

Biosynthesis – Inspiration for Drug Discovery

Shikimate Metabolites

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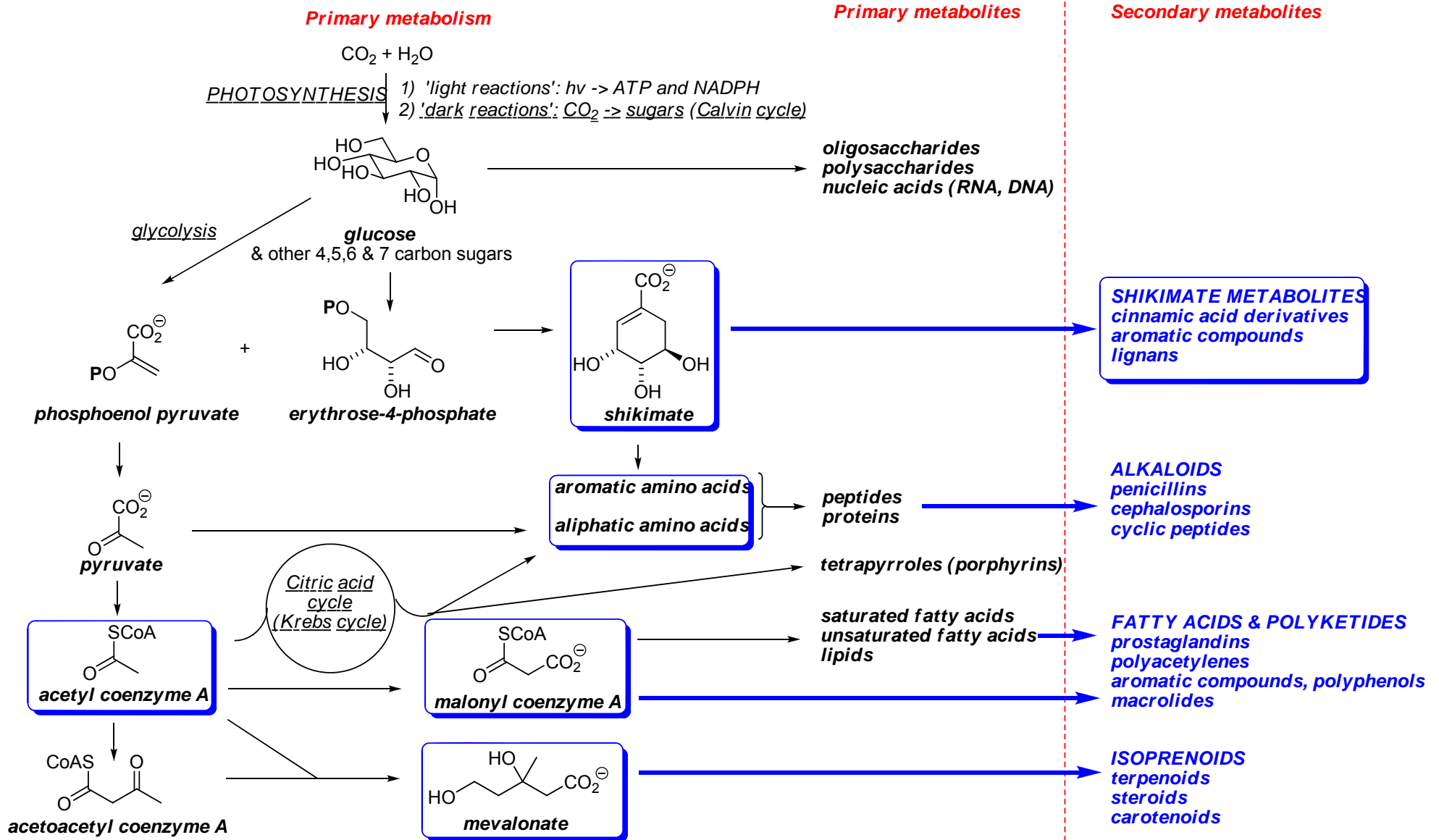
Imperial College
London

