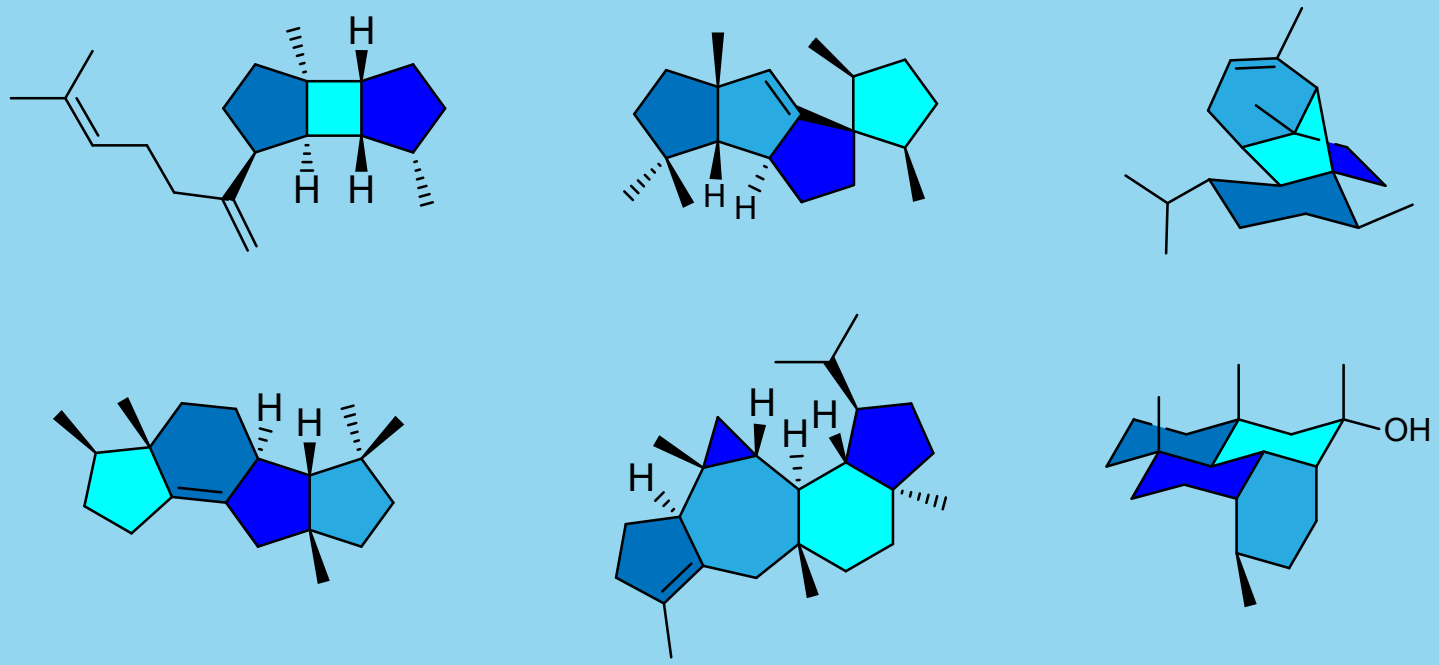


Organic Molecules & Materials

Prof. Dr. Jeroen S. Dickschat

0. Literature

0.1 Textbooks

- Paul M. Dewick, Medicinal Natural Products, Wiley-VCH
- Christopher T. Walsh, Yi Tang, Natural Product Biosynthesis, RSC Publishing

0.2 Journals

- Angewandte, JACS, Chemical Science (recent articles on NPs)
- Journal of Natural Products
- ChemBioChem, Organic & Biomolecular Chemistry
- Natural Product Reports (only reviews)

0.3 Webpages and Software

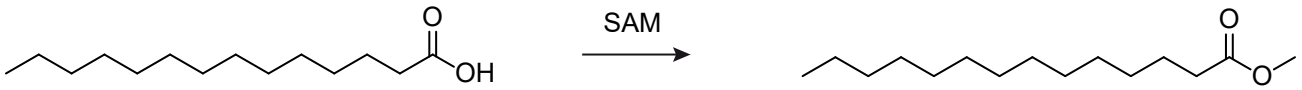
- KEGG Pathways
- NCBI
- Pymol (free 3D structure viewer)

1. Enzymes and Cofactors

1.1 Enzyme classification

EC 1	Oxidoreductases
EC 1.1	CH-OH as electron donor
EC 1.1.1	$NAD(P)^+$ as electron acceptor
EC 1.1.1.1	alcohol dehydrogenase

EC 2	Transferases
EC 2.1.1.15	Fatty acid O-methyltransferase



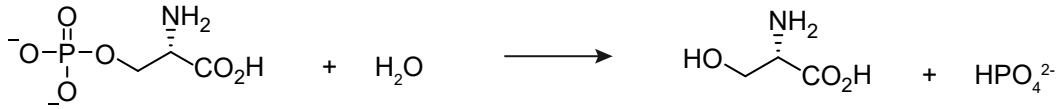
myristic acid | methyl myristate

SAM = Me donor

1. Enzymes and Cofactors

1.1 Enzyme classification

EC 3	Hydrolases
EC 3.1.3.3	Phosphoserine phosphatase



EC 4	Lyases (catalyse eliminations)
EC 4.4.1.3	DMSP lyases

dimethylsulfoniopropionate (DMSP) dimethyl sulfide acrylic acid

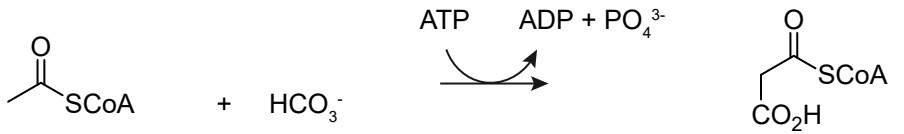
1. Enzymes and Cofactors

1.1 Enzyme classification

EC 5	Isomerases
EC 5.3.3.2	Isopentenyl diphosphate isomerase (IDI)

isopentenyl diphosphate (IPP) dimethylallyl diphosphate (DMAPP)

EC 6	Ligases (catalyse covalent bond formations)
EC 6.4.1.2	Acetyl-SCoA carboxylase



acetyl-SCoA malonyl-SCoA

EC 7	Translocases (catalyse transmembrane transport)

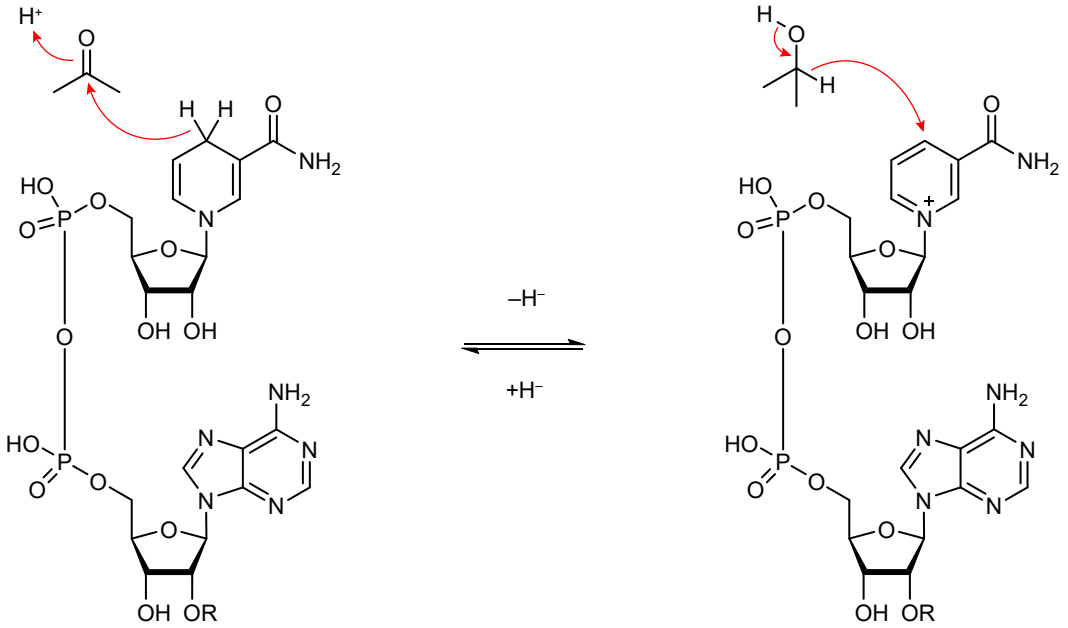
1.2 Enzyme cofactors

1.2.1 Redox cofactors

1.2.1.1 NAD(P)H

reduced form (hydride donor) | oxidised form (hydride acceptor)

nicotineamide adenin dinucleotide (phosphate)



R=H (NADH)
R=PO_3^{2-} (NADPH)

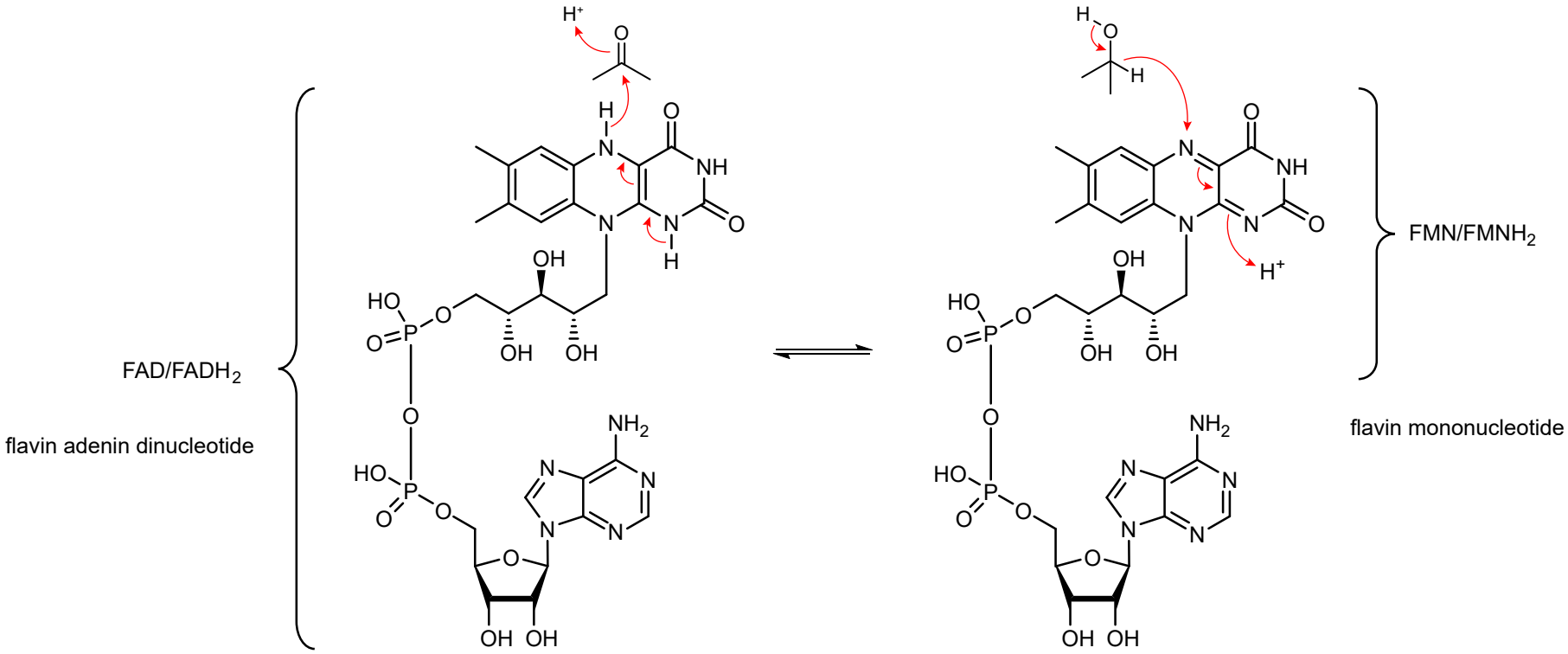
R=H (NAD^+)
R=PO_3^{2-} ($NADP^+$)

1.2 Enzyme cofactors

1.2.1 Redox cofactors

1.2.1.2 FMN and FAD

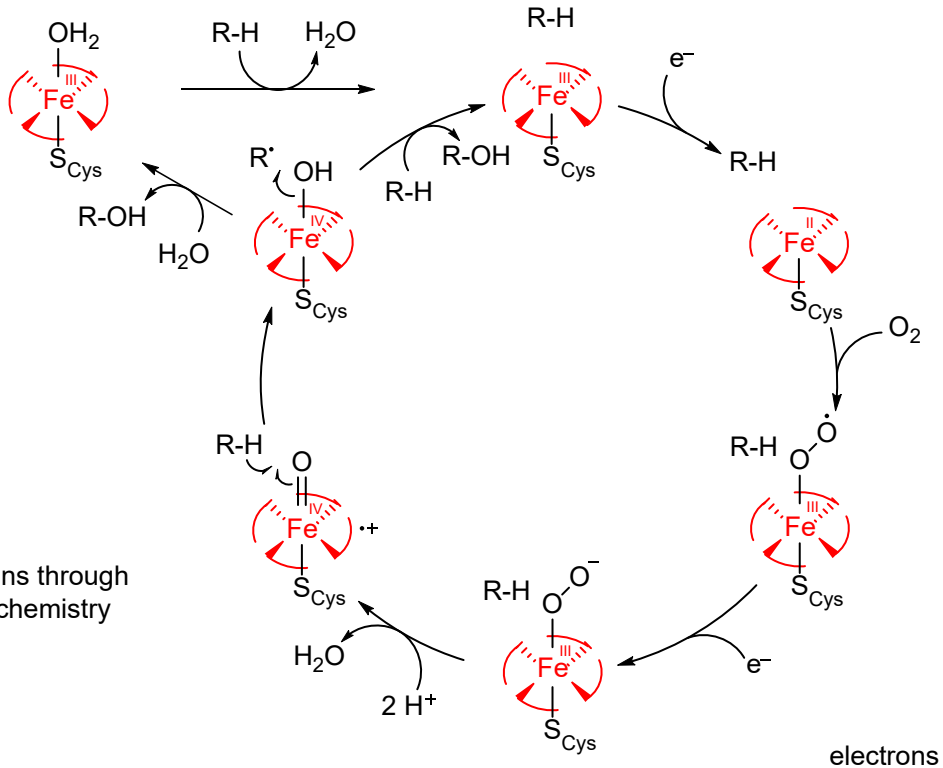
reduced form (hydride donor) oxidised form (hydride acceptor)



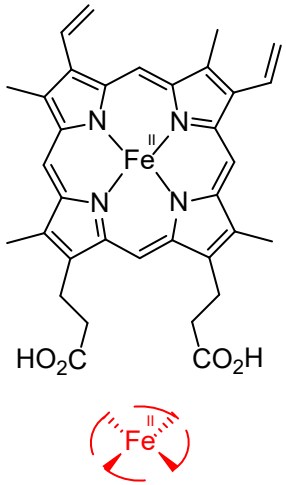
1.2 Enzyme cofactors

1.2.1 Redox cofactors

1.2.1.3 Heme iron complexes: cytochrome P450 monooxygenases



oxidations through radical chemistry



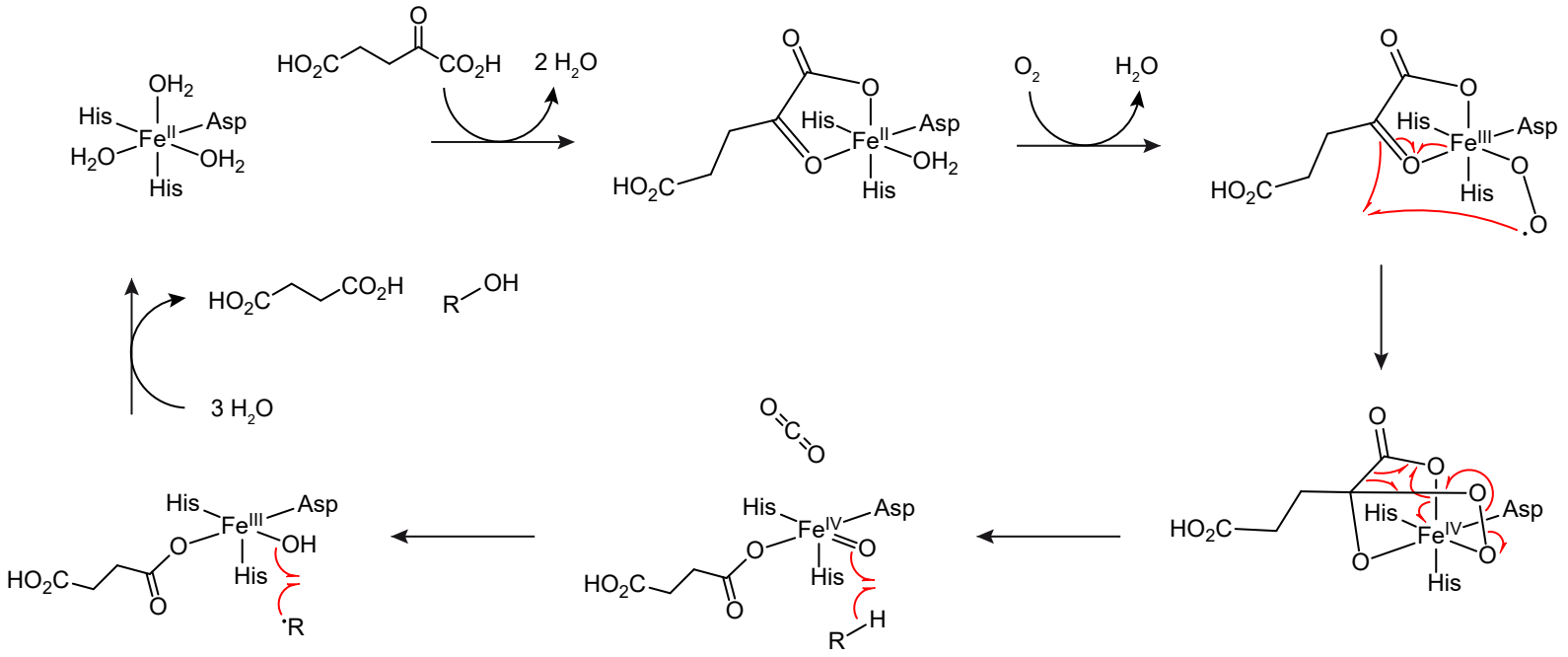
heme iron complex

electrons from NADPH by redox partner proteins

1.2 Enzyme cofactors

1.2.1 Redox cofactors

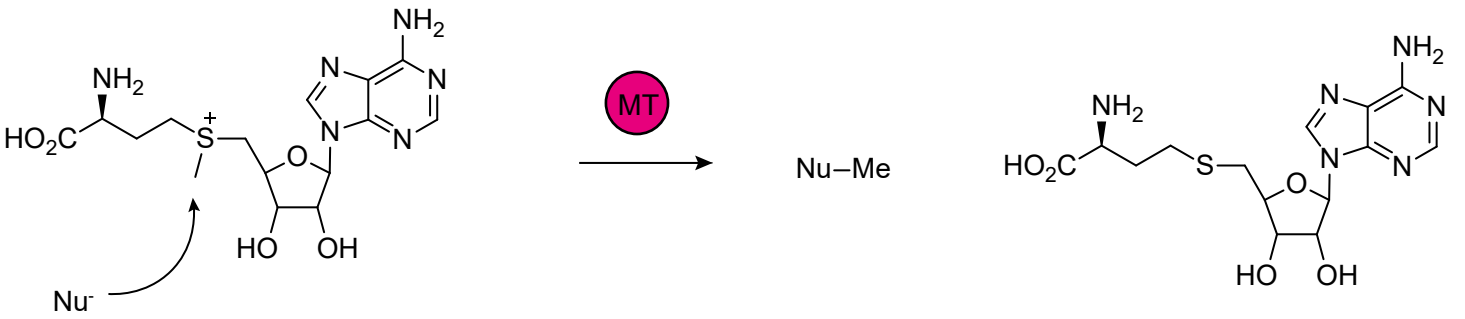
1.2.1.4 α-Ketoglutarate dependent dioxygenases



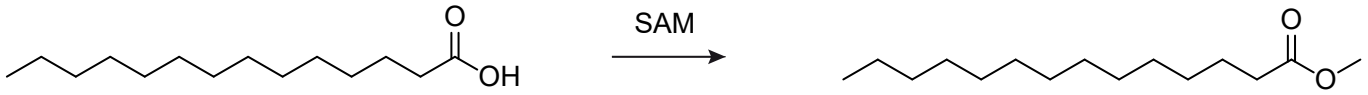
1.2 Enzyme cofactors

1.2.2 Cofactors for alkylations

1.2.2.1 S-Adenosylmethionine (SAM)



S-adenosylmethionine (SAM) S-adenosylhomocysteine (SAH)

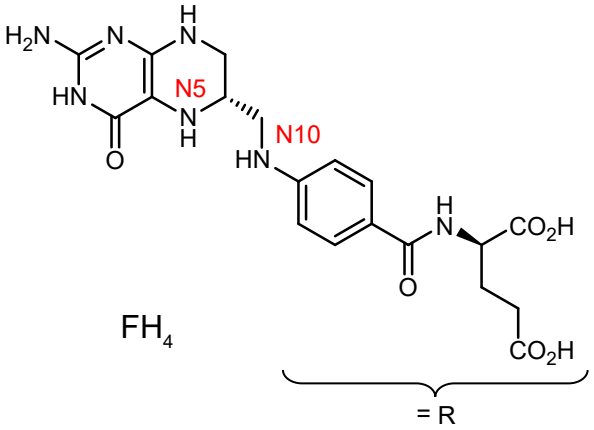


myristic acid methyl myristate

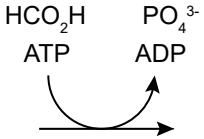
1.2 Enzyme cofactors

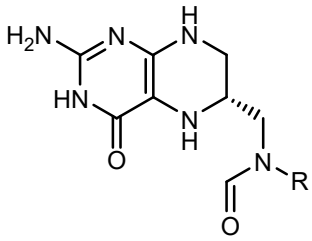
1.2.2 Cofactors for alkylations

1.2.2.2 Tetrahydrofolate (FH_4)

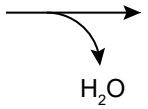


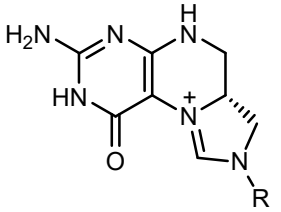
FH_4



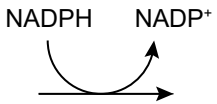


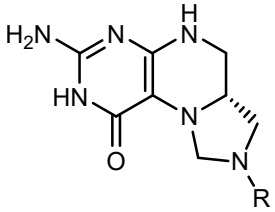
10-Formyl-FH_4



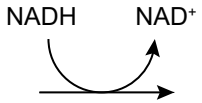


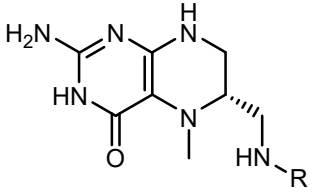
5,10-Methenyl-FH_4





5,10-Methylen-FH_4



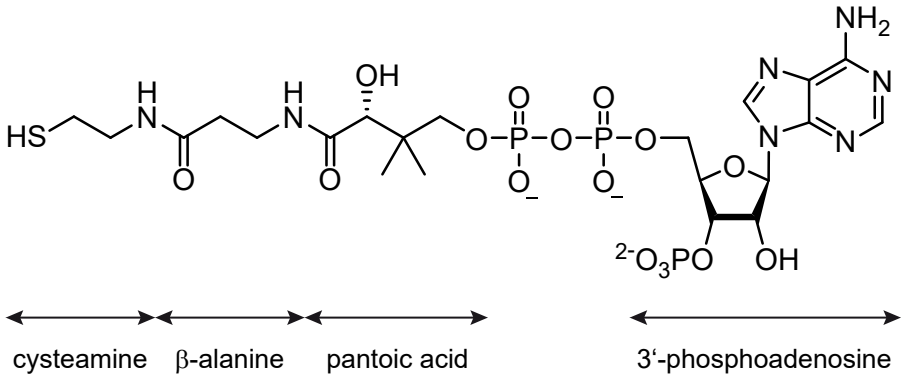


5-Methyl-FH_4

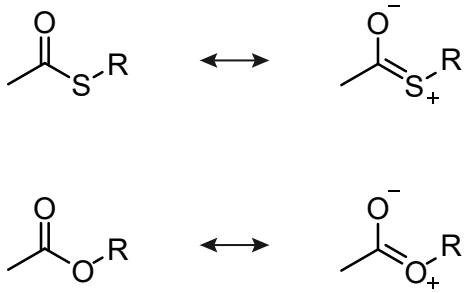
1.2 Enzyme cofactors

1.2.3 Cofactors of acyl group transfer

1.2.3.1 Coenzyme A



coenzyme A



thioesters exhibit

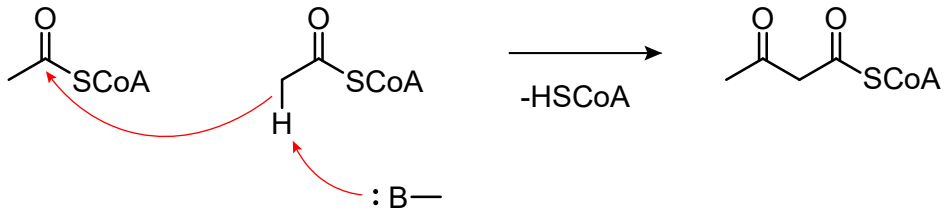
- lower resonance (S >> C, O ≈ C)
- higher C,H acidity
- better leaving group RS^-
- higher reactivity in Claisen- and aldol reaction

