Fischer projection and the story behind

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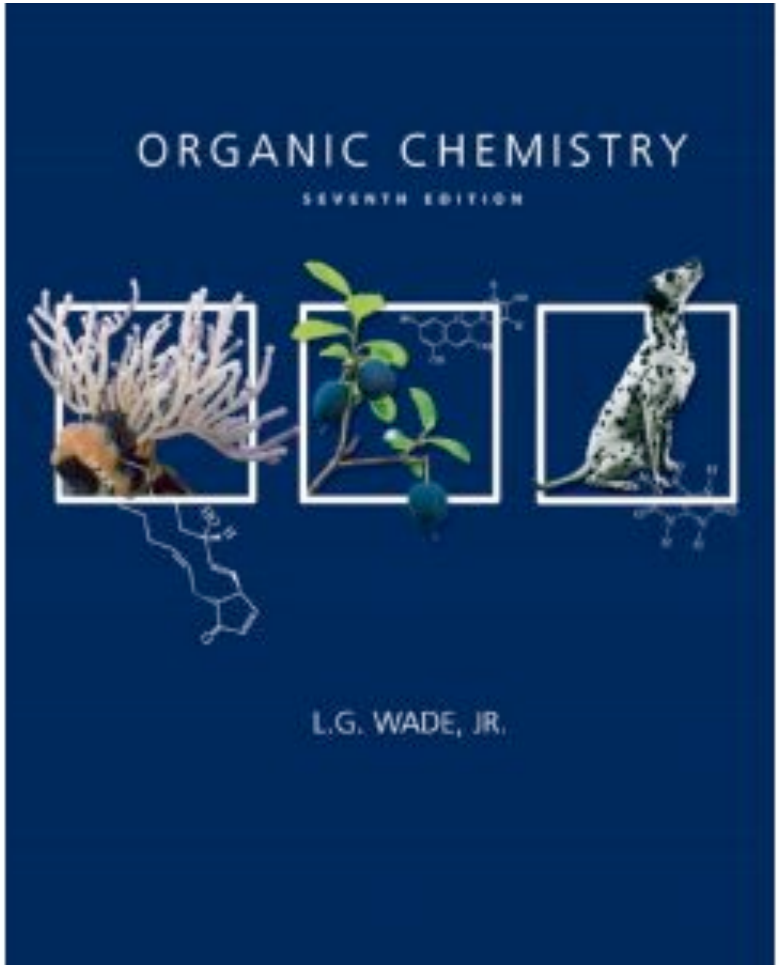
- **Emil Fischer**, “**Syntheses in the purine and sugar group**” Nobel Lecture, December 12, 1902
- **Raymond U. Lemieux** and Ulrike Spohr, “**How Emil Fischer was let to the lock and key concept for enzyme specificity**”. Presentation at the symposium “Emil Fischer: 100 Years of Carbohydrate Chemistry” California, April 5-10, 1992.
- **William Reusch** “Virtual Textbook of Organic Chemistry” Emeritus Faculty from Michigan State University
- Wade “**Organic Chemistry**” 6th edition

- **C. S. Hudson**, "**Emil Fischer's Discovery of the Configuration of Glucose----A Semicentennial Retrospect**" Journal of Chemical Education 1941, 353.



Emil Fischer
(1852-1919)

Biography

- Born in Euskirchen, near Cologne, the son of a businessman. His father compelled him to work in the family business until determining that his son was unsuitable

- attended the University of Strasbourg in 1872. earned his doctorate in 1874 Tutor: Adolf von Baeyer (NB 1905)

- 1875, an assistant in Baeyer's lab at the University of Munich, Then Associate Professor in 1879.

- Professor at University of Erlangen since 1881.

- Refused an offer from company, Even his father made him financially independent.

- Professor of Chemistry at the University of Würzburg and here he remained until 1892, when he was asked to succeed A. W. Hofmann in the Chair of Chemistry at the University of Berlin. Here he remained until his death in 1919.

EF: “The abundance of substances of which animals and plants are composed, the remarkable processes whereby they are formed and then broken down again have claimed the attention of mankind and from the early days they also persistently captivated the interest of chemists.“

Noteworthy successes were not achieved by science until 18th century when men like **Sigismund Marggraf** in Berlin, Lavoisier in Paris and Carl Wilhelm Scheele in Sweden studied it.

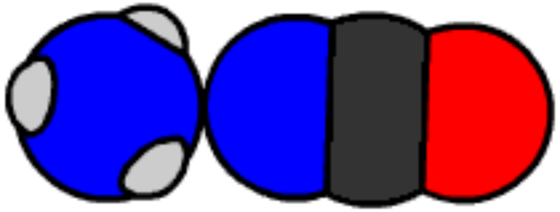
Difficulty and necessity made the research separate from mineral chemistry then became a special branch of our science.

Organic chemistry

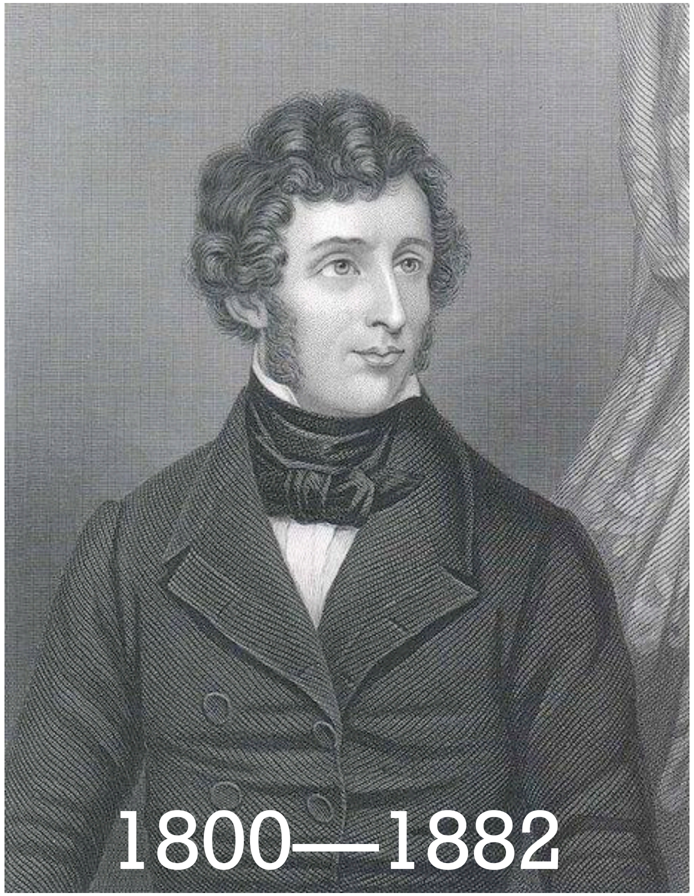
It found the exploration of new avenues more worthwhile. It replaced the animal and vegetable substances by many artificial products such as the hydrocarbons and cyano compounds, wood tar and coal tar, wood alcohol, etc.

Friedrich Wöhler

$[NH_4^+][NCO^-]$



1828



$$AgNCO + NH_4Cl \rightarrow (NH_2)_2CO + AgCl$$

This discovery prompted Wöhler to write triumphantly to Berzelius: "I must tell you that I can make urea without the use of kidneys, either man or dog. Ammonium cyanate is urea."

Chemistry in 19 century

1856 A.D.

New dyes synthesises by William Perkin, Sr. from coal tar. Bessemer's converter revolutionises iron smelting process. Industries boom as a result of chemical progress.

1858 A.D.

Friedrich Kekule defines the concept of valency, and with Couper discovers the tetravalent quality of carbon.

1866 A.D.

Kekule propunds his theory of the molecular structure of benzene.

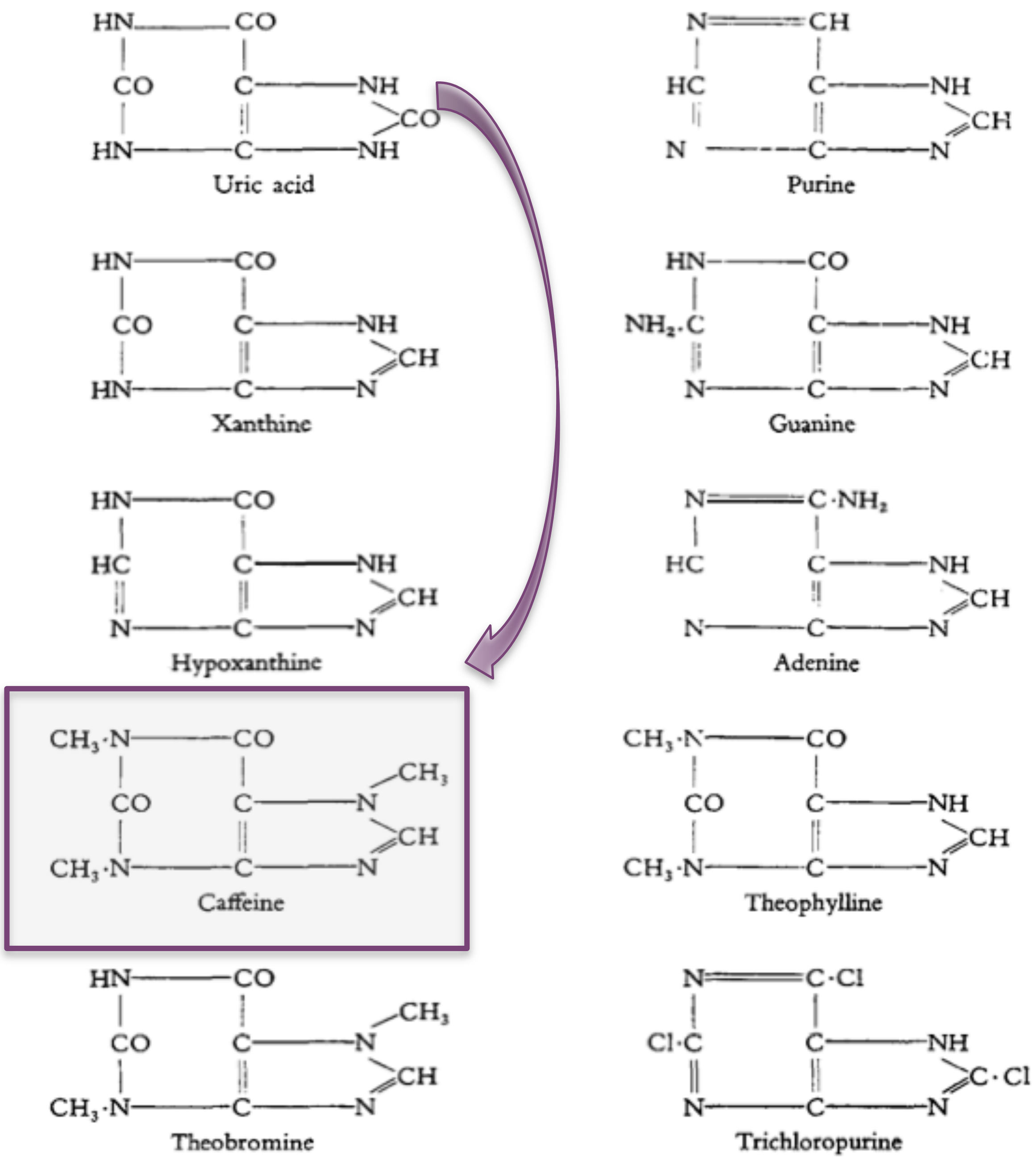
1869 A.D.

The periodic law is put forward by Dmitri Mendeleev and simultaneously and independently by Julius Meyer.

the one-sided study of carbon compounds cannot suffice to elucidate the nature of chemical processes in all aspects

the reversion of organic chemistry to the great problems of biology.

"in recognition of the extraordinary services he has rendered by his work on sugar and purine syntheses"



+ Before Fischer:

- **Research started at the beginning of organic chemistry**
- the first organic products formed in plants from carbon dioxide in the air
- Abundance: surpass all substance that are current in the living world.
- more than a century elapsed from the elucidation of their elementary composition by Lavoisier
- **Slow progress**

Carbohydrate

The reason

- The peculiar difficulties when those substances pose for experimental treatment
- The great profusion of forms which also necessitates a rather complex systematology

+ Known distinction

Monosaccharide

- Grape sugar
- By hydrolysis all polysaccharides can be converted into the simpler monosaccharides

- Conversely monosaccharides can be transformed into the more complex polymers by a process termed dehydratation
- 50 known, 10 in nature

Polysaccharide

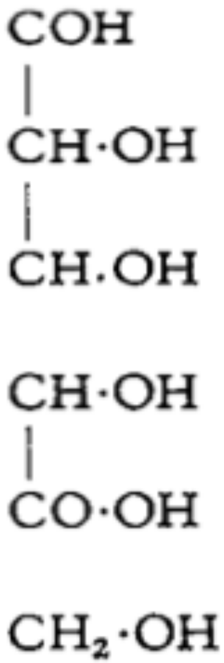
- Starch, Cellulose
- Both hydrolyse to form grape sugar
- With starch, hydrolysis comes about under the action of the gastric and intestinal juices.
- Cellulose hydrolysed by strong sulphuric acid and yields wood sugar

Item	Substrate							
	Broccoli	Carrot	Cauliflower	Celery	Cucumber	Lettuce	Onion	Radish
	g/kg as is							
Dry matter	112.7	124.9	83.9	43.7	29.6	34.2	51.6	43.1
Ethanol insoluble residue	72.4	49.9	48.5	18.8	9.6	13.5	26.1	18.0
Total dietary fiber residue[1]	53.8	36.5	36.5	17.7	7.8	12.2	22.3	16.3
Total dietary fiber[2]	34.9	29.2	24.8	13.5	5.8	8.9	17.6	12.5
	g/kg dry matter							
Total dietary fiber residue	477	292	435	405	264	357	432	378
Total dietary fiber	310	234	296	309	196	260	341	290
Non-starch polysaccharides[3]	223	176	223	217	133	174	256	209
	g/kg total dietary fiber residue							
Organic matter	871	859	888	844	847	840	847	852
Crude protein	222	59	207	80	101	114	55	84
Total dietary fiber	649	800	681	764	746	726	792	768
Cell wall monomers (anhydrous)								
Arabinose	84.3	61.4	94.2	39.1	19.2	14.4	12.4	25.1
Fucose	3.0	TR[4]	3.6	2.0	2.0	2.4	2.8	2.5
Galactose	47.3	107.2	49.3	39.3	85.0	24.1	149.4	23.0
Glucose	133.3	164.2	146.3	179.5	174.6	161.8	161.7	181.6
Mannose	14.2	15.5	15.7	18.3	21.1	17.5	9.0	17.6
Rhamnose	TR	1.8	TR	TR	1.4	5.2	3.2	6.9
Xylose	21.3	7.9	23.1	21.4	36.4	24.5	16.4	20.9
Uronic acids	164.5	244.8	181.2	237.1	164.6	238.7	237.3	275.1
Acetyl	12.9	17.4	16.3	15.6	13.4	13.7	10.2	15.5
Klason lignin	49.5	24.3	24.2	43.2	46.2	76.6	22.6	41.8

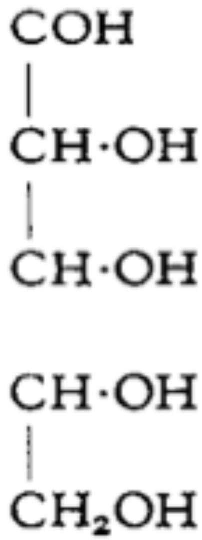
Nutrient Metabolism, 1993, 860

Problem I

The different sugars are using the same chemical structure.



