

Biosynthesis of Natural Products

Biosynthesis of Alkaloids

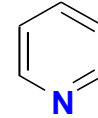
Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College
London

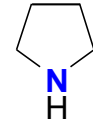
Oct 2019

Format & Scope of Lecture

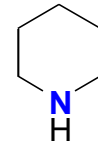
- **What are alkaloids?**
 - definitions, 1° metabolism → α -amino acids (Lys, Orn)
 - the citric acid cycle – oxaloacetate & α -ketoglutarate
 - pyridoxal – transamination, racemisation & decarboxylation
- **Phenylalanine & tyrosine derived alkaloids**
 - benzyloquinolines – e.g. opium, aporphine & erythrina alkaloids
- **Tryptophan derived alkaloids**
 - mixed tryptophan/mevalonate (isoprenoid) alkaloids:
 - secologanin derived: vinca-, strychnos- & quinine alkaloids etc.
- **Non-ribosomal peptides & derivatives**
 - penicillins & cephalosporins



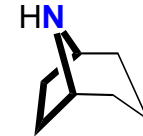
pyridine



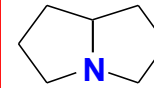
pyrrolidine



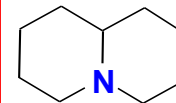
piperidine



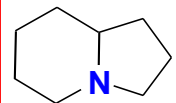
tropane



pyrrolizidine



quinolizidine

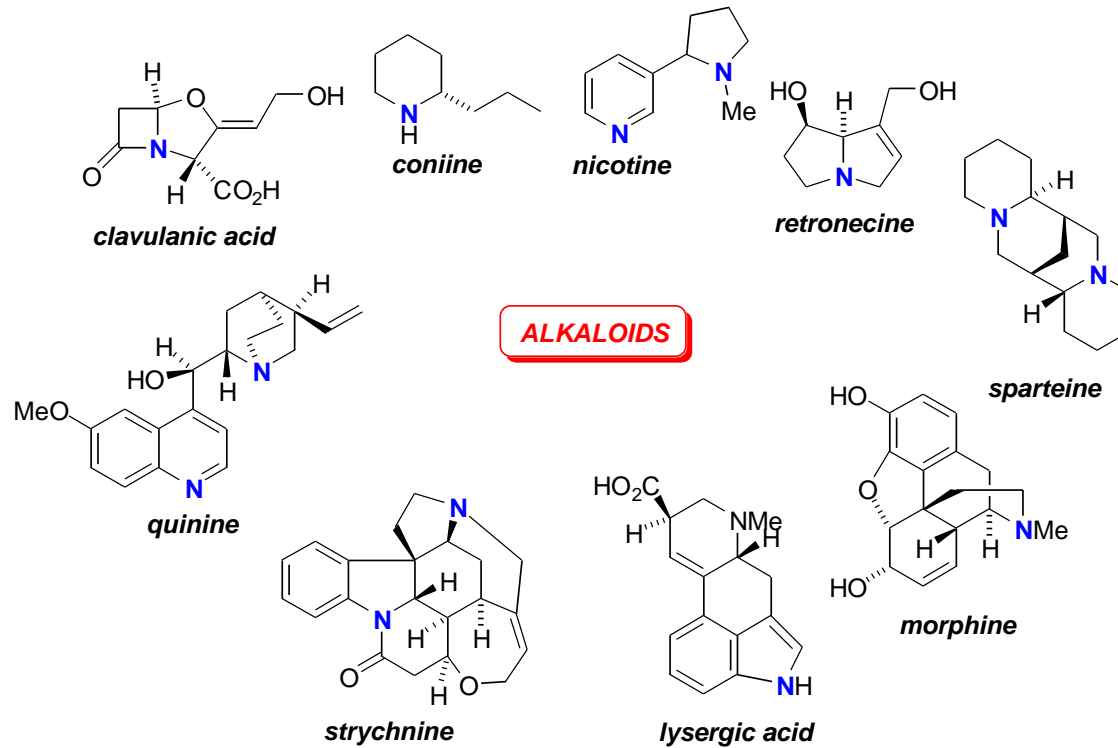


indolizidine

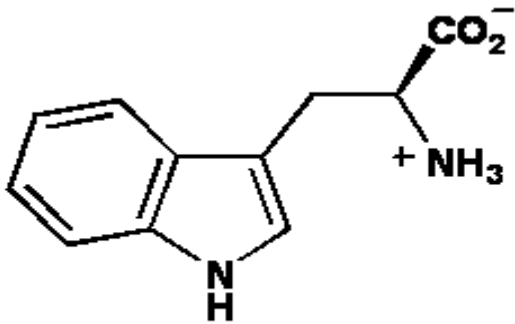
Alkaloids

- **Definitions:**

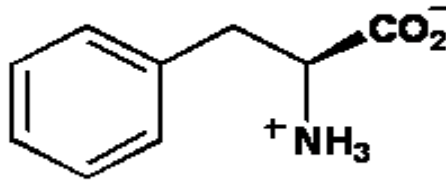
- **originally** – ‘a natural product that could be extracted out of alkaline but not acidic water’ (i.e. containing a basic amine function that protonated in acid)
- **more generally** - ‘any non-peptidic & non-nucleotide nitrogenous secondary metabolite’