1.2 Enzyme cofactors

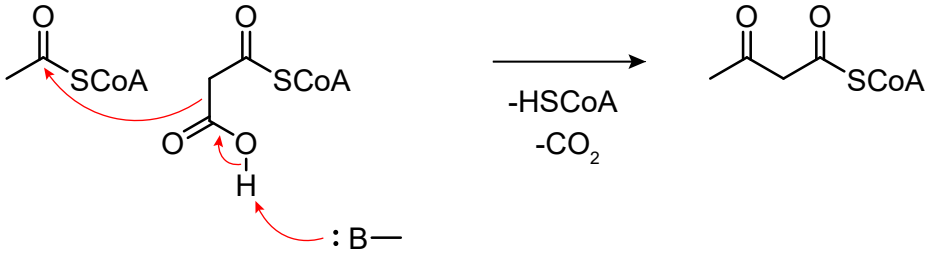
1.2.3 Cofactors of acyl group transfer

1.2.3.1 Coenzyme A

biological Claisen condensation



even higher reactivity with malonyl-SCoA



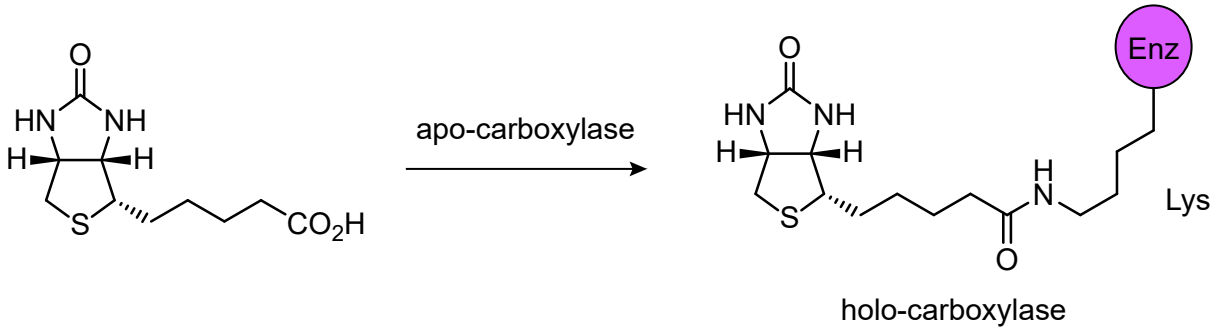
effects of CO_2 formation

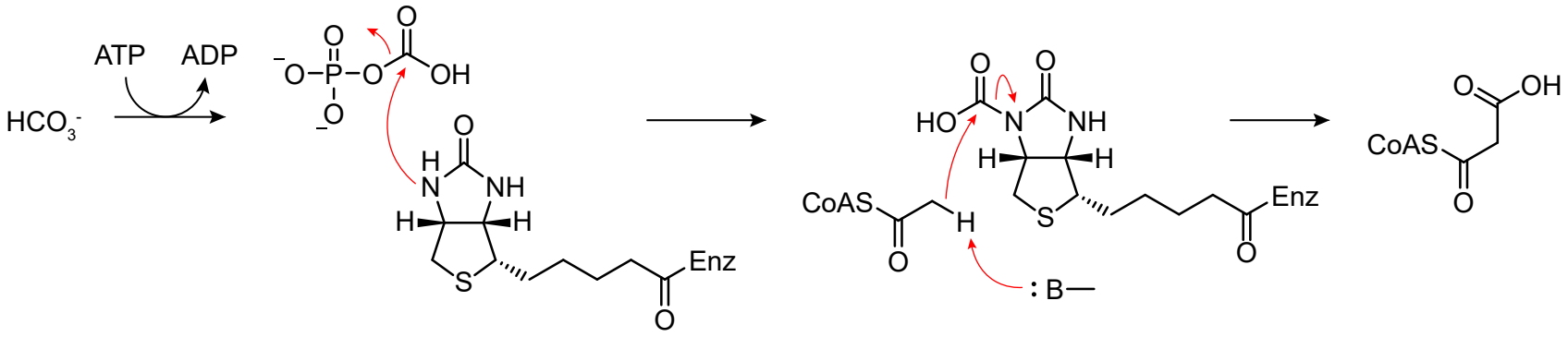
- reaction driven by entropy
- no back reaction possible

1.2 Enzyme cofactors

1.2.3 Cofactors of acyl group transfer

1.2.3.2 Biotin (carboxylation of acetyl-SCoA)

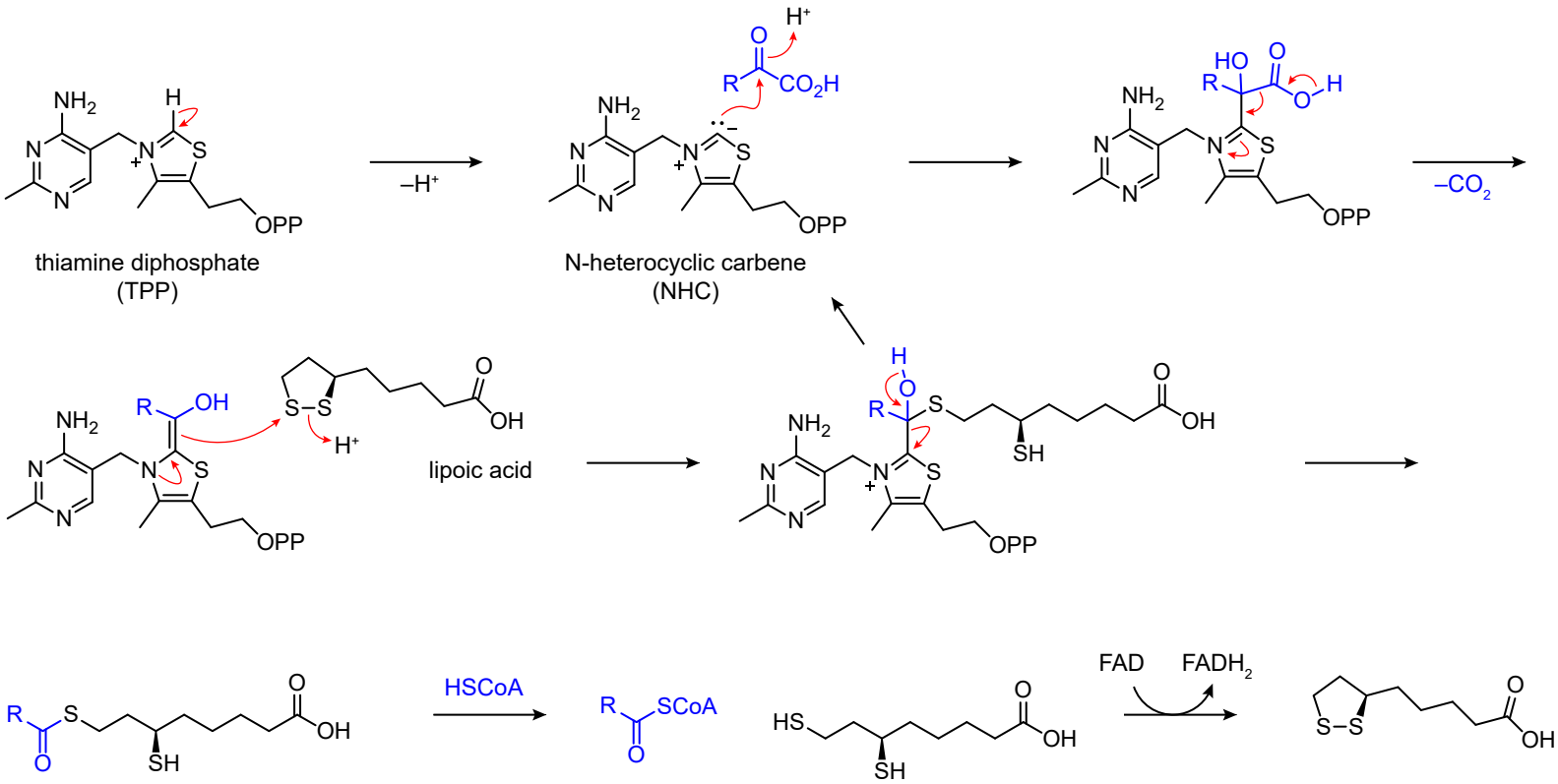




1.2 Enzyme cofactors

1.2.3 Cofactors of acyl group transfer

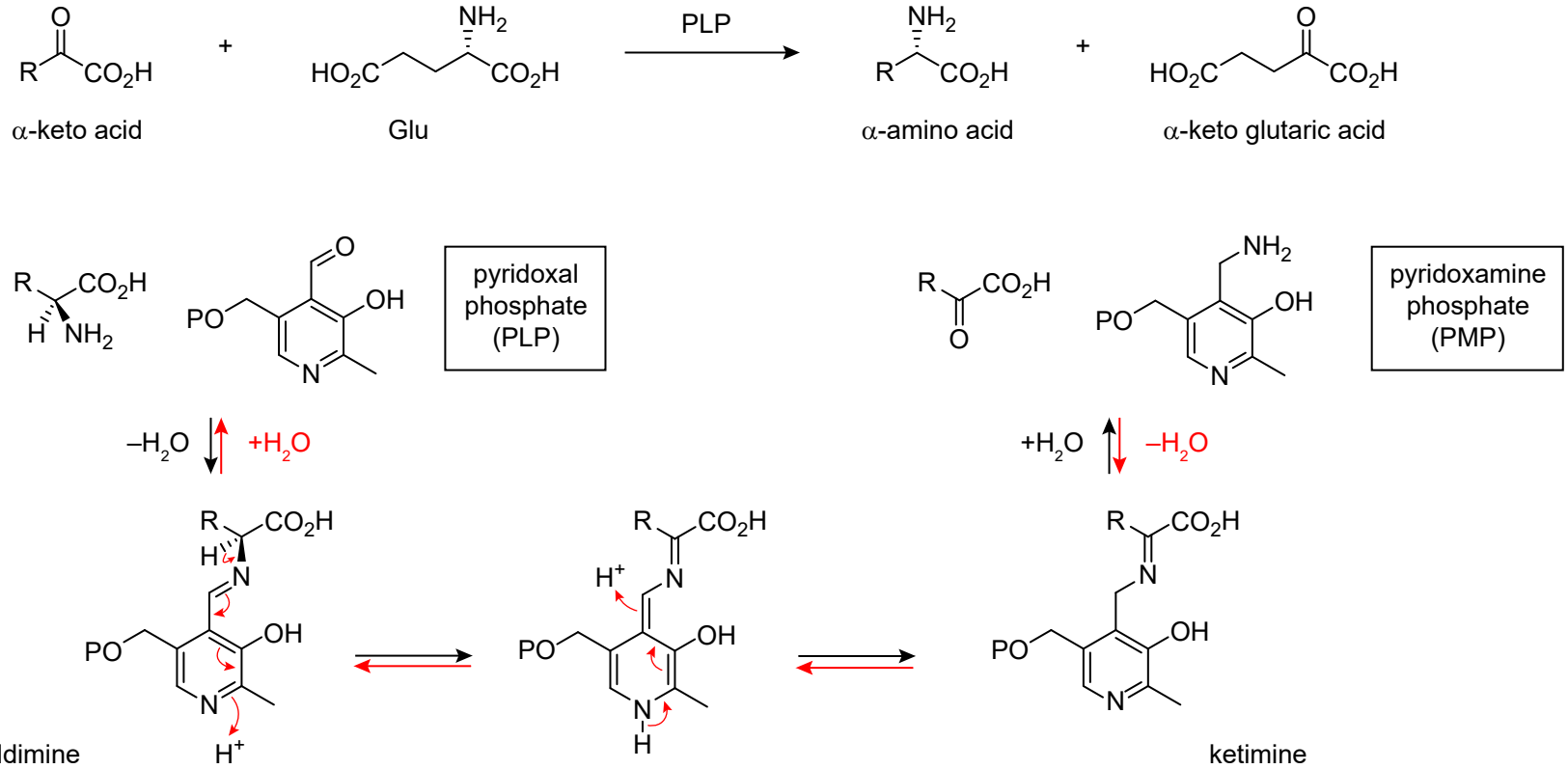
1.2.3.3 Thiamine diphosphate and lipoic acid (oxidative decarboxylation)



1.2 Enzyme cofactors

1.2.4 Cofactors of amino acid metabolism

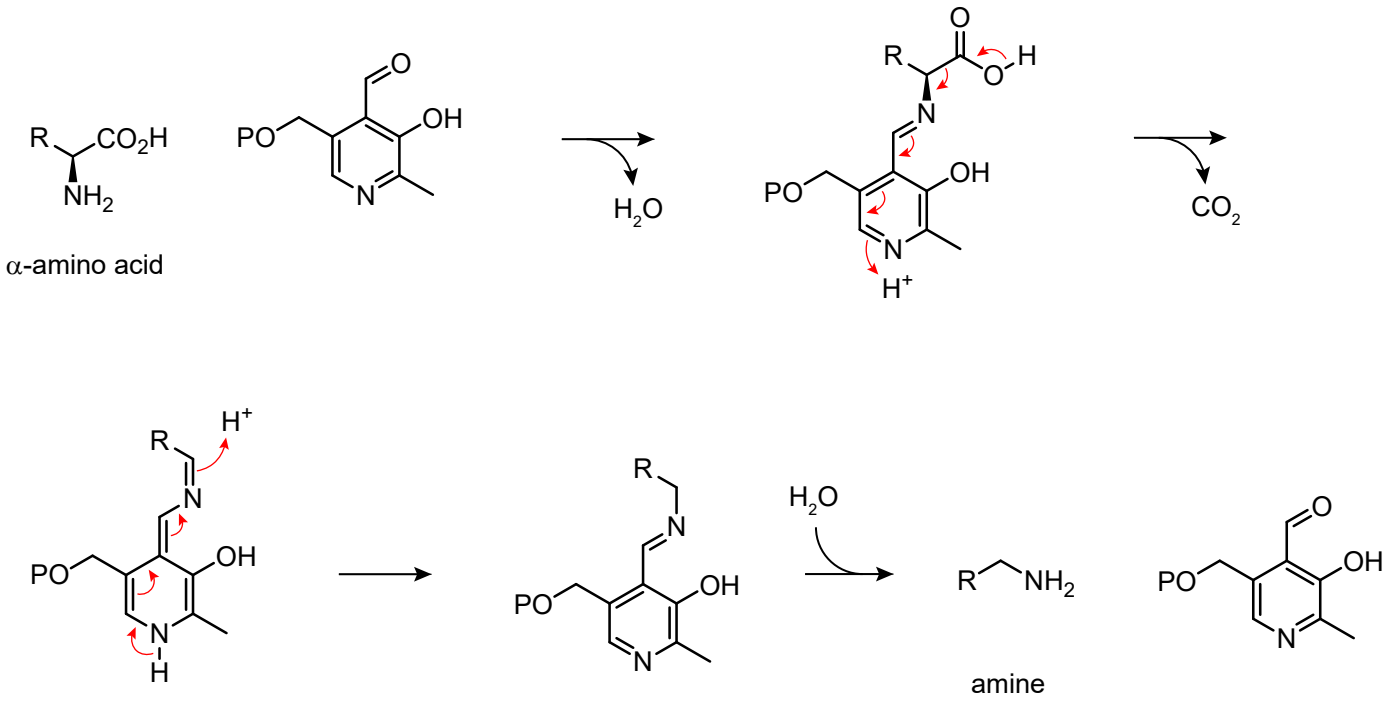
1.2.4.1 Pyridoxal phosphate (transamination)



1.2 Enzyme cofactors

1.2.4 Cofactors of amino acid metabolism

1.2.4.2 Pyridoxal phosphate (decarboxylation)



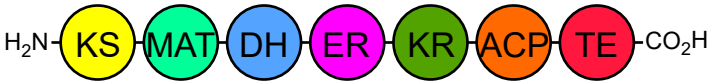
2. Fatty acids

2.1 Biosynthesis of saturated fatty acids

2.1.1 Animals and fungi (type I)

multidomain enzymes (megasynthases)

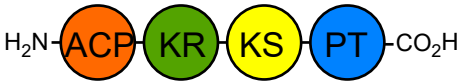
animals: homodimer



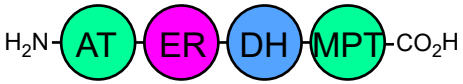
domains (catalytically active units)

KS: ketosynthase
MAT: malonyl/acetyltransferase
DH: dehydratase
ER: enoyl reductase
KR: ketoreductase
ACP: acyl carrier protein
TE: thioesterase

fungi: $\alpha_6\beta_6$ heterododecamer



α subunit



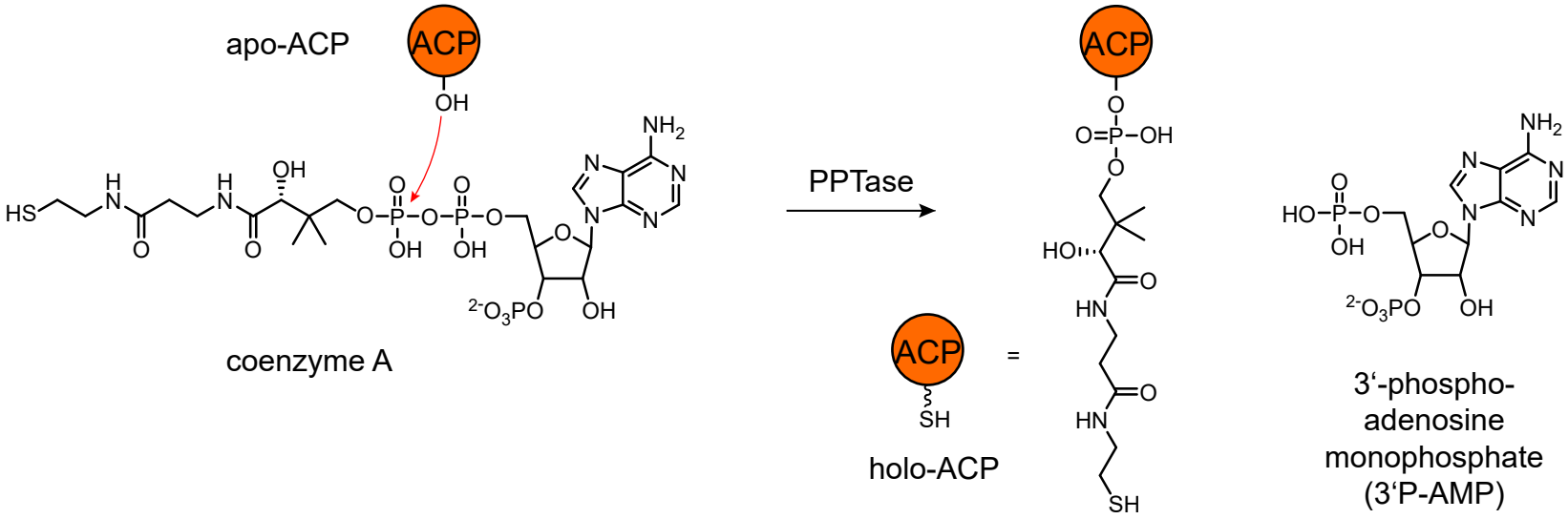
β subunit

PT: phosphopantetheinyl transferase
AT: acetyl transferase (only starter unit)
MPT: malonyl/palmitoyl transferase

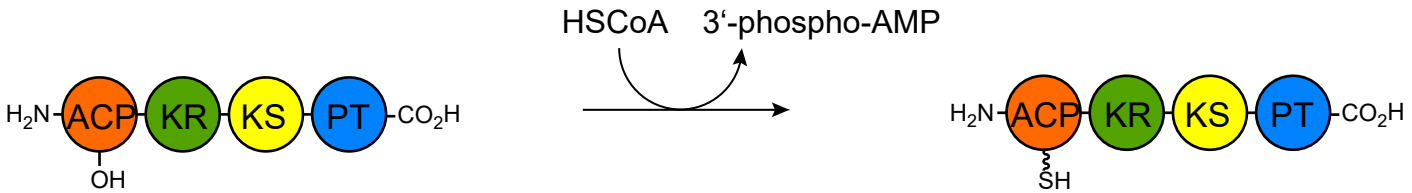
2.1 Biosynthesis of saturated fatty acids

2.1.1 Animals and fungi (type I)

activation of ACP by phosphopantetheinyl transferase (PPTase)

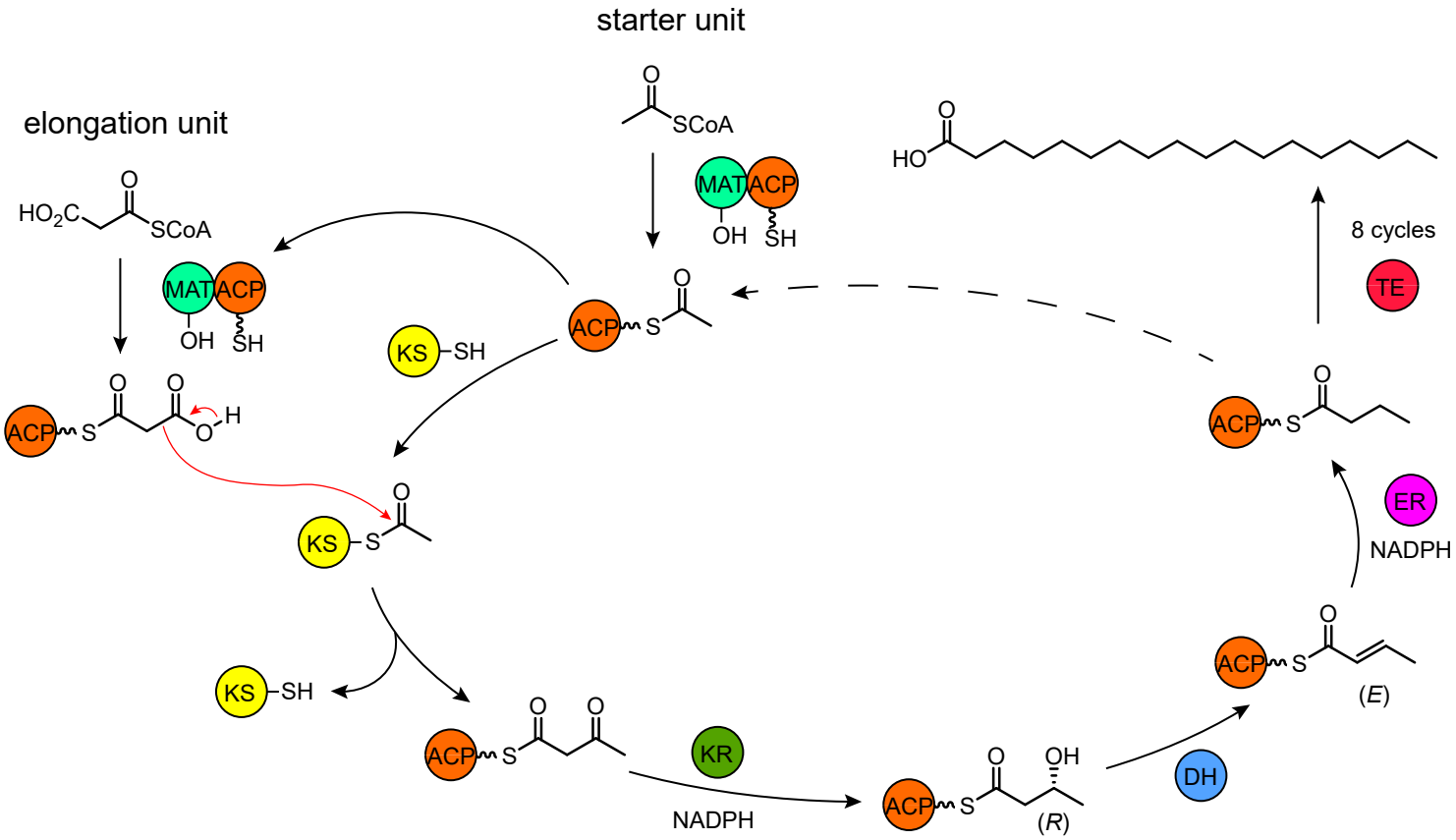


self-activation in fungi



2.1 Biosynthesis of saturated fatty acids

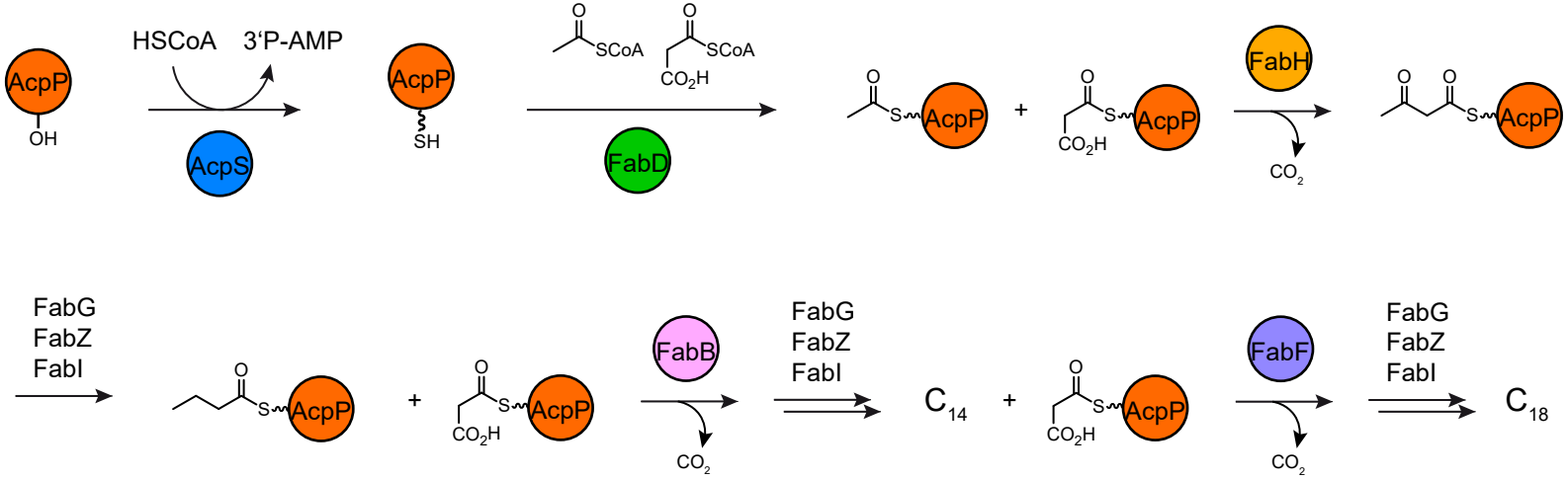
2.1.1 Animals and fungi (type I)