Glucose or galactose



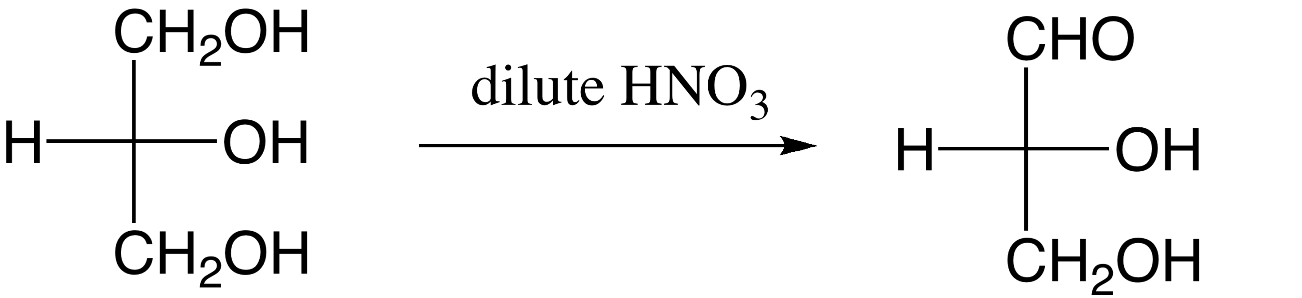
Arabinose and xylose

Problem II

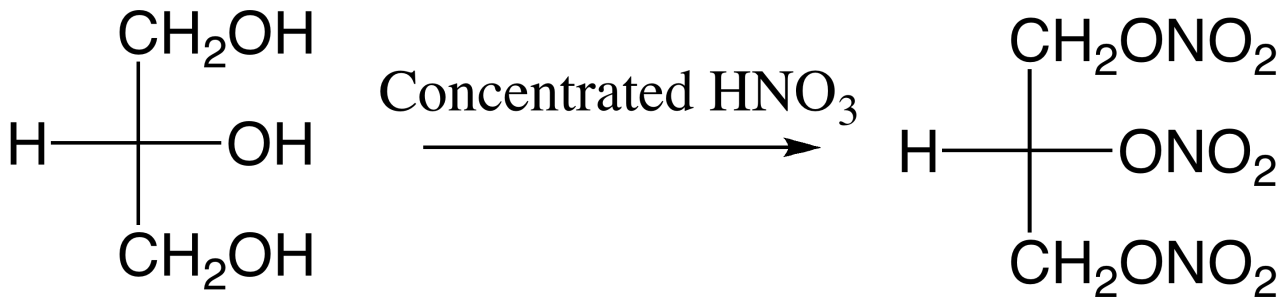
Success of synthesis is extremely scant

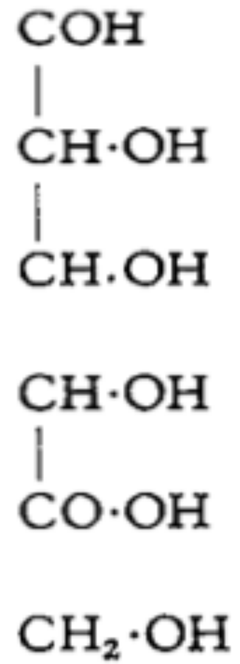
- Only one from literature can stand "modern test".
- the sweet syrup which the Russian chemist Butlerov obtained 40 years ago from formaldehyde by the action of lime water ($Ca(OH)_2 \cdot 2H_2O$)
- a complex mixture and contains only a tiny amount of a substance, closely related to grape sugar
- glycerol.

Relationship of glycerol and sugar



glycerose





Glucose or galactose

Brief review of Stereochemistry

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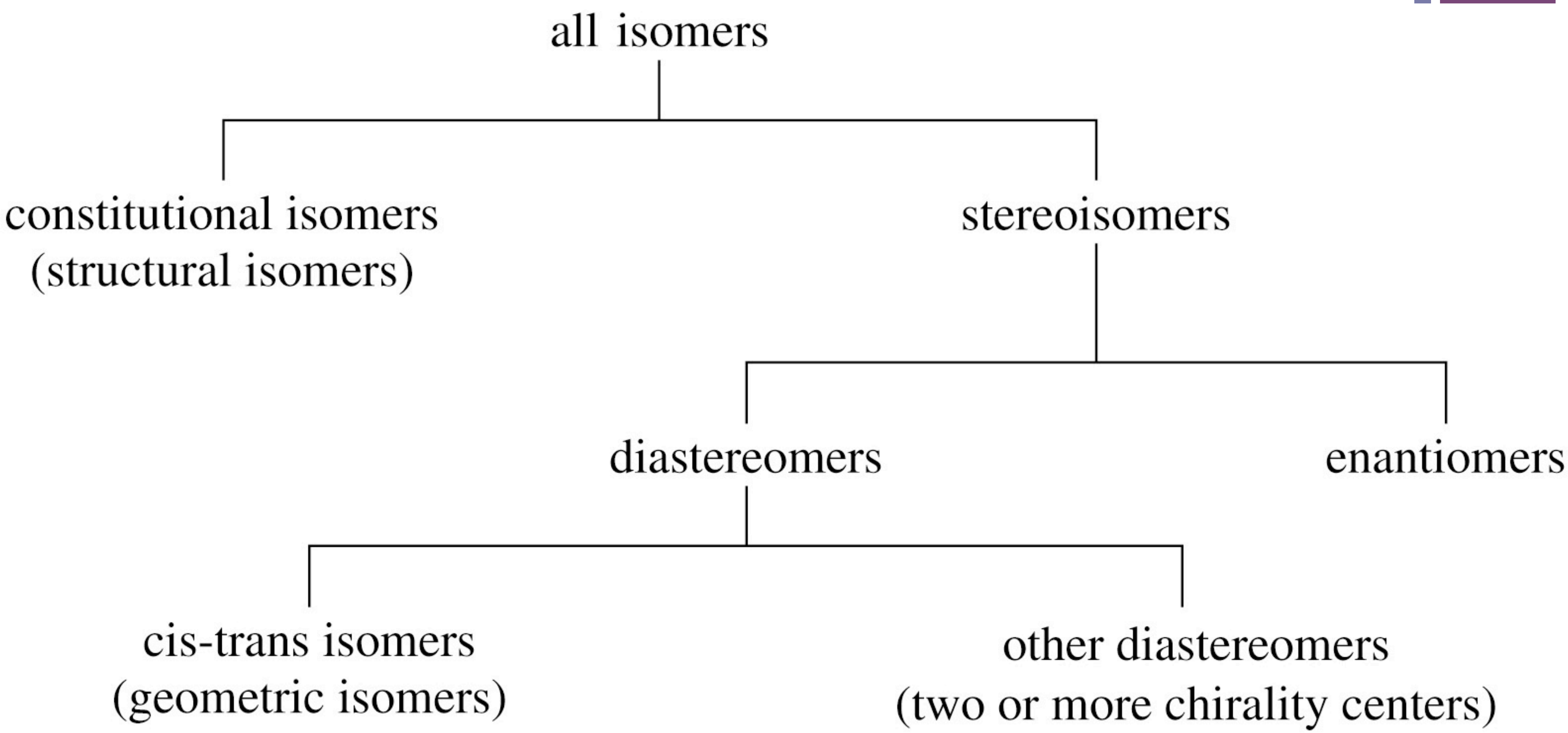
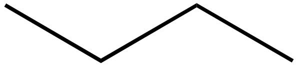
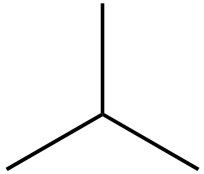
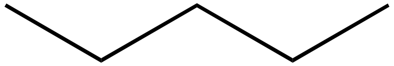
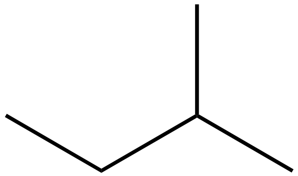
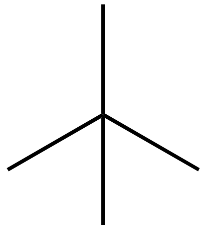

all isomers
constitutional isomers
(structural isomers)
stereoisomers
diastereomers
enantiomers
cis-trans isomers
(geometric isomers)
other diastereomers
(two or more chirality centers)

