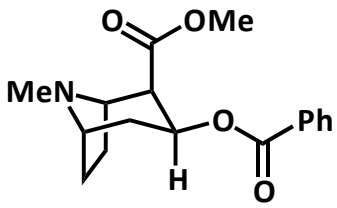
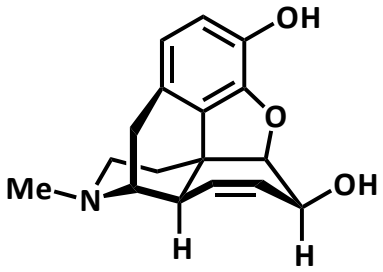
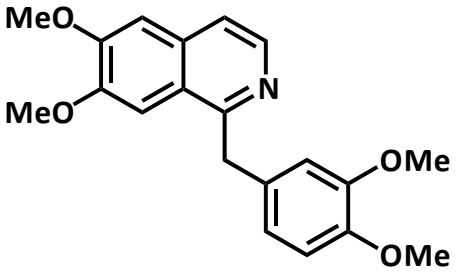
Natural Product Chemistry II
Four Lectures







Synopsis: Recap of pyridoxal phosphate and biosynthesis of some amino acids; lysine and ornithine in biosynthesis of pyrrolidine and piperidine alkaloids; alkaloids derived from phenylalanine and tyrosine; benzylisoquinoline alkaloids; phenol oxidation in the biosynthesis of complex alkaloids; classic examples of biomimetic synthesis

- Chemical Aspects of Biosynthesis, Oxford Chemistry Primer no. 20, John Mann
- The Organic Chemistry of Biological Pathways, John McMurry, Tadhg Begley
- Organic Chemistry, Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers, 1st Edition, Chapters 49, 50 and 51
- Medicinal Natural Products – A Biosynthetic Approach, 2nd Edition, Paul Dewick
- Biomimetic Organic Synthesis, Vols 1 & 2, Eds Erwan Poupon and Bastien Nay

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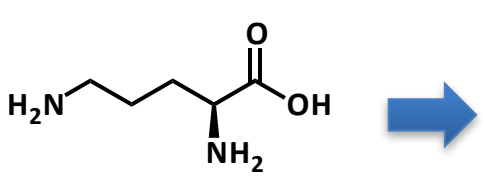
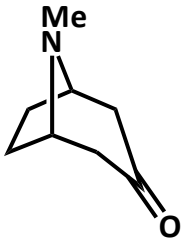
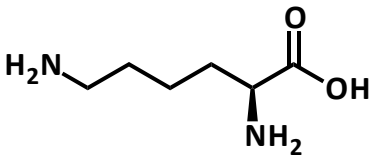
- Alkaloids
- Nitrogen containing secondary metabolites – non-peptidic – non-nucleoside
- Named by Meissner as they were 'like alkali'
- Mostly derived from α-amino acids
- ornithine and lysine - aliphatic alkaloids
- phenyl alanine and tyrosine – aromatic alkaloids and aromatic compounds in general
- tryptophan – indole alkaloids



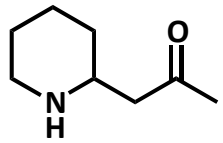
ornithine



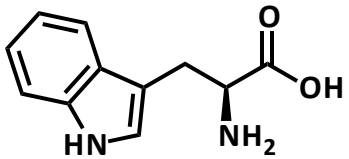
tropinone



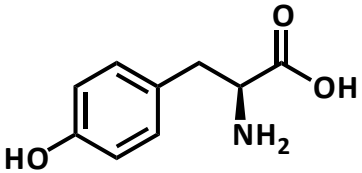
lysine - Lys - K



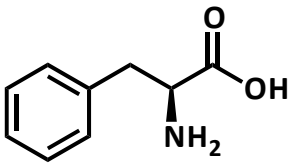
pelletierine



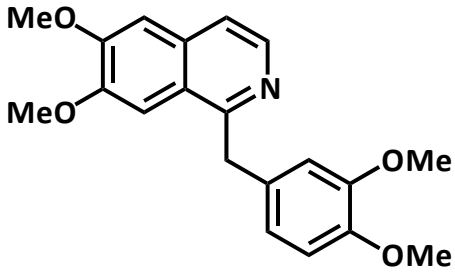
tryptophan - Trp - W



tyrosine - Tyr - Y

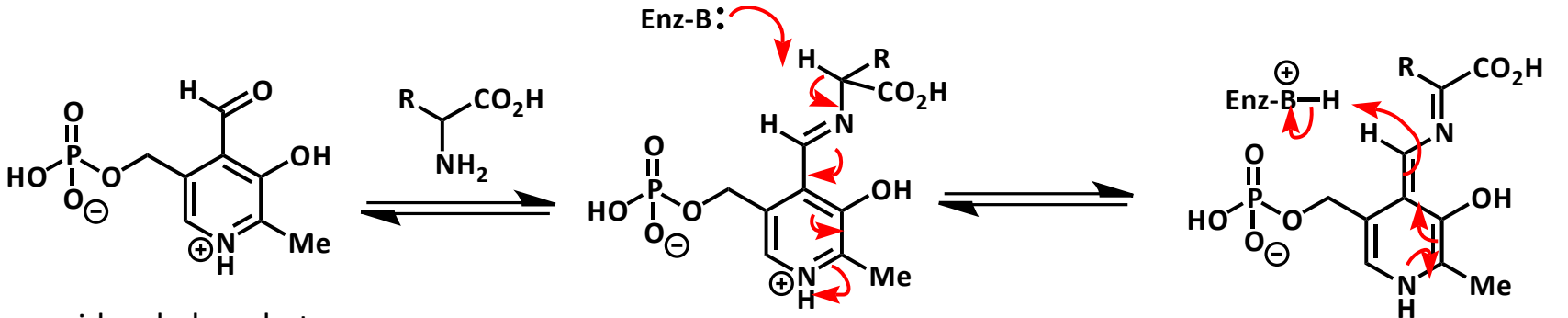


phenyl alanine - Phe - F

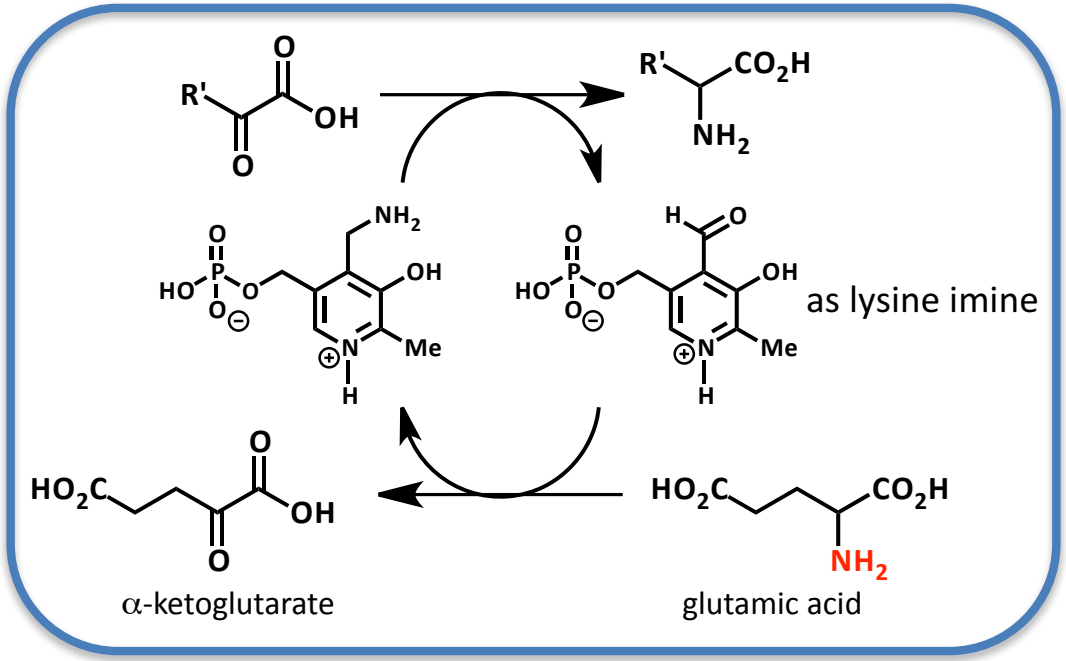


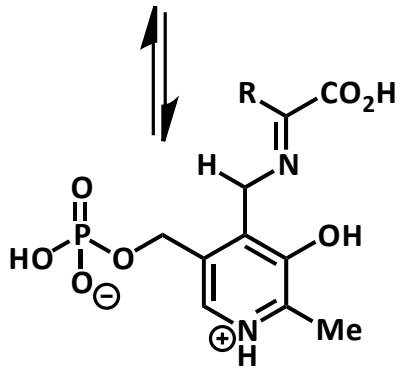
papaverine

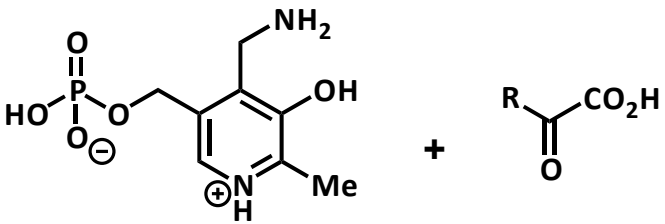
- Biosynthesis of amino acids – amine transfer using pyridoxamine / pyridoxal phosphate and an aminotransferase



pyridoxal phosphate



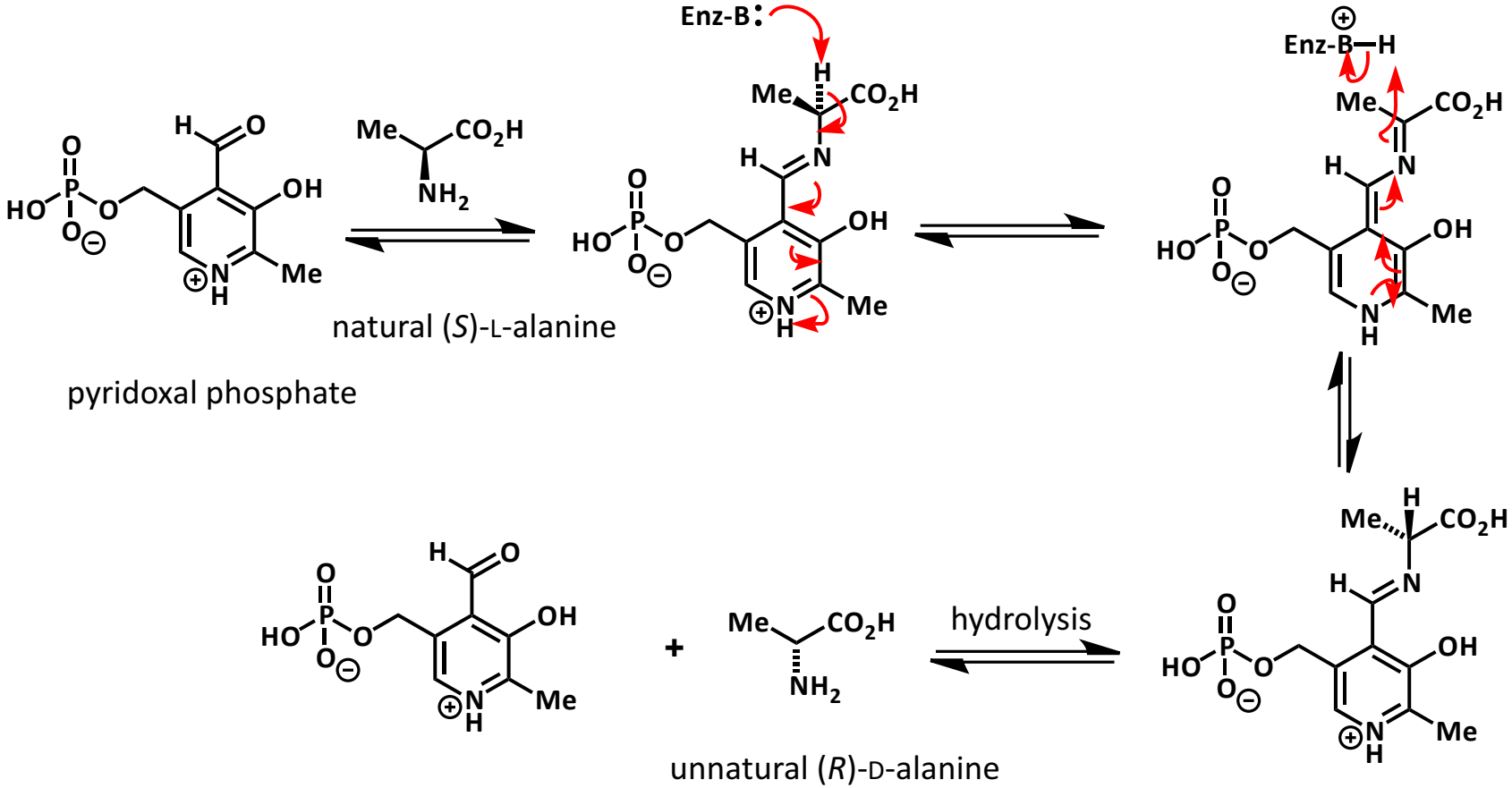




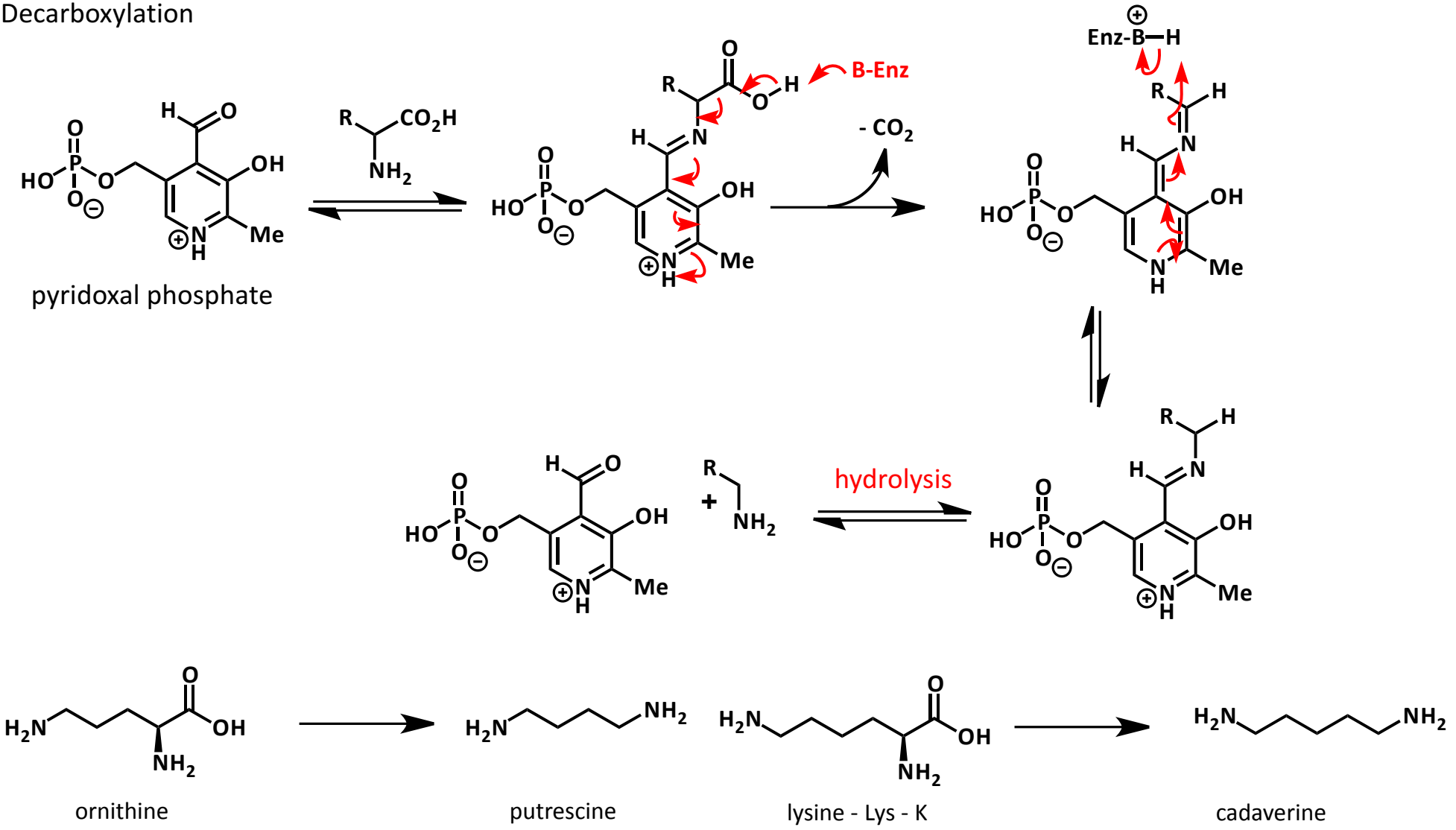
pyridoxamine phosphate

- Overall transamination
- Glutamate acts as nitrogen source –
nitrogen initially introduced by reductive amination of α-ketoglutarate
- Pyridoxal phosphate carried around as the lysine imine

- Pyridoxal phosphate mediates a number of other transformations including racemisation and decarboxylation



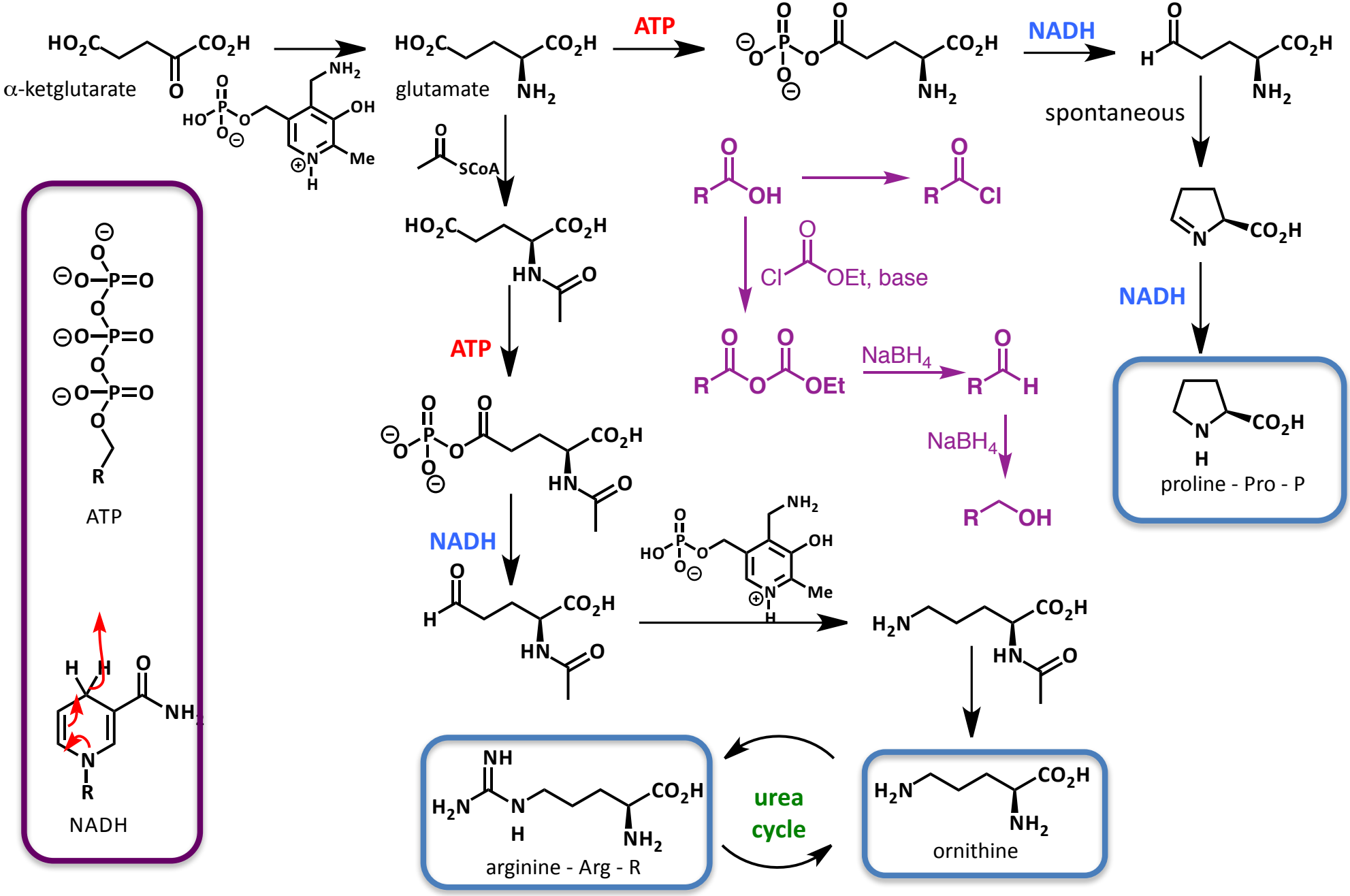
- Decarboxylation



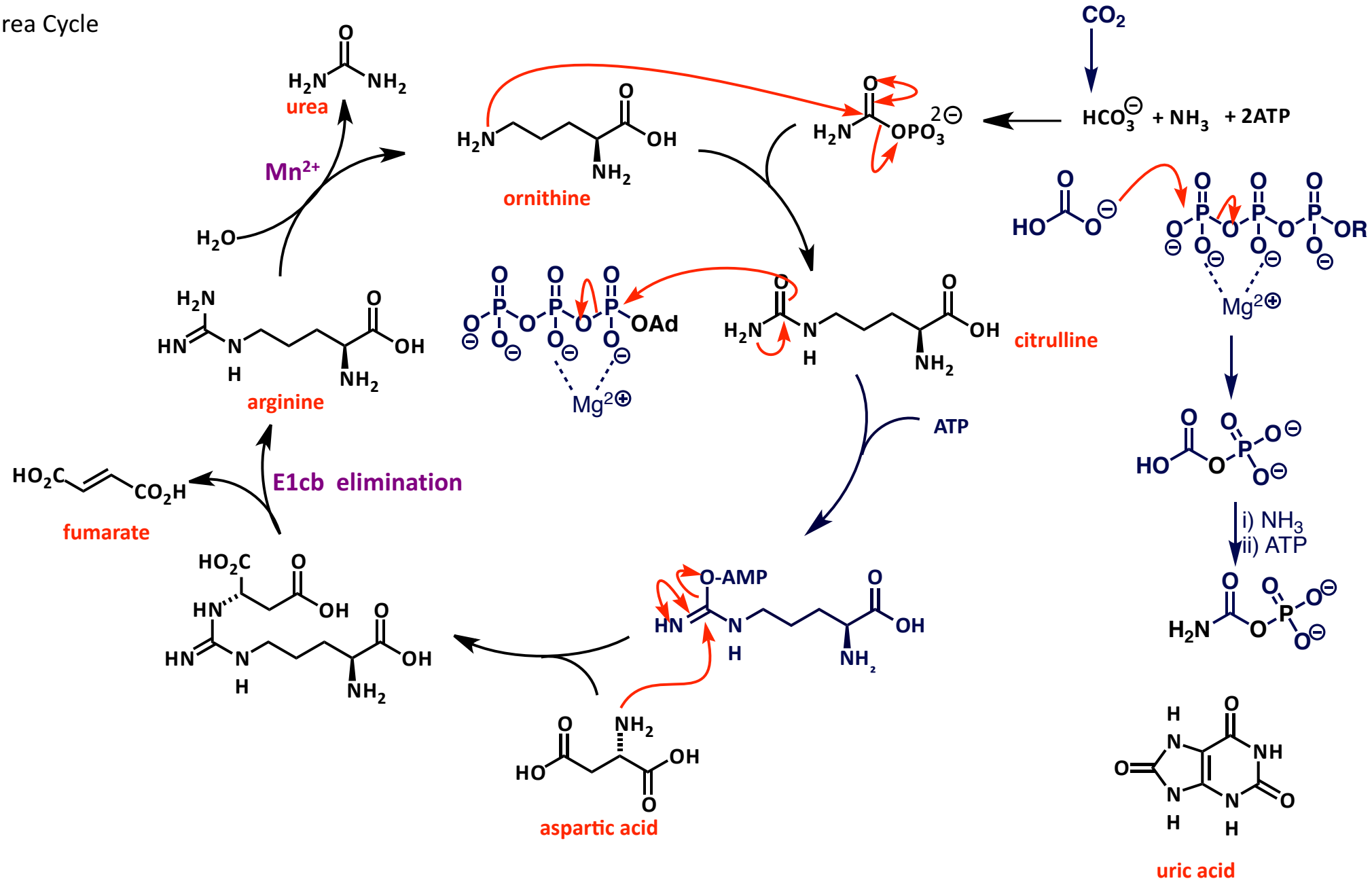
- As their names suggest, putrescine and cadaverine smell of rotting flesh

- Other reactions mediated by pyridoxal phosphate include C-C bond formation, substitution at the β-position of α-amino acids, internal redox reactions between C_α and C_β and between C_α and C_γ, oxidation of a primary amine

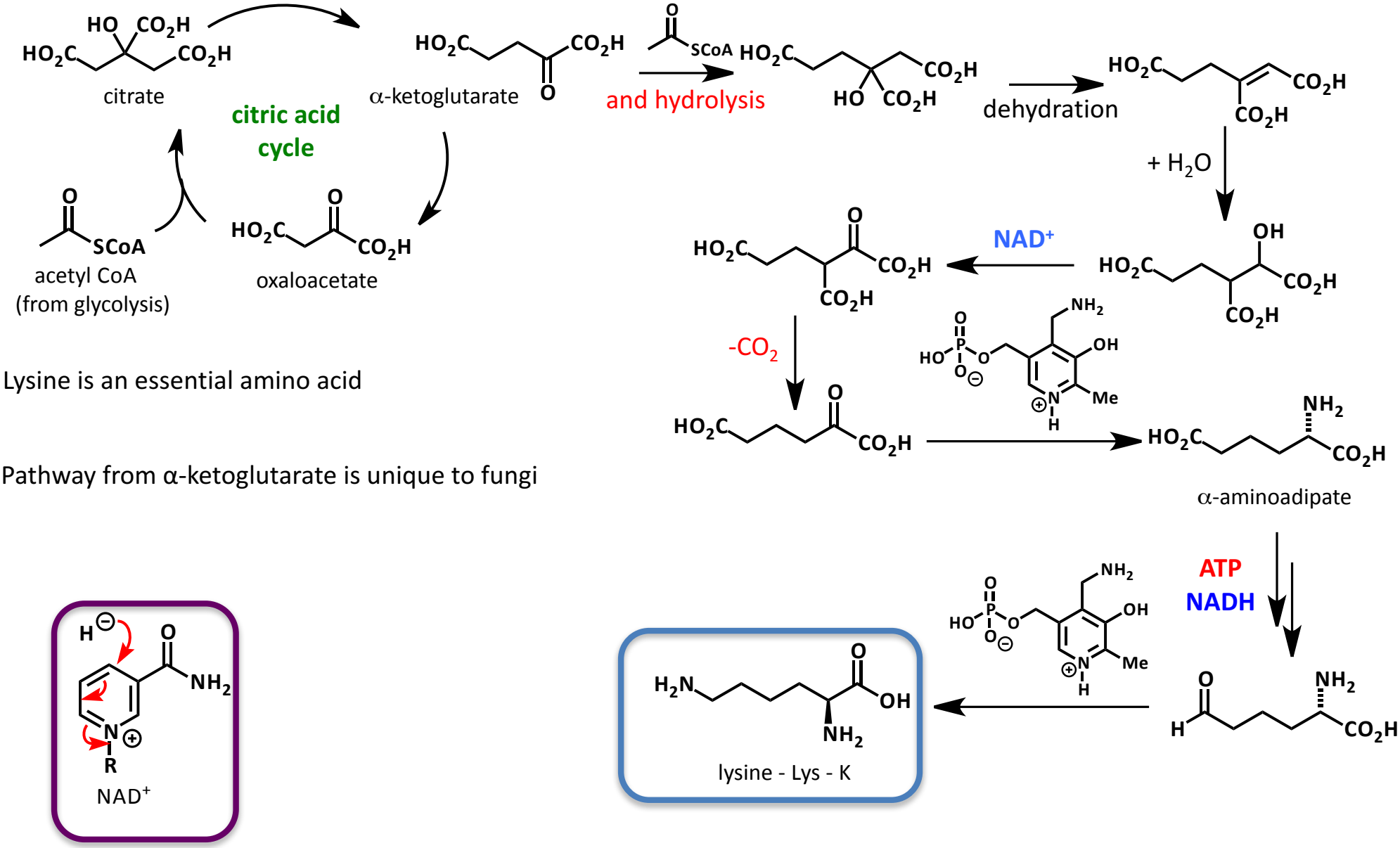
Biosynthesis of some amino acids



Urea Cycle


urea
Mn2+
H2O
ornithine
CO2
HCO3⊖ + NH3 + 2ATP
citrulline
Mg2+
OAd
arginine
ATP
E1cb elimination
fumarate
O-AMP
i) NH3
ii) ATP
aspartic acid
uric acid