2.1 Biosynthesis of saturated fatty acids

2.1.2 Bacteria and plants (type II) - discrete monofunctional enzymes

FabH	KS III (chain elongation C_4)	FabG	KR
FabB	KS I (chain elongations C_6 – C_{14})	FabZ	DH
FabF	KS II (chain elongations C_{16} – C_{18})	FabI	ER
FabD	malonyl-CoA:ACP transacylase		
		AcpP	apo-ACP
FabA	3-hydroxydecanoyl-ACP dehydratase/isomerase	AcpS	holo-ACP synthase

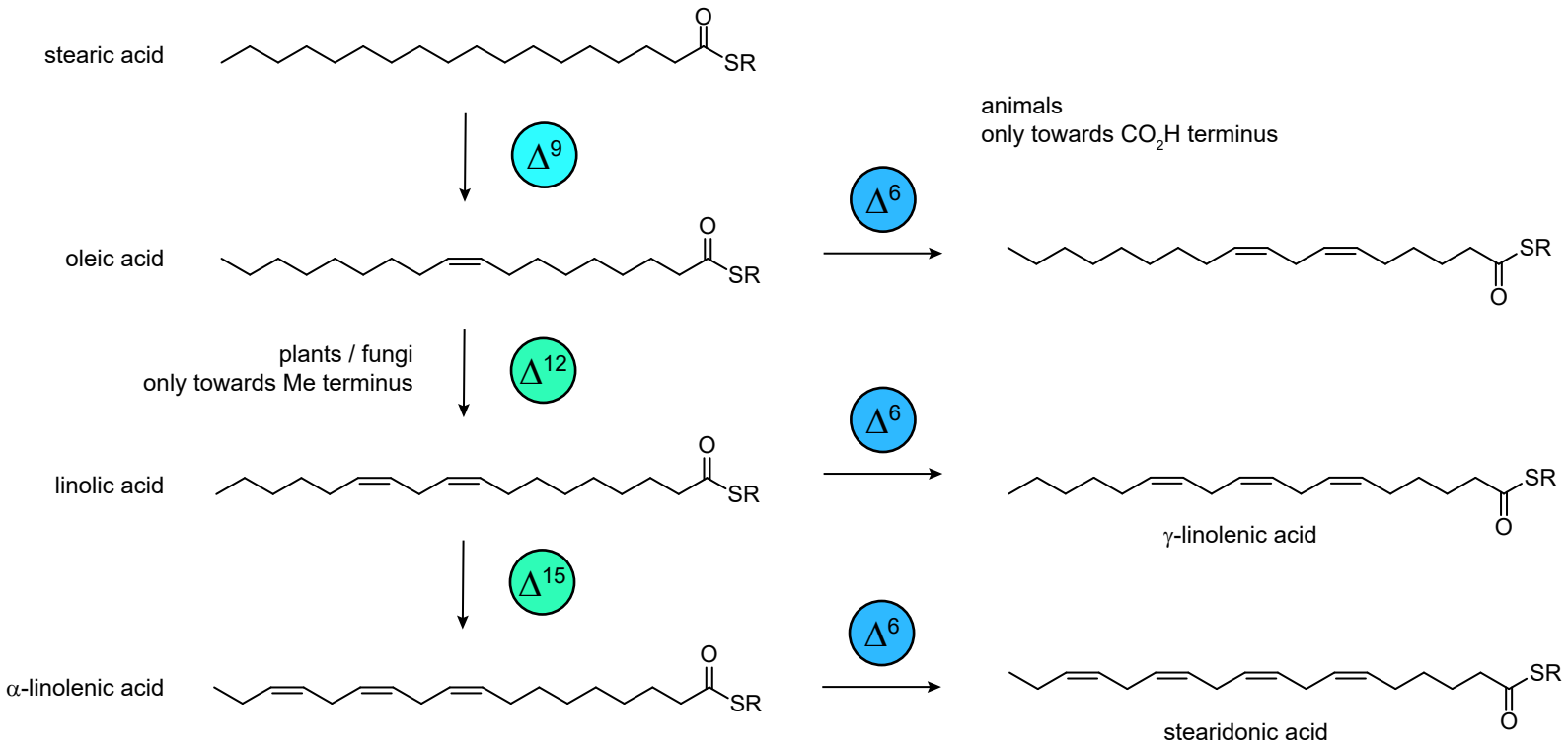


2.2 Biosynthesis of unsaturated fatty acids

2.2.1 Eukaryotes

from saturated fatty acids, by desaturases

ubiquitous: Δ^9 desaturases

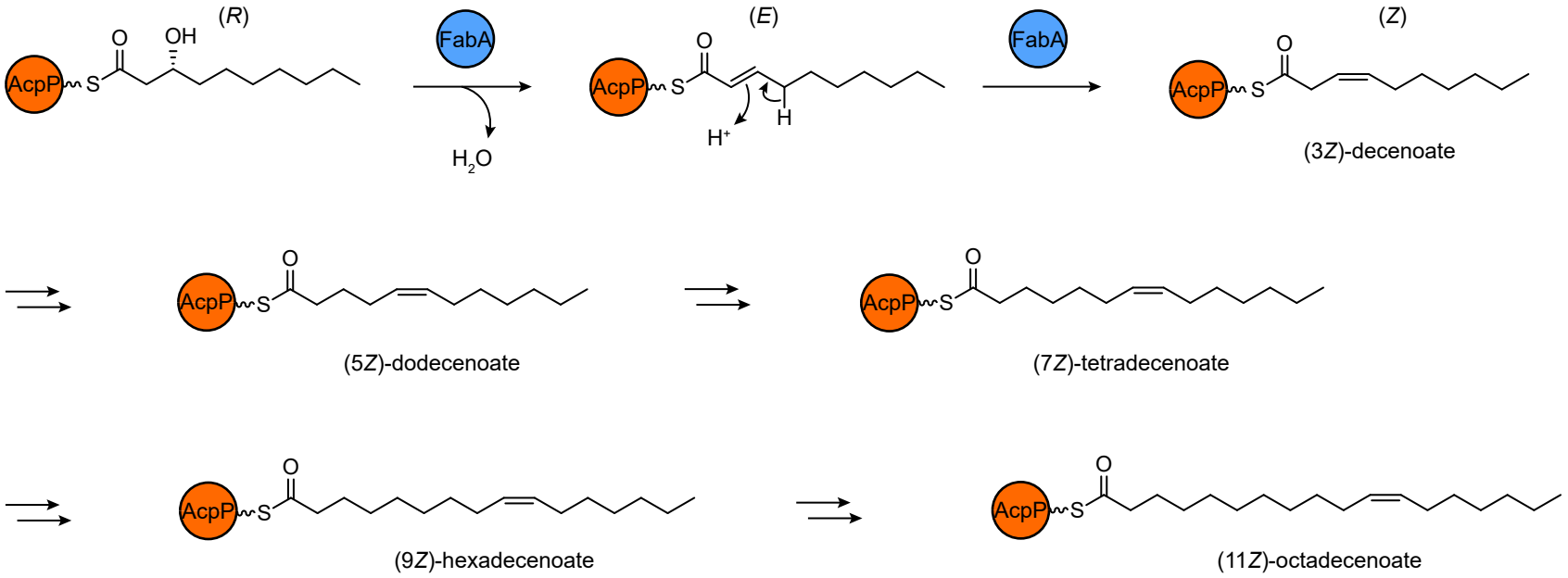


2.2 Biosynthesis of unsaturated fatty acids

2.2.2 Bacteria

anaerobic pathway

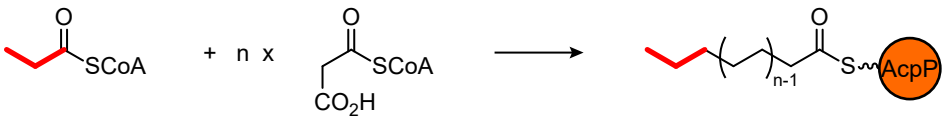
3-Hydroxydecanoyl-ACP dehydratase/isomerase (FabA)



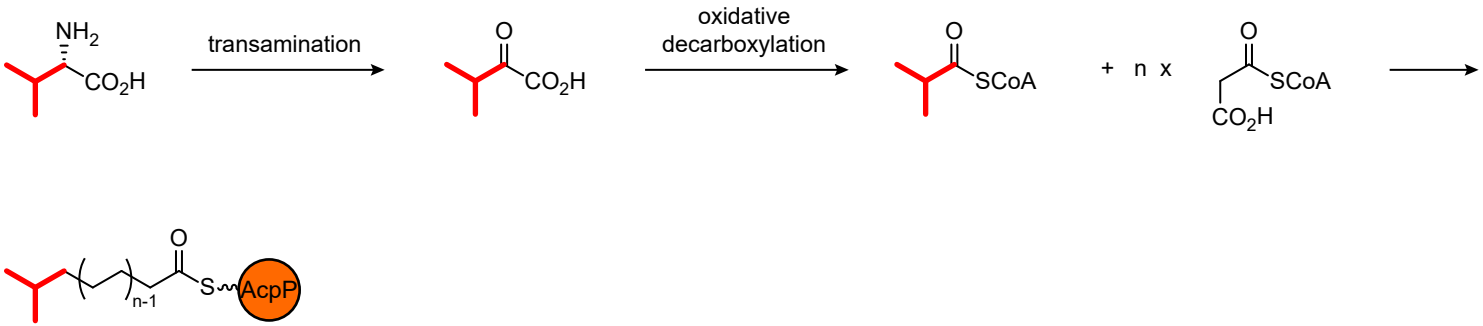
double bond in ω-7 position in all cases