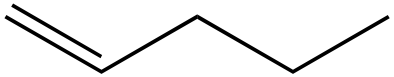

n-butane

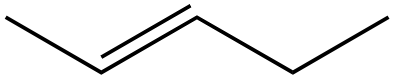

isobutane

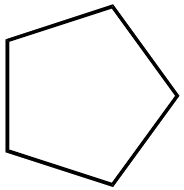

n-pentane

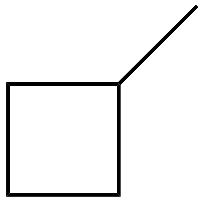

isopentane


neopentane

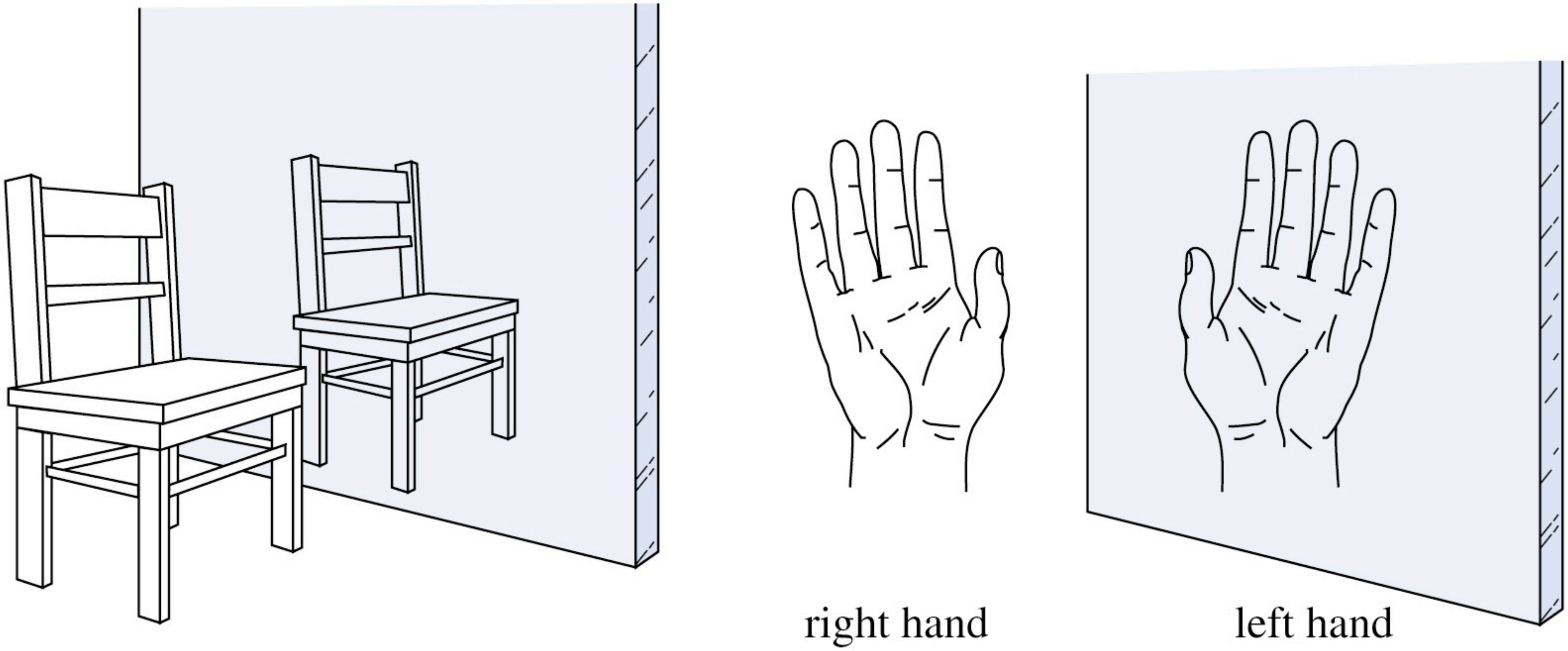

1-pentene


2-pentene

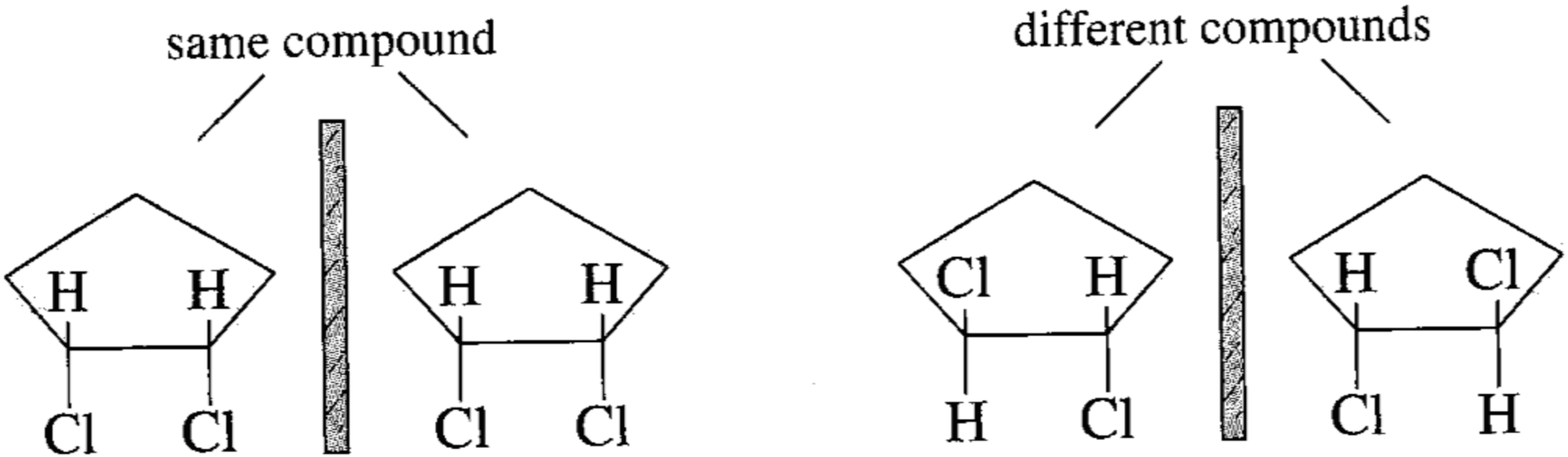

cyclopentane


methylcyclobutane

Chirality

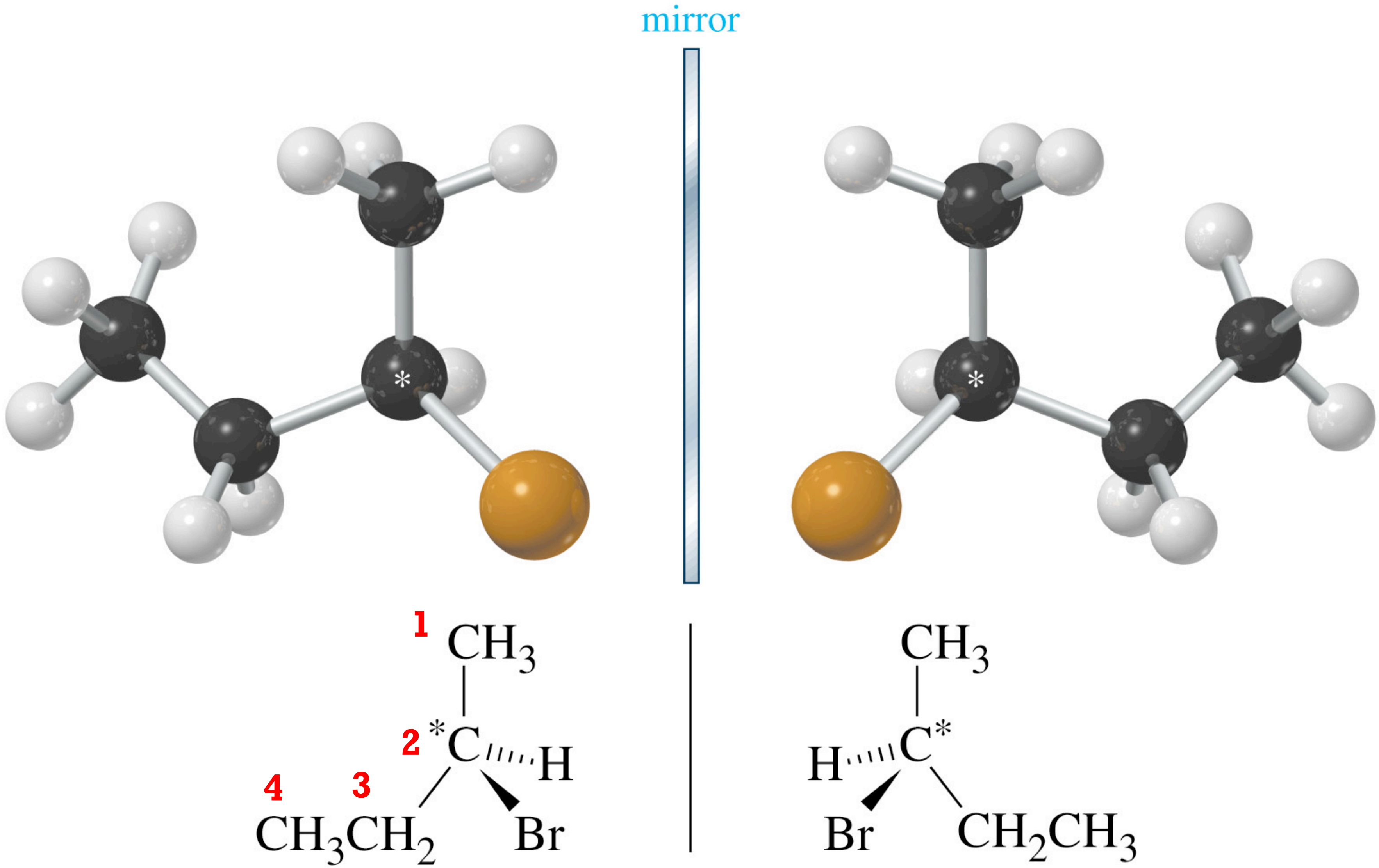


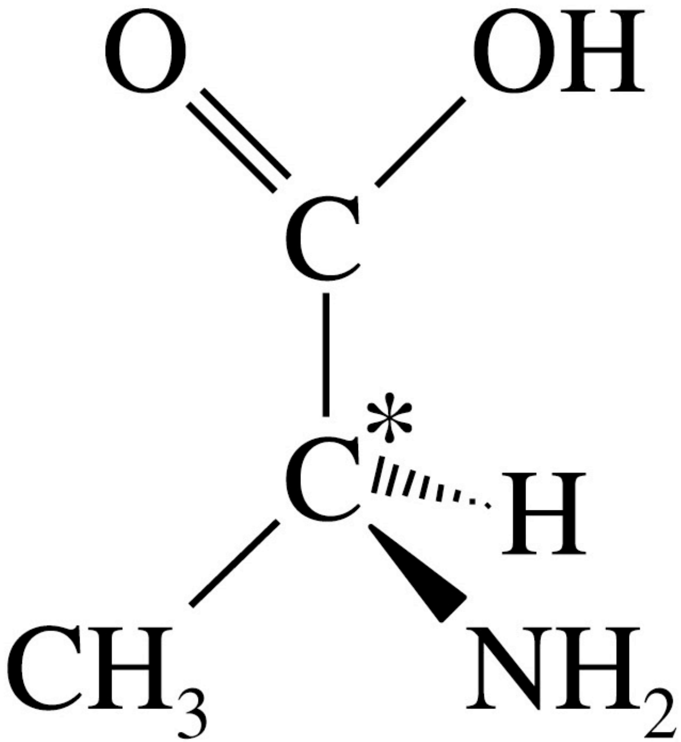
enantiomers



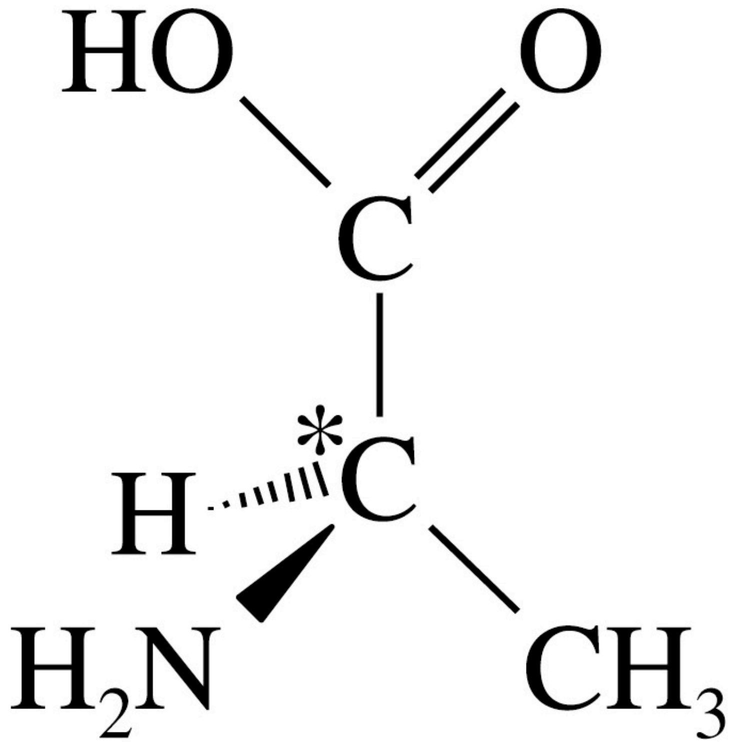
cis-1, 2-dichlorocyclopentane
(achiral)

trans-1, 2-dichlorocyclopentane
(chiral)


mirror
1
CH3
2
*C
H
4 3
CH3CH2
Br
CH3
C*
H
Br
CH2CH3

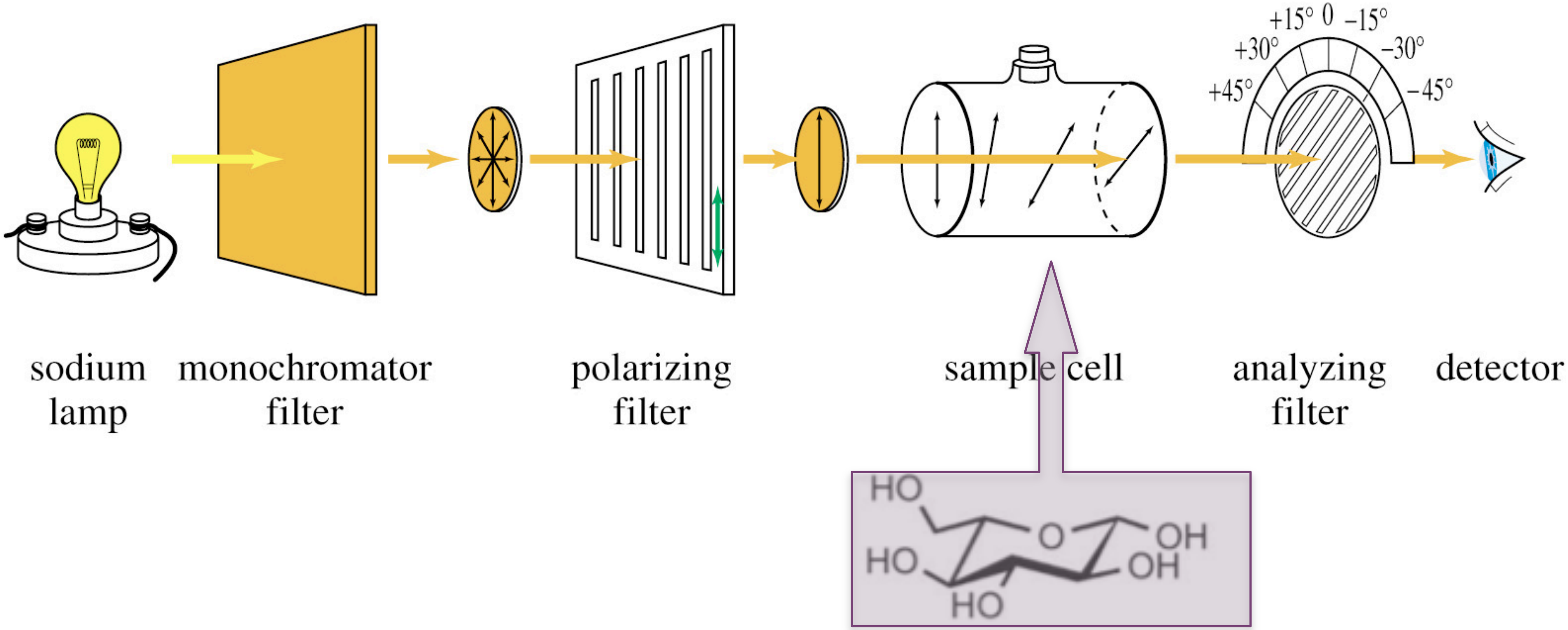


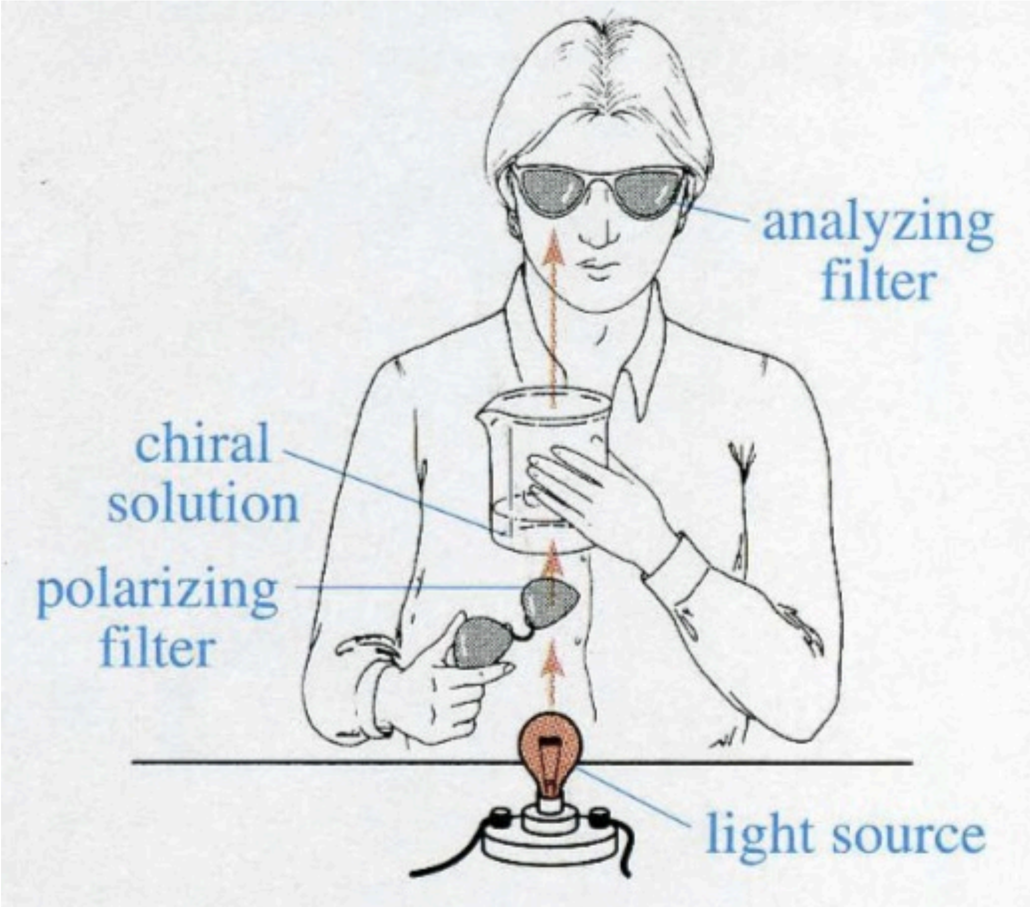
natural alanine



unnatural alanine

Can be metabolized by usual enzyme


+15° 0 −15°
+30°
−30°
+45°
−45°
sodium lamp
monochromator filter
polarizing filter
sample cell
analyzing filter
detector
HO
O
OH
HO
OH
HO



Dextrorotatory (clockwise) rotations are (+). **d**

Levorotatory (counterclockwise) rotations are (−). **l**

+ Characteristic pysical property of one compound, like b.p. and density. Observed α depends on the concentration of the sample solution and the length of the cell and the optical property of the compound

Specific rotation

$$[\alpha] = \frac{\alpha(\text{observed})}{c \cdot l}$$

where

$\alpha(\text{observed})$ = rotation observed in the polarimeter

c = concentration in grams per mL

l = length of sample cell (path length) in decimeters (dm)

Metabolism of tartaric acid

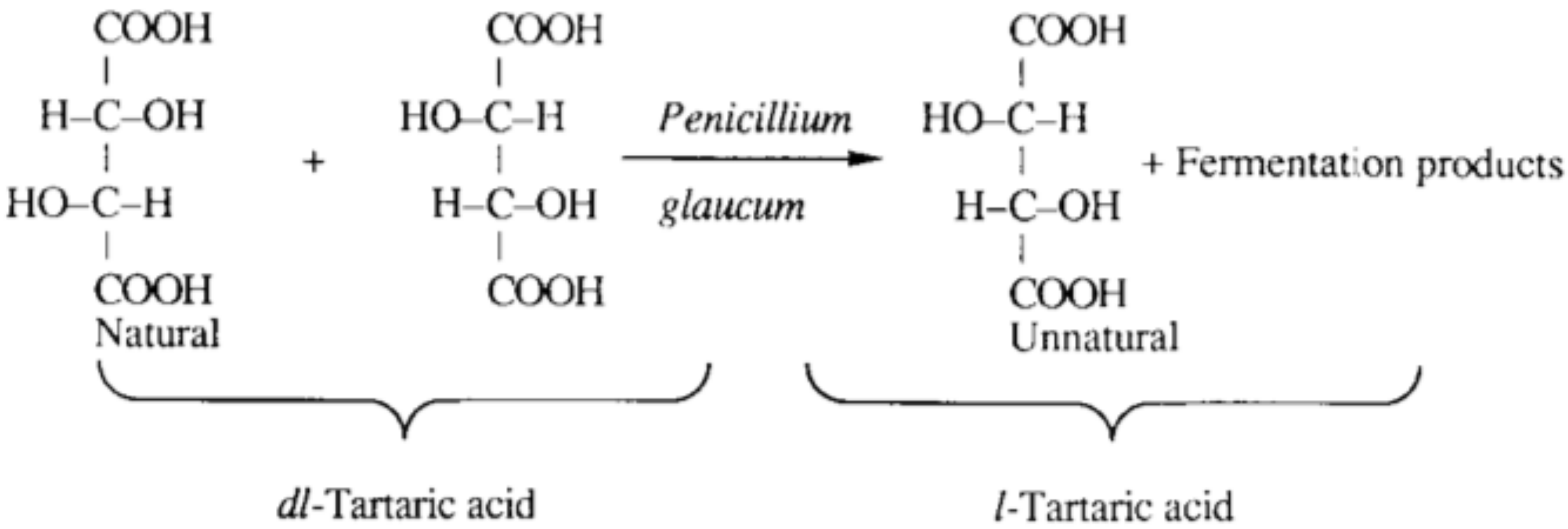


FIG. 2.—Louis Pasteur's preparation of D-(*levo*)-tartaric acid.

