Biosynthesis – Inspiration for Drug Discovery

Biosynthesis of Fatty Acids & Polyketides

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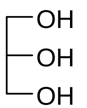
Format & Scope of Lectures

- ***What are fatty acids?***
  - 1° metabolites: fatty acids; 2° metabolites: their derivatives
  - biosynthesis of the building blocks: acetyl CoA & malonyl CoA
- ***Fatty acid synthesis by Fatty Acid Synthases (FASs)***
  - the chemistry involved
  - the FAS protein complex & the dynamics of the iterative synthesis process
- ***Fatty acid secondary metabolites***
  - eiconasiods: prostaglandins, thromboxanes & leukotrienes
- ***What are polyketides?***
  - definitions & variety
- ***Polyketide synthesis by PolyKetide Synthases (PKSs)***
  - the chemistry involved
  - the PKS protein complexes & the dynamics of the iterative synthesis process
- ***Polyketide secondary metabolites***
  - Type I modular metabolites: macrolides – *e.g.* erythromycin
  - Type I iterative metabolites: *e.g.* mevinolin (=lovastatin®)
  - Type II iterative metabolites: aromatic compounds and polyphenols: *e.g.* actinorhodin

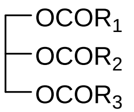
Fatty Acid Primary Metabolites

- ***Primary metabolites:***
  - ***fully saturated, linear carboxylic acids*** & derived ***(poly)unsaturated derivatives:***
    - constituents of essential natural waxes, seed oils, ***glycerides*** (fats) & phospholipids
    - ***structural role*** – ***glycerides*** & phospholipids are essential constituents of cell membranes
    - ***energy storage*** – ***glycerides*** (fats) can also be catabolised into acetate → citric acid cycle
    - ***biosynthetic precursors*** – for elaboration to secondary metabolites



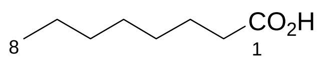
glycerol

⇩ ***3x fatty acids***

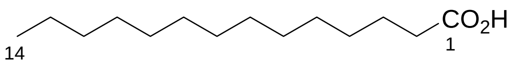


glycerides

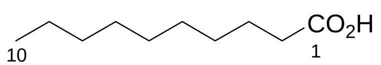
SATURATED ACIDS [$MeCH_2(CH_2CH_2)_nCH_2CO_2H$ (n = 2-8)]
e.g.



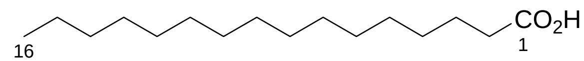
caprylic acid (C8, n = 2)



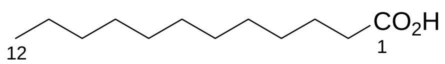
myristic acid (C14, n = 5)



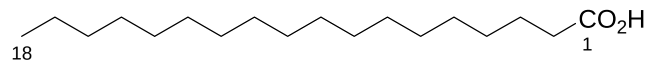
capric acid (C8, n = 3)



palmitic acid (C16, n = 6)

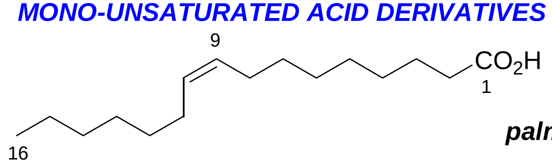


lauric acid (C12, n = 4)

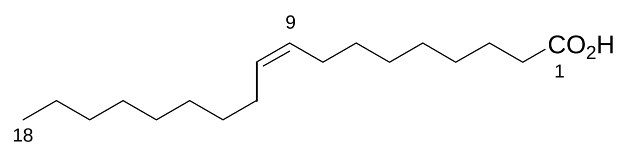


stearic acid (C18, n = 7)

MONO-UNSATURATED ACID DERIVATIVES (MUFAs) e.g.

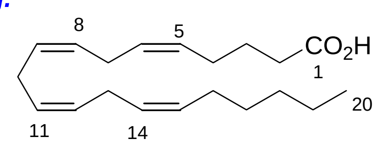


palmitoleic acid (C16, Z -Δ^9)

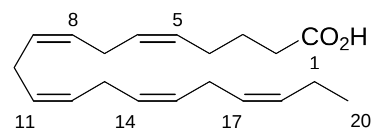


oleic acid (C18, Z-Δ^9)
(>80% of fat in olive oil)

POLY-UNSATURATED ACID DERIVATIVES (PUFAs)
e.g.



arachidonic acid (AA)
(C20, Z -Δ^5, Z -Δ^8, Z -Δ^{11}, Z -Δ^{14})

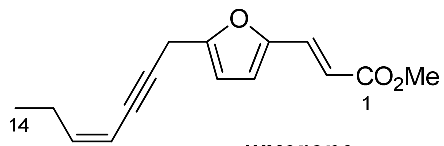


eicosapentaenoic acid (EPA)
(C20, Z-Δ^5, Z -Δ^8, Z-Δ^{11}, Z -$\Delta^{14,}$ Z -Δ^{17})
(in cod liver oil)

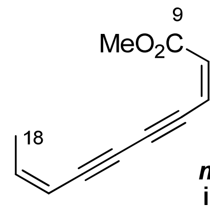
Fatty Acids Derivatives – *Secondary Metabolites*

- ***Secondary metabolites***
  - further ***elaborated*** derivatives of ***polyunsaturated fatty acids (PUFAs)***
    - *e.g.* polyacetylenes & ‘eicosanoids’ (prostaglandins, thromboxanes & leukotrienes)

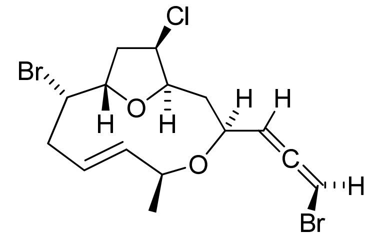
POLYACETYLENES
e.g.



wyerone
anti-fungal

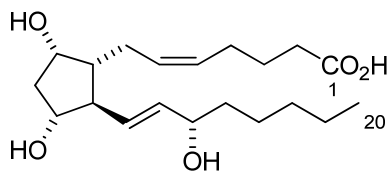


matricaria ester
in chamomile tea



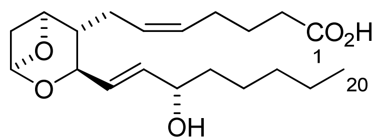
obtucallene II
marine natural product

PROSTAGLANDINS
e.g.