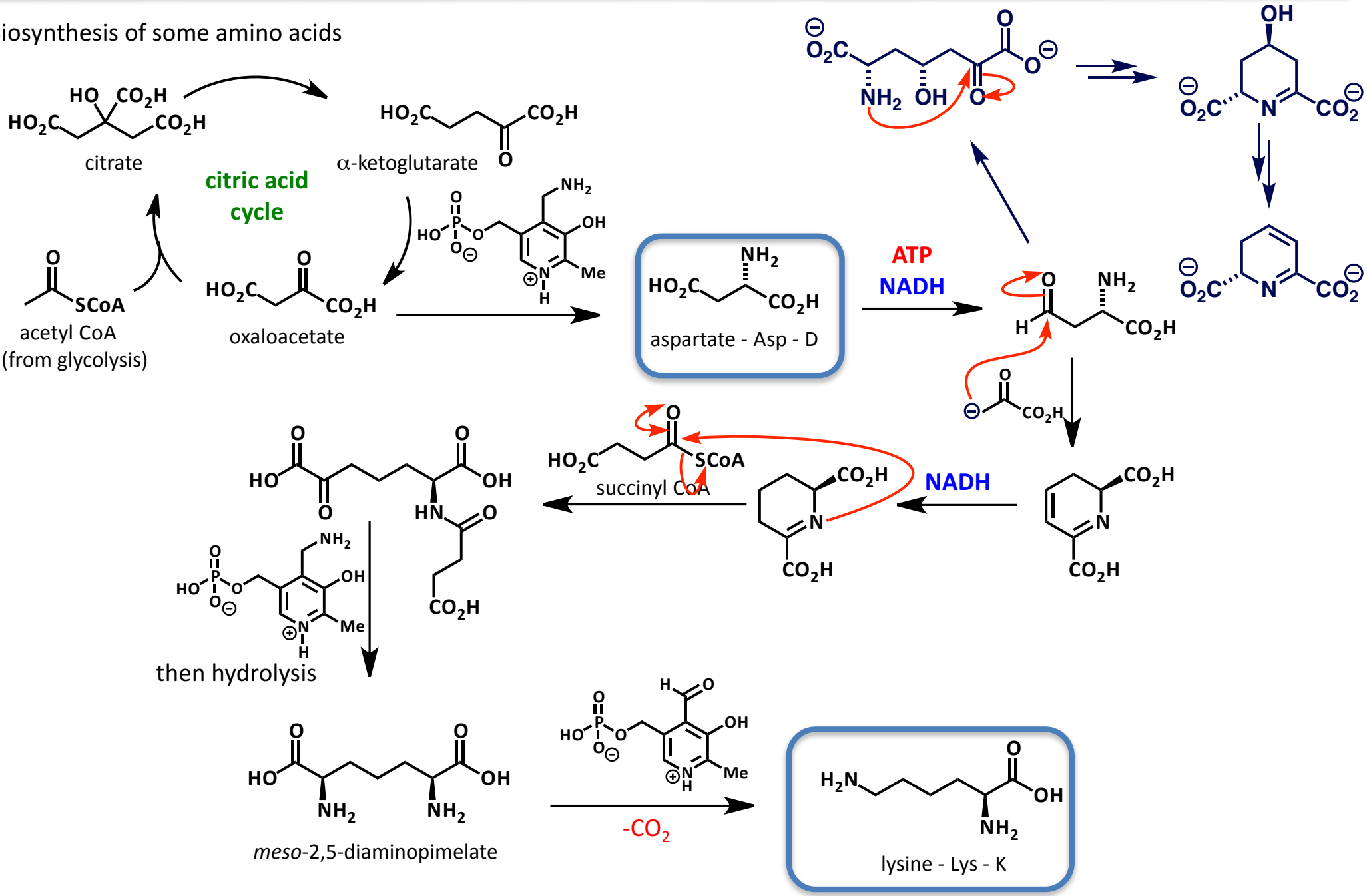
- Biosynthesis of some amino acids



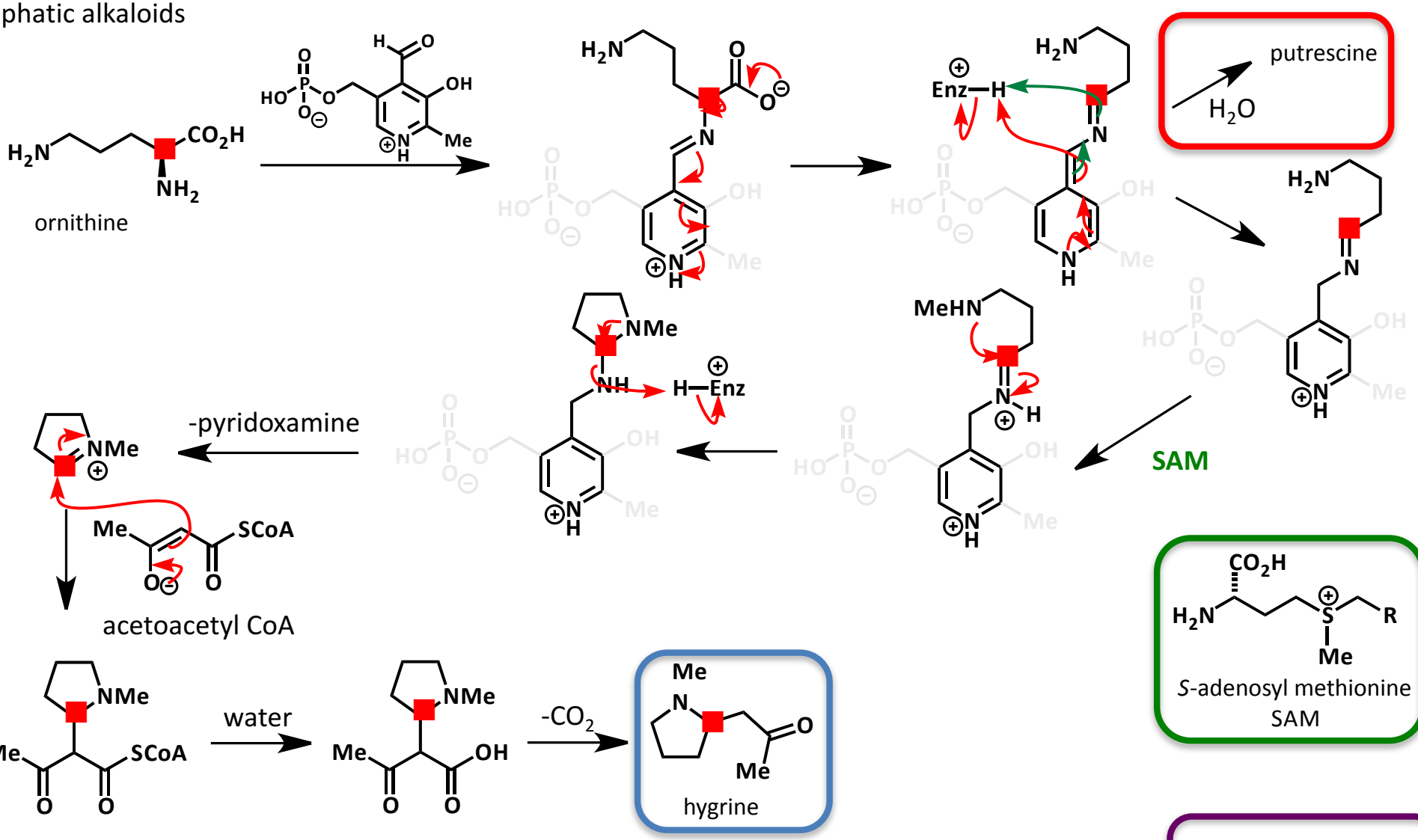
- Lysine is an essential amino acid

- Pathway from α-ketoglutarate is unique to fungi

Biosynthesis of some amino acids

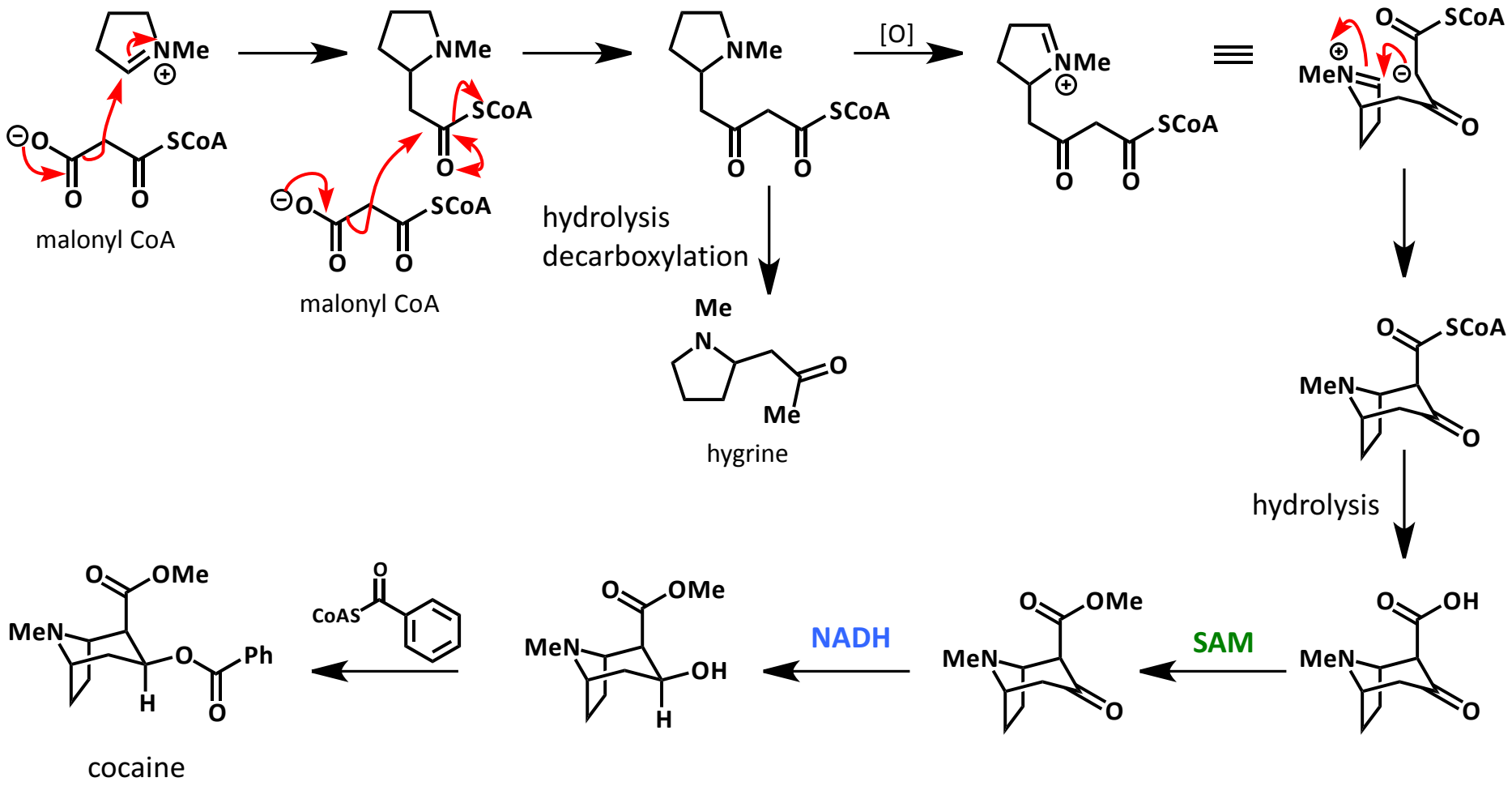


- Aliphatic alkaloids

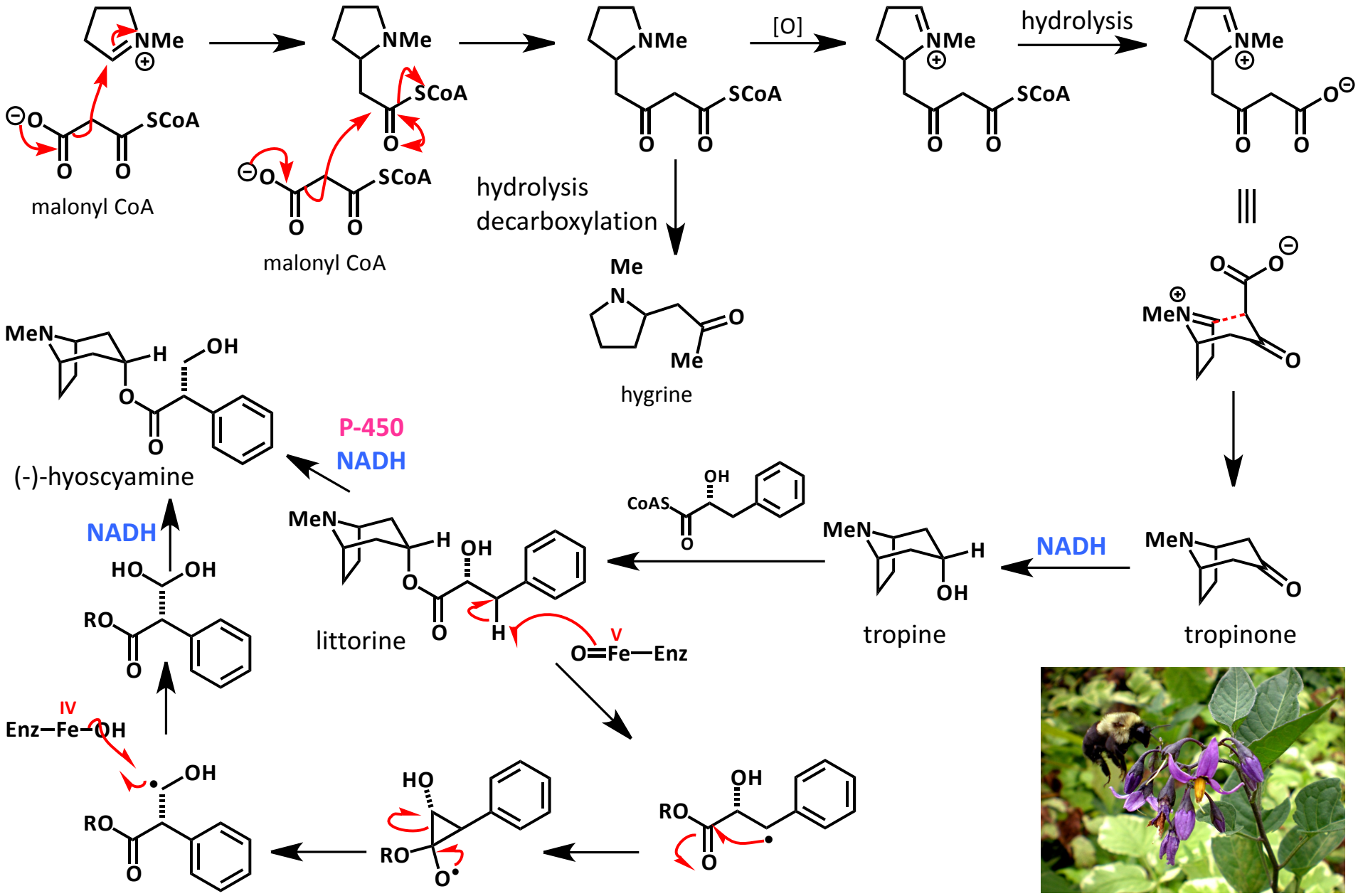


- Also possible is methylation of the cyclic imine formed after release of pyridoxamine
- In this example the reaction does not proceed by way of symmetrical putrescine
- However, symmetrical putrescine is an intermediate in some **plants** (but not others)

Aliphatic alkaloids

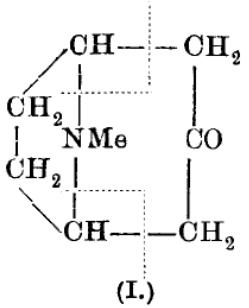


Aliphatic alkaloids – tropinone and tropine

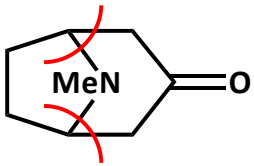


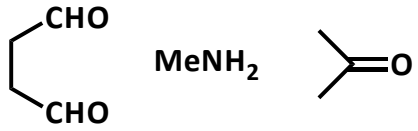
- Robinson's synthesis of tropinone – R. Robinson, *J. Chem. Soc.*, **1917**, 762.

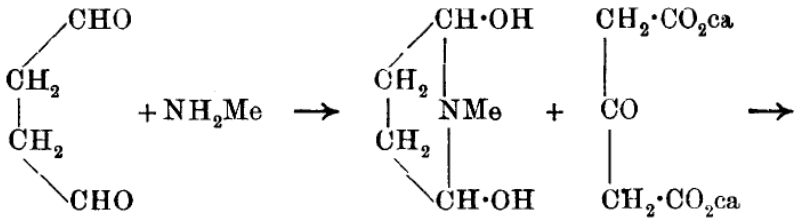
Nevertheless, an inspection of the formula of tropinone (I) discloses a degree of symmetry and an architecture which justify the hope that the base may ultimately be obtained in good yield as the product of some simple reaction and from accessible materials. By imaginary hydrolysis at the points indicated by the dotted lines, the substance may be resolved into succindialdehyde, methylamine, and acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis.

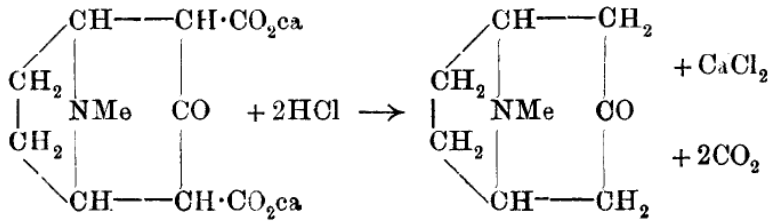


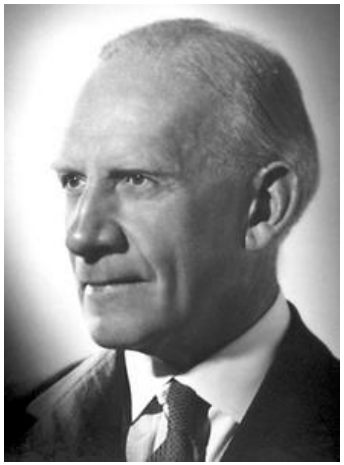
(I.)



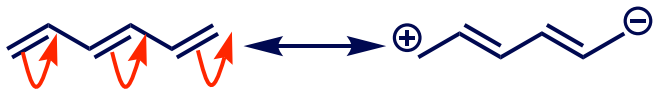




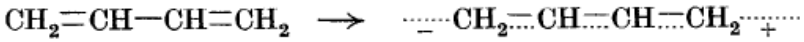




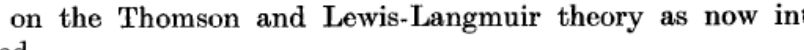
- Sir Robert Robinson (1886-1975)
- Waynflete Professor of Organic Chemistry 1930-1954
- Nobel Prize 1947 for "investigations on plant products of biological importance, especially the alkaloids"
- Inventor of the 'curly arrow'



(*a*) *Conjugation of Ethylene Linkings.*—The representation of the active phase and conjugation of butadiene on the partial valency theory is



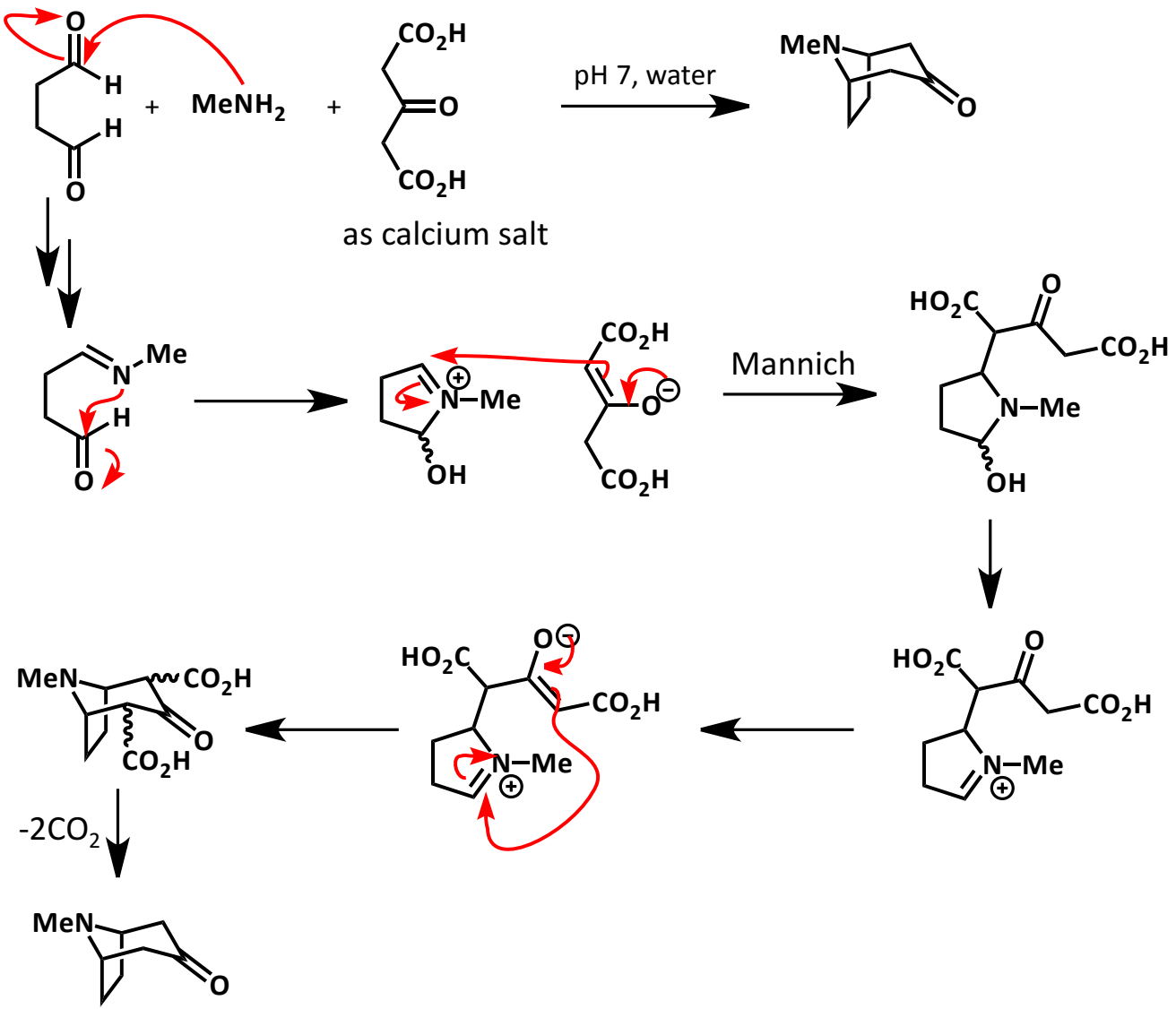
and on the Thomson and Lewis-Langmuir theory as now interpreted



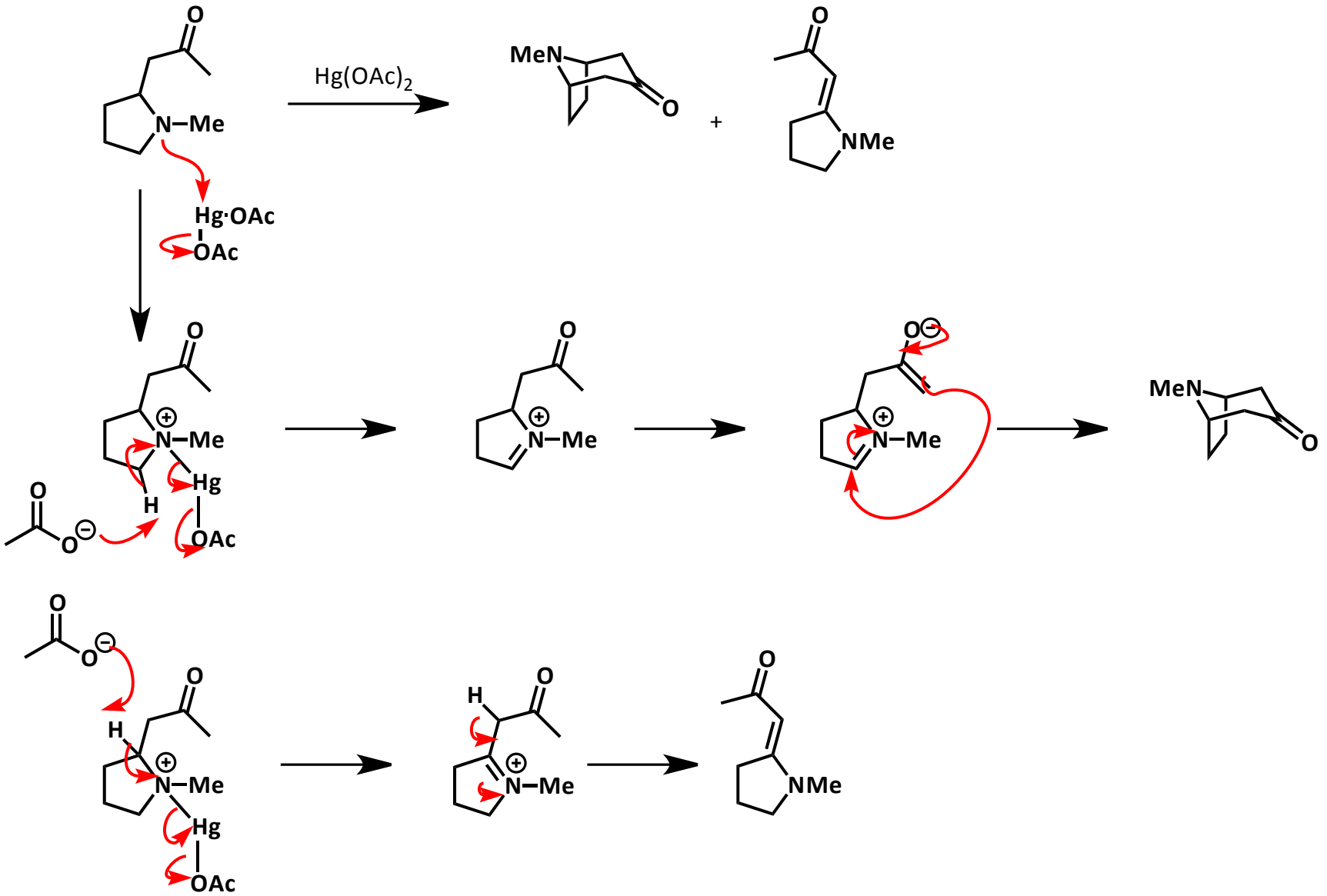
Similarly, the conjugation of three double bonds, supposing such to occur, would be represented thus :—

J. Chem. Soc, **1922**, *121*, 427.

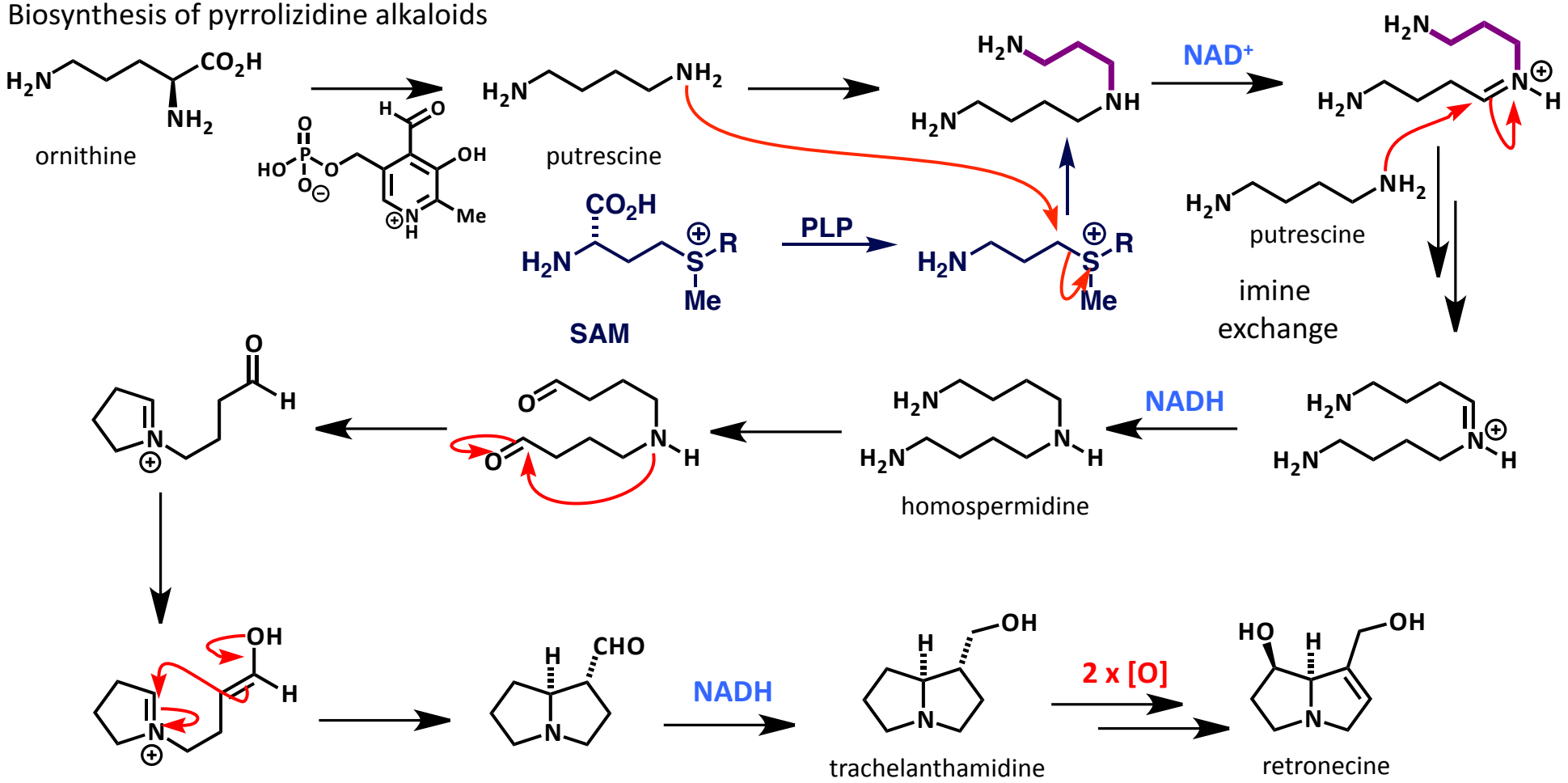
- Robinson's biomimetic synthesis of tropinone – R. Robinson, *J. Chem. Soc.*, **1917**, 762.



