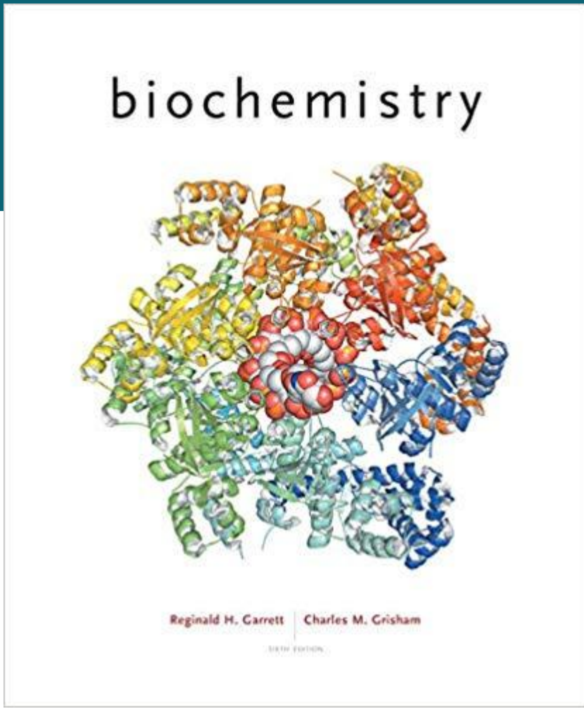

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Chapter 22 – Part 2
Pentose Phosphate Pathway

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The pentose phosphate pathway

Also called the **hexose monophosphate shunt** or the **phosphogluconate pathway**

Cells require NADPH for reductive biosynthetic reactions

The **pentose phosphate pathway** allows glucose to provide reducing power (electrons in the form of NADPH) and carbon compounds for biosynthetic reactions

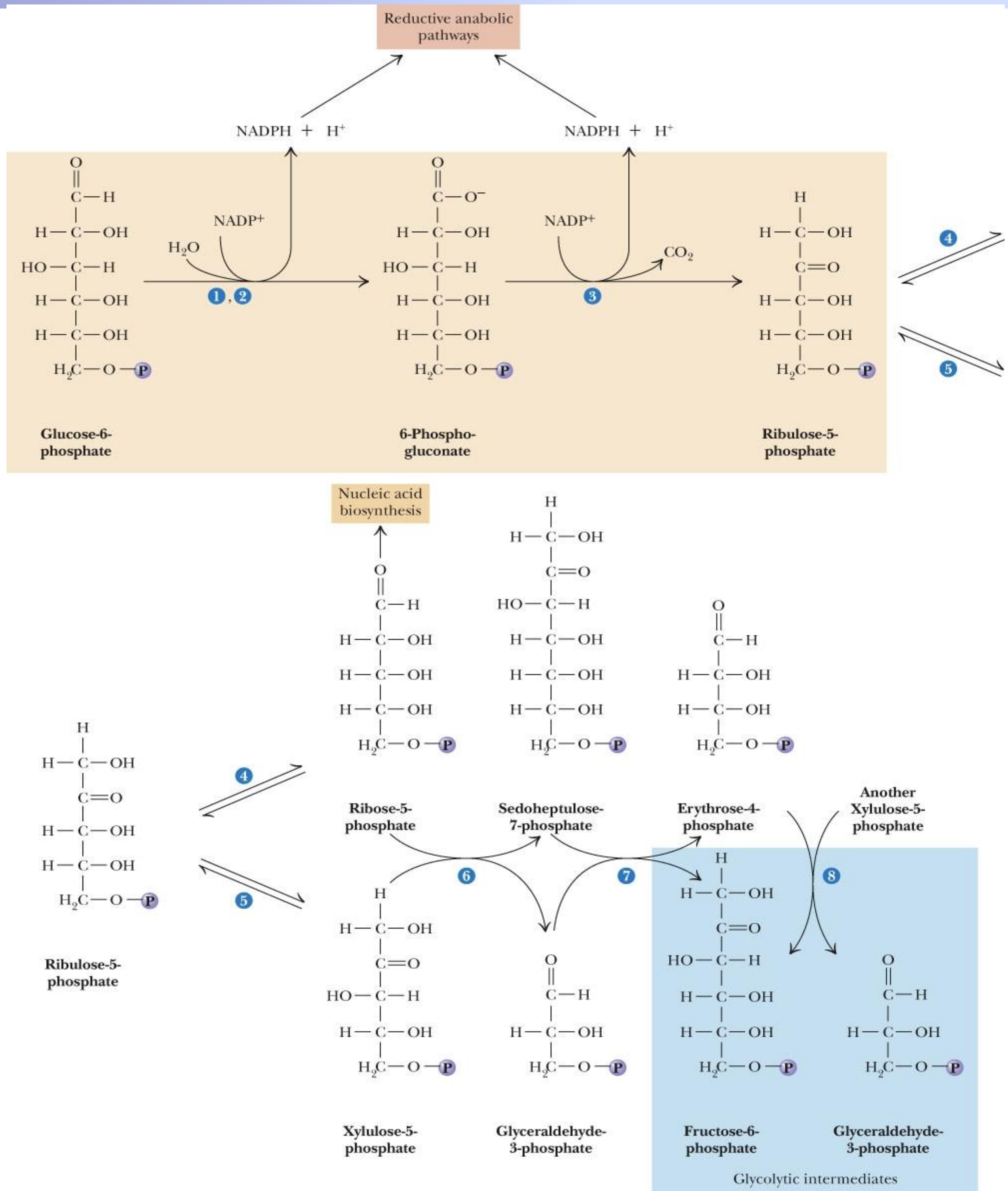
This pathway also produces ribose-5-P

This pathway consists of two oxidative processes (3 steps) followed by five non-oxidative steps