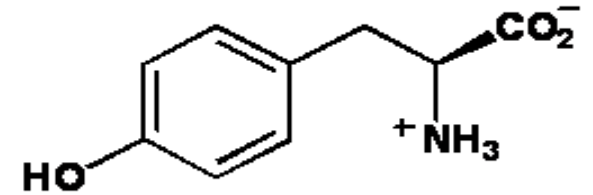
α -Amino Acids used to make Alkaloids



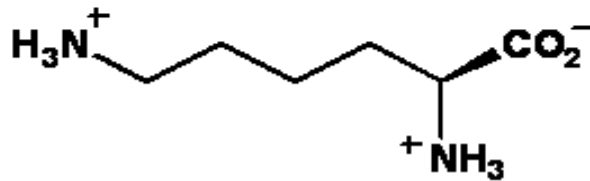
tryptophan



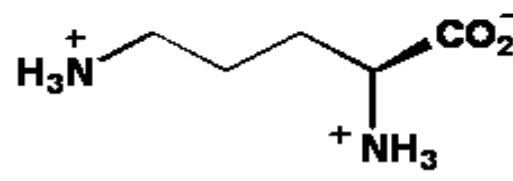
phenylalanine



tyrosine

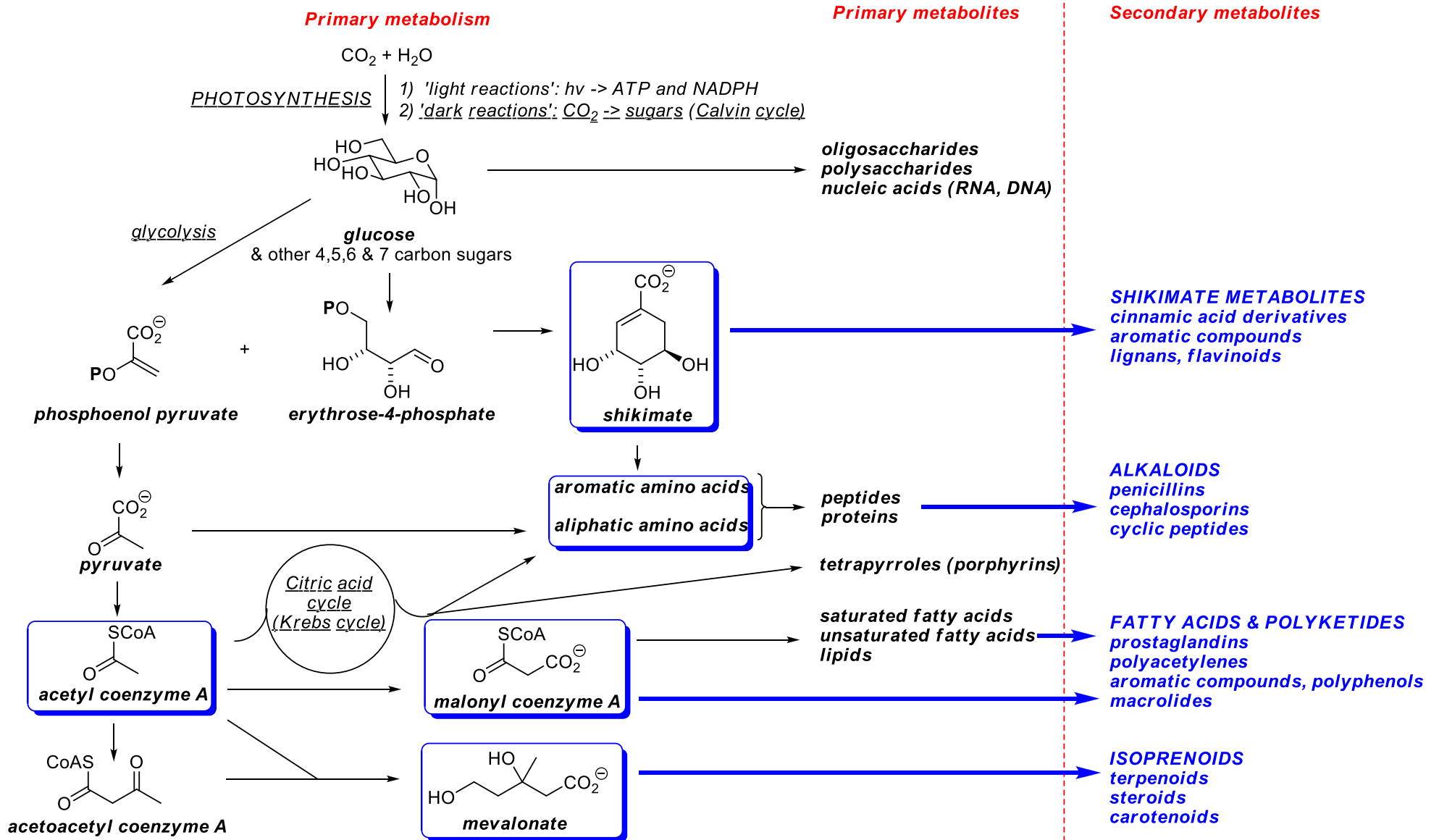


lysine



ornithine

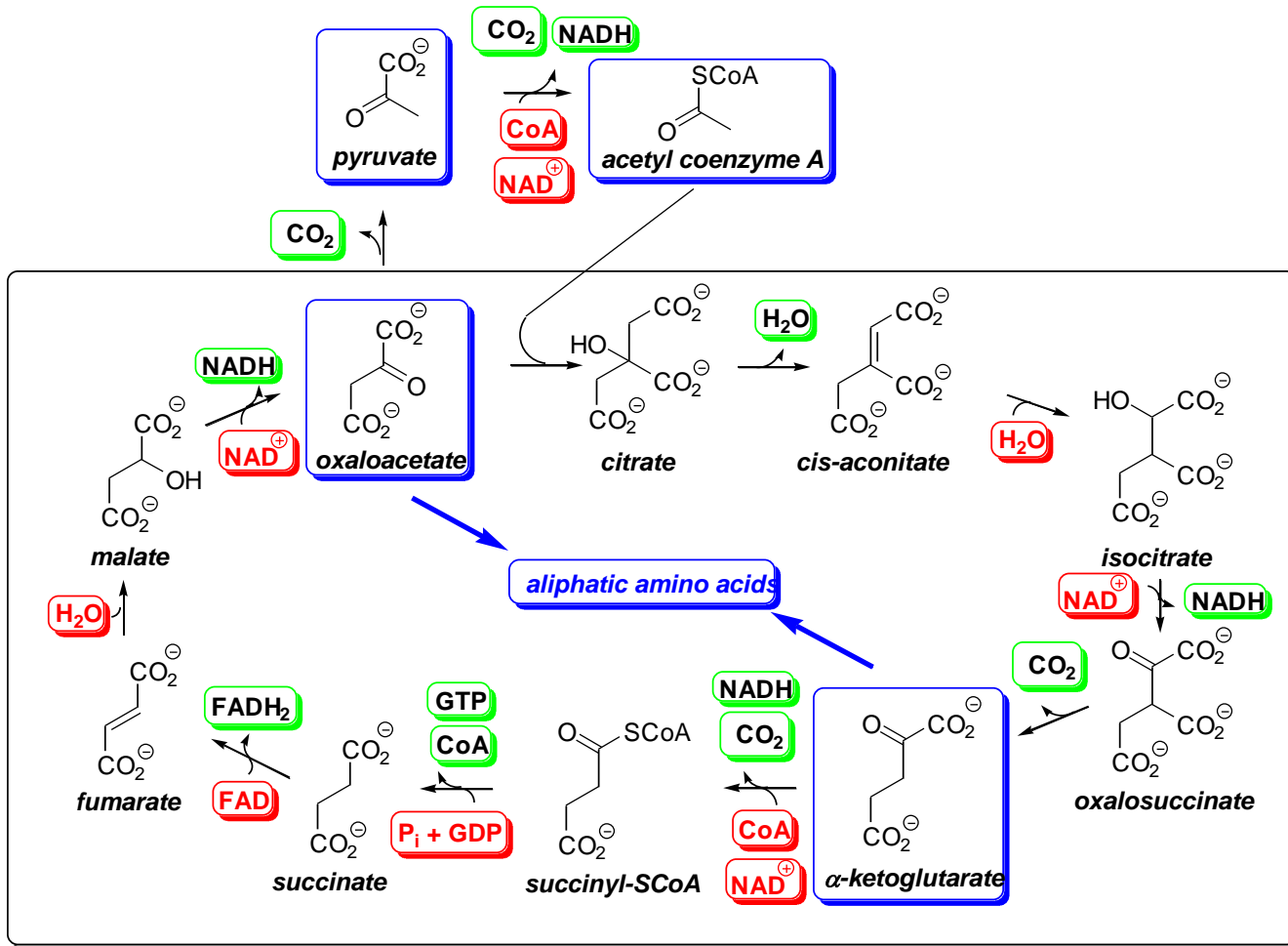
Primary Metabolism - Overview



For interesting animations' of e.g. photosynthesis see: <http://www.johnkyrk.com/index.html>

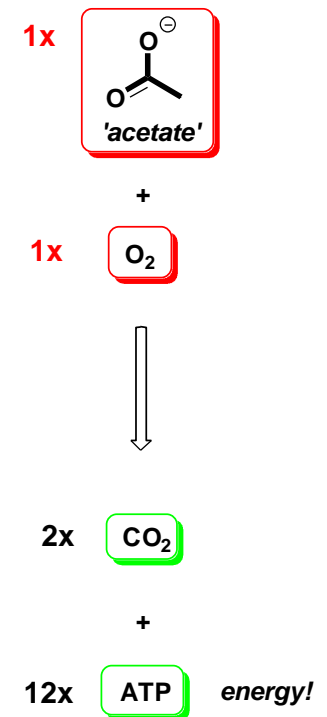
The Citric Acid Cycle

- **The citric acid (Krebs) cycle** is a major catabolic pathway of 1° metabolism that provides two key building blocks for aliphatic amino acid biosynthesis - **oxaloacetate** & **α -ketoglutarate**:



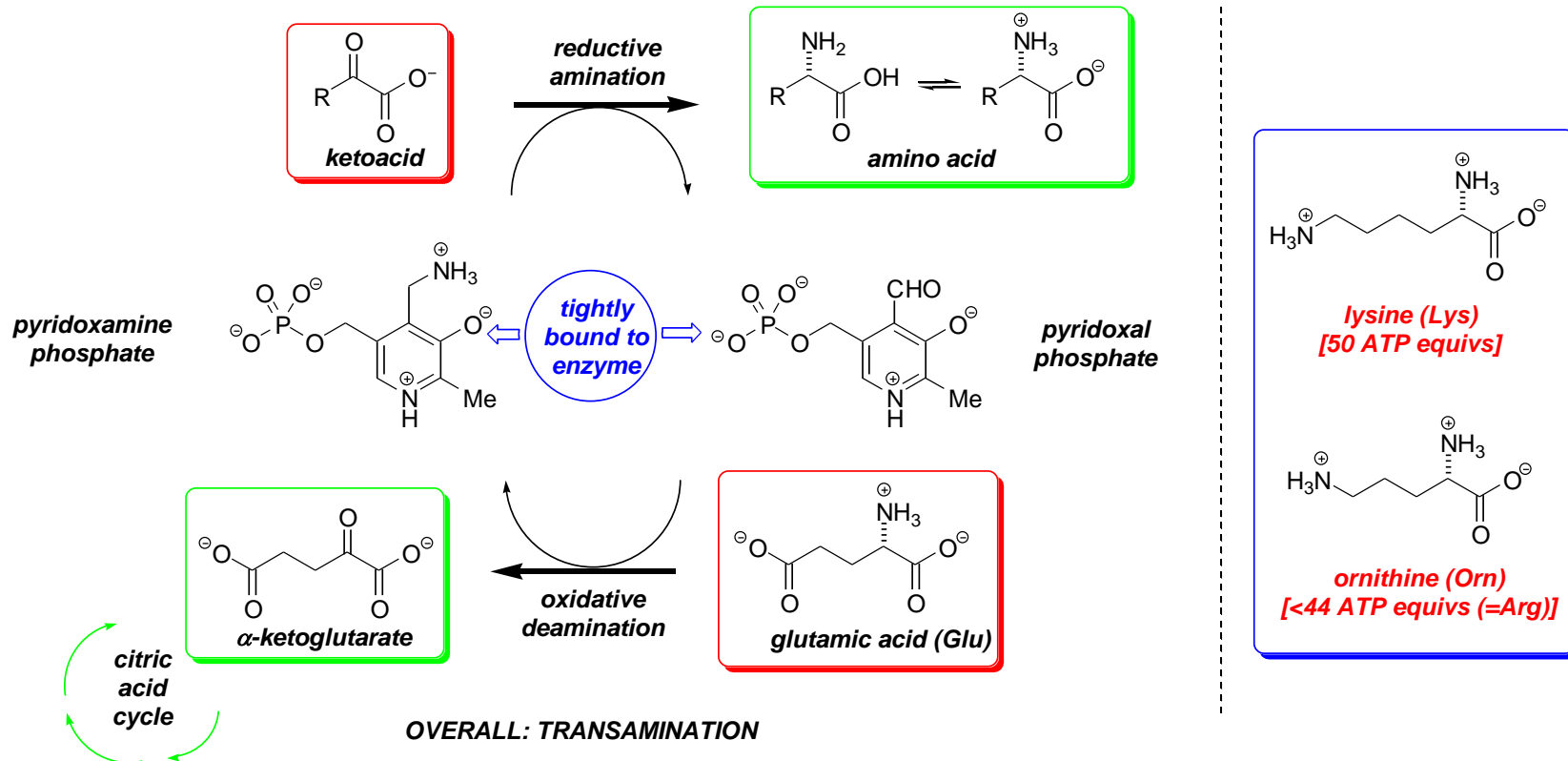
THE CITRIC ACID CYCLE

OVERAL STOICHIOMETRY



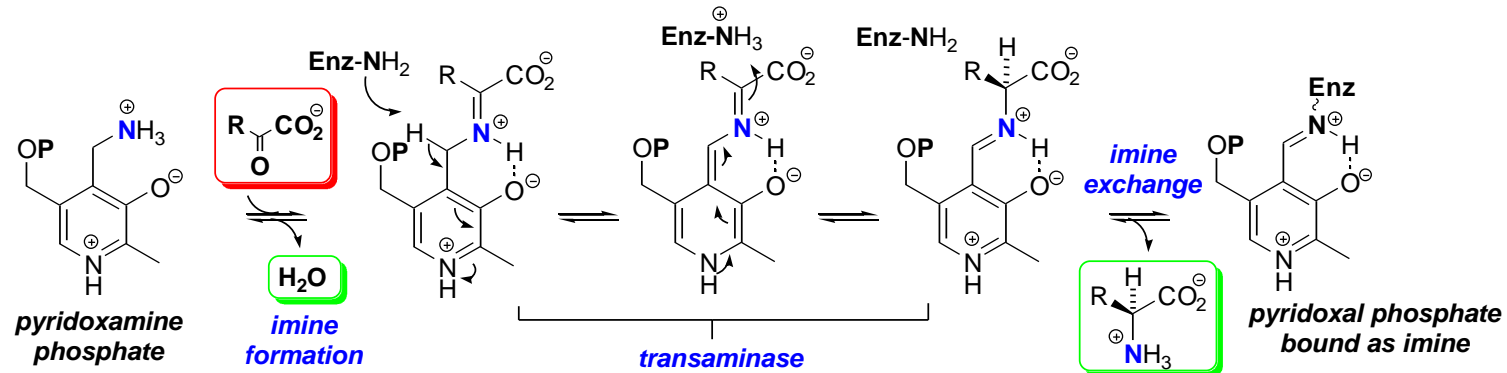
The Biosynthesis of Lysine & Ornithine

- **Lysine & ornithine** - the two most significant, *non-aromatic* α -amino acid **precursors to alkaloids**:
 - NB. lysine (Lys) is proteinogenic whereas ornithine (Orn) is not
 - phenylalanine (Phe), tyrosine (Tyr) & tryptophan (Trp) from **shikimate** are the other important precursors
 - biosynthesis is *via* reductive amination of the appropriate α -ketoacid mediated by **pyridoxal-5'-phosphate (PLP)**

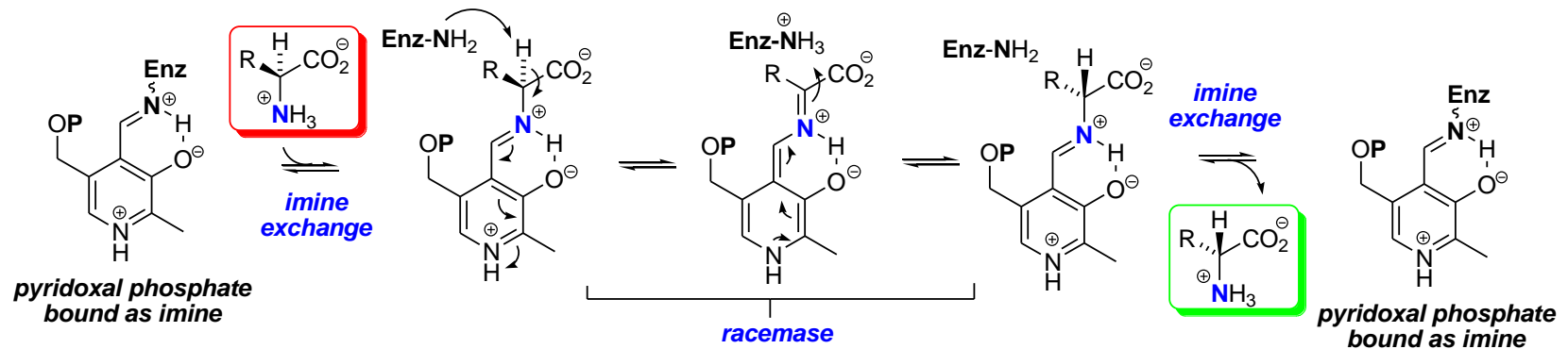


PLP Chemistry – *Transamination & Racemisation*

- Transamination** – LHS → RHS (*reductive amination*); RHS → LHS (*oxidative deamination*):