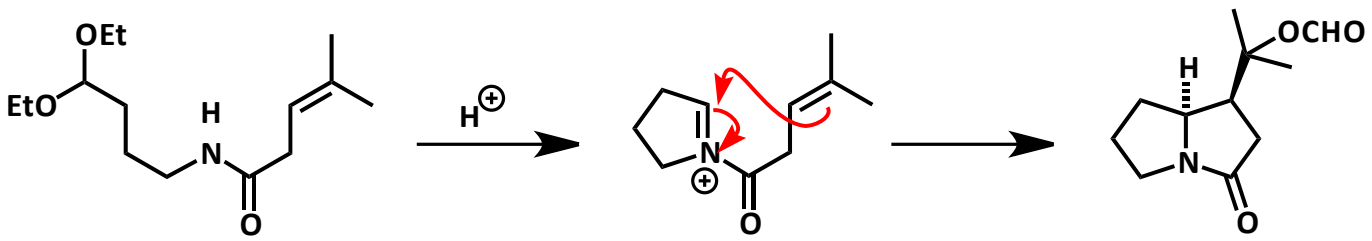
- Biomimetic synthesis of tropinone by pyrrolidine oxidation: E. Leete, S. H. Kim, *J. Chem. Soc., Chem. Commun*. **1989**, 1899.



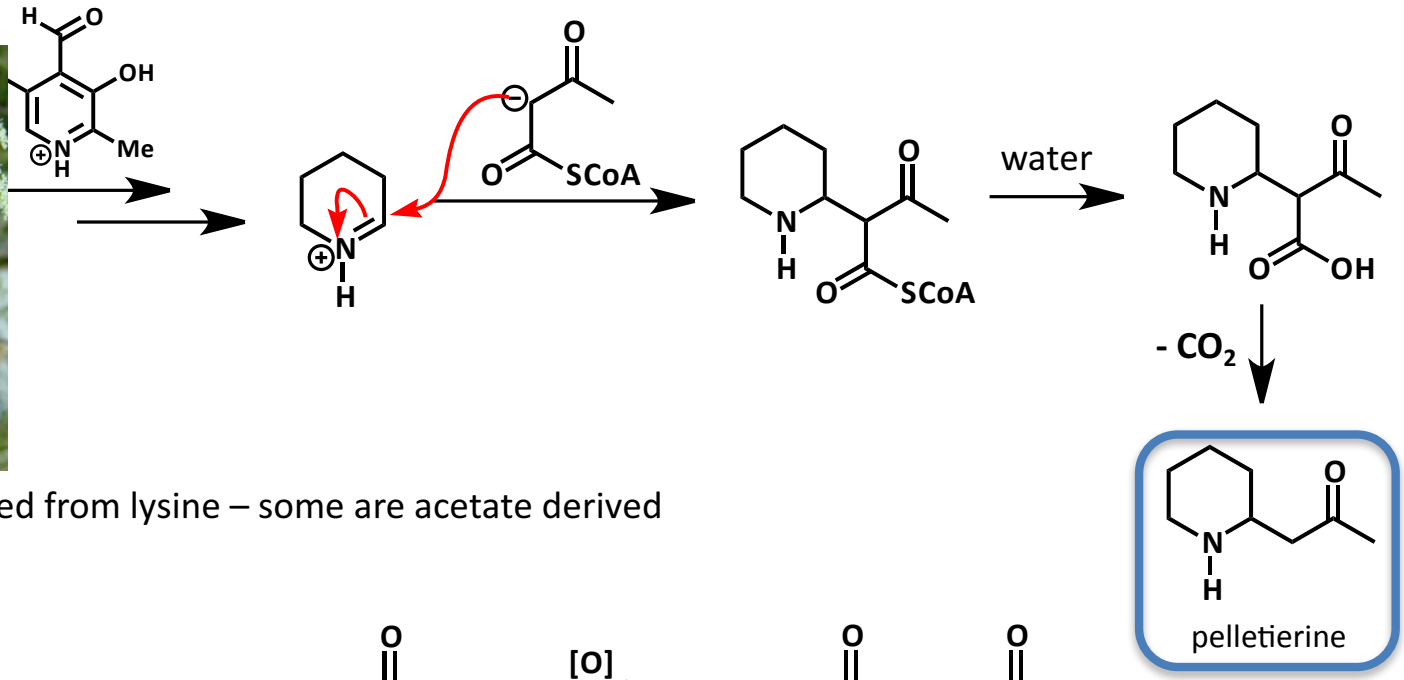
Biosynthesis of pyrrolizidine alkaloids



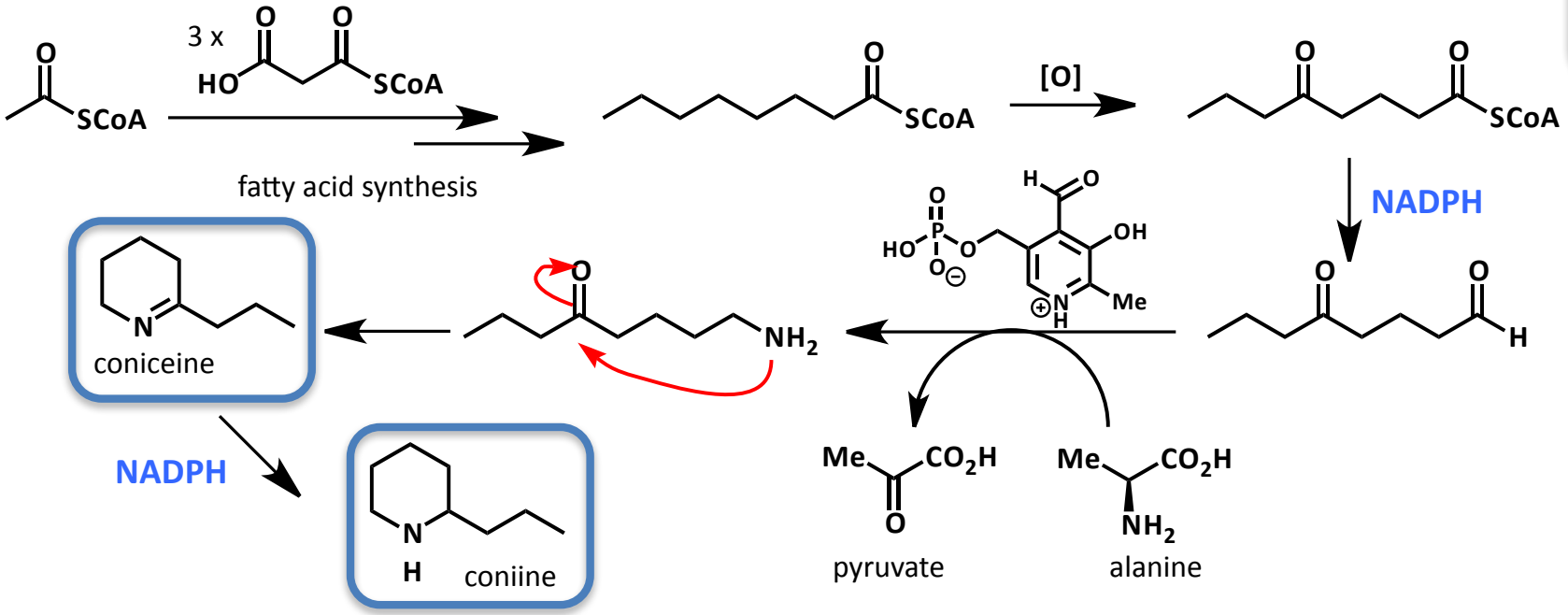
Biomimetic synthesis of pyrrolizidine alkaloids



- Biosynthesis of piperidine alkaloids
- In a similar manner to ornithine, lysine gives rise to piperidine alkaloids



- Not all piperidine alkaloids are derived from lysine – some are acetate derived

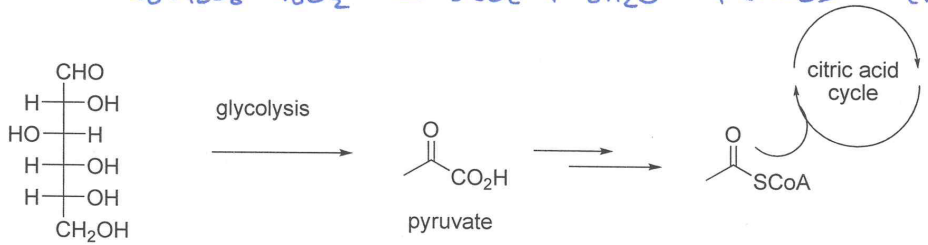


Glycolysis

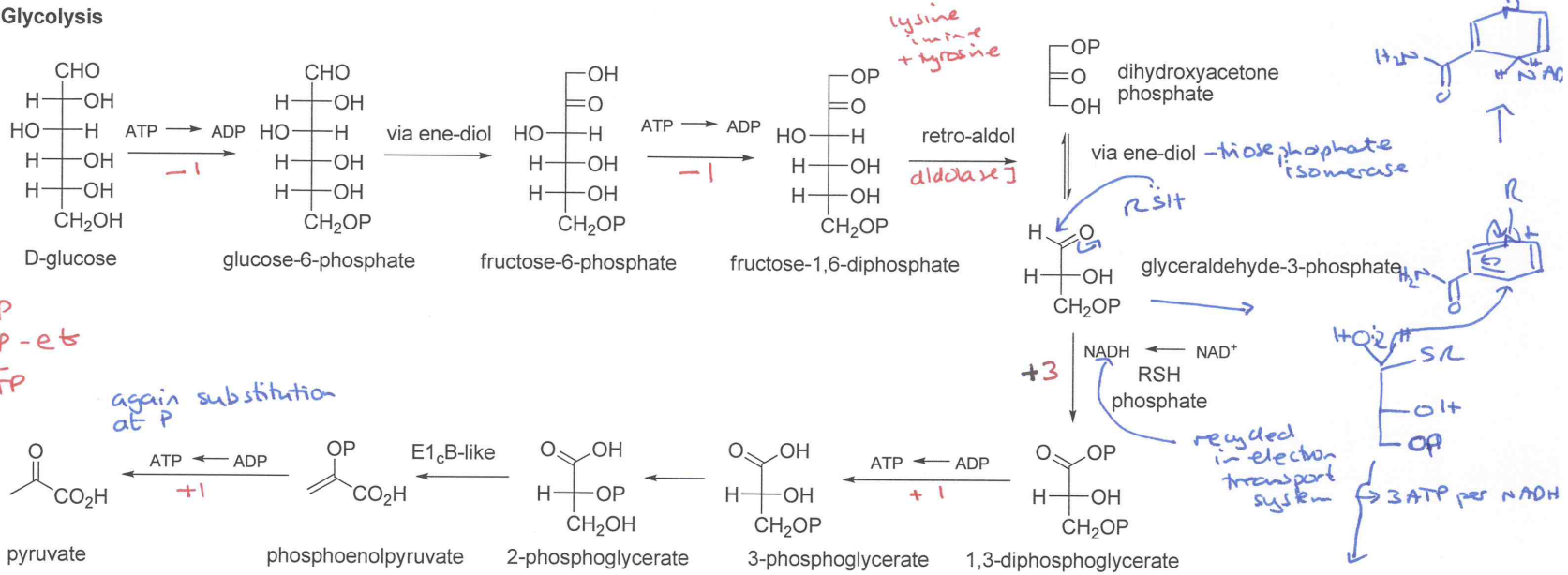
$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + energy (36 ATP)

● = ATP

overview

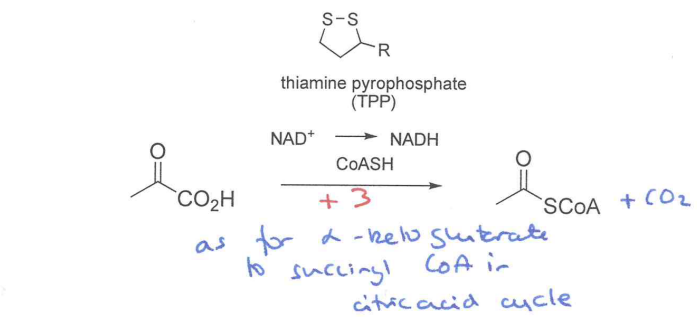


Glycolysis

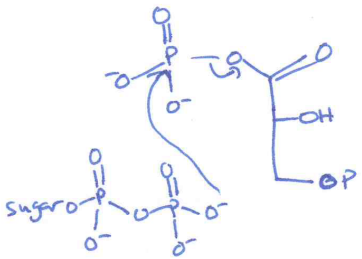


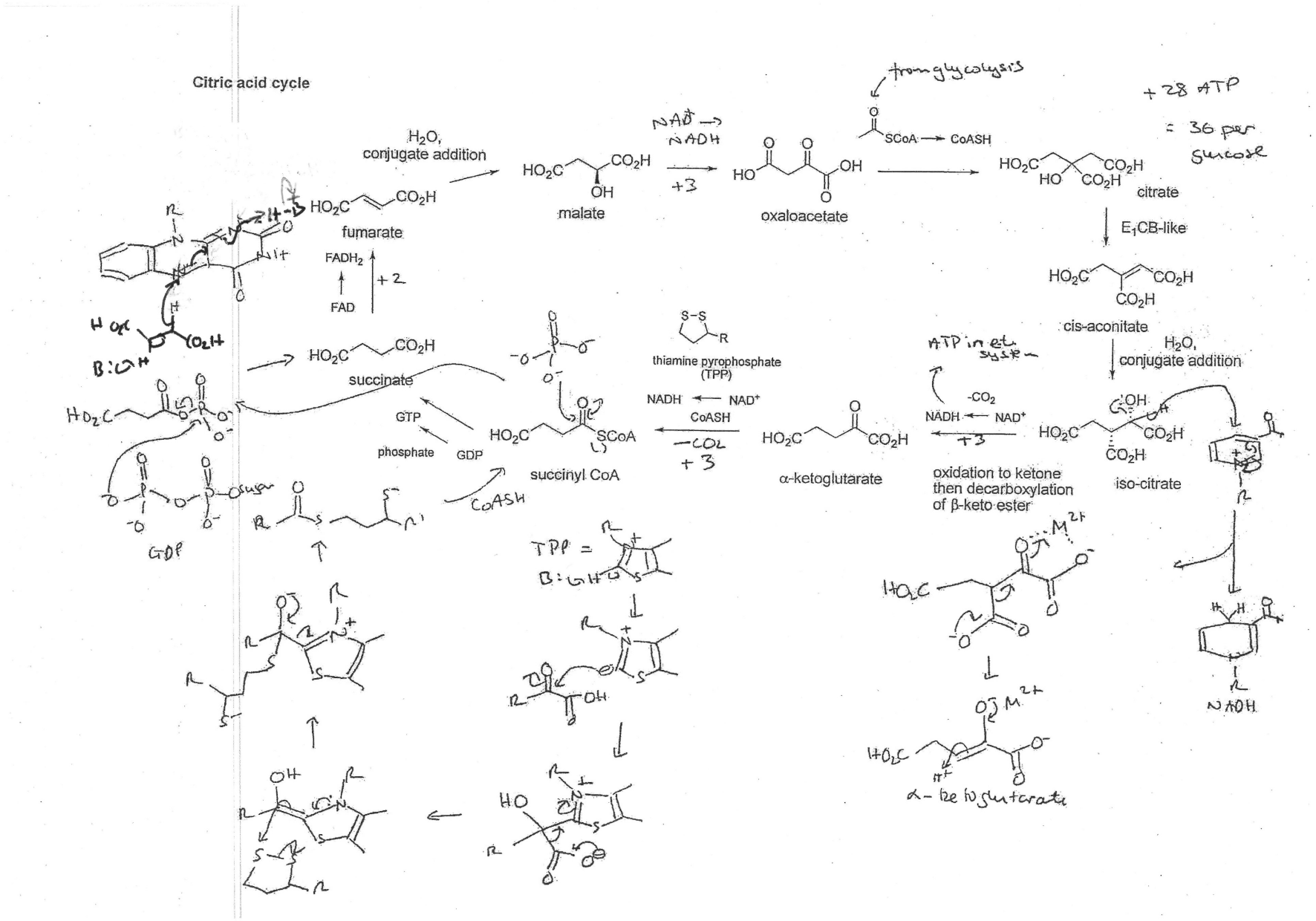
+ 2 ATP
+ 6 ATP - et
8 ATP

again substitution at P

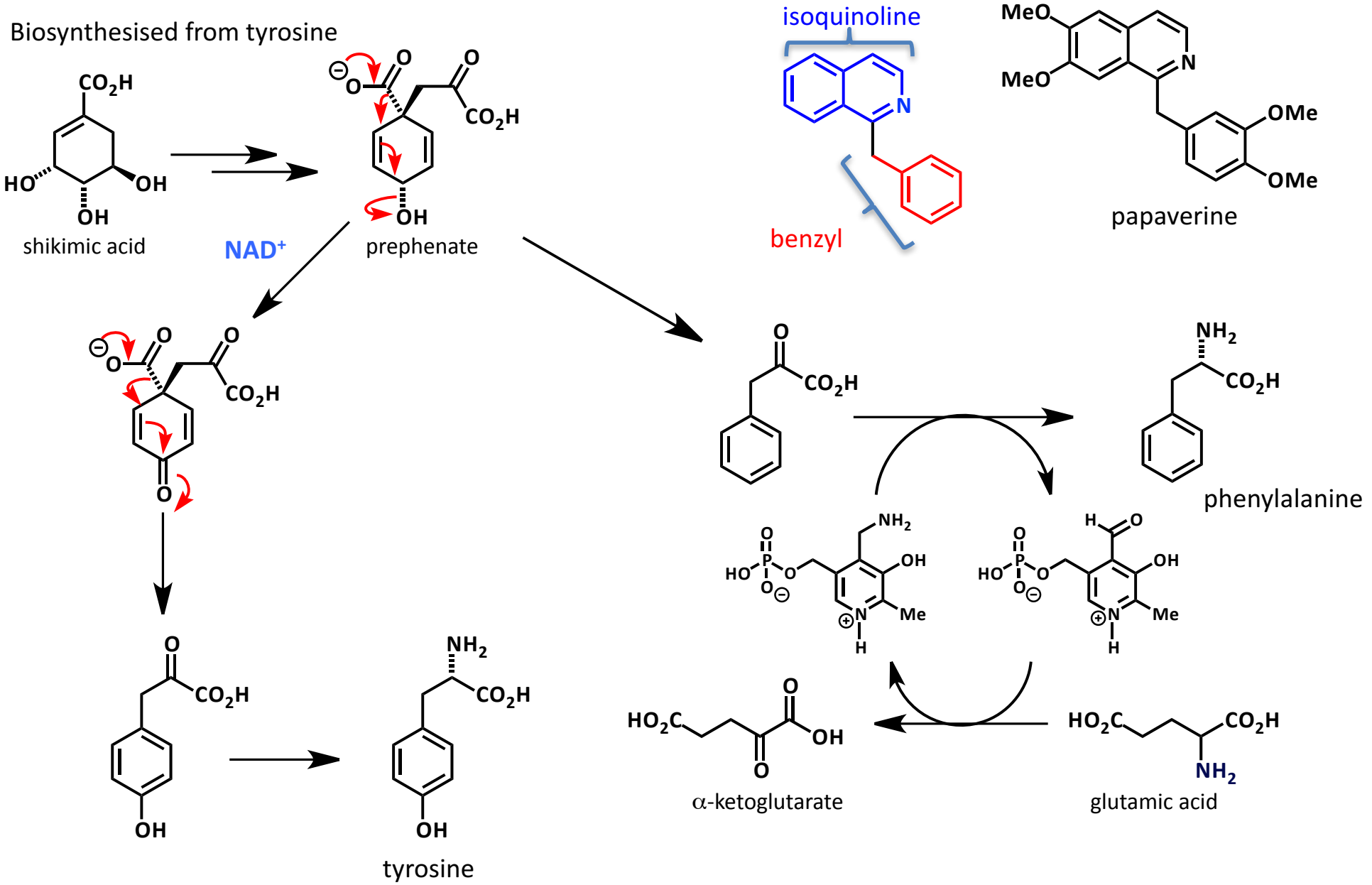


as for α-keto glutarate to succinyl CoA in citric acid cycle

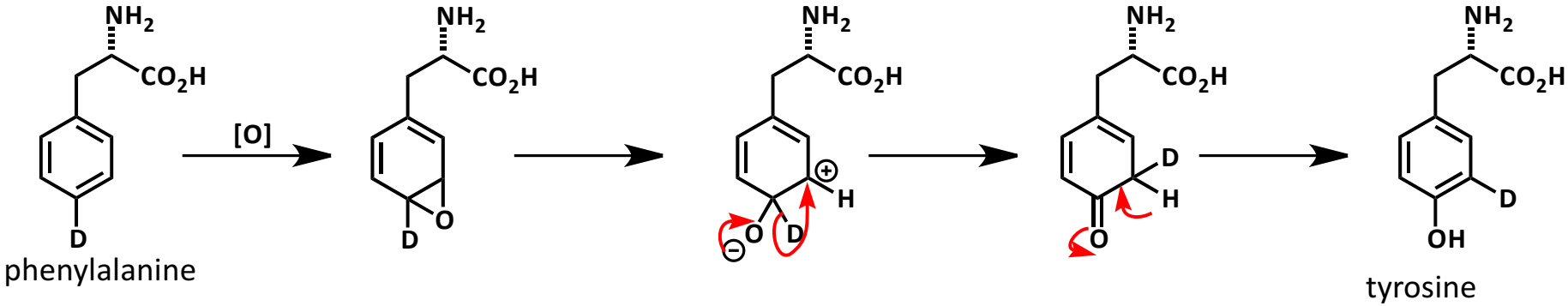



Citric acid cycle
H_2O, conjugate addition
fumarate
malate
NAD → NADH
+3
oxaloacetate
from glycolysis
SCoA → CoASH
citrate
+28 ATP
= 36 per glucose
E_1CB-like
cis-aconitate
H_2O, conjugate addition
iso-citrate
ATP in et. syste
$-CO_2$
NADH ← NAD^+
+3
oxidation to ketone then decarboxylation of β-keto ester
α-ketoglutarate
$-CO_2$
+3
NADH ← NAD^+
CoASH
succinyl CoA
thiamine pyrophosphate (TPP)
GTP
phosphate
GDP
succinate
$FADH_2$
FAD
+2
GDP
CoASH
TPP =
NADH

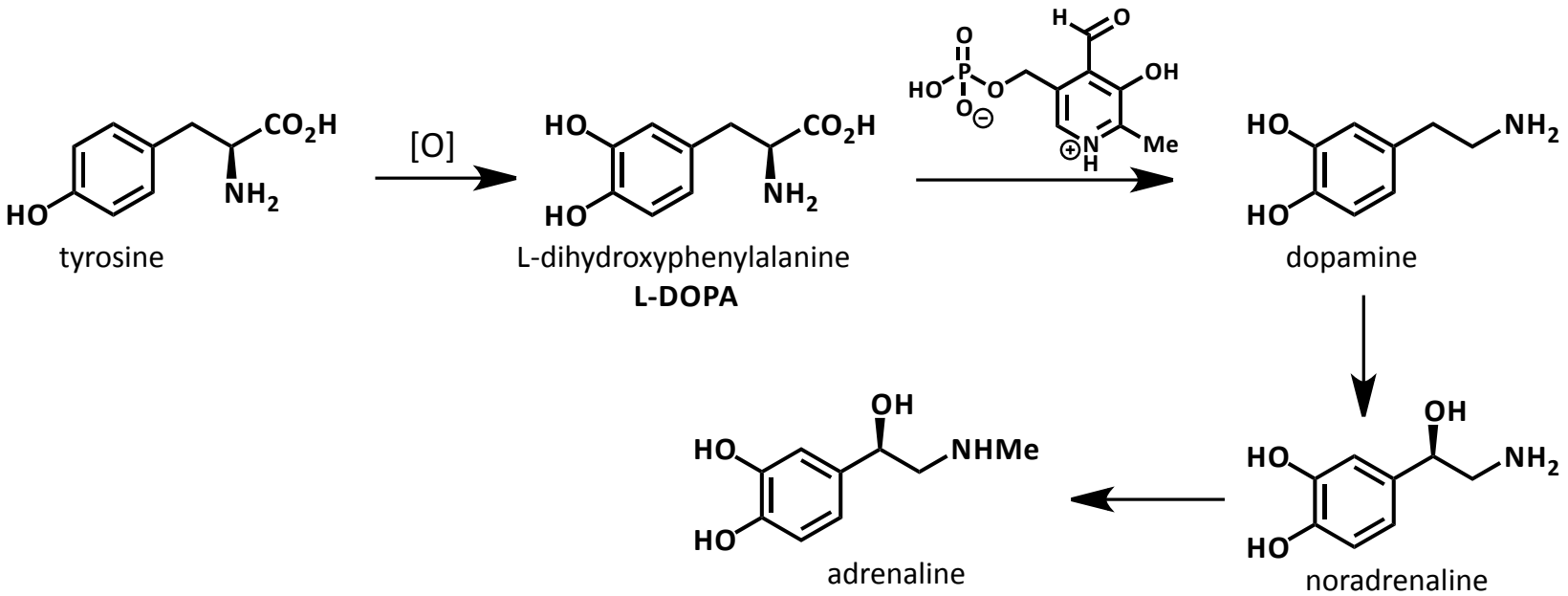
- Biosynthesis of benzylisoquinoline alkaloids
- Biosynthesised from tyrosine



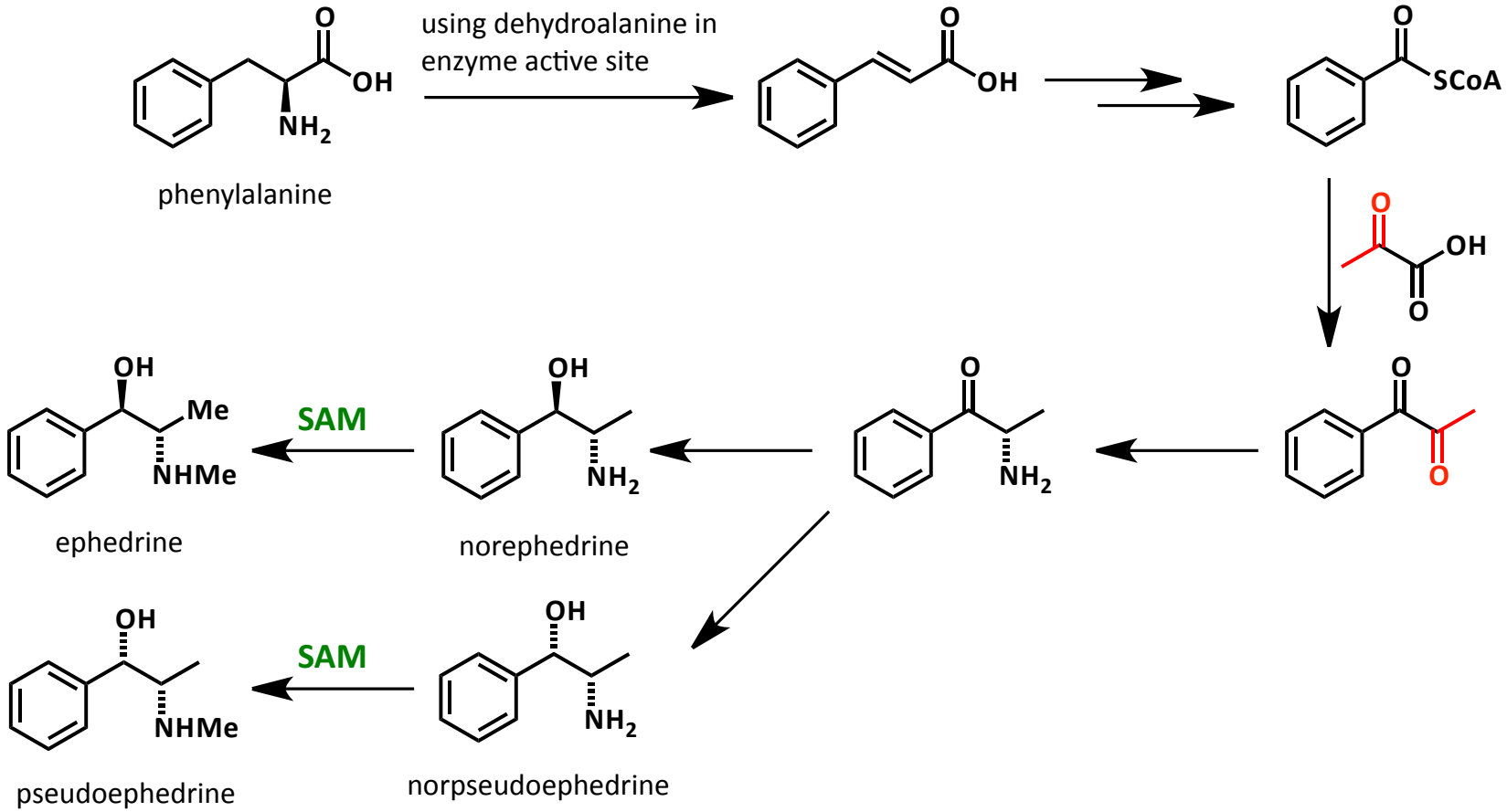
- Tyrosine can also be biosynthesised directly from phenylalanine by oxidation (and NIH shift)
- Hydride (deuteride) transferred to cation followed by enolisation
- Hydride transfer mechanism discovered the National Institute of Health, Bethesda, USA.