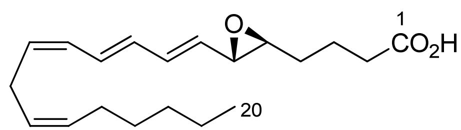
prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

THROMBOXANES
e.g.



thromboxane A_2 (TXA_2)

LEUKOTRIENES
e.g.

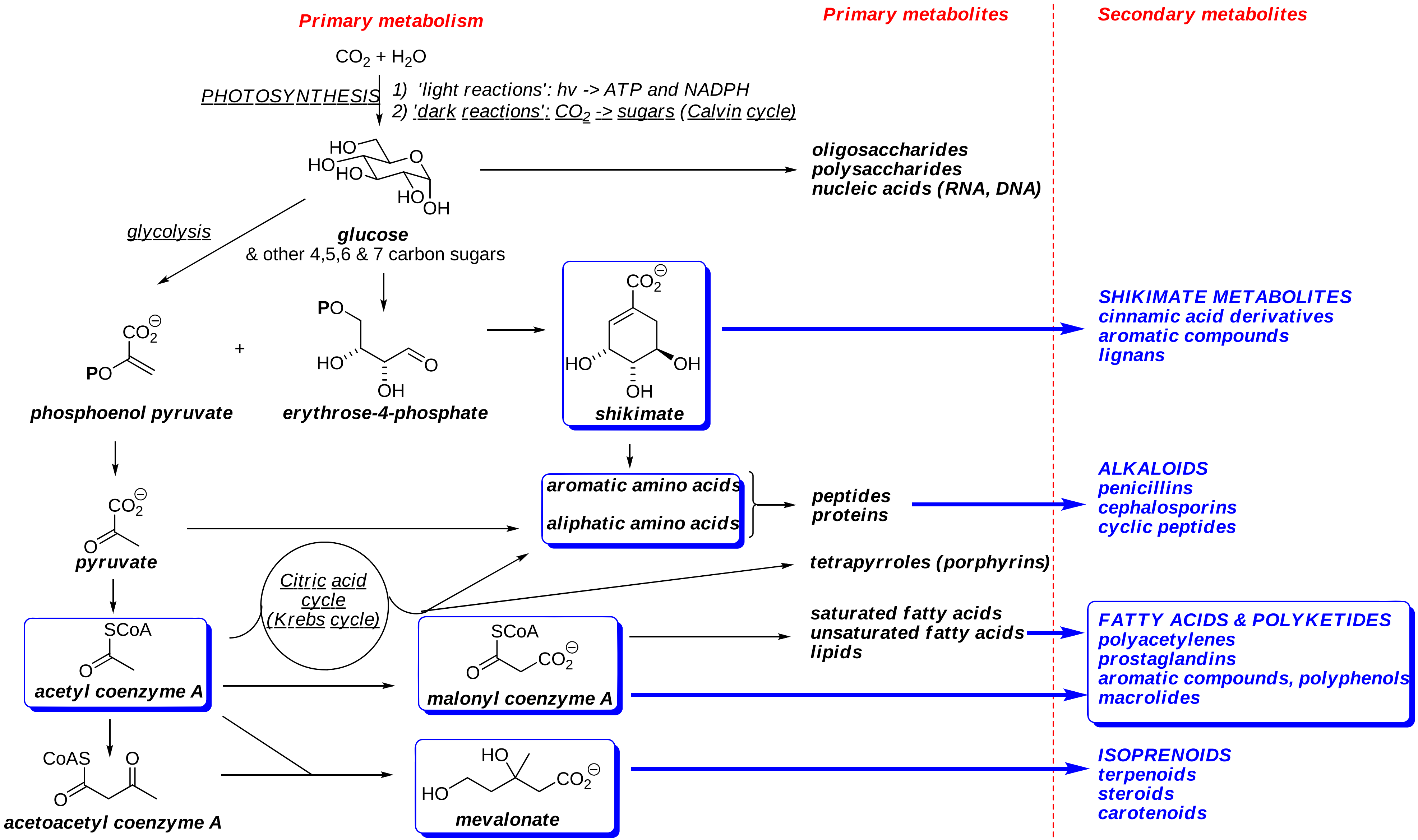


leukotriene A_4(LTA_4)

leukotriene A_4 (LTA_4)

