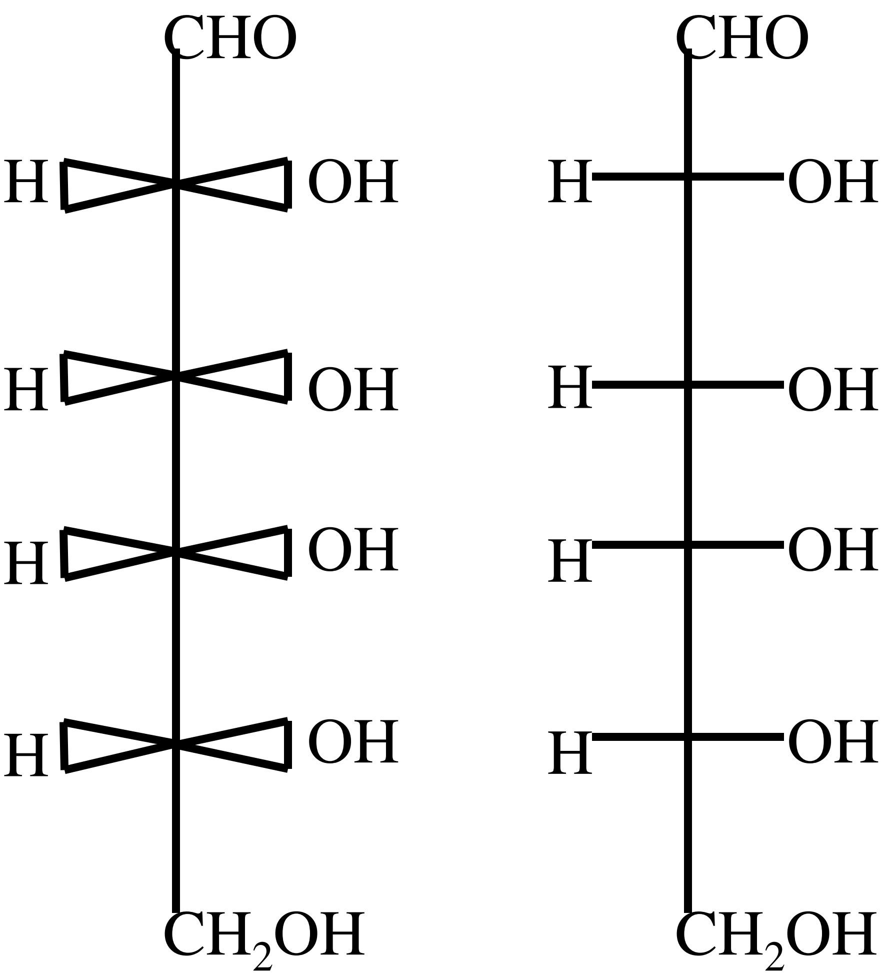
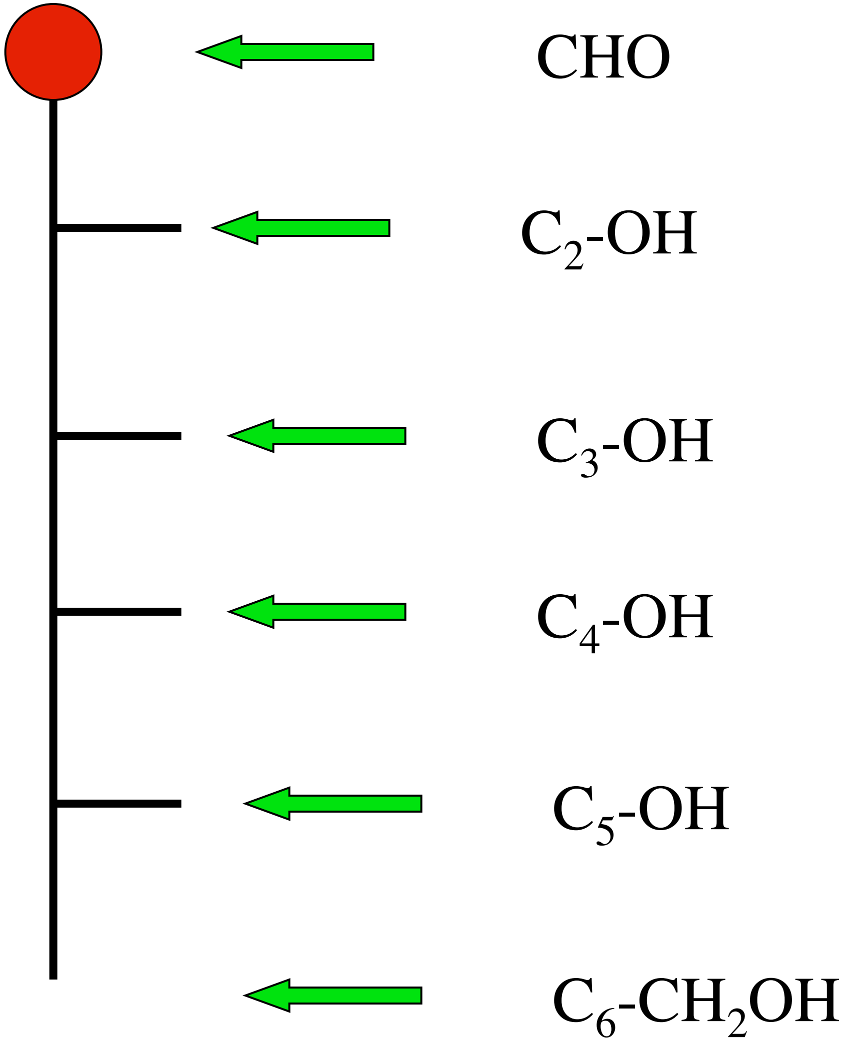
The Carbohydrates
$[C(H_2O)]_n$

Emil Hermann Fischer (1852-1919)

The Fischer-Rosanoff Convention



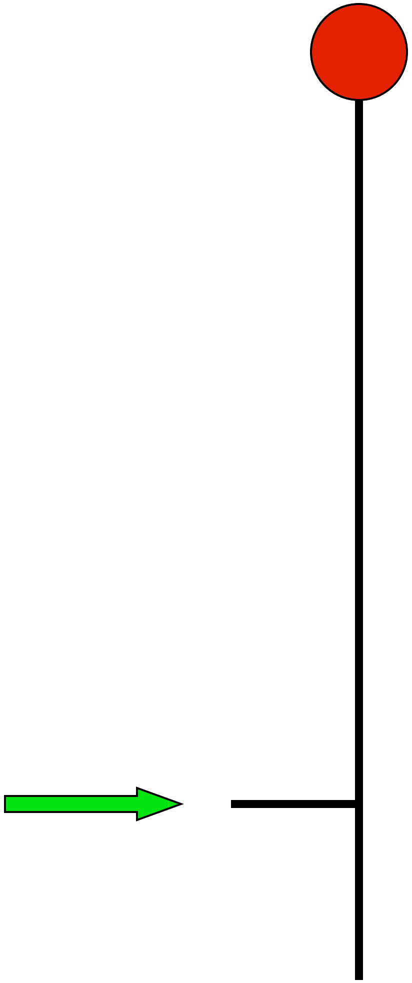
Fischer Projections



Rosanoff Modification

Fischer-Rosanoff D- and L-Series

OH on the right of the highest
numbered chiral carbon = D-series.



OH on the left of the highest
numbered chiral carbon = L-series.

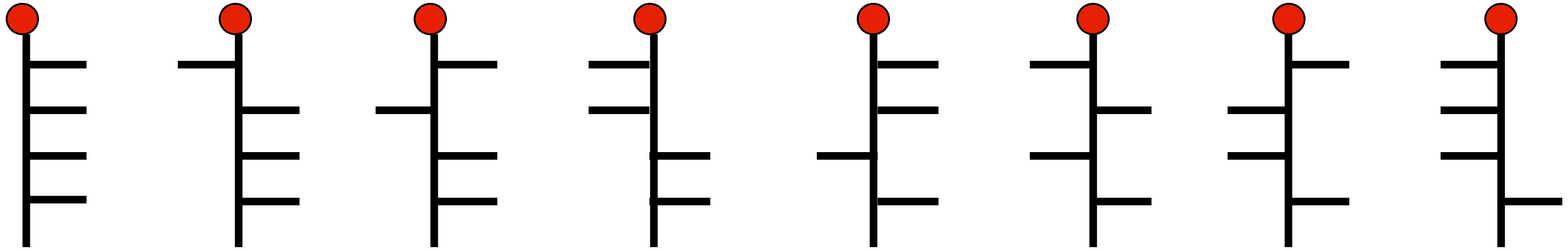
The D-Aldohexoses

C_5 8 right

C_4 4 right 4 left

C_3 2 right 2 left 2 right 2 left

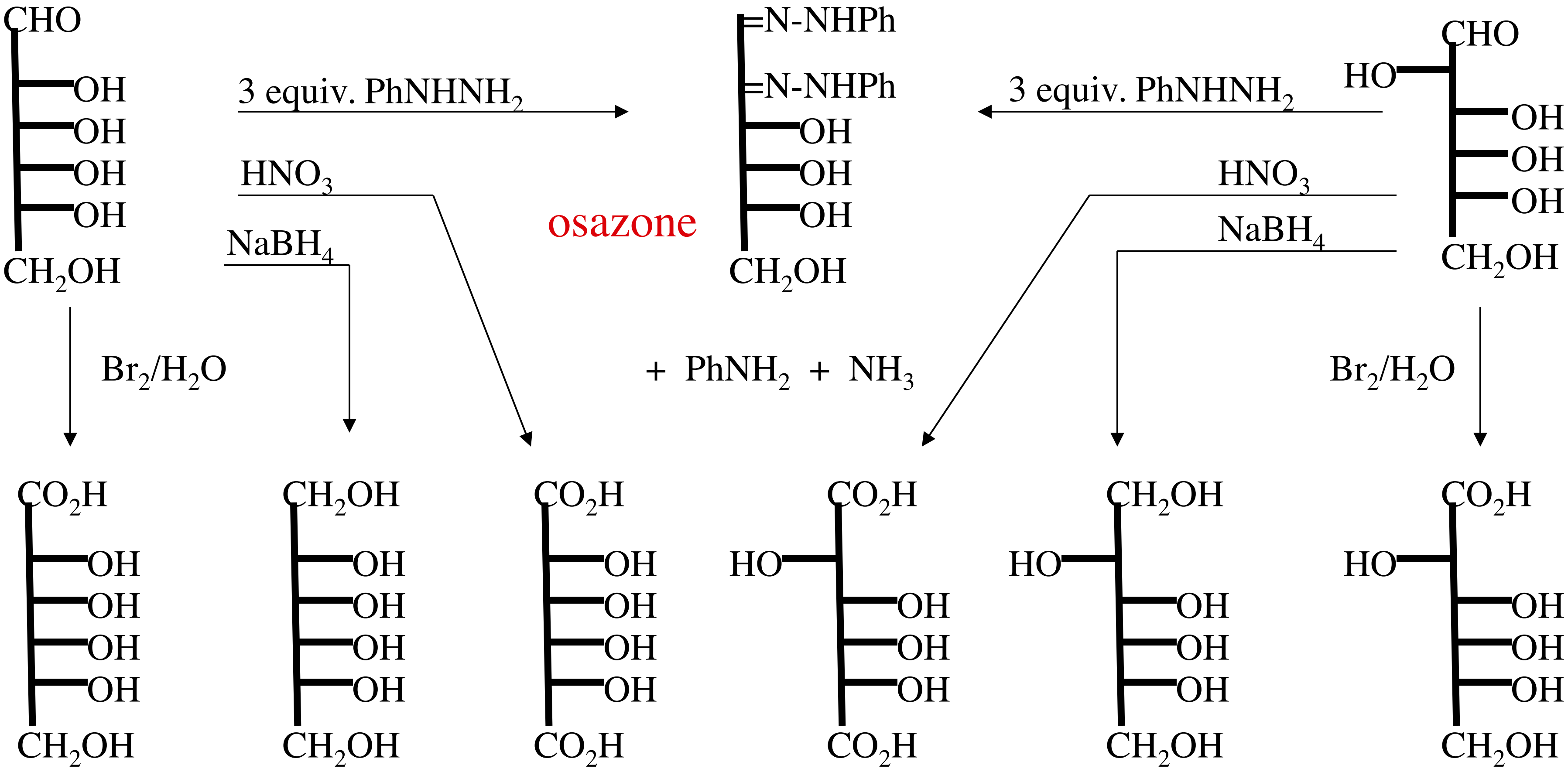
C_2 right left right left right left right left



Allose Altrose Glucose Mannose Gulose Idose Galactose Talose

All altruists gladly make gum in gallon tanks [L. Fieser]

Reactions of Aldoses



osazone

aldonic acid

alditol
achiral

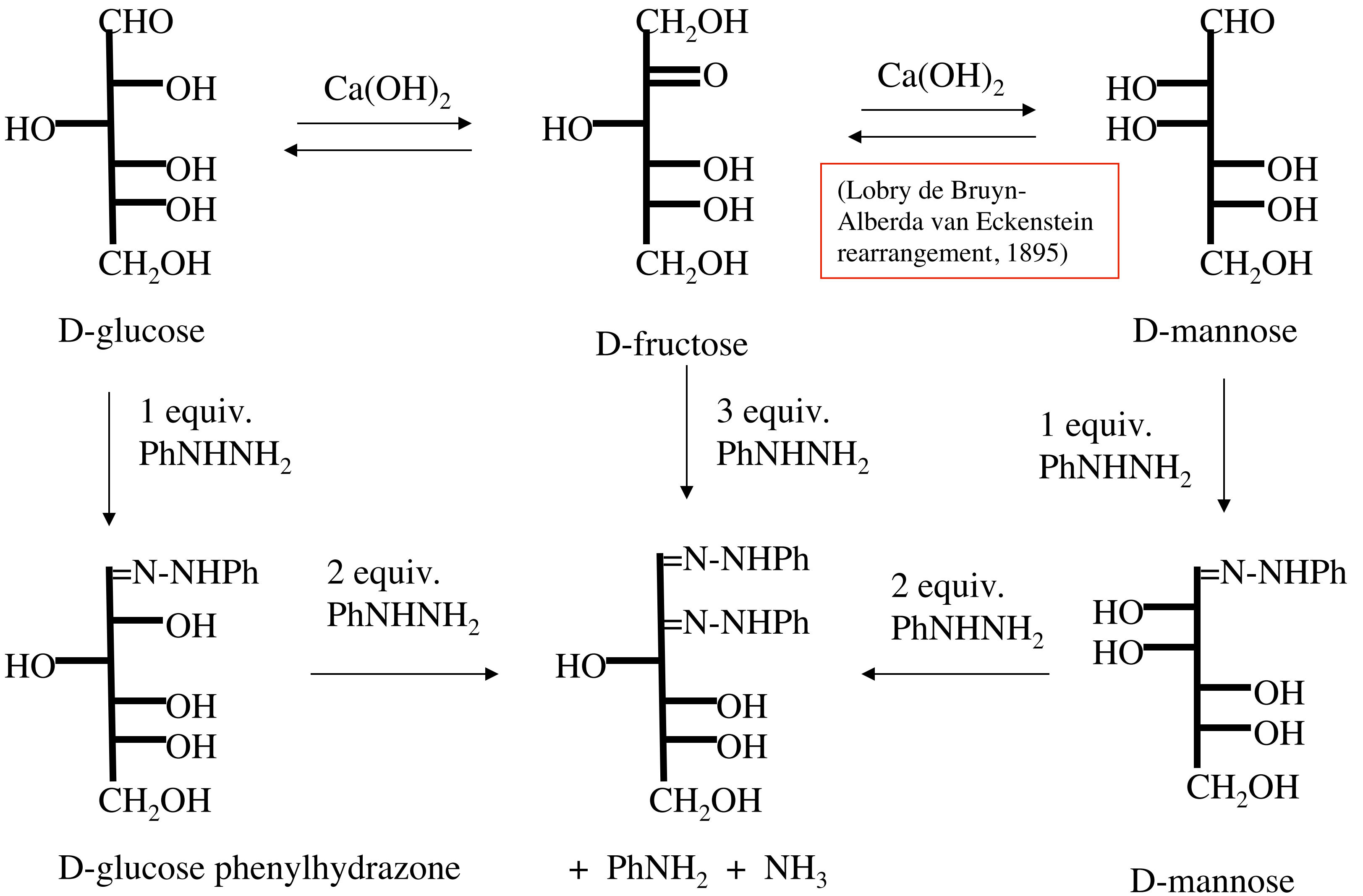
aldaric acid
achiral

aldaric acid

alditol

aldonic acid

More on Osazones



(Lobry de Bruyn-Alberda van Eckenstein rearrangement, 1895)