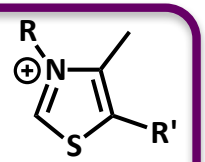
- Biosynthesis of L-dopa and adrenaline

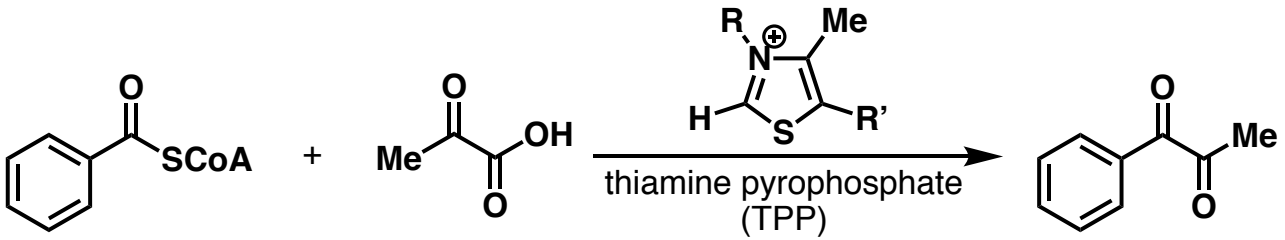


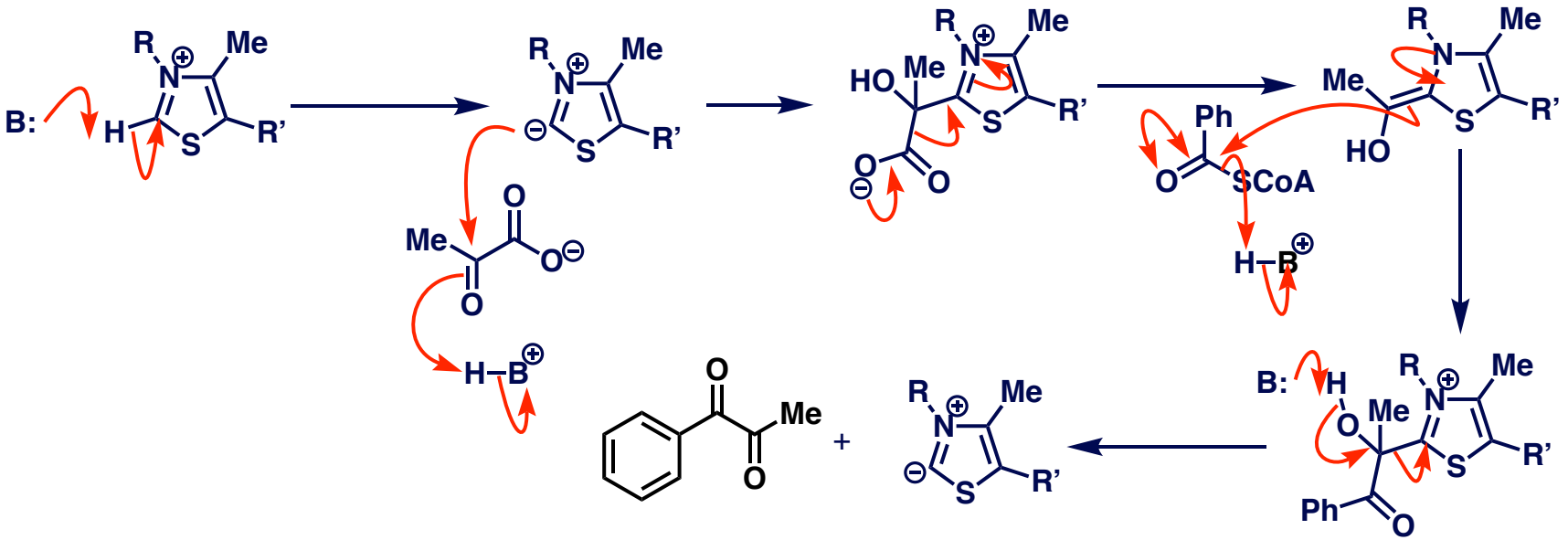
- The related ephedrine, from a number of *Ephedra* species, has a very different biogenesis involving pyruvate



thiamine pyrophosphate

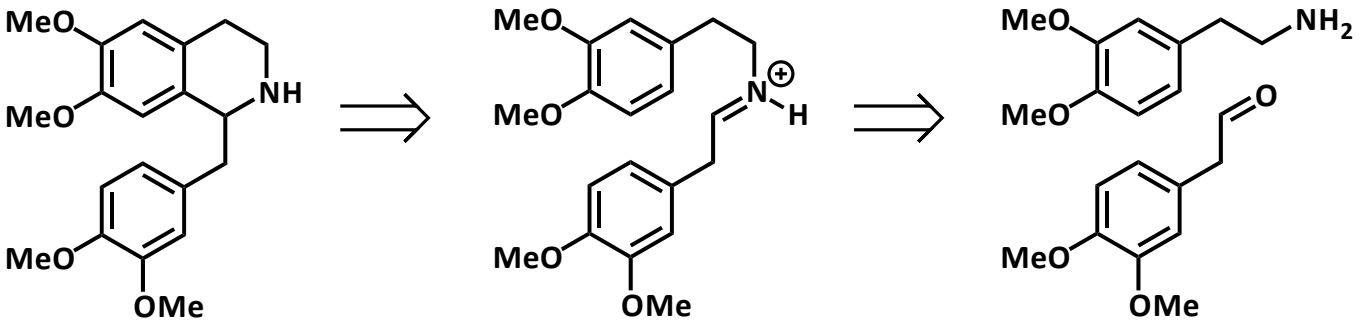






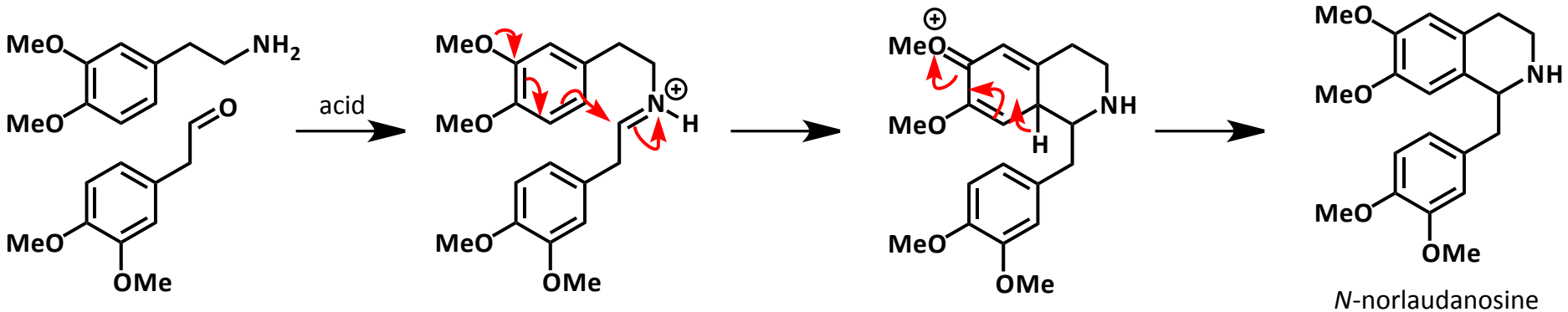
- **TPP** acts like cyanide:
  - good nucleophile
  - stabilises adjacent negative charge
  - good leaving group

- Retrosynthetic analysis of a benzylisoquinoline alkaloid.

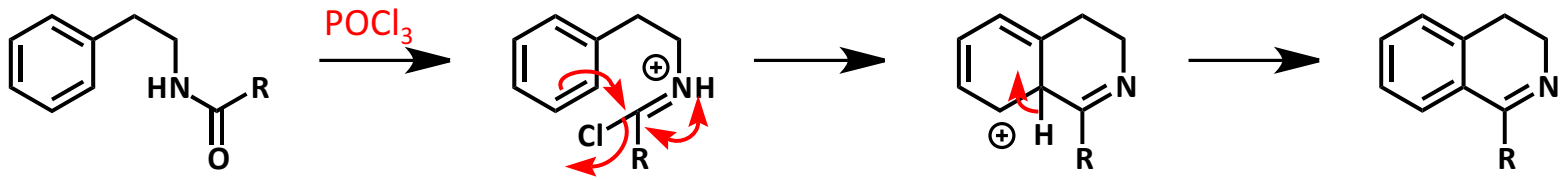


N-norlaudanosine

Pictet Spengler

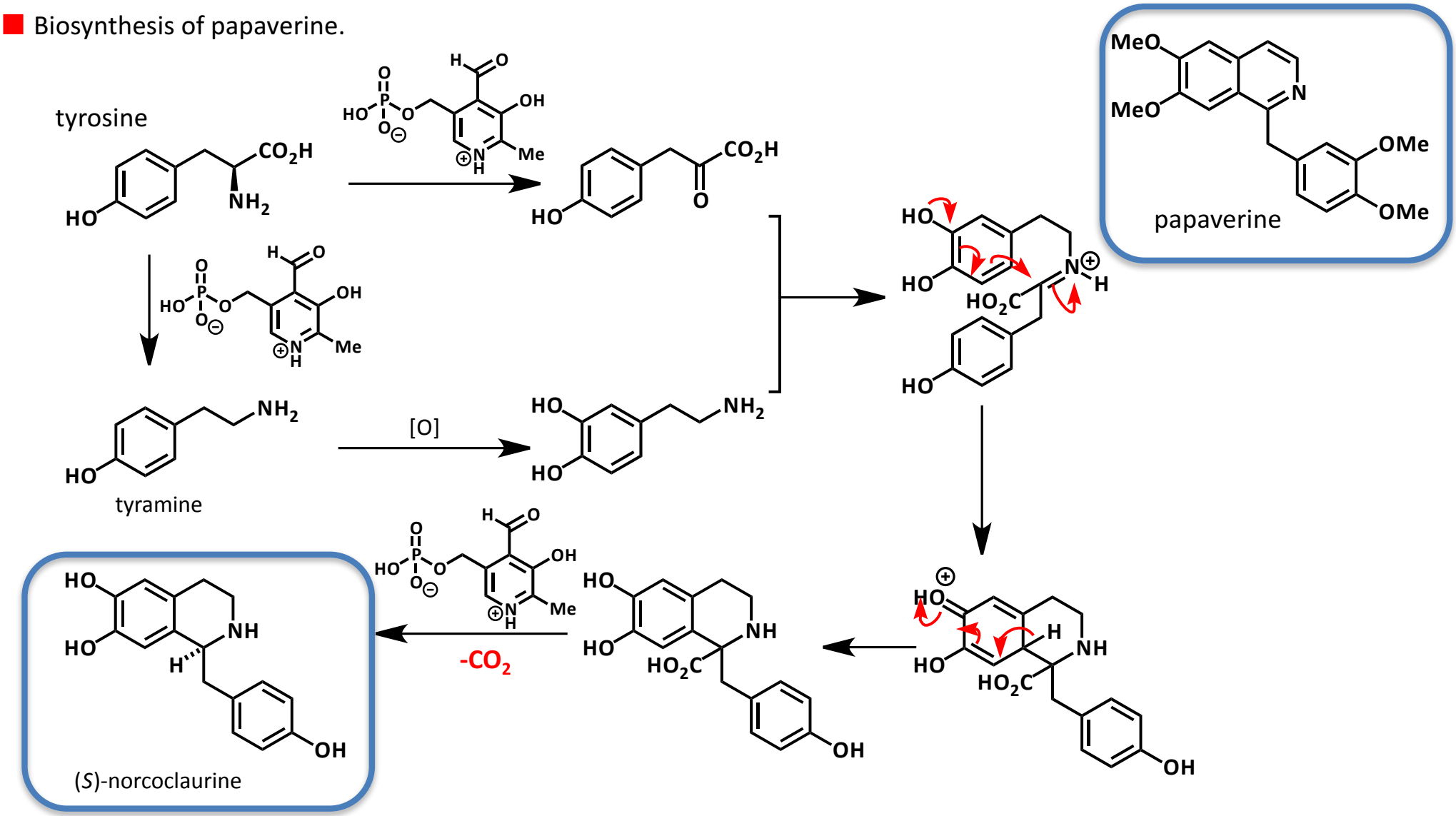


N-norlaudanosine

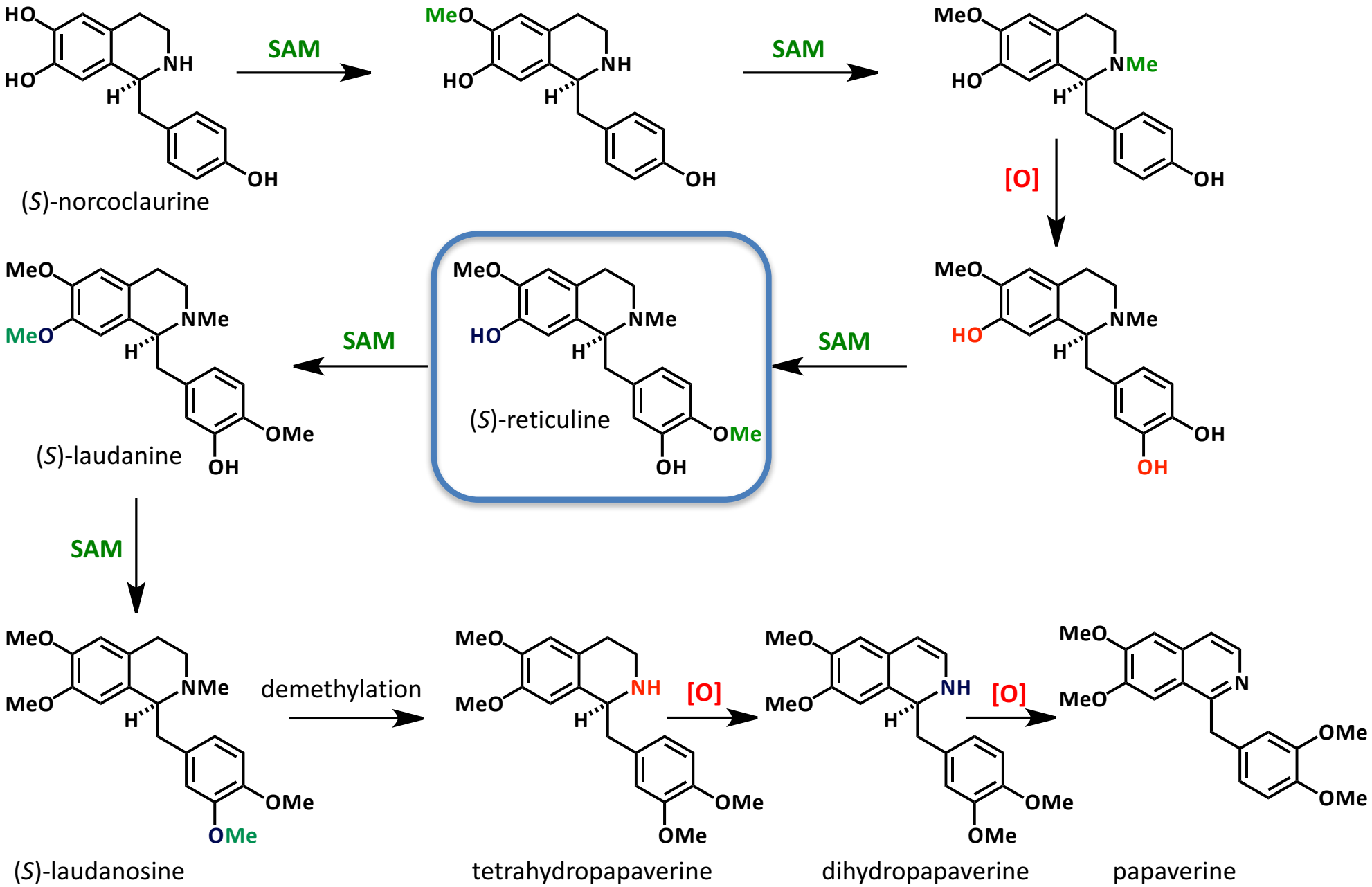


Bischler Napieralski

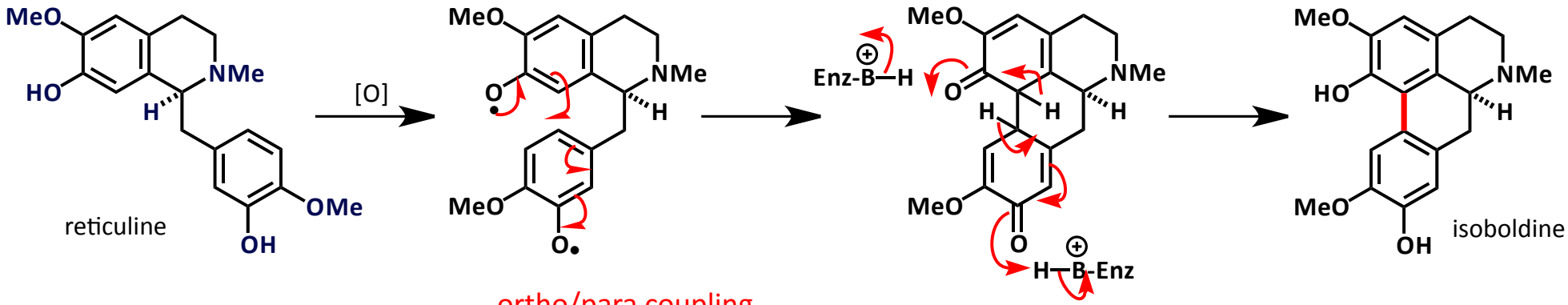
- Biosynthesis of papaverine.

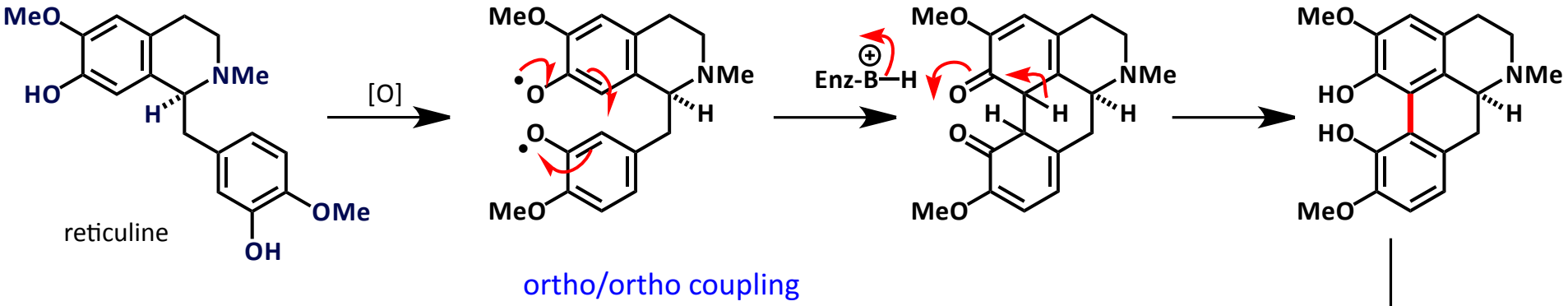


- Biosynthesis of papaverine – a recent study reveals the following plausible biosynthesis – *Phytochemistry*, **2010**, *71*, 1305.



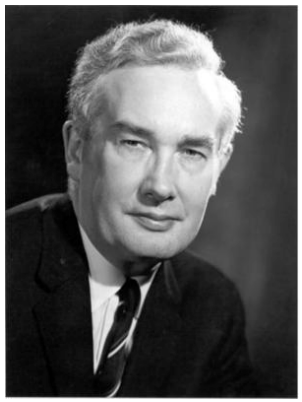
- Complex alkaloids can be readily formed biosynthetically and in the laboratory by oxidative radical coupling.





- ortho or para **couplings** to phenols are acceptable mechanistically and biosynthetically

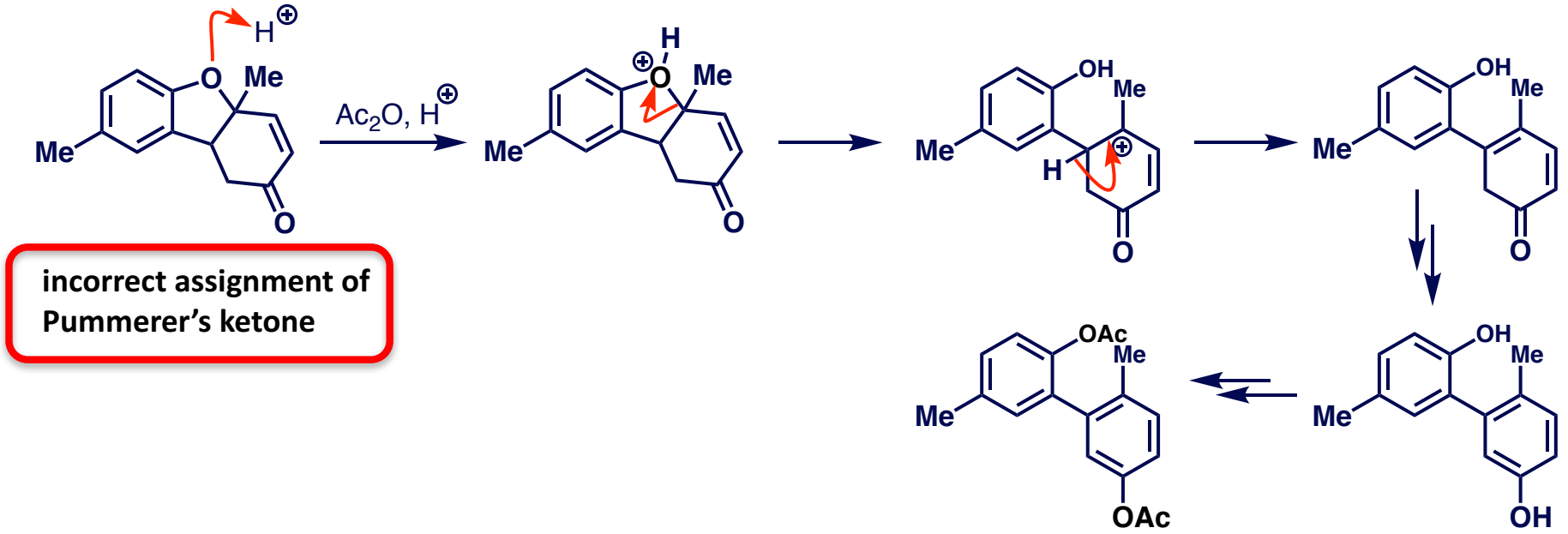
- Pummerer's ketone and its relation to biosynthesis
- Initial incorrect structure assignment based on reasonable mechanism