Nov 2008

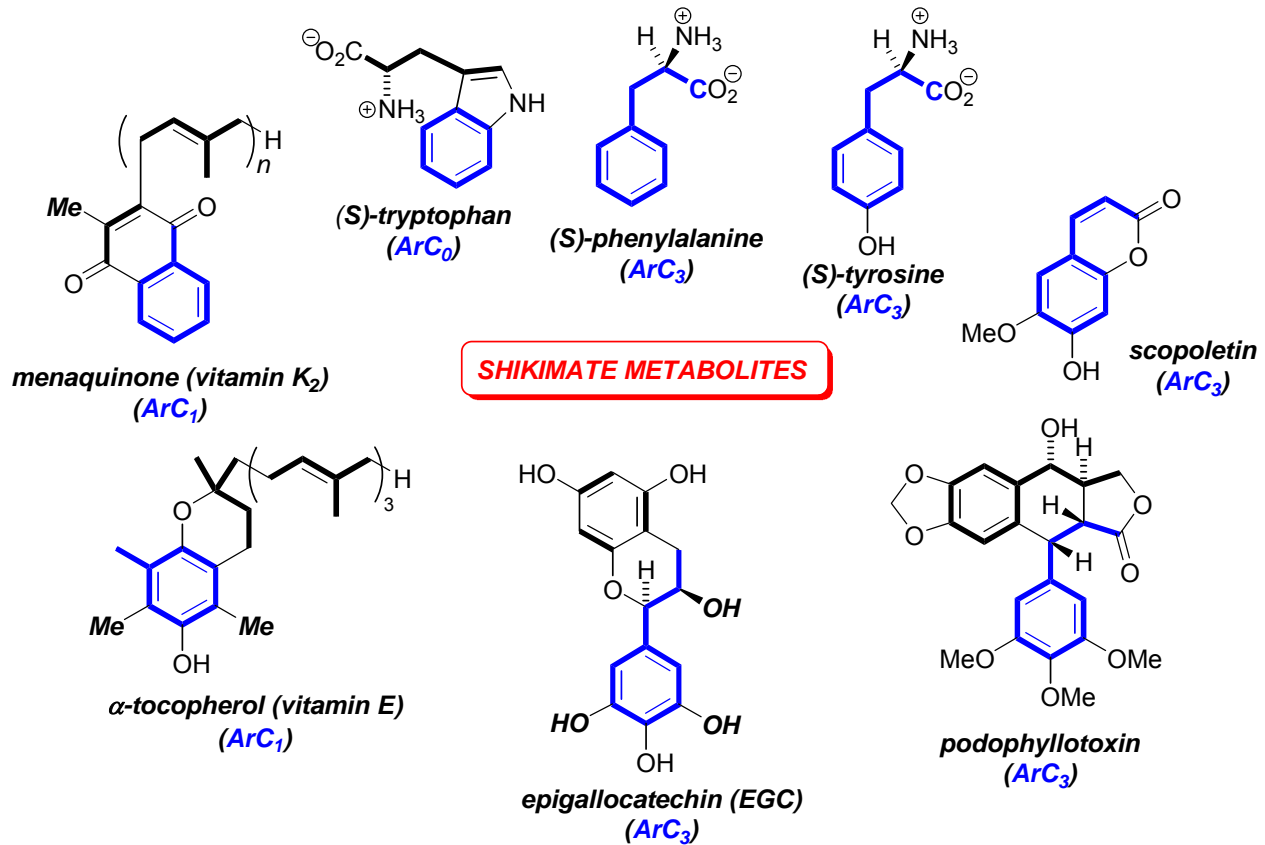
Format & Scope of Lecture

- ***The shikimate biosynthetic pathway***
 - the core shikimate pathway - mechanisms of the key enzymes
 - aromatic amino acids: Phe, Tyr & Trp
 - ArC₃ metabolites – coumarins, lignans & lignins