"I am convinced that life as we know it has arisen out of asymmetrical processes in the universe. The universe is asymmetric."

van’t Hoff-Le Bel theory of the asymmetric carbon atom

1874

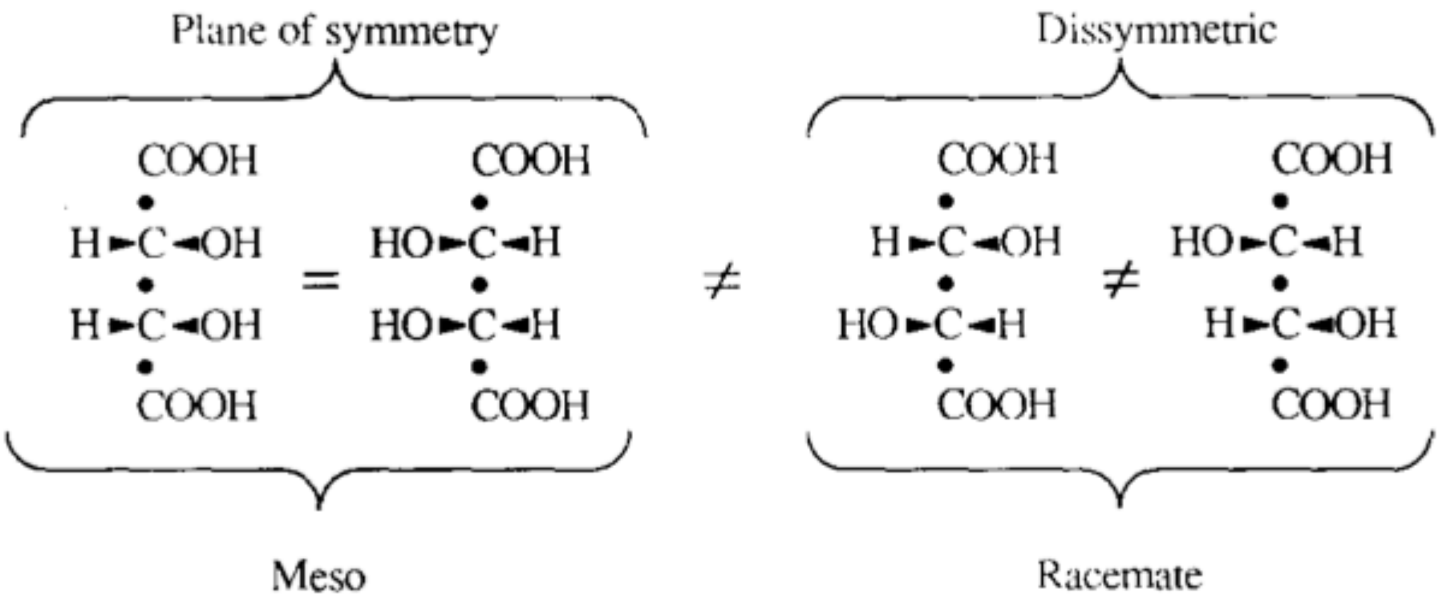
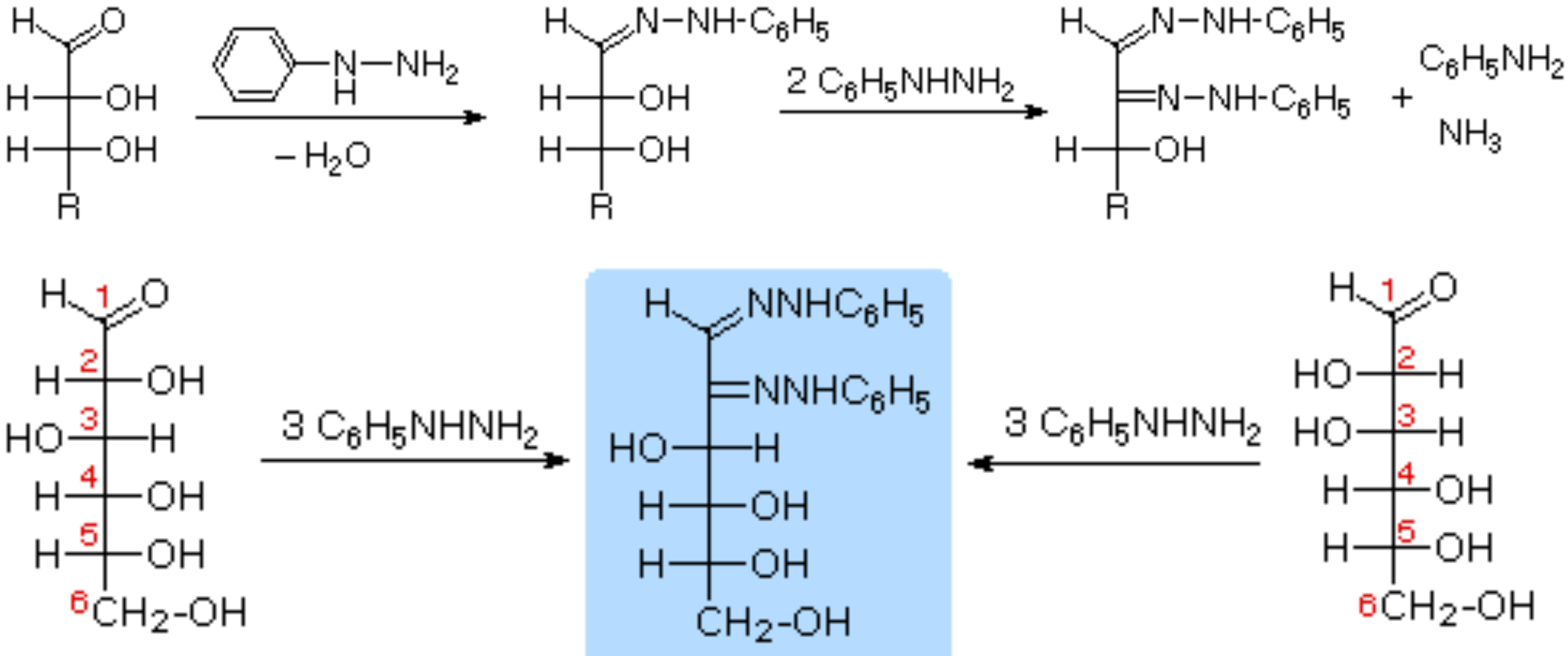


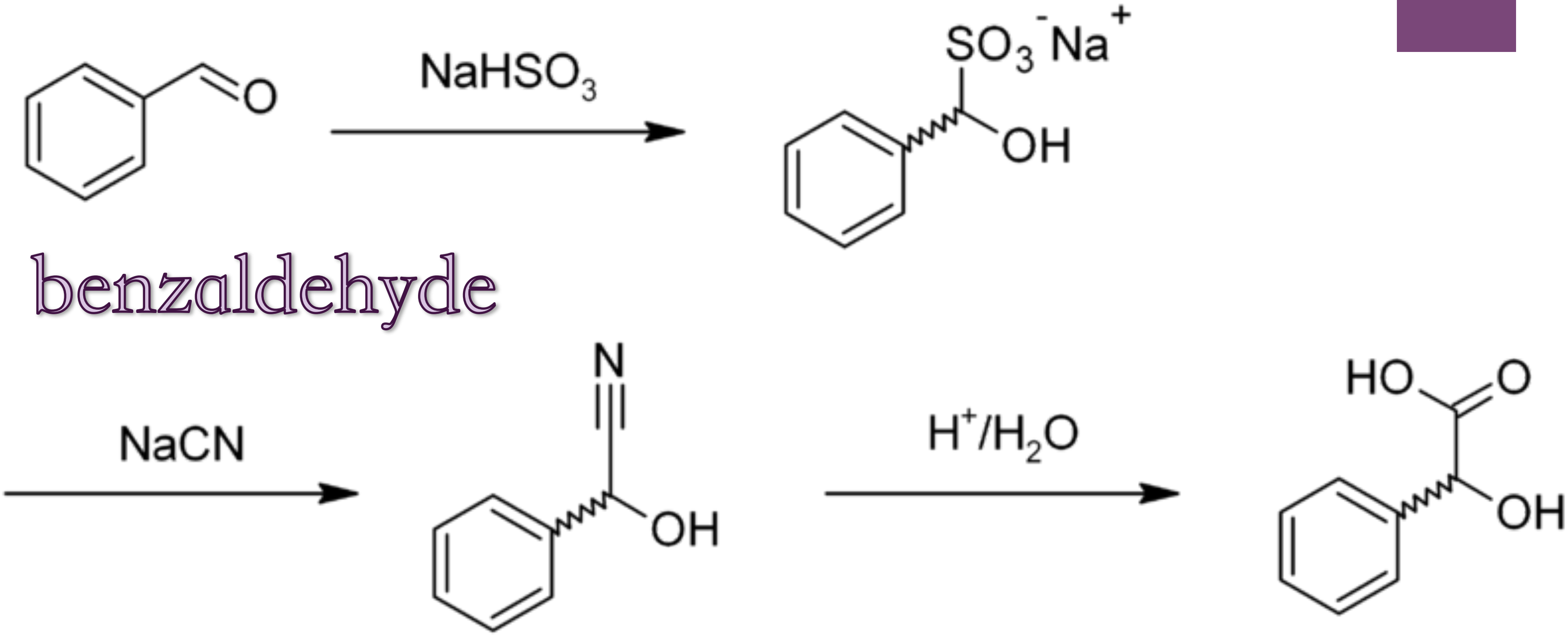
FIG. 3.—The basic assumption for Fischer’s research of the optical isomerism of sugars.