D-glucose

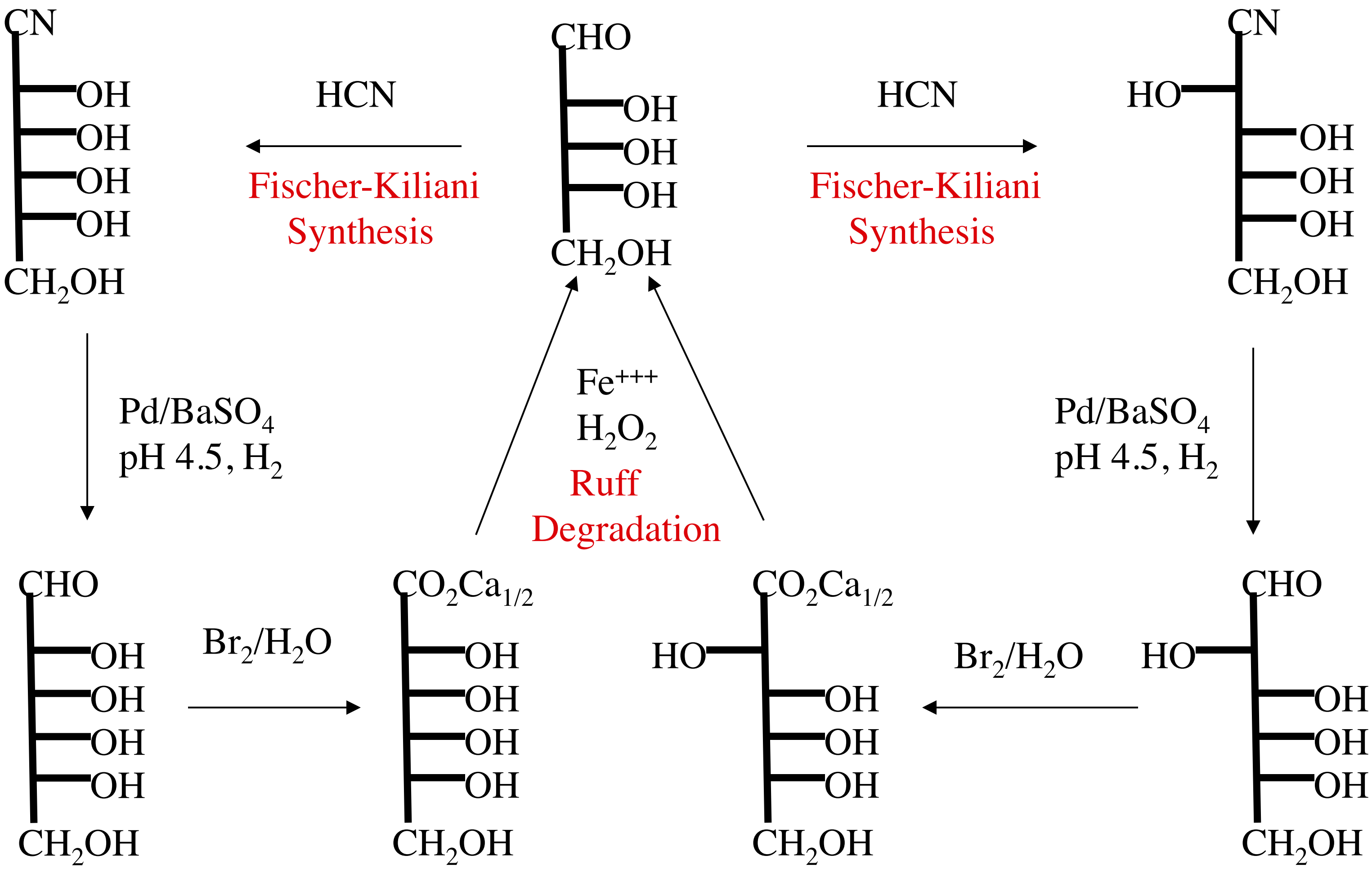
D-fructose

D-mannose

D-glucose phenylhydrazone

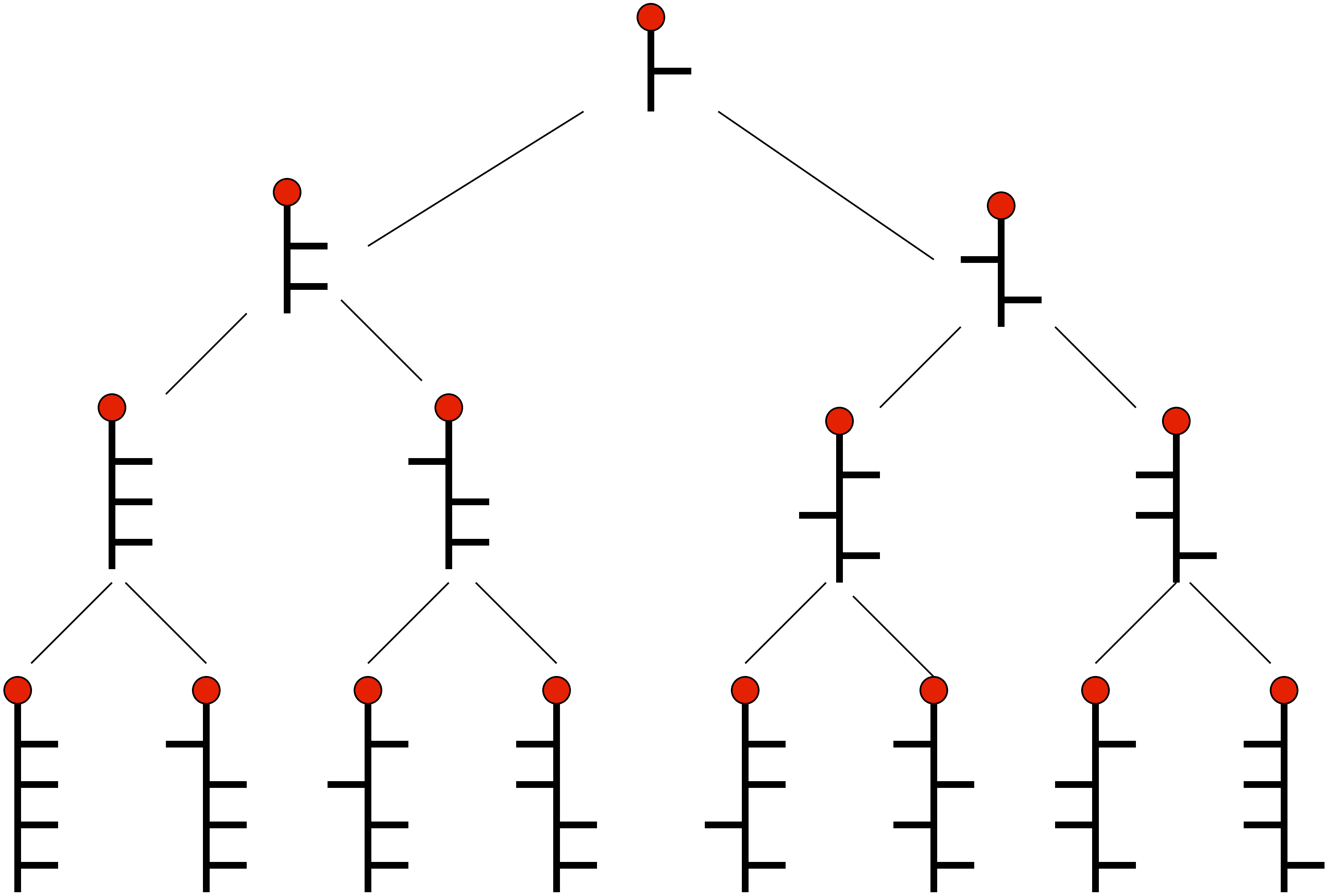
D-mannose phenylhydrazone

Chain Lengthening and Shortening of Aldoses



Aldonic acid as Ca salt

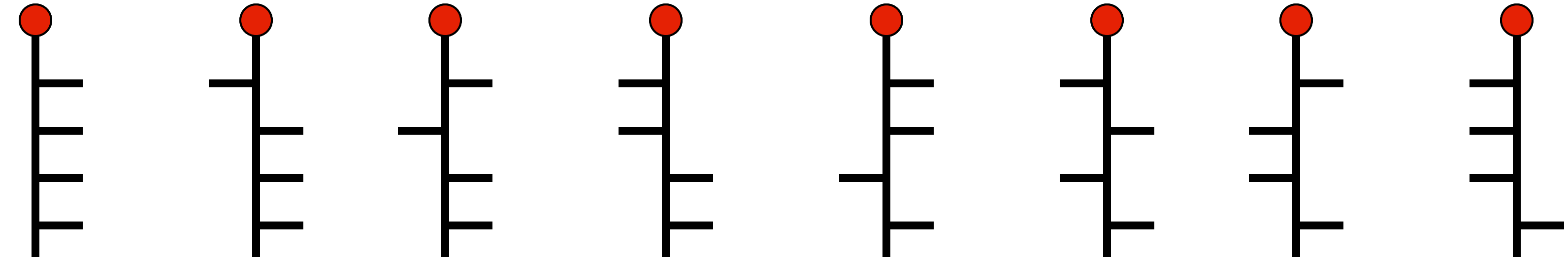
Interrelationship of the D-Series of Aldoses via Chain Lengthening and Degradation



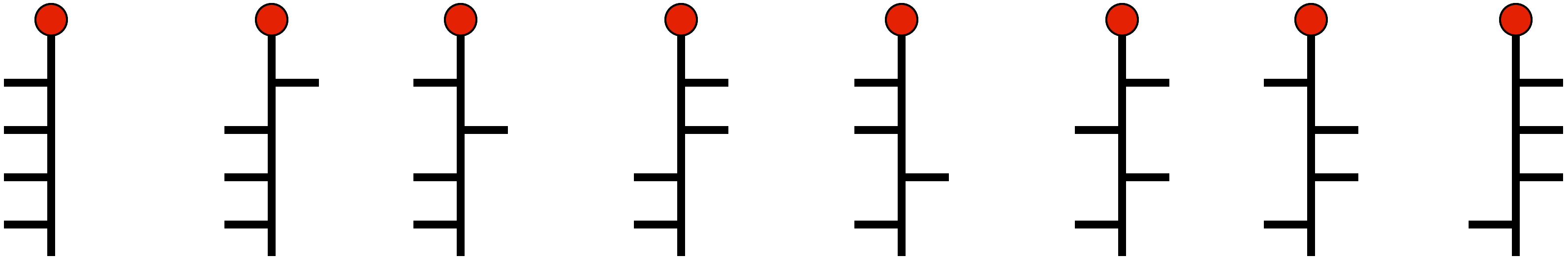
The Aldohexoses

But which one is (+)-glucose?

D-series

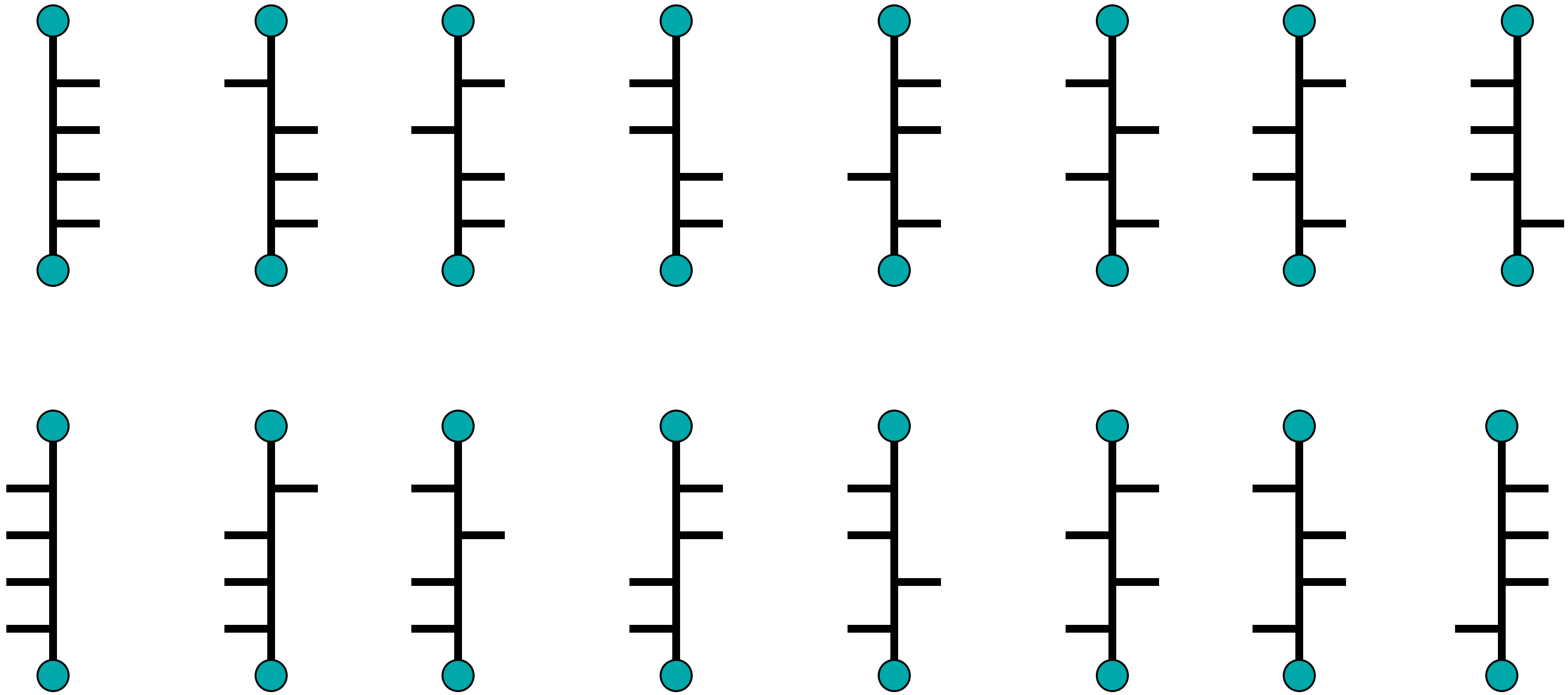


L-series



Rosanoff Formulation of C_6 Aldaric Acids and Alditols

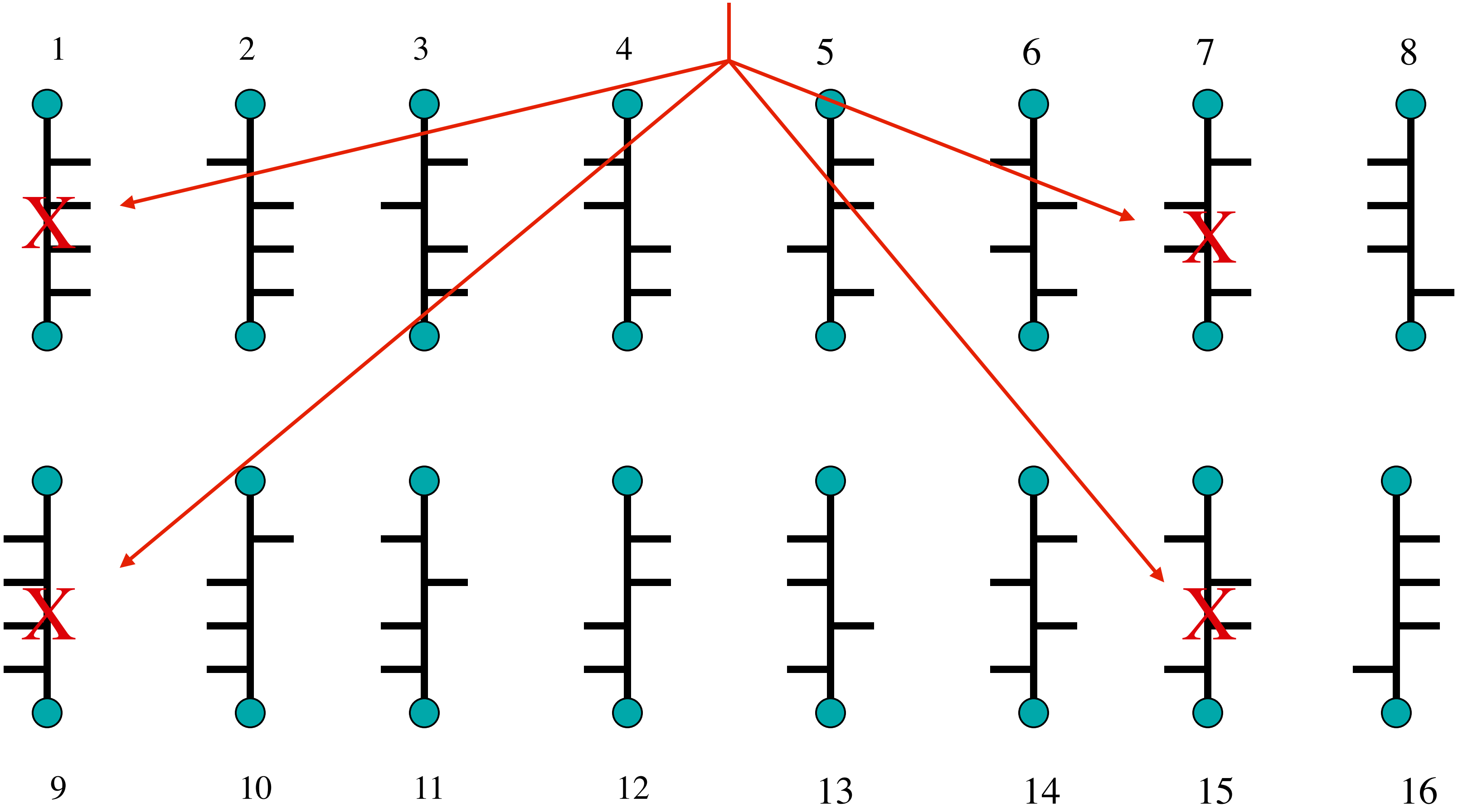
Terminal groups identical; CO_2H or CH_2OH



Fischer’s Proof: Part 1

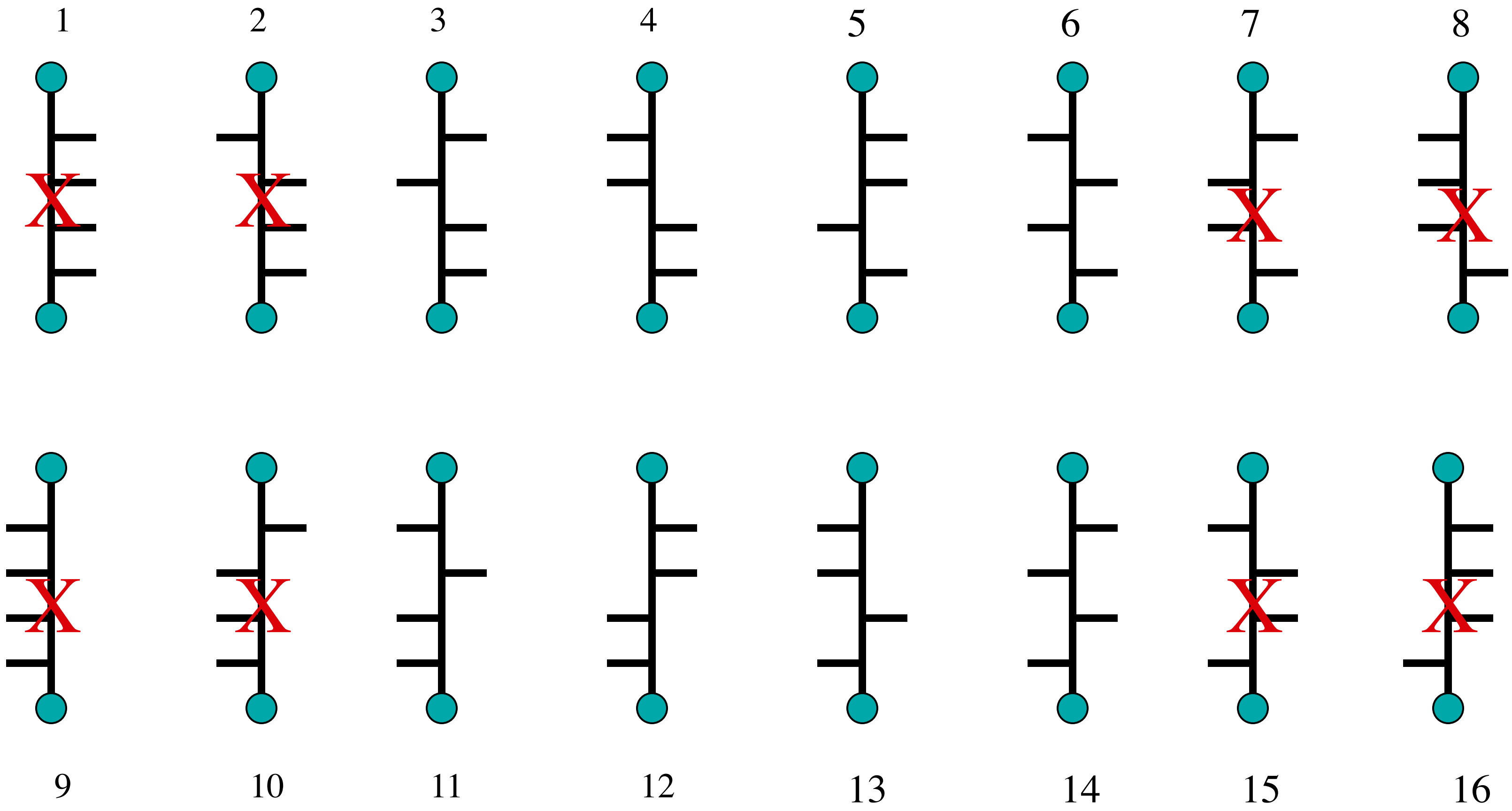
(+)-Glucose forms an optically active aldaric acid and optically active alditol.