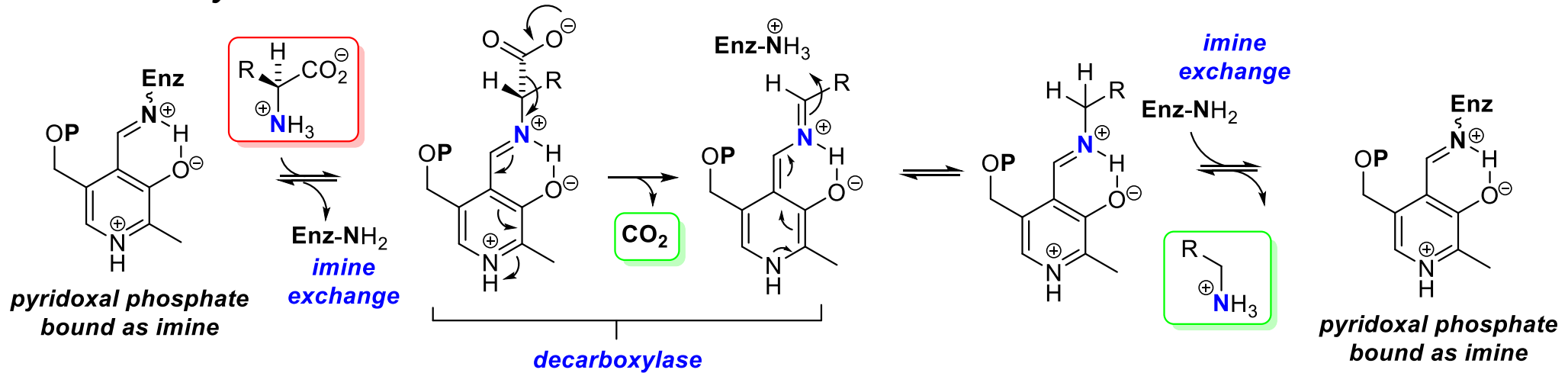


- Racemisation/inversion of configuration:**

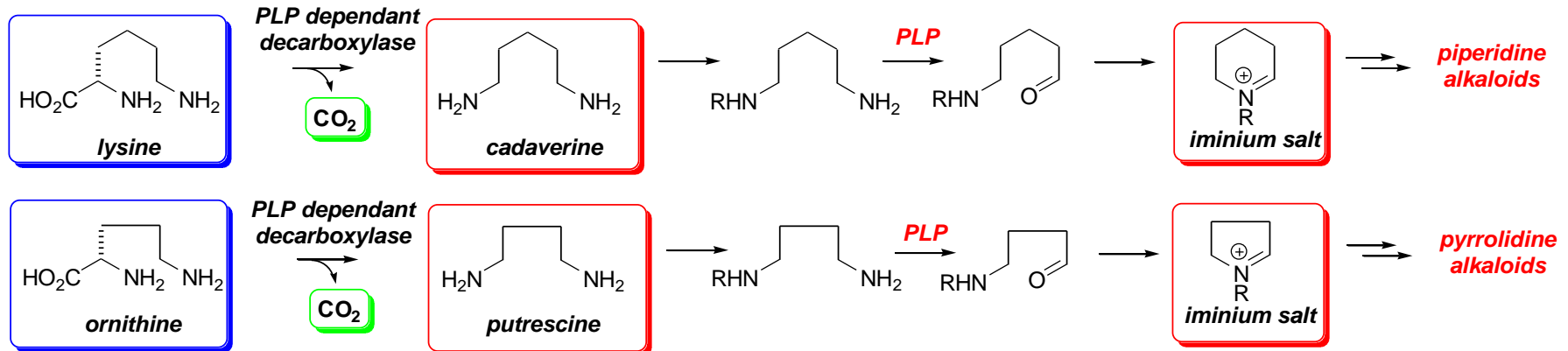


PLP Chemistry – Decarboxylation

- Decarboxylation:**

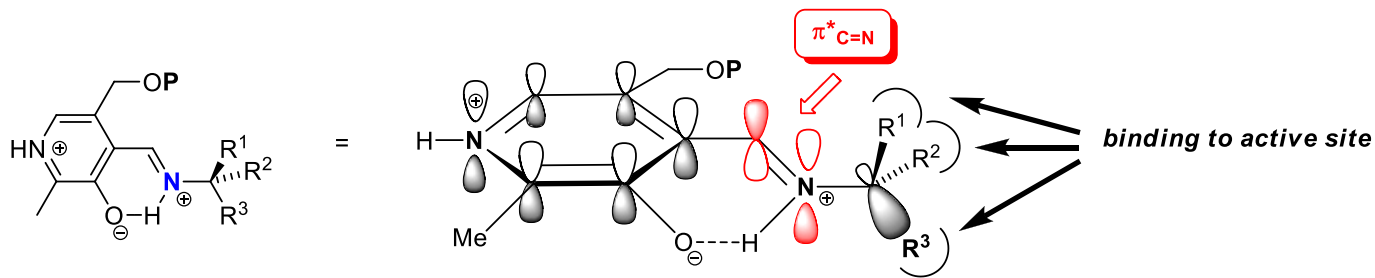


- Decarboxylation of **lysine** & **ornithine**:

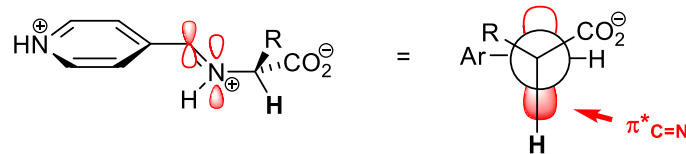


Control of PLP Activity – Stereoelectronics

- How does an enzyme control whether the PLP co-factor effects *racemisation or decarboxylation*?
 - i.e.* which bond will be cleaved?

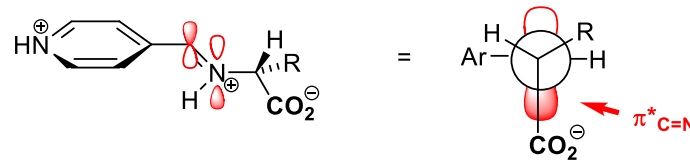


racemisation
(α proton loss)



$\sigma_{C-H} \rightarrow \pi^*_{C=N}$ *anti peri planar*

decarboxylation

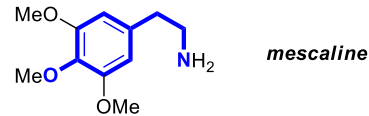


$\sigma_{C-C} \rightarrow \pi^*_{C=N}$ *anti peri planar*

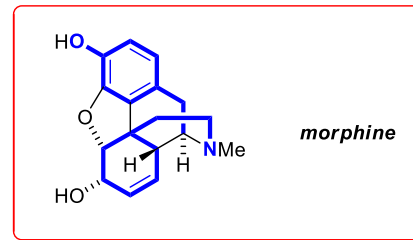
Phenylalanine & Tyrosine Derived Alkaloids

- **Alkaloids (generally) containing an ArC_2N subunit ($\pm ArC_2/ArC_1$):**
 - Skeleta built up by **reductive amination, decarboxylation, oxidation** (e.g. **phenolic coupling, hydroxylation**)
 - **Major classes:**