It operates mostly in the cytosol of liver and adipose cells

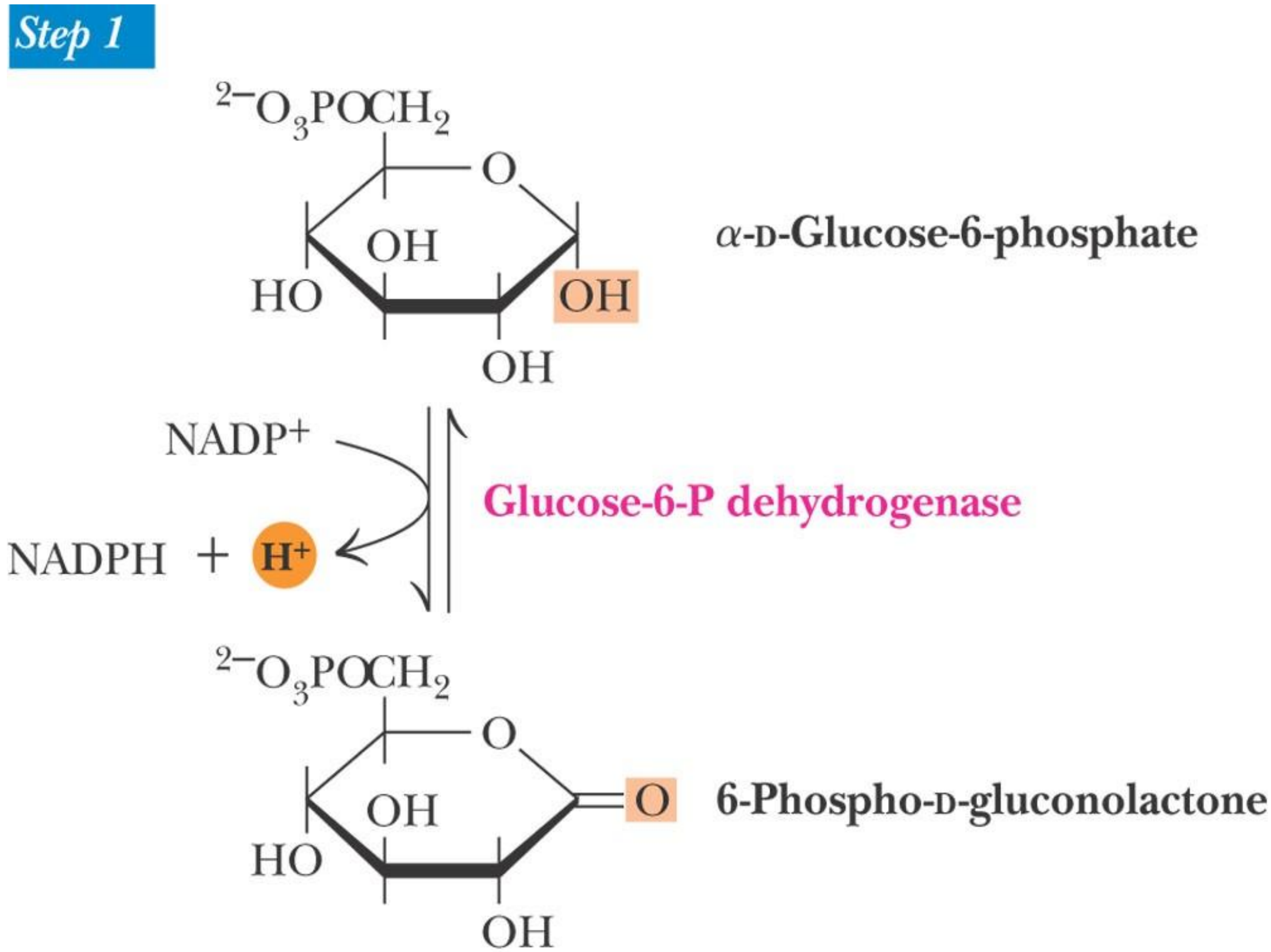
NADPH is used in cytosol for fatty acid synthesis

The pentose phosphate pathway



Step 1 - Glucose-6-phosphate dehydrogenase

Oxidation of glucose-6-phosphate to 6-phosphor-gluconolactone, $NADP^+$ is reduced to NADPH

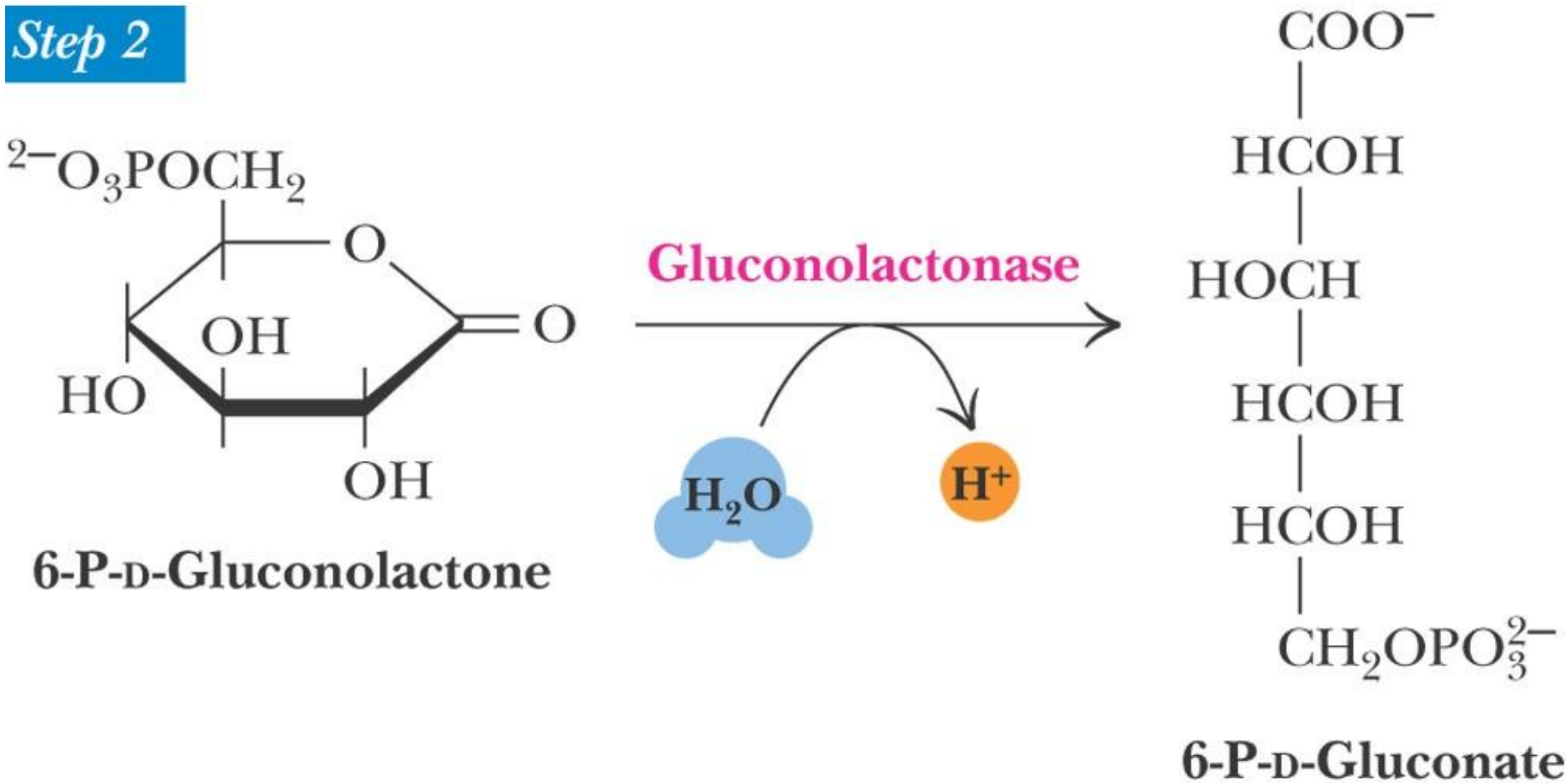


The cyclic form of 6-phospho-gluconate is a **lactone** called 6-phospho-D-gluconolactone.