- 1, 7, 9, 15 eliminated: plane of symmetry, achiral



Fischer’ s Proof: Part 2

(+)-Glucose and (+)-mannose form the same osazone. If 1, 7, 9, and 15 are not related to (+)-glucose, then they are not related to (+)-mannose nor are 2, 8, 10, and 16 related to (+)-glucose.

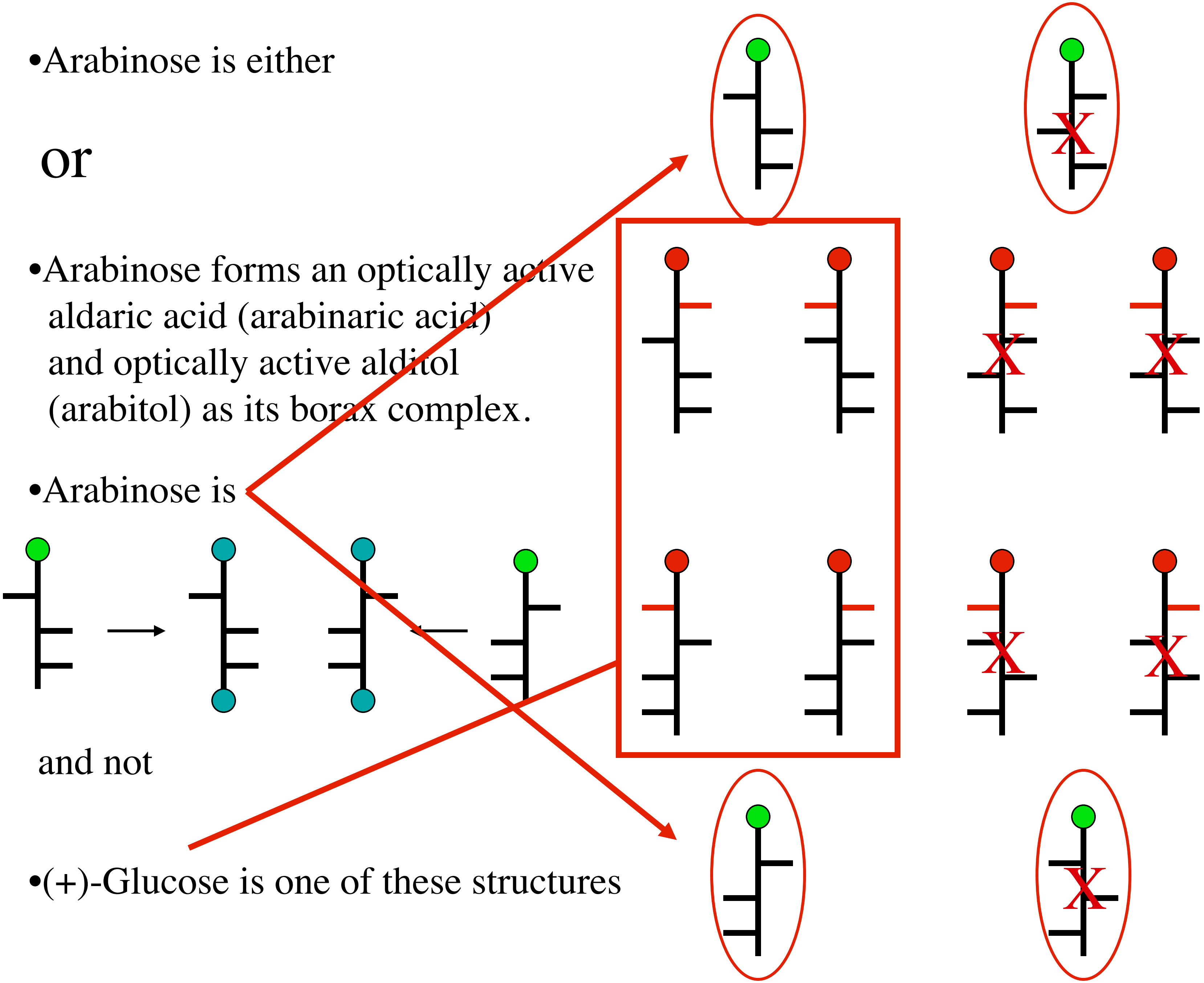


Fischer’ s Proof: Part 3

(+)-Arabinose affords (-)-glucose and (-)-mannose by Kiliani-Fischer synthesis.

(+)-Arabinose must be of the opposite series (D/L)as (+)-glucose and have the same absolute configuration at $C_{3\text{-}5}$ as (-)-glucose and (-)-mannose.

What is the structure of arabinose?



- Arabinose is either

or

- Arabinose forms an optically active aldaric acid (arabinaric acid) and optically active alditol (arabitol) as its borax complex.

- Arabinose is

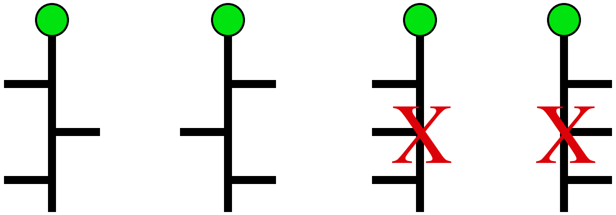
and not

- (+)-Glucose is one of these structures

Fischer's Proof: Part 4

The pentose (+)-xylose affords optically inactive xylaric acid and optically inactive xylitol as its borax complex.

- (+)-Xylose can only be one of the following:



Fischer-Kiliani synthesis of (+)-xylose leads to two new hexoses, (+)-gulose and (+)-idose, both of which form optically active aldaric acids.

- These enantiomers cannot be (+)-xylose because their Fischer-Kiliani hexoses (already eliminated) would lead to one optically active and one optically inactive aldaric acid.

- (+)-Xylose must be one of the remaining two structures.

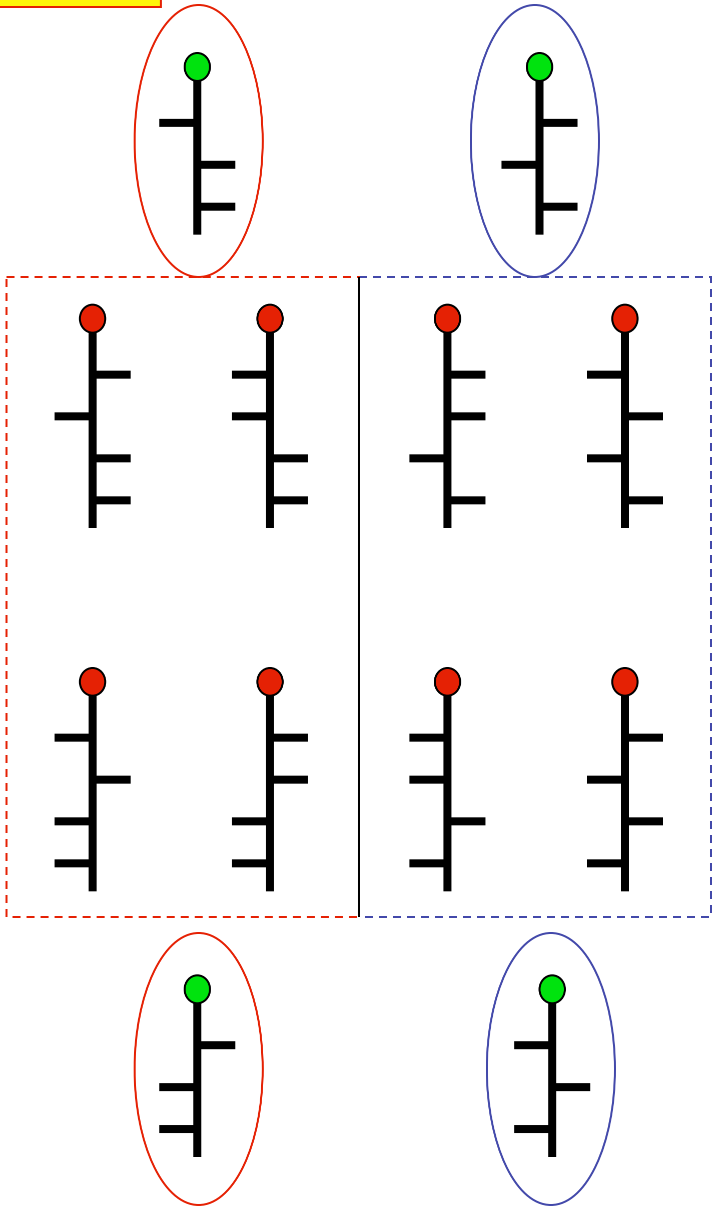
Fischer’ s Proof: Part 5

- (+)-Arabinose

- (+)-Glucose/(+)-Mannose

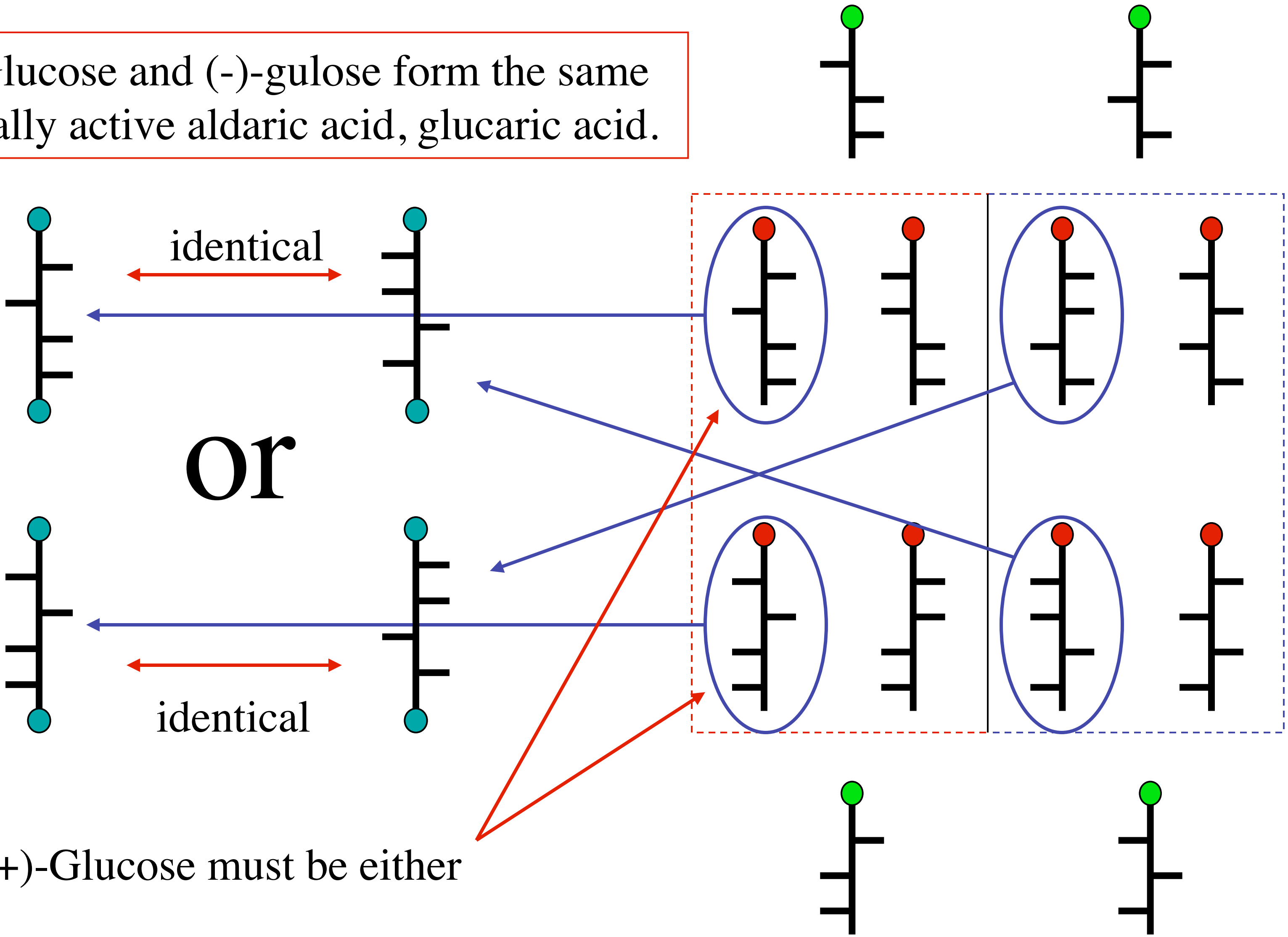
- (+)-Xylose

- (+)-Gulose/(+)-Idose



Fischer’ s Proof: Part 5

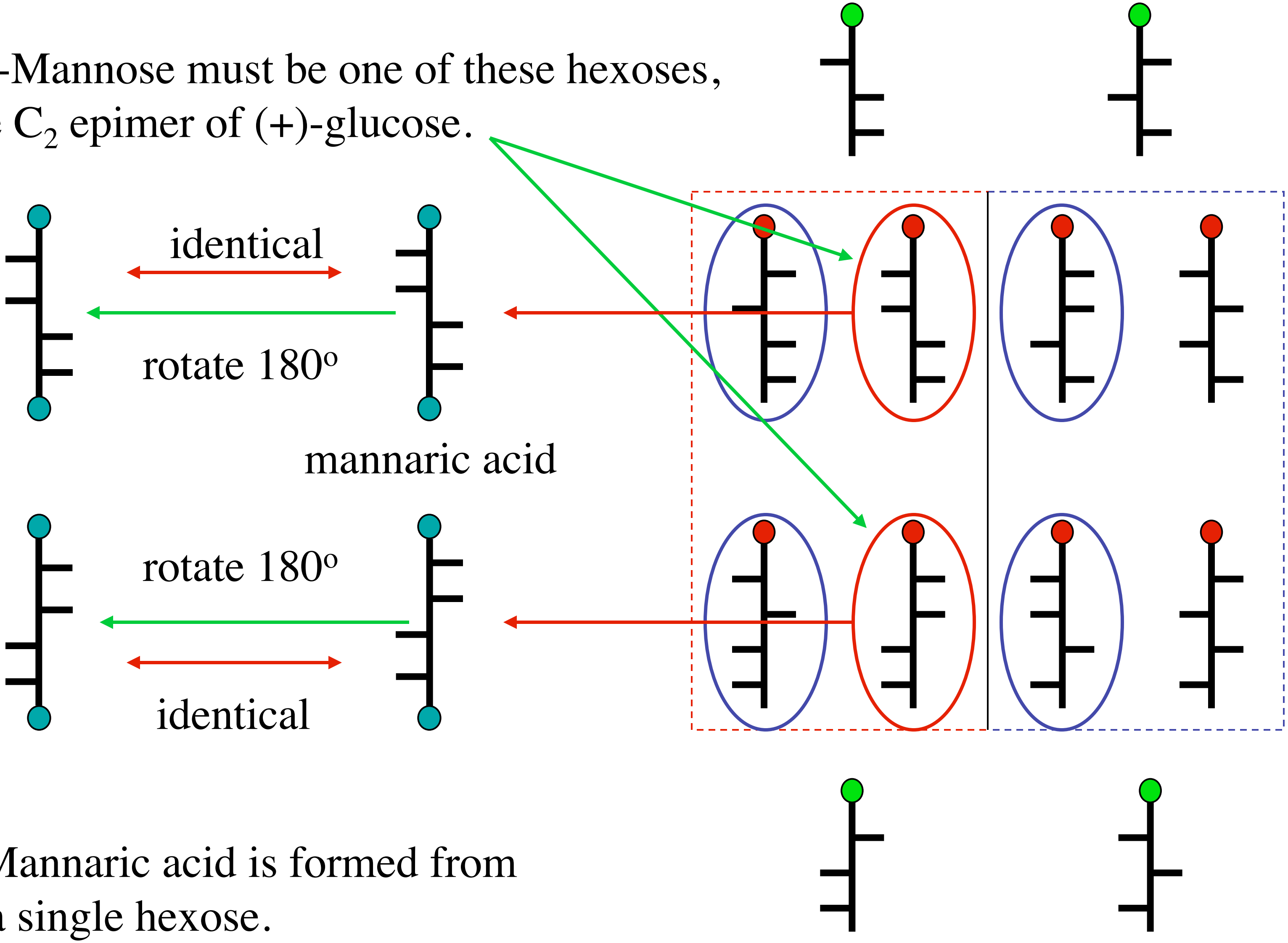
(+)-Glucose and (-)-gulose form the same optically active aldaric acid, glucaric acid.



- (+)-Glucose must be either

Fischer's Proof: Part 5

- (+)-Mannose must be one of these hexoses, the C_2 epimer of (+)-glucose.

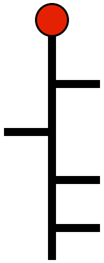


- Mannaric acid is formed from a single hexose.

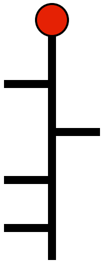
Fischer's Proof: Part 6

But which enantiomer of glucose is (+)-glucose?

Just Guess!