Primary Metabolism - Overview

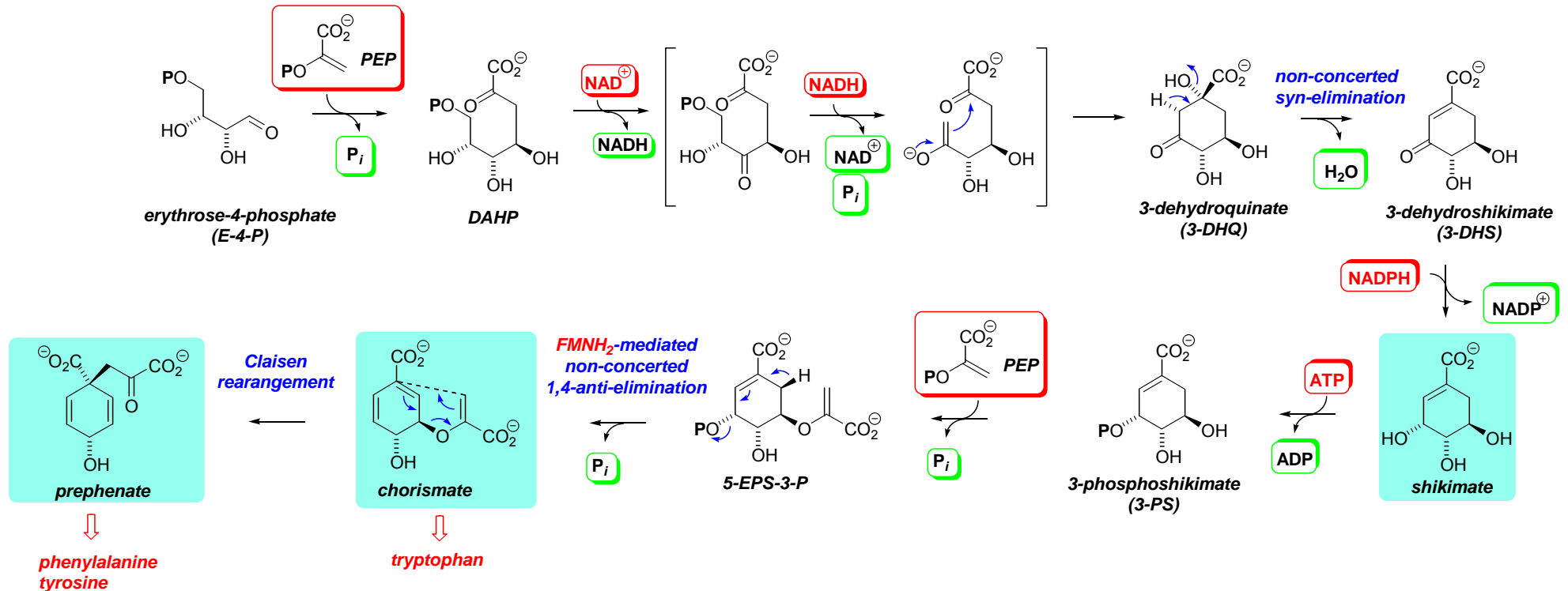


Shikimate Metabolites



The Shikimate Biosynthetic Pathway - Overview

- **Phosphoenol pyruvate & erythrose-4-phosphate → shikimate → chorismate → prephenate:**

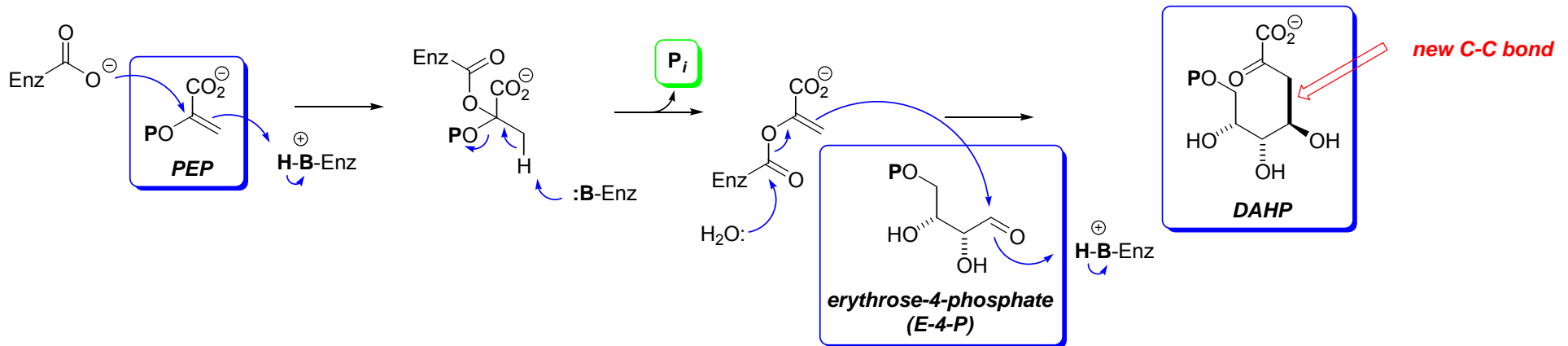


– The detailed mechanisms of these steps have been studied intensively. Most are chemically complex and interesting. For additional details see:

- Mann *Chemical Aspects of Biosynthesis* Oxford Chemistry Primer No. 20, **1994** (key details)
- Haslam *Shikimic Acid – Metabolism and Metabolites* Wiley, **1993** (full details and primary Lit. citations)
- <http://www.chem.qmul.ac.uk/iubmb/enzyme/reaction/misc/shikim.html> (interesting web-site with many biosynthetic pathways)