1884， The first publication of sugar by Fischer



Phenylhydrazine

1832 Winckler

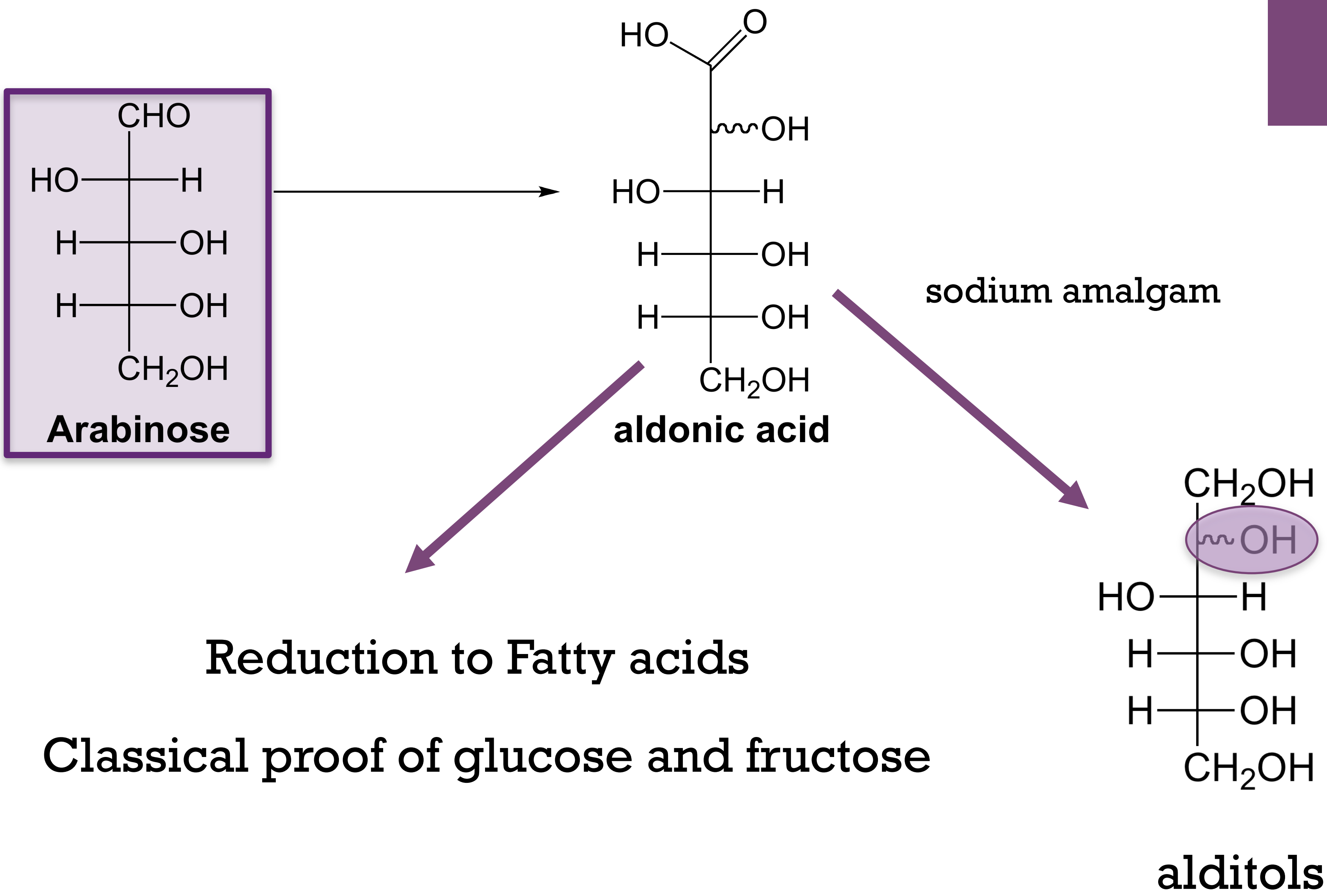


benzaldehyde

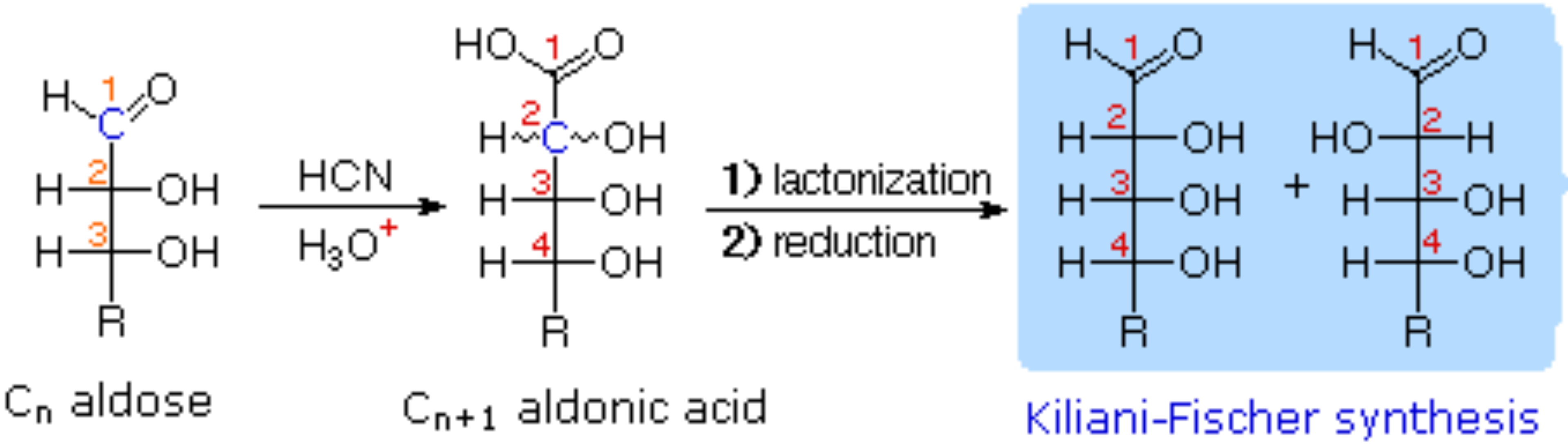
cyanohydrin

Mandelic acid

+ Contribution of Kiliani

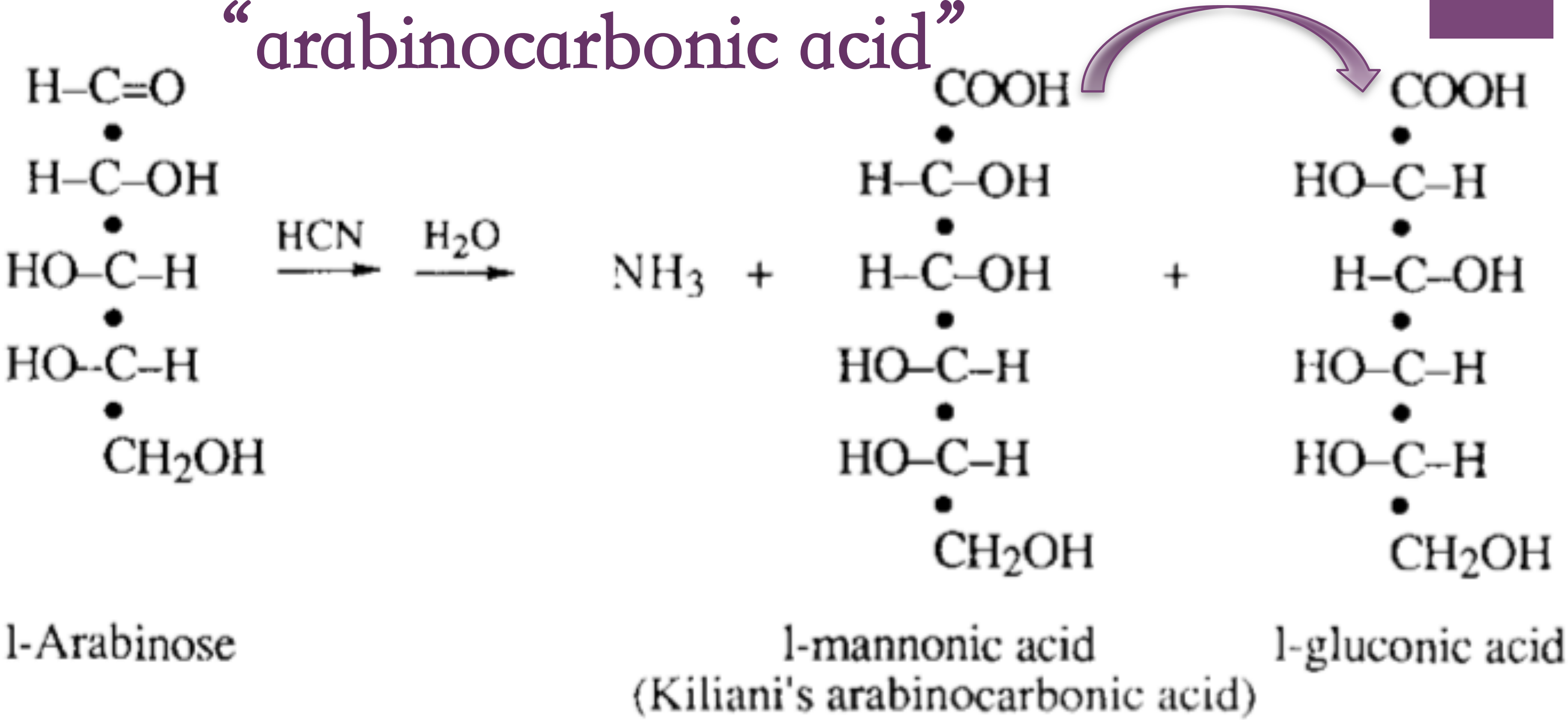


Kiliani-Fischer reaction



Mixture of C-2 epimers

Fischer characterized "arabinocarbonic acid"



quinoline

+

He managed to synthesize sugars from C2 to C9.

Complexity	**Simple Carbohydrates** monosaccharides		**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides		
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.				
Reactivity	**Reducing** sugars oxidized by Tollens' reagent (or Benedict's or Fehling's reagents). **Non-reducing** sugars not oxidized by Tollens' or other reagents.				

