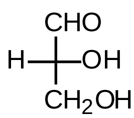
The Fischer proof of the structure of (+)-glucose

Started in 1888, 12 years after the proposal that carbon was tetrahedral, and thus had stereoisomers.
Tools:

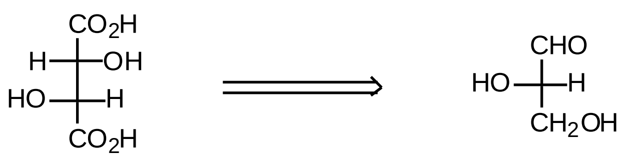
- melting points
- optical rotation (determine whether a molecule is optically active)
- chemical reactions

Fischer knew:

- (+)-glucose is an aldohexose.
- Therefore, there are 4 stereocenters and 2^4 = 16 stereoisomers (8 D-sugars and 8 L-sugars)
- At this time could not determine the actual configuration (D or L) of sugars
- Fischer arbitrarily assigned D-glyceraldehyde the following structure.



- In 1951 Fischer was shown to have guessed correctly.



L-Tartaric acid L-glyceraldehyde

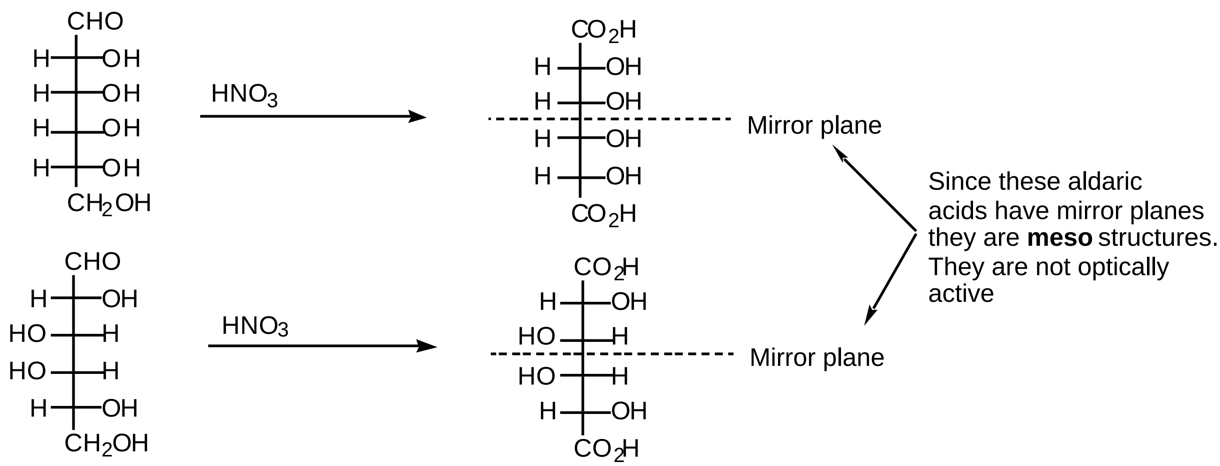
Which of the 8 D-aldohexoses is (+)-glucose???

1) Oxidation of (+)-glucose with nitric acid gives an aldaric acid, glucaric acid, that is optically active. Therefore (+)-glucose cannot have structures **1** or **7**, which would give optically inactive aldaric acids.

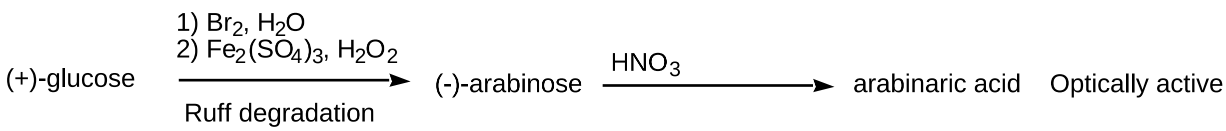
(+)-glucose $\xrightarrow{HNO_3}$ Glucaric acid Optically active