2.3 Fatty acids from alternative starters

- odd fatty acids: starter unit propionyl-CoA

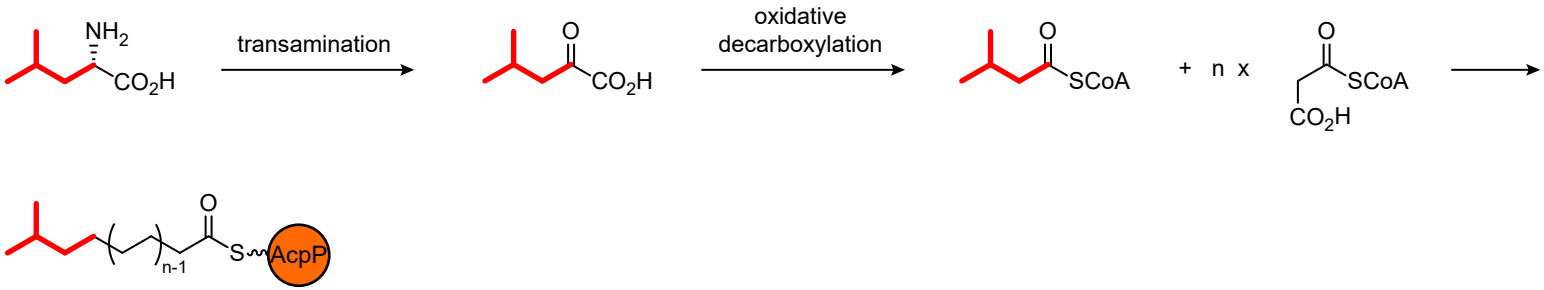


- *iso*-even fatty acids: starter unit from valine

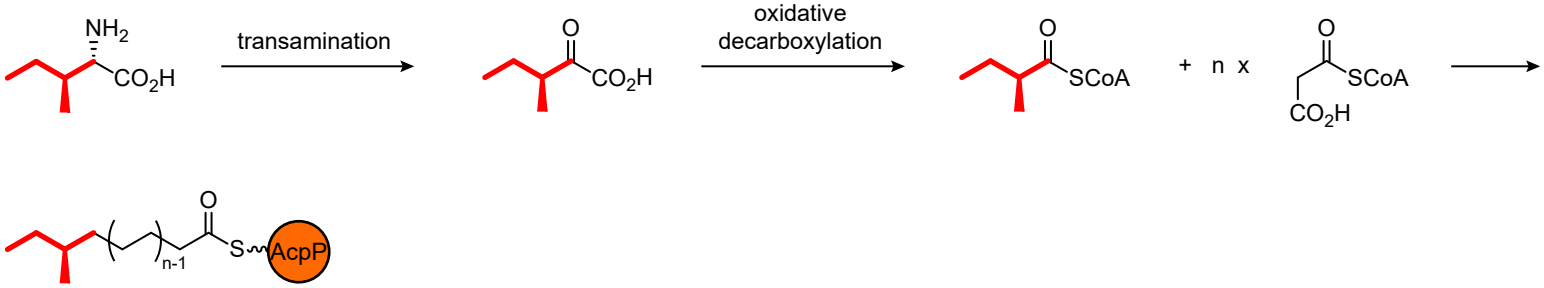


2.3 Fatty acids from alternative starters

- *iso*-odd fatty acids: starter unit from leucine

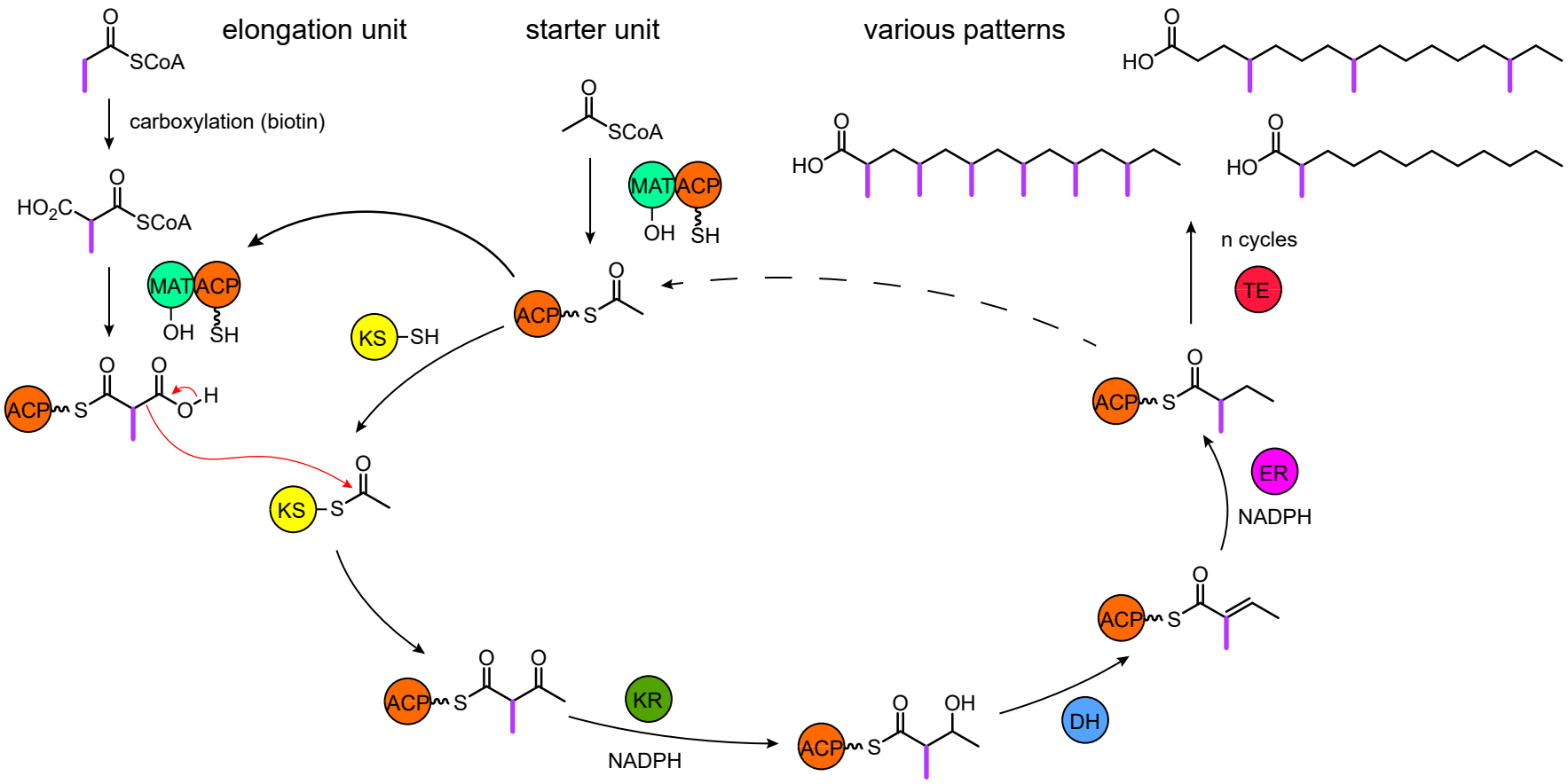


- *anteiso*-odd fatty acids: starter unit from isoleucine

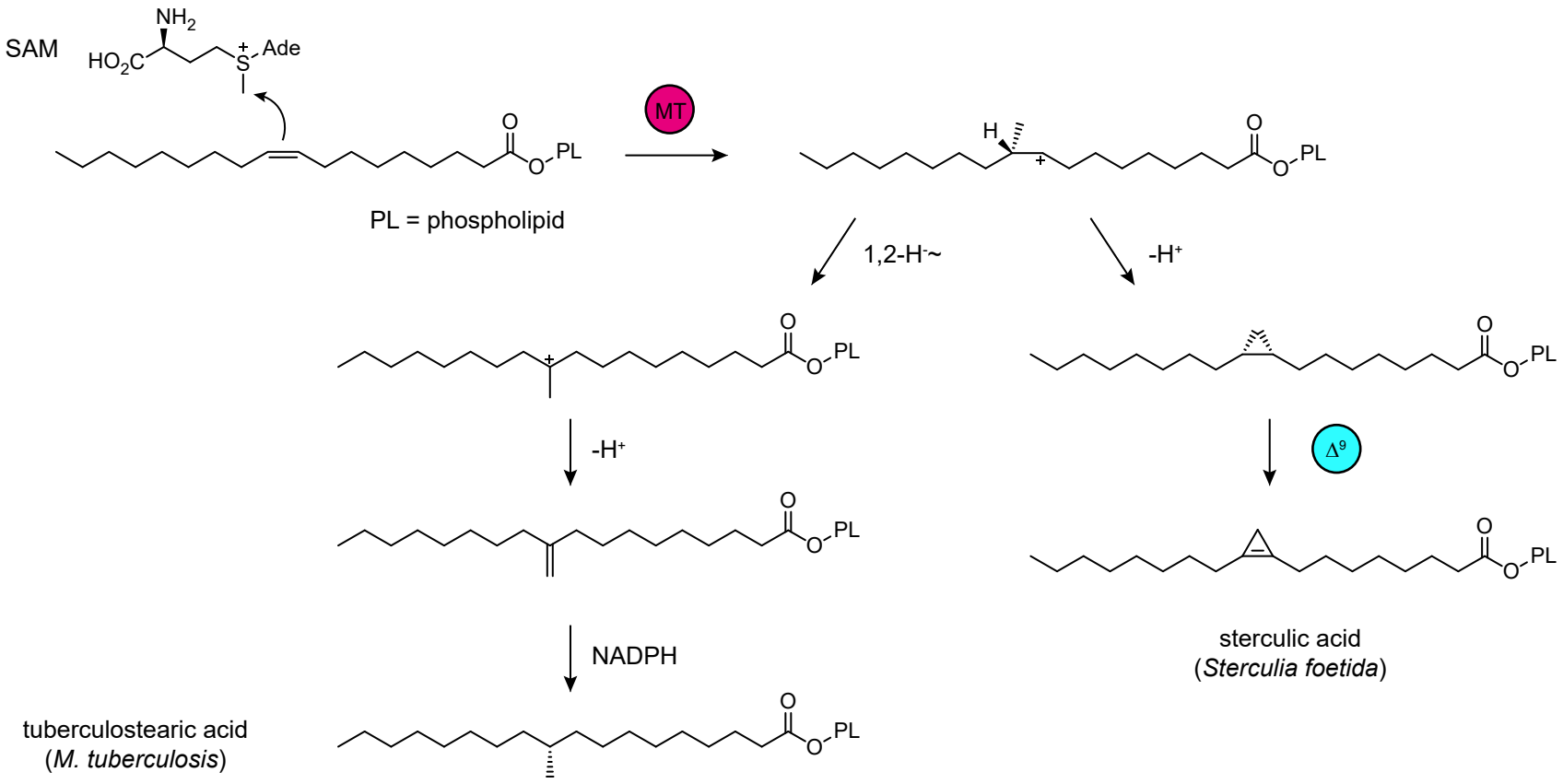


2. Fatty acids

2.4 Me branched and cyclopropyl fatty acids

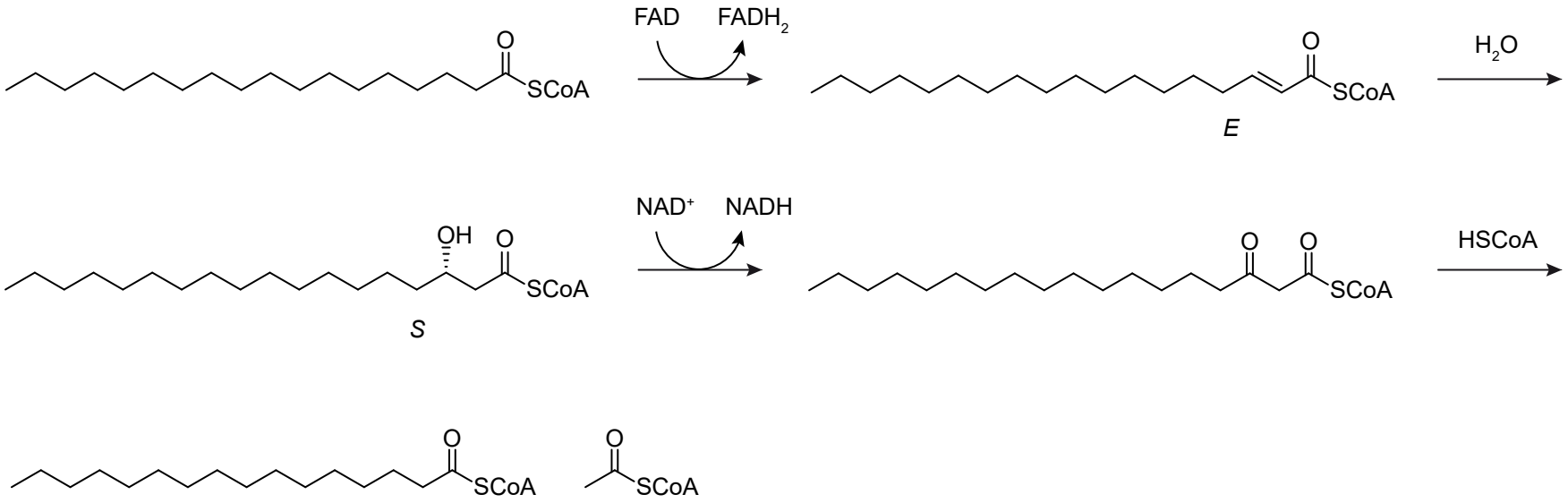


2.4 Me branched and cyclopropyl fatty acids



2.5 Fatty acid catabolism

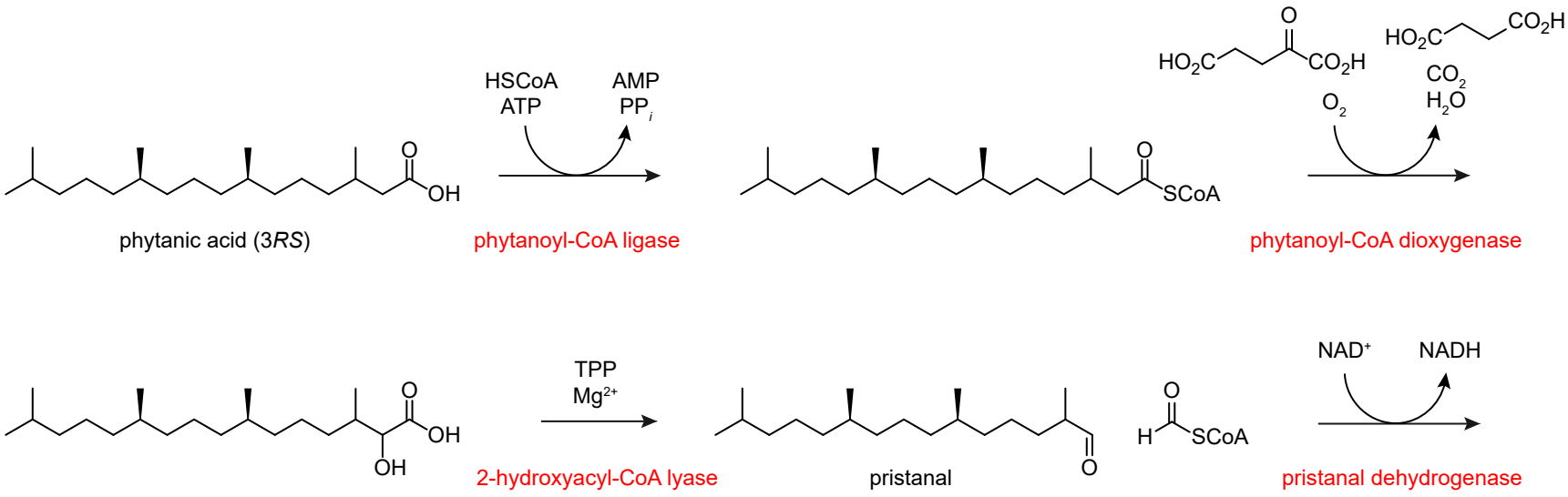
- inversion of fatty acid biosynthesis
- own enzymes
- substrates: SCoA esters (not ACP bound)
- stereochemistry different

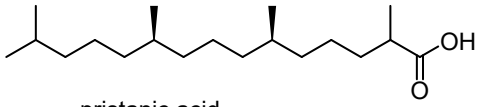


2.5 Fatty acid catabolism

2.5.2 α-Oxidation - fatty acid degradation by one carbon

phytanic acid catabolism (β-oxidation is blocked)





Refsum disease:
impaired α-oxidation leads to phytanic acid accumulation
severe neurological disorders
treatment: phytanic acid restricted diet

3. Polyketides

3.1 Definition

acetic acid derived natural products, formally „polymers of ketene“

3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

megasynthases (multidomain enzymes, cf. FAS from plants and fungi)

a) iterative (iPKS) - mostly fungal, but also known from bacteria

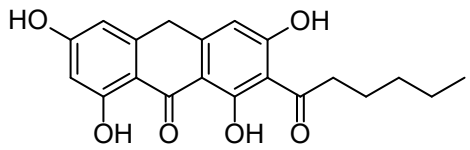
- aa) non-reducing (NR-iPKS)
- ab) partially reducing (PR-iPKS)
- ac) highly reducing (HR-iPKS)

b) modular PKS - bacterial

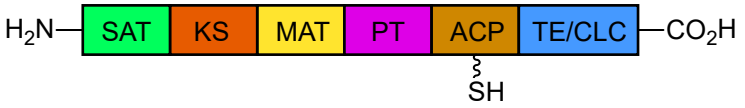
3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.1 non-reducing iterative PKS (NR-iPKS)



norsolorinic acid anthrone (*Aspergillus flavus*)

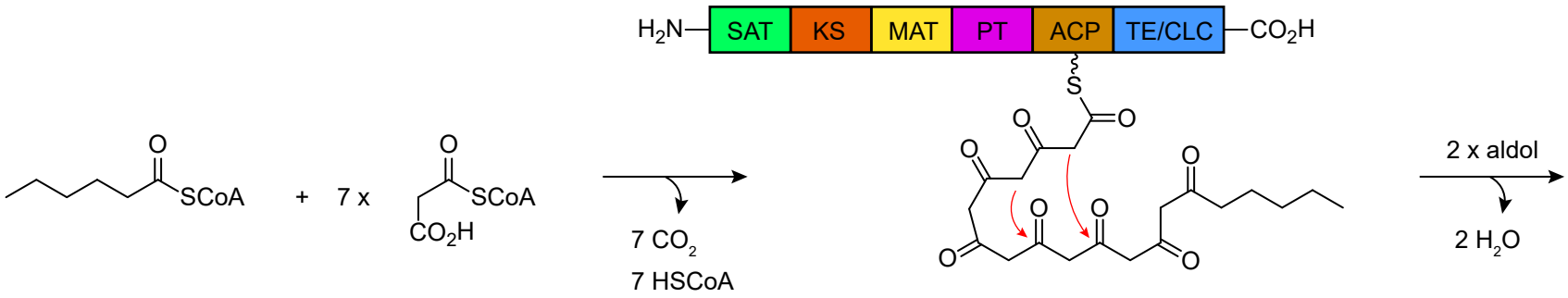


SAT: starter unit:ACP transacylase

MAT: malonyl-CoA:ACP transacylase

PT: product template (folds and protects growing polyketide chain)

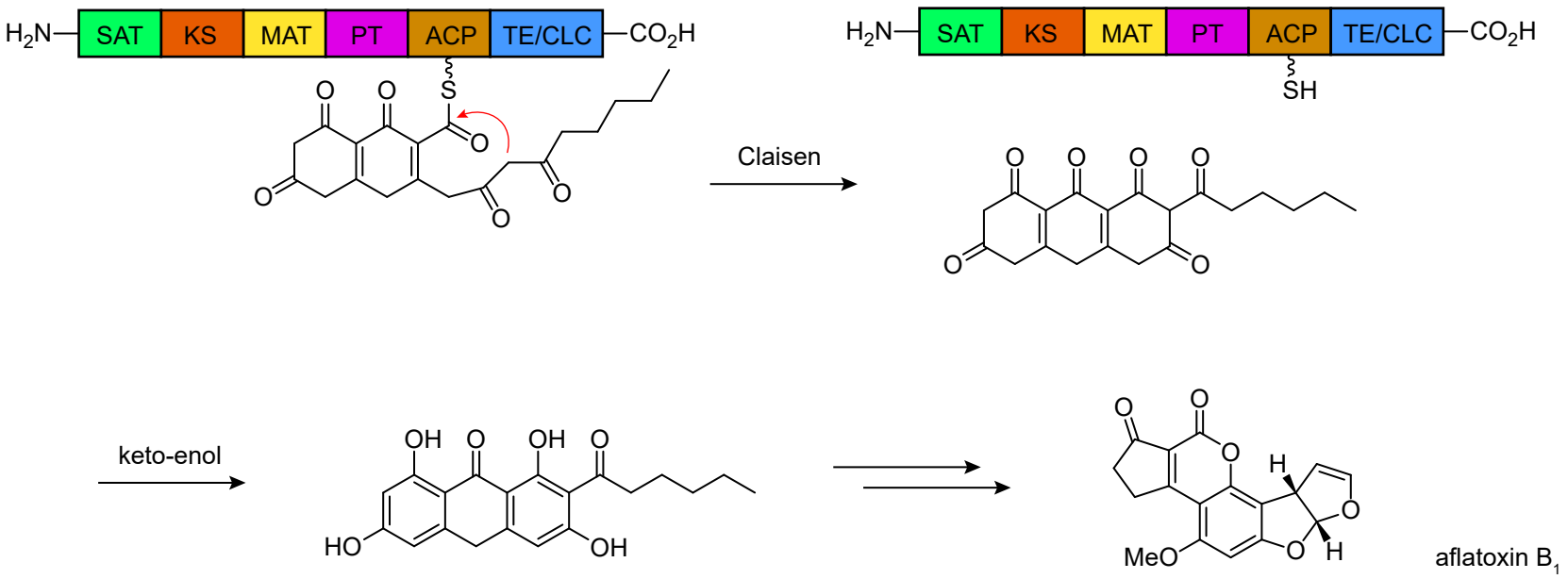
TE/CLC: thioesterase/Claisen condensation domain



3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

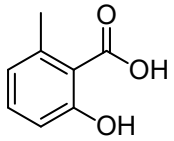
3.2.1.1 non-reducing iterative PKS (NR-iPKS)



3.2 Polyketide synthases (PKS)

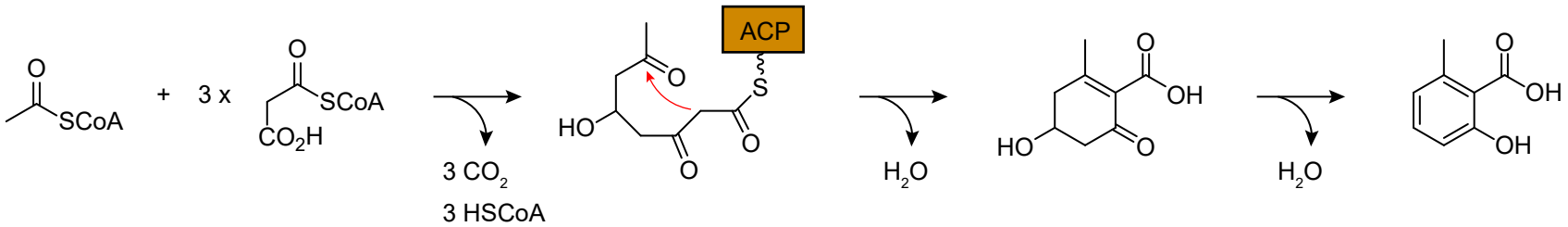
3.2.1 Type I PKS

3.2.1.2 partially reducing iterative PKS (PR-iPKS)



6-methylsalicylic acid

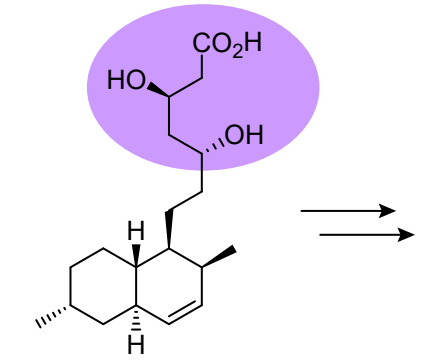
6-methylsalicylic acid synthase (6-MSAS)



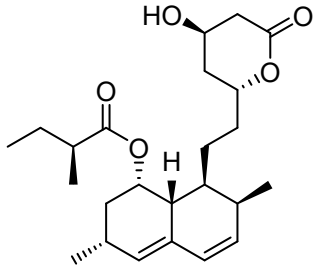
3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

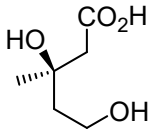
3.2.1.3 highly reducing iterative PKS (HR-iPKS)



dihydromonacolinic acid



lovastatin

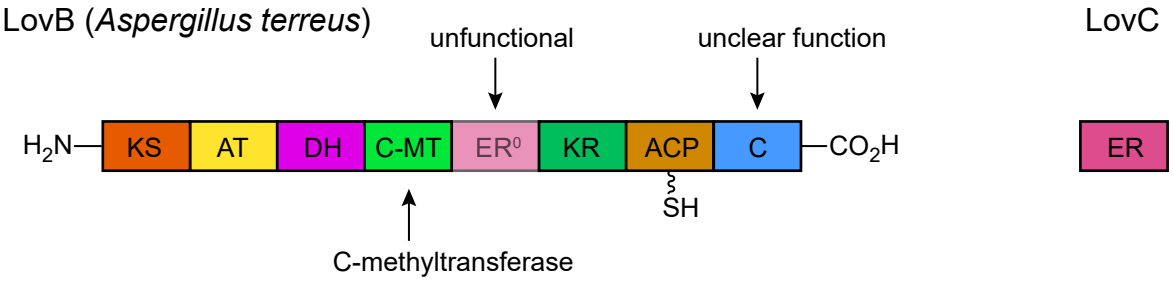


terpenes

structurally related to mevalonic acid

statin (cholesterol-lowering drug)

inhibitor of HMG-CoA reductase

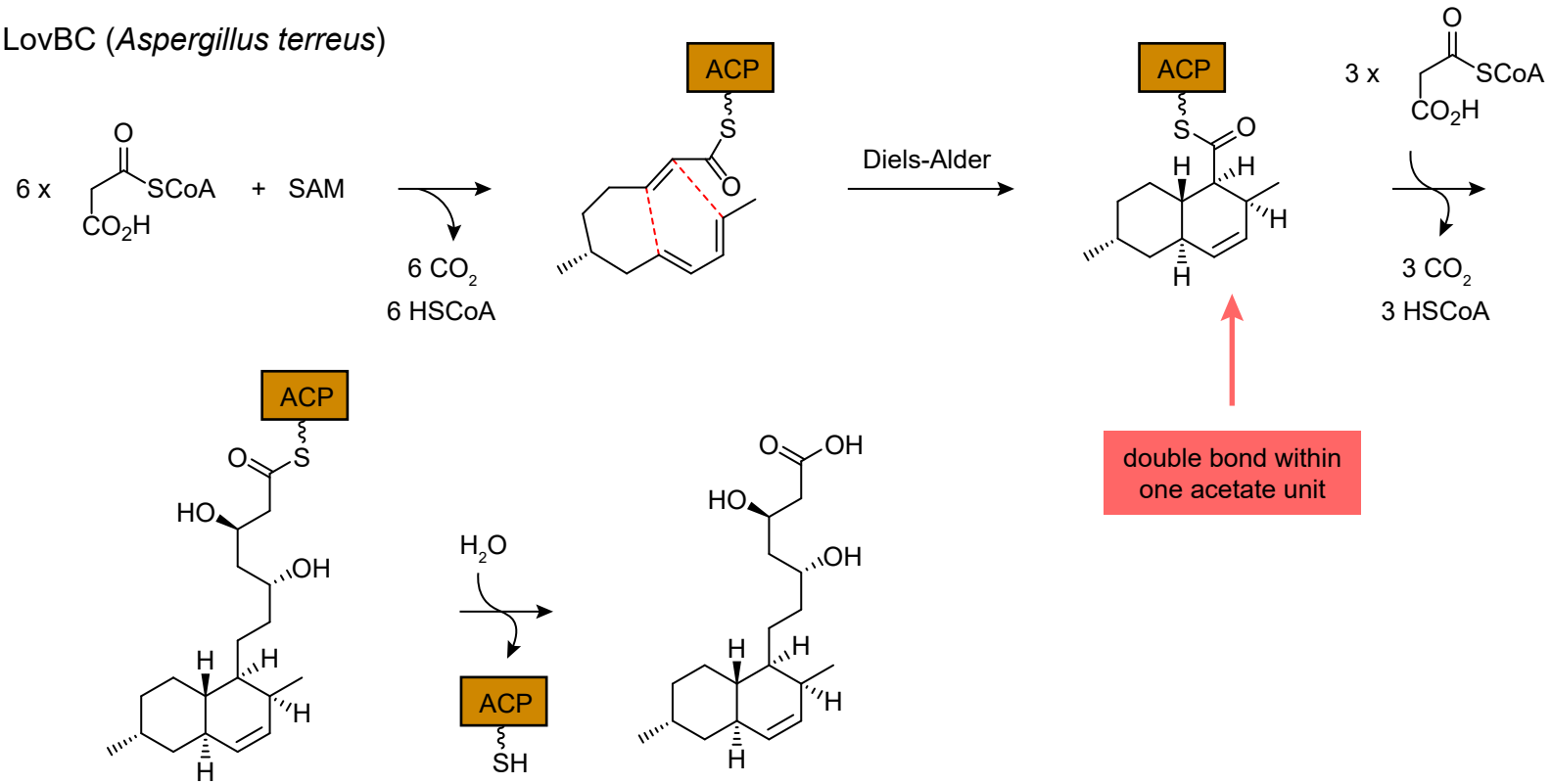


3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.3 highly reducing iterative PKS (HR-iPKS)

LovBC (*Aspergillus terreus*)



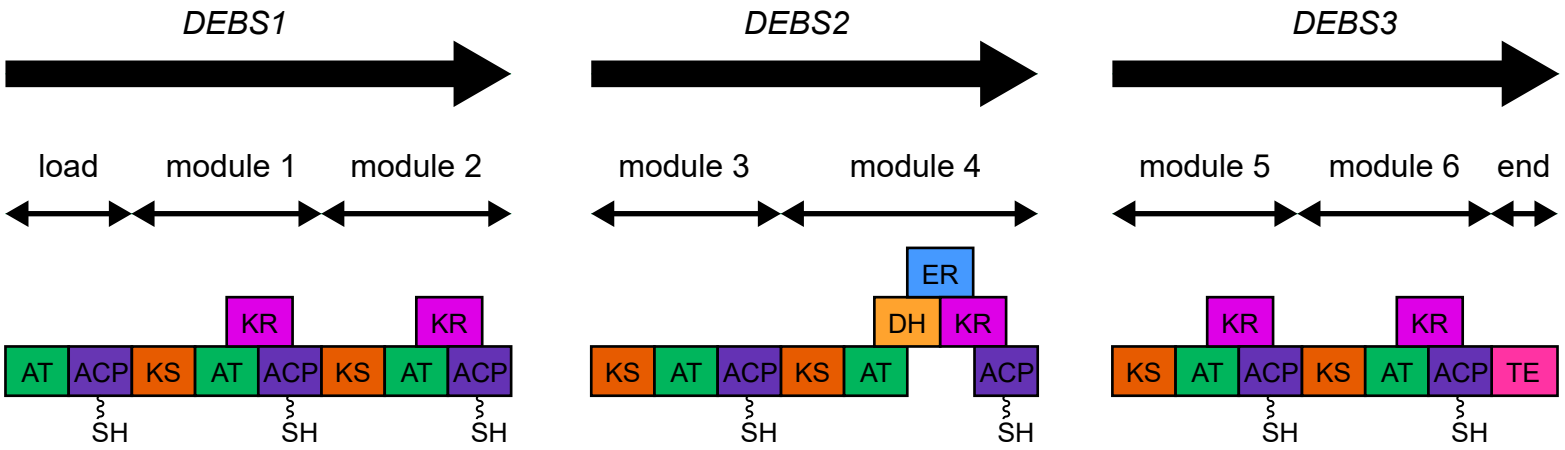
3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.4 modular PKS

first example: erythromycin (*Saccharopolyspora erythraea*)

macrolide antibiotic, binds to the bacterial ribosome and inhibits protein biosynthesis

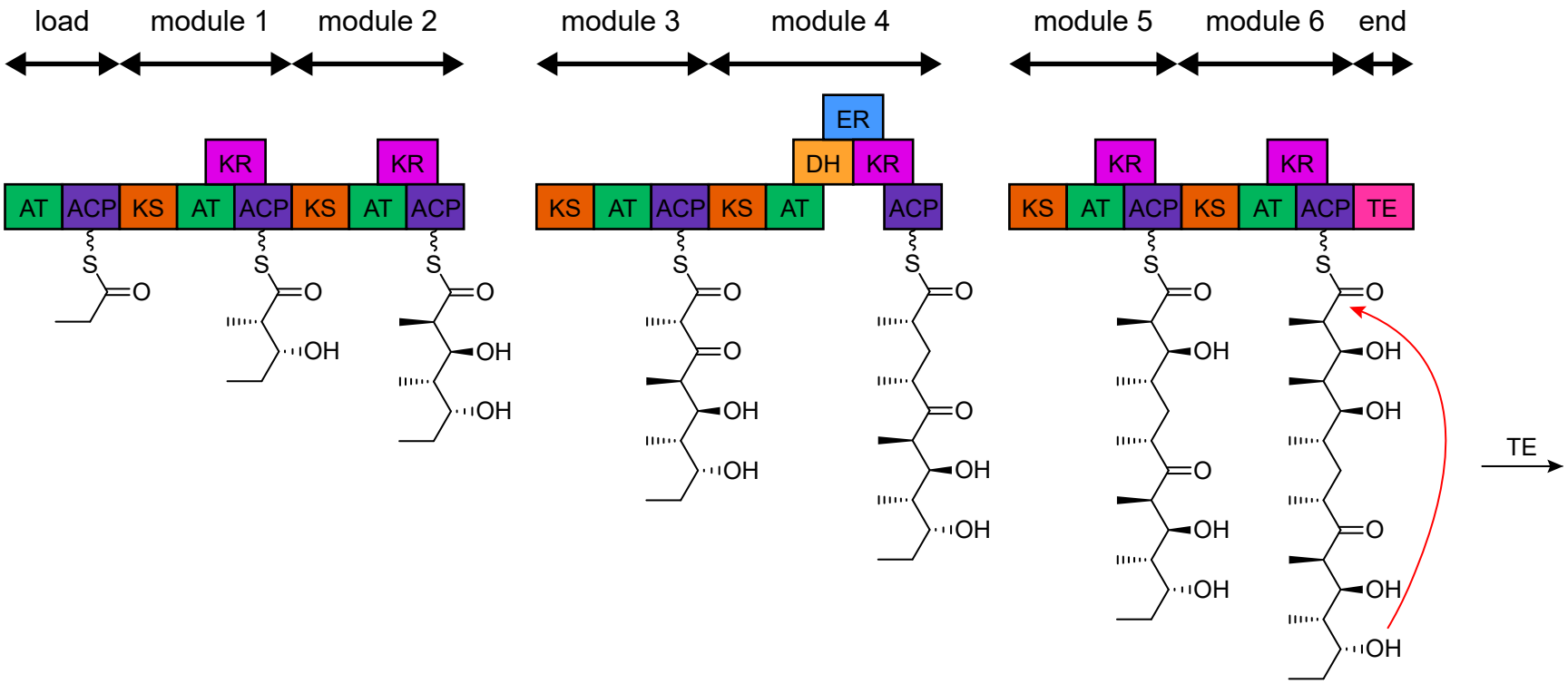


each module incorporates one unit, processing can be predicted from presence of optional domains