The lactone is unstable and spontaneously is hydrolyzed to the linear form,

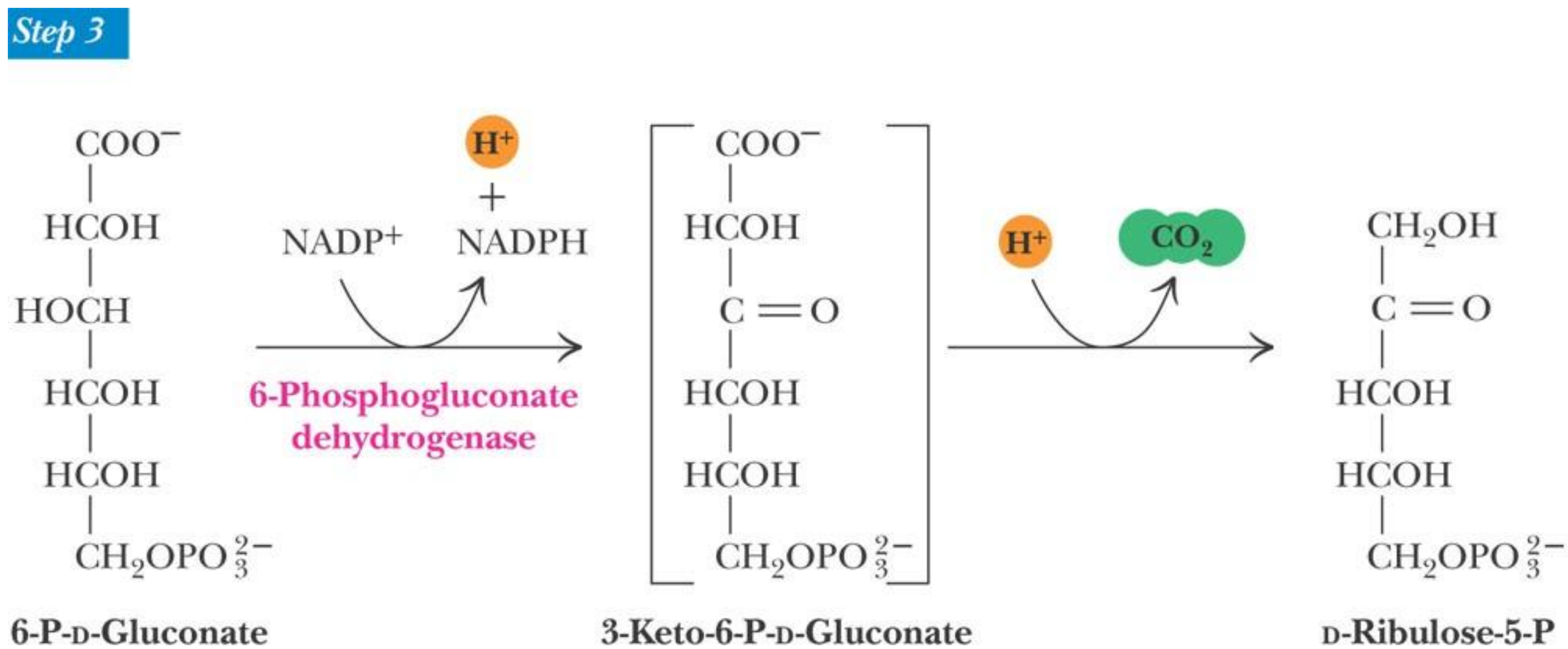
The enzyme glucolactonase (Step 2) accelerates the opening of the ring

Step 2 - Glucolactonase



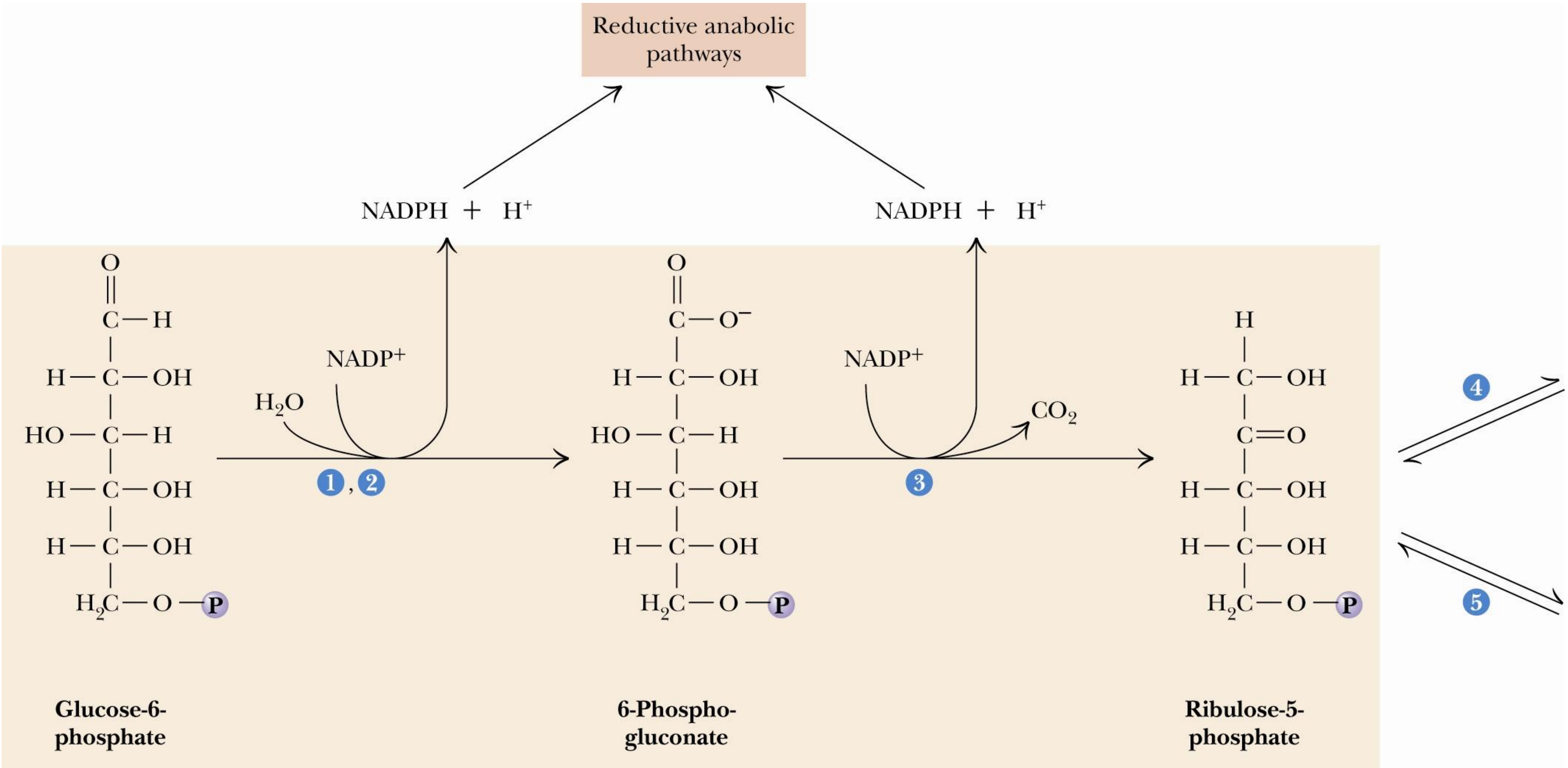
This hydrolysis also occurs spontaneously