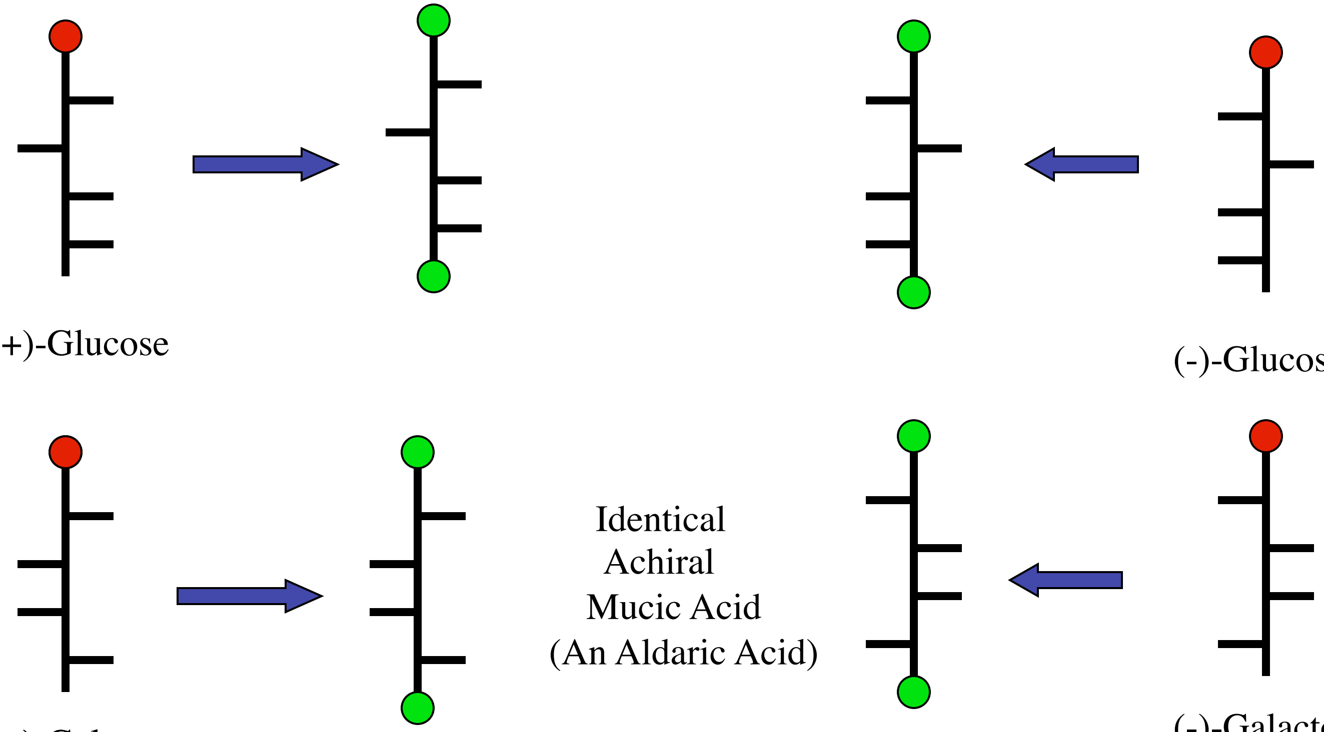
D-glucose



L-glucose

- Fischer arbitrarily assigned the D-series to the dextrorotatory enantiomer.
- Sixty years later (1951), he was proved correct when Bijvoet related (+)-glucose to (+)-tartaric acid.
- Fischer: All sugars related to D-(+)-glucose by chemical correlation belong to the D-series.

A Flaw in the Fischer Scheme



(+)-Glucose

(-)-Glucose

Identical
Achiral
Mucic Acid
(An Aldaric Acid)

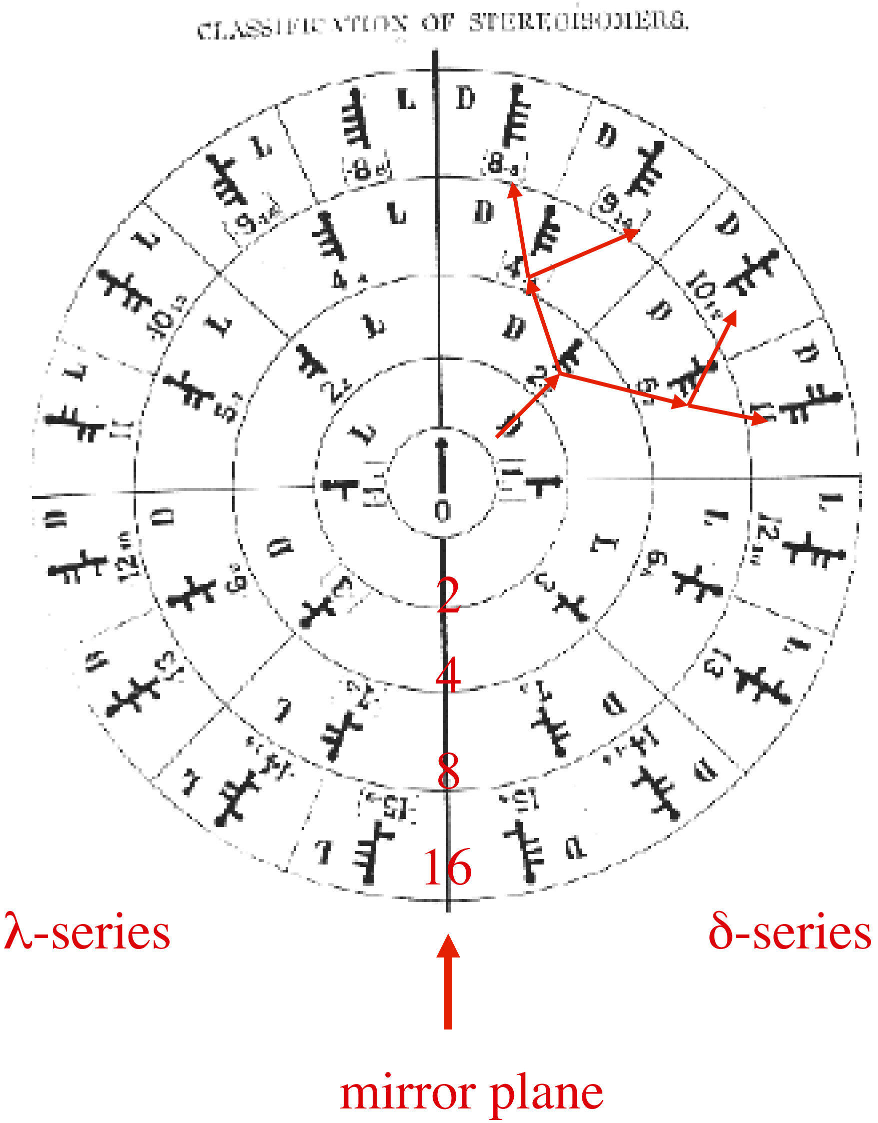
(+)-Galactose

(-)-Galactose

"Two aldoses can produce the same dibasic acid only if they belong to the same stereochemical family. That this, however, is erroneous as a general proposition, may be readily seen from the fact that the two enantiomorphous galactoses - plainly belong to the opposite families - yield the same mucic acid." A. M. Rosanoff-1906

Rosanoff’s Reorganization of the Carbohydrates

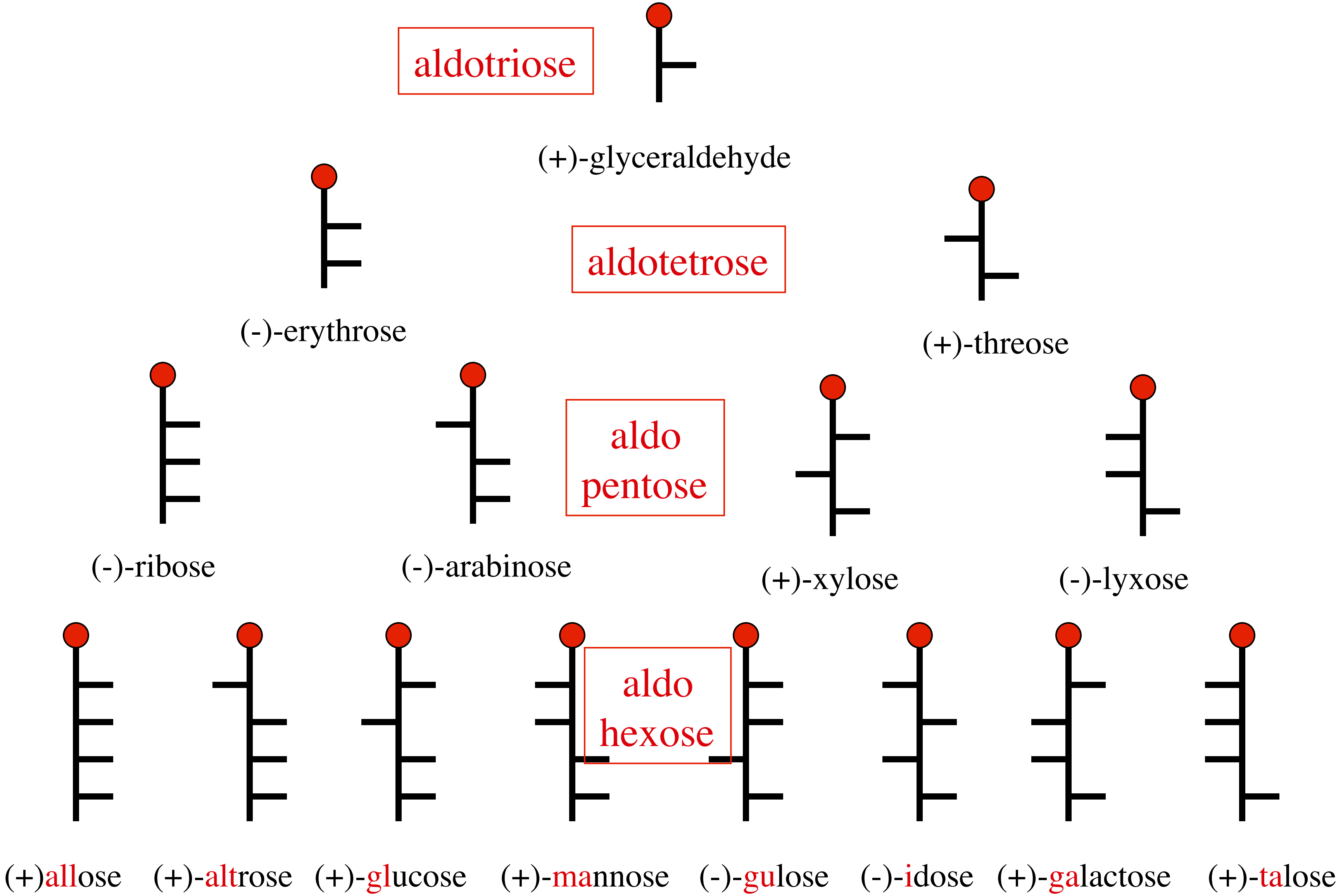
- Arranged by successive Kiliani syntheses
- The D- and L- assignments were Fischer’s based on chemical correlation with D-(+)-glucose, an unreliable scheme.



Evolution of Signage

	Optical Activity	Configuration
Fischer-1891	+/-	d,l
Rosanoff-1906	+/-	δ,λ ↓
Today	+/- = d,l	D,L

The D-Series of Aldoses



aldotriose

(+)-glyceraldehyde

aldotetrose

(-)-erythrose

(+)-threose

aldo pentose

(-)-ribose

(-)-arabinose

(+)-xylose

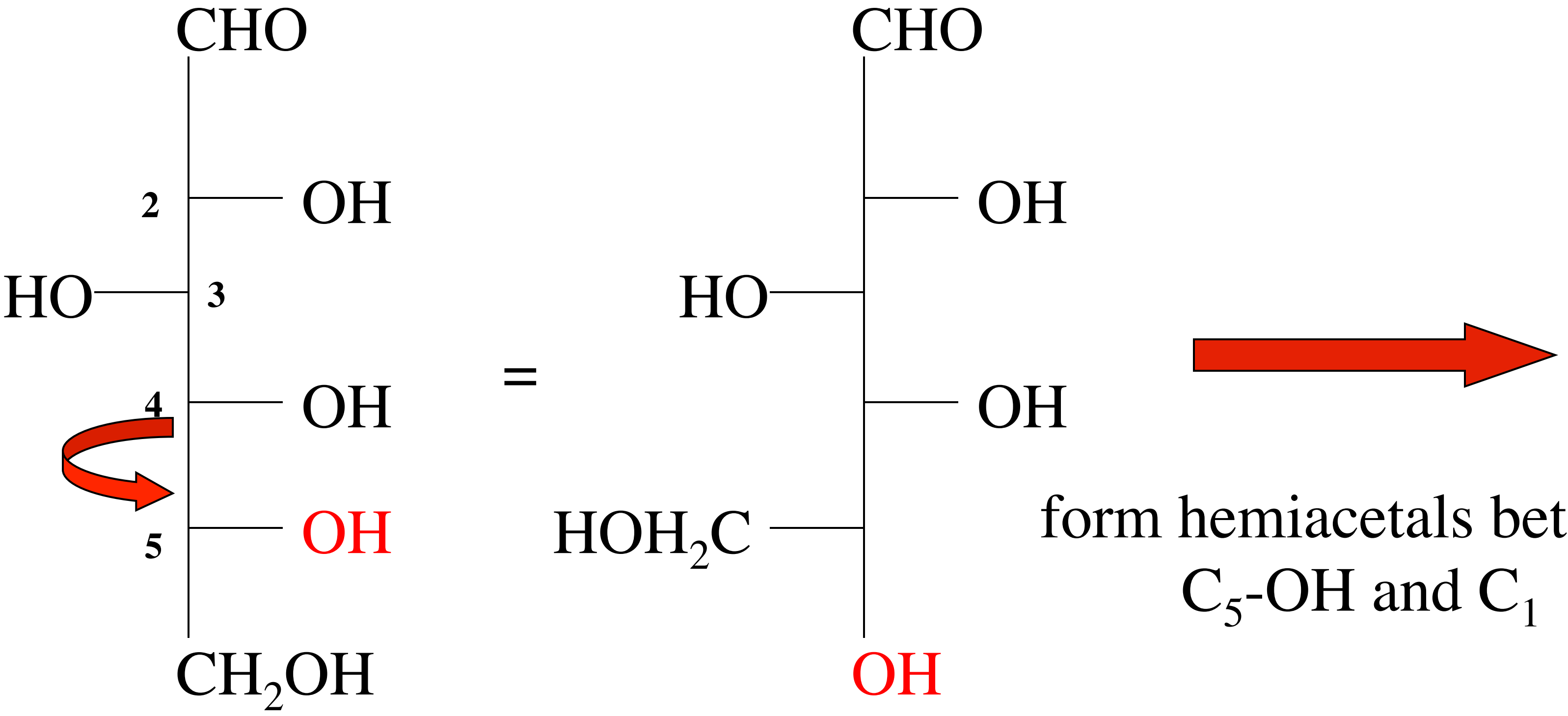
(-)-lyxose

aldo hexose

(+)allose (+)-altrose (+)-glucose (+)-mannose (-)-gulose (-)-idose (+)-galactose (+)-talose

All altruists gladly make gum in gallon tanks [L. Fieser]