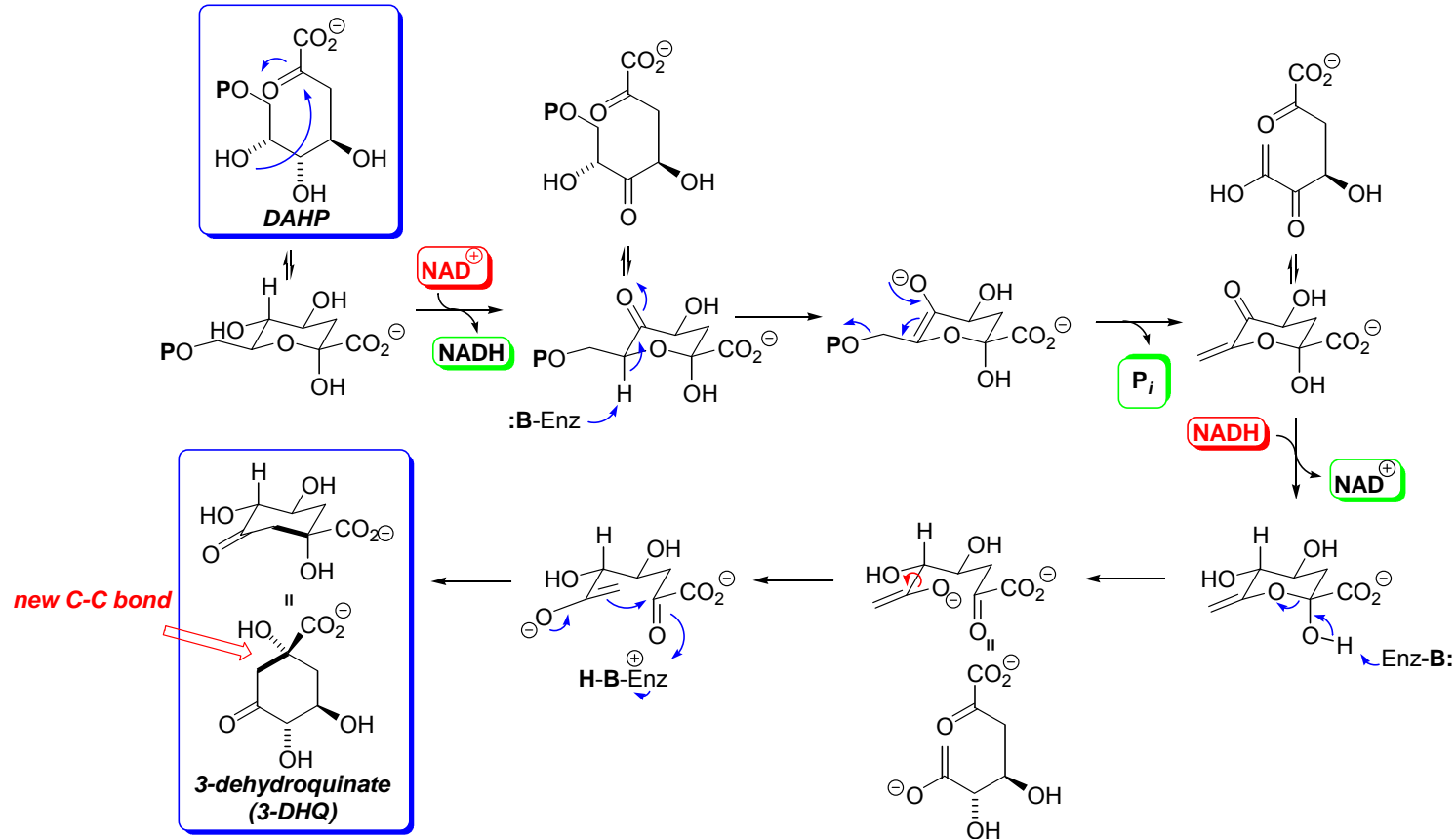
- **Phosphoenol pyruvate (PEP) + erythrose-4-phosphate (E-4-P) → 3-deoxy-D-arabino-heptulosonate-7-phosphate (DHAP)**
- **Enzyme: 3-deoxy-7-phosphoheptulosonate synthase = DAHP synthase [EC 2.5.1.54]**
 - *chemistry catalysed: an aldol reaction*



– Floss *et al.* *J. Biol. Chem.* **1972**, 247, 736 ([DOI](#))