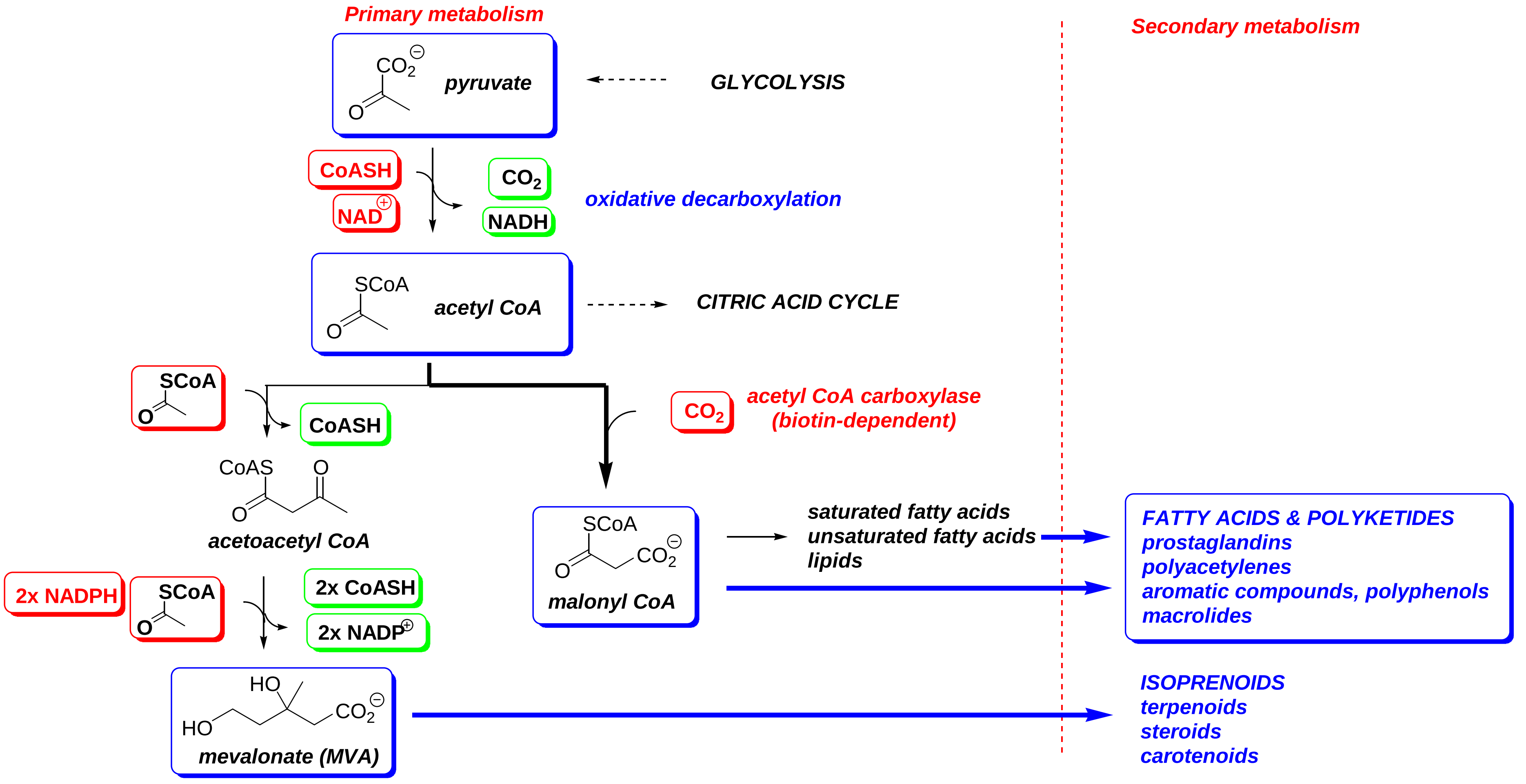
EICOSANOIDS

Primary Metabolism - *Overview*



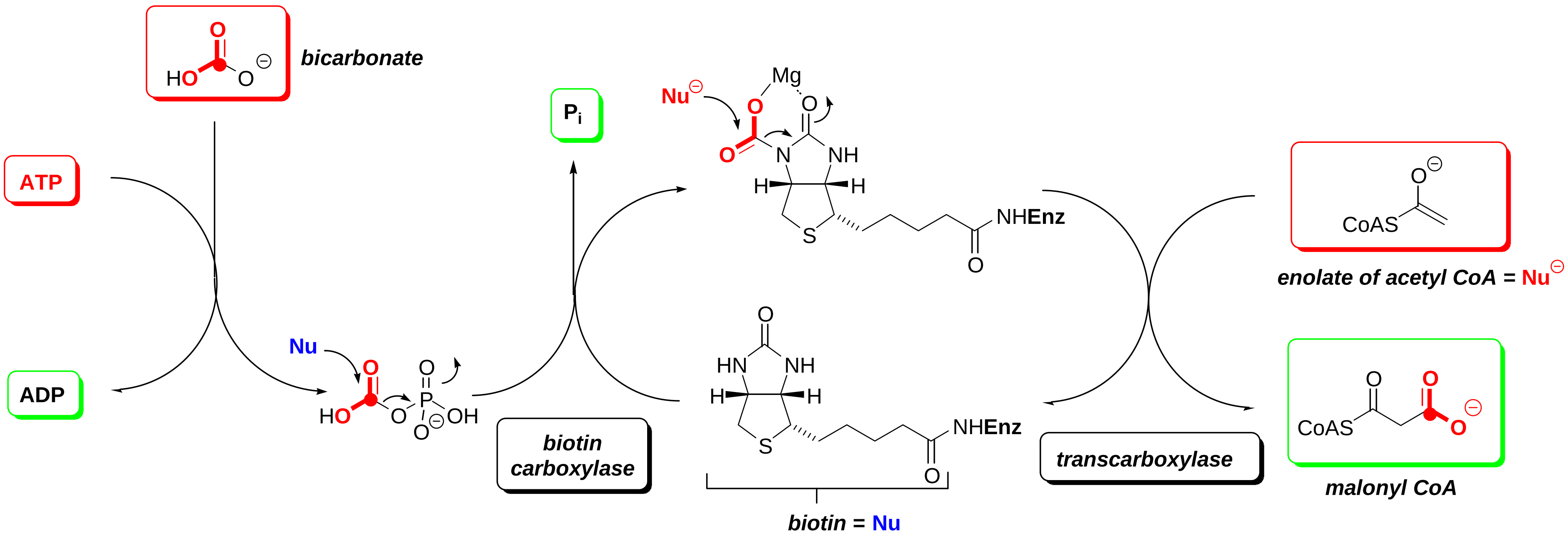
Biosynthesis of Malonyl Coenzyme A

- ***Malonyl coenzyme A*** is the key ***'extender unit'*** for the biosynthesis of ***fatty acids (& polyketides):***
  - is formed by the ***carboxylation*** of ***acetyl coenzyme A*** mediated by a ***biotin-dependent enzyme***
  - this is the ***first committed step of fatty acid/polyketide biosynthesis*** (& is a rate controlling step)