Step 3 - Phospho-gluconate dehydrogenase



- Oxidative decarboxylation of 6-phospho-gluconate to ribulose-5-phosphate (a pentose phosphate).
- The reaction generates NADPH.
- The intermediate 3-Keto-6-P-D-gluconate is very susceptible to decarboxyation

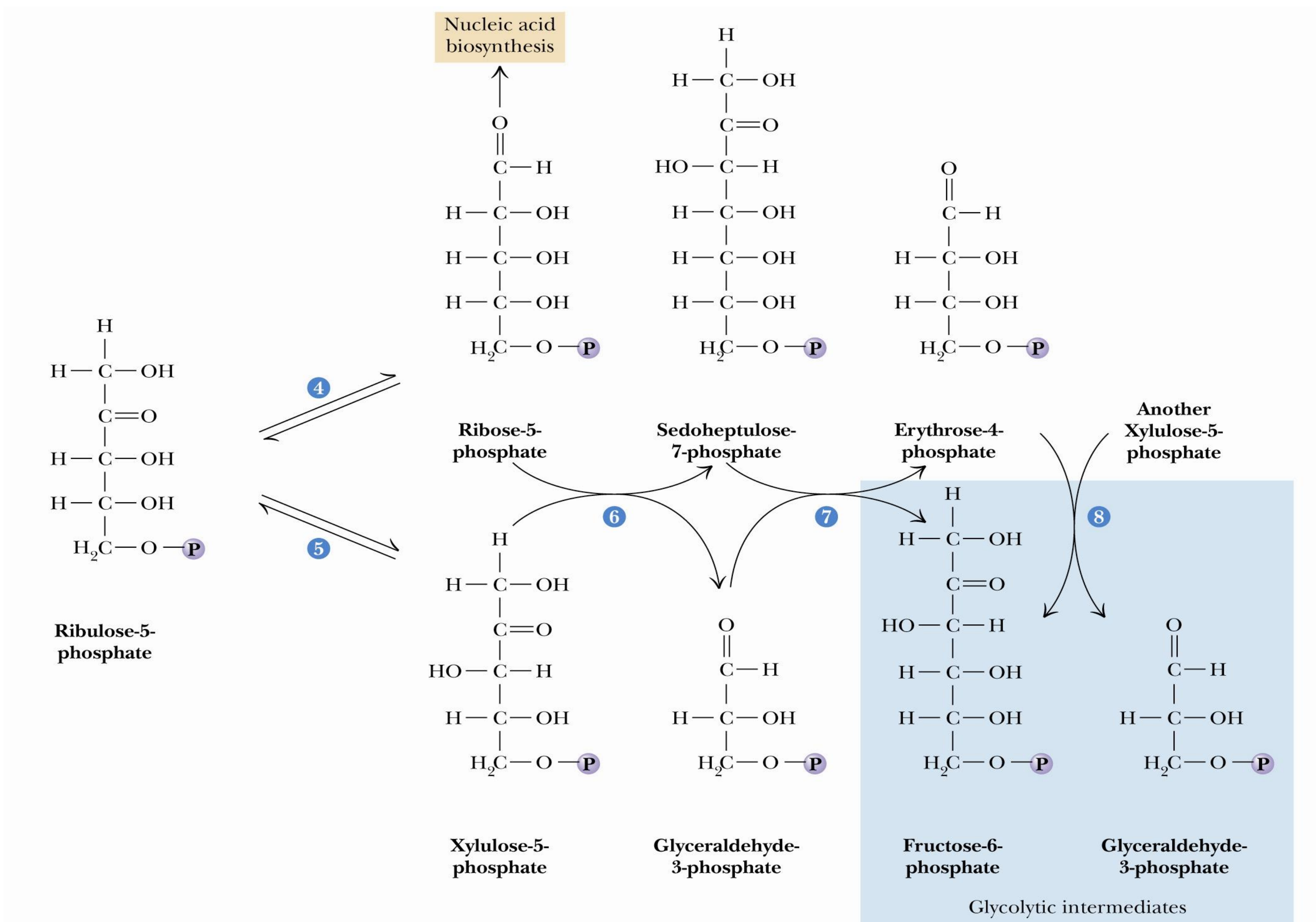
NADP synthesis for anabolic/biosynthetic reactions



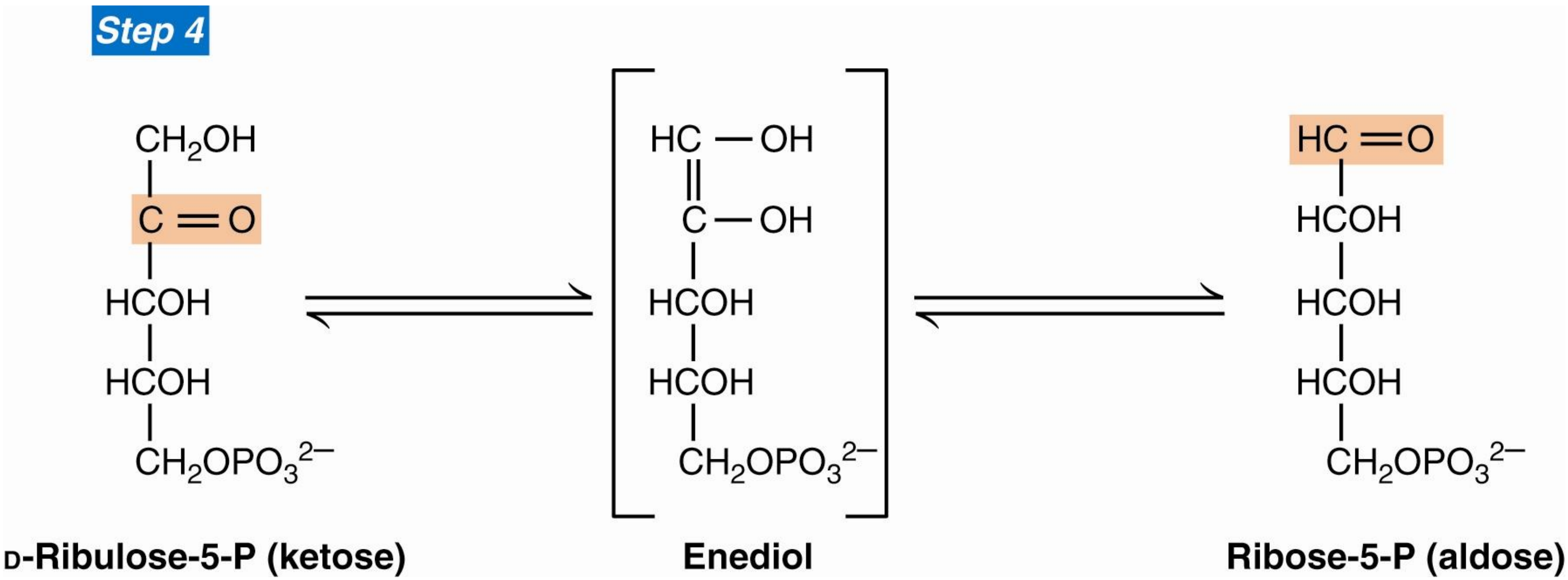
The first two reactions (3 steps) are oxidations coupled to the reduction of $NADP^+$ to NADPH, to be used in biosynthetic reactions. D-ribulose-5-P, is the substrate for the non-oxidative reactions of the pentose phosphate pathway