DAHP → 3-DHQ

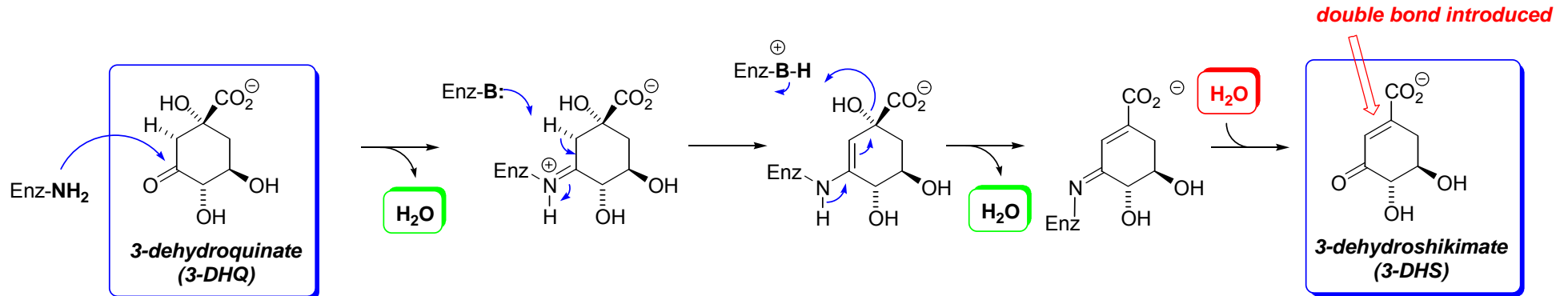
- **3-Deoxy-D-arabino-heptulosonate-7-phosphate (DHAP) → 3-dehydroquinate (3-DHQ)**
- **Enzyme: 3-dehydroquinase synthase [EC 4.2.3.4]**
 - *chemistry catalysed: alcohol → ketone → alcohol redox cycle & cyclisation via aldol reaction*



- Knowles *et al.* *Biochemistry* **1989**, 28, 7555 ([DOI](#))

3-DHQ → 3-DHS

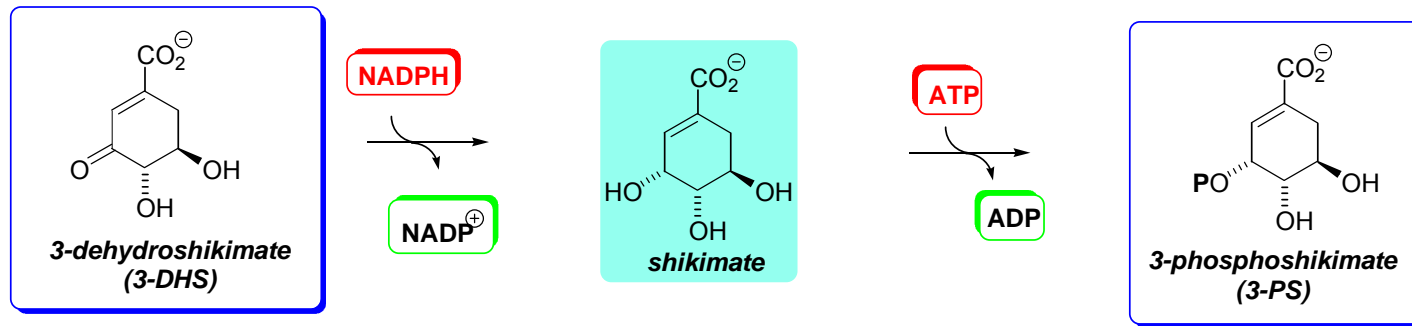
- **3-Dehydroquinate (3-DHQ) → 3-dehydroshikimate (3-DHS)**
- **Enzyme: 3-dehydroquinate dehydratase [EC 4.2.1.10]**
 - *chemistry catalysed: stereoselective syn-elimination*



- Abell *et al. Biochem. J.* **1996**, 319, 333 ([DOI](#))
- Coggins *et al. J. Biol. Chem.* **1995**, 270, 25827 ([DOI](#))
- Coggins *et al. Nature Struct. Biol.* **1999**, 6, 521 ([DOI](#))