Biosynthesis of Malonyl Coenzyme A

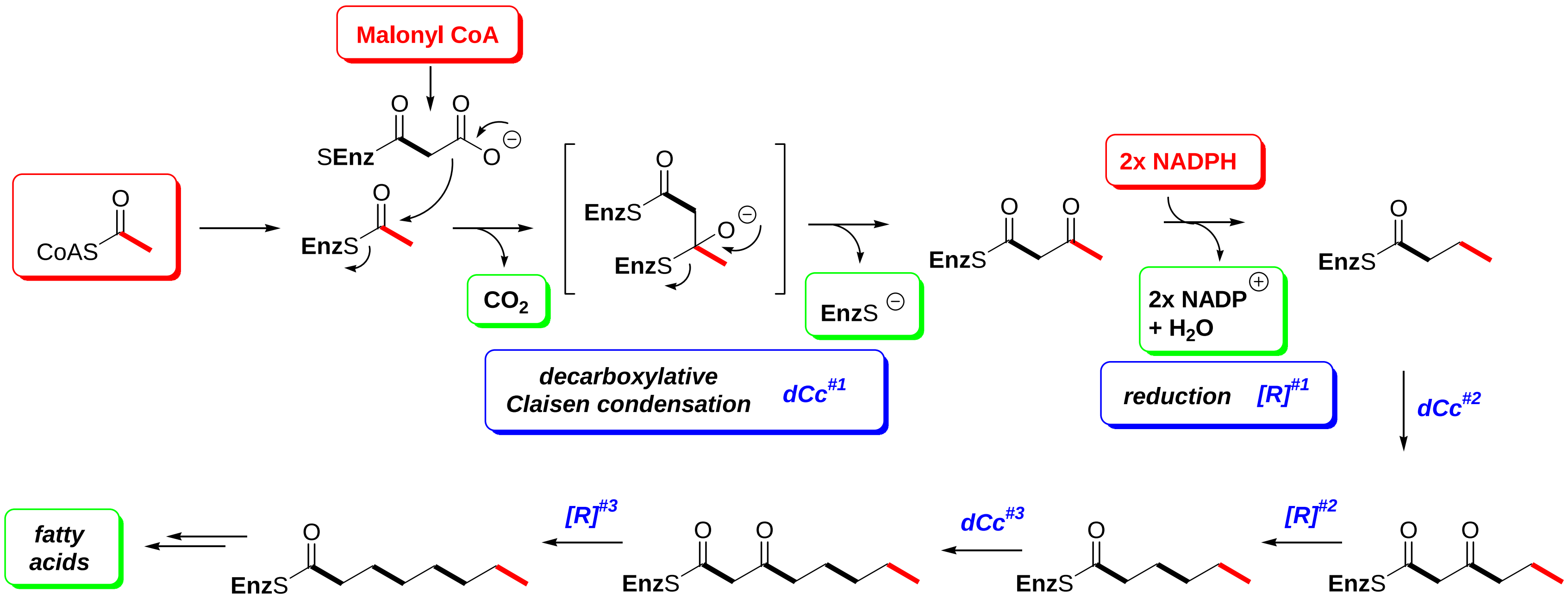
- ***Bicarbonate*** is the source of the ***CO_2***:
  - the bicarbonate is first ***activated*** via ***phosphorylation*** by ***ATP***
  - then the ***phosphorylated bicarbonate*** carboxylates ***biotin*** to give ***carboxybiotin***
  - then the ***carboxybiotin*** carboxylates the enolate of ***acetyl CoA*** to give ***malonyl CoA:***



  - the carboxylation of biotin & acetyl CoA are mediated by a ***single biotin-dependent enzyme (complex)*** having both ***biotin carboxylase*** and ***transcarboxylase active sites***
  - *NB.* coupling to ATP ‘hydrolysis’ provides ***energy*** to drive carboxylation processes

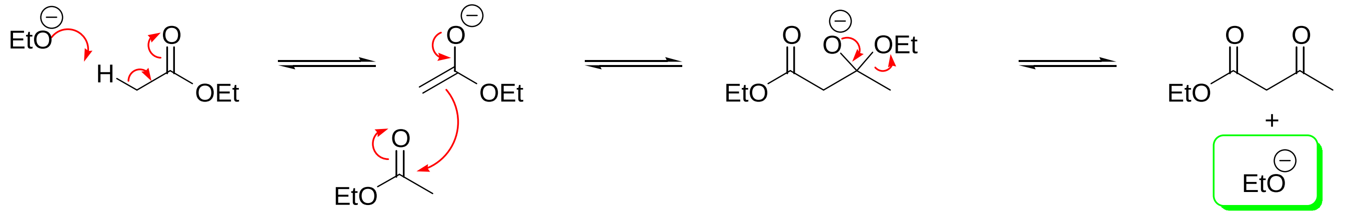
Biosynthesis of Fatty Acids – *Iterative Oligomerisation*

- ***fatty acids*** are biosynthesised from ***acetyl CoA*** as a ***starter unit*** by ***iterative*** 'head-to-tail' ***oligomerisation*** involving:
  - condensation with ***malonyl CoA*** as an ***extender unit*** (with loss of ***CO_2***) – a ***decarboxylative Claisen condensation***
  - 3-step ***reduction*** of the resulting ***ketone*** → ***methylene***
- after **n = 2-8 iterations** the ***C8-20 saturated fatty acid*** is released from the enzyme(s):

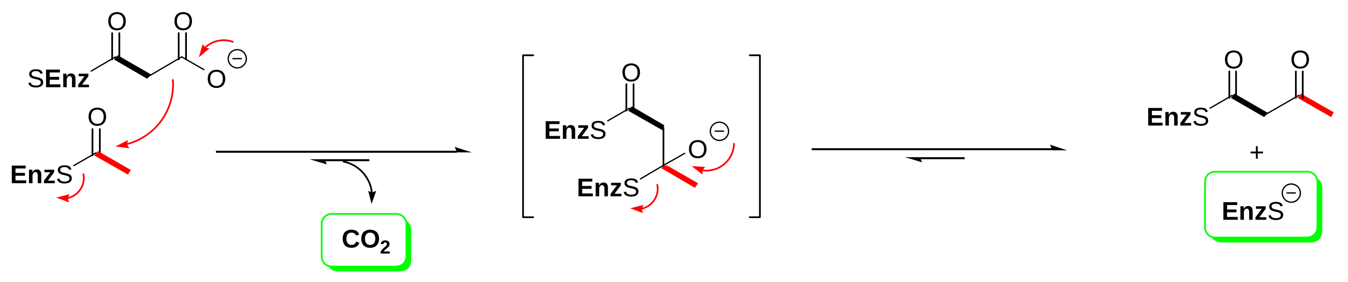


The Decarboxylative Claisen Condensation (dCc)

- *in vitro* – the classical ***Claisen condensation***:



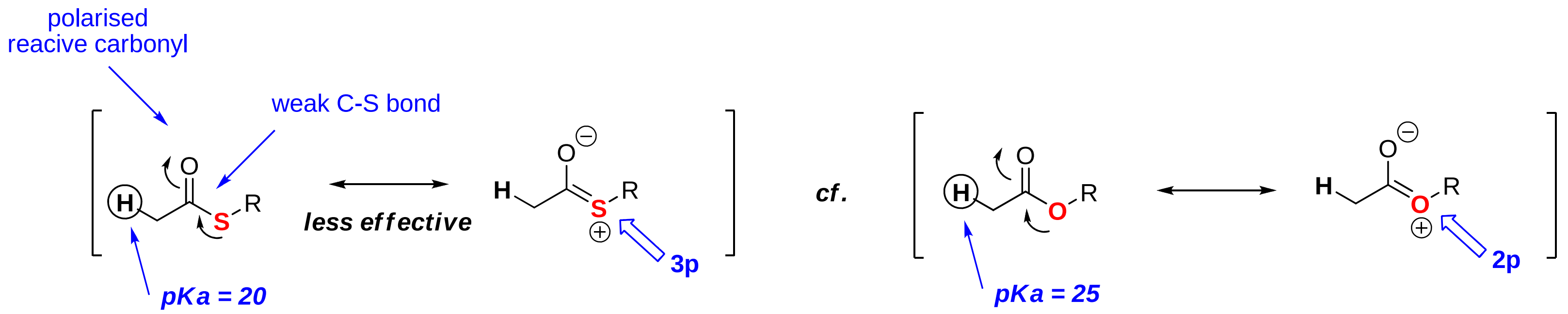
- *in vivo* - the ***decarboxylative Claisen condensation*** catalysed by a ***ketosynthase (KS)***



  - the energy released upon loss of CO_2 provides a driving force for the condensation
  - thioesters are also particularly reactive partners in this type of condensation...

The Claisen Condensation - *Why Thioesters*?

- recall the chemistry of ***coenzyme A*** (1st lecture) – properties of ***alkyl thioesters*** (*cf.* alkyl esters)
  - ***highly electrophilic carbonyl*** (~ ketone)
  - ***high acidity of protons*** α ***to the carbonyl of thioesters*** (*cf.* ester)
  - ***weak C-S bond*** (*cf.* C-O bond):
    - due to poor orbital overlap between the p-orbital lone pair on sulfur (n_S) [*cf.* n_O] and the carbonyl anti bonding orbital $\pi^*_{C=O}$; (*i.e.* minimal 'resonance' $n_S \rightarrow \pi^*_{C=O}$)

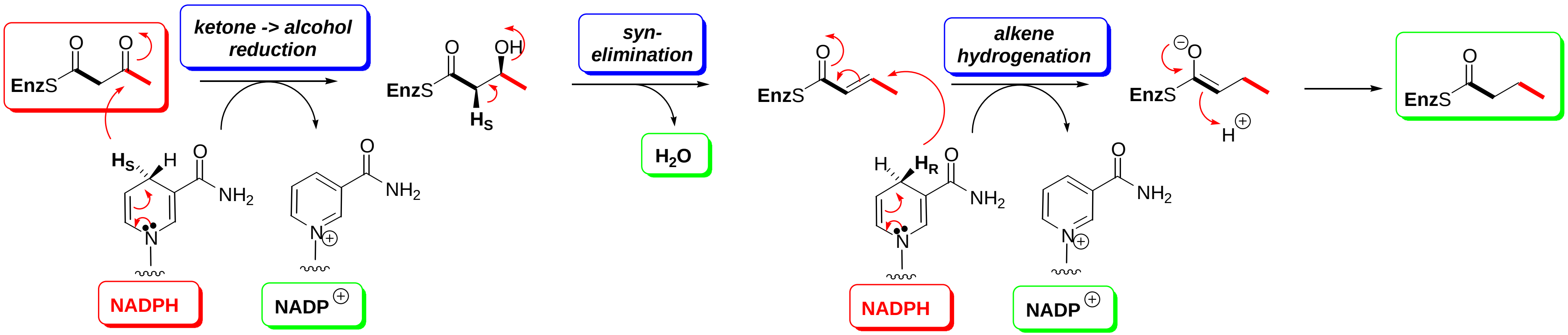


  - ***good leaving group ability of RS⁻*** (*cf.* RO⁻)
    - due to pK_a (RSH) ~10 *cf.* pK_a (ROH) ~16

Ketone → Methylene - *Reduction*

- ***ketone*** → ***methylene*** reduction is achieved *via* a ***3-step process:***

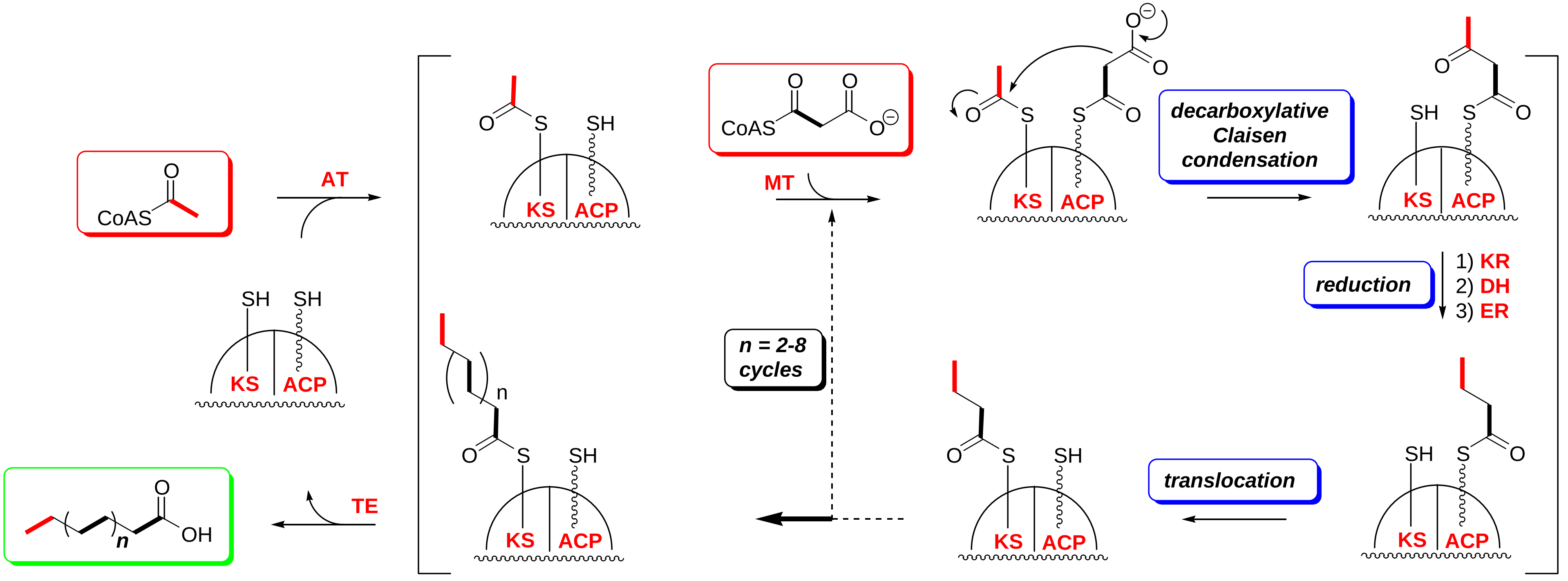
  1. ***NADPH***-mediated ***ketone*** → ***alcohol reduction*** catalysed by a ***keto reductase (KR)***
  2. ***syn-eliminataion*** of water catalysed by a ***dehydratase (DH)***
  3. ***NADPH***-mediated ***hydrogenation*** of the double bond catalysed by an ***enoyl reductase (ER)***