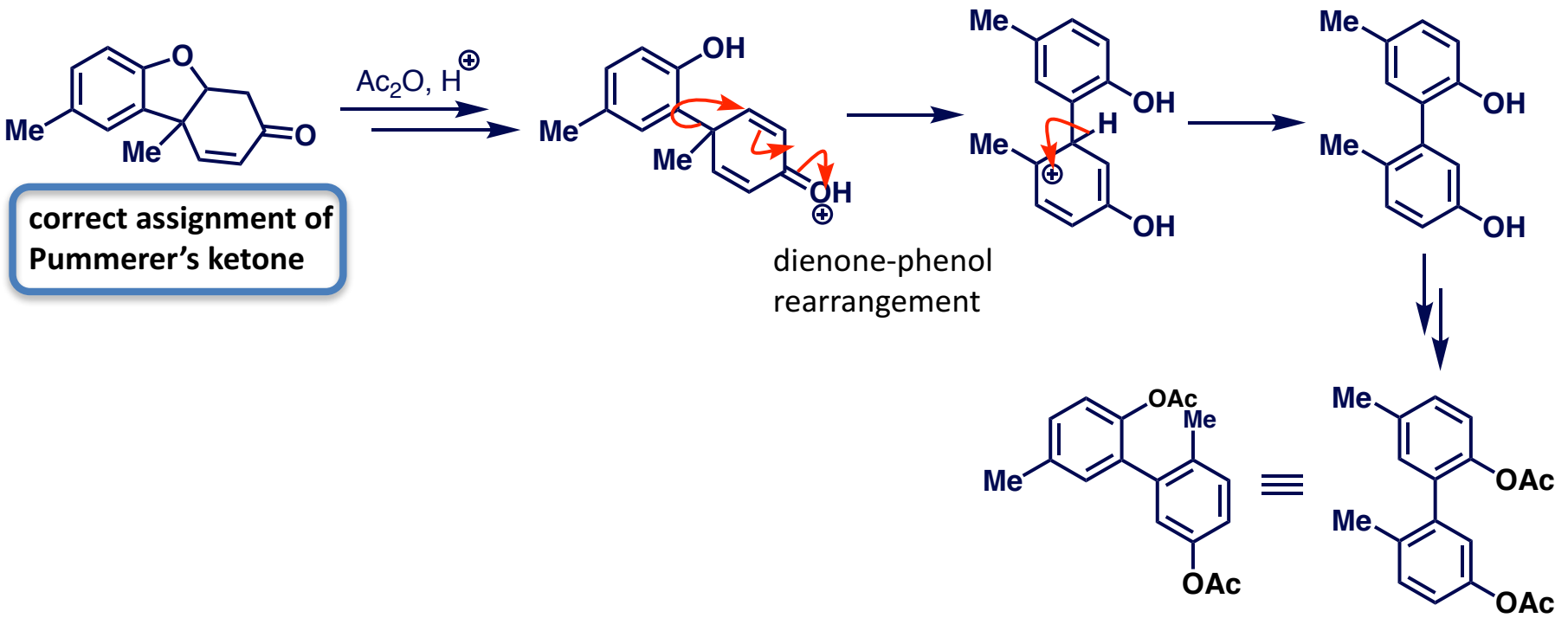
- Sir Derek Barton (1918-1998)
- Professor of Organic Chemistry, Imperial College, London 1957-1970
- Hofmann Professor of Organic Chemistry, Imperial College, London 1970-1978
- Nobel Prize 1969 with Odd Hassel for 'development of the concept of conformation and its application in chemistry'

incorrect original assignment for Pummerer's ketone

correct structure of Pummerer's ketone



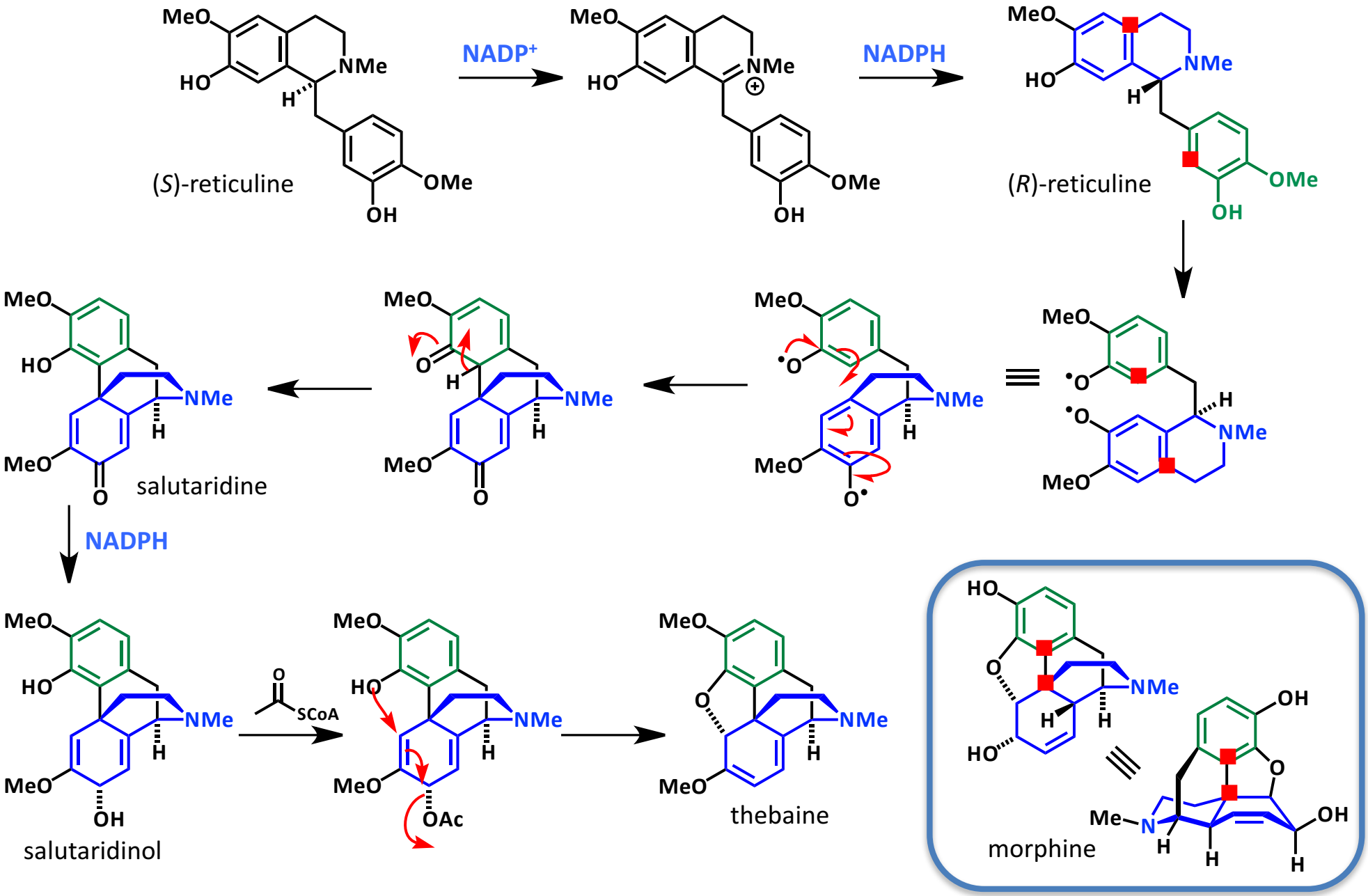
incorrect assignment of Pummerer's ketone



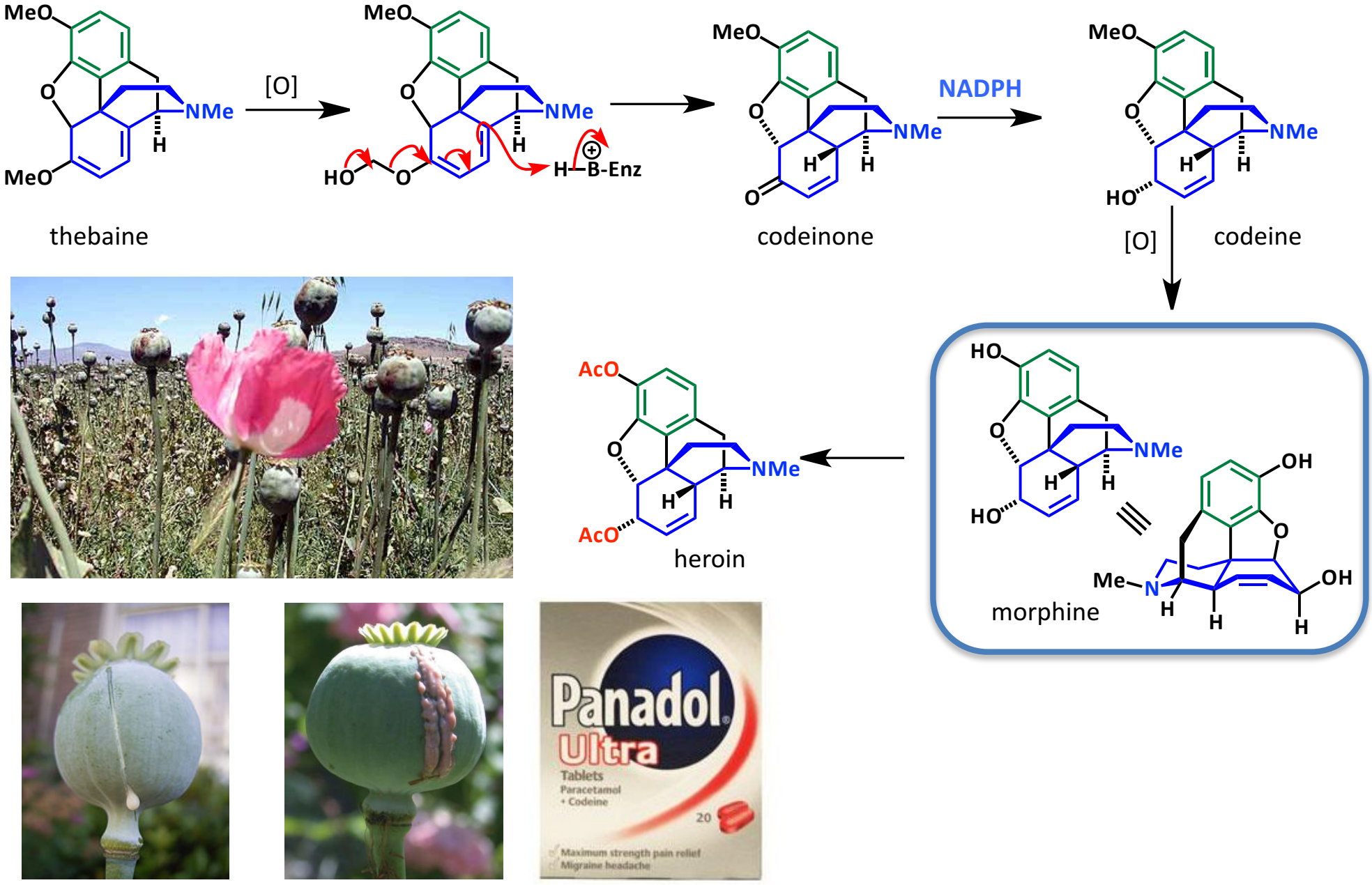
correct assignment of Pummerer's ketone

dienone-phenol rearrangement

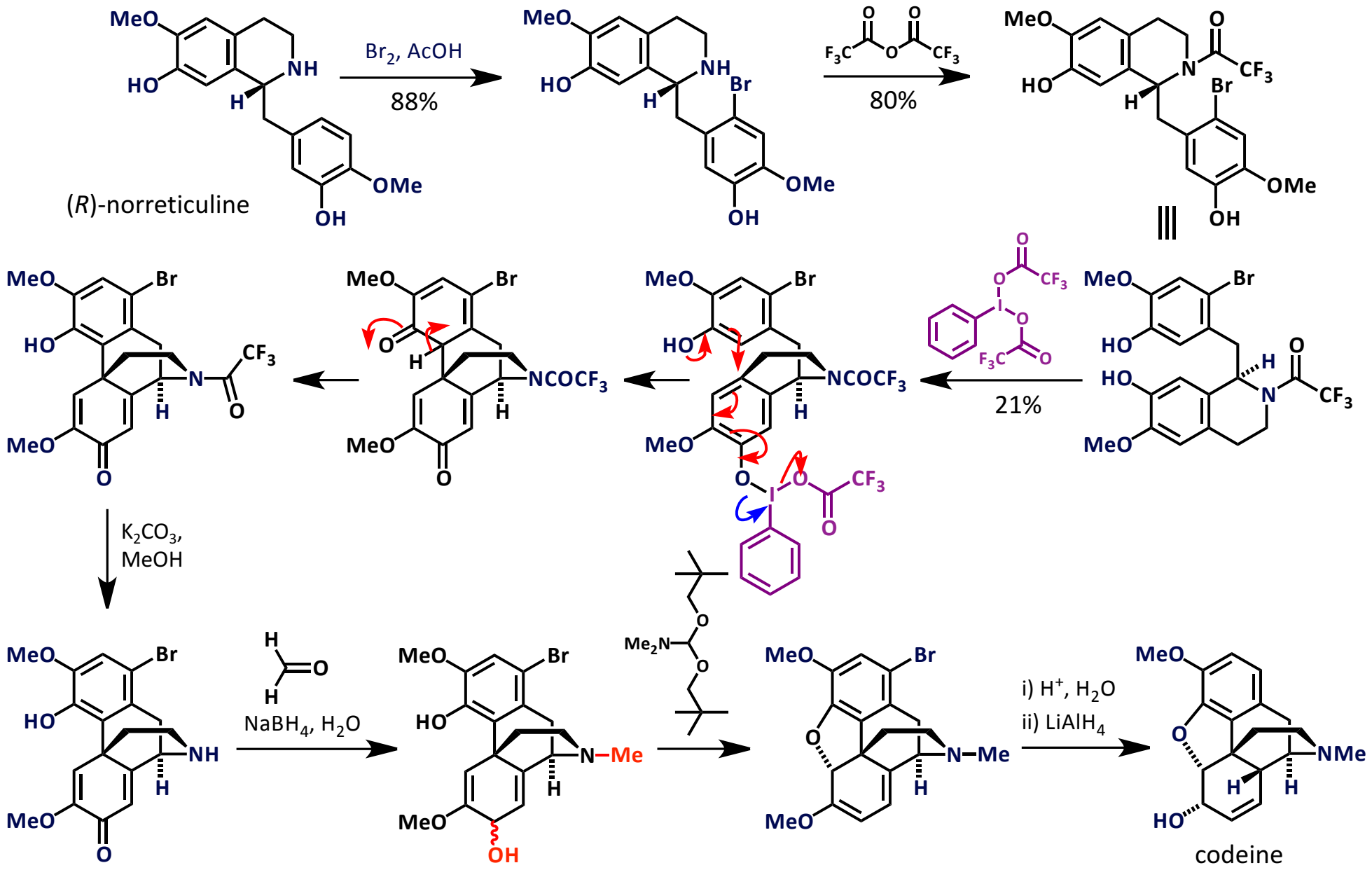
Biosynthesis of the opium alkaloids



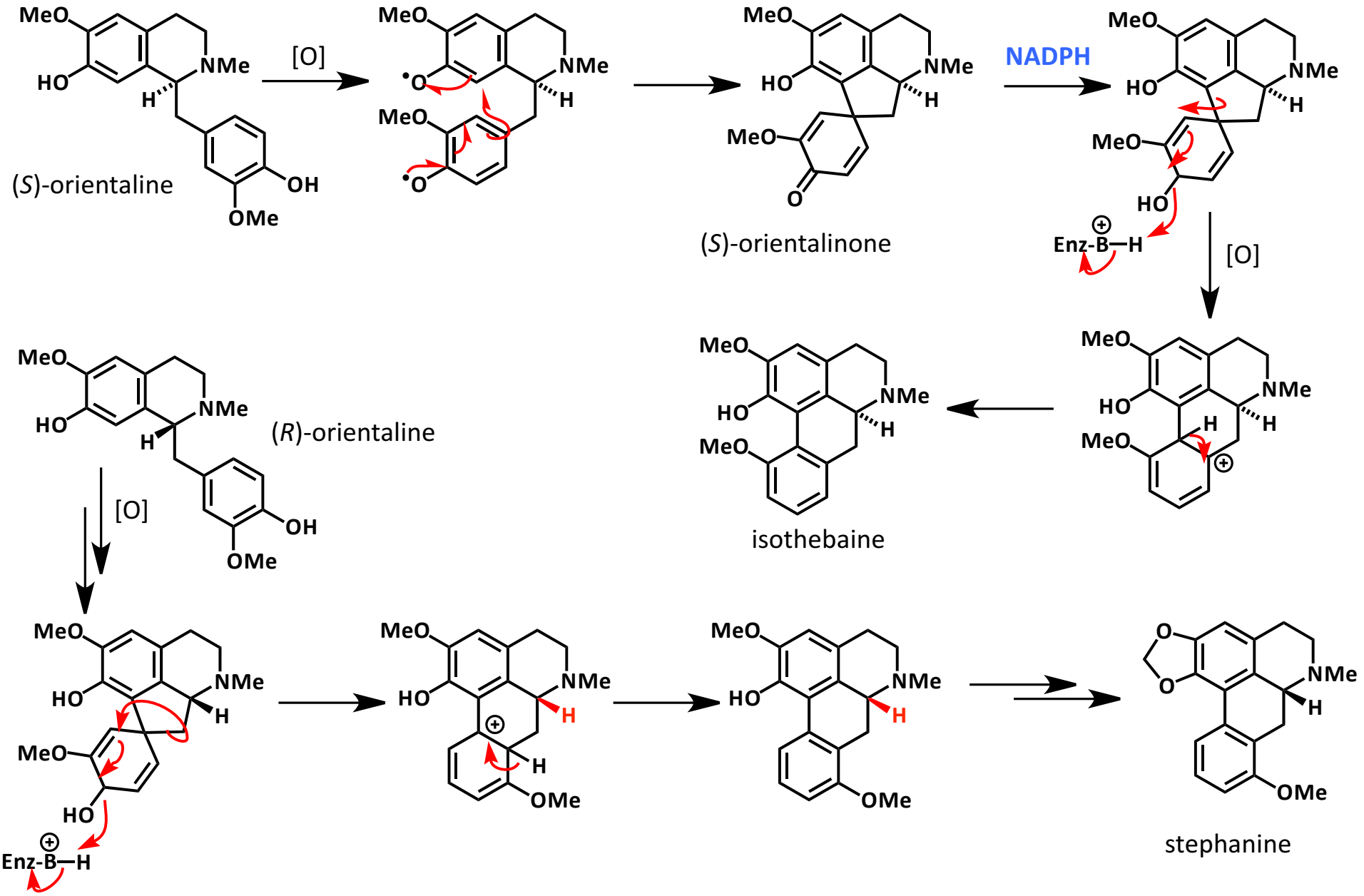
Biosynthesis of the opium alkaloids



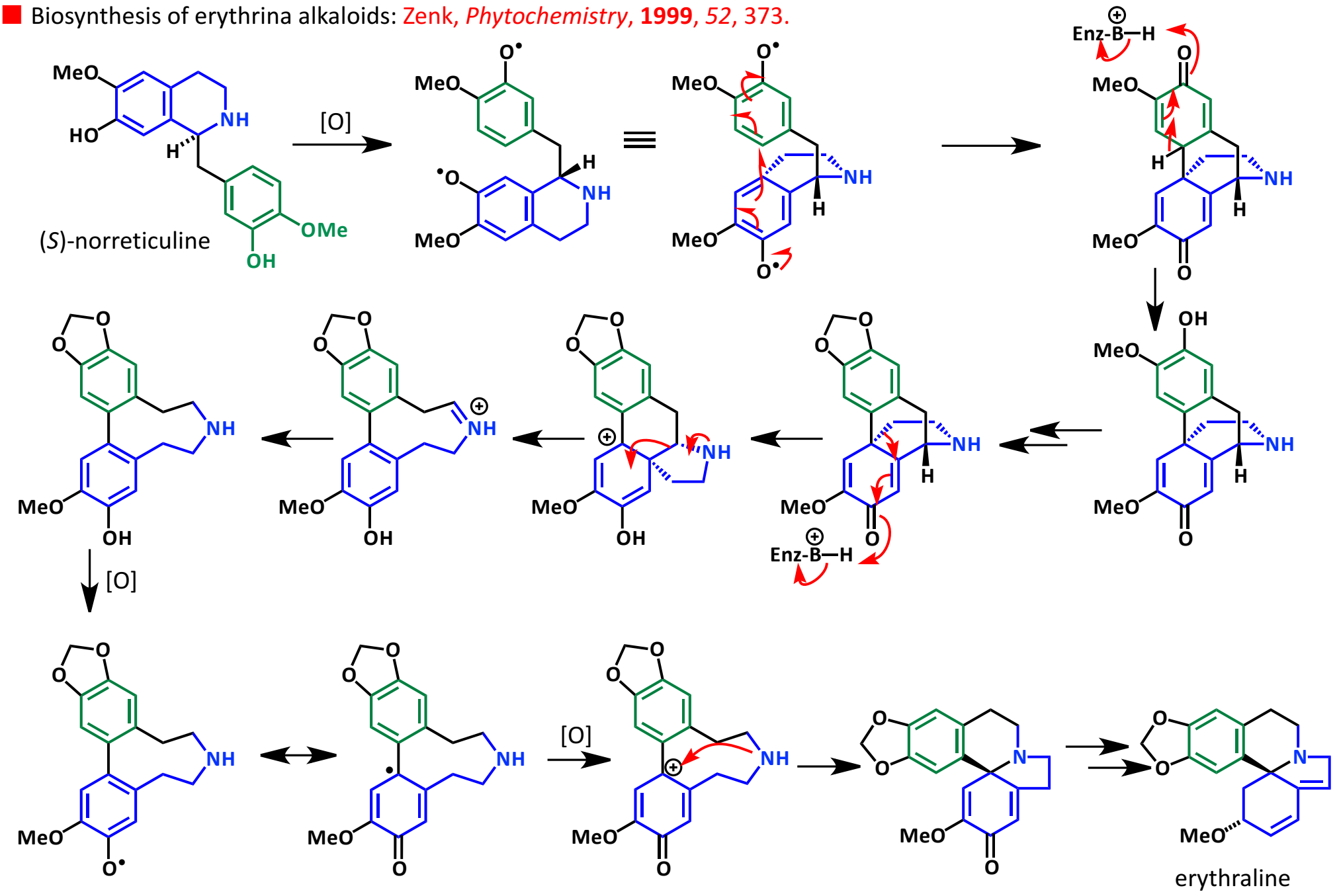
- Biomimetic synthesis of codeine White *et. al. Tetrahedron* **1983**, *39*, 2393.



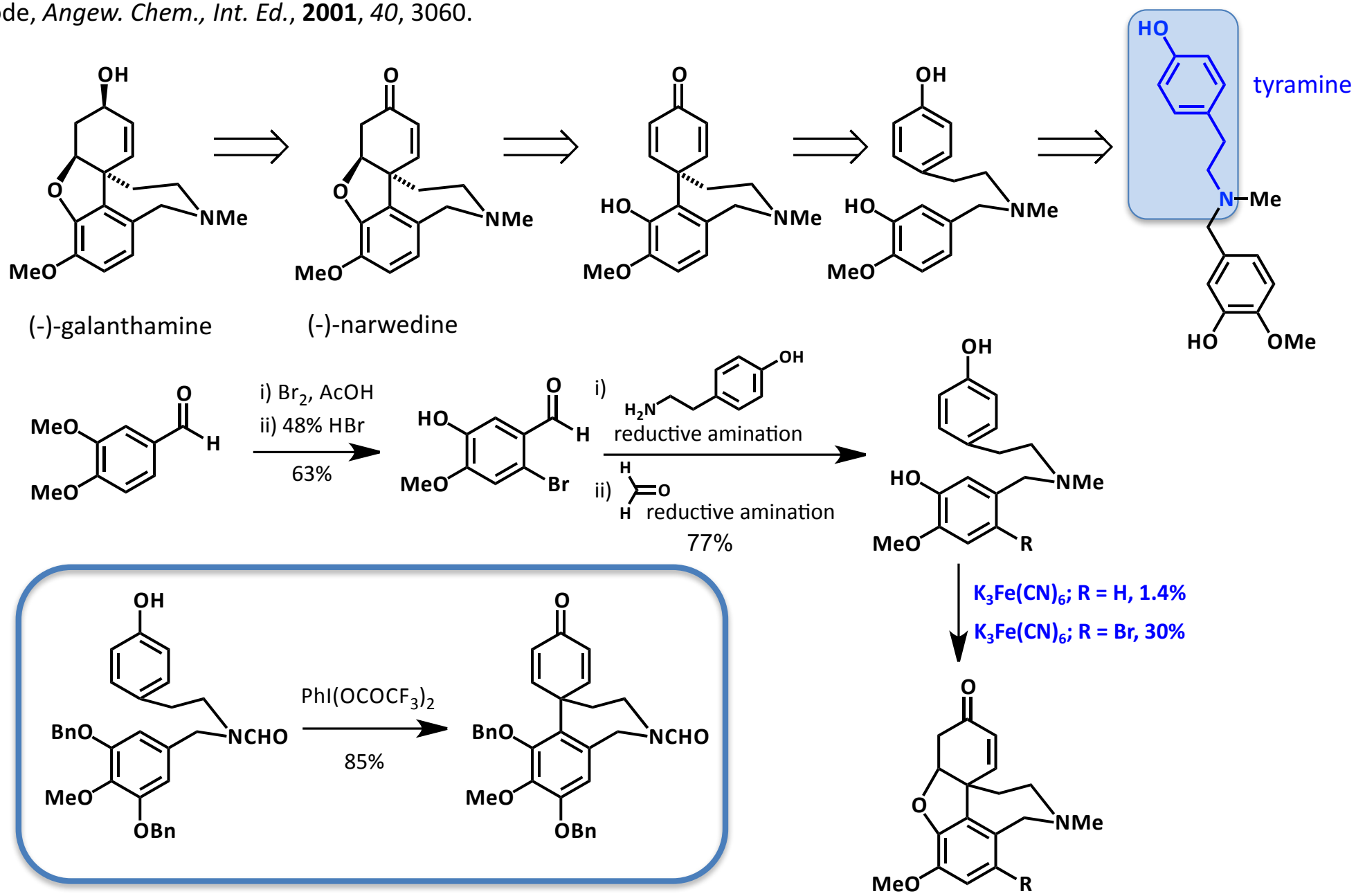
- To solve a 'meta' coupling, do an ortho/para coupling and a dienone-phenol rearrangement



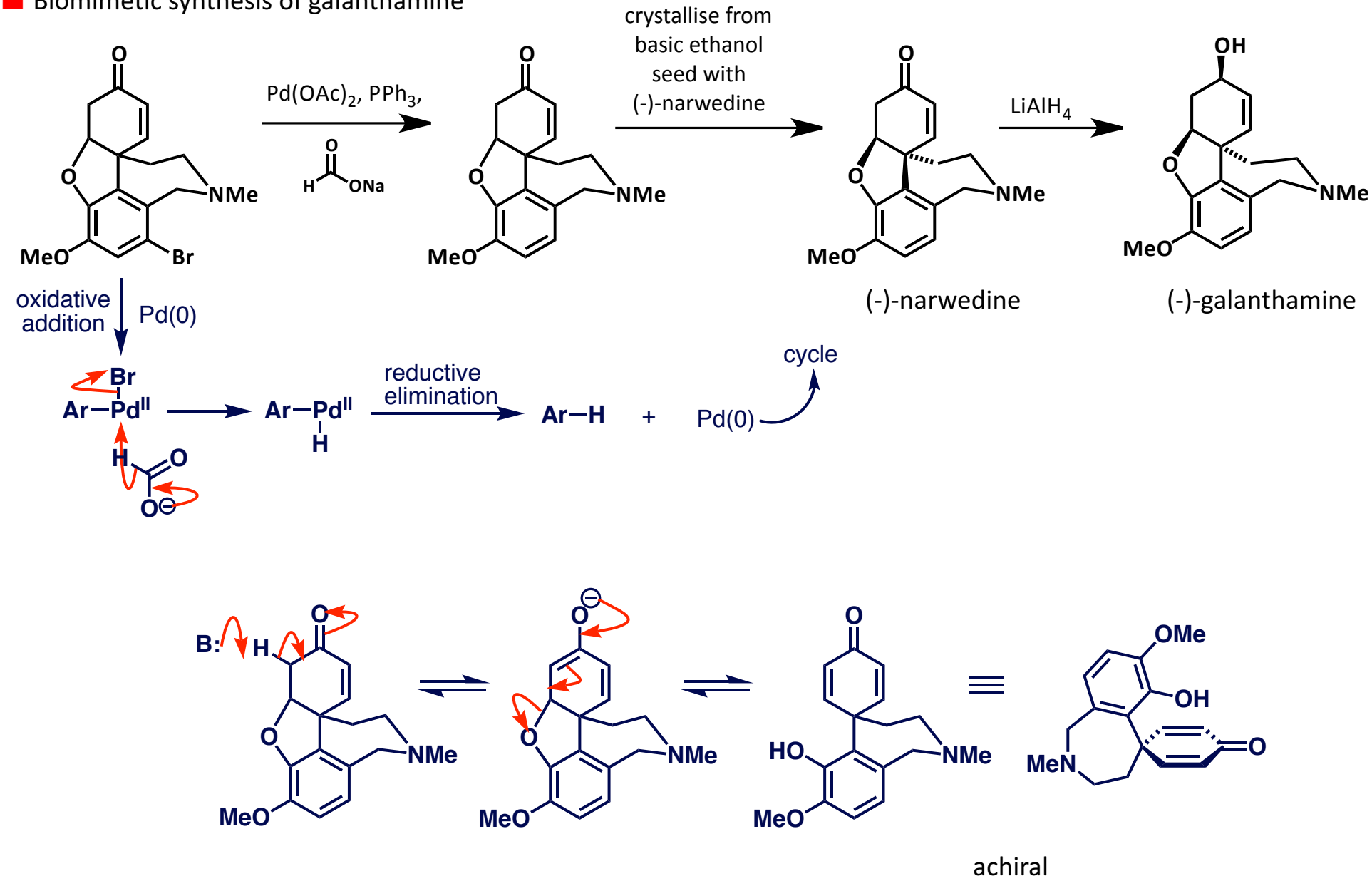
■ Biosynthesis of erythrina alkaloids: Zenk, *Phytochemistry*, **1999**, *52*, 373.