3-DHS → 3-PS

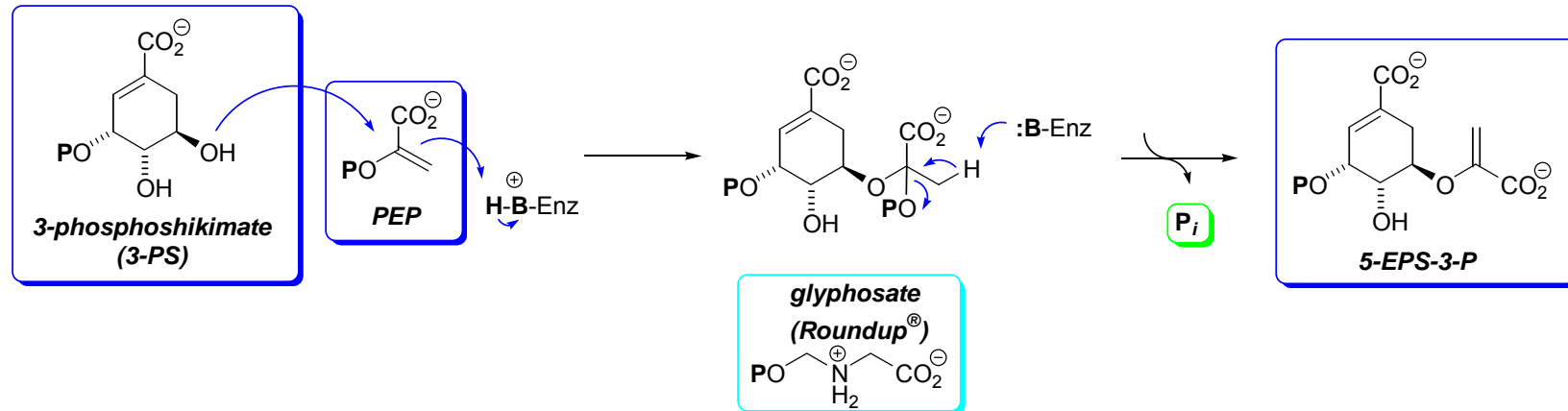
- **3-Dehydroshikimate (3-DHS) → shikimate → 3-phosphoshikimate (3-PS)**
- **Enzymes: shikimate dehydrogenase** [EC 1.1.1.25] then **shikimate kinase** [EC 2.7.1.71]
 - *chemistry catalysed:* stereoselective reduction of ketone → alcohol then alcohol phosphorylation



- Ye *et al.* *J. Bacteriol.* **2003**, 185, 4144 ([DOI](#))
- Morell *et al.* *J. Biol. Chem.* **1968**, 243, 676 ([DOI](#))

3-PS → 5-EPS-3-P

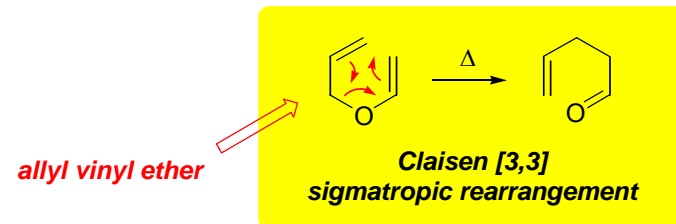
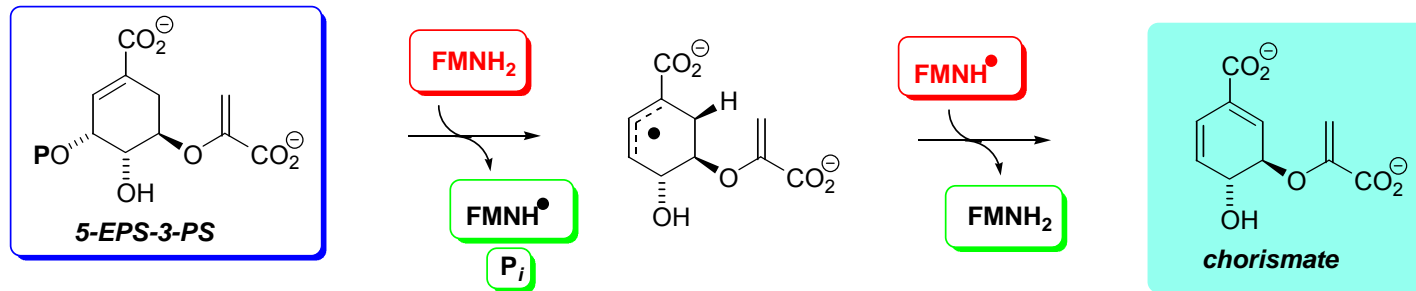
- **3-Phosphoshikimate (3-PS) → 5-enolpyruvylshikimate-3-phosphate (5-EPS-3P)**
- **Enzyme: 3-phosphoshikimate 1-carboxyvinyltransferase [EC 2.5.1.19]**
 - *chemistry catalysed: vinyl ether formation*