3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.4 modular PKS

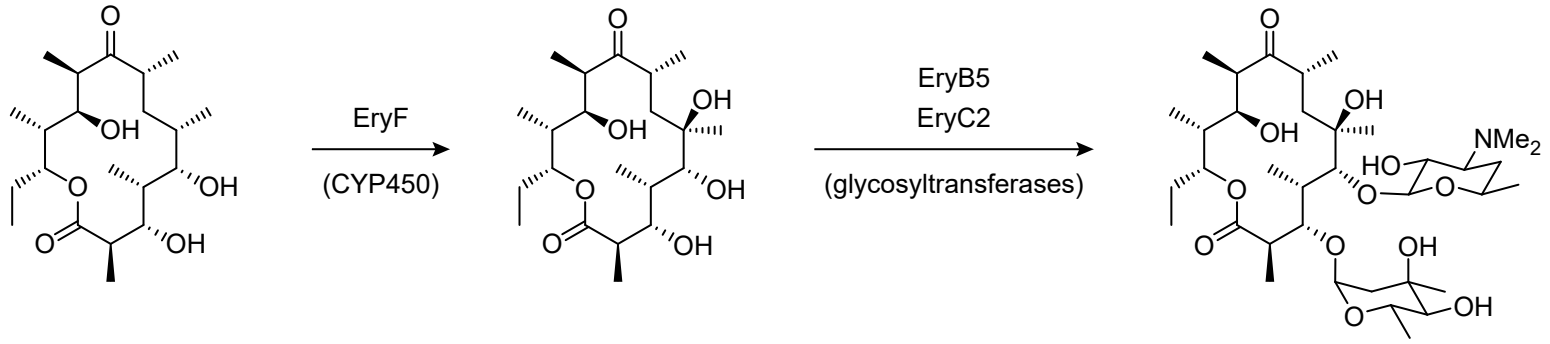


3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.4 modular PKS

tayloring steps of erythromycin biosynthesis



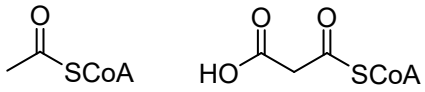
6-deoxyerythronolide B | erythronolide B | erythromycin D

3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

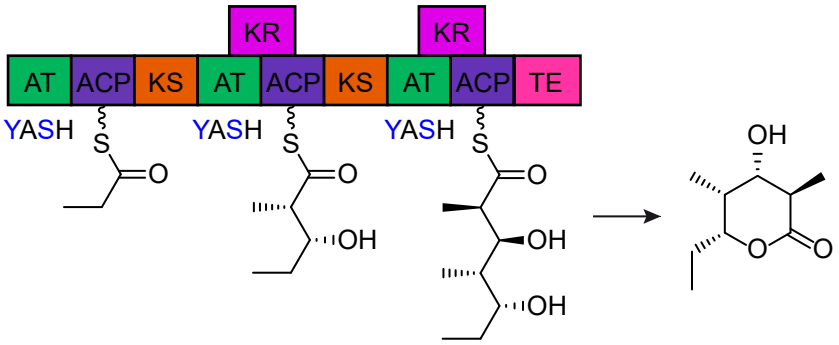
3.2.1.4 modular PKS

AT domains: substrate specificity indicated by highly conserved motifs



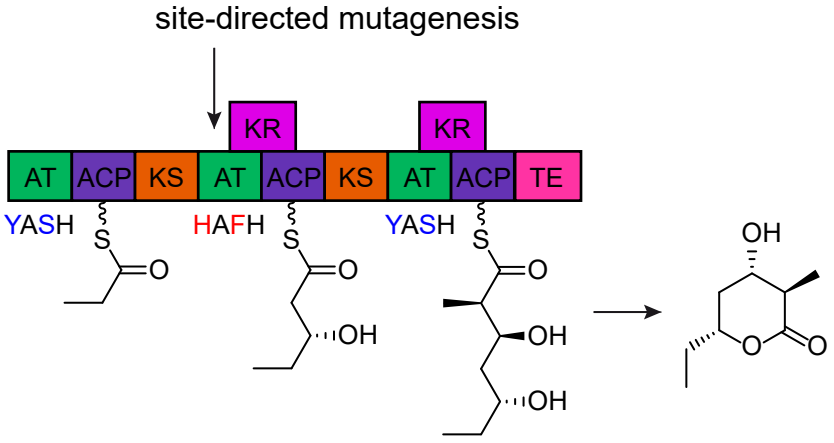
HAFH

YASH



DEBS1-TE

site-directed mutagenesis



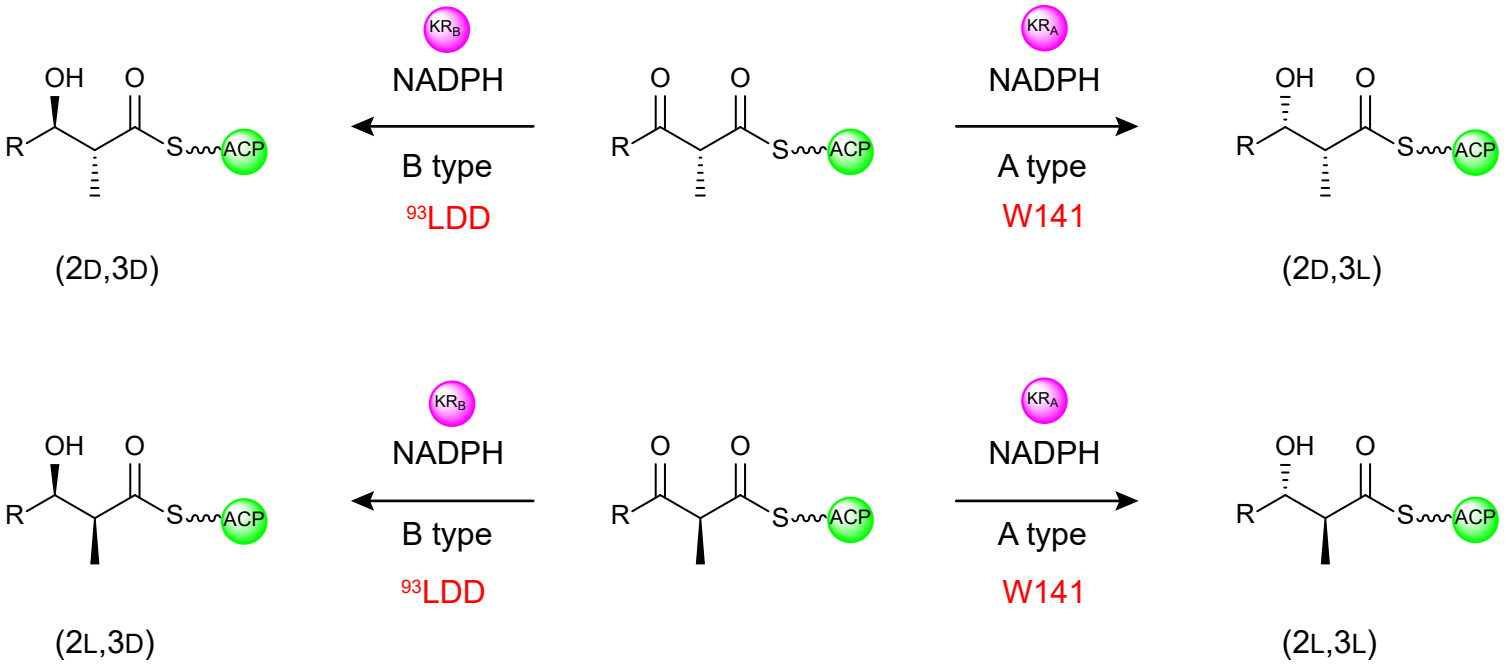
DEBS1-TE

3.2 Polyketide synthases (PKS)

3.2.1 Type I PKS

3.2.1.4 modular PKS

KR domains: stereospecificity is indicated by highly conserved motifs



3.2 Polyketide synthases (PKS)

3.2.2 Type II PKS

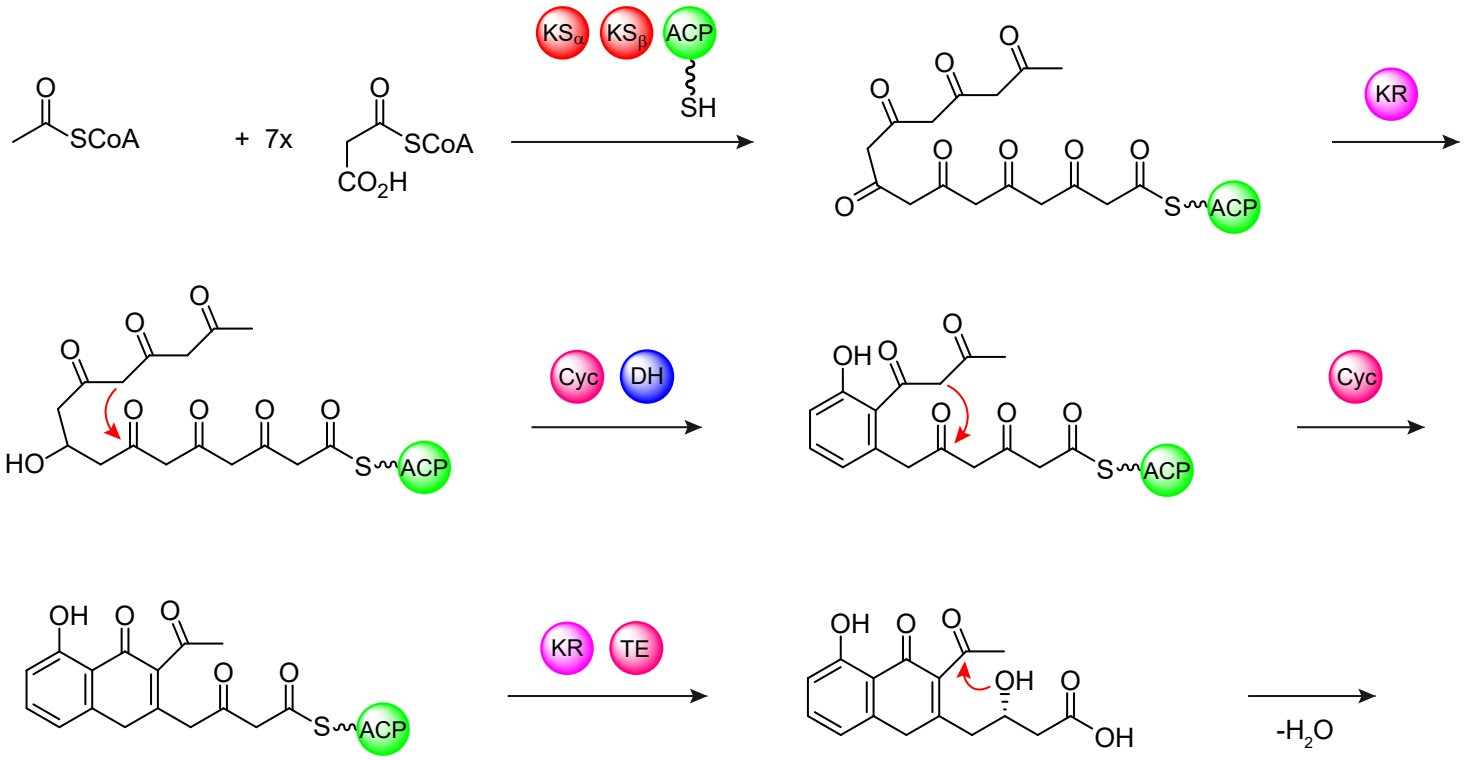
occur in bacteria (mainly Gram-positives, actinomycetes)

discrete enzymes (cf. FAS in bacteria)

3.2 Polyketide synthases (PKS)

3.2.2 Type II PKS

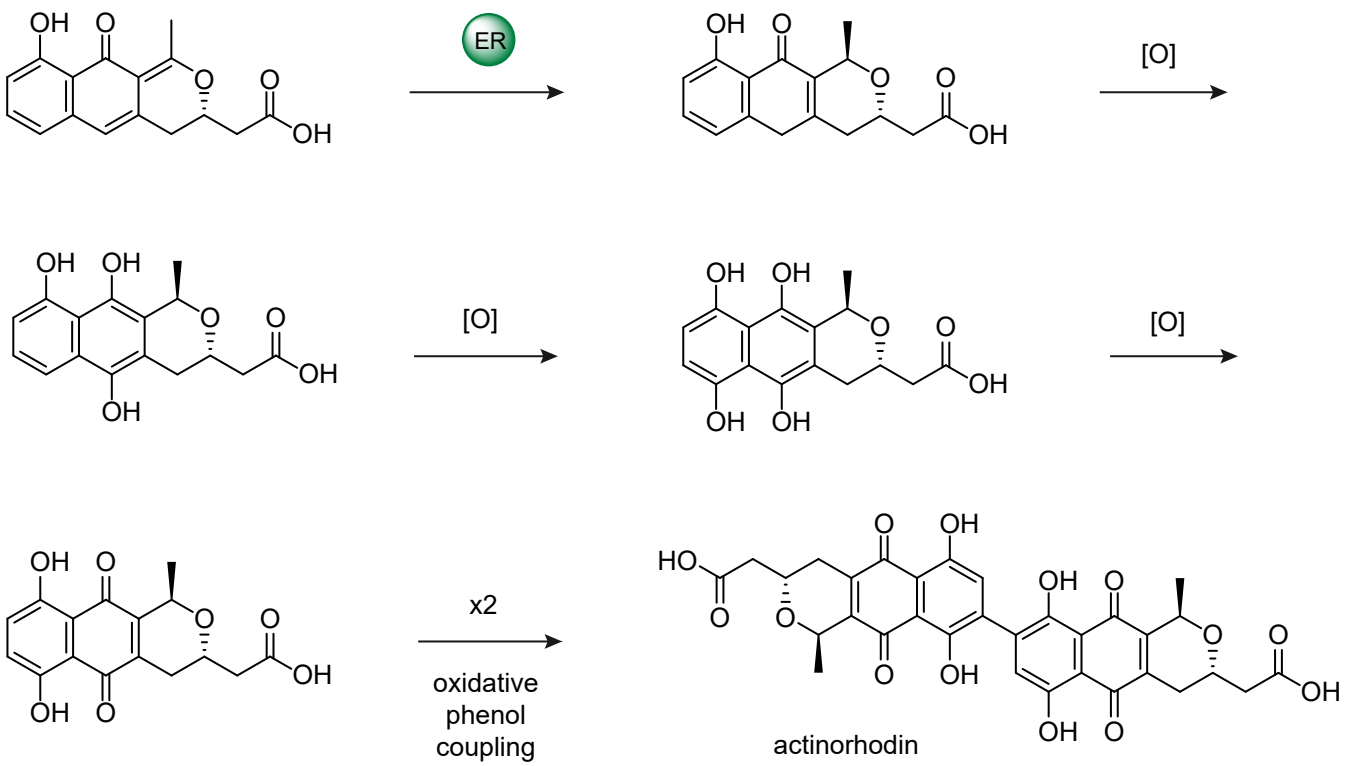
first example: actinorhodin



3.2 Polyketide synthases (PKS)

3.2.2 Type II PKS

first example: actinorhodin

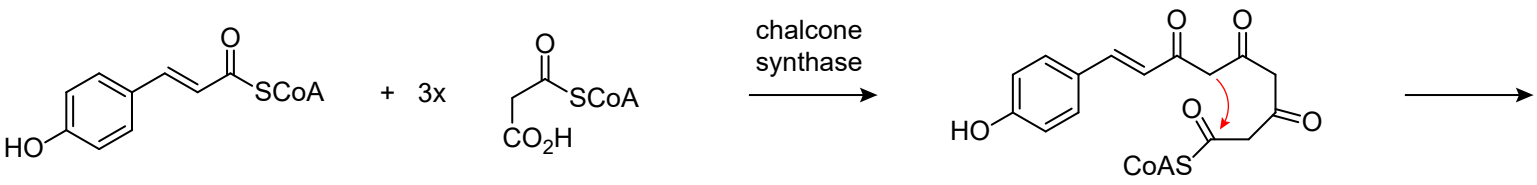


3.2 Polyketide synthases (PKS)

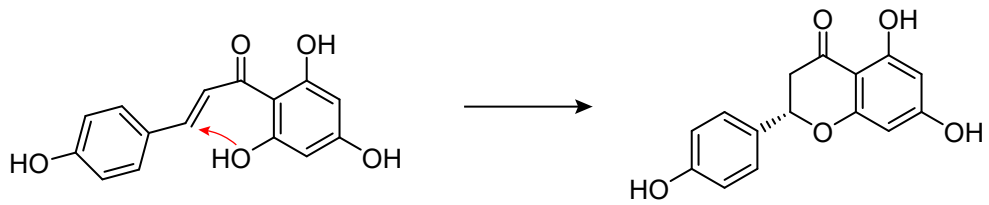
3.2.3 Type III PKS

chalcone synthases (plants, bacteria)

similar to FabH (= KSIII) of FAS in plants and bacteria, intermediates = CoA thioesters



coumaroyl-SCoA

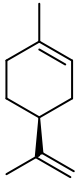


naringenin-chalcone naringenin

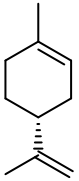
4. Terpenes

4.1 Occurrence, biological activity and nomenclature

> 80,000 known compounds (largest NP class)

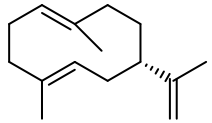


(*S*)-limonene
(*Abies nobilis*)



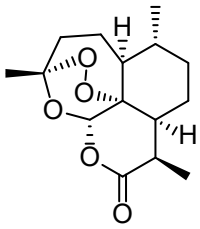
(*R*)-limonene
(*Citrus sinensis*)

aroma compounds

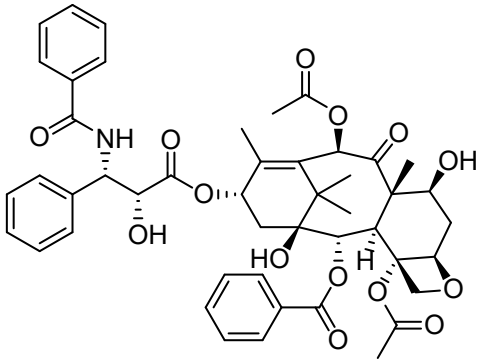


(–)-germacrene A
(*Therioaphis maculata*)

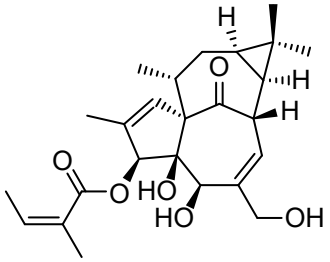
alarm pheromone



artemisinin (*Artemisia annua*)
anti-malaria



taxol (*Taxus brevifolia*)
anti-cancer



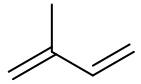
ingenol 3-angelate (*Euphorbia peplus*)
anti-cancer

4. Terpenes

4.1 Occurrence, biological activity and nomenclature

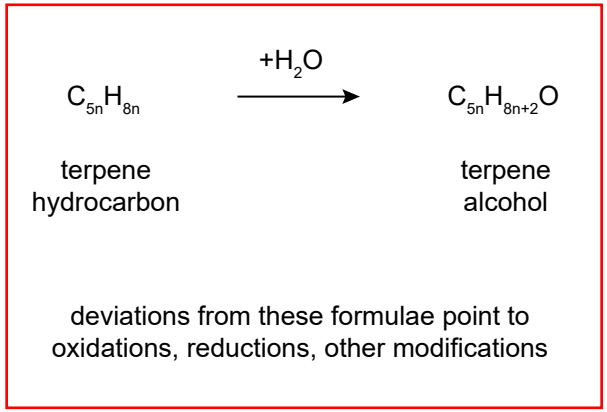
classification

terpenes are built from Me branched C_5 units (isoprene rule, Wallach 1885, Bonn)



isoprene

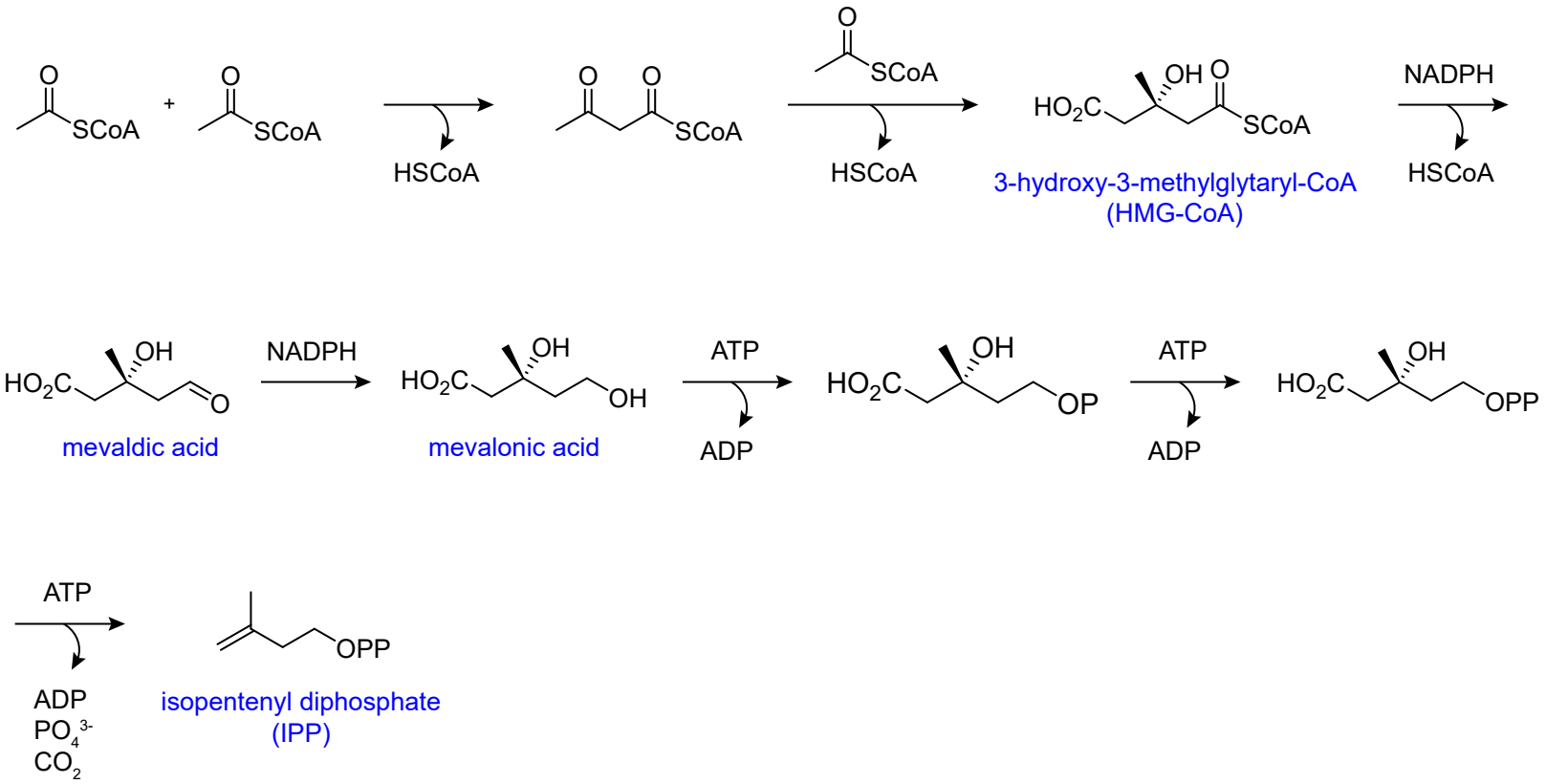
C_5H_8	hemiterpenes
$C_{10}H_{16}$	monoterpenes
$C_{15}H_{24}$	sesquiterpenes
$C_{20}H_{32}$	diterpenes
$C_{25}H_{40}$	sesterterpenes
$C_{30}H_{48}$	triterpenes
$C_{35}H_{56}$	sesquarterpenes
$C_{40}H_{64}$	tetraterpenes