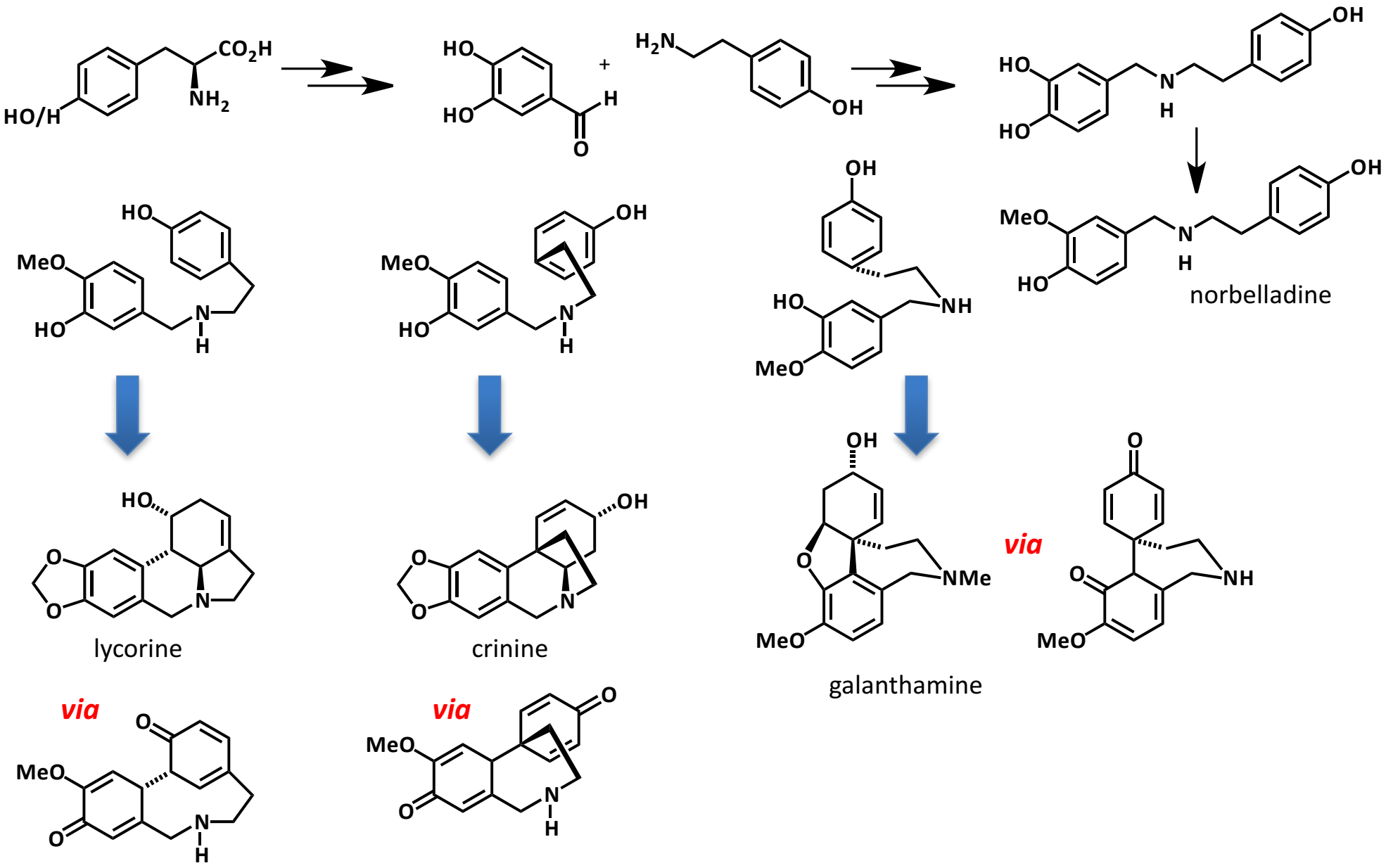
■ Biomimetic synthesis of galanthamine. Barton, *J. Chem. Soc.*, **1962**, 806; Chaplin & Tiffin, *Tet. Lett.*, **1997**, *38*, 7931; Node, *Angew. Chem., Int. Ed.*, **2001**, *40*, 3060.



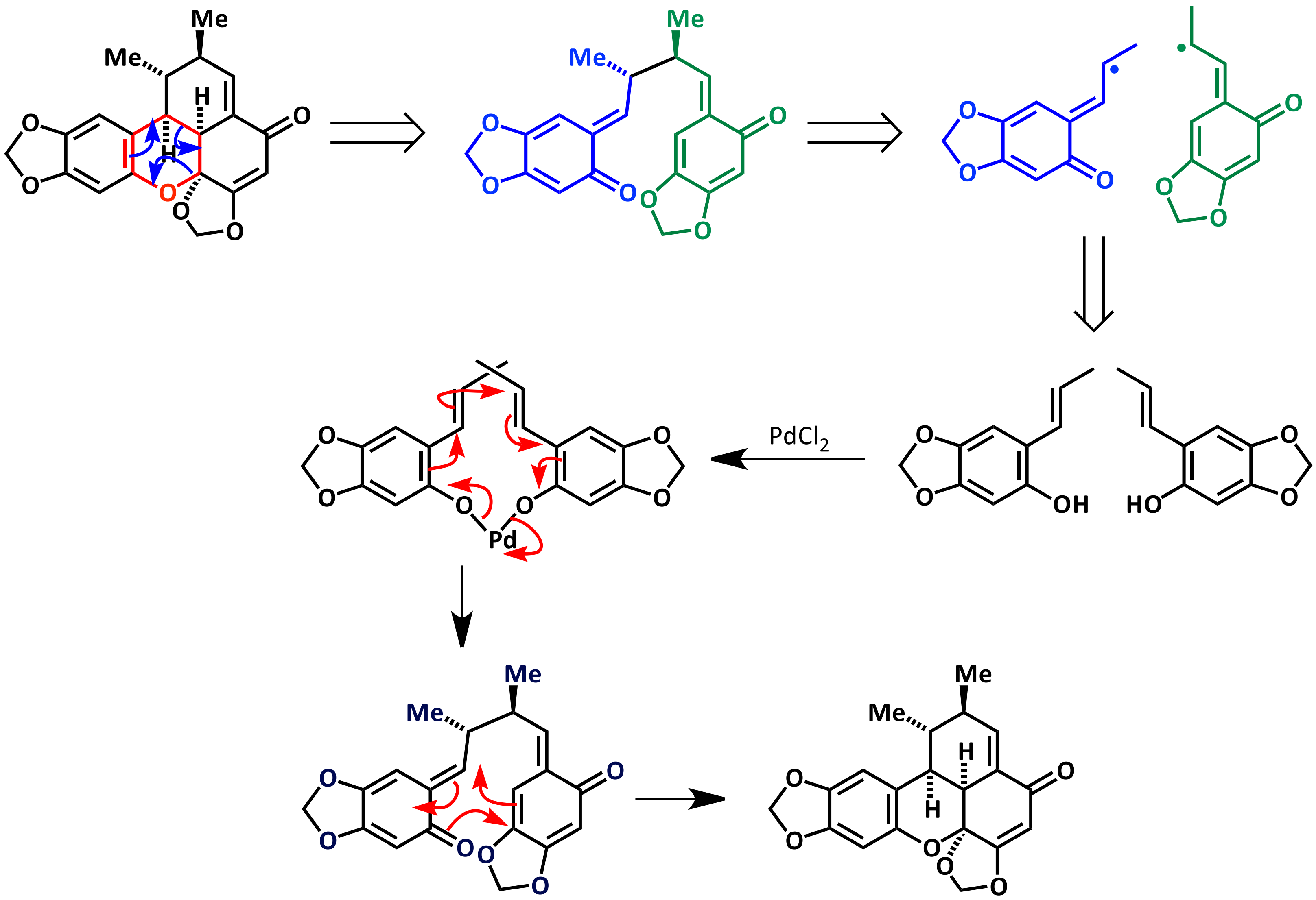
Biomimetic synthesis of galanthamine



- Biosynthetic overview of amaryllidaceae alkaloids from the daffodil family

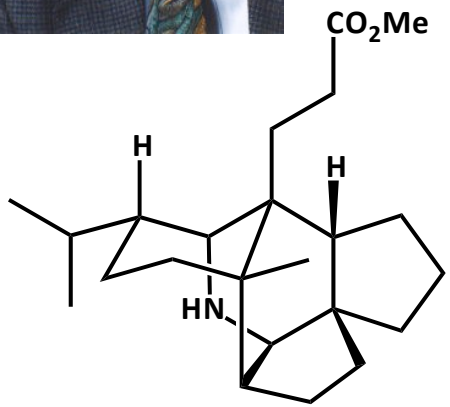


- Biosynthesis as a guide for retrosynthesis
- Carpanone; Chapman, *J. Am. Chem. Soc.*, **1971**, *93*, 6696.

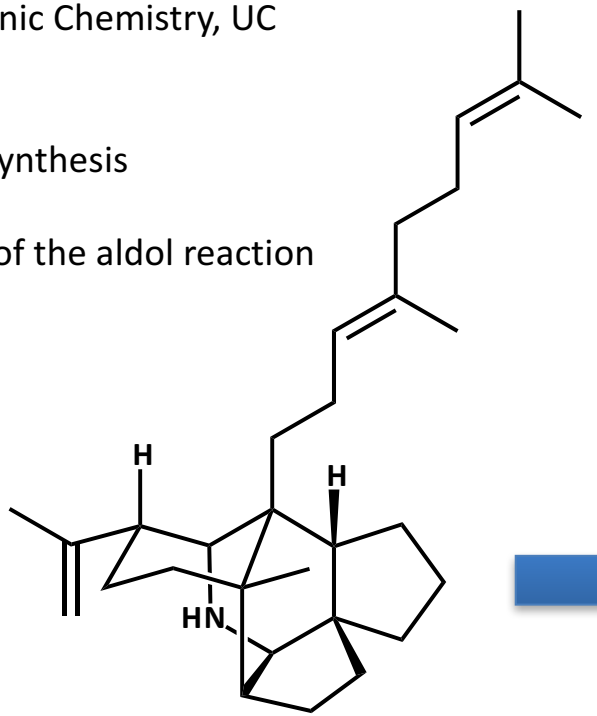


- Alkaloids from Yuzuriha – Clayton Heathcock Review, *Angew. Chem. Int. Ed.*, **1992**, *31* 665-681; Classics in Total Synthesis, K. C. Nicolaou, E. J. Sorensen, Chapter 26.

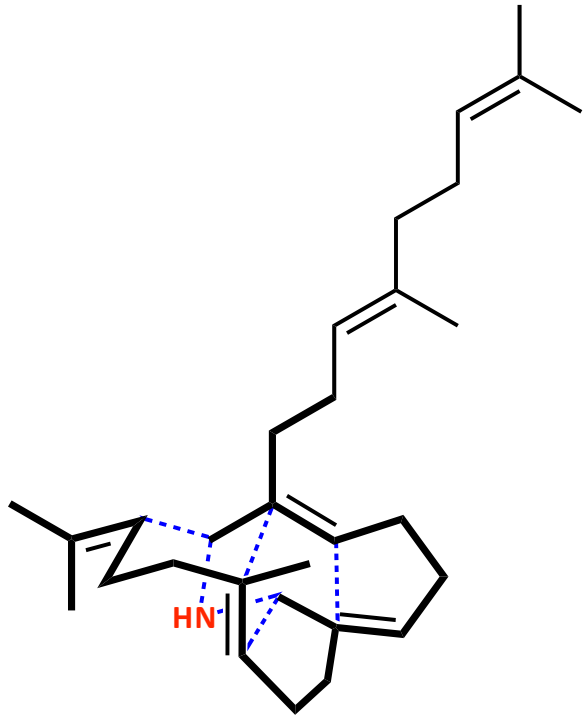
- Professor Clayton Heathcock
- Professor of Organic Chemistry, UC Berkeley
- Natural product synthesis
- Stereochemistry of the aldol reaction

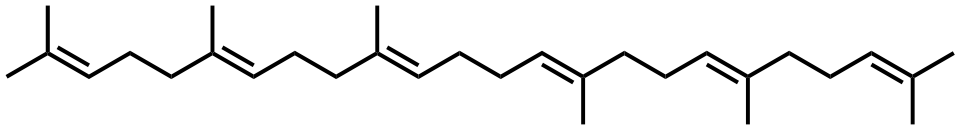


methyl homosecodaphniphylate



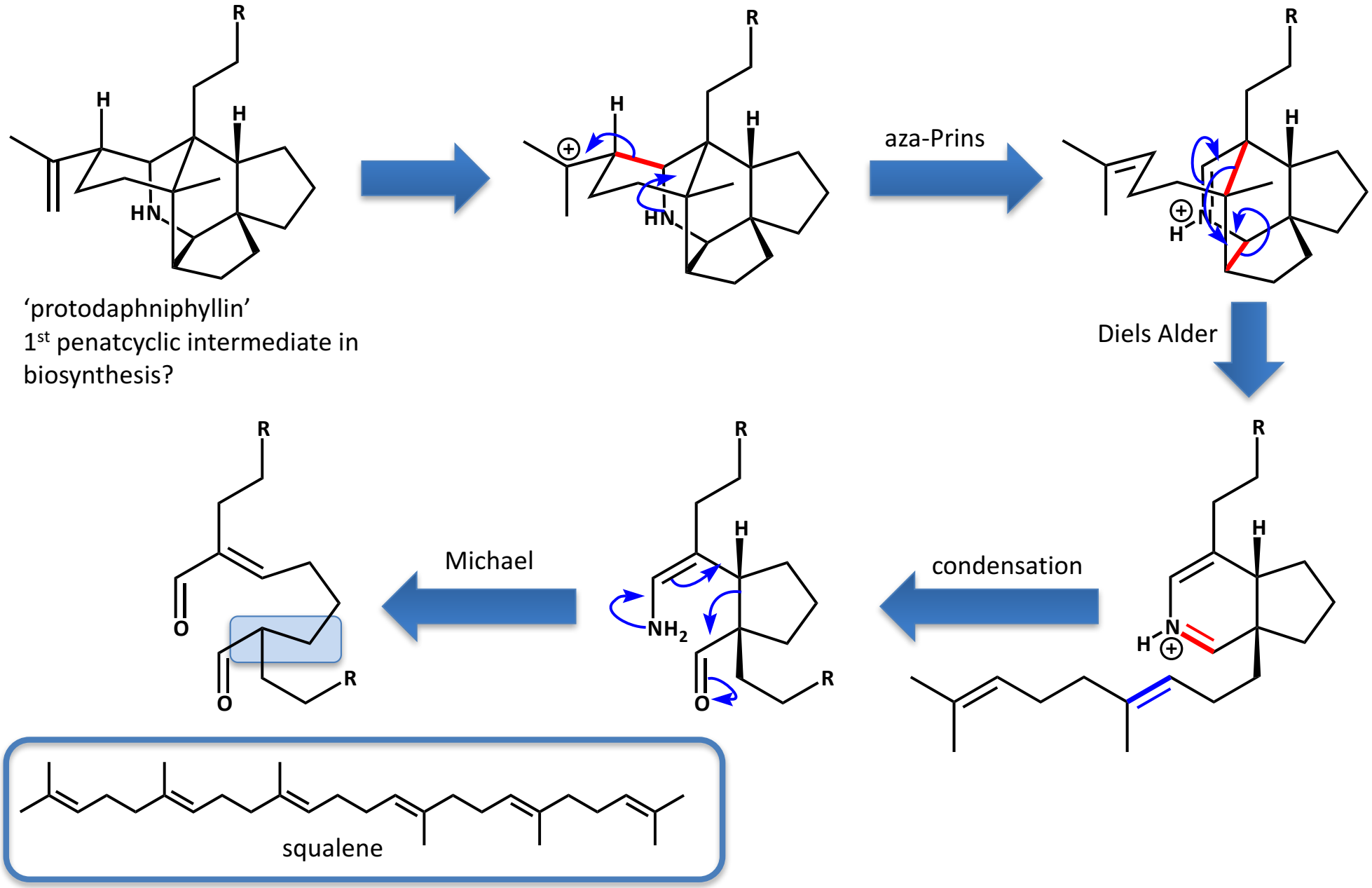
'protodaphniphyllin'
1st pentacyclic intermediate in biosynthesis?





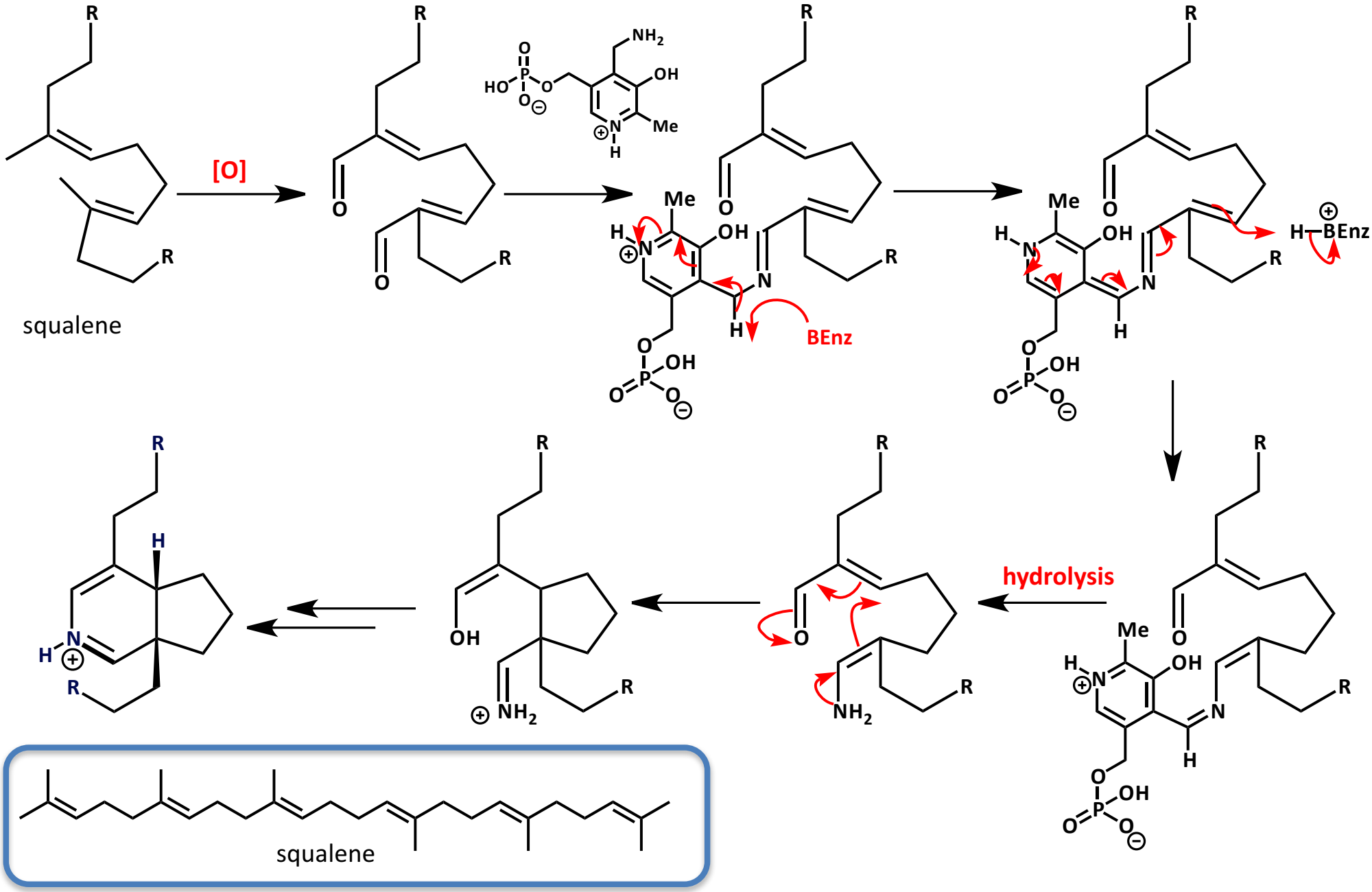
squalene

- Plausible biogenesis / retrosynthesis - high molecular complexity reduced to linear precursor

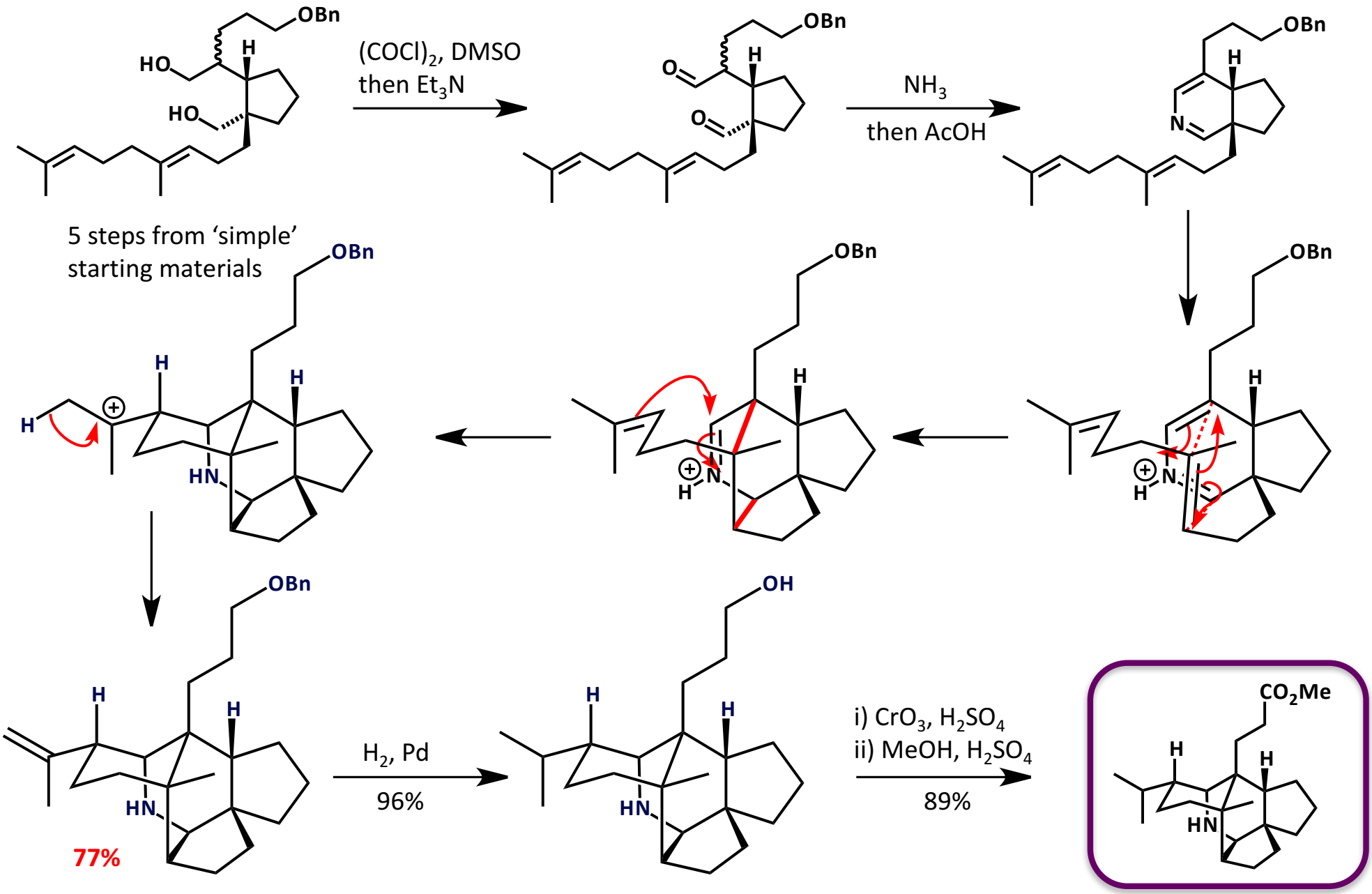


'protodaphniphyllin'
1st penatcyclic intermediate in biosynthesis?