- **Glyphosate ('Roundup')** – a Monsanto agrochemical is a potent inhibitor of this biosynthetic step
 - a non-selective herbicide
- Lewis *et al. Biochemistry* **1999**, 38, 7372 ([DOI](#))
- Jakeman *et al. Biochemistry* **1998**, 37, 12012 ([DOI](#))

5-EPS-3-P → Chorismate

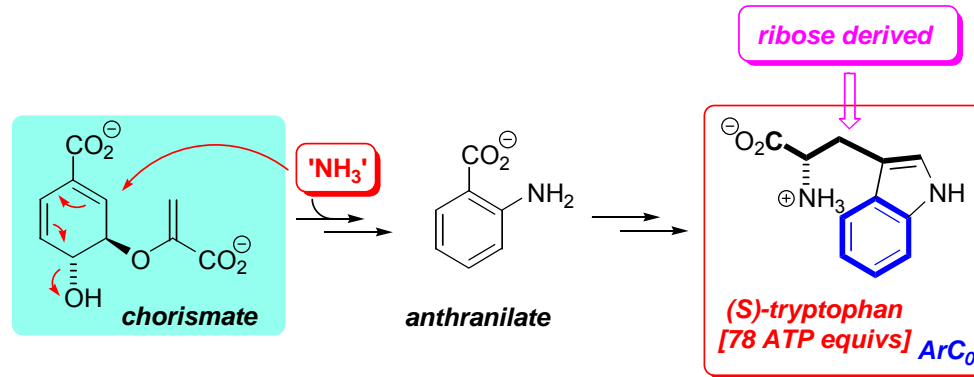
- **5-Enolpyruvylshikimate-3-phosphate (5-EPS-3P) → chorismate**
- **Enzyme: chorismate synthase** [EC 4.2.3.5]
 - *chemistry catalysed: non-concerted anti-1,4-elimination*



- Abell *et al.* *Bioorg. Chem.* **2000**, 282, 191 ([DOI](#))
- Abell *et al.* *J. Biol. Chem.* **2000**, 275, 35825 ([DOI](#))
- Bornemann *et al.* *Biochemistry* **1996**, 35, 9907 ([DOI](#))

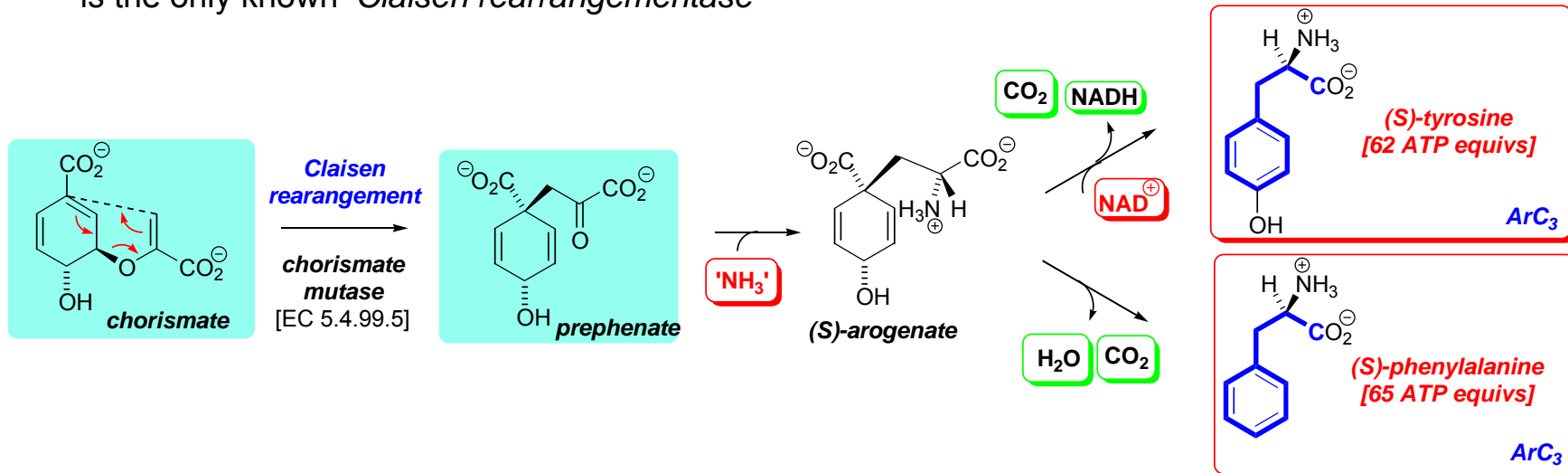
Chorismate → Tryptophan, Tyrosine & Phenylalanine