Let's look at the logic of Fischer

COH

|

CH·OH

|

CH.OH

CH·OH

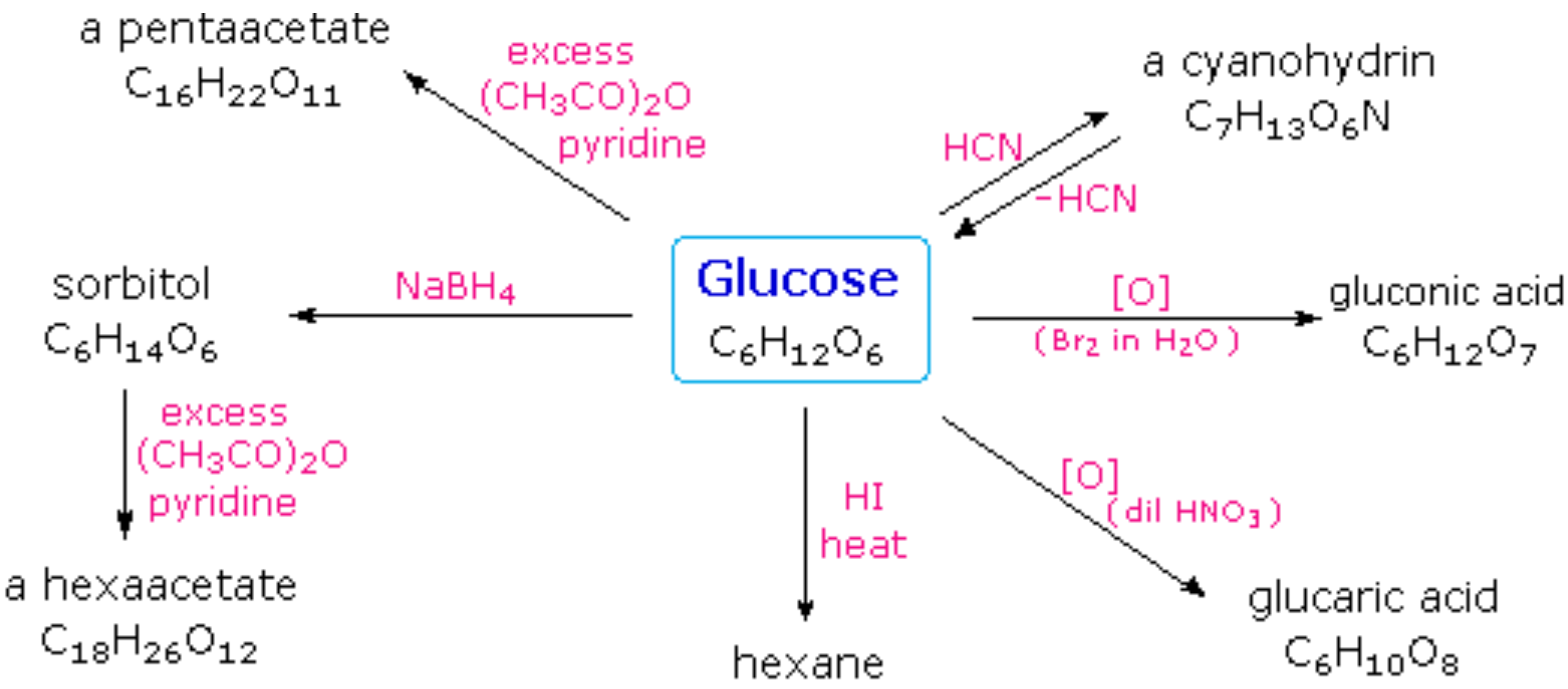
|

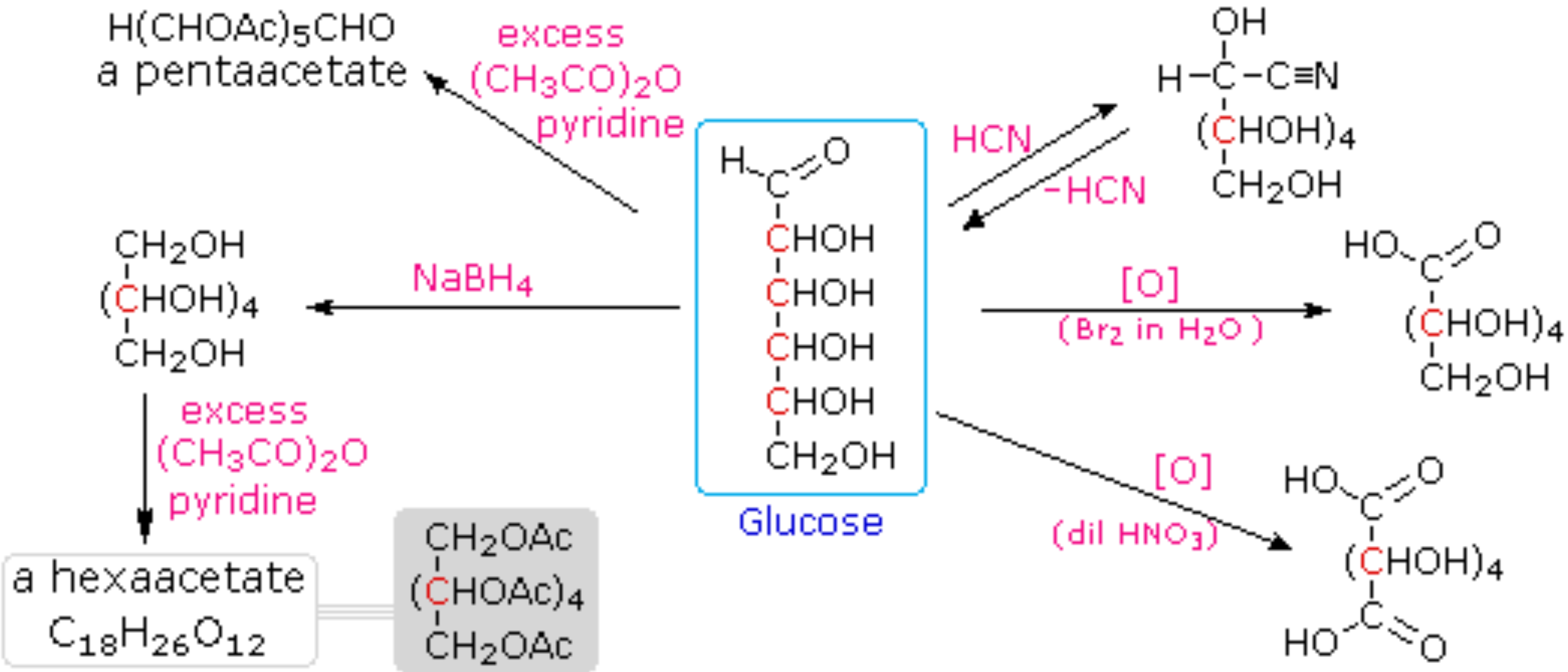
CO·OH

CH_2·OH

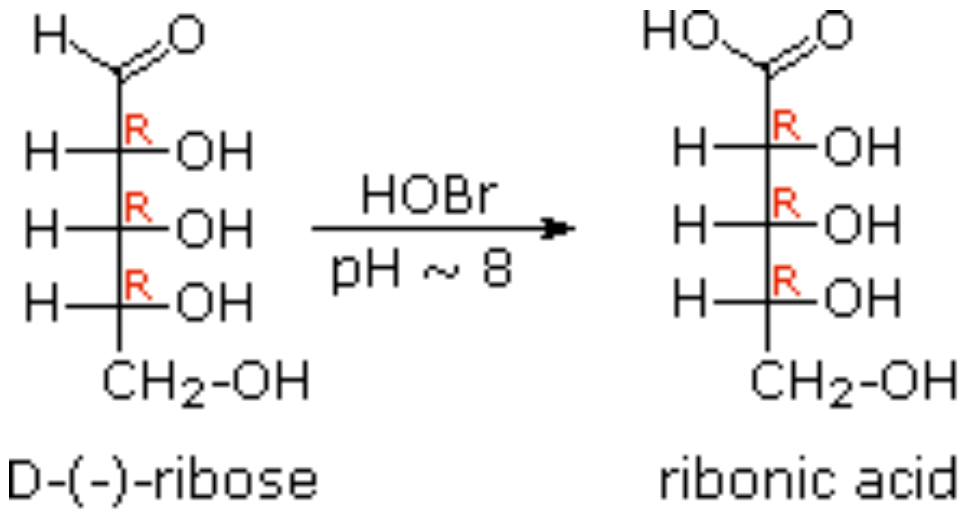
Glucose or galactose

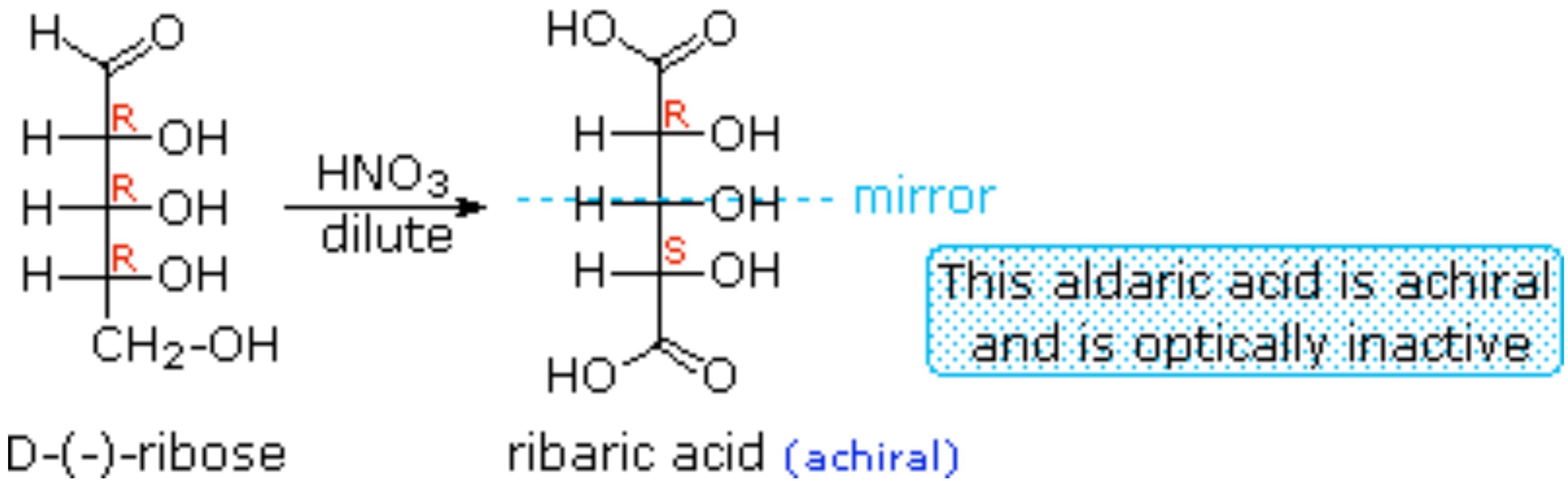
Known chemistry



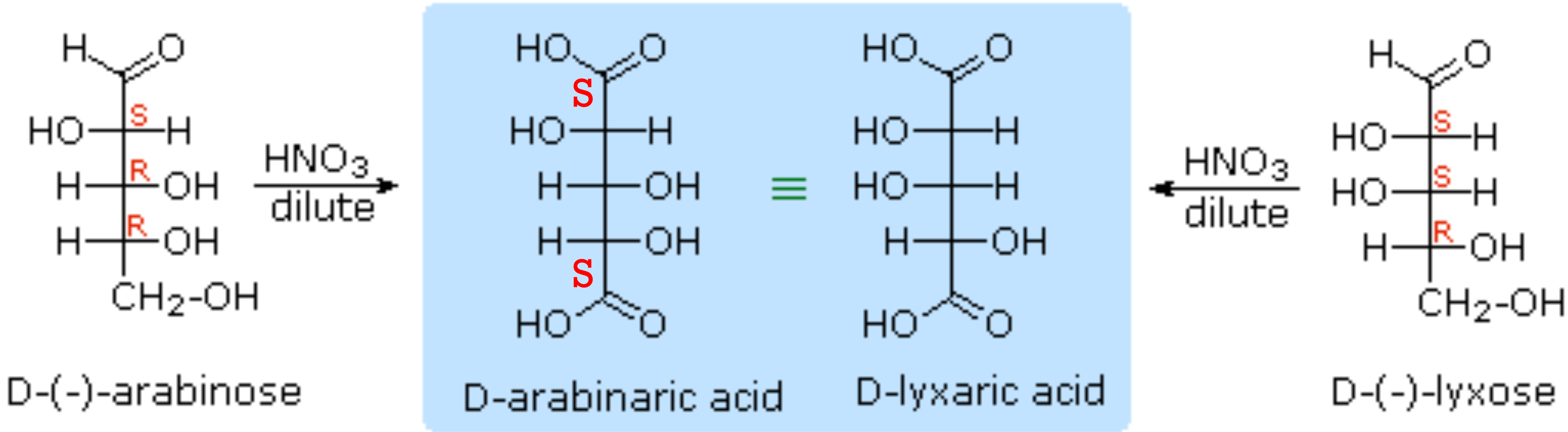

H(CHOAc)5CHO
a pentaacetate
excess
(CH3CO)2O
pyridine
HCN
-HCN
OH
H-C-C≡N
(CHOH)4
CH2OH
CH2OH
(CHOH)4
CH2OH
NaBH4
H
C
O
CHOH
CHOH
CHOH
CHOH
CH2OH
Glucose
[O]
(Br2 in H2O)
HO
C
O
(CHOH)4
CH2OH
excess
(CH3CO)2O
pyridine
[O]
(dil HNO3)
HO
C
O
(CHOH)4
C
HO
O
a hexaacetate
C18H26O12
CH2OAc
(CHOAc)4
CH2OAc

Known chemistry





Known chemistry



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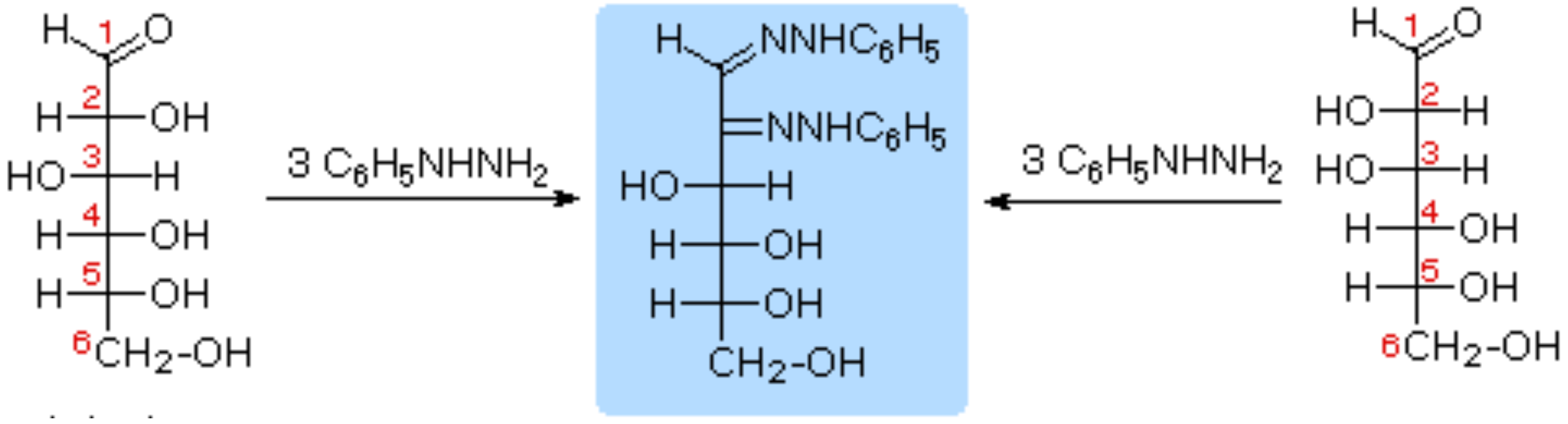
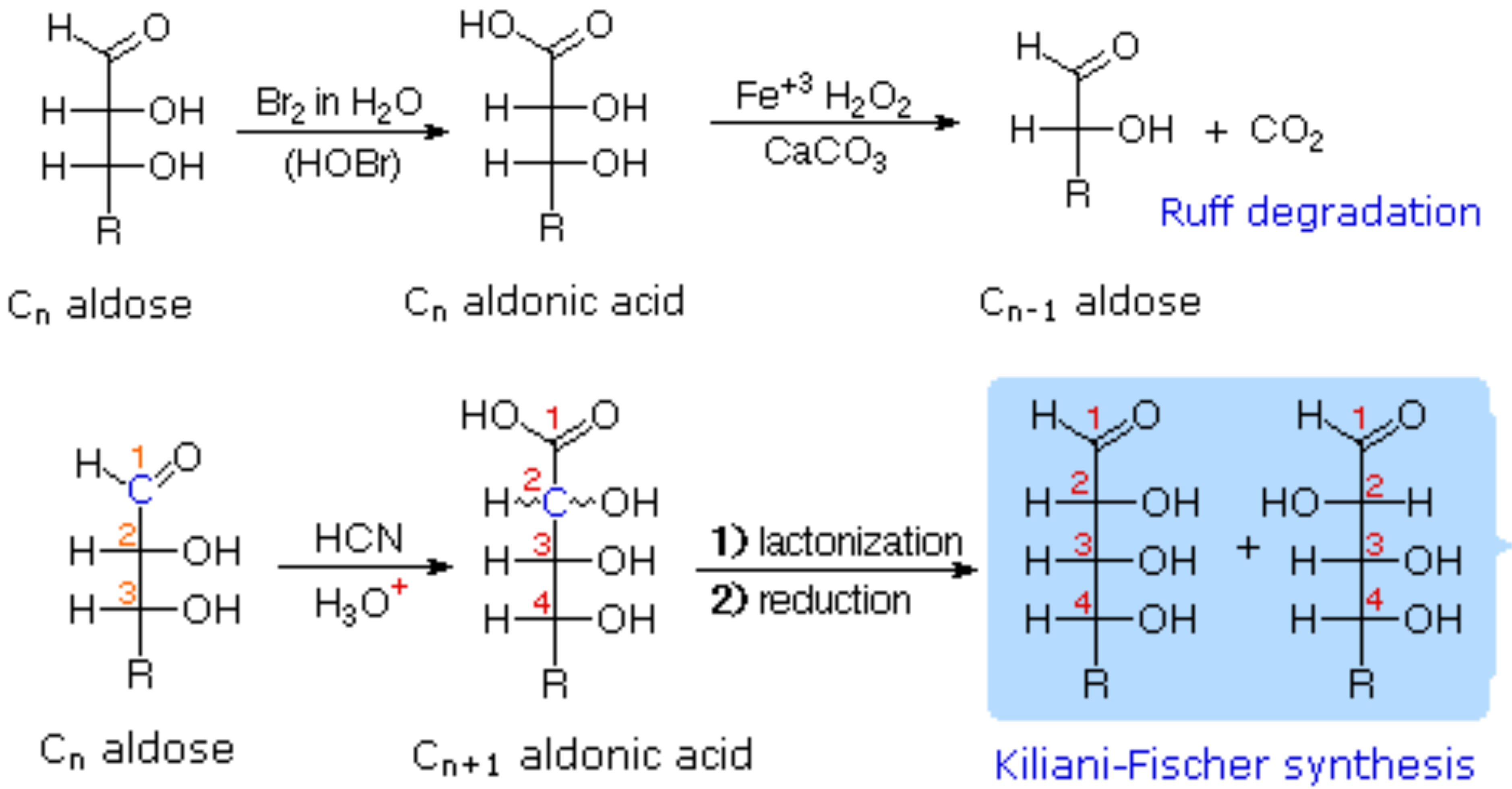
Derivatives of $HOCH_2(CHOH)_nCHO$

HOBr Oxidation	⟶	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	⟶	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	⟶	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Osazone reaction
Same pdt from Glucose & Mannose

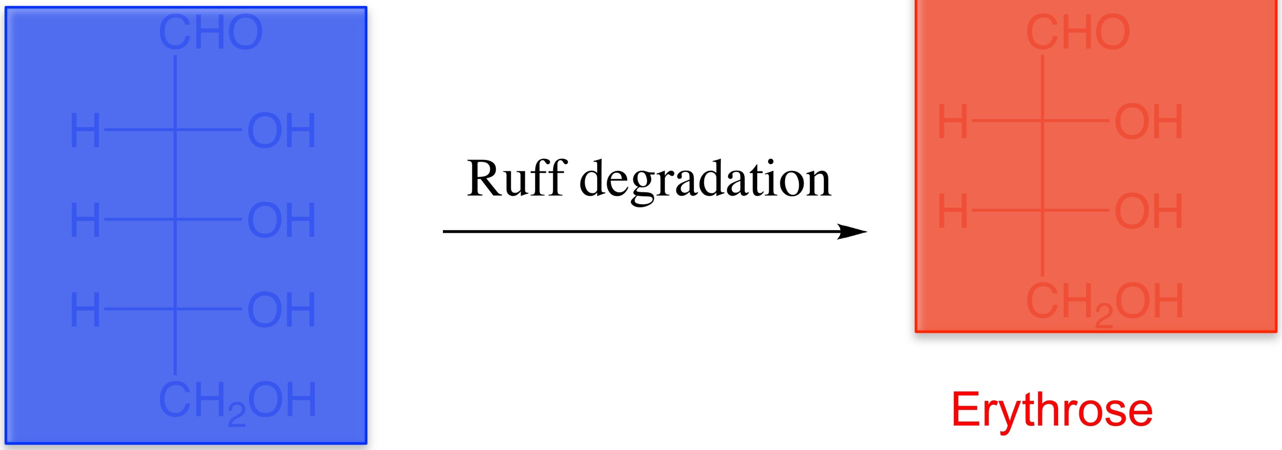


Chain Shortening and Lengthening

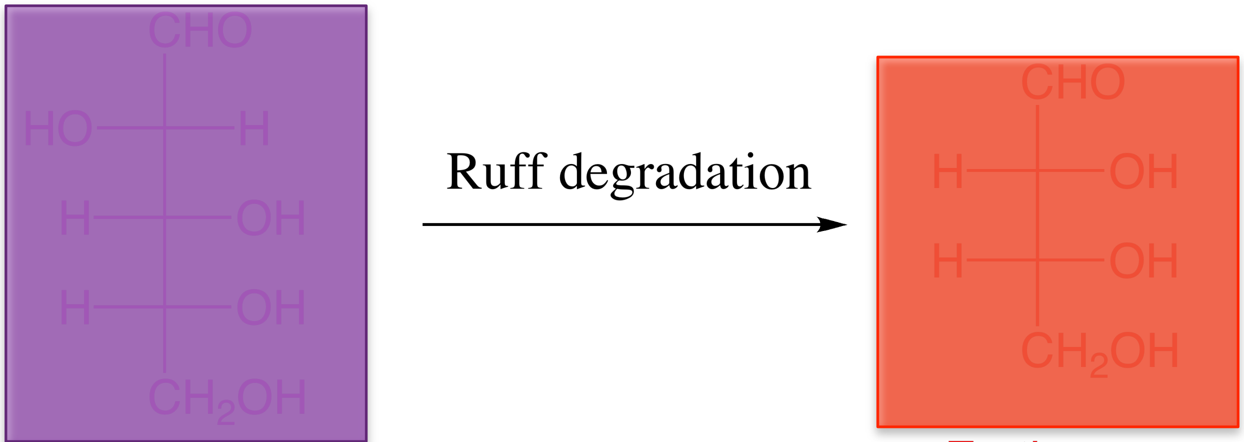


+ Train of logic-1

Ribose and arabinose (pentoses) both gave erythrose on Ruff degradation.