Steps 4-8: Non-oxidative reactions

These steps of the pathway produce ribose-5-phosphate for nucleic acid and coenzyme (NADH, NADPH, FAD) biosynthesis
Some carbon is directed to glycolysis or gluconeogenesis

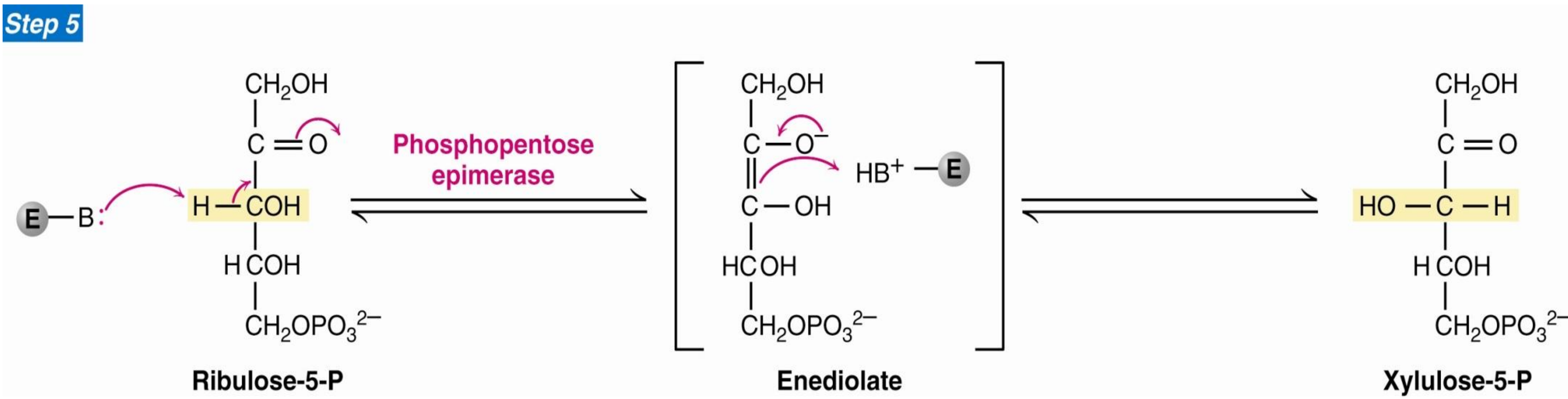


Steps 4: Phosphopentose isomerase



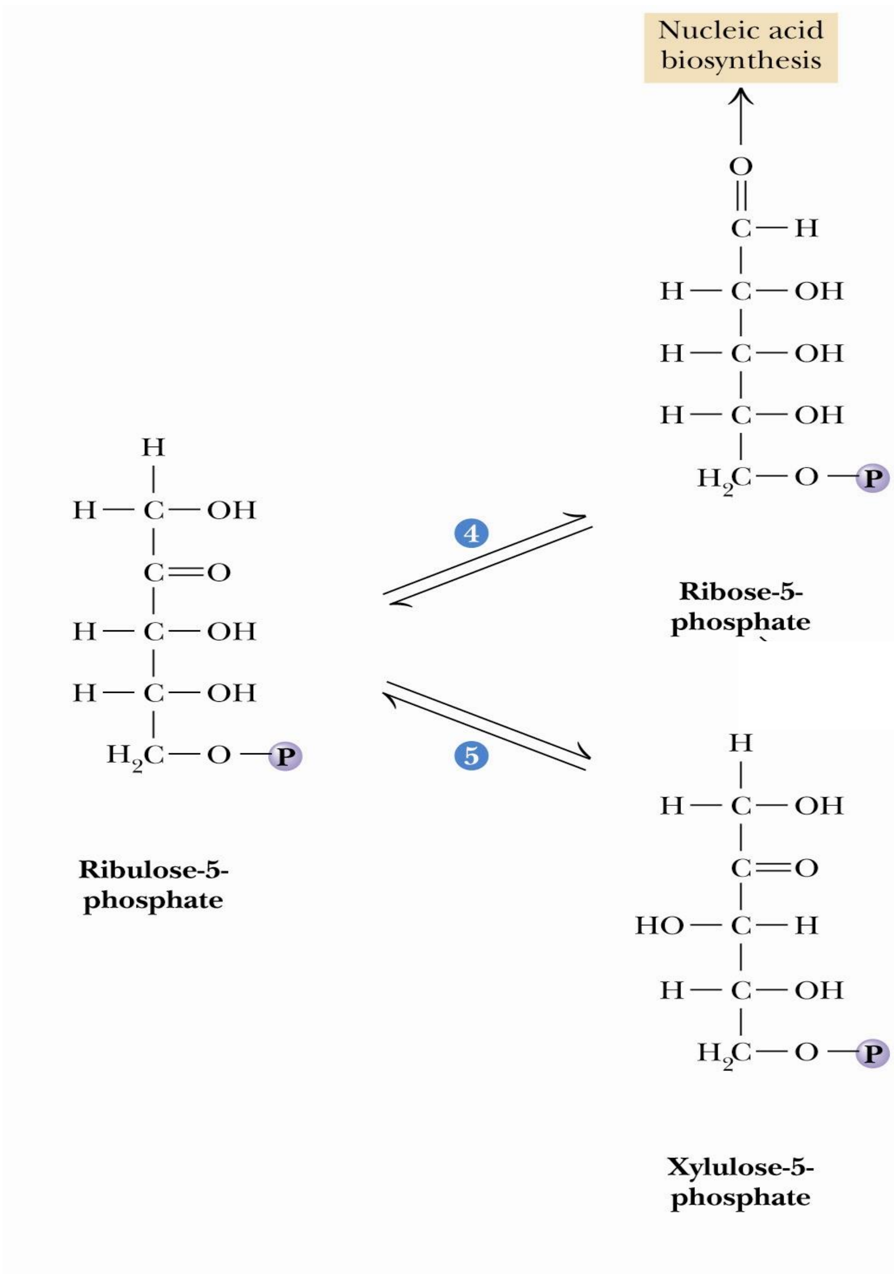
The phosphopentose isomerase reaction converts D-ribulose-5-P (a ketose) to Ribose-5-P (an aldose). The reaction involves an ene-diol intermediate.

