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.

\[
\begin{align*}
\text{CHO} & \\
\text{H} & \text{OH} \\
\text{CH}_2\text{OH} & \\
\end{align*}
\]

- In 1951 Fischer was shown to have guessed correctly.

\[
\begin{align*}
\text{CO}_2\text{H} & \\
\text{HO} & \text{OH} \\
\text{H} & \\
\end{align*} \quad \rightarrow \quad \begin{align*}
\text{CHO} & \\
\text{HO} & \text{H} \\
\text{CH}_2\text{OH} & \\
\end{align*}
\]

L-Tartaric acid \quad \rightarrow \quad 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.

\[
\begin{align*}
\text{(+)-glucose} & \xrightarrow{\text{HNO}_3} \text{Glucaric acid} \\
& \quad \text{Optically active}
\end{align*}
\]
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.
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???

5) Fischer had previously developed a method to interchange the ends of a sugar (the aldehyde is converted to a CH$_2$OH and the CH$_2$OH 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 structure 3 is (+)-mannose!!!**