Fischer Projections of Glucose

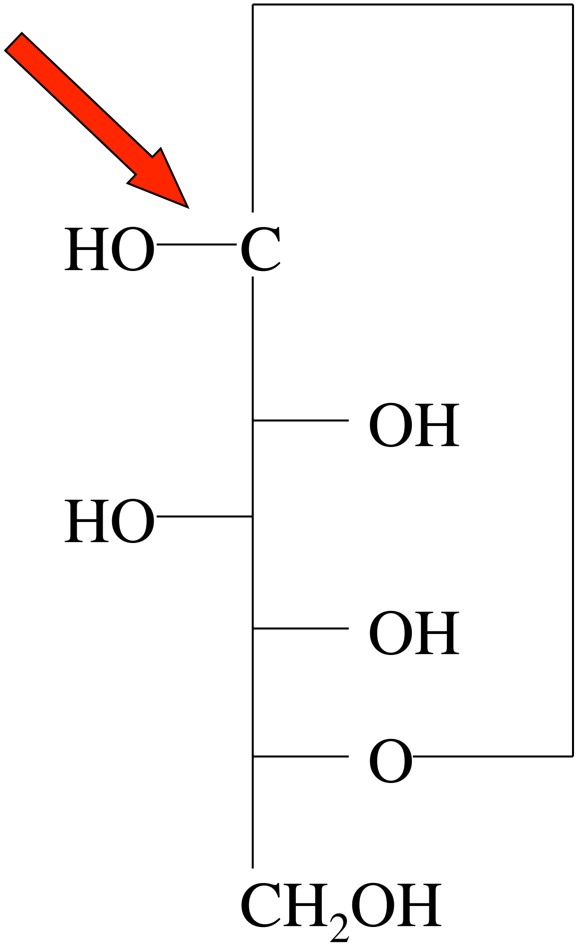


form hemiacetals between C_5-OH and C_1

D-(+)-Glucose

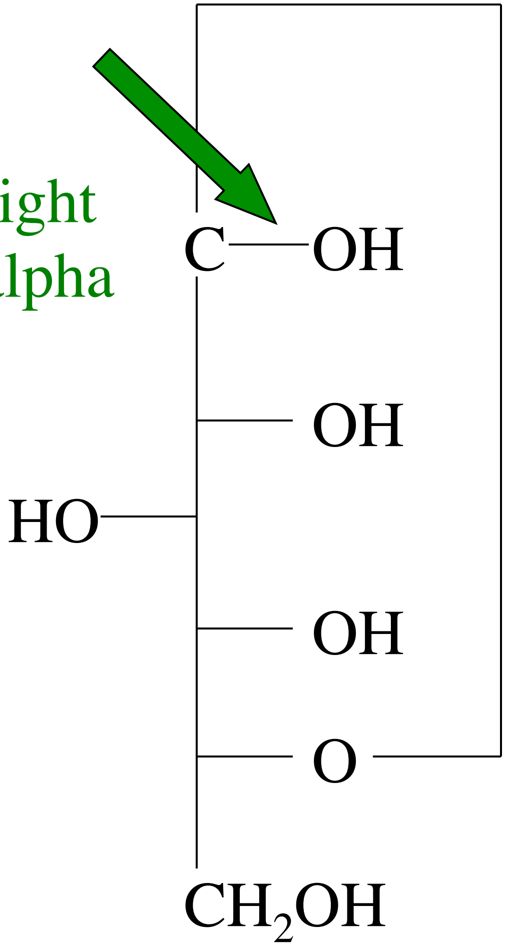
rotate C_5 about C_4 by 120°

Fischer Projections of Glucopyranose Anomers



left
beta

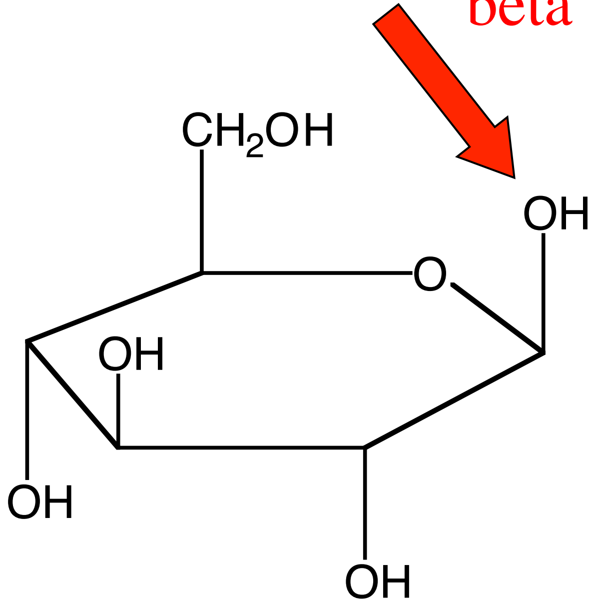
β-D-(+)-Glucopyranose



right
alpha

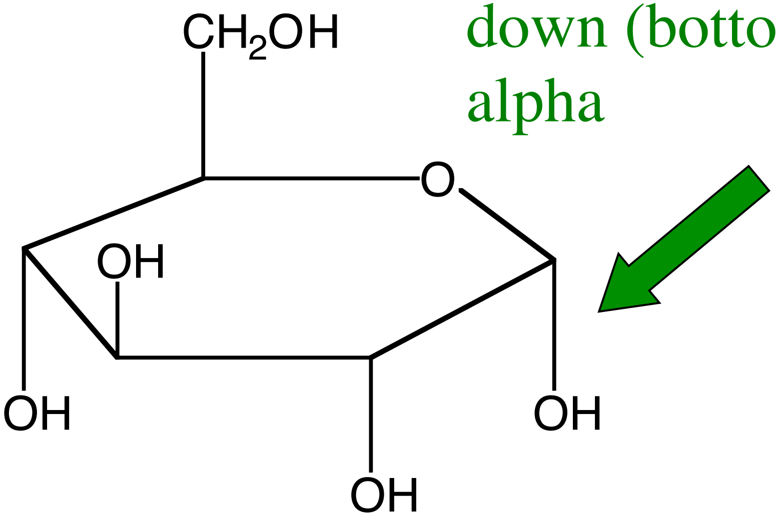
α-D-(+)-Glucopyranose

Haworth Projections of Glucopyranose Anomers



up (top)
beta

β-D-(+)-Glucopyranose

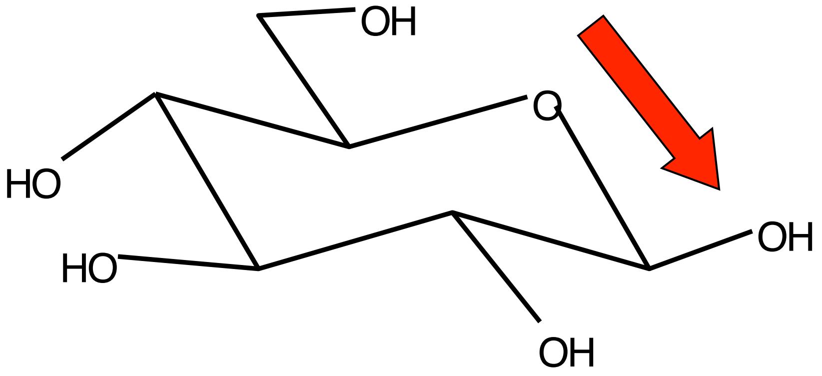


down (bottom)
alpha

α-D-(+)-Glucopyranose

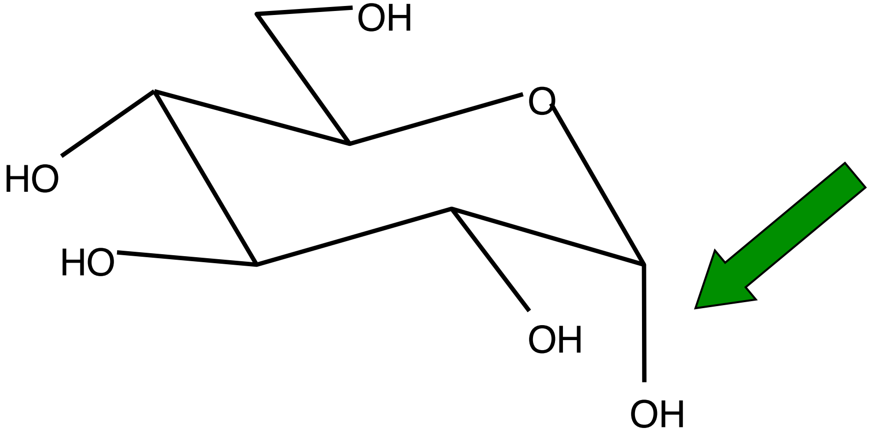
Chair Conformations of Glucopyranose Anomers

up (top)
beta



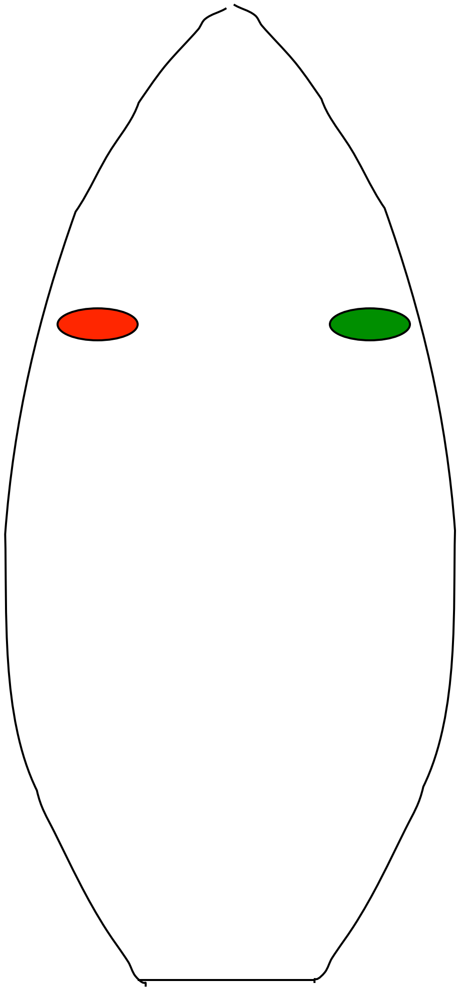
β-D-(+)-Glucopyranose

down (bottom)
alpha



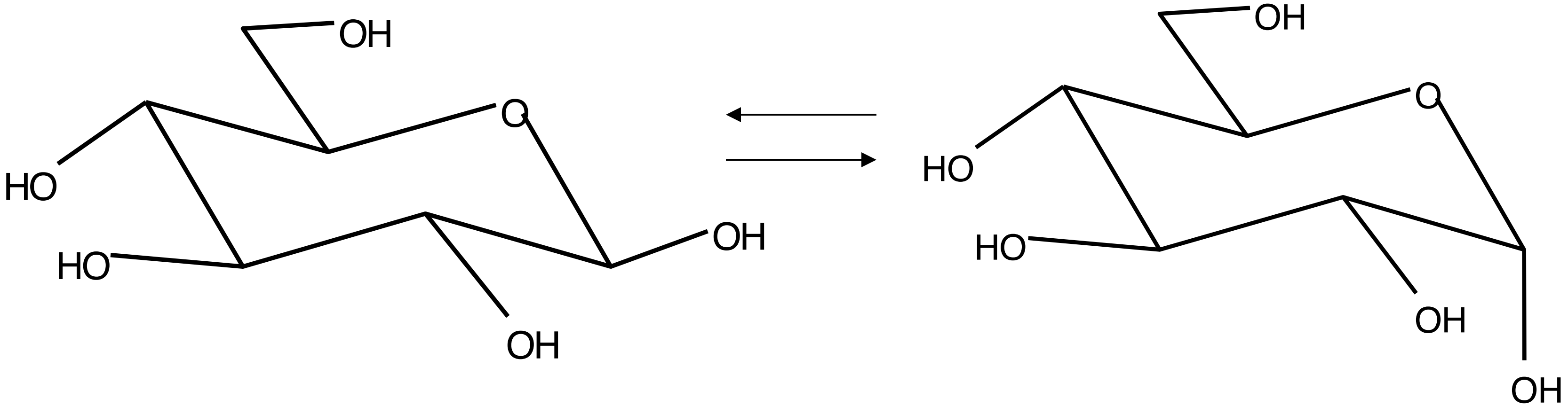
α-D-(+)-Glucopyranose

How an Old Salt Remembers



port	starboard
left	right
red light	green light
fewer letters	more letters
beta	alpha
up	down
top	bottom

Mutarotation of Anomers



β-D-(+)-Glucopyranose

Crystallizes above 98°C

α-D-(+)-Glucopyranose

Crystallizes below 98°C

pure β-anomer
mp 150°C
$[\alpha]_D = +18.7^o$

$\xrightarrow{H_2O}$

equilibrium
mixture
$[\alpha] = +52.6^o$

$\beta/\alpha = 64/36$

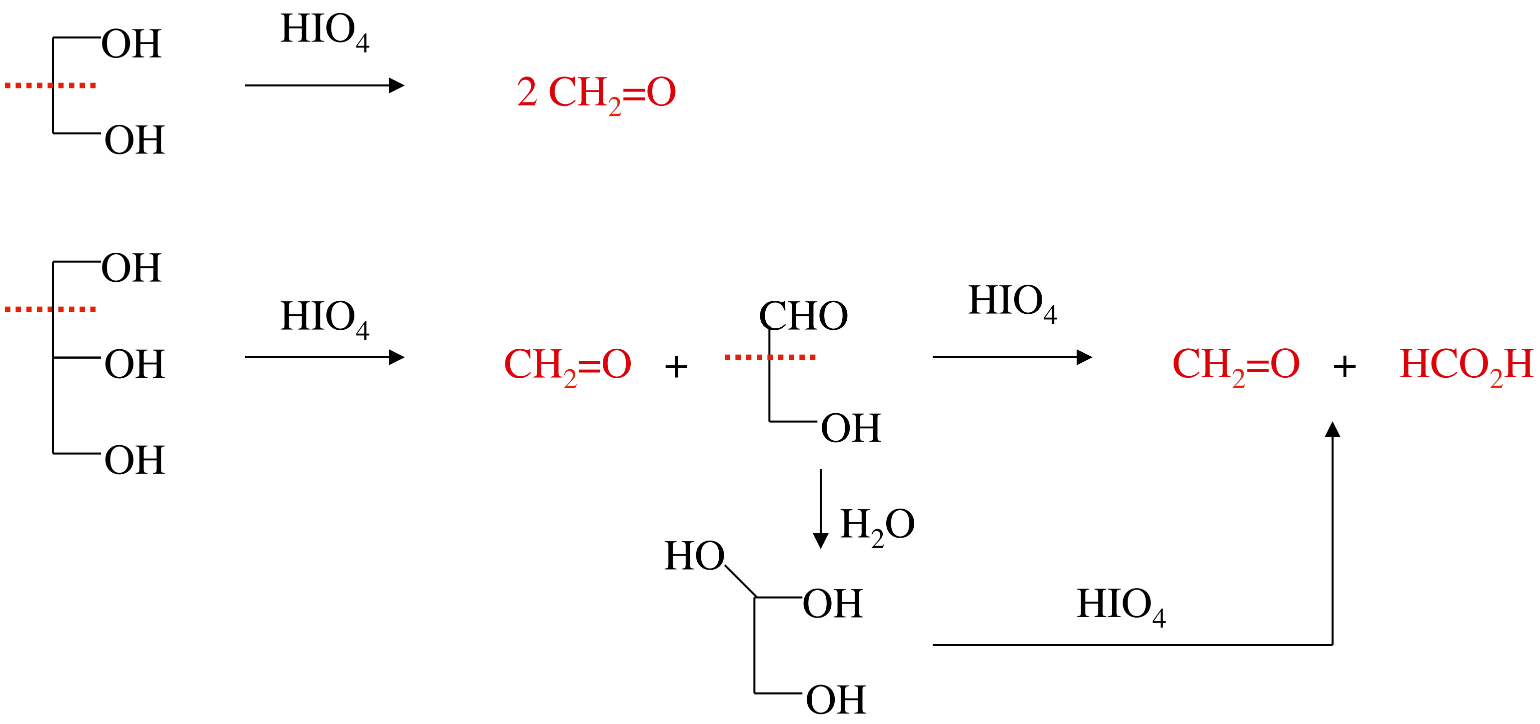
$\xleftarrow{H_2O}$

pure α-anomer
mp 146°C
$[\alpha]_D = +112.2^o$

Ring Sizes of Hexoses

Hexose	***Pyranose Form (%α/%β)***	***Furanose Form***
allose	92	8
altrose	70	30
glucose	~100(36.5/63.5)	<1
mannose	~100(67/33)	<1
gulose	97	3
idose	75	25
galactose	93(27.5/72.5)	7
talose	69	31
fructose	67	33

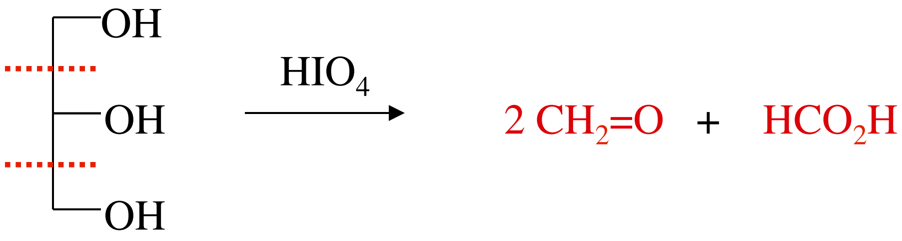
Periodic Acid Cleavage of Carbohydrates as a Diagnostic Tool



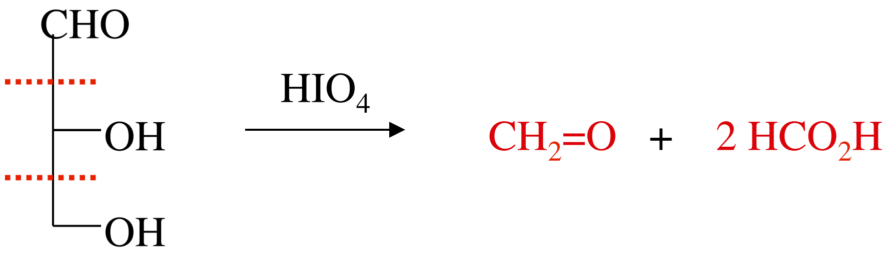
Formaldehyde (CH_2O) arises from a primary alcohols

Formic acid (HCO_2H) arises from a secondary alcohols

Periodic Acid Cleavage of Carbohydrates as a Diagnostic Tool

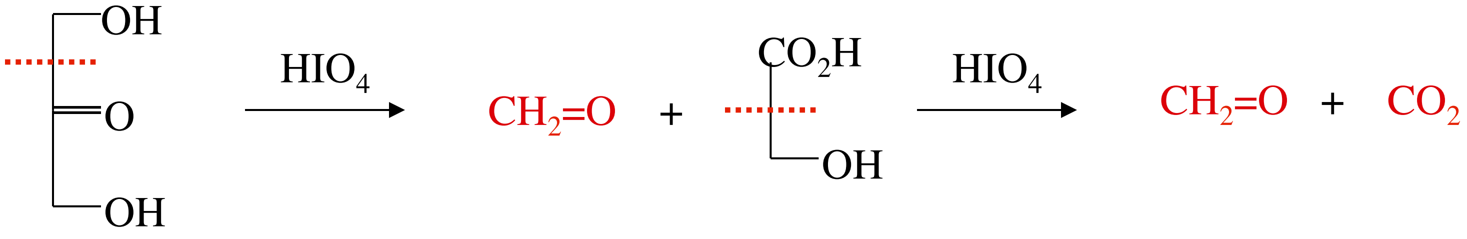


$\xrightarrow{HIO_4}$ $2\ CH_2{=}O + HCO_2H$



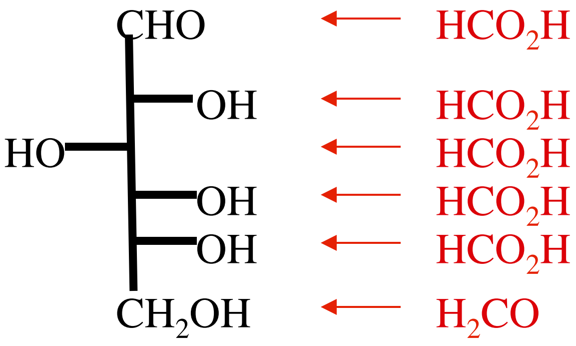
$\xrightarrow{HIO_4}$ $CH_2{=}O + 2\ HCO_2H$

- $RCH_2OH \longrightarrow CH_2{=}O$
- $R_2CHOH \longrightarrow HCO_2H$
- $RCH{=}O \longrightarrow HCO_2H$
- $R_2C{=}O \longrightarrow CO_2$