4.2 Biosynthesis of monomers and acyclic precursors

4.2.1 Mevalonate pathway

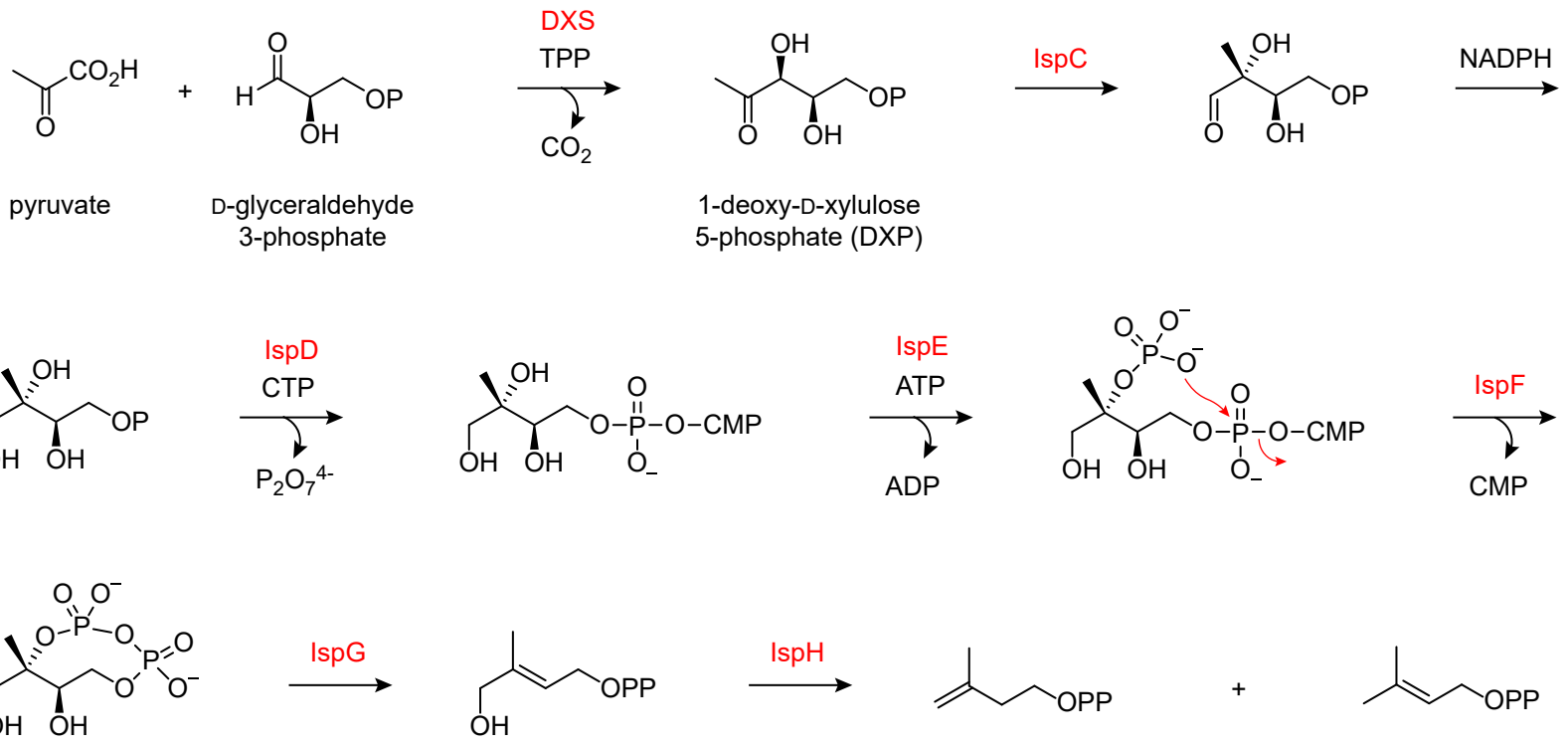
in fungi and animals, in the cytosol of plants, in bacteria (rare)



4.2 Biosynthesis of monomers and acyclic precursors

4.2.2 Deoxyxylulose phosphate pathway

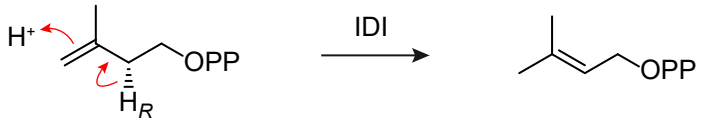
in plants (in the plastids), in most bacteria



4.2 Biosynthesis of monomers and acyclic precursors

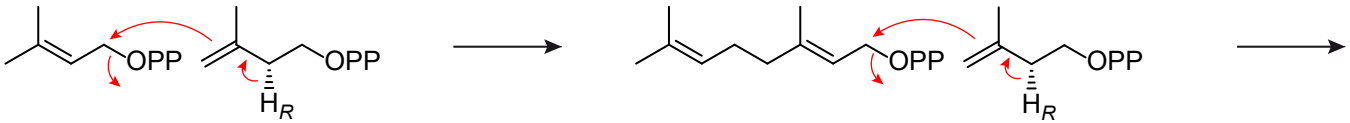
4.2.3 Polyisoprenoid biosynthesis

4.2.3.1 Isopentenyl diphosphate isomerase (IDI)



IPP DMAPP

4.2.3.2 Polyisoprenoid synthases



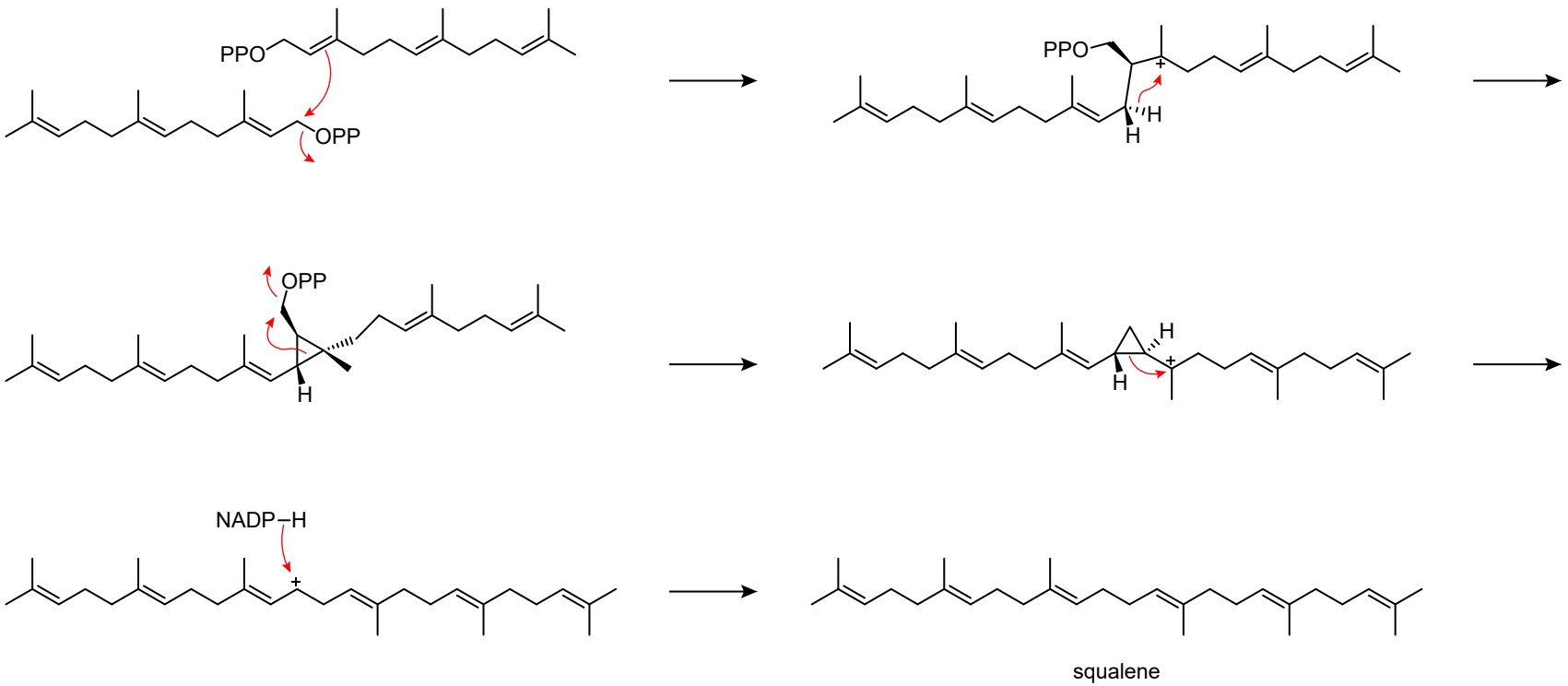
geranyl diphosphate (GPP)

farnesyl diphosphate (FPP) geranylgeranyl diphosphate (GGPP)

4.2 Biosynthesis of monomers and acyclic precursors

4.2.3 Polyisoprenoid biosynthesis

4.2.3.3 Squalene synthase



4.3 Terpene synthases

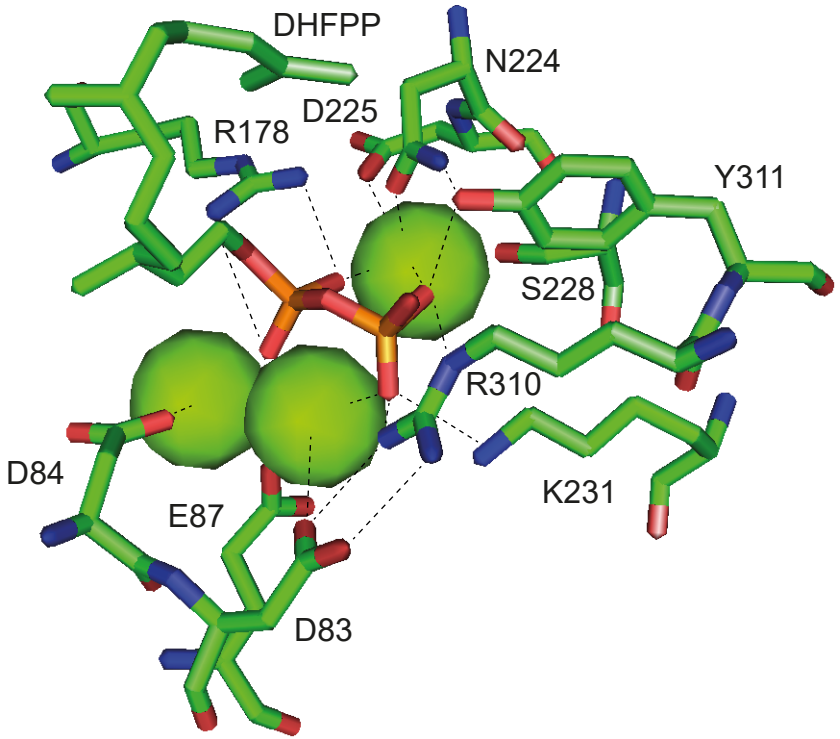
4.3.1 Type I

highly conserved motifs

DDXXD
R
NDLXSXXXE
RY

Mg^{2+}-dependent

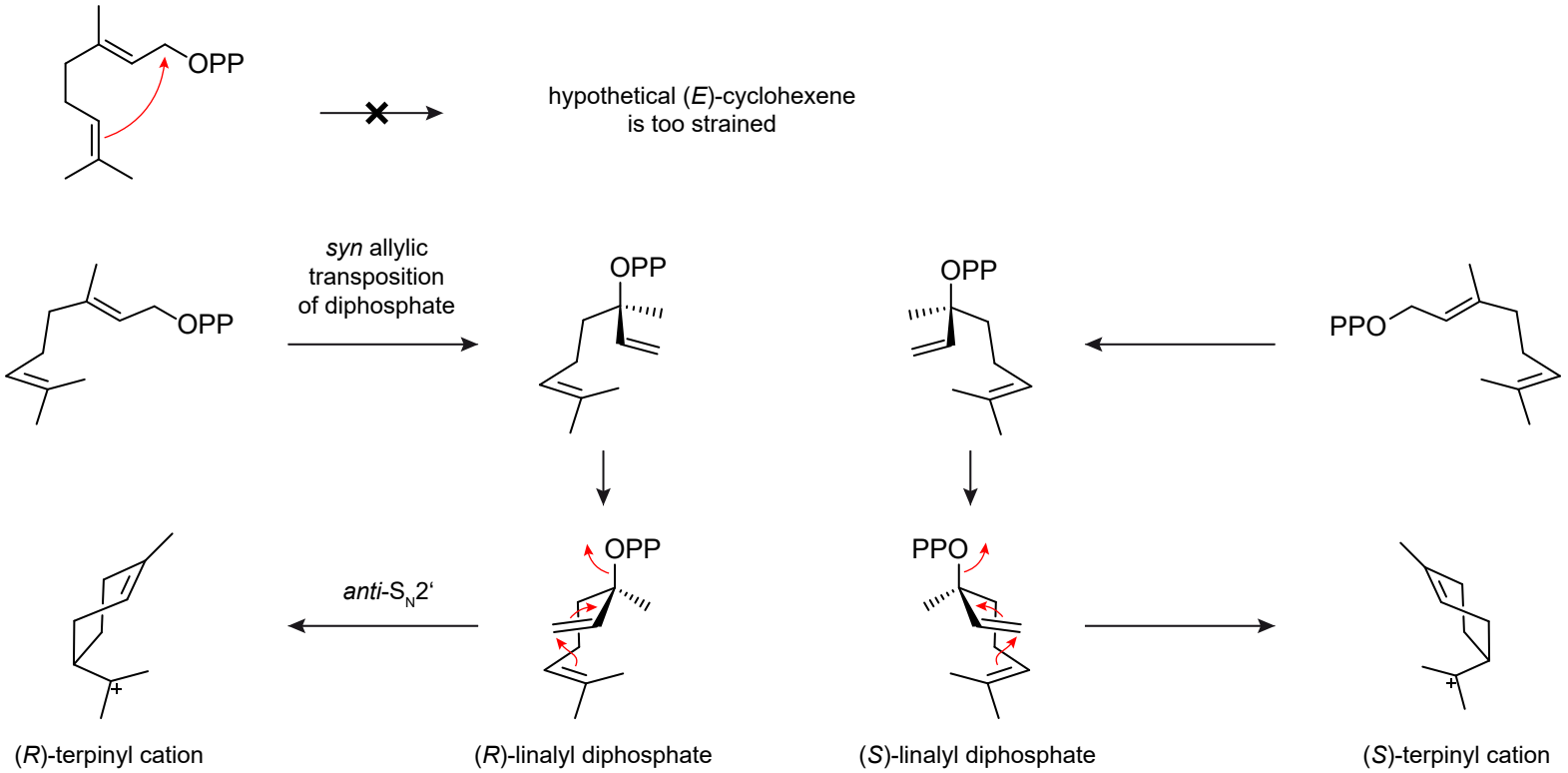
ionisation by abstraction
of diphosphate



4.3 Terpene synthases

4.3.1 Type I

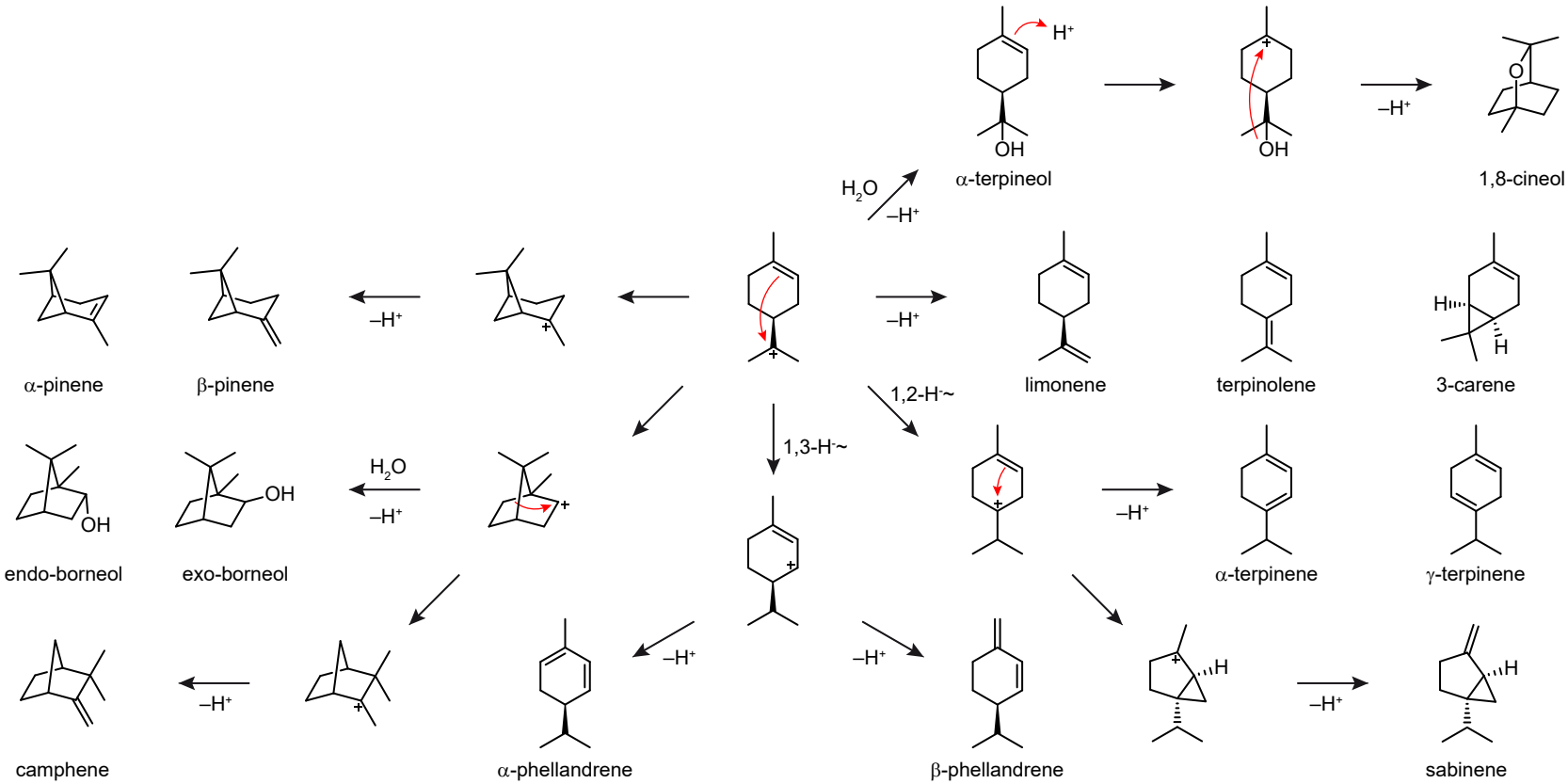
4.3.1.1 Monoterpene biosynthesis



4.3 Terpene synthases

4.3.1 Type I

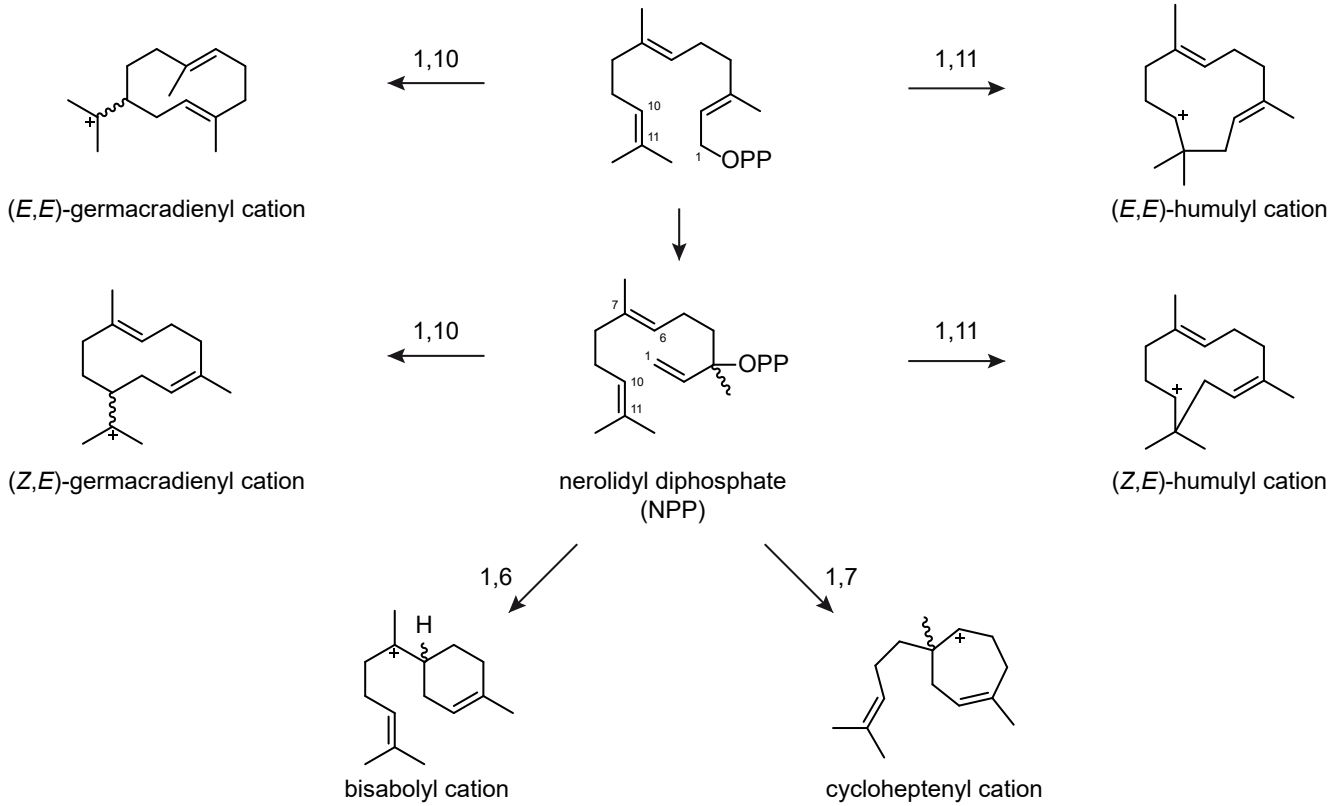
4.3.1.1 Monoterpene biosynthesis



4.3 Terpene synthases

4.3.1 Type I

4.3.1.2 Sesquiterpene biosynthesis

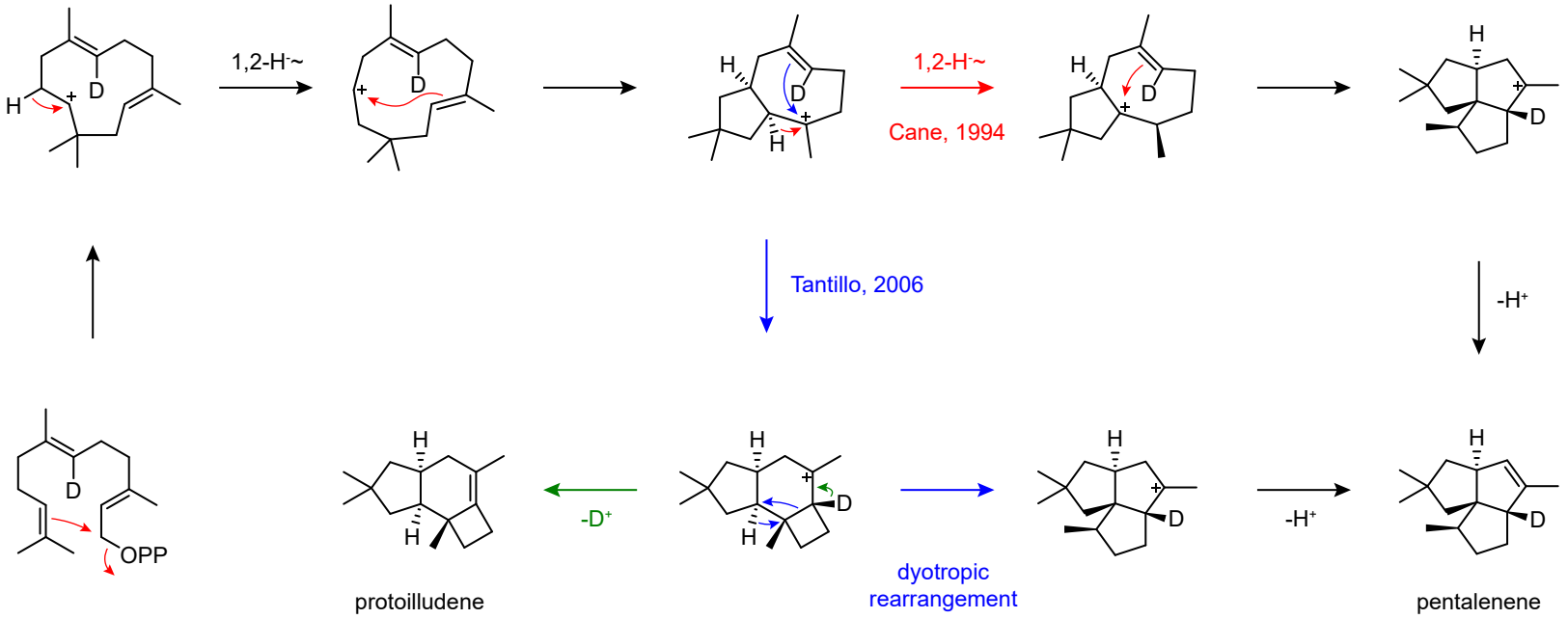


4.3 Terpene synthases

4.3.1 Type I

4.3.1.2 Sesquiterpene biosynthesis

Pentalenene synthase (*Streptomyces exfoliatus*)



