunomycin have been remarkably effective in the treatment of a wide variety of human cancers. They now constitute a cornerstone of combination cancer chemotherapy. The aglycon part of these systems is a linear tetracyclic framework incorporating an anthraquinone moiety (derived from anthracene). The amino sugar is called daunosamine.

An unusual group of antibiotics, the aminoglycoside antibiotics, is based on oligosaccharide structures. Of particular therapeutic importance is streptomycin (an antituberculosis agent), isolated in 1944 from cultures of the mold *Streptomyces griseus*. The molecule consists of three subunits: the furanose streptose, the glucose derivative 2-deoxy-2-methylamino-L-glucose (an example of the rare L form), and streptidine, which is actually a hexasubstituted cyclohexane.



Adriamycin (R = OH)
Daunomycin (R = H)



Streptomycin