1

7

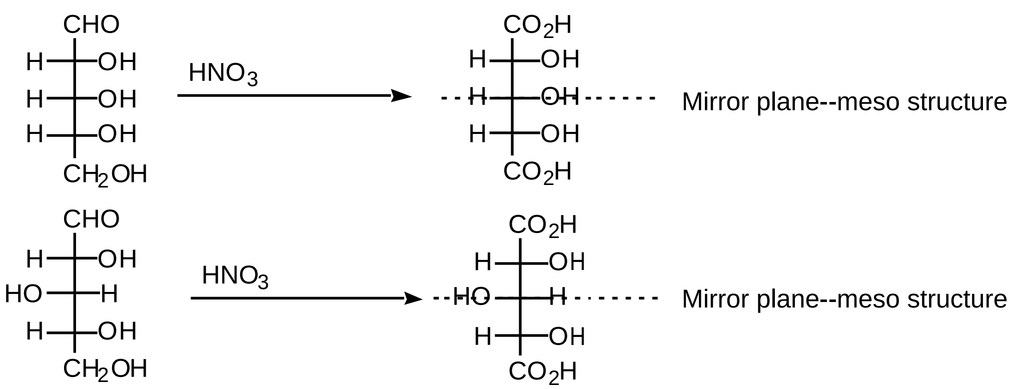


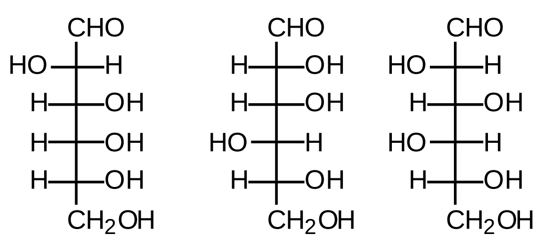
2) Ruff degradation of (+)-glucose gives (-)-arabinose. Oxidation of (-)-arabinose with nitric acid gives arabanaric acid, which is optically active. Therefore, (-)-arabinose cannot have structures **9** or **11**, which would give optically inactive aldaric acids. If arabinose cannot be **9** or **11**, (+)-glucose cannot be **2** (**1** was already eliminated), **5** or **6**, which would give **9** or **11** in a Ruff degradation.