- all steps are generally stereospecific but stereospecificity varies from organism to organism
  - indicated specificities are for ***human FAS***

Biosynthesis of Fatty Acids – *Overview of FAS*

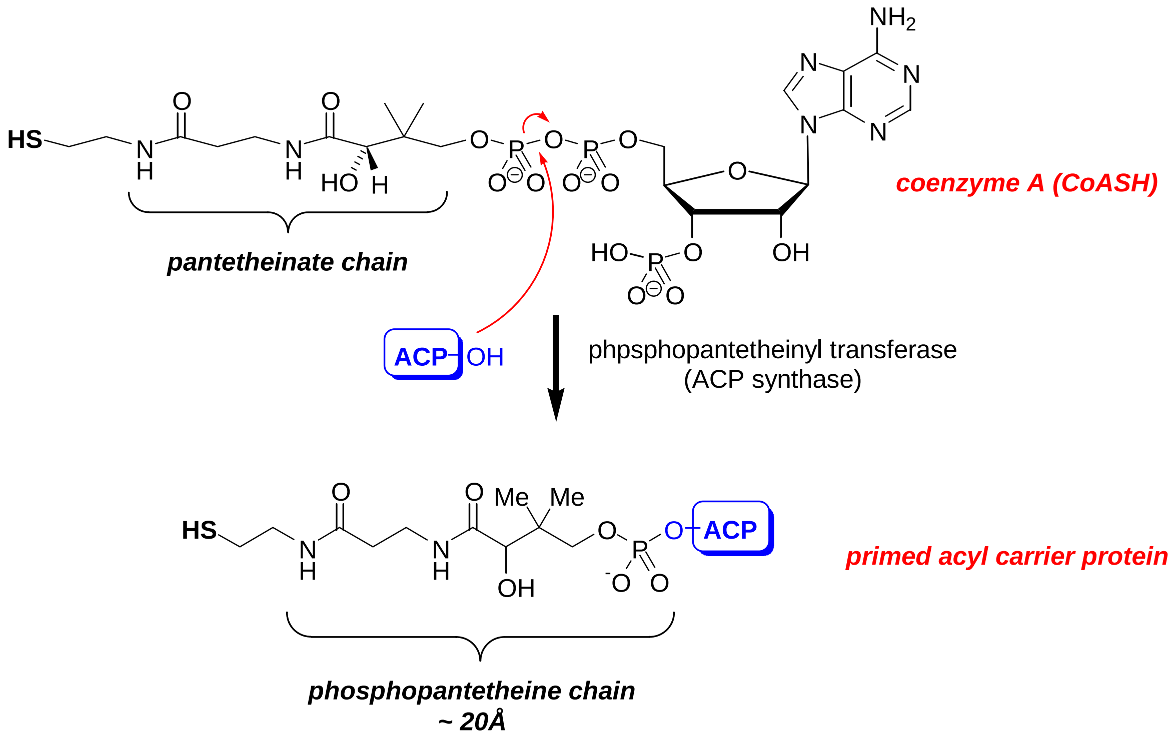
- The *in vivo* process by which all this takes place involves a 'molecular machine' - ***Fatty Acid Synthase (FAS)***
  - ***Type I FAS: single multifunctional protein complex*** (*e.g.* in mammals incl. humans)
  - ***Type II FAS: set of discrete, dissociable single-function proteins*** (*e.g.* in bacteria)
  - ***All FASs*** comprise ***8 components*** (ACP & 7× catalytic activities): ***ACP***, ***KS***, ***AT***, ***MT***, ***KR***, ***DH***, ***ER*** & [***TE***] :



KS = keto synthase (also known as **CE** = condensing enzyme); **AT** = acetyl transferase; **MT** = malonyl transferase; **KR** = keto reductase; **DH** = dehydratase; **ER** = enoyl reductase; **TE** = thioesterase; **ACP** = acyl carrier protein

The Acyl Carrier Protein (ACP)