Steps 5: Phosphopentose epimerase



The **phosphopentose <u>epimerase</u>** reaction interconverts ribulose-5-P and xylulose-5-phosphate. The mechanism involves an ene-diol intermediate and occurs with inversion at C-3 (epimers)

Steps 4-5

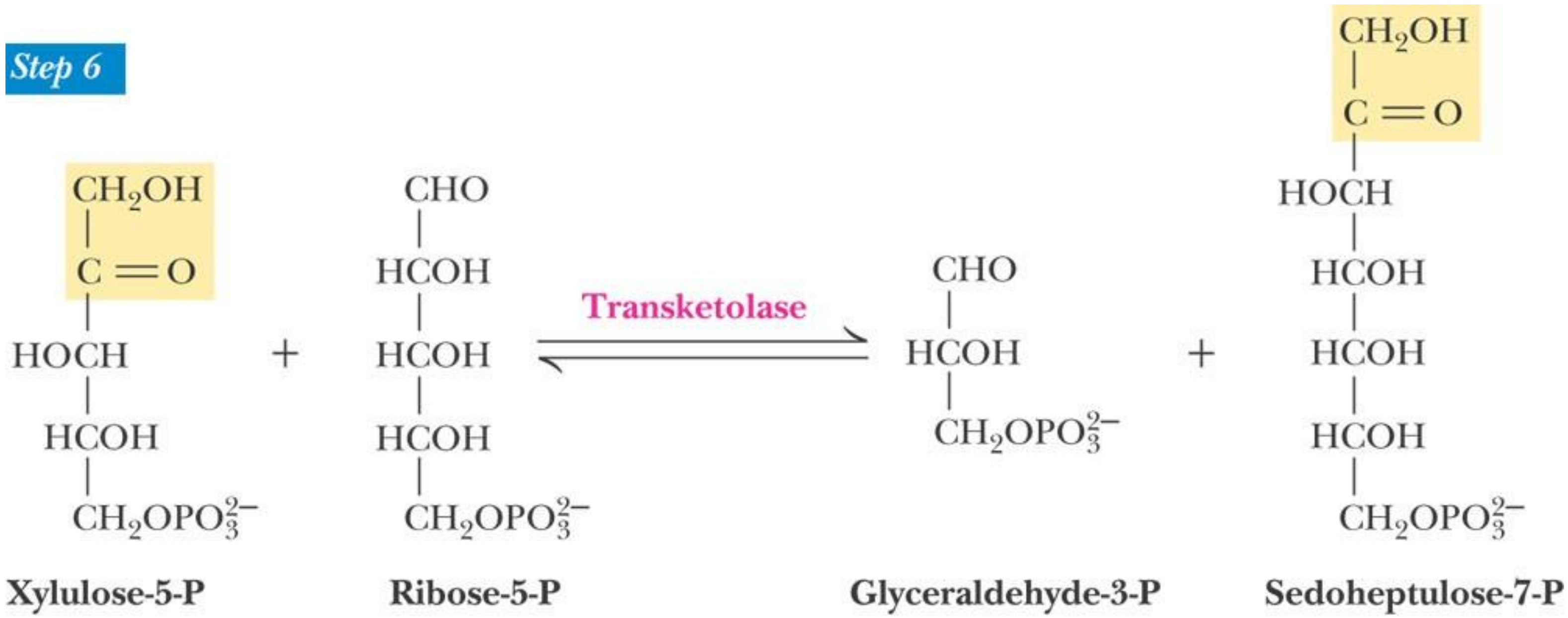


Steps 4-5 are reversible

→ the three pentose phosphates are in equilibrium

Step 4 is an **isomerization** (exchange of groups between carbons);
Step 5 is an **epimerization** (exchange of groups on a single carbon)