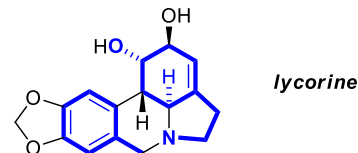
- **monocyclic alkaloids**
- phenethylamines (e.g. mescaline)]



- **Benzylisoquinolines**
- opium alkaloids (e.g. papaverine, morphine)
- aporphine alkaloids
- erythrina alkaloids

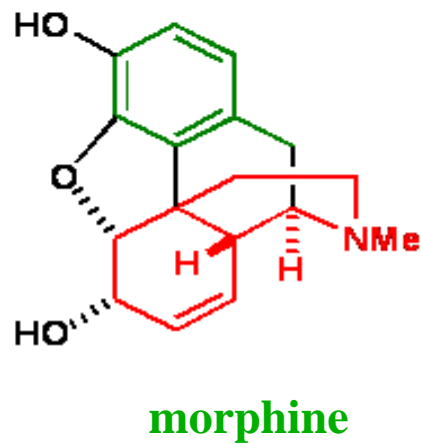
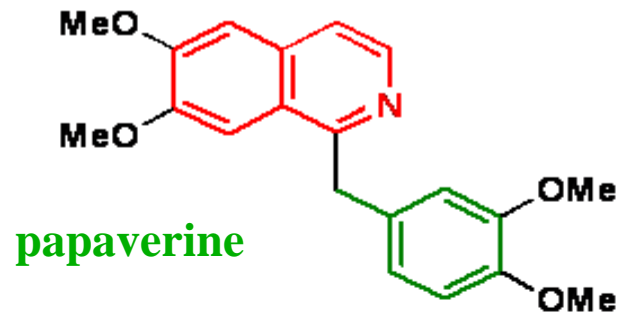


- **amaryllidaceae alkaloids**
- e.g. lycorine, galanthamine



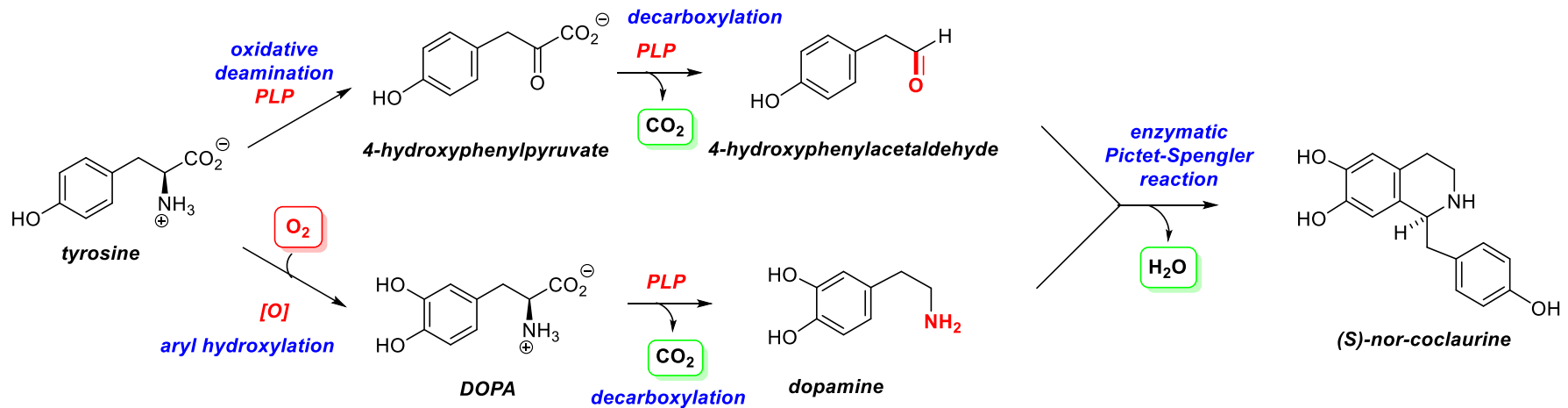
Benzyloquinoline Opium Alkaloids

Benzyloquinoline Alkaloids

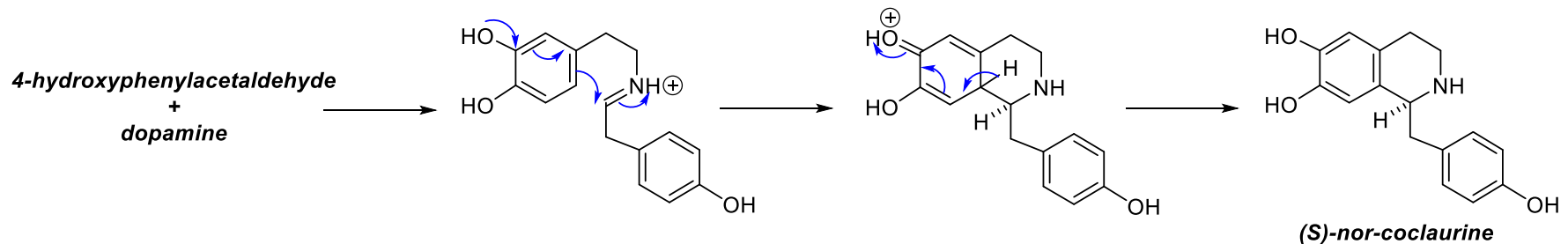


Benzylisoquinoline Alkaloids – *Ring Formation*

- **Benzylisoquinoline alkaloids** constitute an extremely large and varied group of alkaloids
 - many, particularly the *opium alkaloids* (e.g. papaverine, morphine) are **biosynthesised** from two molecules of tyrosine via ***nor-coclaurine*** (and then ***nor-laudanosoline***).

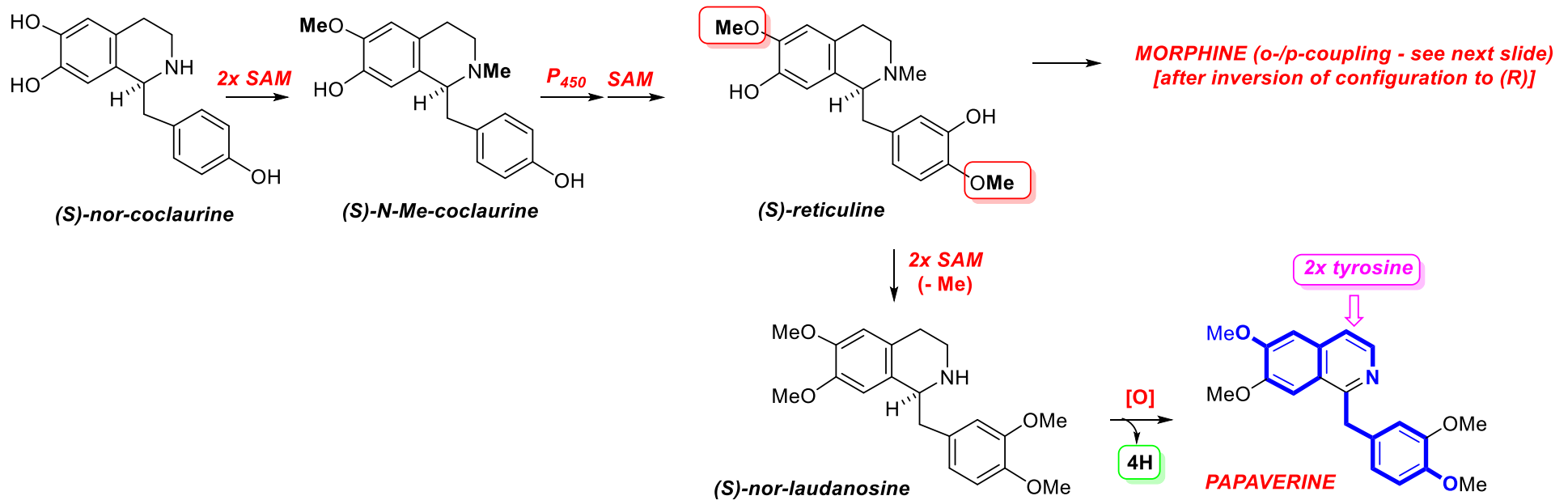


– Mechanism of Pictet Spengler reaction:



Benzylisoquinoline Alkaloids - *Papaverine*

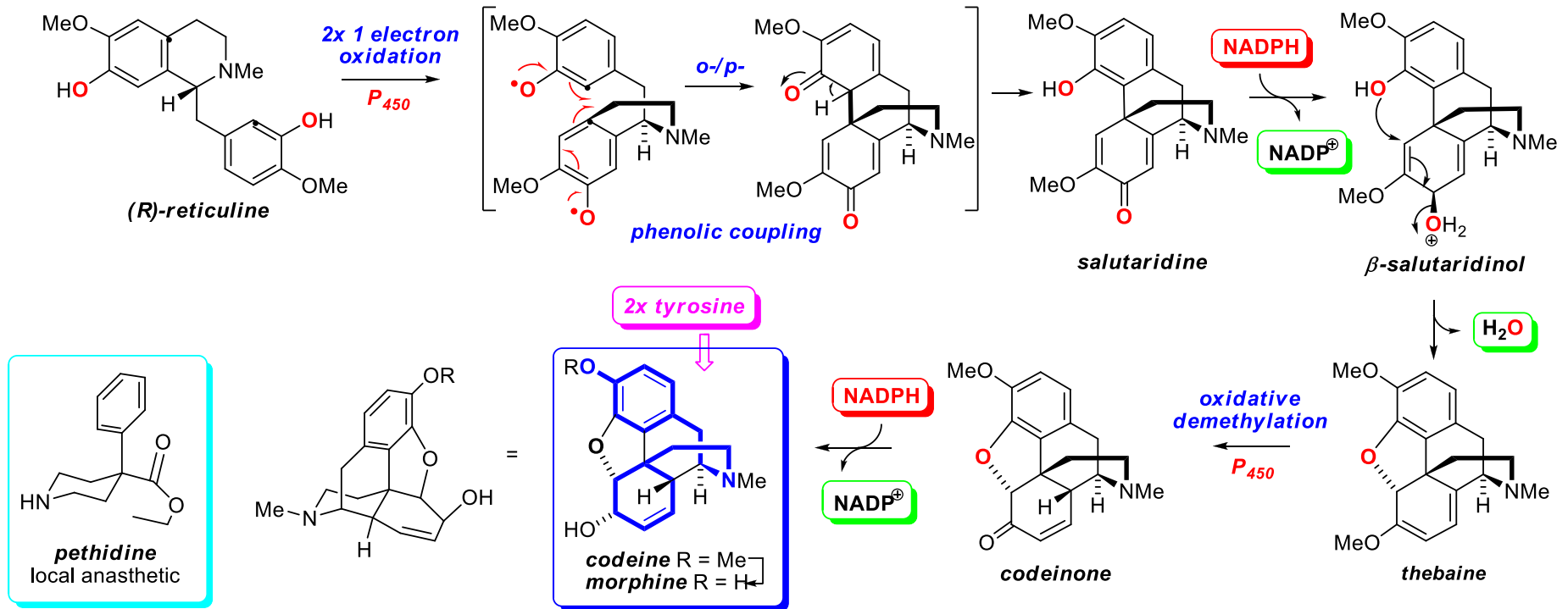
- ***Papaverine***: analgesic constituent of the **opium poppy** (*Papaver somniferum*):
 - **biosynthesis**:



- **NB.** The prefix **nor** means **without a methyl group**. Coclaurine, reticuline and laudanosine are the *N*-methyl compounds

Oxidative Phenolic Coupling – Morphine

- **Morphine:** analgesic & sedative constituent of the **opium poppy** (*Papaver somniferum*):
 - **biosynthesis:** *o*-/*p*- oxidative phenolic coupling of **reticuline**:



- Morphine acts by activating the **opiate receptors** in the brain (IC_{50} 3 nM)
- The natural ligands for these receptors are peptides: e.g. Leu-enkephalin (Tyr–Gly–Gly–Phe–Leu) (IC_{50} 12 nM)

Tryptophan Derived Alkaloids

- **Alkaloids containing an indole subunit:**

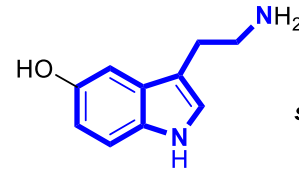
- Skeleta built up by **reductive amination, decarboxylation & hydroxylation**)

- **Major classes:**

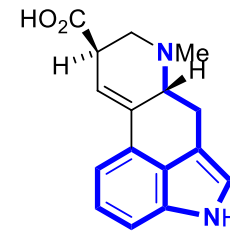
- **simple derivatives** (e.g. serotonin, bufotenine)

- **mixed Trp/mevalonate alkaloids** e.g.

- **ergot** [DMAPP derived] (e.g. ergoline, lysergic acid)



serotonin



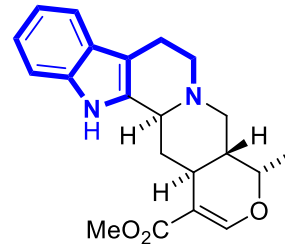
**lysergic acid
(ergot)**

- **vinca** [secologanin derived]

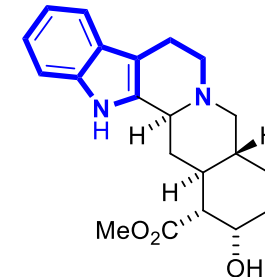
- **yohimbine** [secologanin derived]

- **strychnos** [secologanin derived]

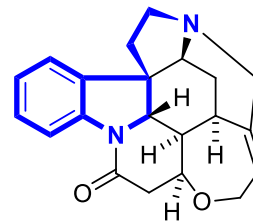
- **quinine** [secologanin derived]