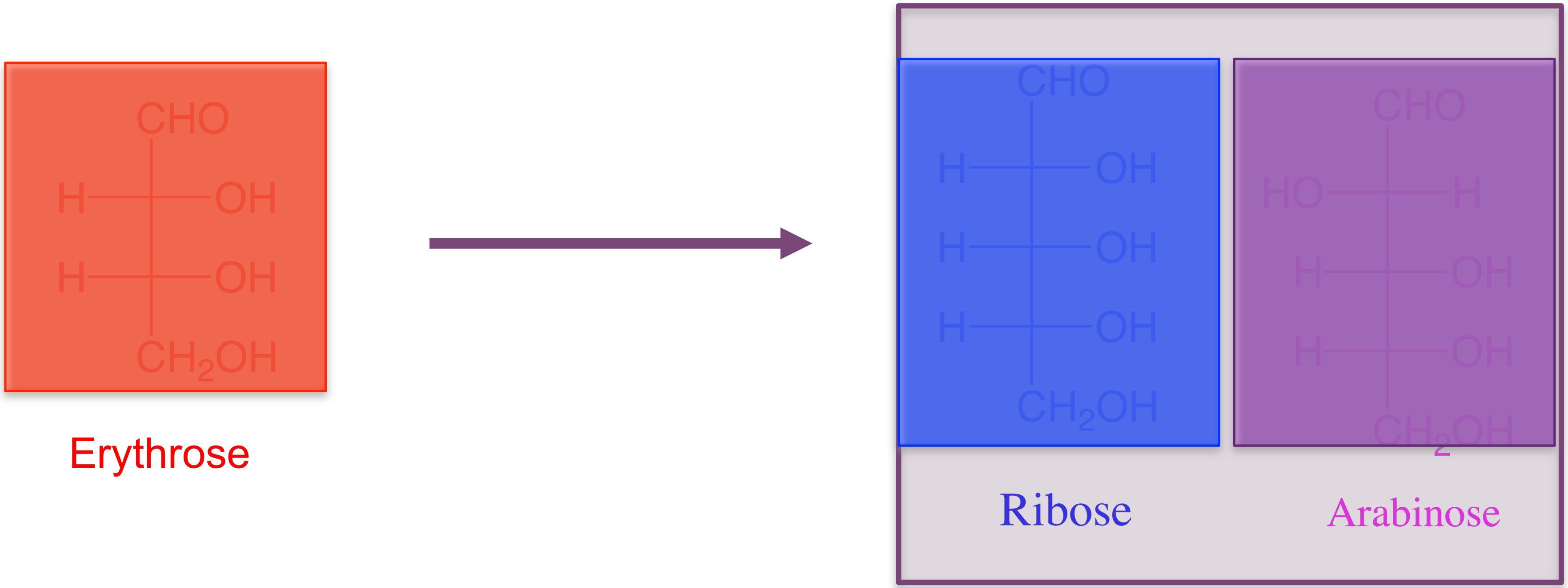
Ribose



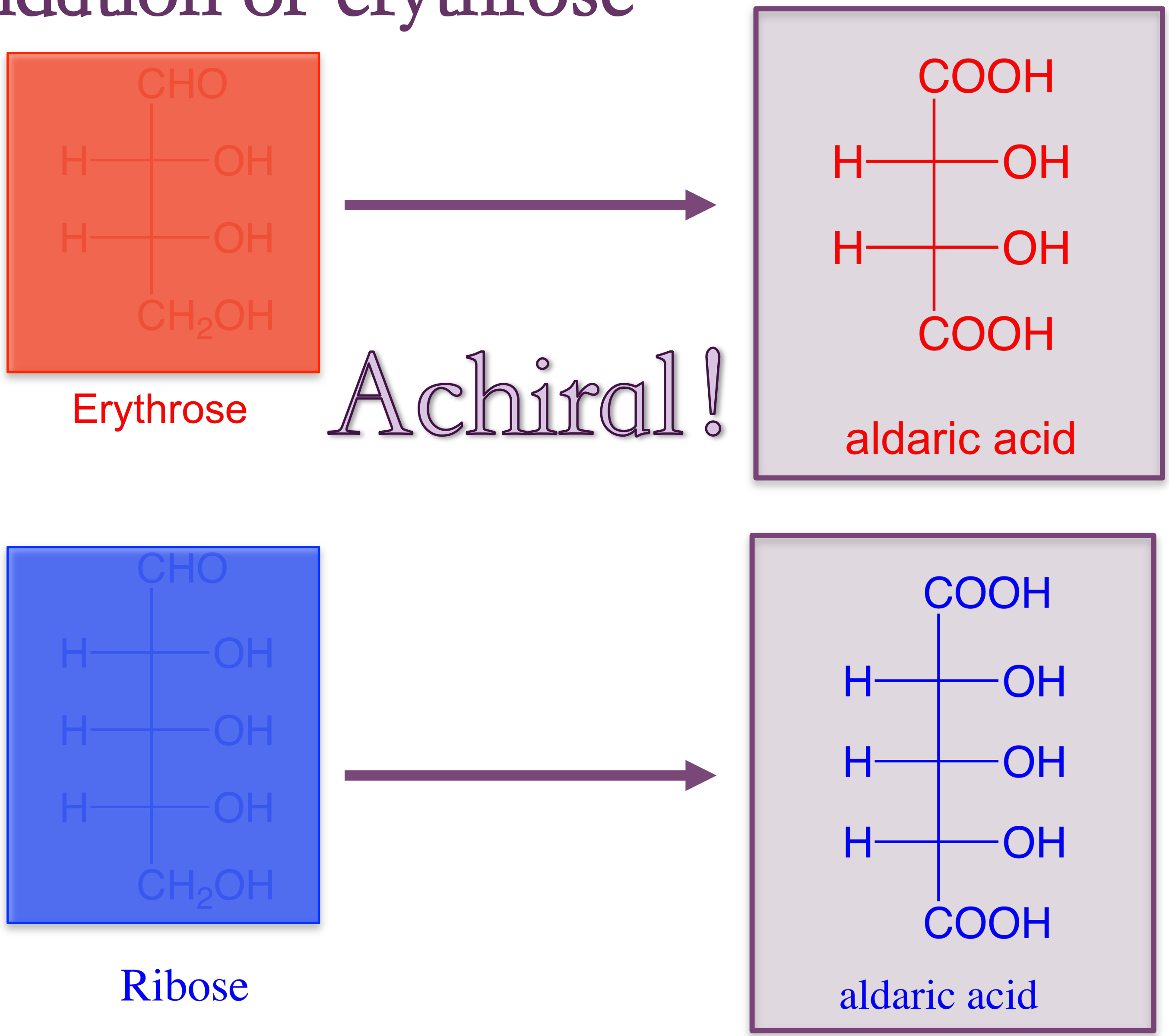
Arabinose

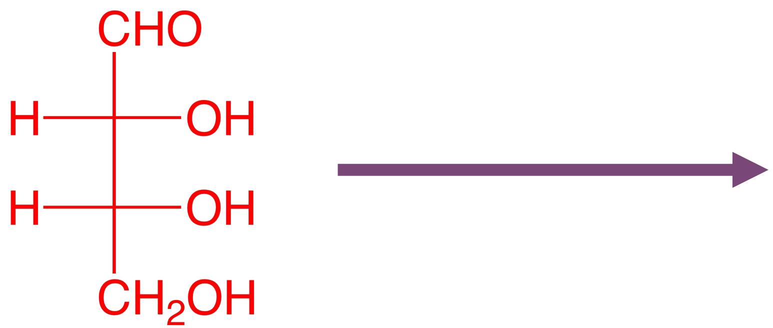
Erythrose

Kiliani-Fischer synthesis applied to erythrose gave a mixture of ribose and arabinose

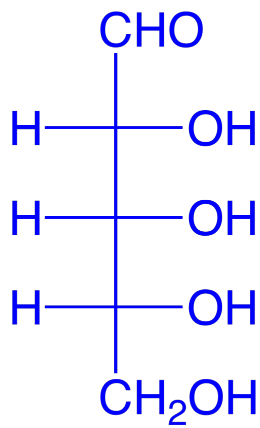


+ Train of logic-2
Oxidation of erythrose

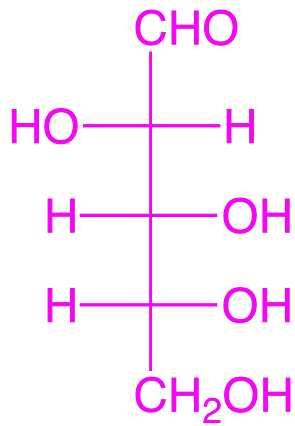




Erythrose

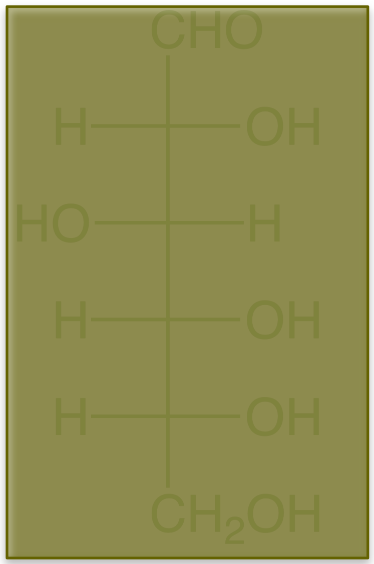


Ribose

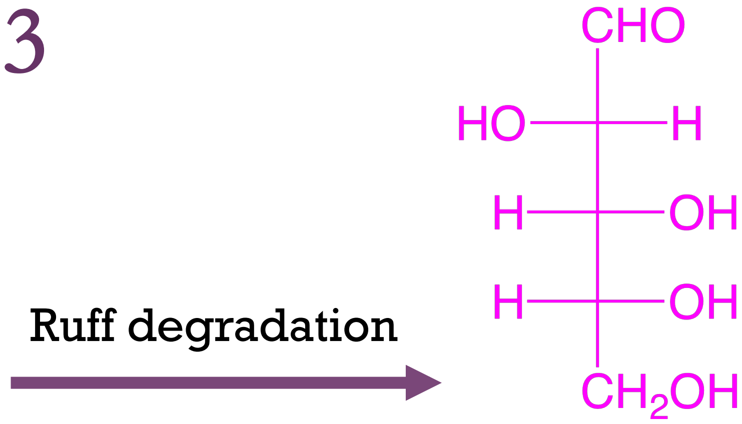


Arabinose

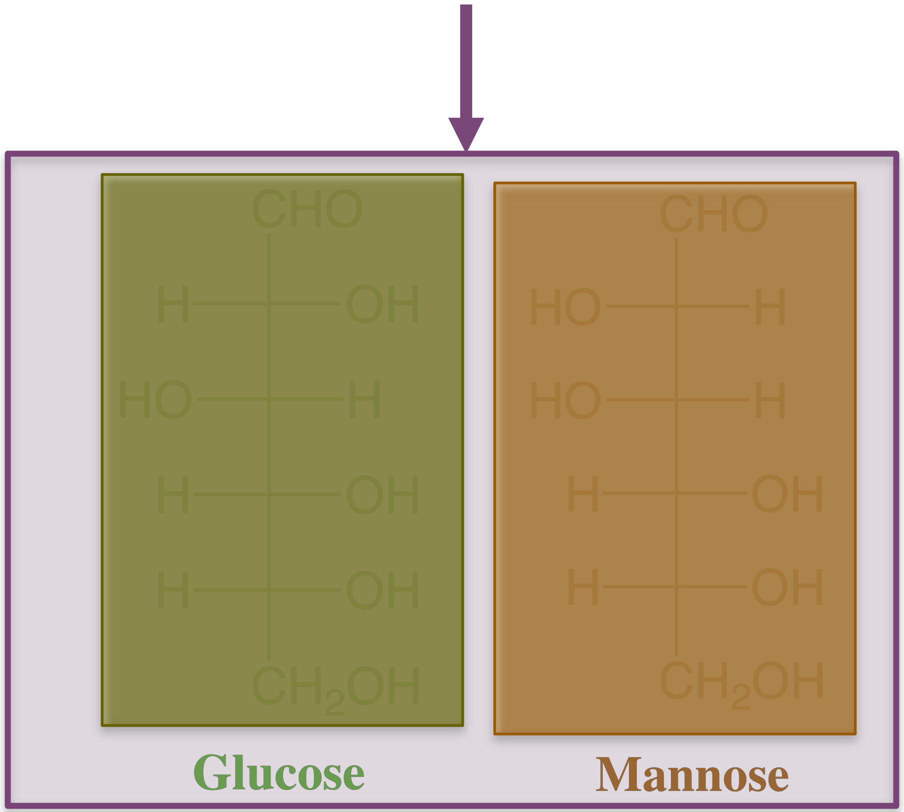
+ Train of logic-3



Glucose

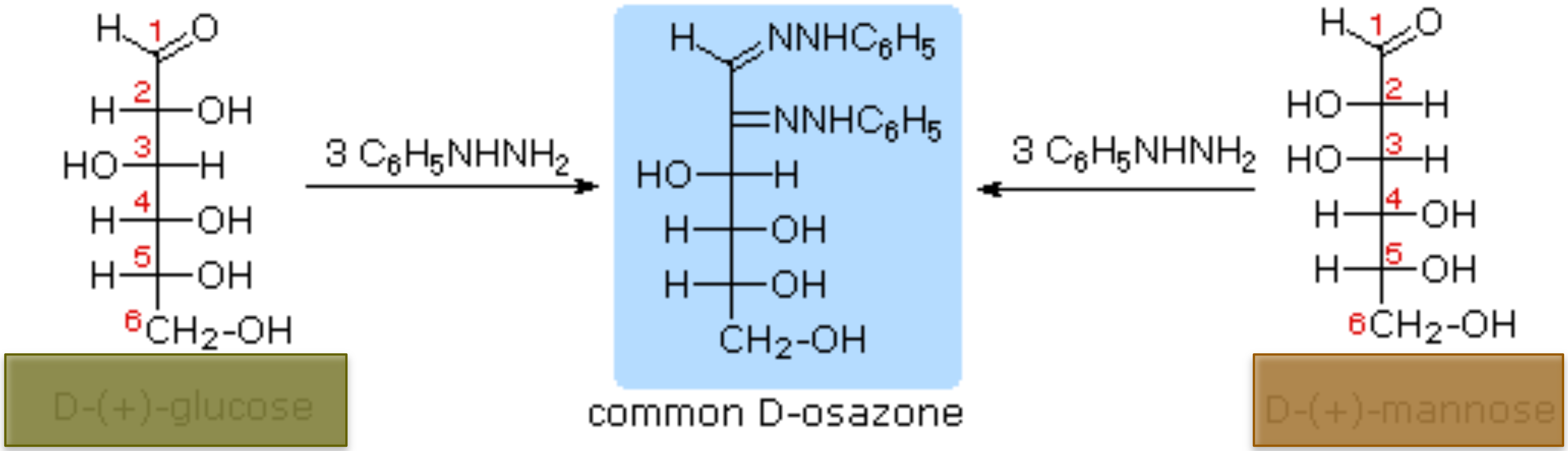


Arabinose



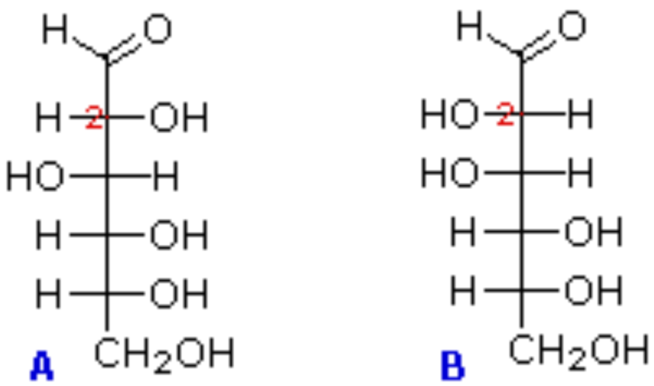
epimers at C-2

Also confirmed by

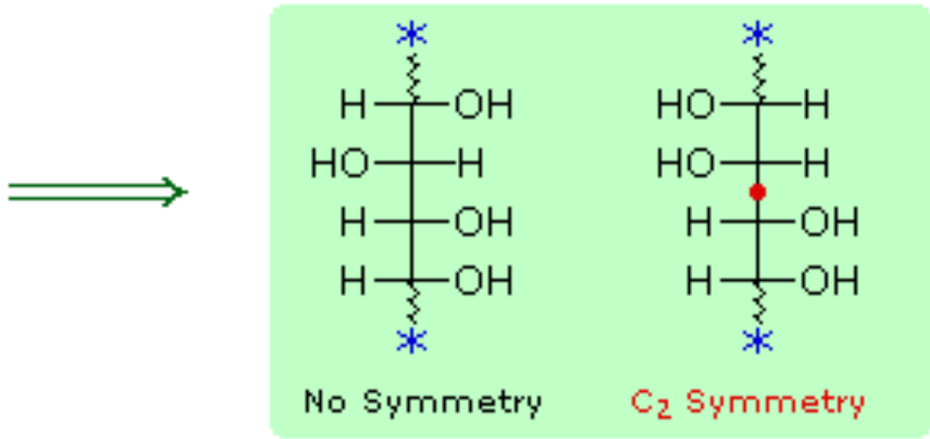


But which is mannose and which is glucose?