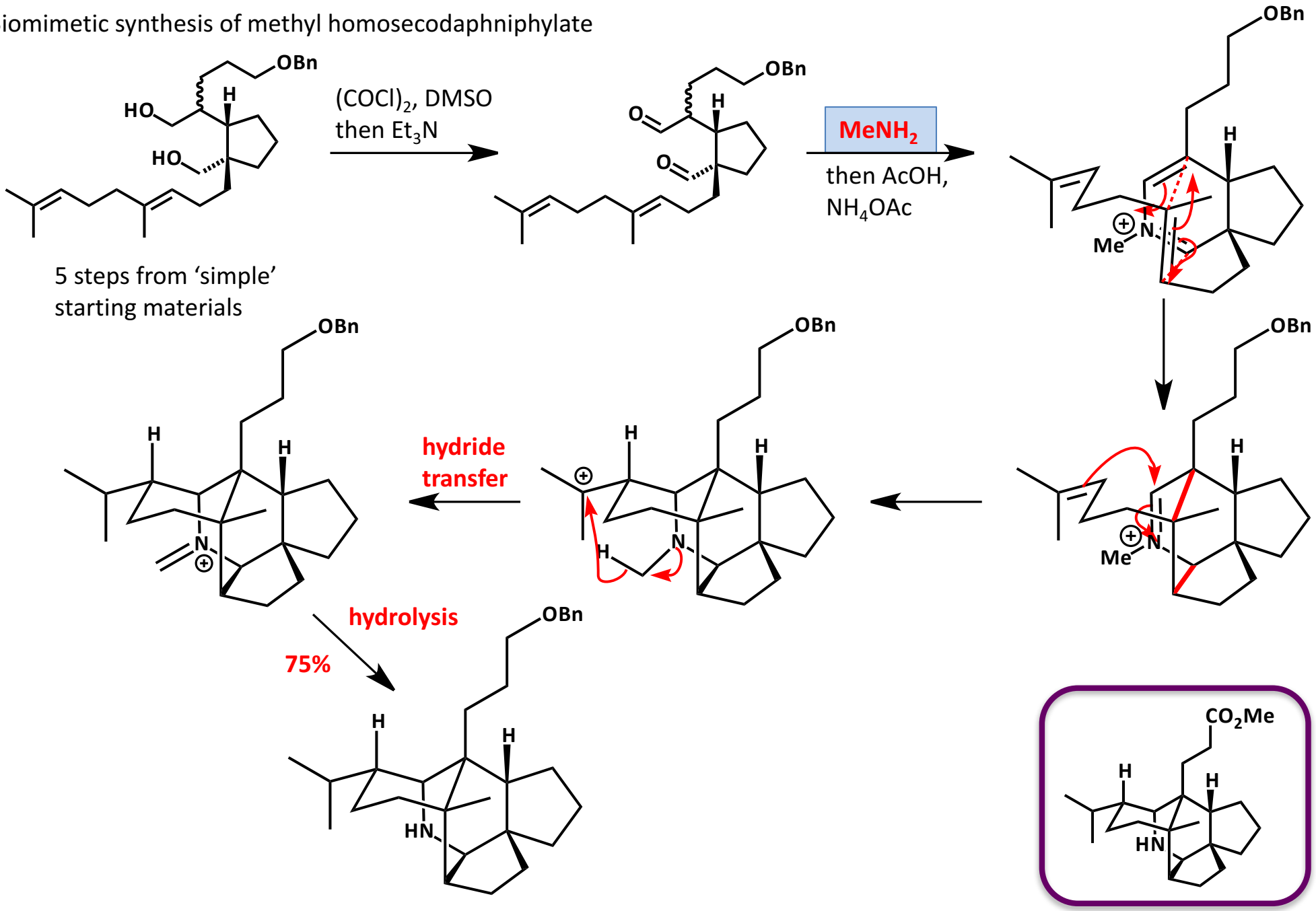
- Plausible retro-biosynthesis / retrosynthesis - high molecular complexity reduced to linear precursor



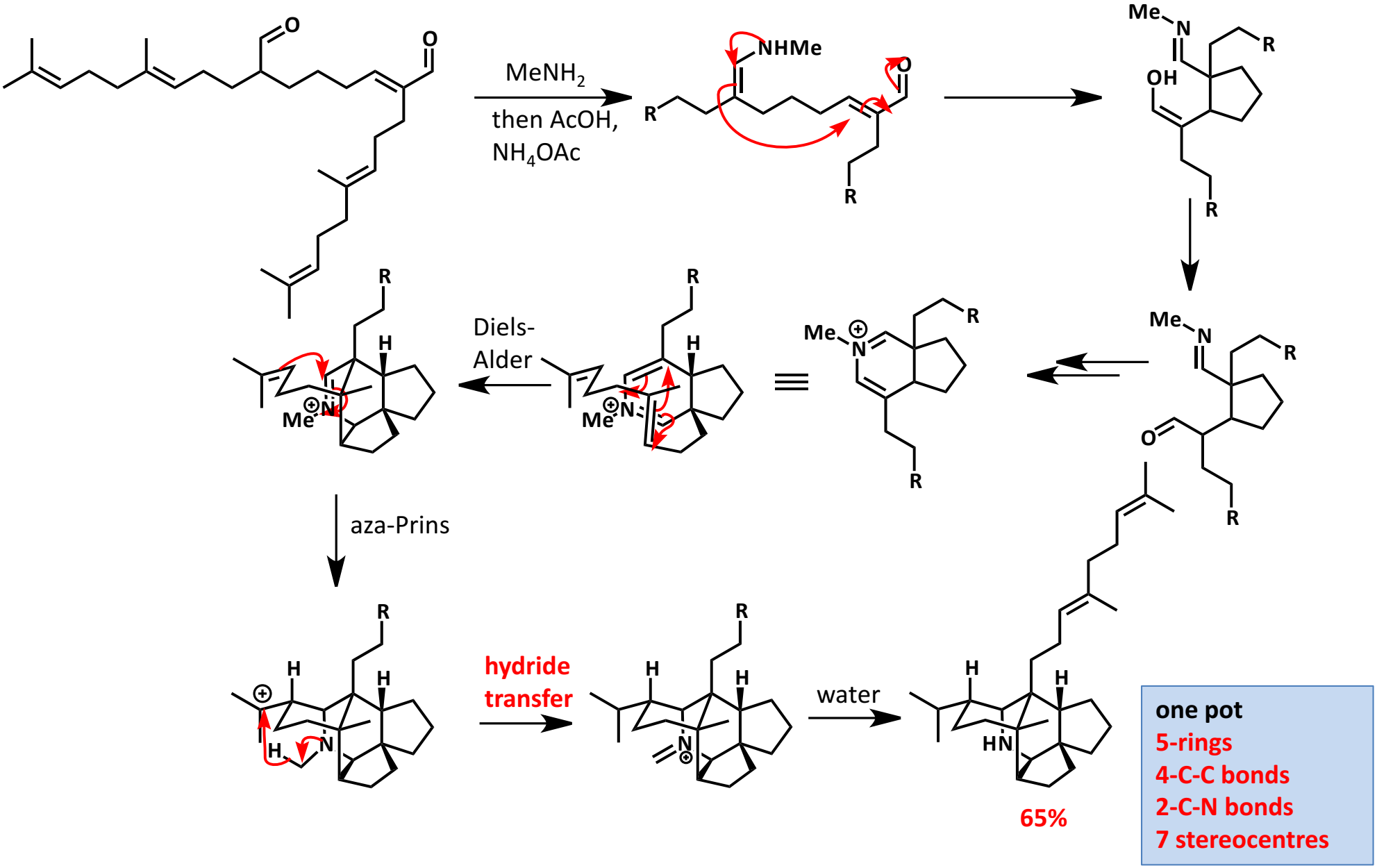
Biomimetic synthesis of methyl homosecodaphniphylate



Biomimetic synthesis of methyl homosecodaphniphylate



Biomimetic “one step” synthesis of dihydro ‘protodaphniphyllin’



- Manzamine alkaloids - cytotoxic

- Isolation of manzamine A, *J. Am. Chem.* Soc., **1986**, *108*,
"Moreover, its provenance is problematical as there appears to be no obvious biogenetic path."

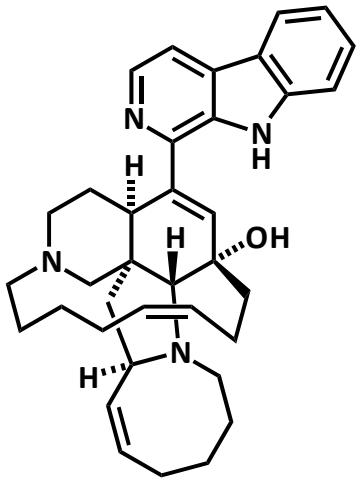
- Biogenesis of the manzamine alkaloids,
J. E. Baldwin, R. C. Whitehead, *Tetrahedron Lett.*, **1992**, *33*, 2059
"In fact the structural analysis of these substances reveals that they may be derived *in vivo* from three building blocks…..

- Sir Jack Baldwin

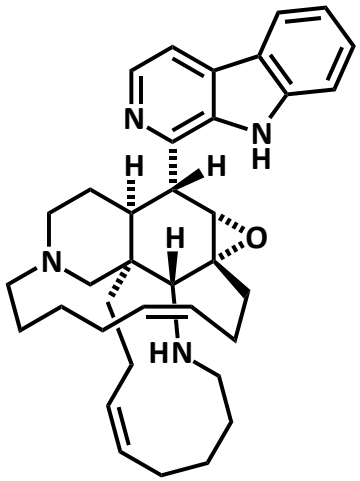
- Waynflete Professor of Organic Chemistry 1978-2005

- Baldwin's Rules

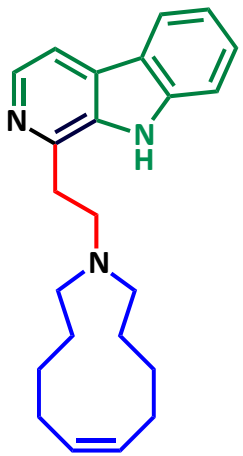
- Biosynthesis of penicillins



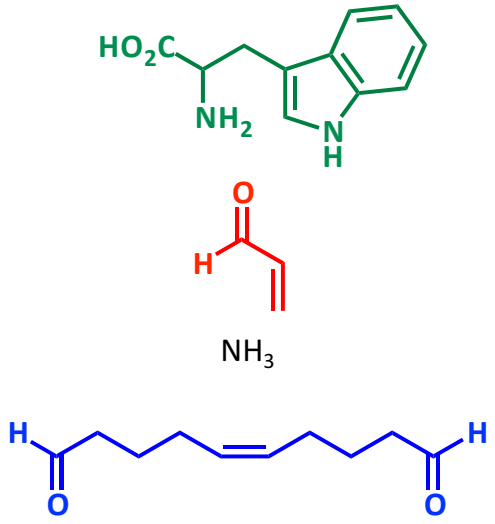
manzamine A



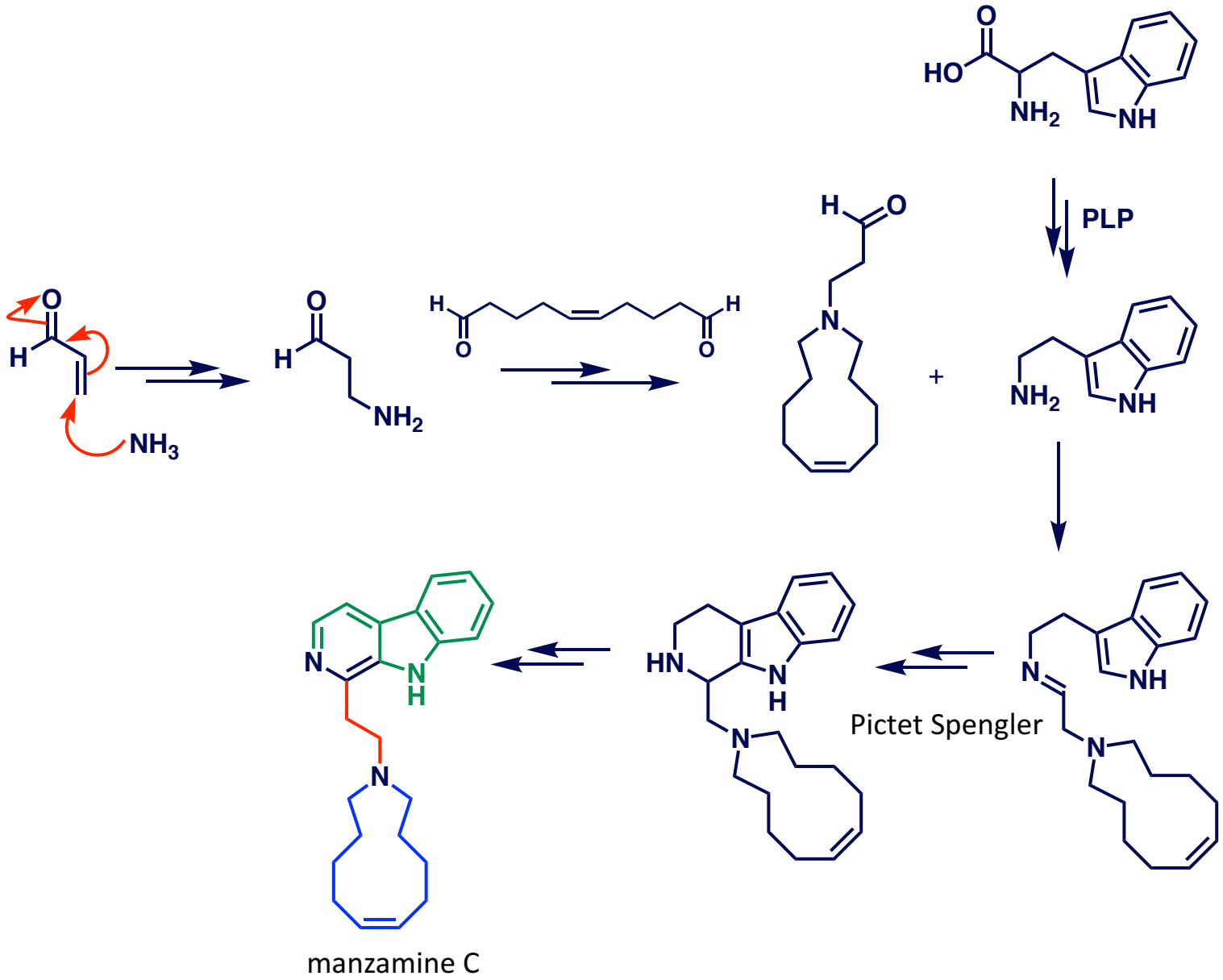
manzamine B



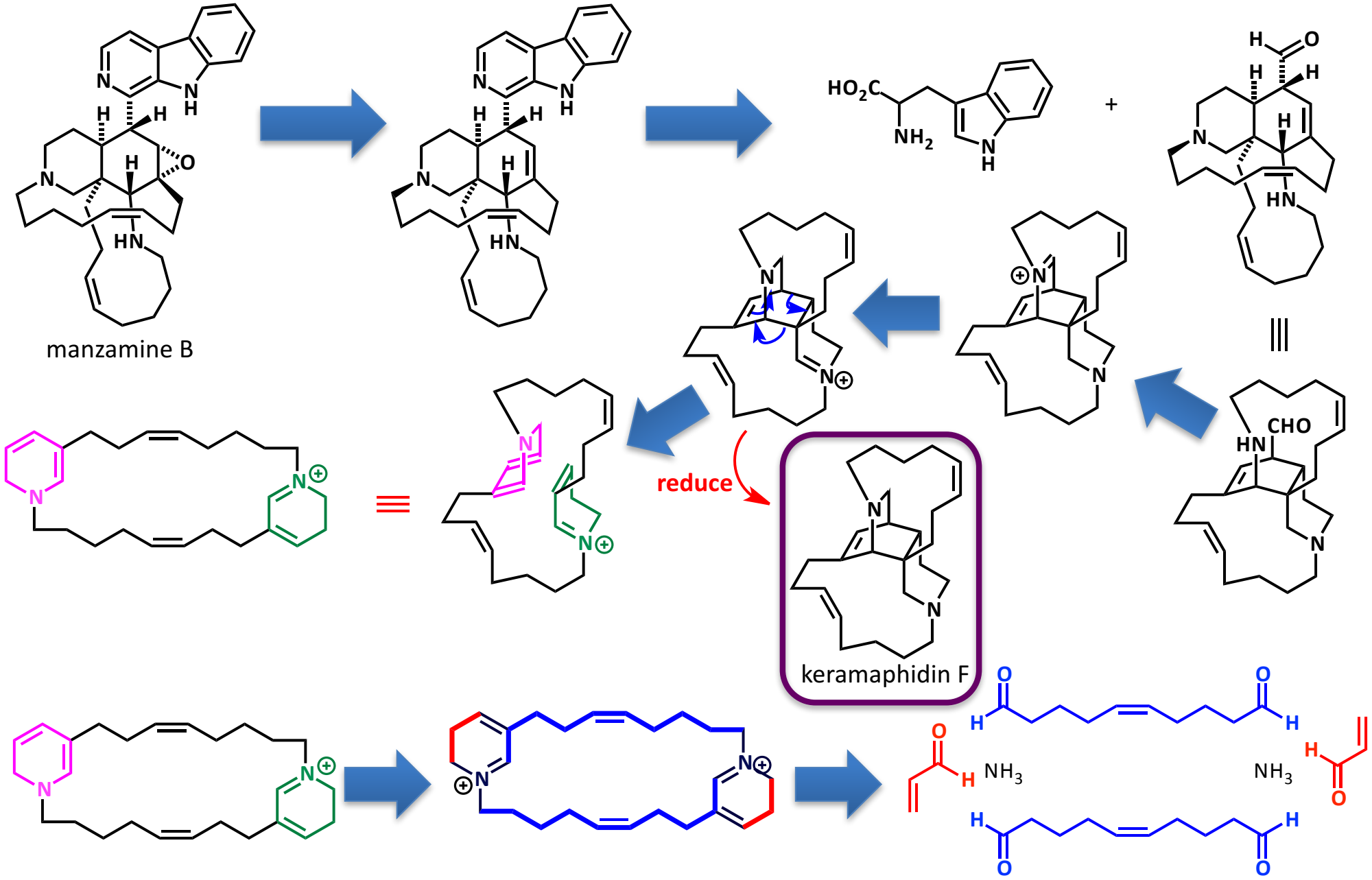
manzamine C



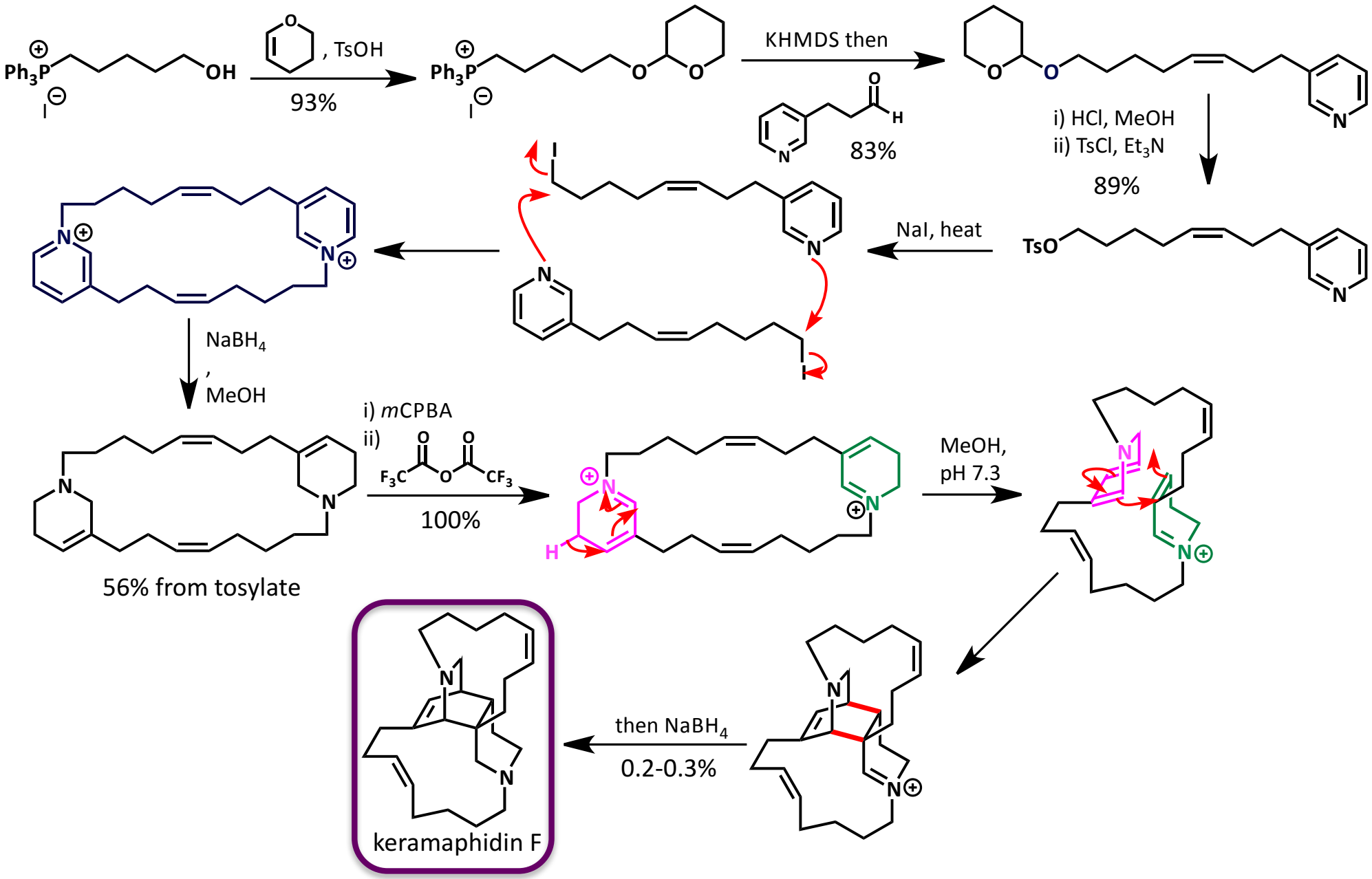
- "Biogenetically an aldehyde function is equivalent to an α-ketoacid or an α-amino acid. The simplest of these has been used in this treatment."

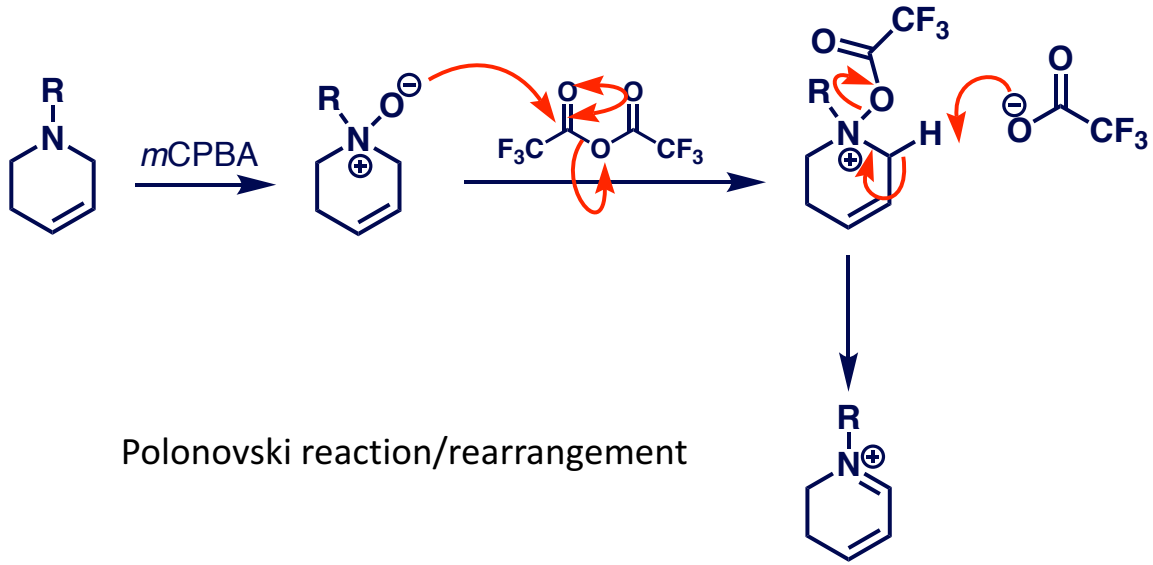

HO
O
NH2
NH
PLP
H
O
N
+
NH2
NH
NH3
NH2
H
O
H
O
N
HN
N
H
N
N
H
N
Pictet Spengler
manzamine C

- Biogenesis of the manzamine alkaloids, J. E. Baldwin, R. C Whitehead, *Tetrahedron Lett.*, **1992**, *33*, 2059



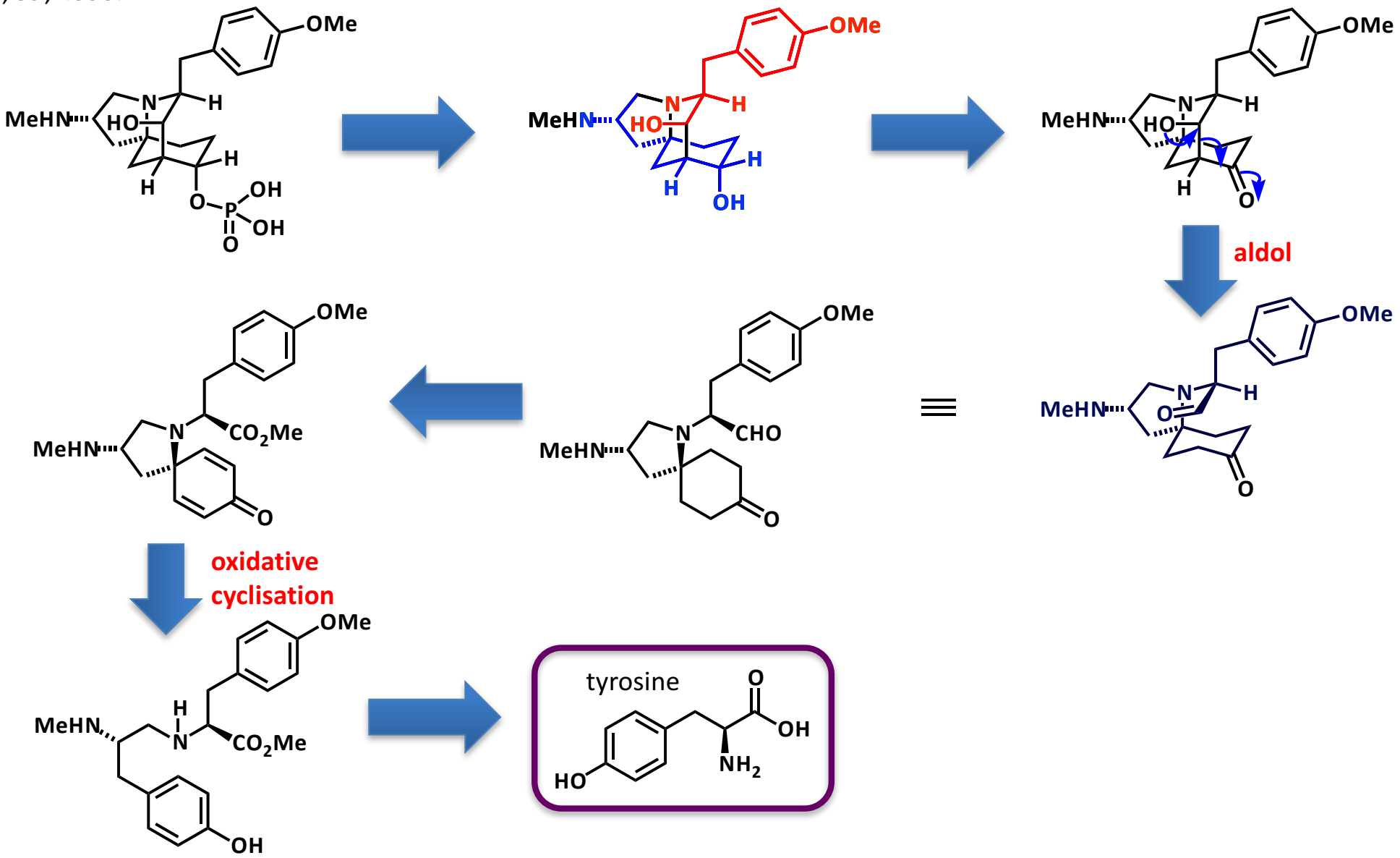
■ Biosynthetic synthesis of keramaphidin B, J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, *Angew. Chem. Int. Ed.*, **1998**, *37*, 2661.