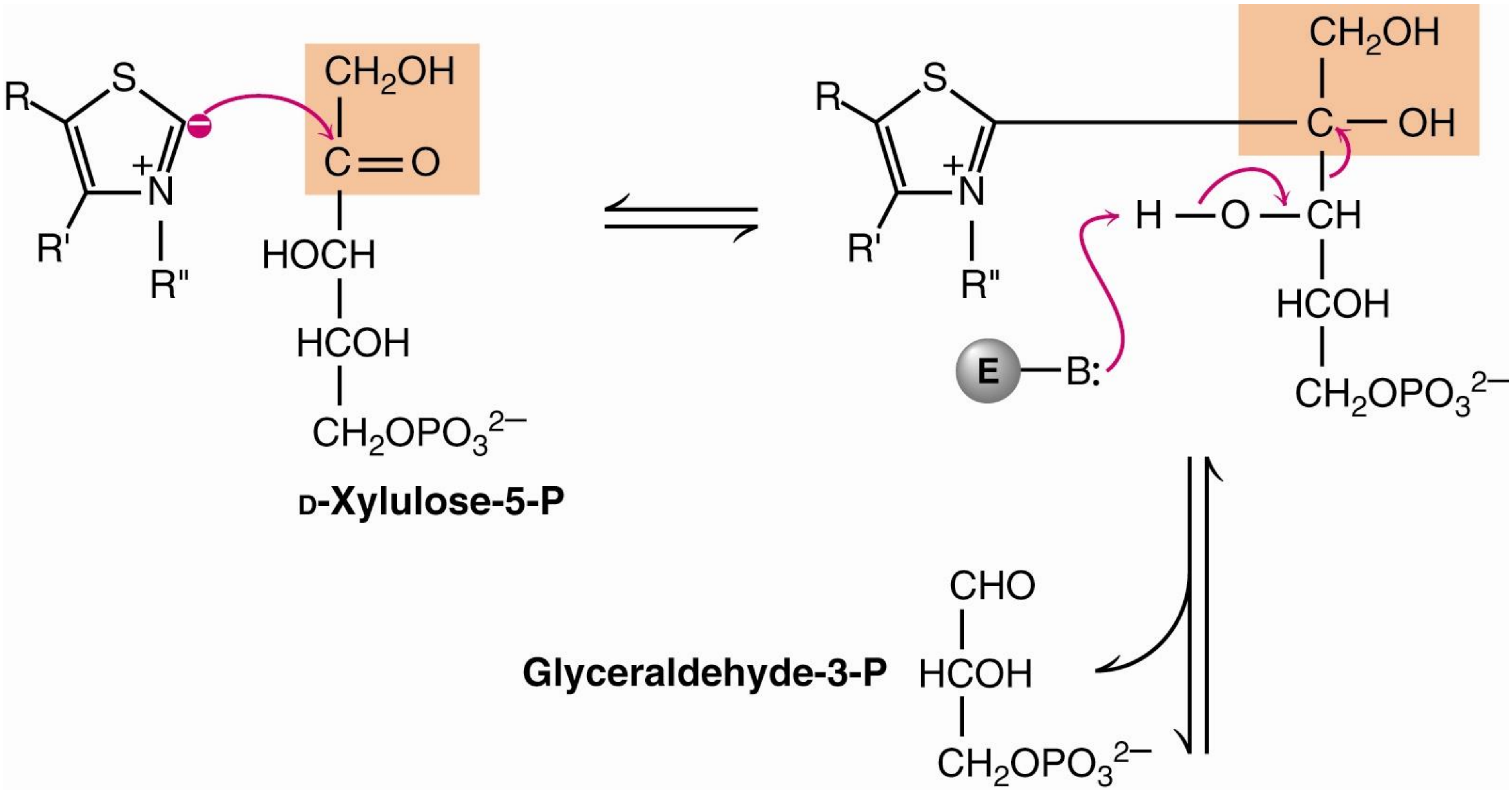
Step 6: Transketolase



The transketolase reaction involve the transfers of a 2-carbon unit to generate glyceraldehyde-3-phosphate and a seven carbon phosphorylated sugar (Sedoheptulose-7-P)

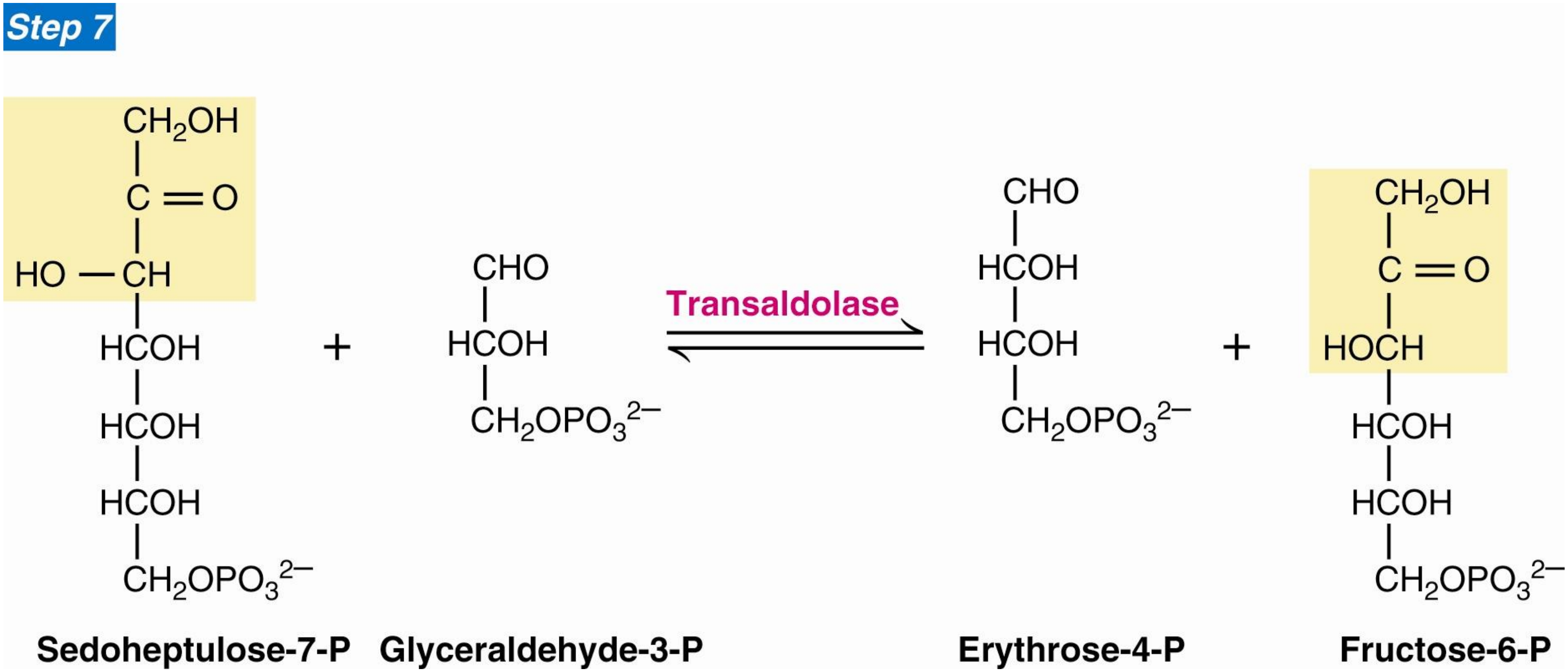
This reactions requires thiamine pyrophosphate as a coenzyme.