Fischer made use of the inherent C_2 symmetry in the four-carbon dissymmetric core of one epimer (B)

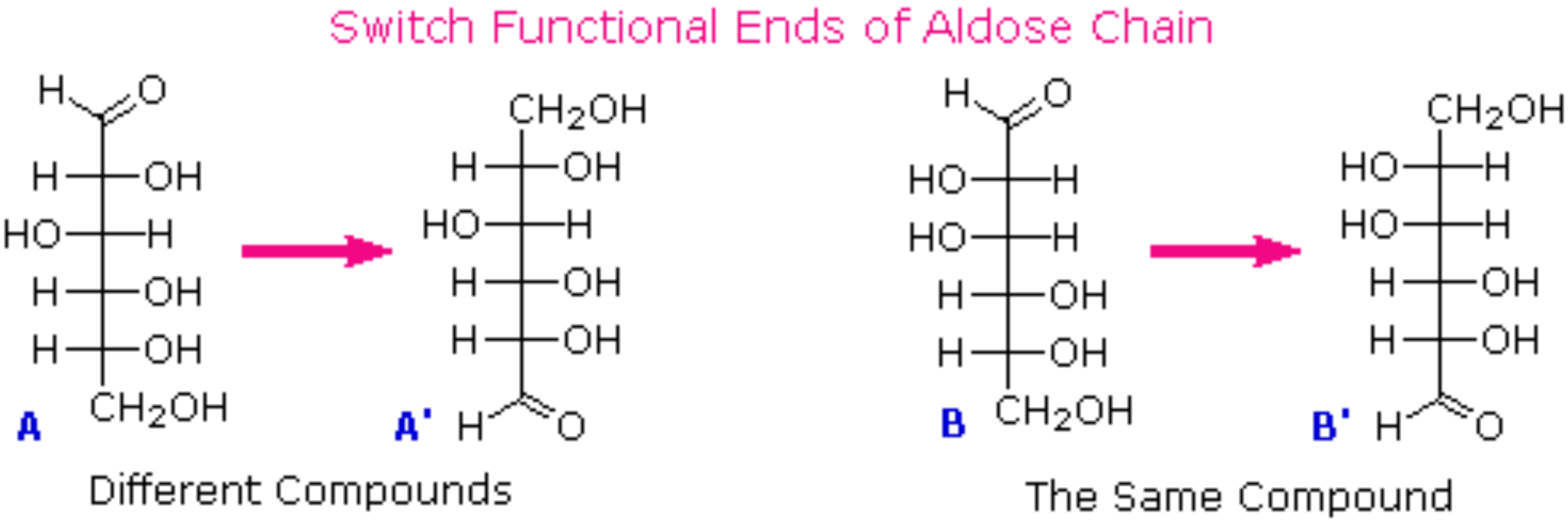


A pair of C-2 epimers.
One is glucose, the other is mannose.



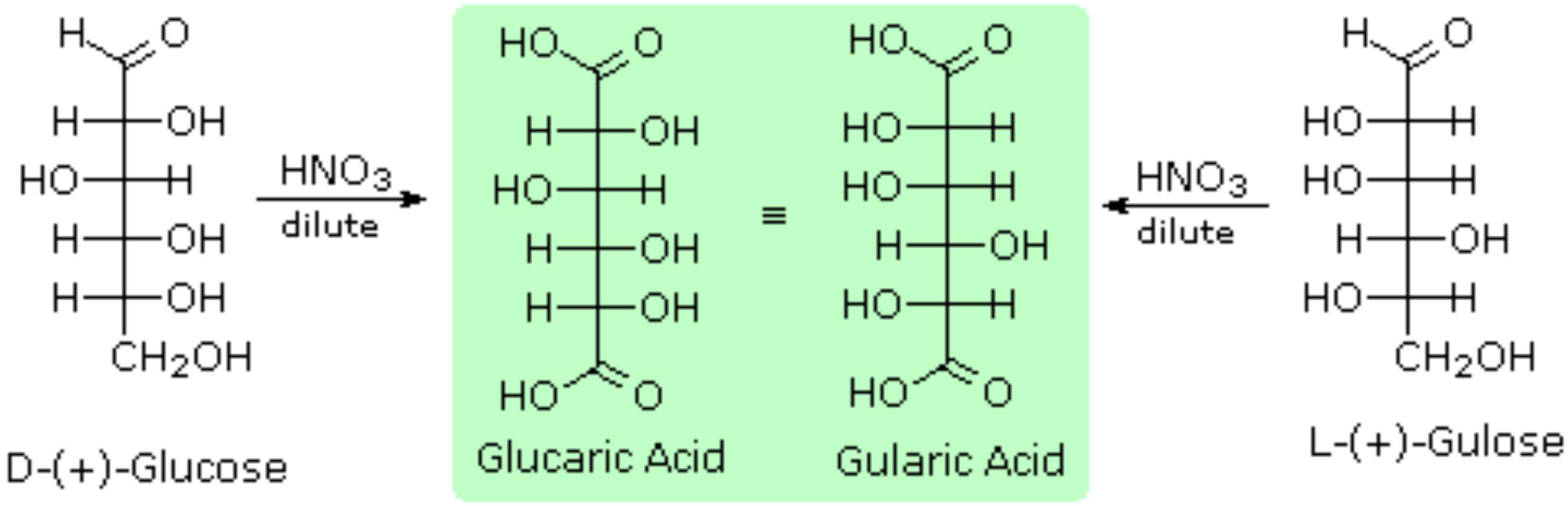
Four-Carbon Dissymmetric Core

+



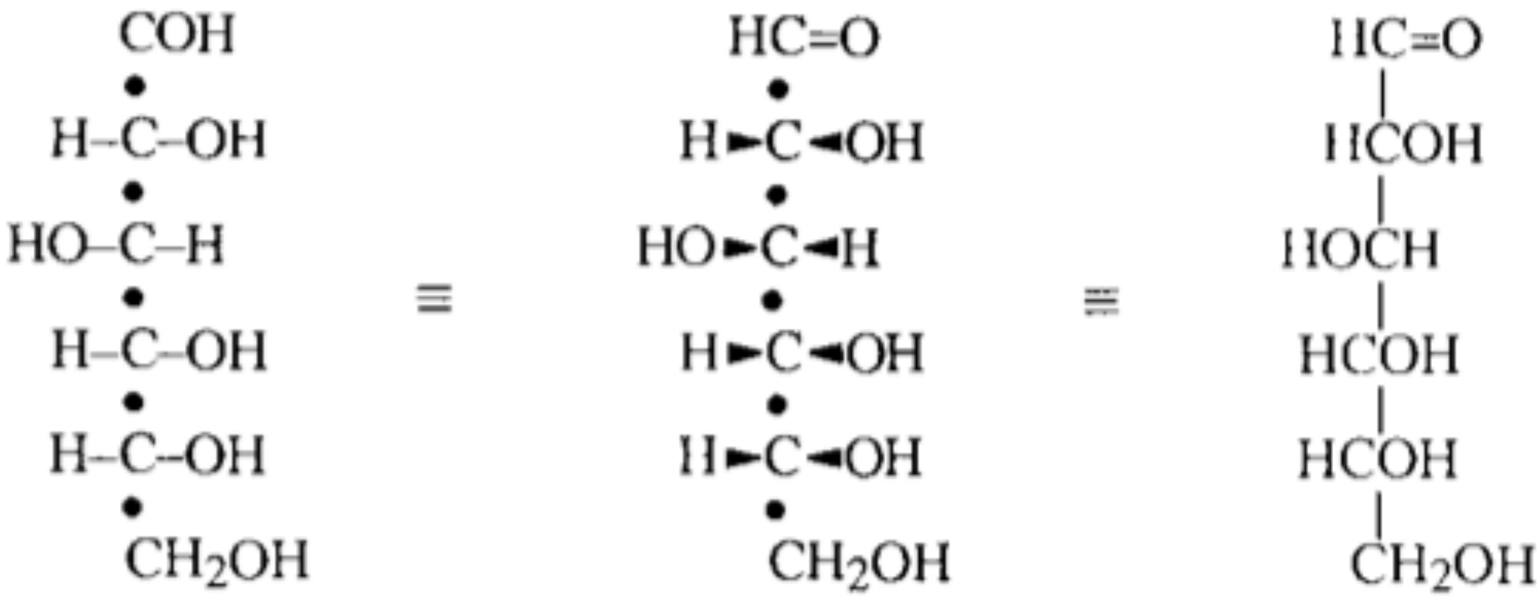
Switch Functional Ends of Aldose Chain
A
A'
Different Compounds
B
B'
The Same Compound

Fischer found L-(+)-Gulose



1891"On the Configuration of Glucose and Related Compounds"

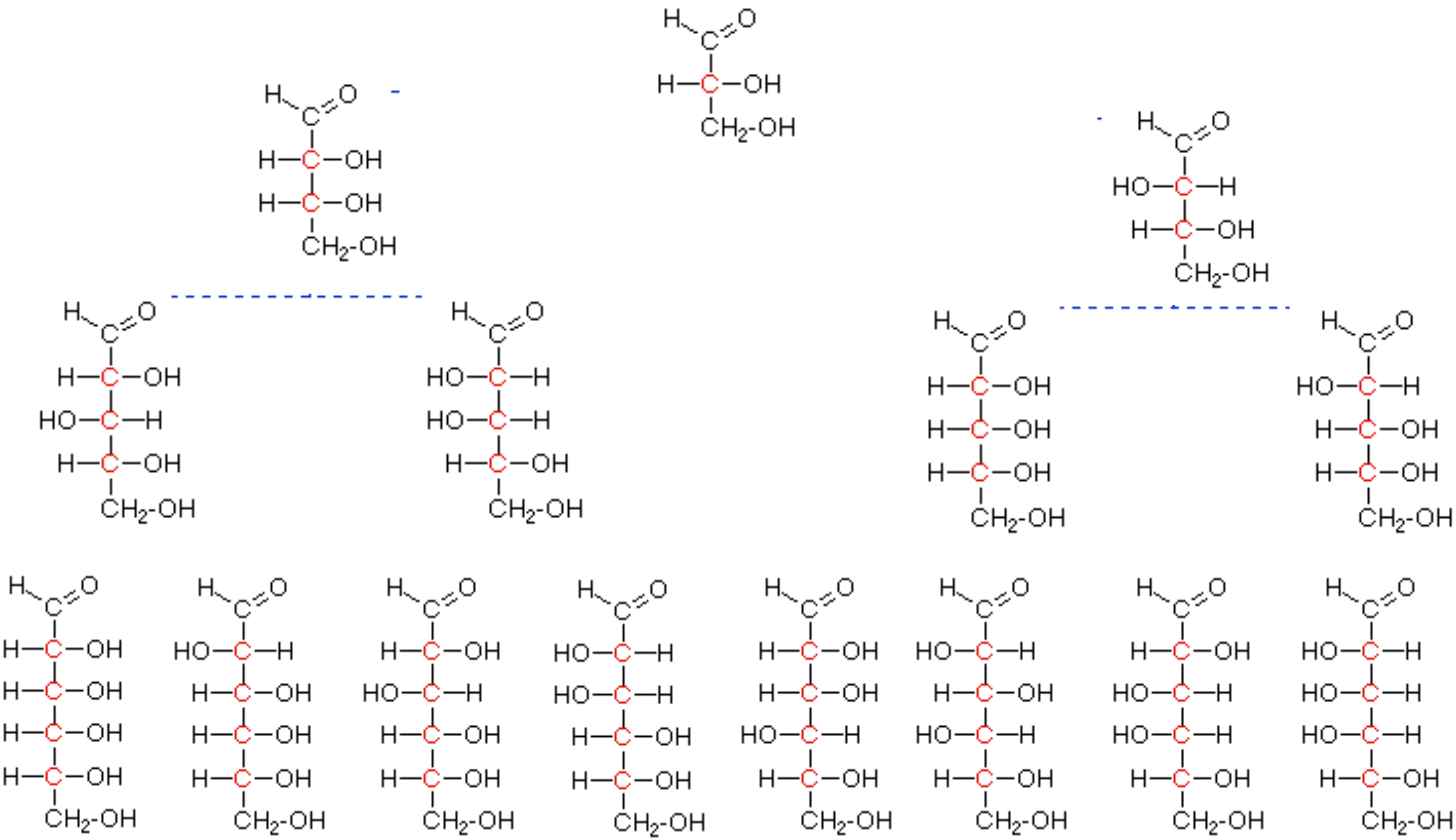
Fischer Projection

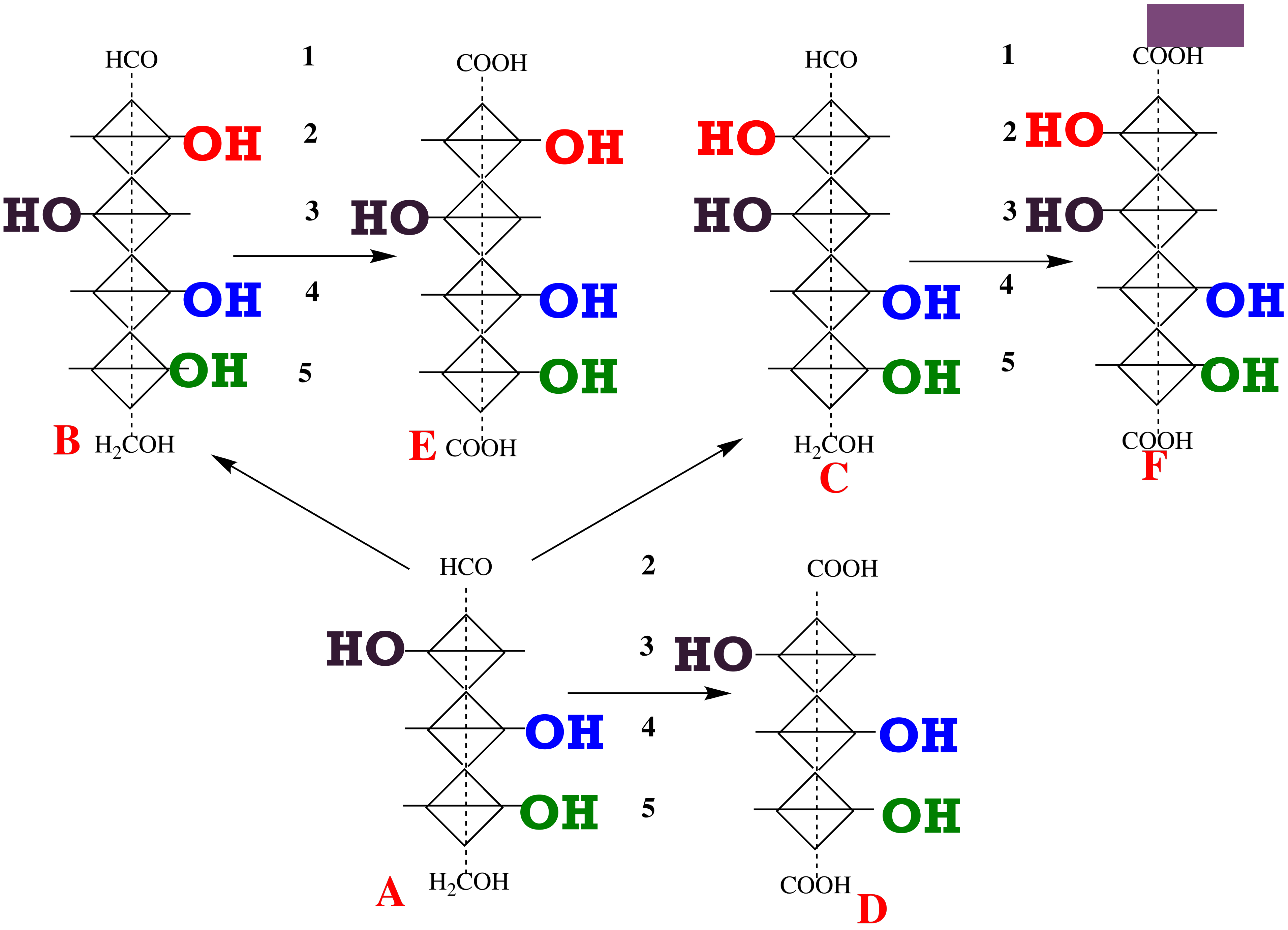


3 4 5

dextro-Glucose

Identified 4 chiral carbons， 2^4 isomer arbitrarily assigned D-sugar





HCO
OH
HO
OH
OH
B
H2COH
1
2
3
4
5
COOH
OH
HO
OH
OH
E
COOH
HCO
HO
HO
OH
OH
H2COH
C
1
2
3
4
5
COOH
HO
HO
OH
OH
COOH
F
HCO
HO
OH
OH
A
H2COH
2
3
4
5
COOH
HO
OH
OH
COOH
D