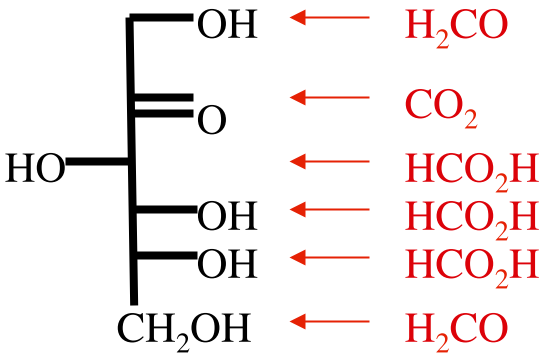


$\xrightarrow{HIO_4}$ $CH_2{=}O$ + $\xrightarrow{HIO_4}$ $CH_2{=}O + CO_2$

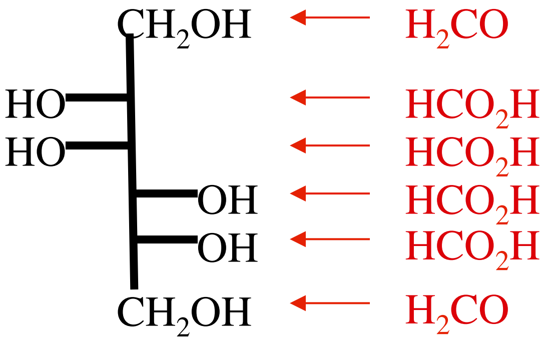
Periodic Acid Cleavage of Carbohydrates



D-glucose

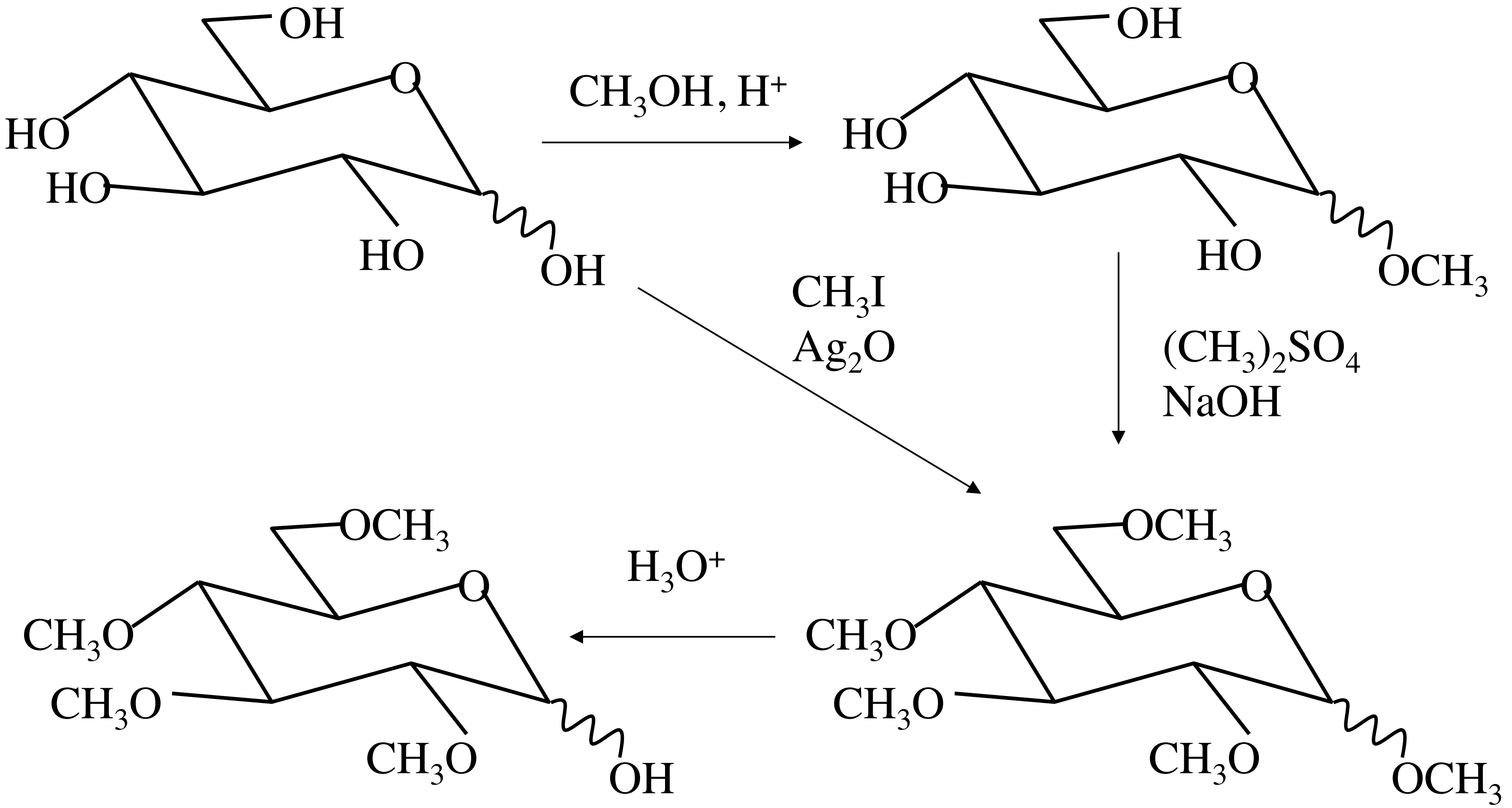


D-fructose

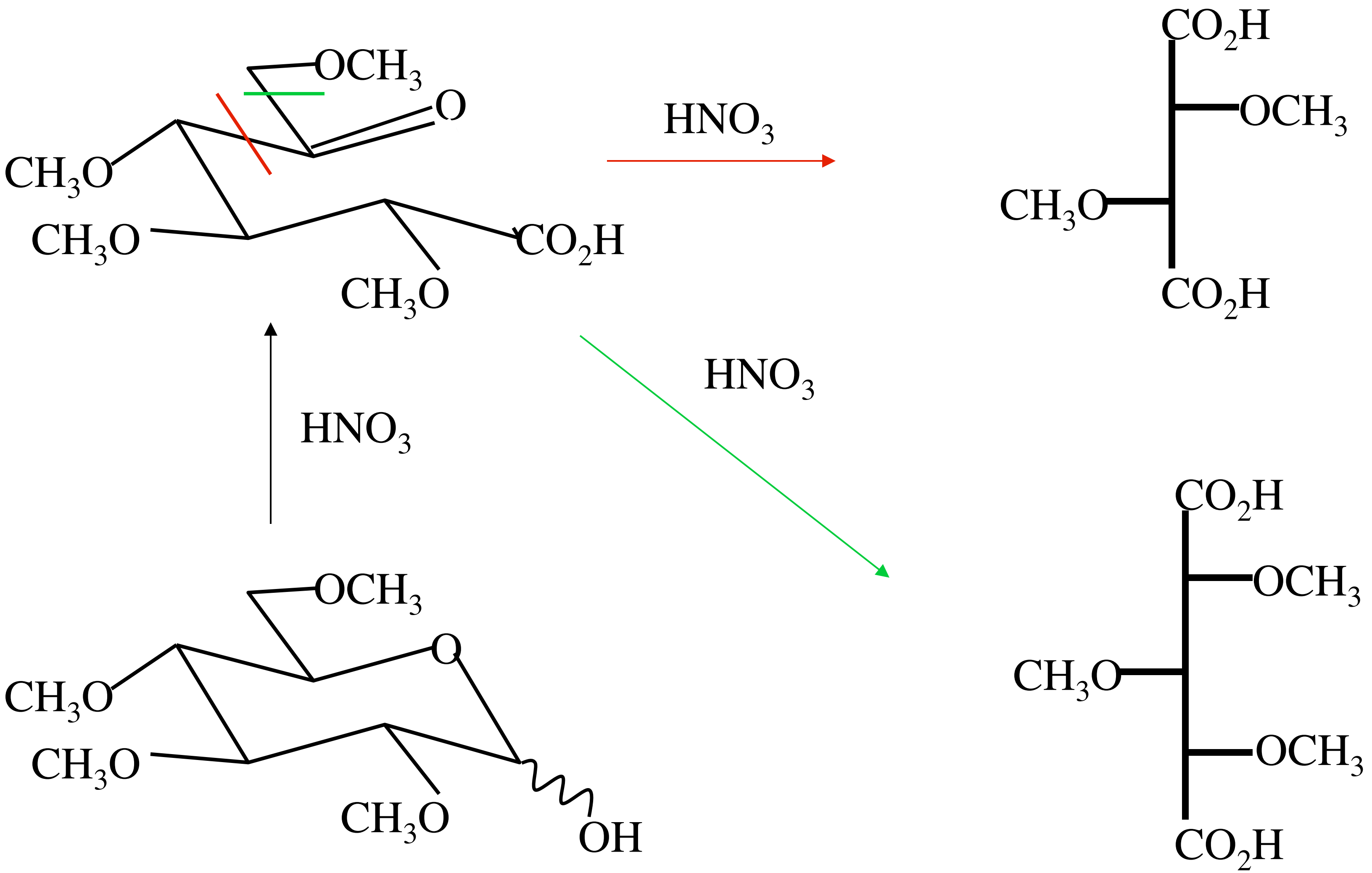


D-mannitol

Methylation of Pyranoses: Pyranosides

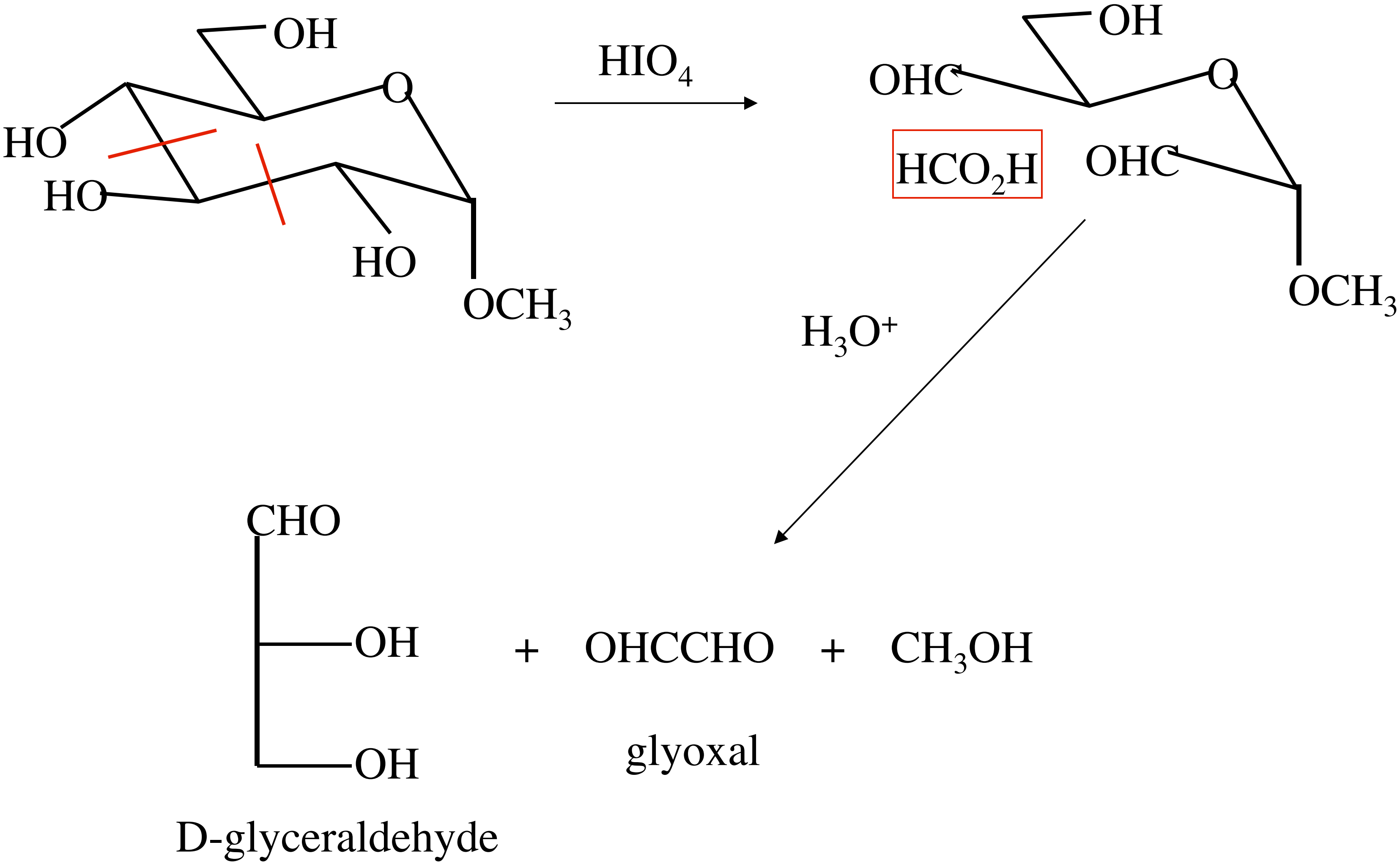


Ring Size of Pyranosides

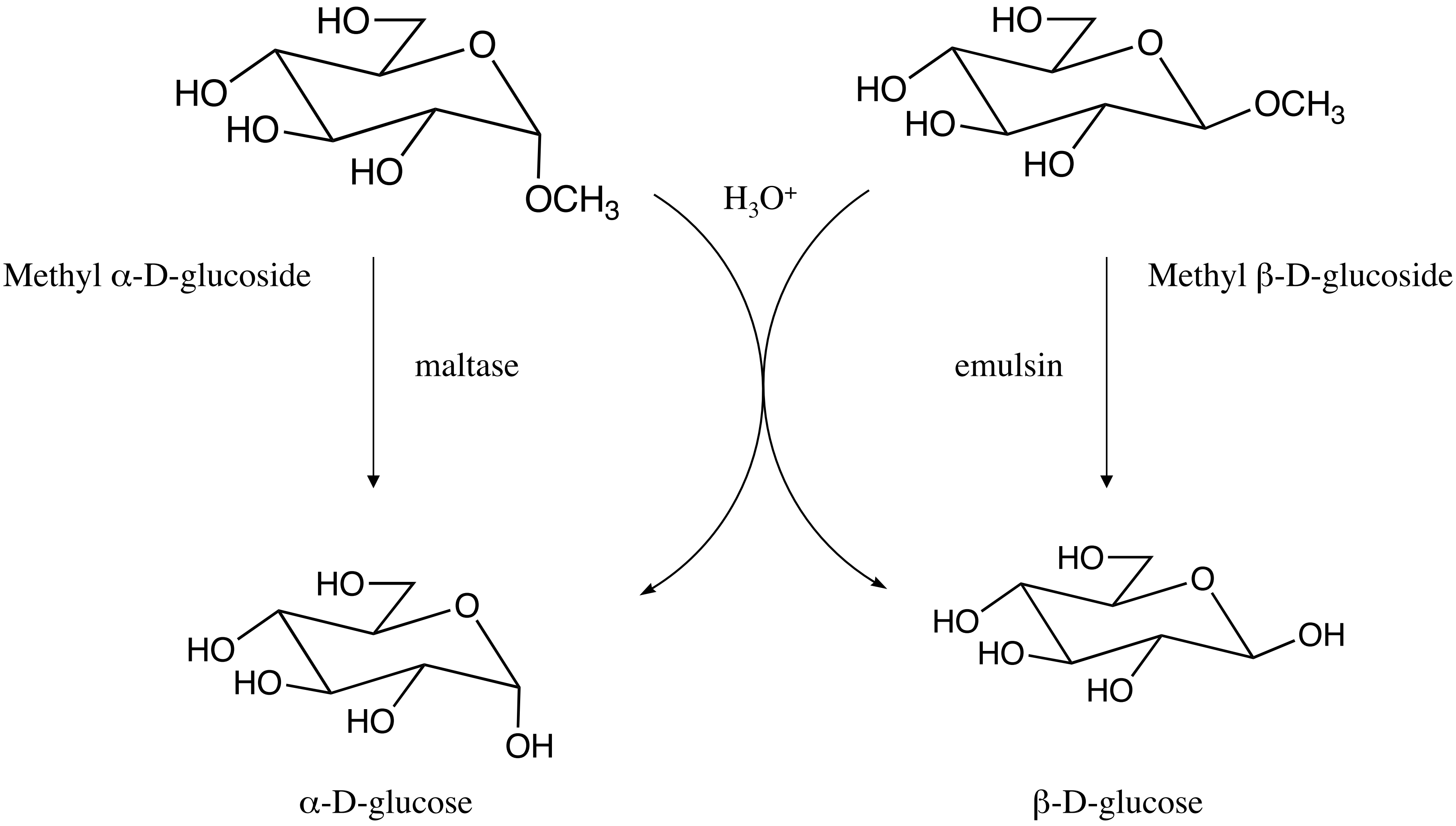


via oxidation of the enol of the ketone

Periodic Acid Cleavage of Methyl α-Glucopyranoside



Enzymatic Cleavage of Glucosides



Methyl α-D-glucoside

maltase

H_3O^+

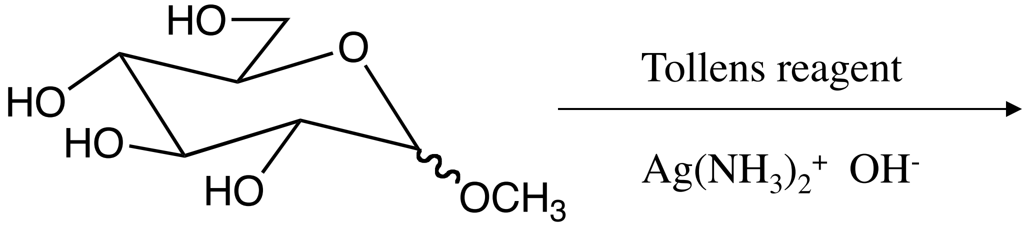
Methyl β-D-glucoside

emulsin

α-D-glucose

β-D-glucose

The Silver Mirror Test



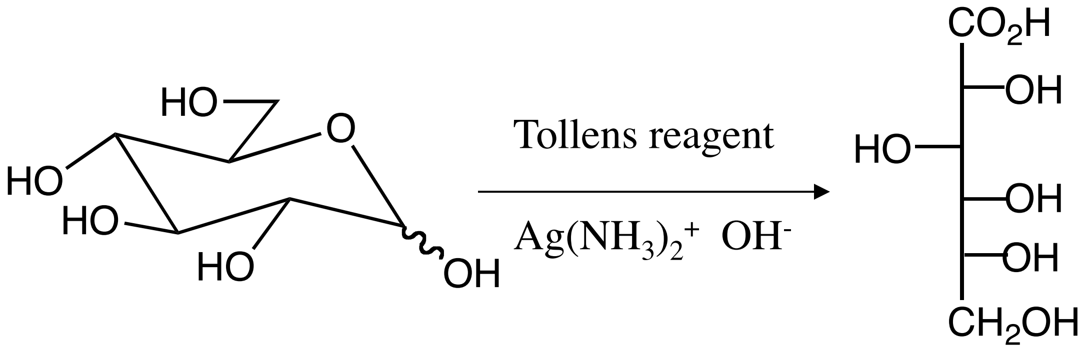
Tollens reagent

$Ag(NH_3)_2^+$ OH^-

no reaction

Methyl -D-glucoside

non-reducing sugar (a glycoside)