Step 6: Mechanism



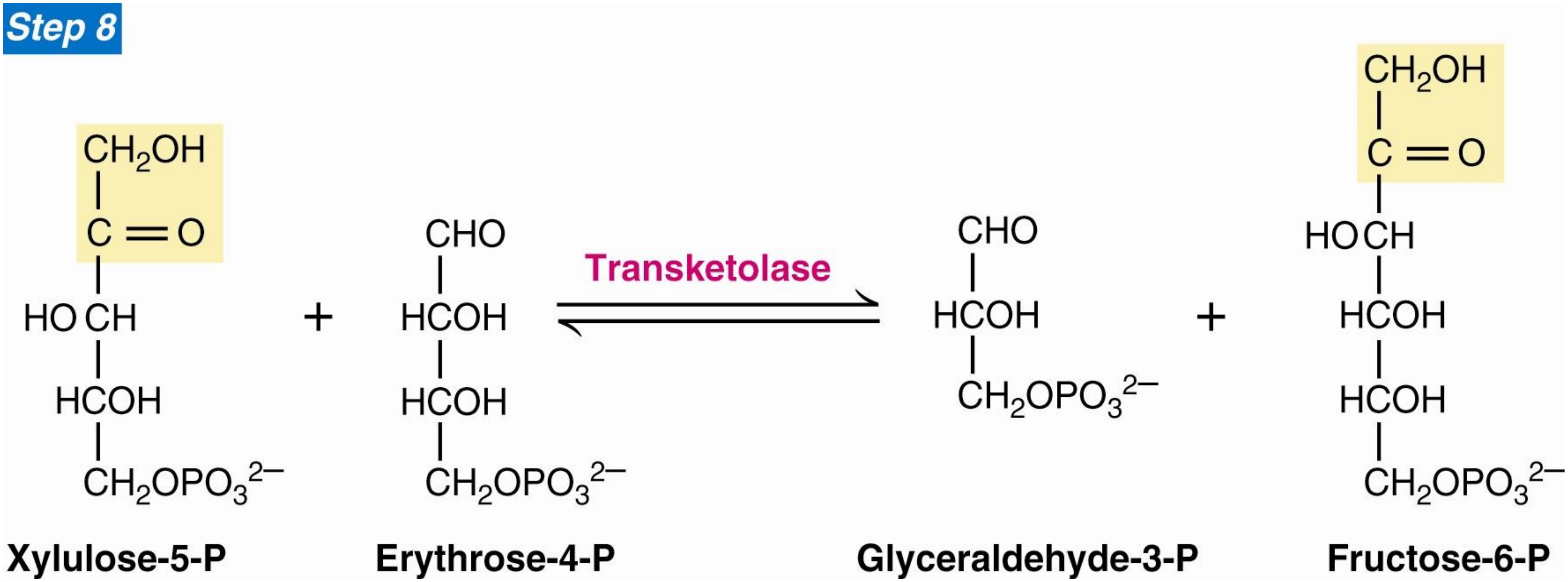
The group transferred is an aldol

Step 7: Transaldolase



- The transaldolase reaction transfers a 3-carbon unit to generate 4C and 6C phospho-sugars
- Erythrose-4-phosphate can be used for synthesis of the aromatic amino acids
- Fructose-6-phosphate can enter glycolysis or gluconeogenesis

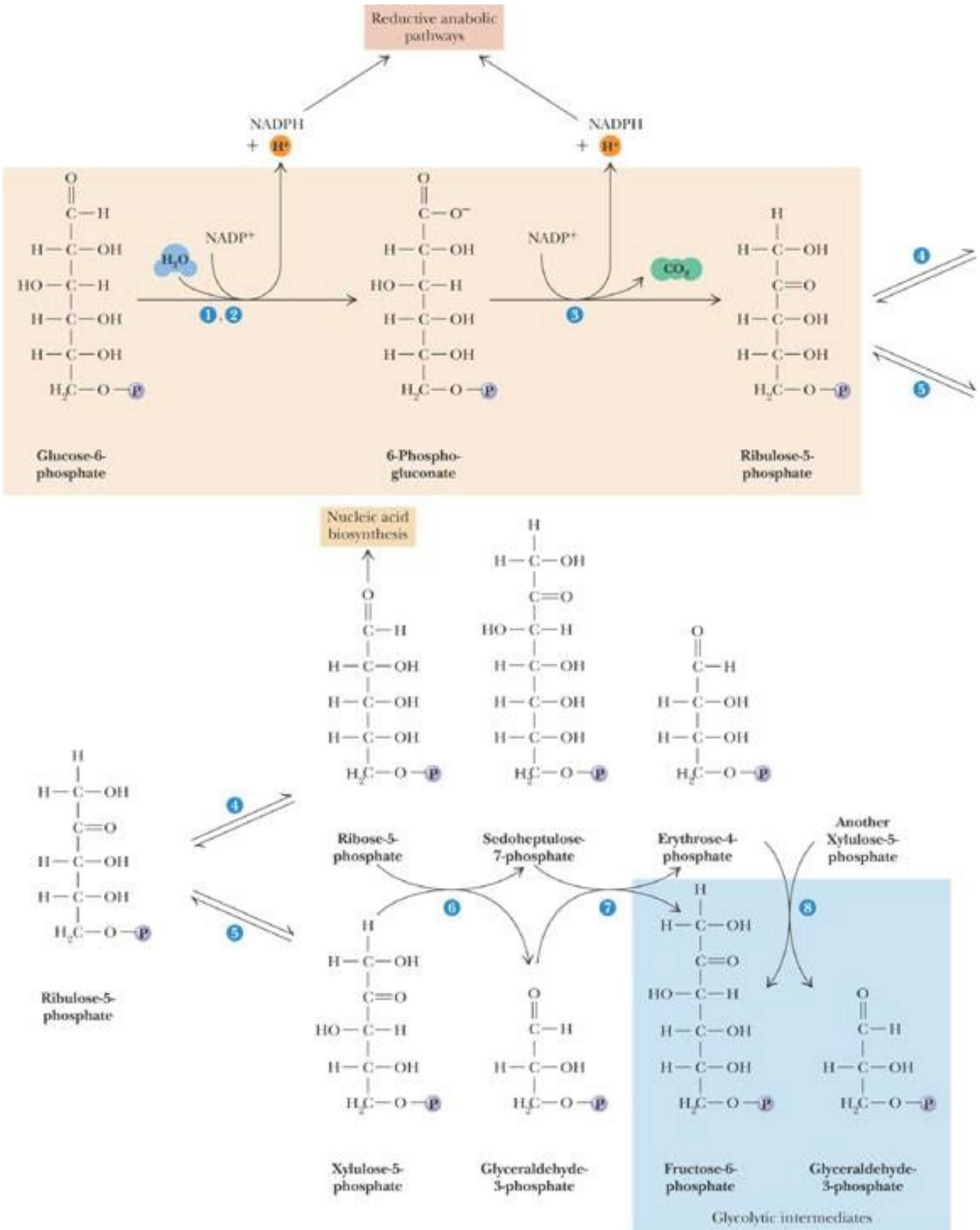
Step 8: Transketolase



This is another two-carbon transfer catalyzed by transketolase, and it also requires TPP as a coenzyme.

The products, Fructose-6-phosphate and glyceraldehyde-3-P, can enter glycolysis or gluconeogenesis

Pentose phosphate pathway regulation



Glucose-6-phosphate dehydrogenase is allosterically inhibited by NADPH and intermediates of fatty acid biosynthesis

This, and other regulatory mechanisms help to partition glucose between glycolysis and the pentose phosphate pathway according to the cell requirements

Pentose phosphate pathway regulation

When both ribose-5-P and NADPH are required
The oxidative reactions of the pathway predominate, ribose-5-P and NADPH are used for biosynthesis, no carbon is returned to glycolysis.

When more ribose-5-P than NADPH is required
Fructose-6-P and glyceraldehyde-3-P from glycolysis are fed into the non-oxidative branch of the pentose phosphate pathway, which can run in reverse to make ribose-5-P with no generation of NADPH. No carbon is returned to glycolysis

Pentose phosphate pathway regulation

When more NADPH than ribose-5-P is required

6 glucose-6-P $\rightarrow$ 6 ribose-5-P + 12 NADPH + by 6 CO_2
the pentose phosphate pathway

6 ribose-5-P $\rightarrow$ 4 fructose-6-P + 2 glyceraldehyde-3-P

4 fructose-6-P + 2 glyceraldehyde-3-P $\rightarrow$ 5 glucose-6-P
by gluconeogenesis

Net reaction is complete oxidation of glucose with production of NADPH:

Glucose-6-P + 12 $NADP^+$ $\longrightarrow$ 6 CO_2 + 12 NADPH

When both NADPH and ATP are needed, but ribose-5-P is not
As before but the fructose-6-P and glyceraldehyde-3-P are fed into glycolysis to generate ATP