9

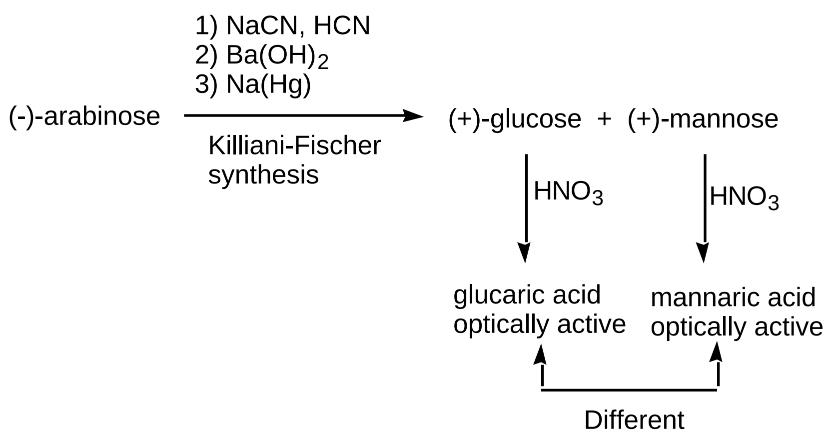
11

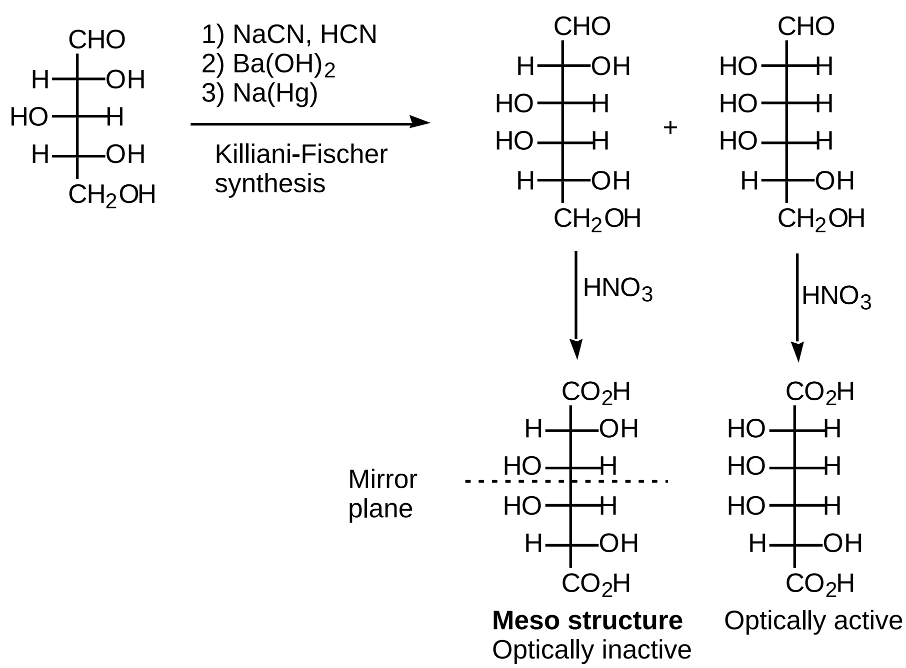




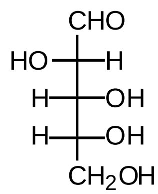
2 **5** **6**

3) Killiani-Fischer chain extension of (-)-arabinose gives (+)-glucose and (+)-mannose. Both of which give optically active aldaric acids when oxidized with nitric acid. Therefore, (-)-arabinose cannot be structure **12**. **12** would give **7** and **8** in a Killiani-Fischer chain extension. **8** would give an optically active aldaric acid, but **7** would give an optically inactive aldaric acid.

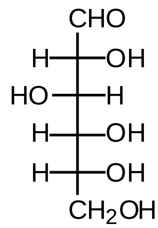




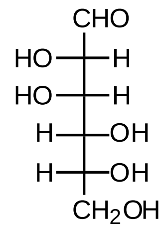
4) The structure of arabinose is **10**. Therefore the structures of (+)-glucose and (+)-mannose are **2** and **3**, but which is which????



10
(-)-aribinose

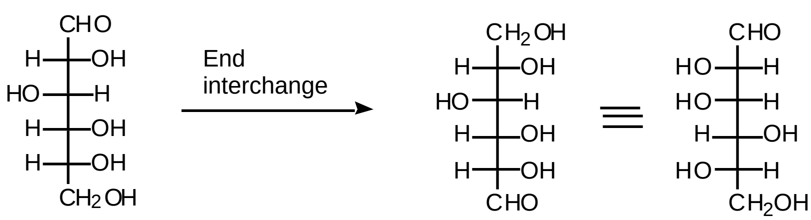


2



3
(+)-glucose and (+)-mannose

5) Fischer had previously developed a method to interchange the ends of a sugar (the aldehyde is converted to a CH_2OH and the CH_2OH is converted to an aldehyde, but we won't worry about how this is done). Fischer reasoned that if ends of **2** were interchanged, a new L-aldohexose would be obtained. On the other hand, if the ends of **3** were interchanged, the product would be the same (structure **3**). When the ends of (+)-glucose were interchanged a new sugar was obtained, which Fischer named L-gulose. When the ends of (+)-mannose were interchanged, the product was (+)-mannose. **Therefore the structure of (+) glucose is structure 2, and strucutre 3 is (+)-mannose!!!**



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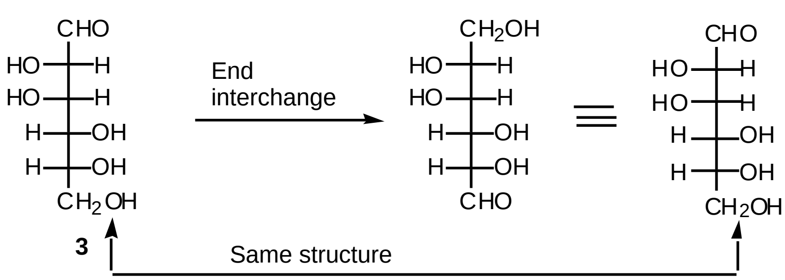

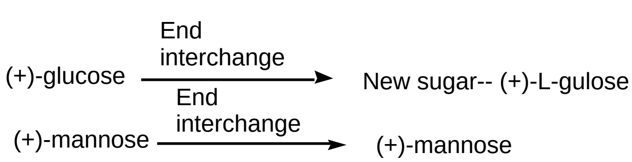

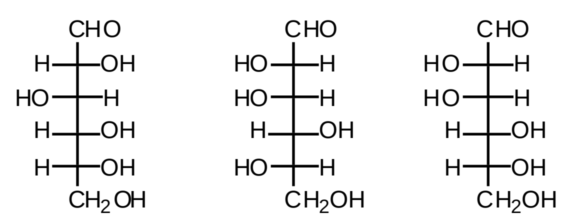

D-(+)-glucose L-(+)-gulose D-(+)-mannose