Tollens reagent

$Ag(NH_3)_2^+$ OH^-

+ Ag^o ↓

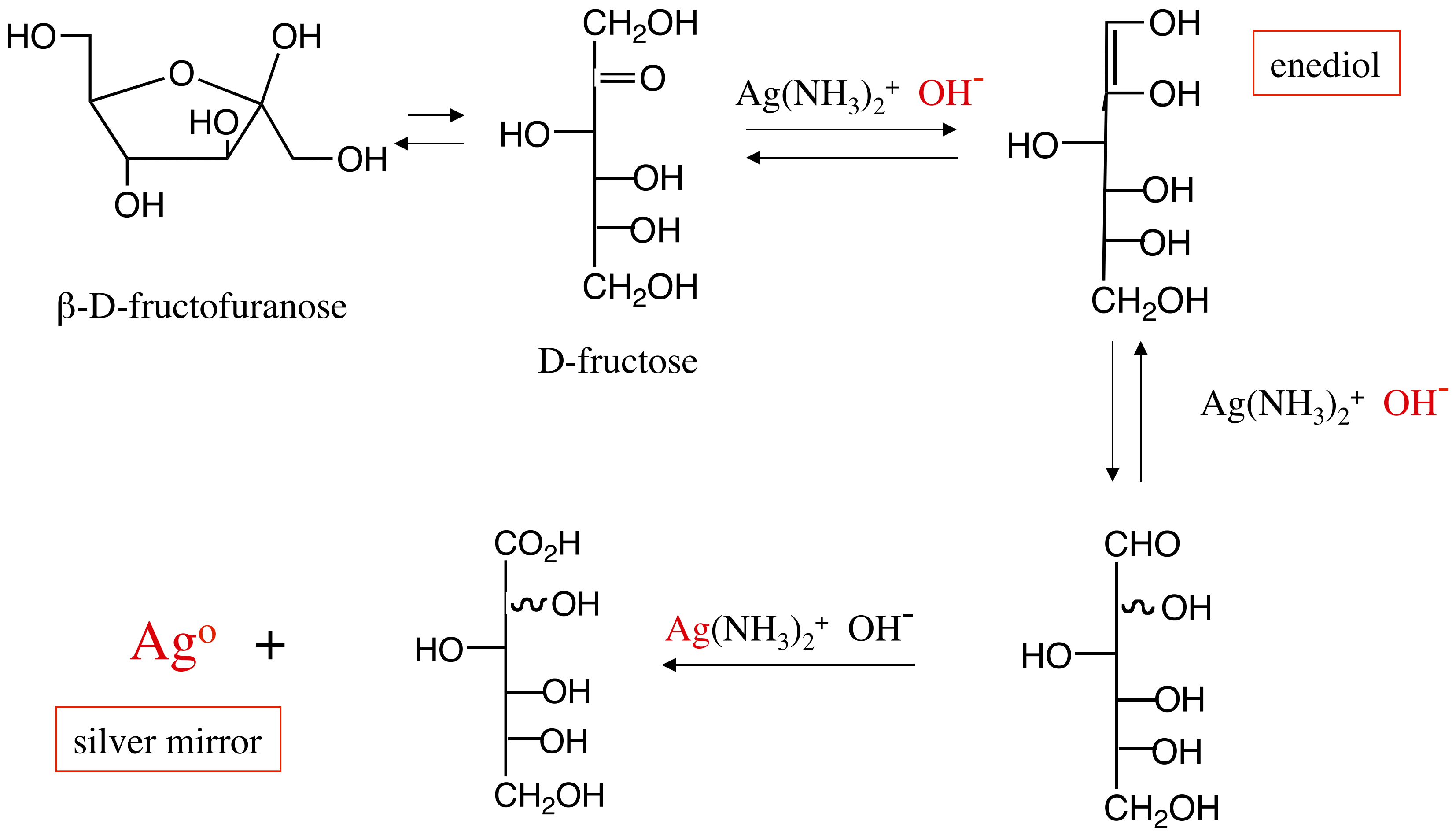
silver mirror

D-glucose

reducing sugar (an aldose)

www.chem-pics.co.uk/download.htm

The Silver Mirror Test



β-D-fructofuranose

D-fructose

enediol

$Ag(NH_3)_2^+$ OH^-

$Ag(NH_3)_2^+$ OH^-

$Ag(NH_3)_2^+$ OH^-

Ag^o +

silver mirror

Aldoses and ketoses are reducing sugars

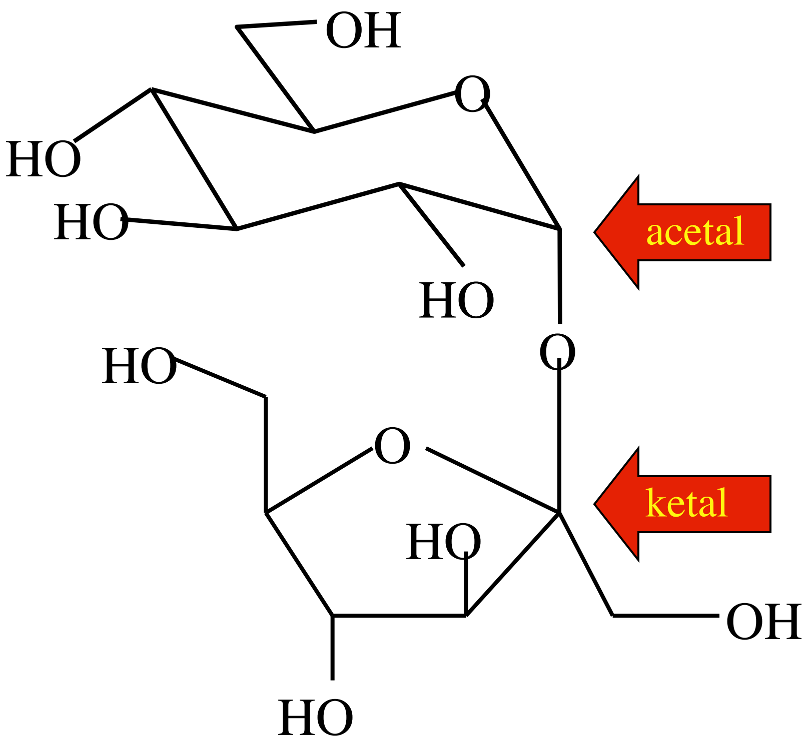
Disaccharides

and

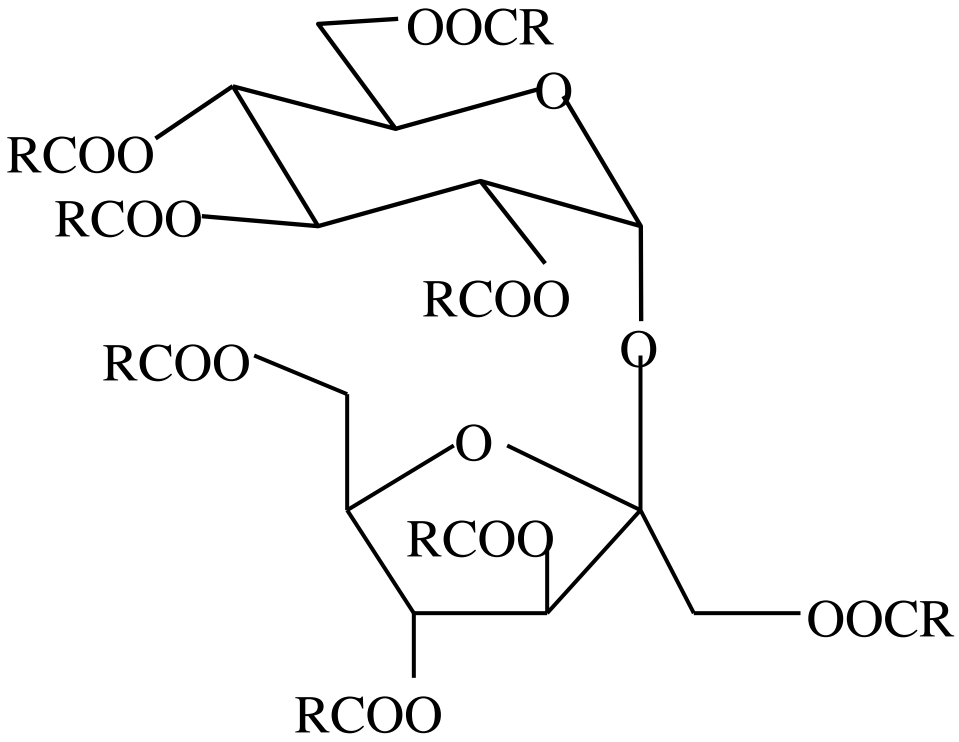
Polysaccharides

α-D-Glucopyranosyl- β -D-fructofuranoside

or β-D-Fructofuranosyl-α-D-glucopyranoside



Sucrose
(non-reducing sugar)



Olestra
(R=n-C_nH_{2n+1}; n=6-8)

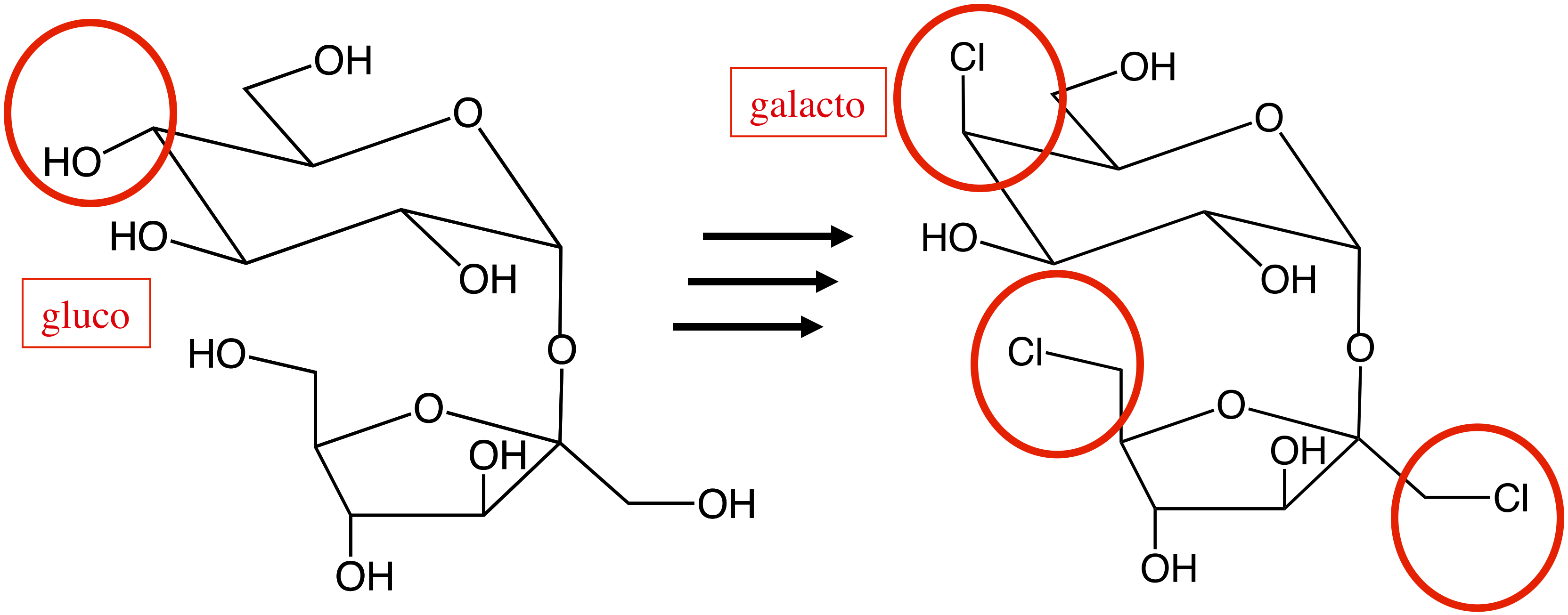
Sucrose is Formed from Glucose and Fructose

This discussion brings to mind a wonderful story told to me by Professor Harry Wasserman (Yale), who during the late 1940's was a graduate student of Professor R. B. Woodward at Harvard. Apparently Woodward had received a notice of a $1,000 prize for the first person to accomplish a chemical synthesis of sucrose. He went into the laboratory and said to his students that all they had to do was connect two molecules of glucose together [...and lose a molecule of water] and they would have themselves $1,000. One student, obviously not overwhelmed by Woodward's stature in the field even at such a young age, replied that if you did it that way,

the prize would be $2,000!

Sucralose

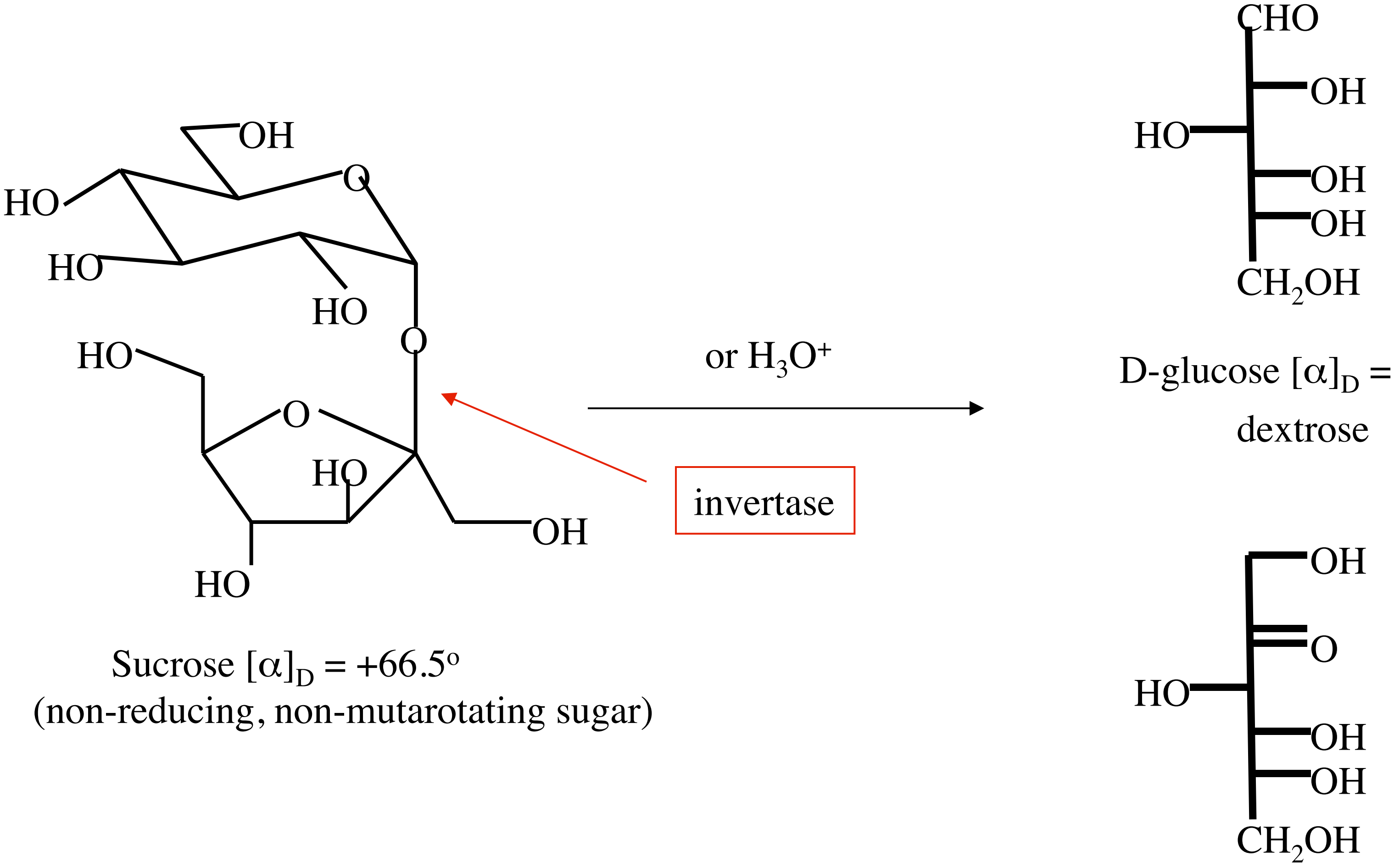
1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside



Sucrose
(non-reducing sugar)

Sucralose
(600 times sweeter than sucrose)

Bees Do It



invertase

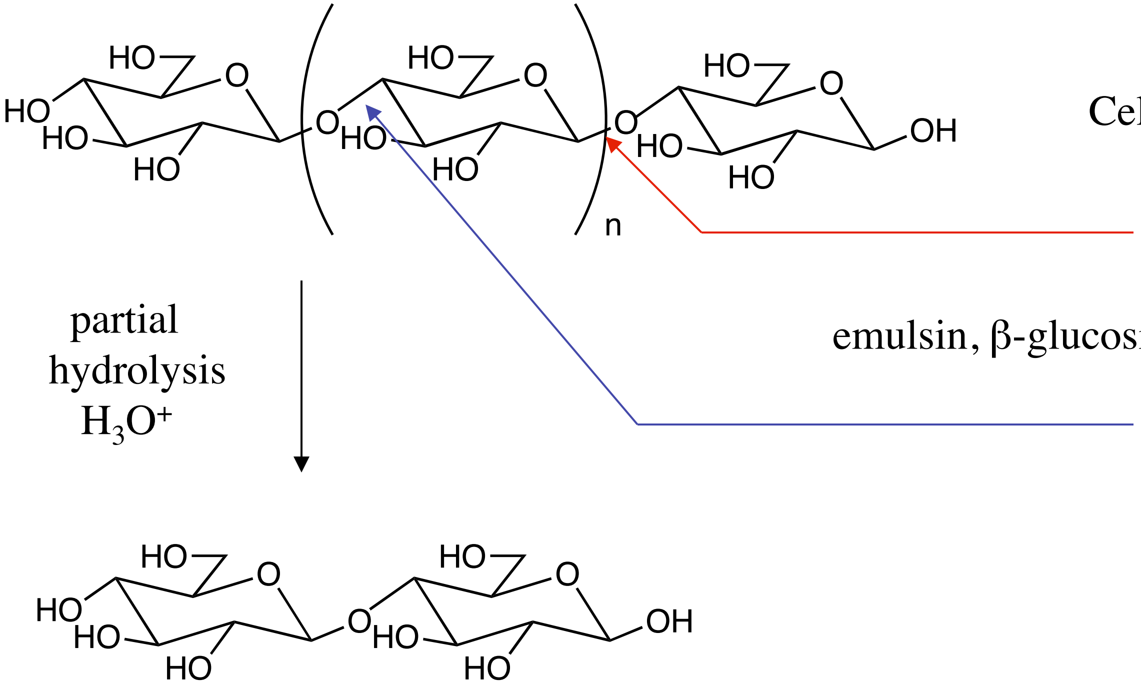
or H_3O^+

Sucrose $[\alpha]_D = +66.5^o$
(non-reducing, non-mutarotating sugar)

D-glucose $[\alpha]_D = +52.7^o$
dextrose

D-fructose $[\alpha]_D = -92.4^o$
levulose

Disaccharides-Cellobiose



Cellulose (polysaccharide)

β-acetal linkage

emulsin, β-glucosidase (termites, ruminants)

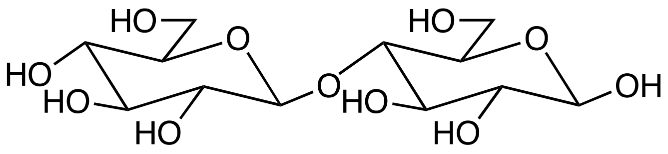
4-*O*-attachment

partial
hydrolysis
H_3O^+

Cellobiose (disaccharide)

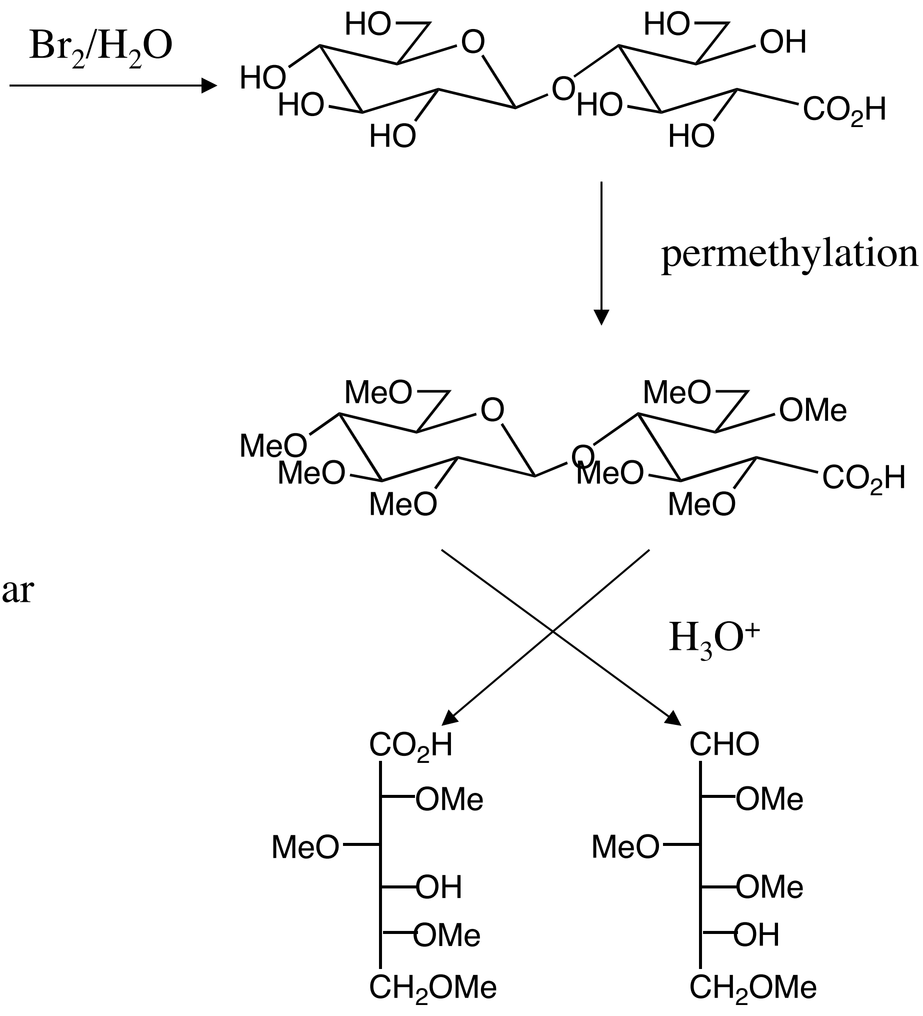
4-*O*-(β-D-glucopyranosyl)-D-glucopyranose