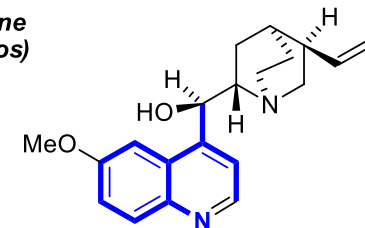
**ajmalicine
(vinca)**



yohimbine



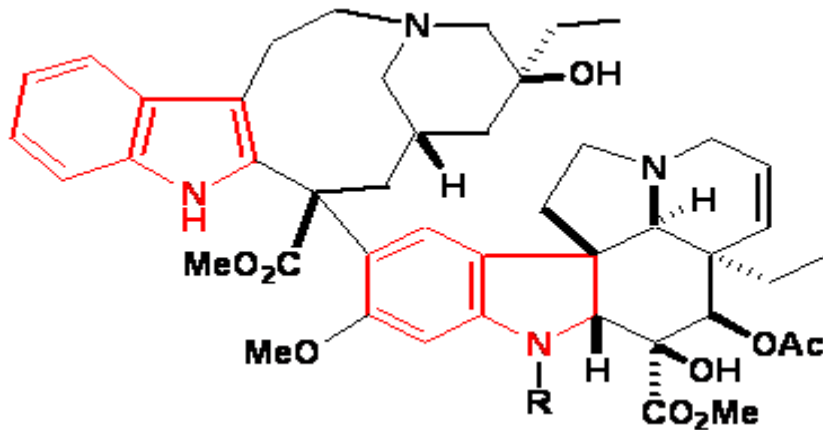
**strychnine
(strychnos)**



quinine

Dimeric Indole Alkaloids – *Vinca* extracts

Dimeric Indole Alkaloids



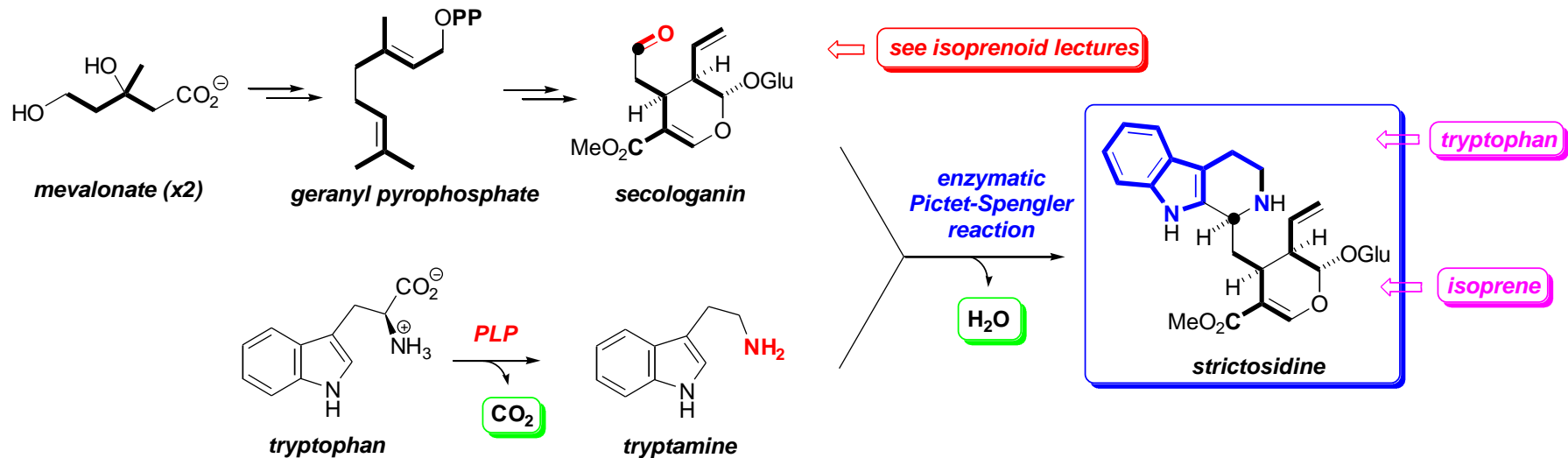
vinblastine (R = Me)
vincristine (R = CHO)



Potent **anti tumour** alkaloids used in **cancer chemotherapy**

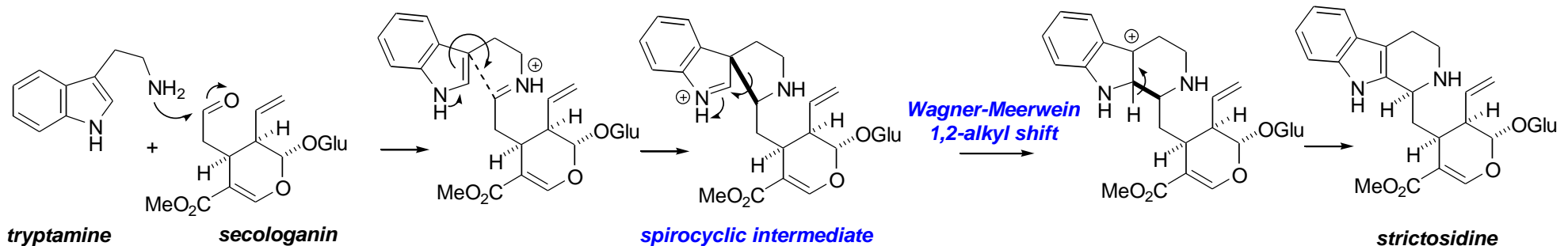
Tryptamine + Secologanin → Strictosidine

- Most alkaloids of **mixed Tryptophan/mevalonate biogenesis** (>1200) are derived from **strictosidine**:
 - Strictosidine** is derived from the condensation of **tryptamine** with the iridoid C₁₀ monoterpene **secologanin**:



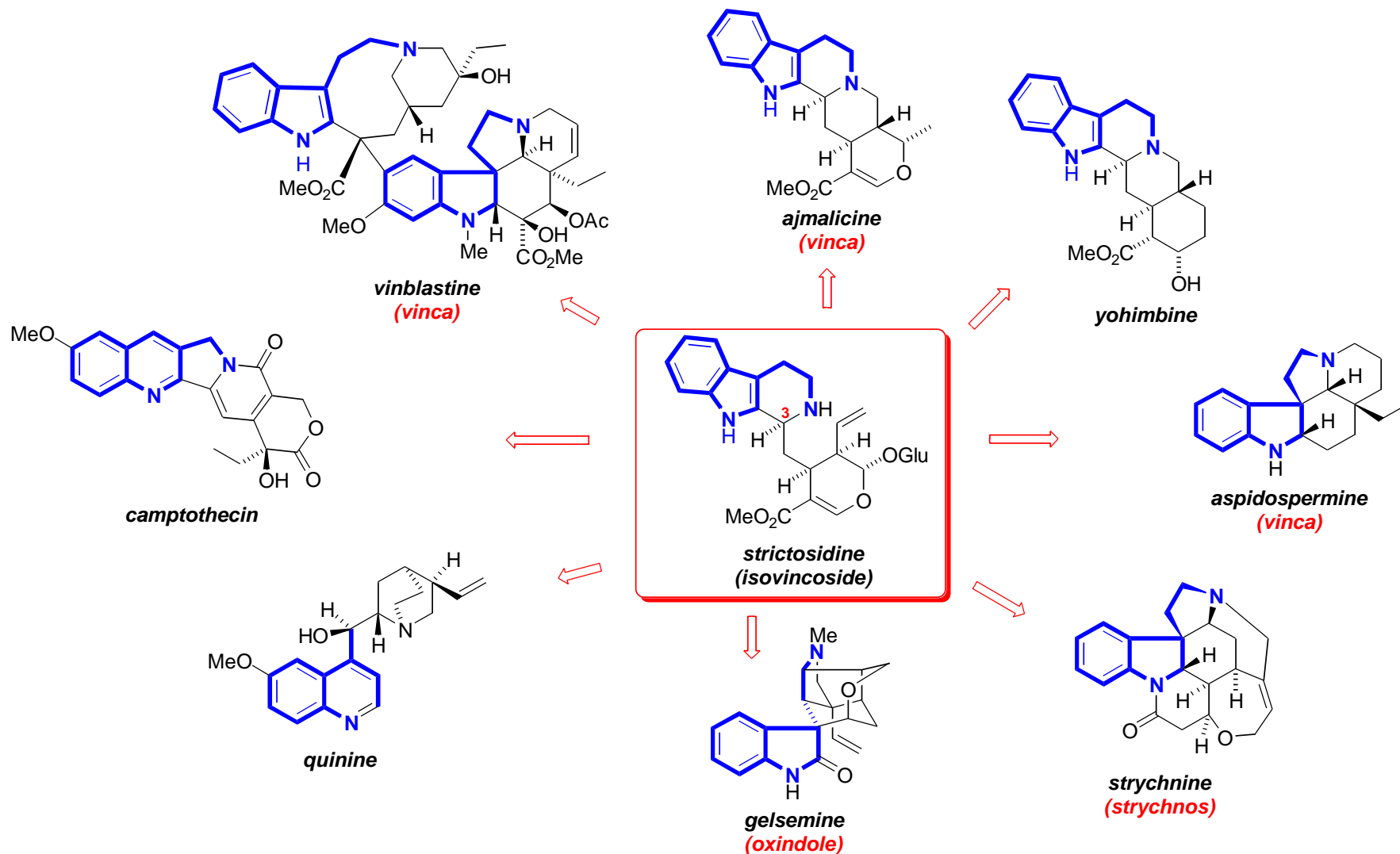
Mechanism of Pictet-Spengler reaction:

- via **spirocyclic** intermediate then **Wagner-Meerwein 1,2-alkyl shift**:



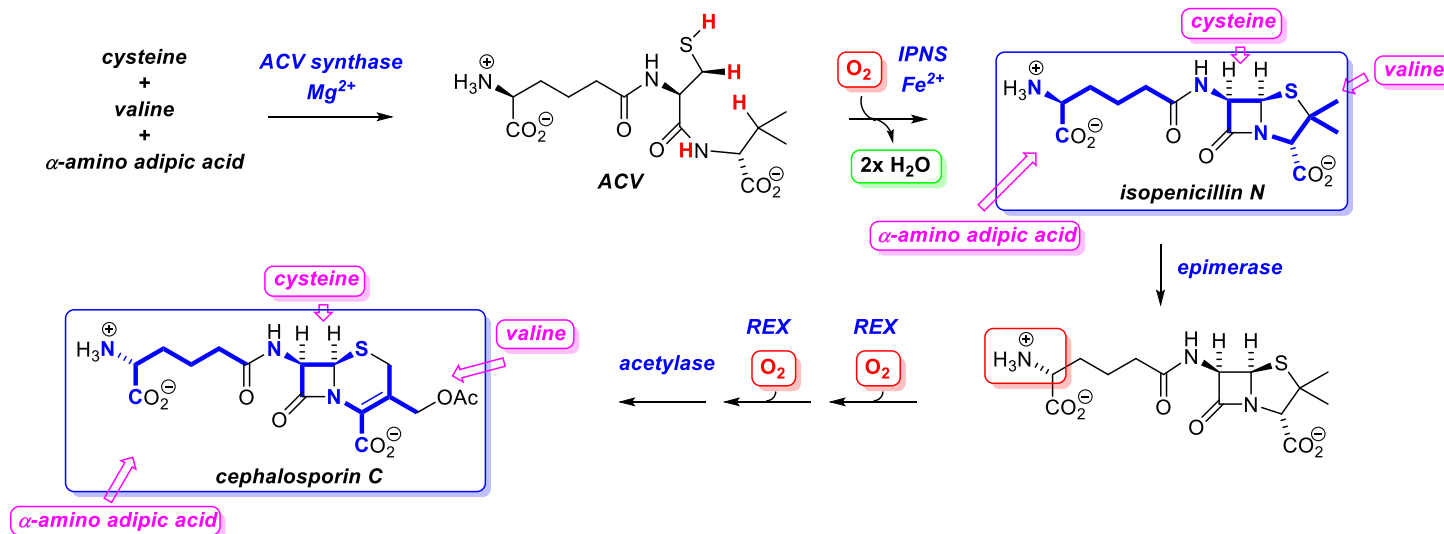
Strictosidine → *Vinca*, *Strychnos*, *Quinine* etc.

- The diversity of alkaloids derived from **strictosidine** is stunning and many pathways remain to be fully elucidated:

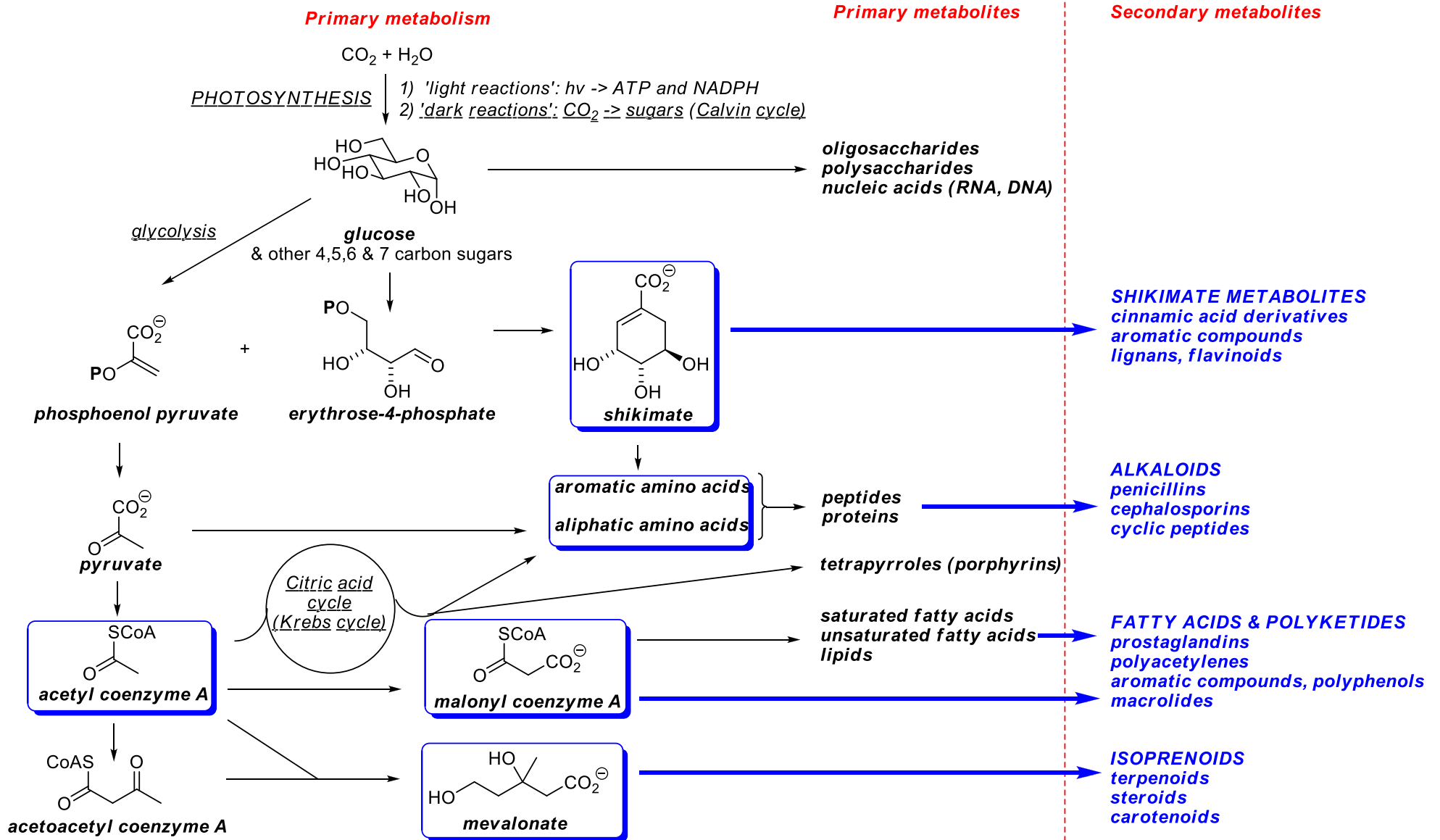


Penicillins & Cephalosporins

- Famous story of the antibiotic penicillin:
 - **discovery** by bacteriologist **Alexander Fleming** at St Mary's Hospital, London (published in **1929**)
 - **isolation & development** by **Howard Florey & Ernst Chain** at the Dunn School of Pathology Oxford University (**1939-1945**)
 - E. Lax 'The mould in Dr Florey's coat' Little Brown & Co., **2004**, [ISBN 0316859257]
 - **biosynthesis** extensively studied by Baldwin:
 - Baldwin *J. Het. Chem.* **1990**, 27, 71 & Baldwin *et al. Nature* **1995**, 375, 700



Primary Metabolism - Overview



For interesting animations' of e.g. photosynthesis see: <http://www.johnkyrk.com/index.html>