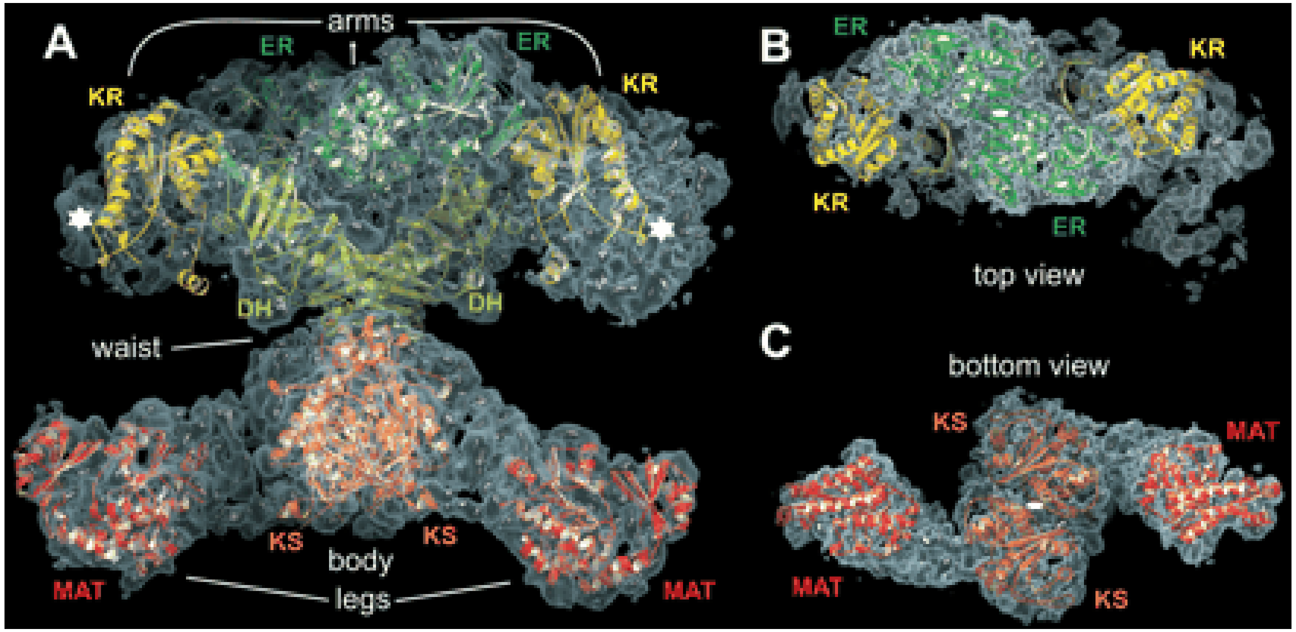
- the ***Acyl Carrier Protein (ACP)*** is the key protein that allows the growing oligomer to access the appropriate active sites
- The ACP is first ***primed*** by the post-translational modification of one of its serine hydroxyl groups:
  - the introduction of a ***phosphopantetheine 'swinging-arm'*** by reaction with ***acetyl coenzyme A:***



  - this swinging-arm provides ***flexibility*** for module-module acyl transfer & provides ***binding energy*** for catalysis
  - the ACP is inactive prior to priming

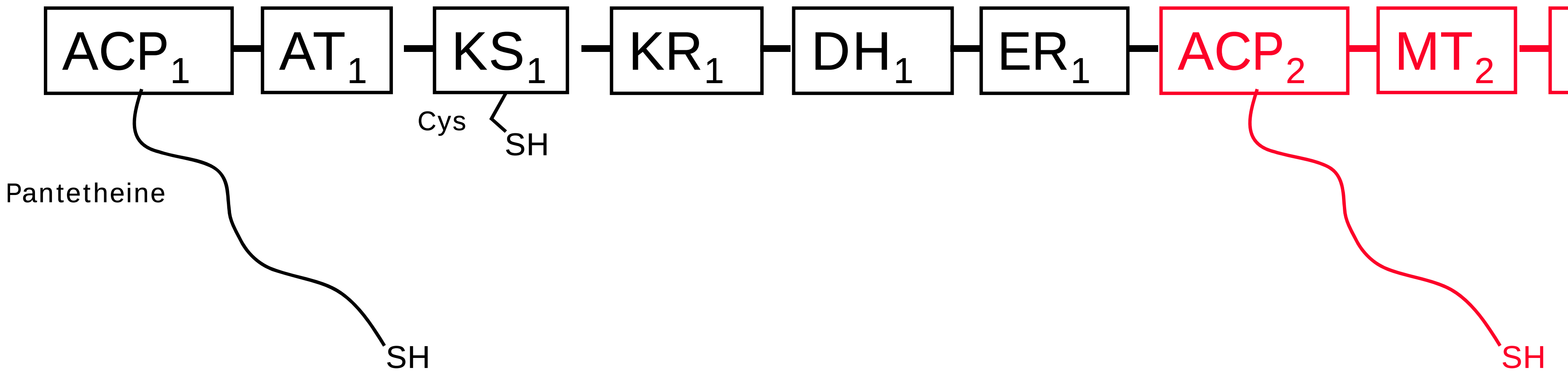
Human Fatty Acid Synthase (FAS)

- the first three-dimensional structure of human fatty acid synthase (272 kDa) at 4.5 Å resolution by X-ray crystallography:
  - Maier, Jenni & Ban *Science* **2006**, *311*, 1258 (DOI) ; also Fungal FAS @ 3.1 Å resolution see: Jenni *et al. Science* **2007**, *316*, 254 & 288



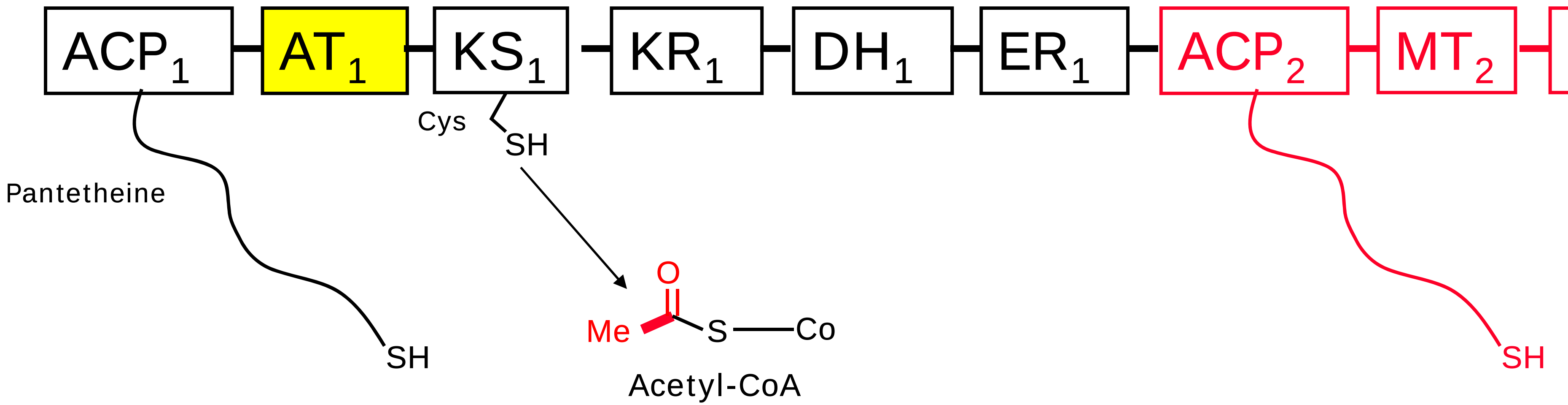
Structural overview. (**A**) Front view: FAS consists of a lower part comprising the KS (lower body) and MAT domains (legs) connected at the waist with an upper part formed by the DH, ER (upper body), and KR domains (arms). (**B**) Top view of FAS with the ER and KR domains resting on the DH domains. (**C**) Bottom view showing the arrangement of the KS and MAT domains and the continuous electron density between the KS and MAT domains