4.3 Terpene synthases

4.3.2 Type II

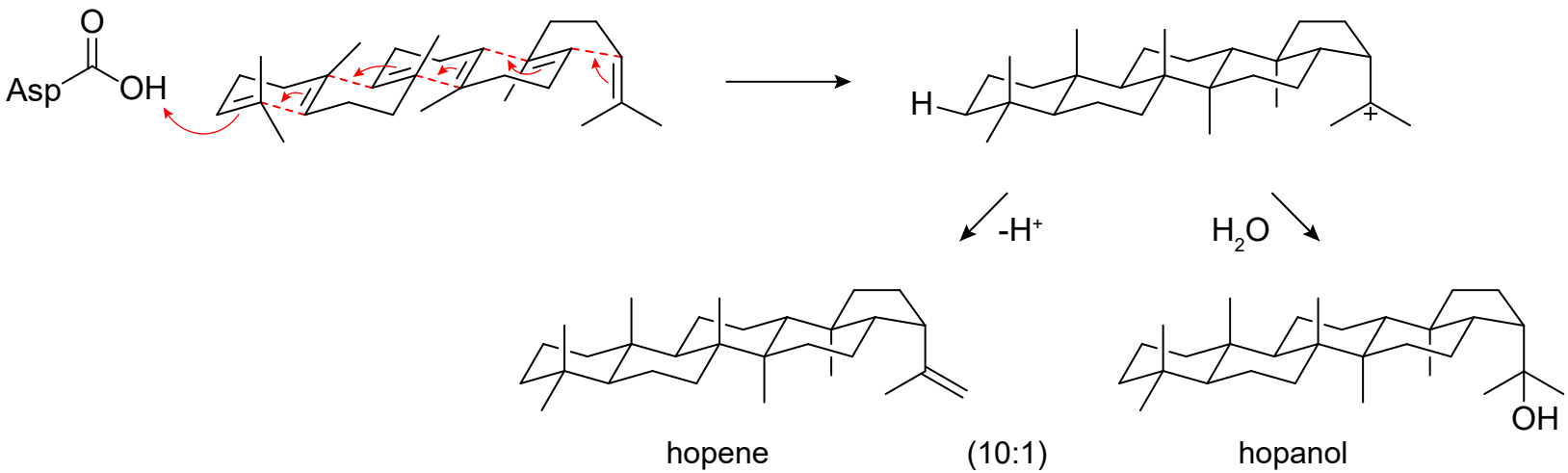
substrate activation by protonation

highly conserved motif DXDD

↑

proton donor

squalene-hopene cyclase

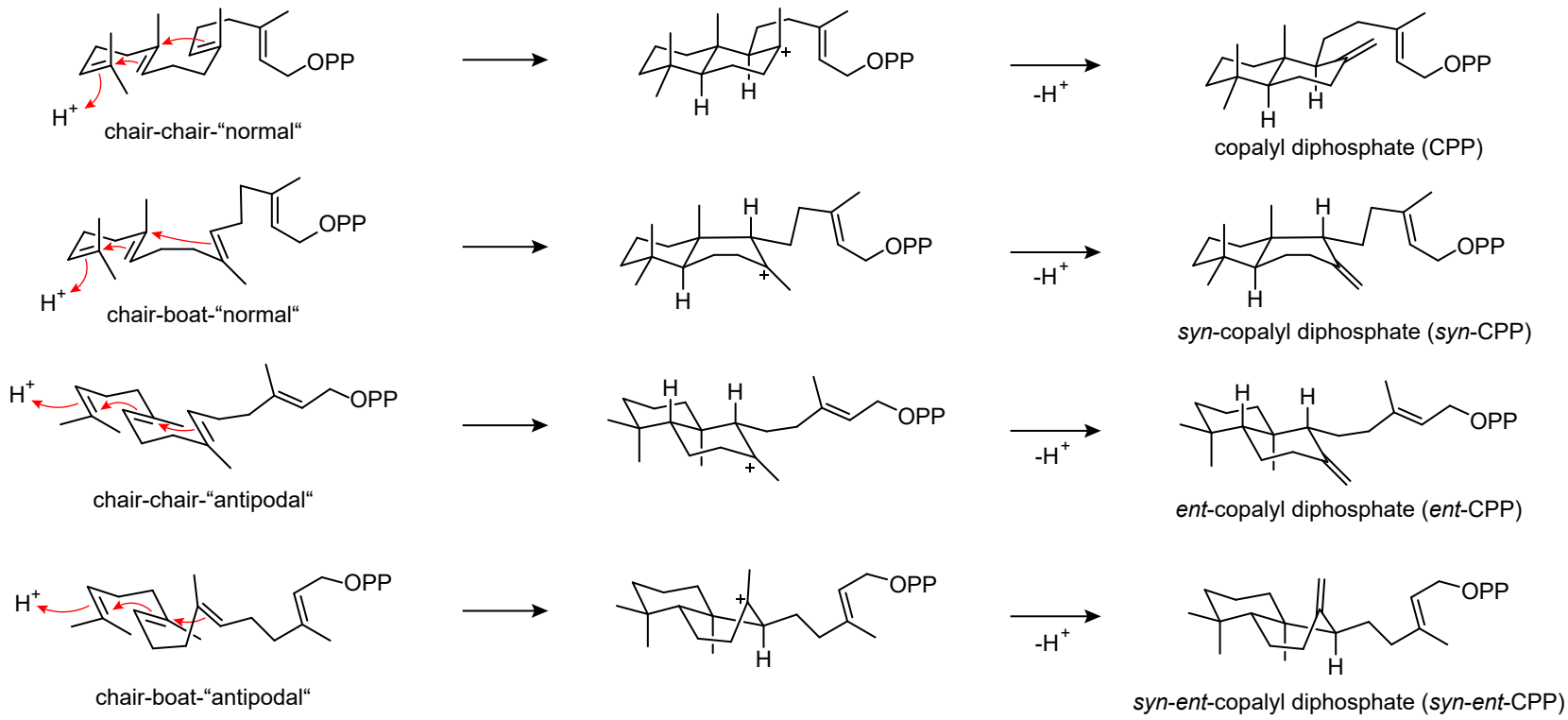


hopene (10:1) hopanol

4.3 Terpene synthases

4.3.2 Type II

labdane related diterpenes

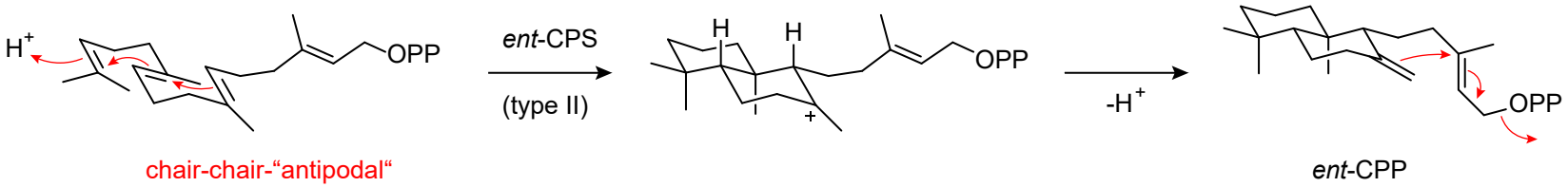


4.3 Terpene synthases

4.3.2 Type II

labdane related diterpenes - further cyclisation by type I terpene synthase possible

discrete type II and type I terpene synthases (in plants and bacteria) or bifunctional enzyme (in fungi)



chair-chair-“antipodal“

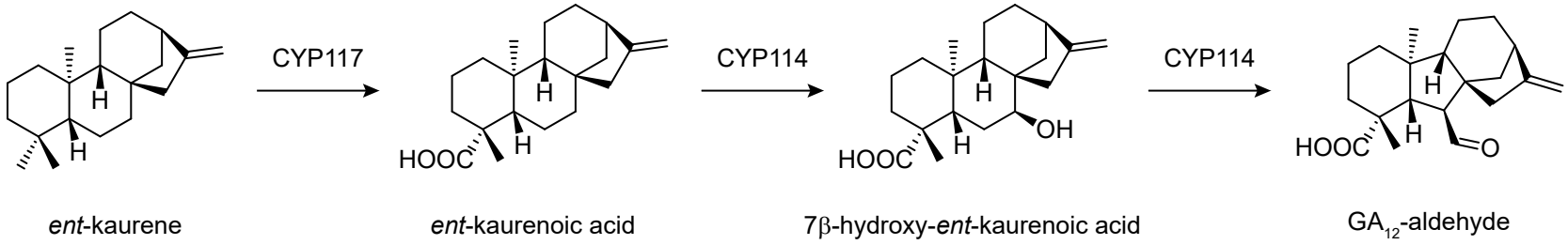
ent-CPP

ent-kaurene

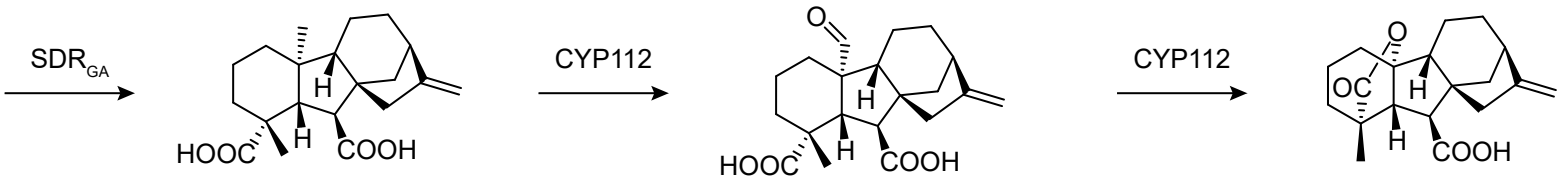
4.3 Terpene synthases

4.3.1 Type II

gibberellin biosynthesis - downstream oxidation steps



ent-kaurene — *ent*-kaurenoic acid — 7β-hydroxy-*ent*-kaurenoic acid — GA_{12}-aldehyde

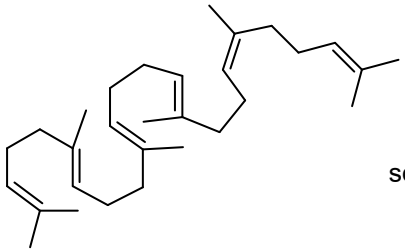


GA_{12} — GA_{24} — GA_9

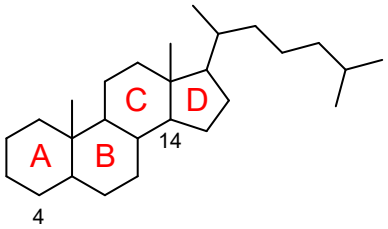
4.3 Terpene synthases

4.3.2 Type II

steroid biosynthesis: lanosterol synthase

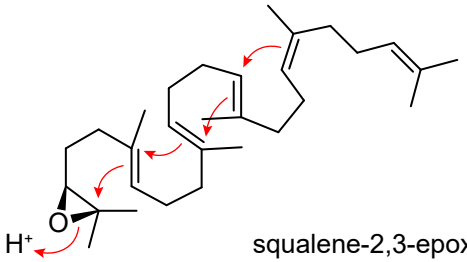


squalene



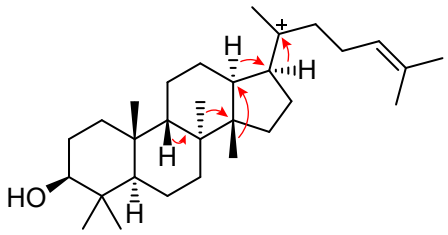
tetracyclic ring system
Me groups at C4 and C14 missing

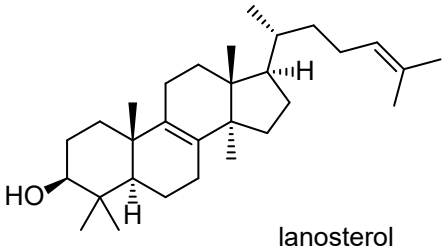
CYP450



squalene-2,3-epoxide

LS



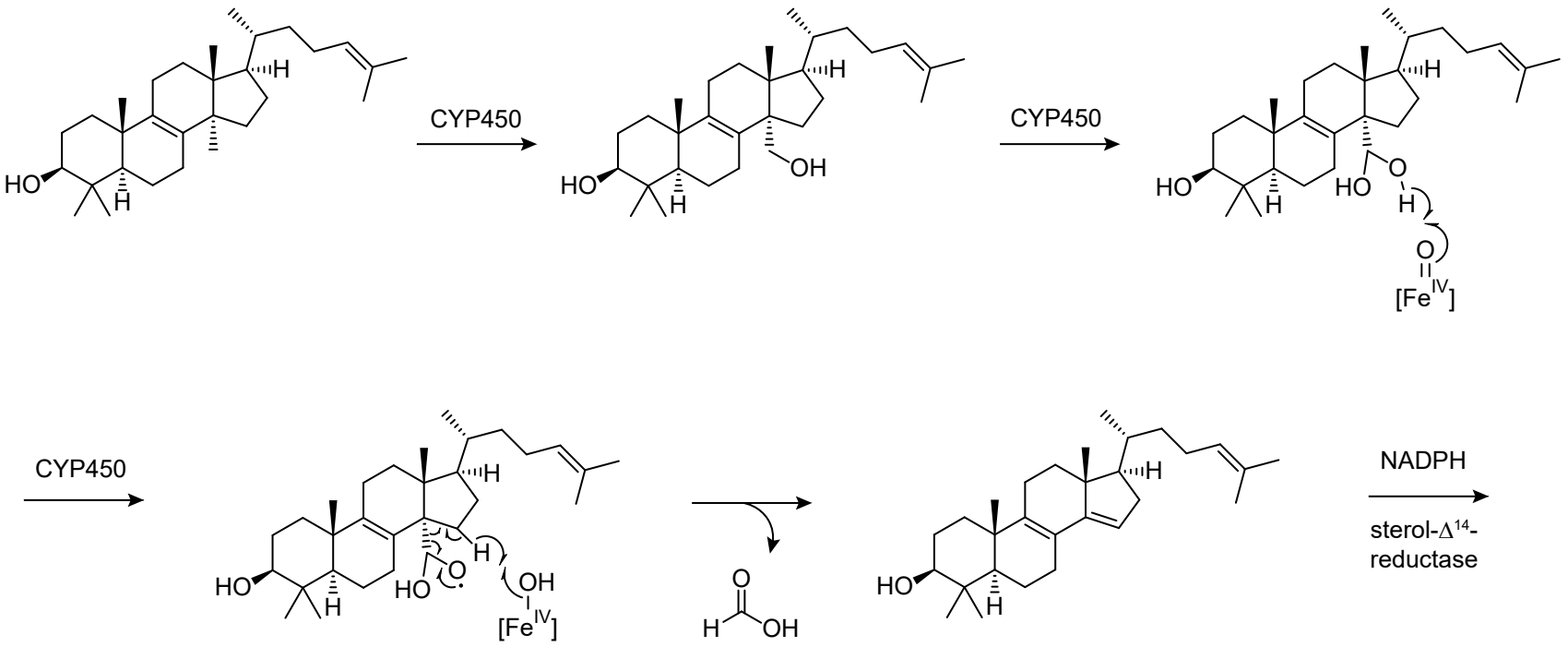


lanosterol

4.3 Terpene synthases

4.3.2 Type II

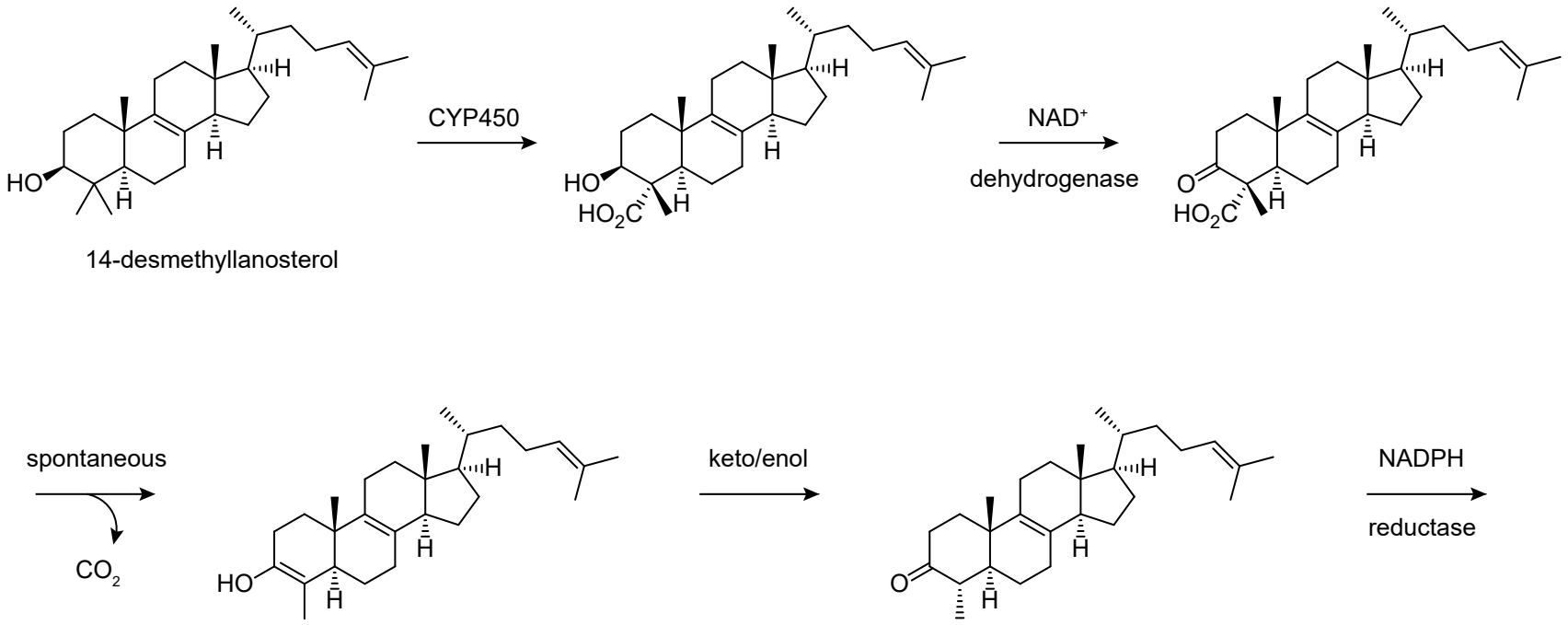
steroid biosynthesis: demethylation of lanosterol



4.3 Terpene synthases

4.3.2 Type II

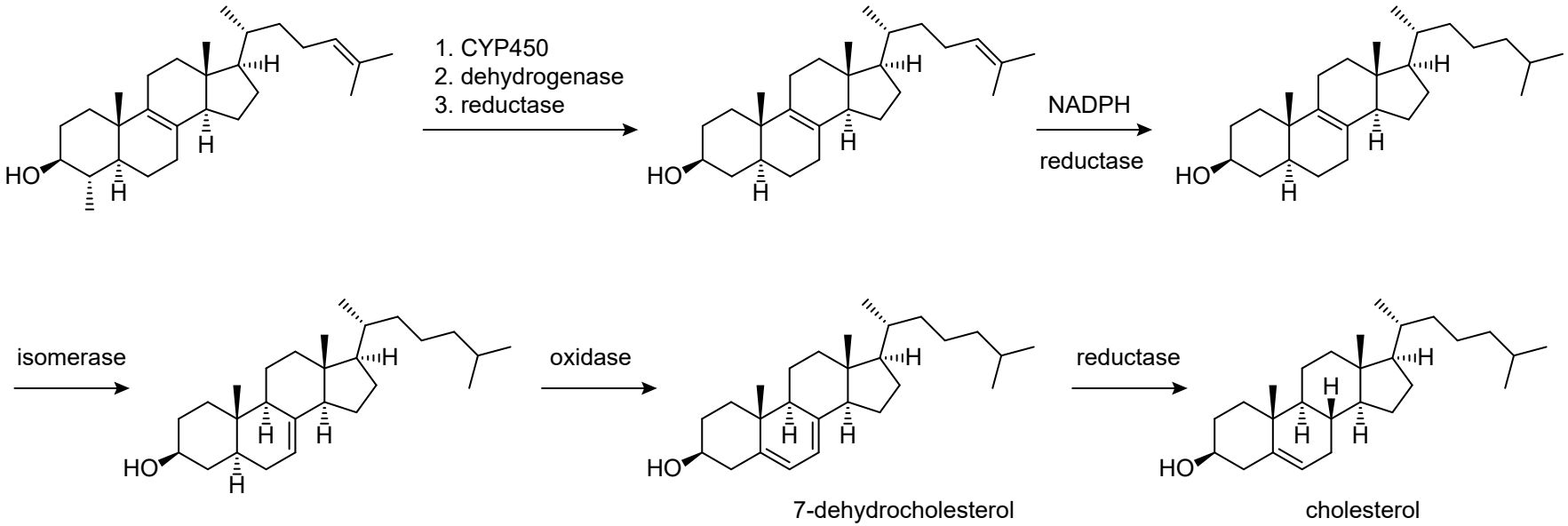
steroid biosynthesis: demethylation of lanosterol