- **Chorismate** → **anthranilate** → **tryptophan**



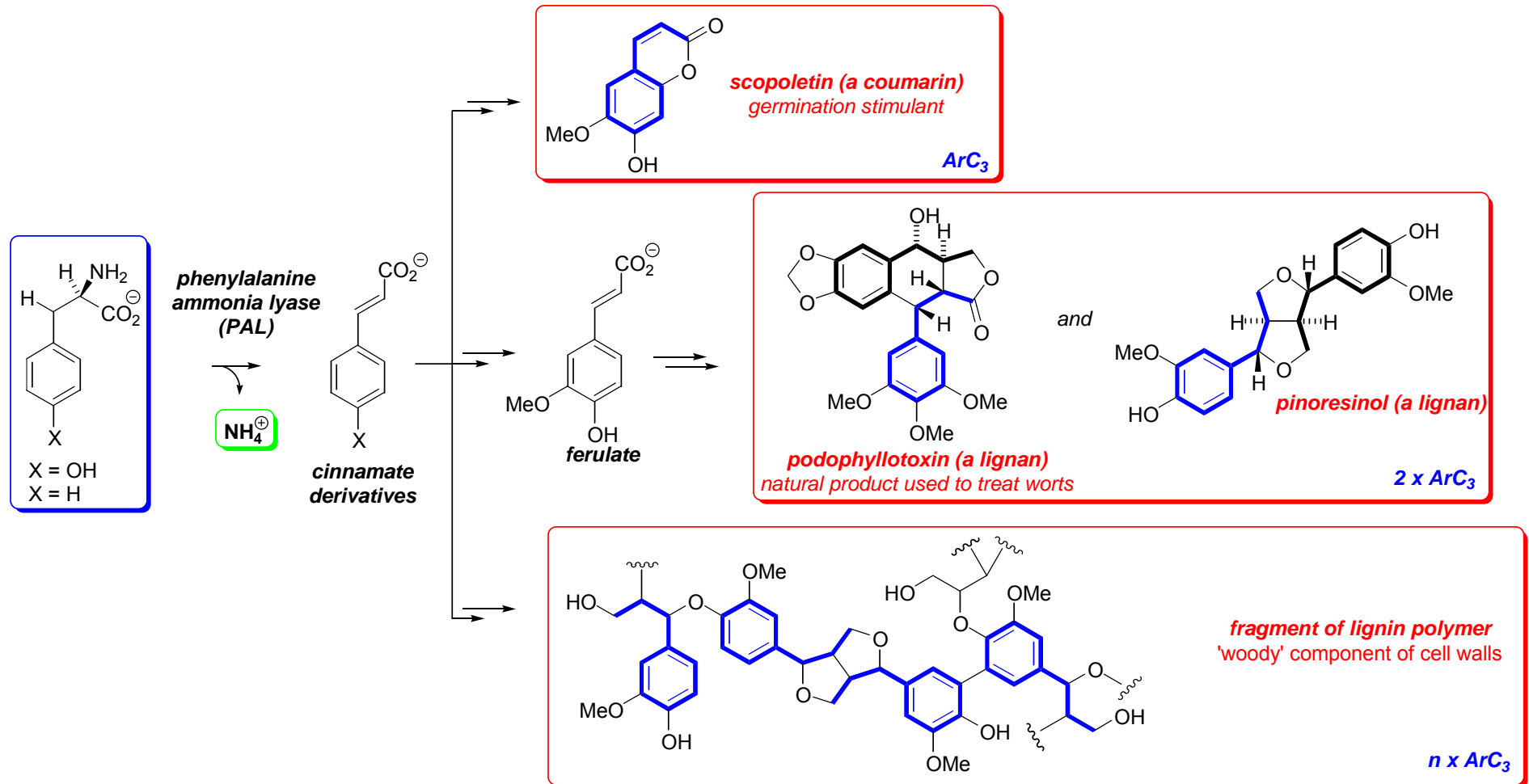
- **Chorismate** → **prephenate** → **tyrosine** & **phenylalanine**

– NB. The enzyme *chorismate mutase* [EC 5.4.99.5] which mediates the conversion of chorismate to prephenate is the only known 'Claisen rearrangementase'



Tyrosine/Phenylalanine → ArC₃ Metabolites

- Tyrosine & phenylalanine → cinnamate derivatives → ArC₃ metabolites
 - coumarins, lignans (stereoselective enzymatic dimerisation) & lignins (stereorandom radical polymerisation)



Primary Metabolism - Overview