Cellobiose-Structure Proof



Cellobiose

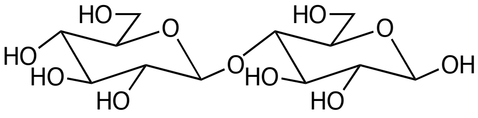
- •hydrolysis ----> only D-glucose
- •emulsin ----> β-glucoside
- •positive Tollens test ----> reducing sugar
- •shows mutarotation

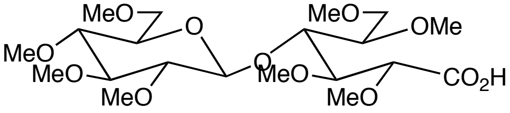


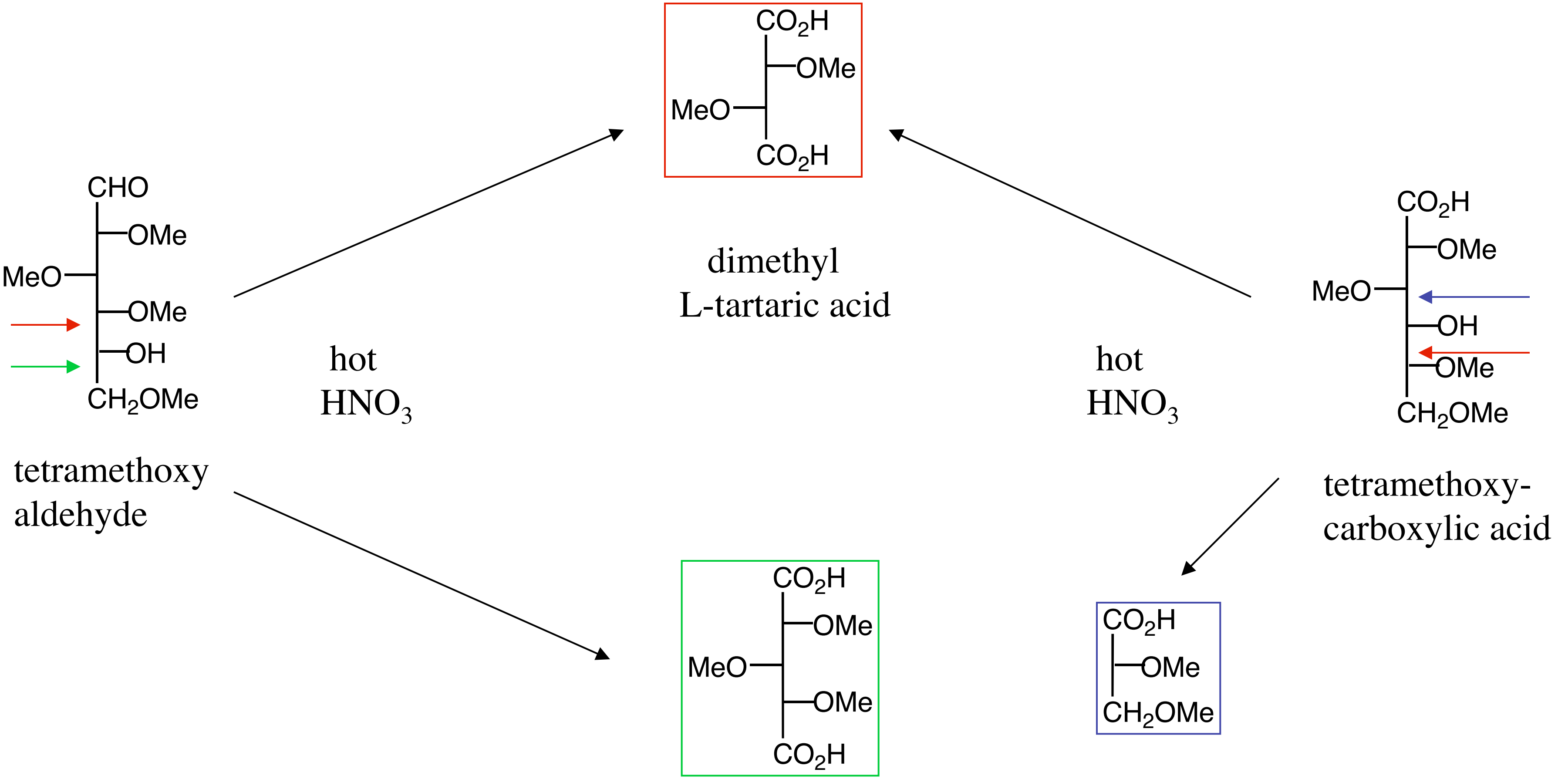
tetramethoxy-
carboxylic acid

tetramethoxy
aldehyde

Cellobiose-Structure Proof







tetramethoxy aldehyde

hot HNO_3

dimethyl L-tartaric acid

hot HNO_3

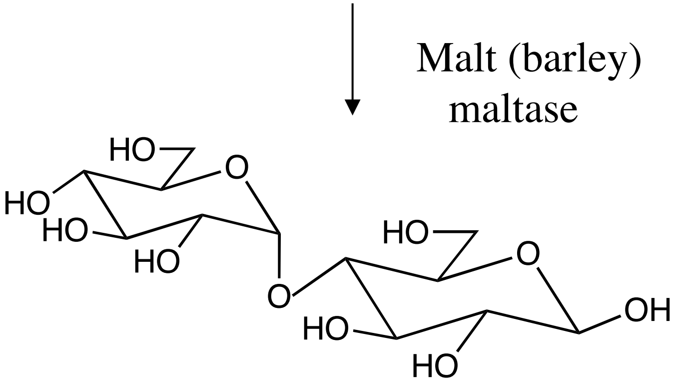
tetramethoxy-carboxylic acid

trimethyl xylaric acid

dimethyl D-glyceric acid

Disaccharides: Maltose

Starches: poly-α-D-glucosides



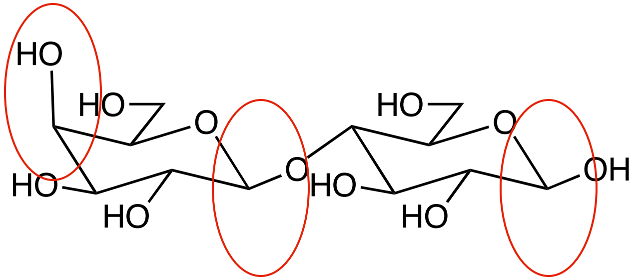
Malt (barley)
maltase

- hydrolysis ----> only D-glucose
- maltase ----> α-glucoside
- positive Tollens test ----> reducing sugar
- shows mutarotation
- differs from cellobiose at the glycosidic anomeric center

Disaccharides: Lactose

4-*O*-(β-D-galactopyranosyl)-D-glucose

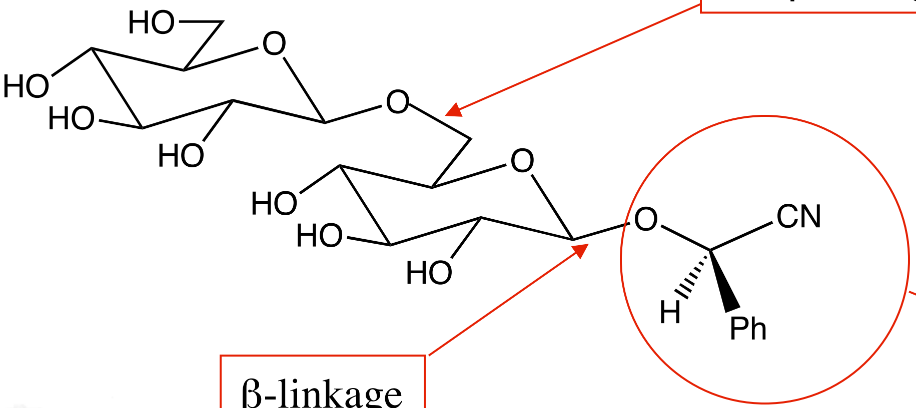
~5% of human and cow milk



- hydrolysis ----> D-glucose and D-galactose
- β-galactosidase (lactase) ----> β-galactoside
- lactose intolerance
- positive Tollens test ----> reducing sugar
- shows mutarotation

Disaccharides: Amygdalin

Laetrile (laevorotatory mandelonitrile), “vitamin 17”



1,6-β-linkage

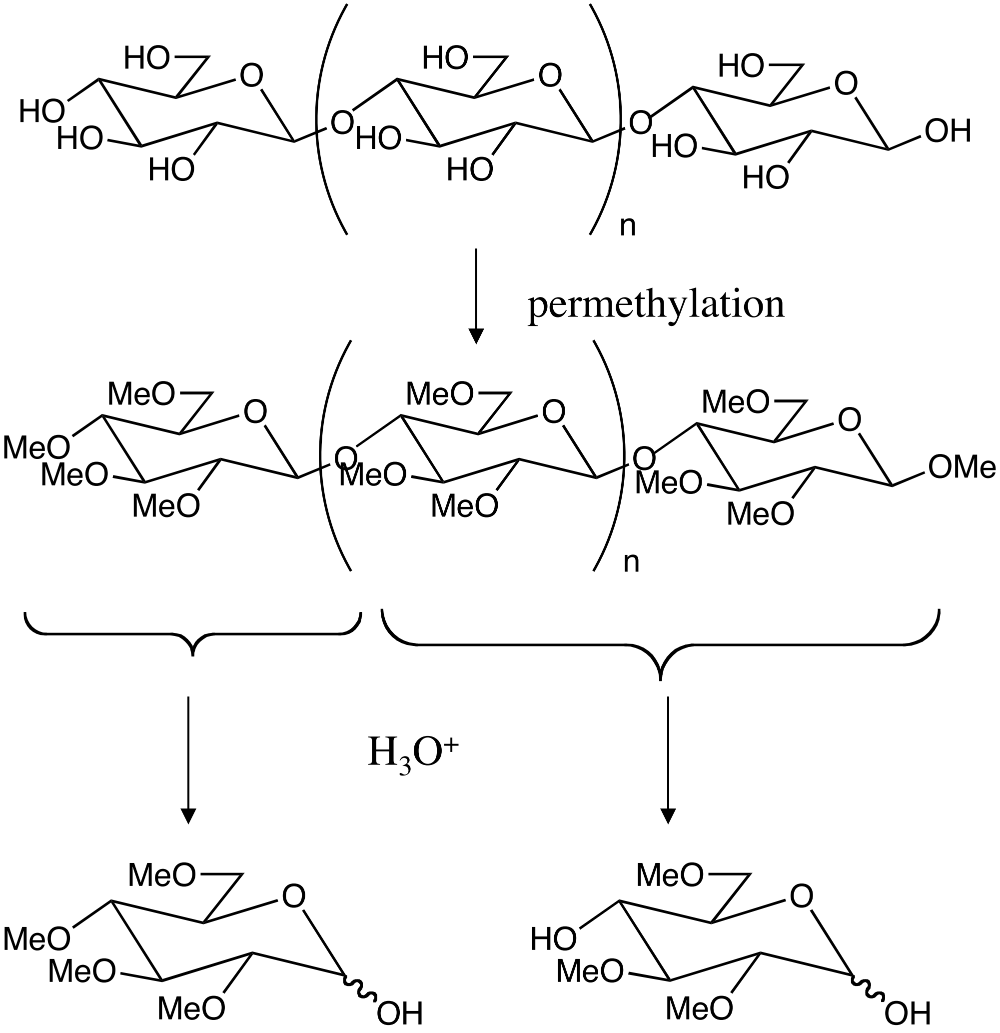
β-linkage

cyanohydrin of benzaldehyde

1836 - Isolated from bitter almonds by Wohler. Demonstrated that emulsin produces glucose, benzaldehyde and prussic acid (HCN)

Touted in some circles as a treatment for cancer.

Cellulose: Chain Length



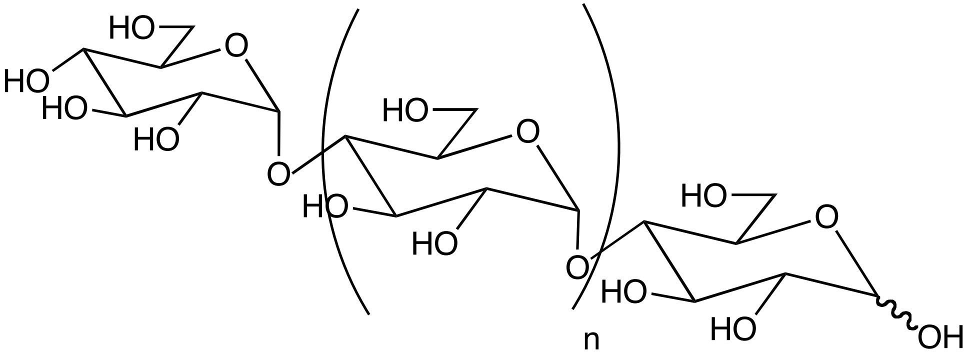
2,3,4,6-tetra-*O*-
methyl D-glucose
(terminal)

0.6%

99.4%

2,3,6-tri-*O*-
methyl D-glucose
(chain)
100-200 units

Starches: Plant Polysaccharides



Amylose :

- ~20% water soluble starch; poly 4-*O*-(α-D-glucoside)

- forms helical structure; blue complex with iodine

Starches: Plant Polysaccharides

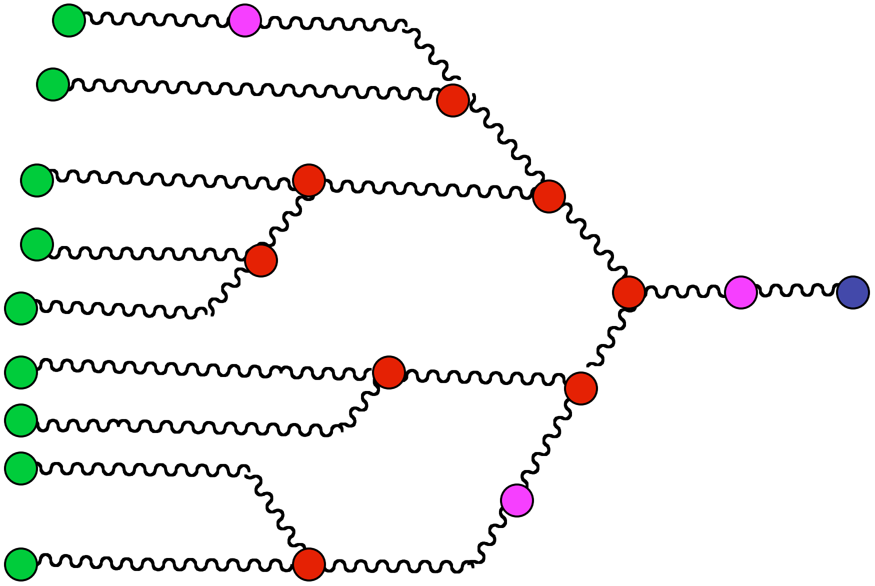
Amylopectin:

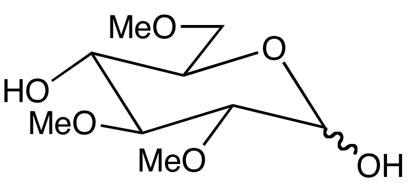
- ~80% water insoluble starch branched poly-4-*O*-(α-D-glucoside)
- permethylation/hydrolysis

🟣 90% 2,3,6-tri-*O*-methyl-D-glucose

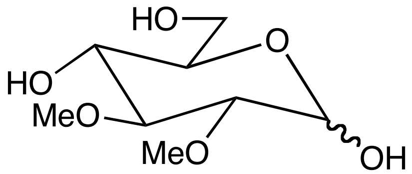
🔴 ~5% 2,3-di-*O*-methyl-D-glucose

🟢 ~5% 2,3,4,6-tetra-*O*-methyl-D-glucose

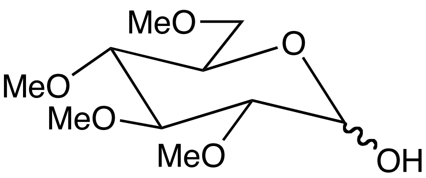




chain



junction



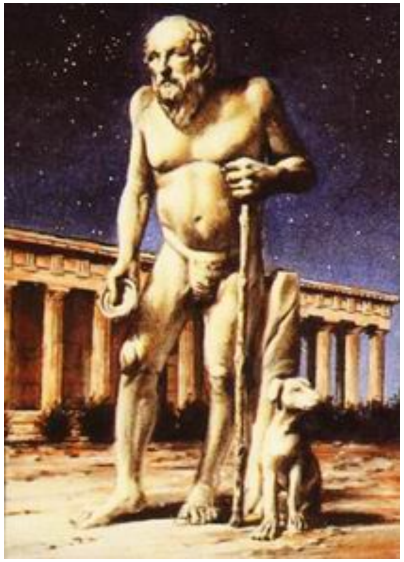
terminus

Average 20 glucose units /chain

And Finally, a True Story

In March of 1986 I was in California visiting several universities. While at Stanford University, I stopped at the health center to have a swollen foot examined. The young resident was very attentive. To assess his qualifications, I asked him where he had attended college. “M.I.T.,” he responded. “So you must have had Professor Kemp for organic chemistry,” I countered. “Yes, I did,” he said. Then I asked, *“What D-aldohexose forms the same osazone as glucose?”*

Like Diogenes the Cynic in search of an honest man (person), I have posed this question to many a practitioner of the medical and dental professions. Neither Diogenes nor I have fulfilled our quests. However, the responses to my query were often amusing.



Response:	My thought:
“I really enjoyed organic chemistry!”	Really?
“Organic, don’t remind me!”	An honest man?
“I know the mechanism of the aldol condensation.”	Wrong chapter!
“I know what a Grignard reagent is.”	Wrong test!
“Wait! Give me some time.”	“It’s only an hour exam.”

The Moral of the Story

Somewhere,…sometime…someone might ask you this question.

What D-aldohexose forms the same osazone as D-glucose?

Your answer will be...

D-Mannose!

The

End