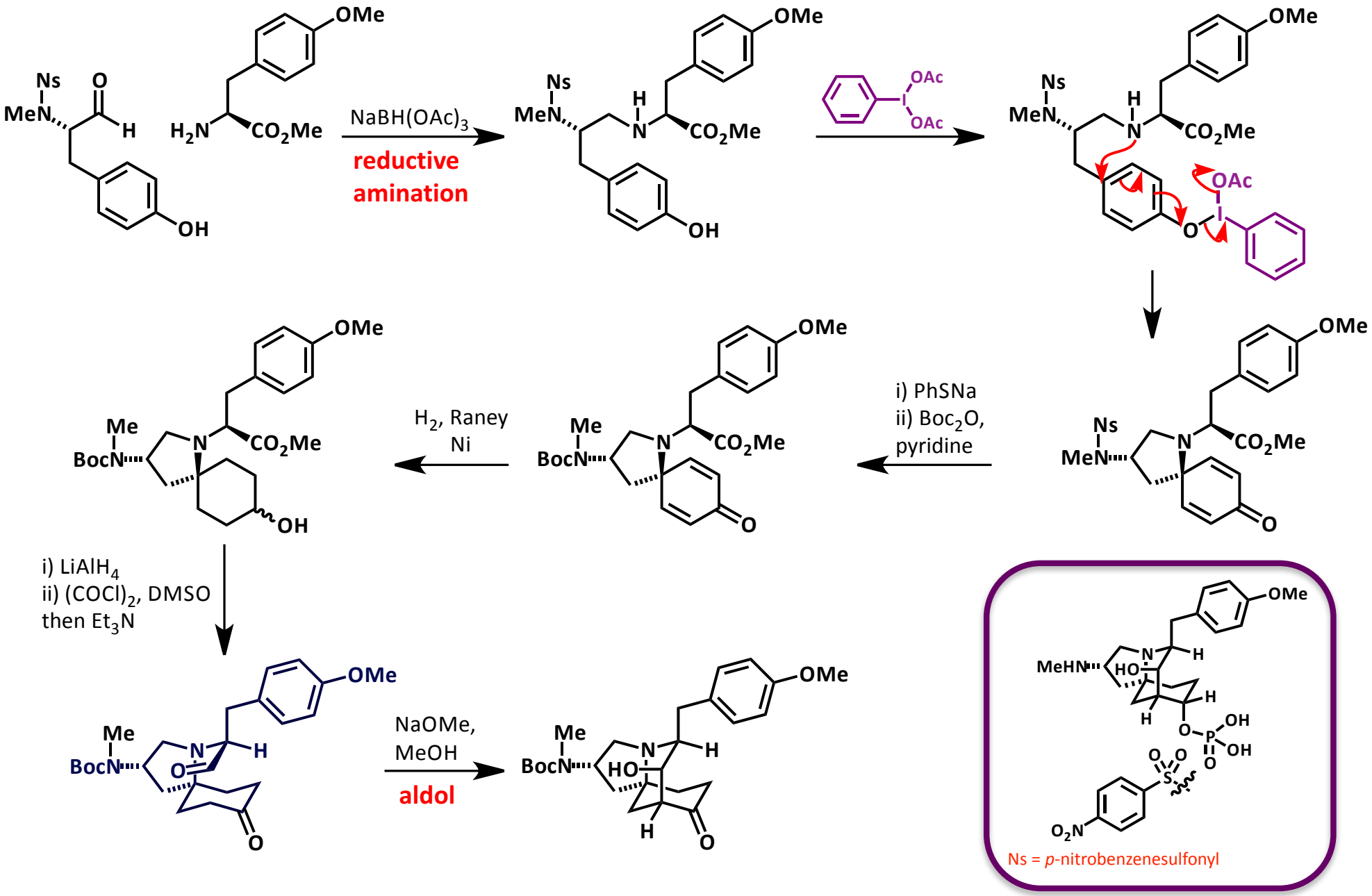


Polonovski reaction/rearrangement

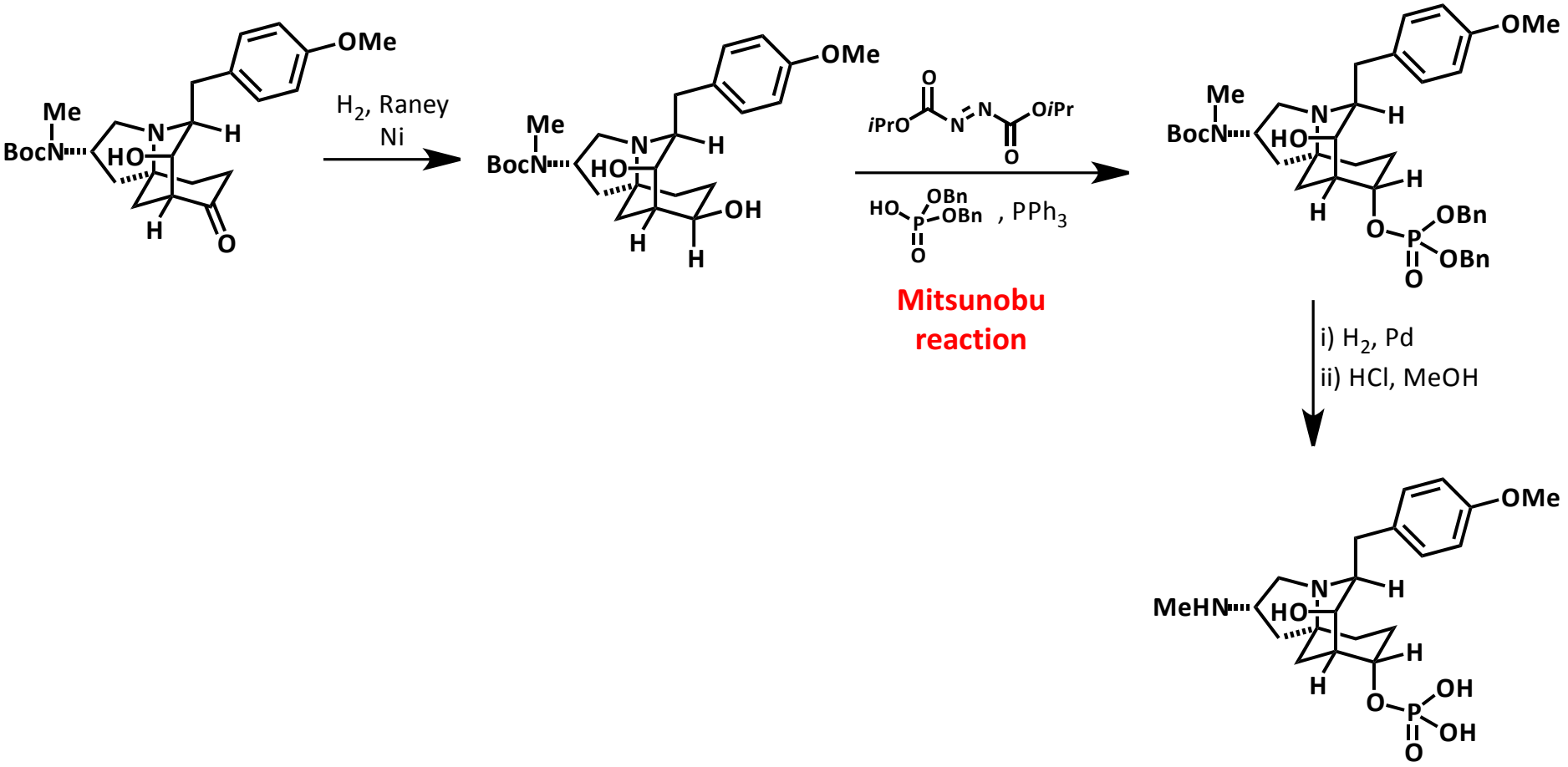
■ FR-901483 – potent immunosuppressant; Snider, *J. Am. Chem. Soc.*, **1999**, *121*, 7778; Sorensen, *Angew. Chem. Int.. Ed.*, **2000**, *39*, 4593.



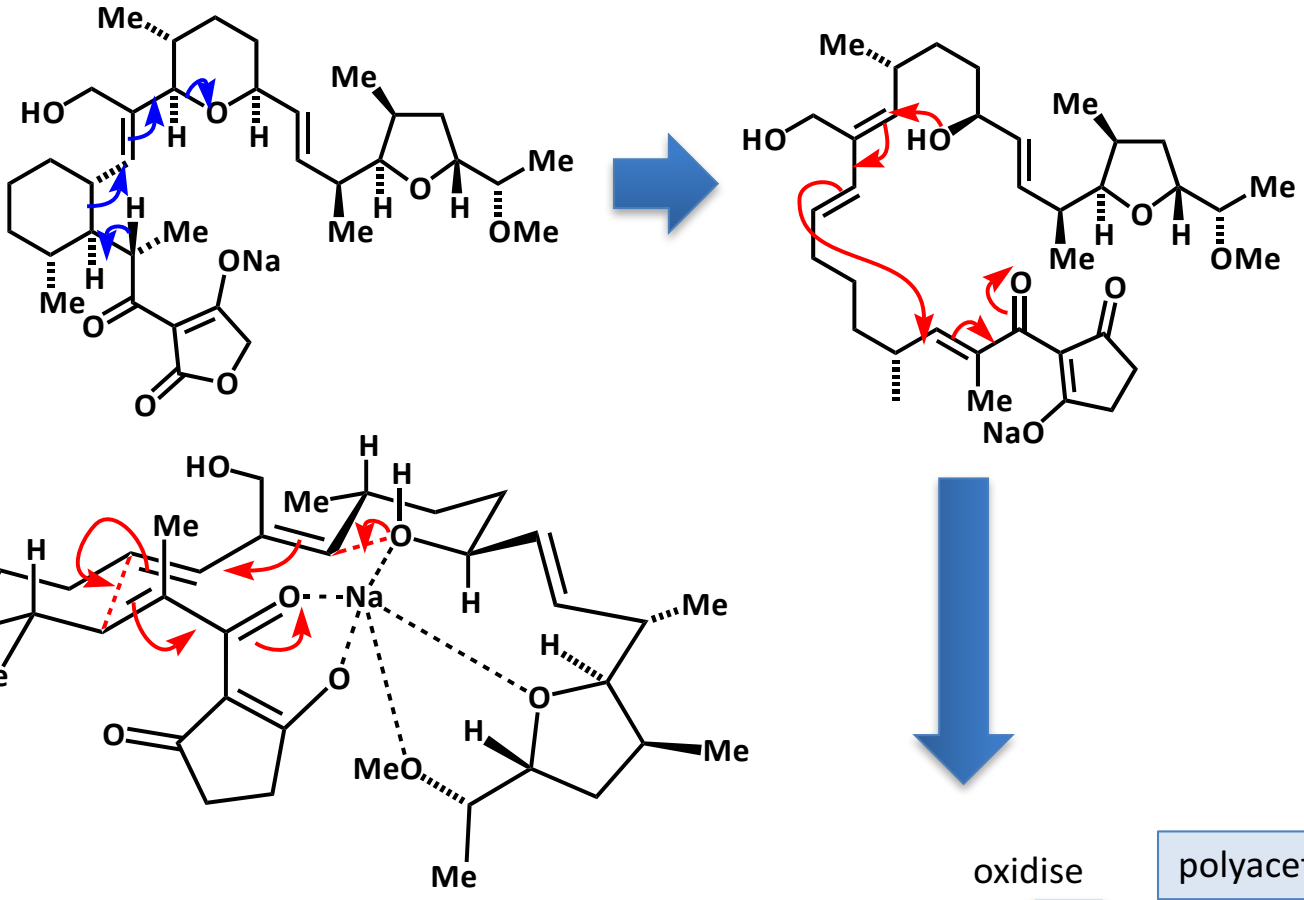
- FR-901483 – potent immunosuppressant; Sorensen, *Angew. Chem. Int.. Ed.*, **2000**, *39*, 4593.



- FR-901483 – potent immunosuppressant; Sorensen, *Angew. Chem. Int.. Ed.*, **2000**, *39*, 4593.



■ Tetronasin – ionophore antibiotic – biosynthesis – Ley and Staunton, *Tetrahedron Lett.*, **1994**, *35*, 307 (and following papers), synthesis, Ley *J. Chem. Soc., Perkin 1*, **1998**, 2259.

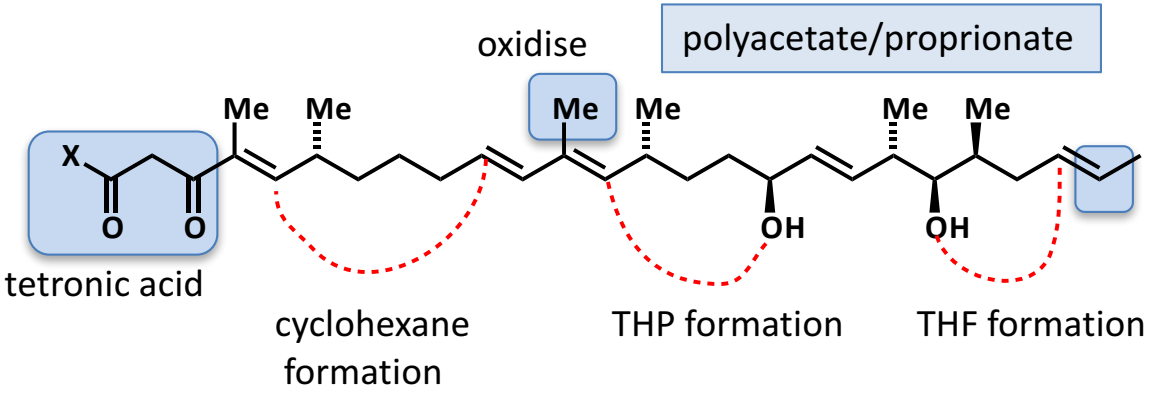


■ Professor Steven Ley, FRS

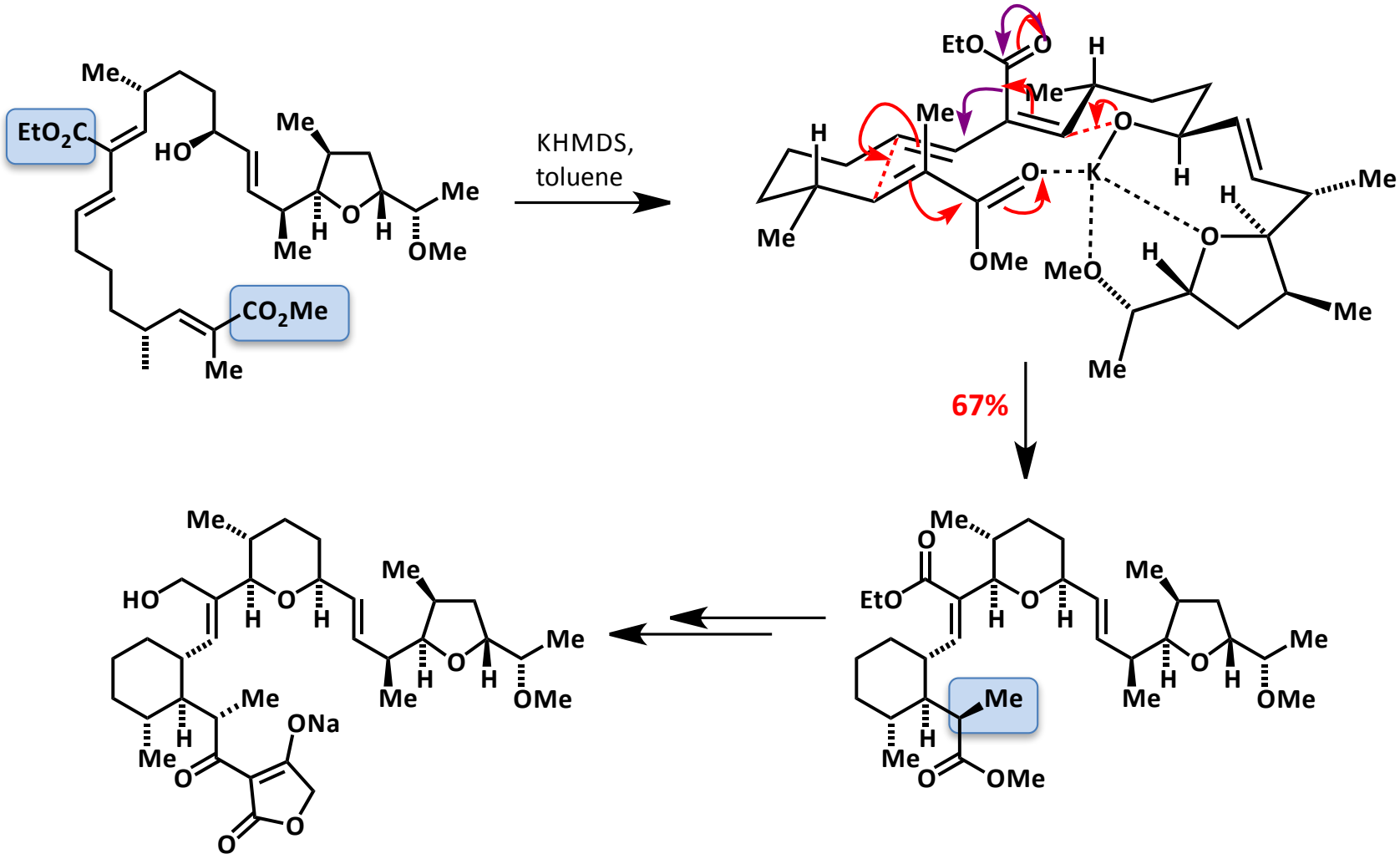
■ BP 1702 Chair, University of Cambridge, **1992-**

■ Professor at Imperial College, London, 1983-1992

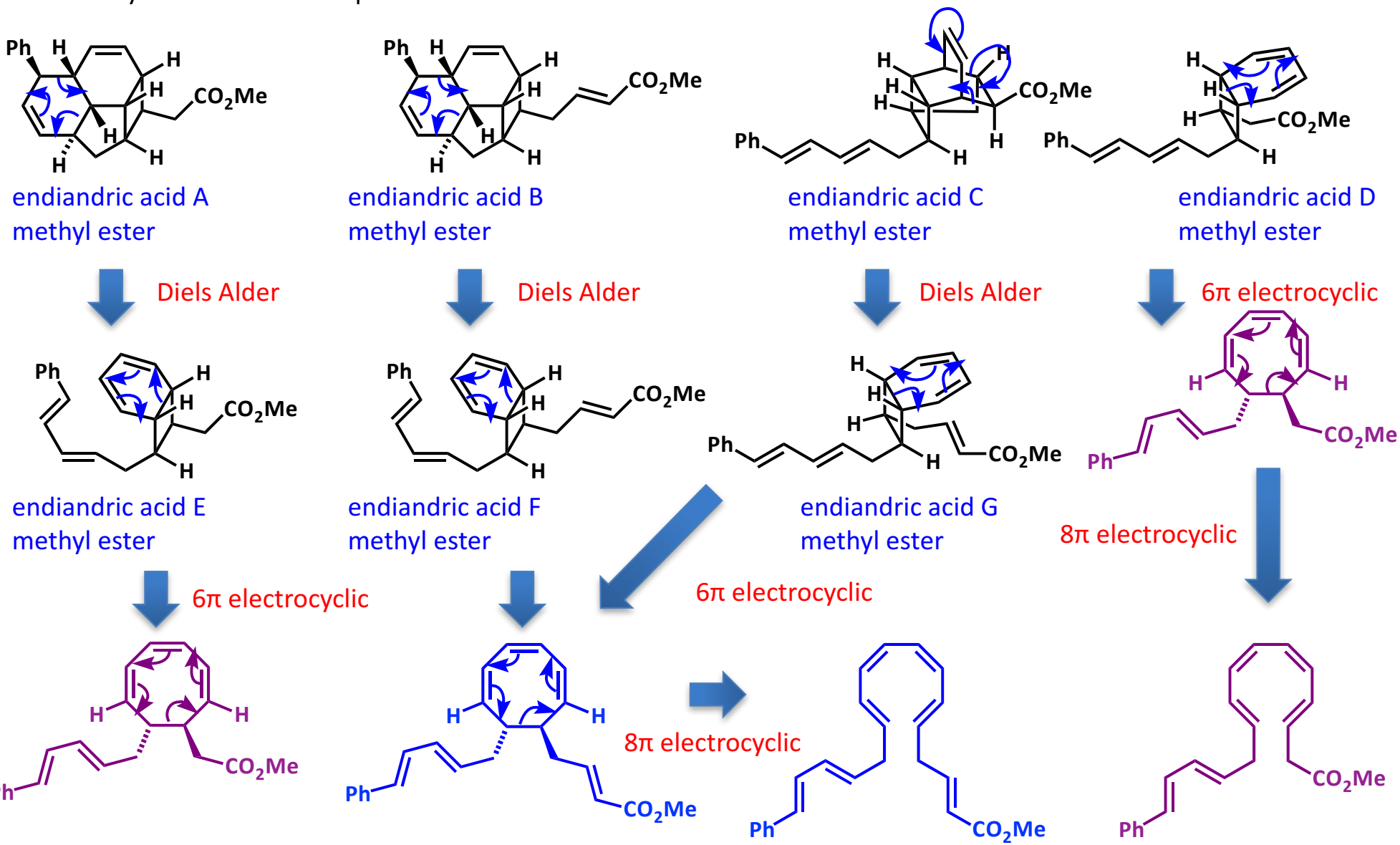
■ Natural product synthesis, methodology: TPAP, supported reagents, flow chemistry



■ Tetronasin – ionophore antibiotic – biosynthesis – Ley and Staunton, *Tetrahedron Lett.*, **1994**, *35* 307 (and following papers), synthesis, Ley *J. Chem. Soc., Perkin 1*, **1998**, 2259.

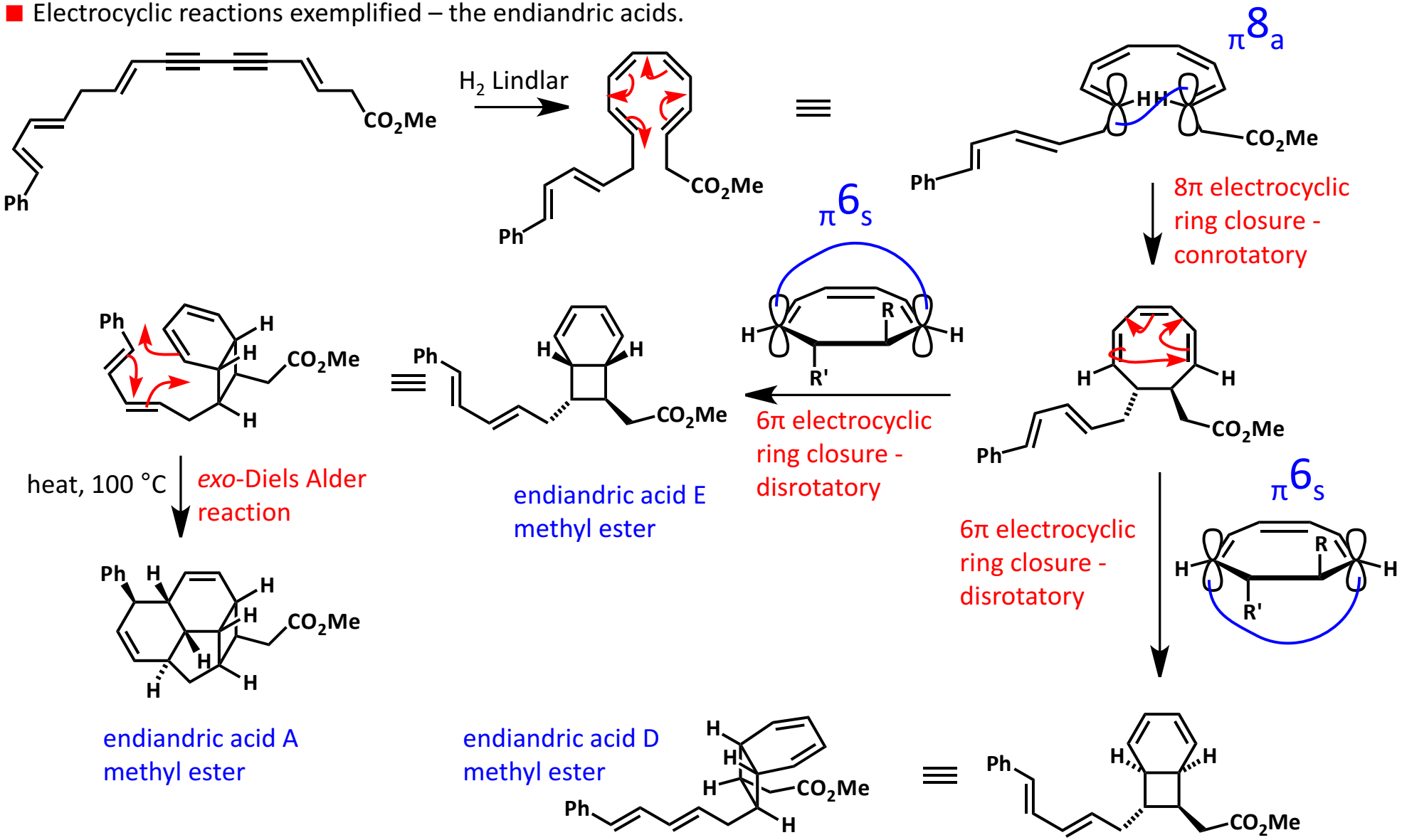


- Electrocyclic reactions exemplified – the endiandric acids.

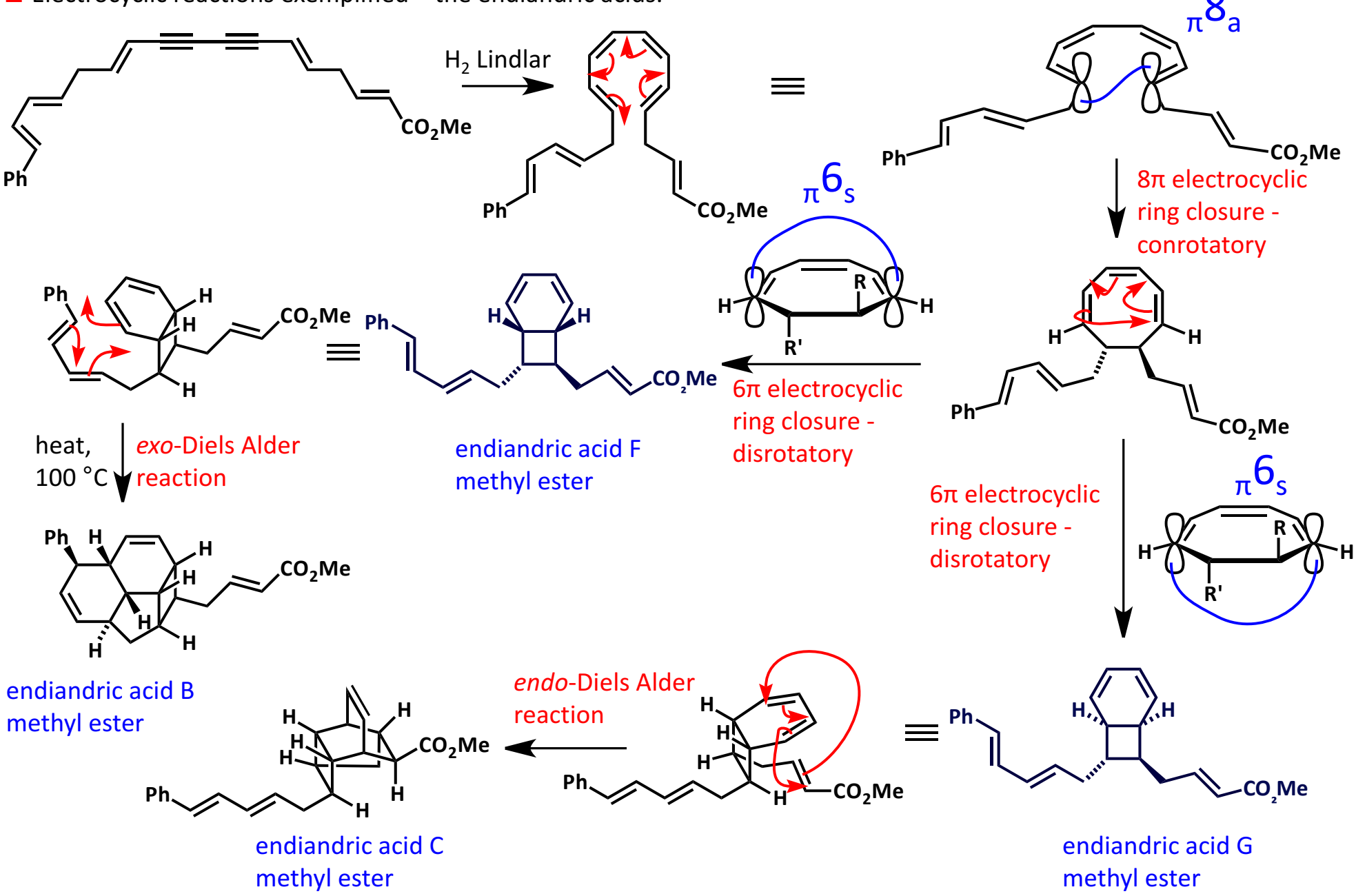


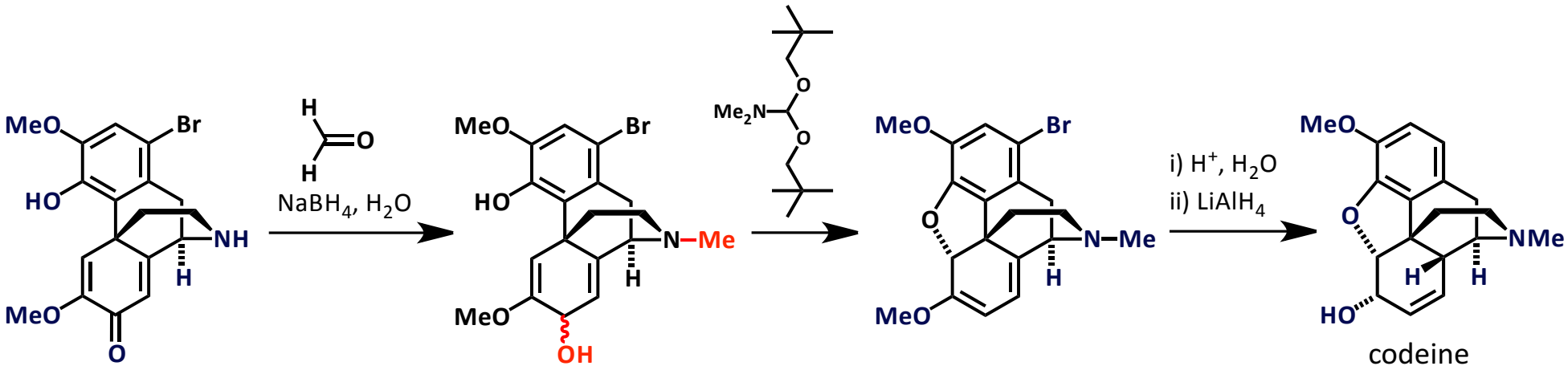
- Biosynthesis proposed by Black *J. Chem. Soc., Chem. Commun.*, **1980**, 902.
- Biomimetic synthesis by K. C. Nicolaou, *J. Am. Chem. Soc.*, **1982**, *104*, 5558.

■ Electrocyclic reactions exemplified – the endiandric acids.



■ Electrocyclic reactions exemplified – the endiandric acids.




MeO
Br
HO
NH
H
MeO
O
H
O
NaBH4, H2O
MeO
Br
HO
N–Me
H
MeO
OH
Me2N
O
O
MeO
Br
O
N–Me
H
MeO
i) H+, H2O
ii) LiAlH4
MeO
O
NMe
H
H
HO
codeine

- The related ephedrine, from a number of *Ephedra* species, has a very different biogenesis involving pyruvate