4.3 Terpene synthases

4.3.2 Type II

steroid biosynthesis: demethylation of lanosterol



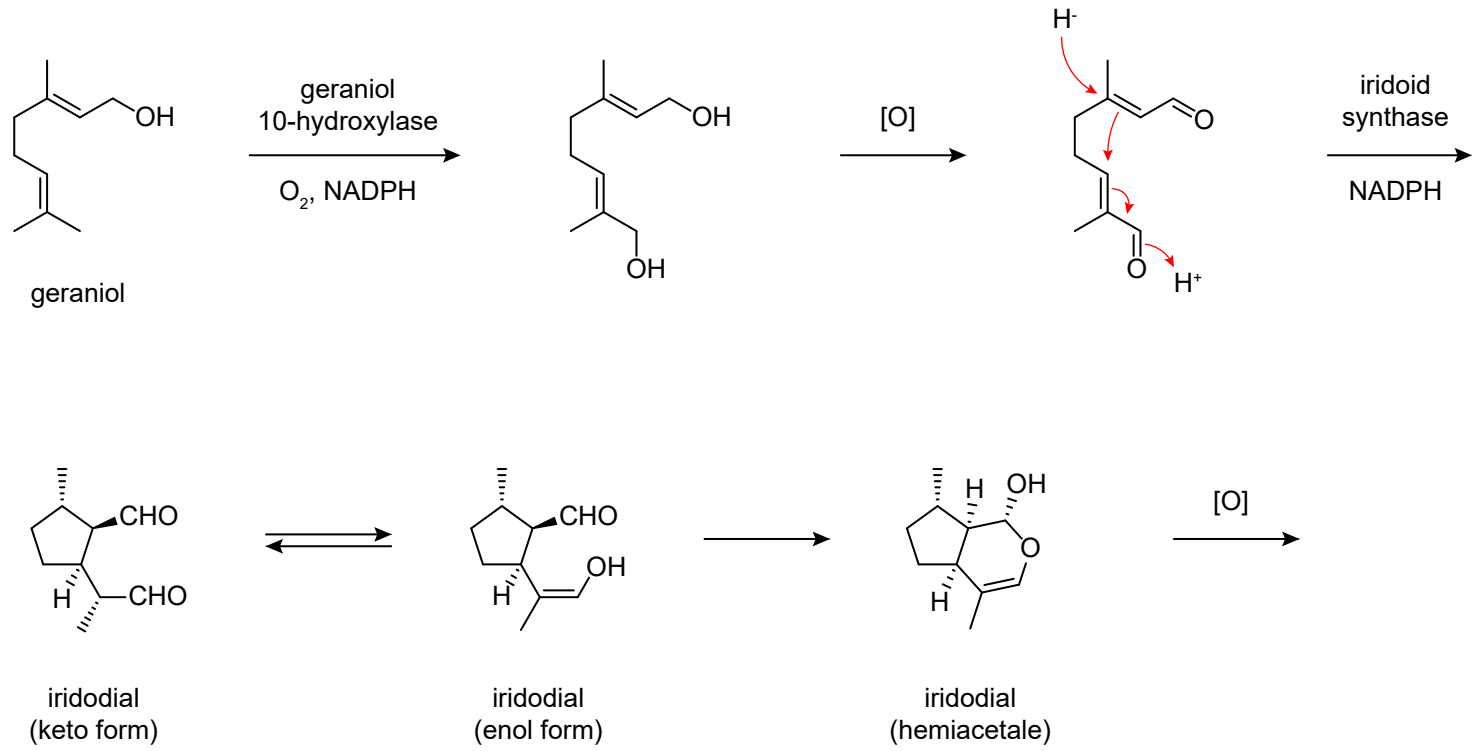
membrane constituent

biosynthetic precursor of steroid hormones

4.3 Terpene synthases

4.3.3 Iridoid synthase

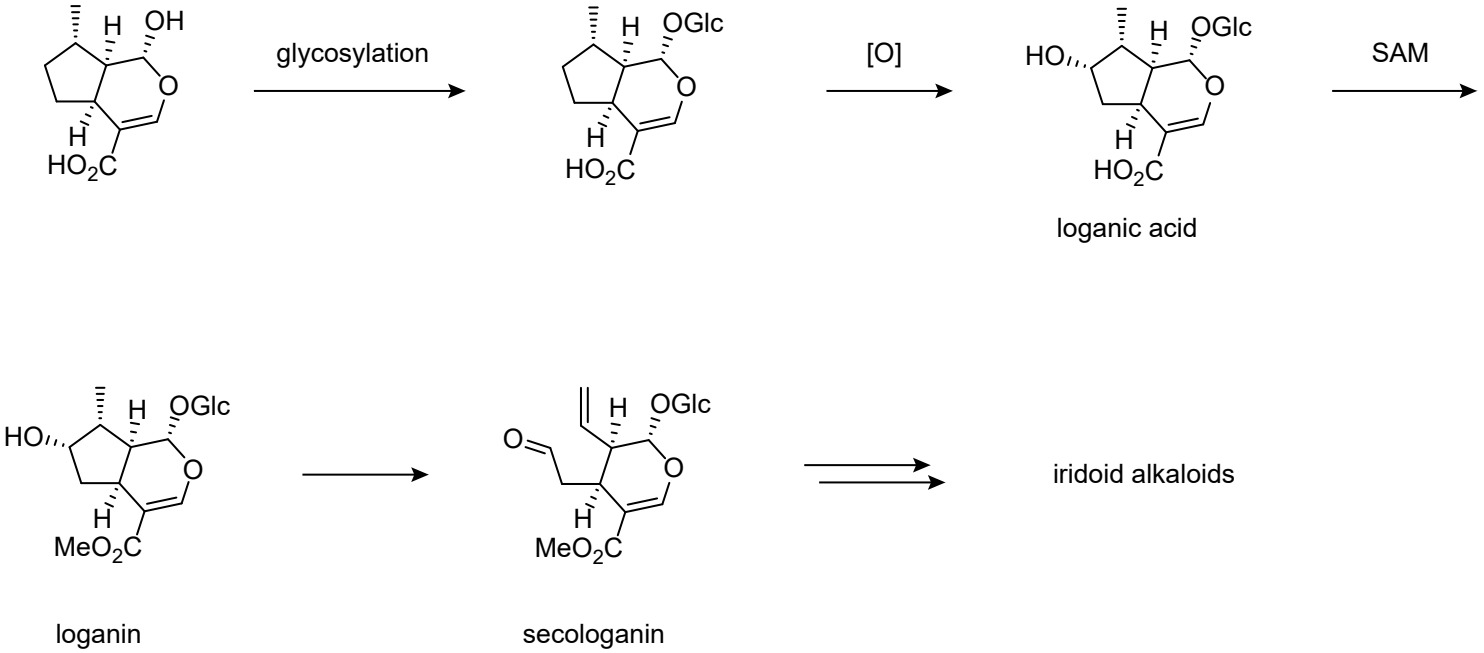
Iridoids = special form of monoterpenes



4.3 Terpene synthases

4.3.3 Iridoid synthase

Iridoids = special form of monoterpenes



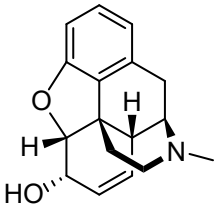
5. Alkaloids

5.1. Definition, occurrence, biological activity

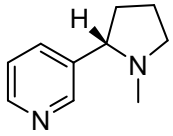
ca. 30,000 known compounds

nitrogen containing

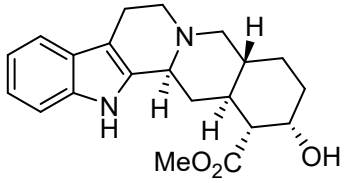
heterogeneous class of natural products



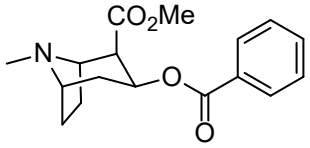
morphine
(*Papaver somniferum*)
strong pain killer



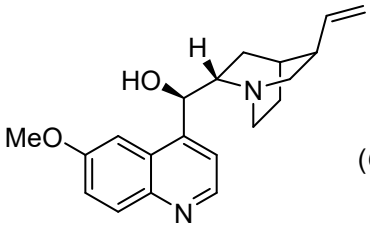
nicotine
(*Nicotiana tabacum*)
intoxicant



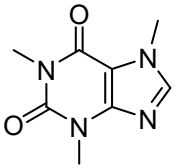
yohimbine
(*Pausinystalia yohimbe*)
aphrodisiac



cocaine
(*Erythroxylum coca*)
intoxicant and pain killer



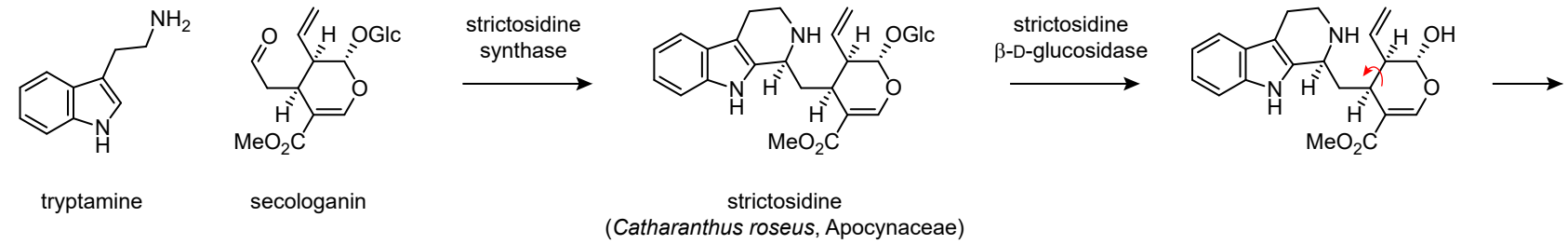
quinine
(*Chinchona officinalis*)
anti-malaria drug

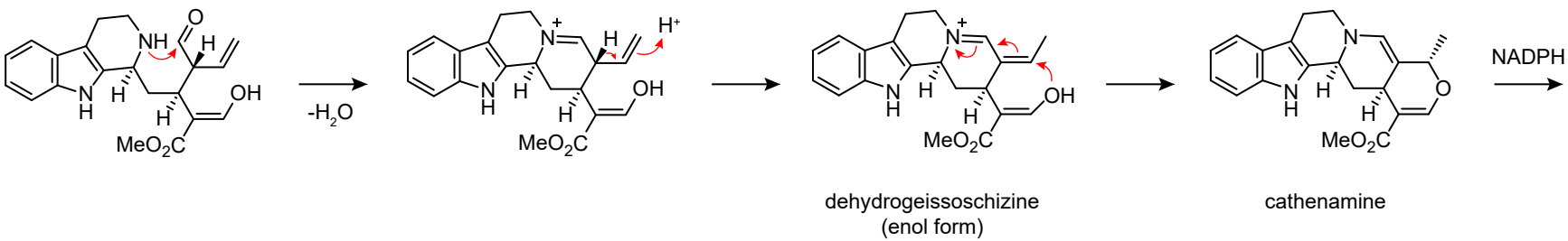


caffeine
(*Coffea arabica*)
stimulans

5.2. Indole alkaloids

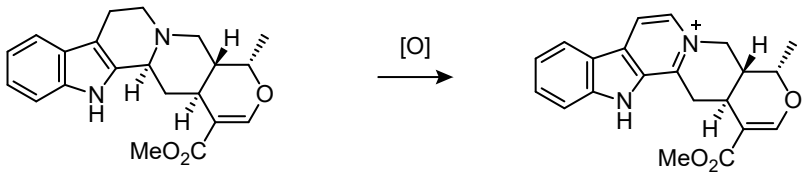
Strictosidine and terpene indole alkaloids





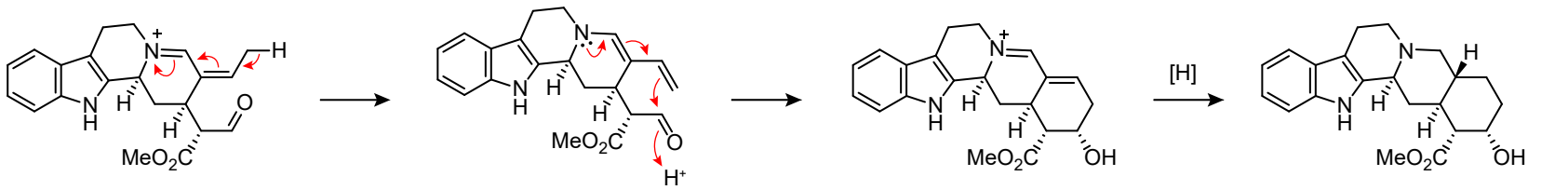
5.2. Indole alkaloids

Strictosidine and terpene indole alkaloids



ajmalicine
(*Rauwolfia serpentia*, Apocynaceae)

serpentine
(*Rauwolfia serpentia*)

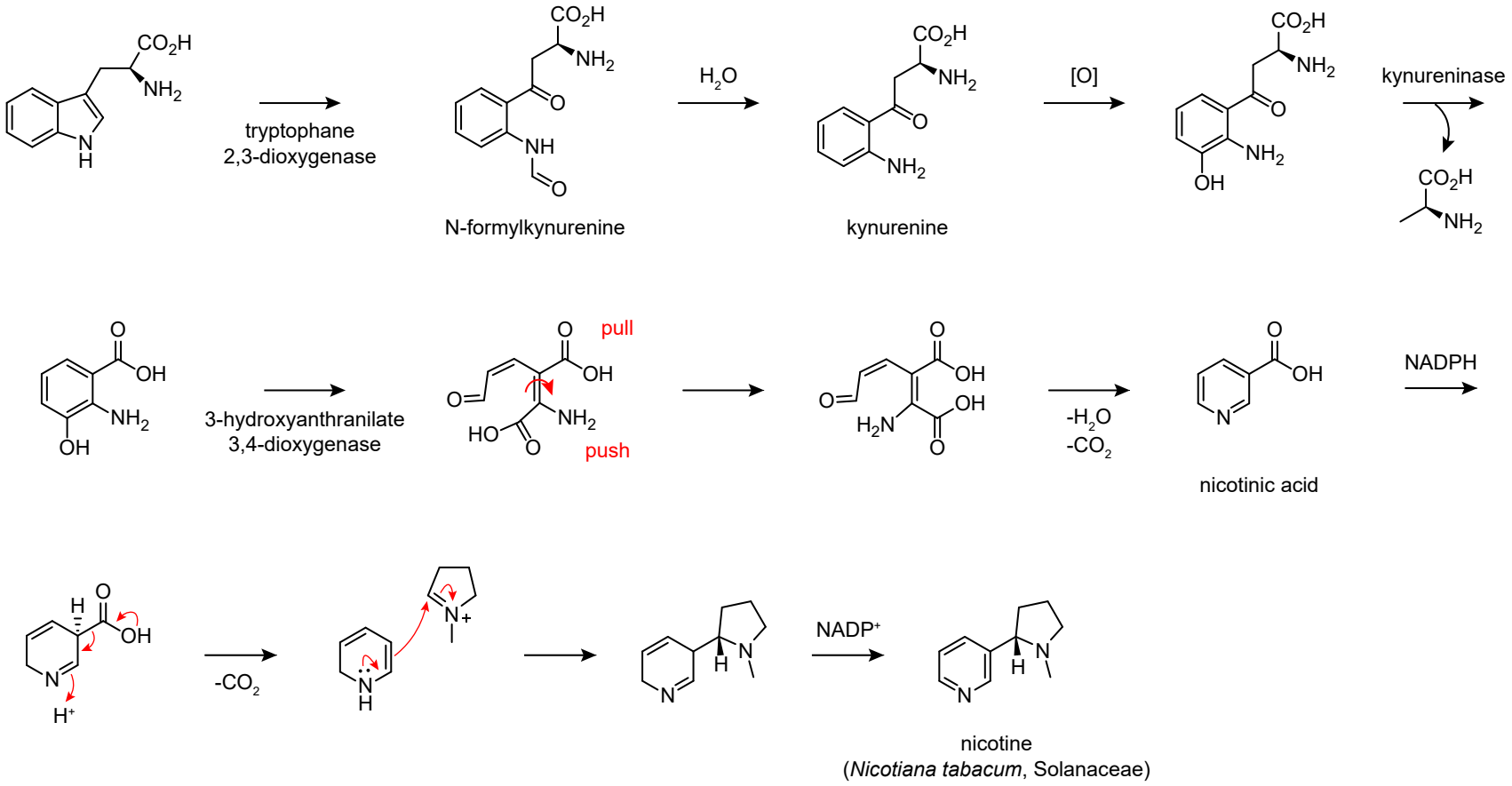


dehydrogeissoschizine
(keto form)

yohimbine
(*Pausinystalia yohimbe*, Rubiaceae)

5.3 Pyridine alkaloids

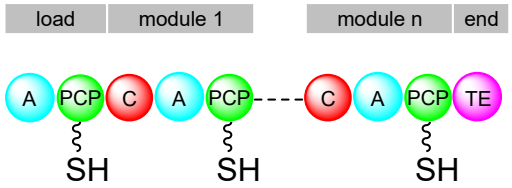
Nicotine (from Solanaceae)



6. Non-ribosomal peptides

6.1 Enzymology: Non-ribosomal peptide synthases (NRPS)

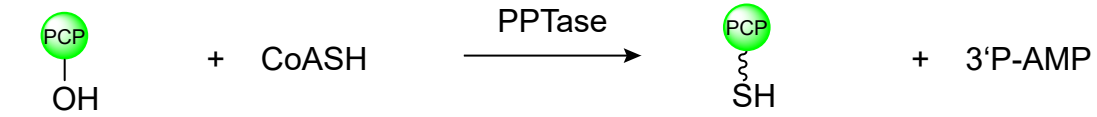
modular (as for modular type I PKS)



A	adenylation domain	(PKS: AT)
PCP	peptidyl carrier protein	(PKS: ACP)
C	condensation domain	(PKS: KS)
TE	thioesterase	(PKS: TE)

PCP

highly conserved serine, requires activation by PPTase



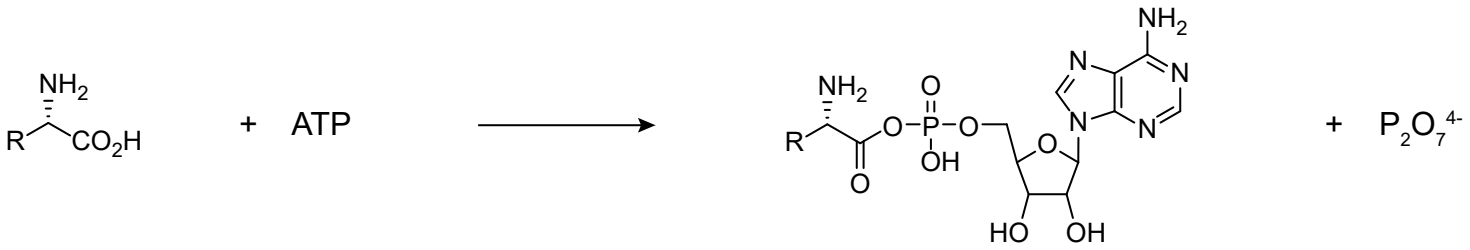
apo-PCP holo-PCP

6. Non-ribosomal peptides

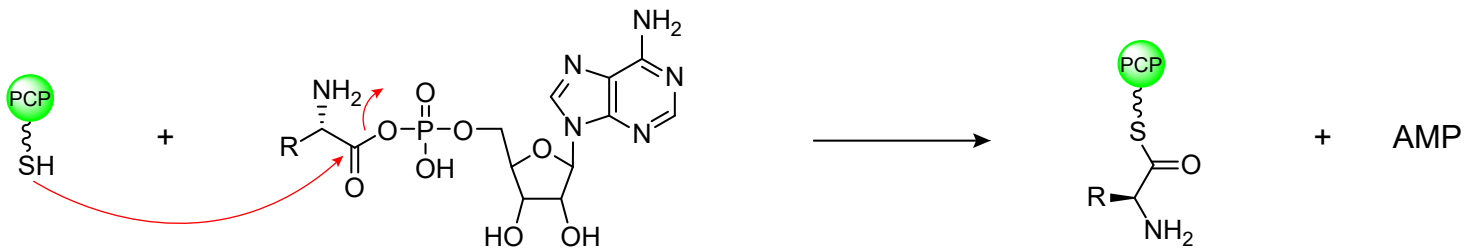
6.1 Enzymology: Non-ribosomal peptide synthases (NRPS)

A domains

substrate activation



upload to PCP

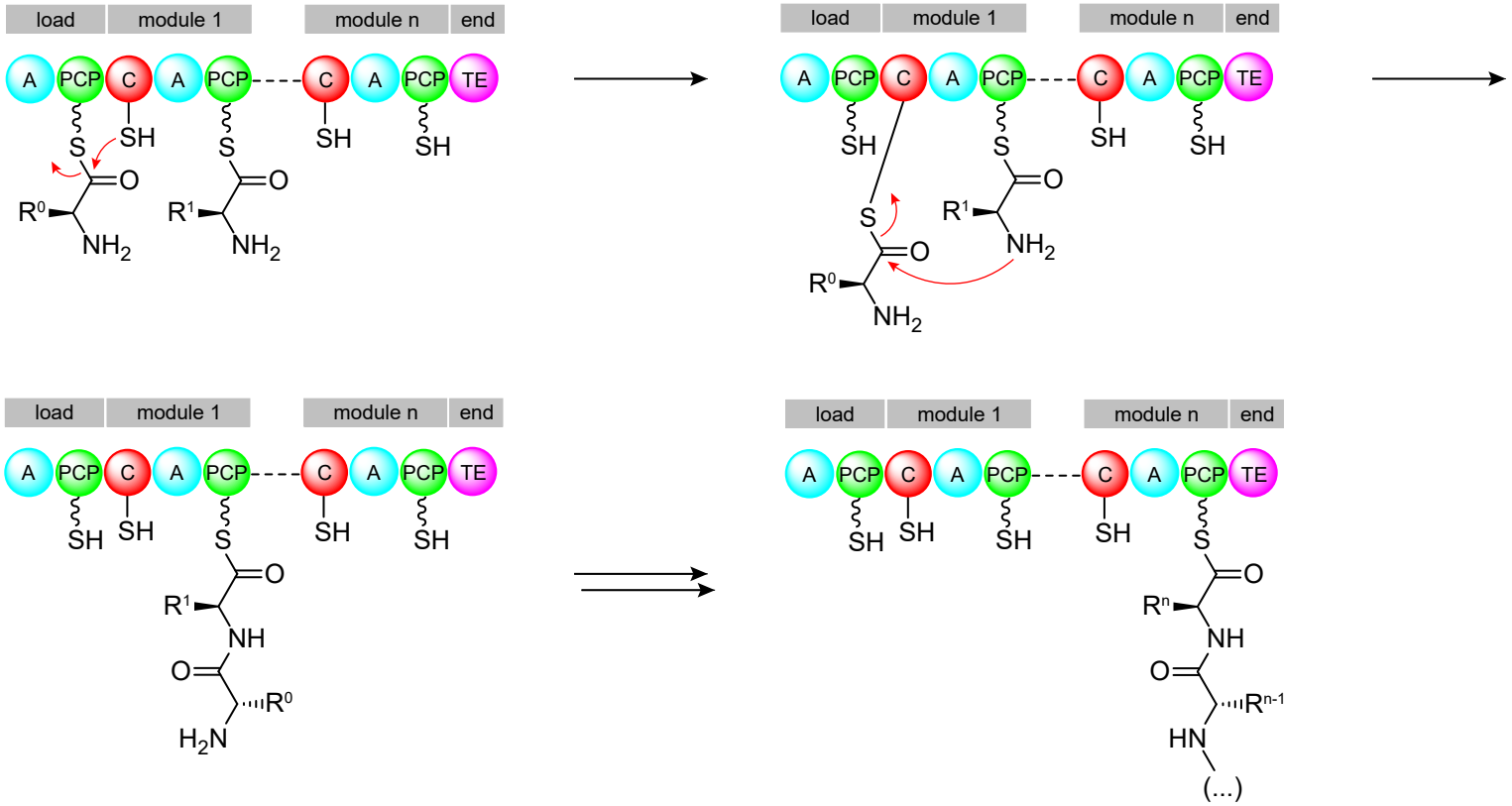


6. Non-ribosomal peptides

6.1 Enzymology: Non-ribosomal peptide synthases (NRPS)

C domains

condensation of amino acid units (peptide bond formation), highly conserved cysteine

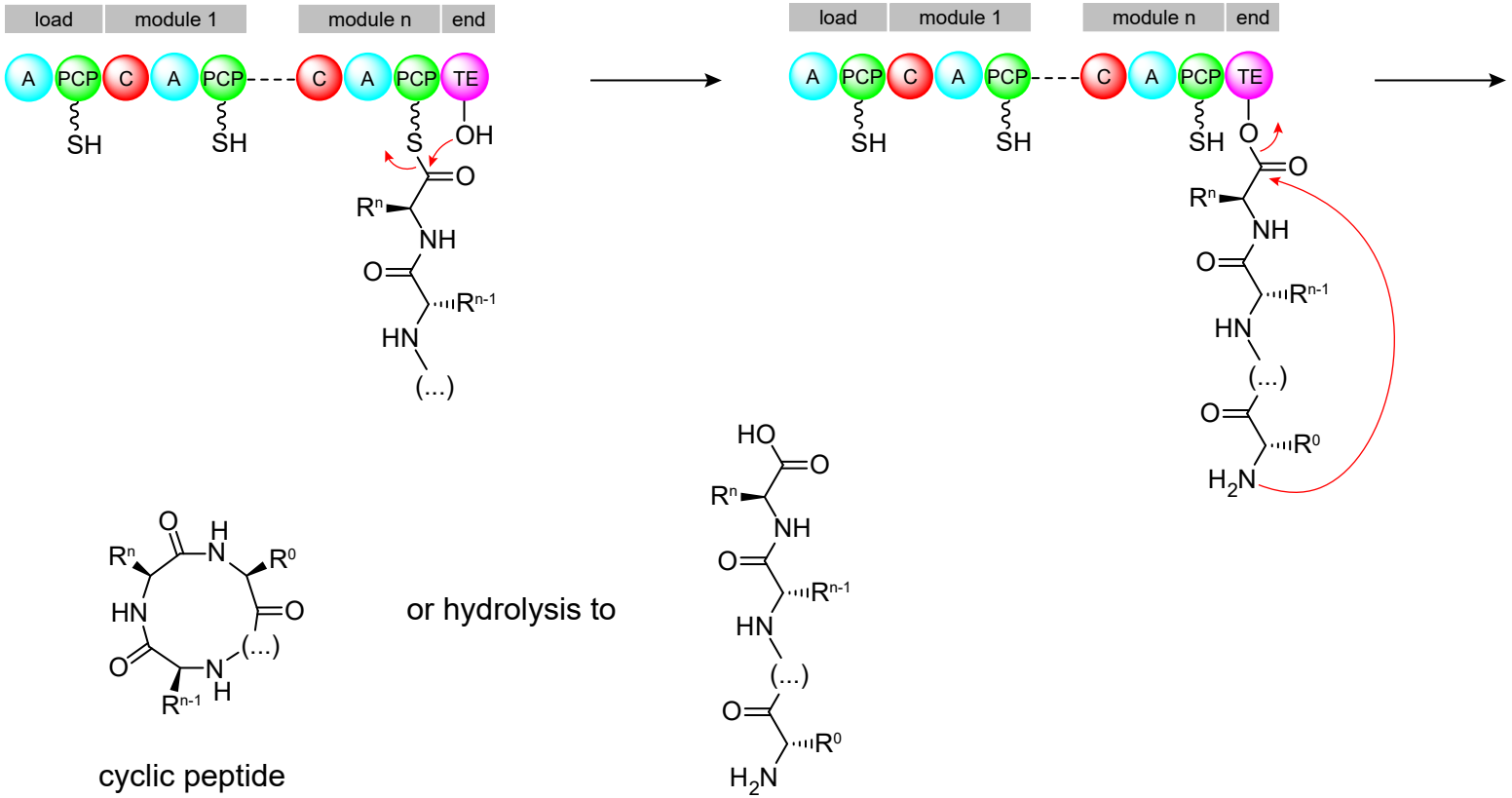


6. Non-ribosomal peptides

6.1 Enzymology: Non-ribosomal peptide synthases (NRPS)

TE domains

product release, highly conserved serine



cyclic peptide

6. Non-ribosomal peptides

6.2 Vancomycin biosynthesis

NRPS