FATTY ACID BIOSYNTHESIS (type II FAS)



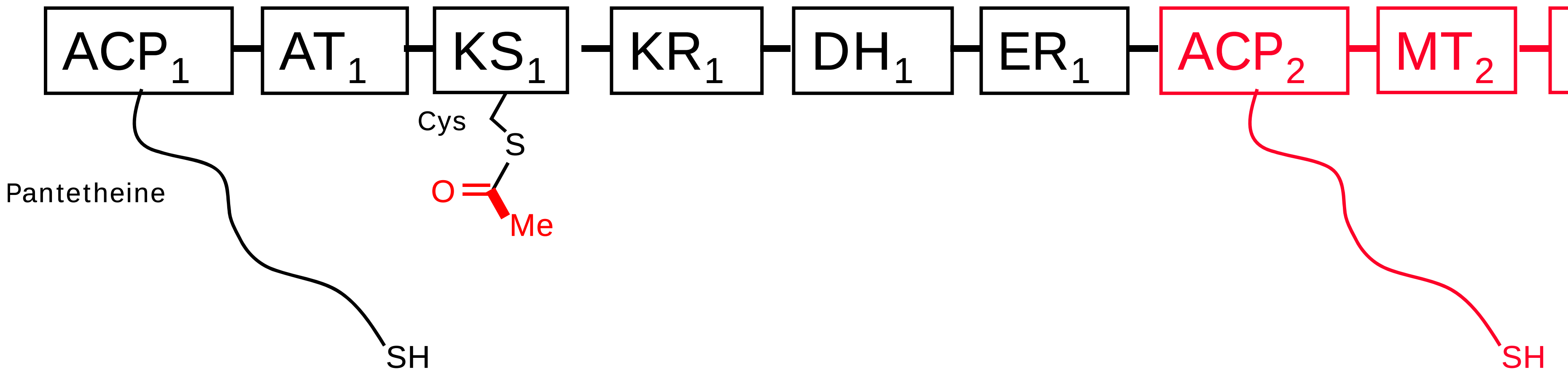
NB. the following sequence of slides have been adapted from: http://www.courses.fas.harvard.edu/%7echem27/

FATTY ACID BIOSYNTHESIS

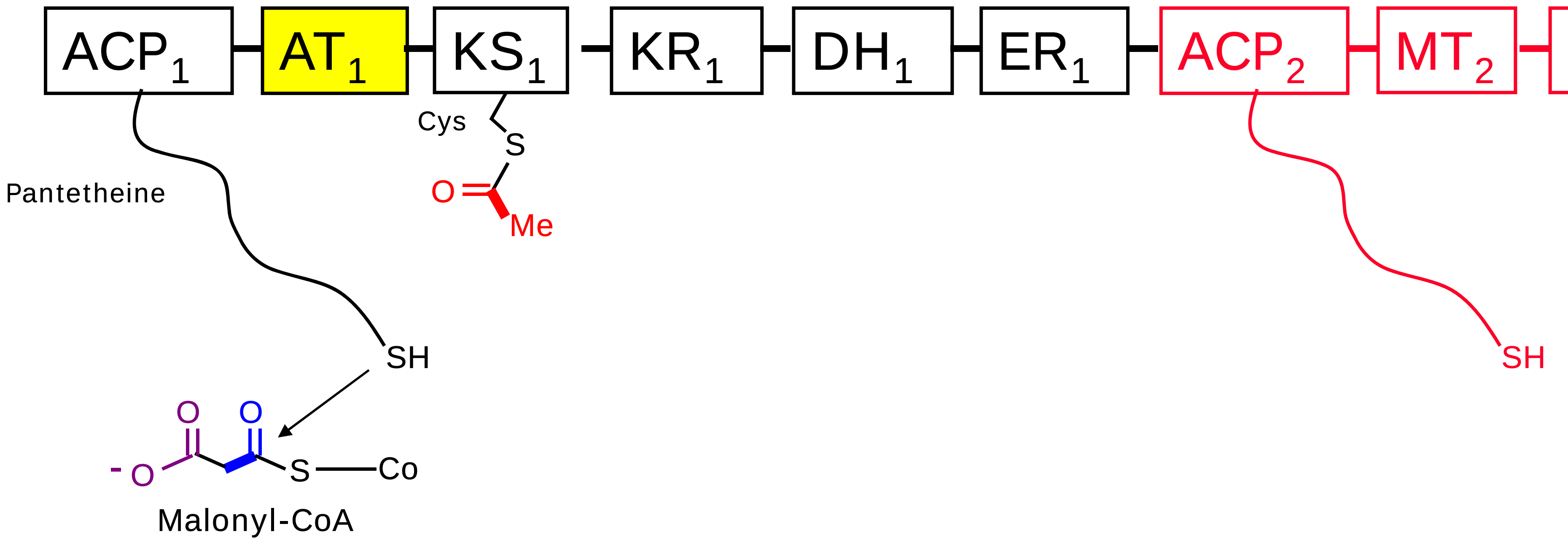


- AT_1 loads acetyl group onto KS_1

FATTY ACID BIOSYNTHESIS

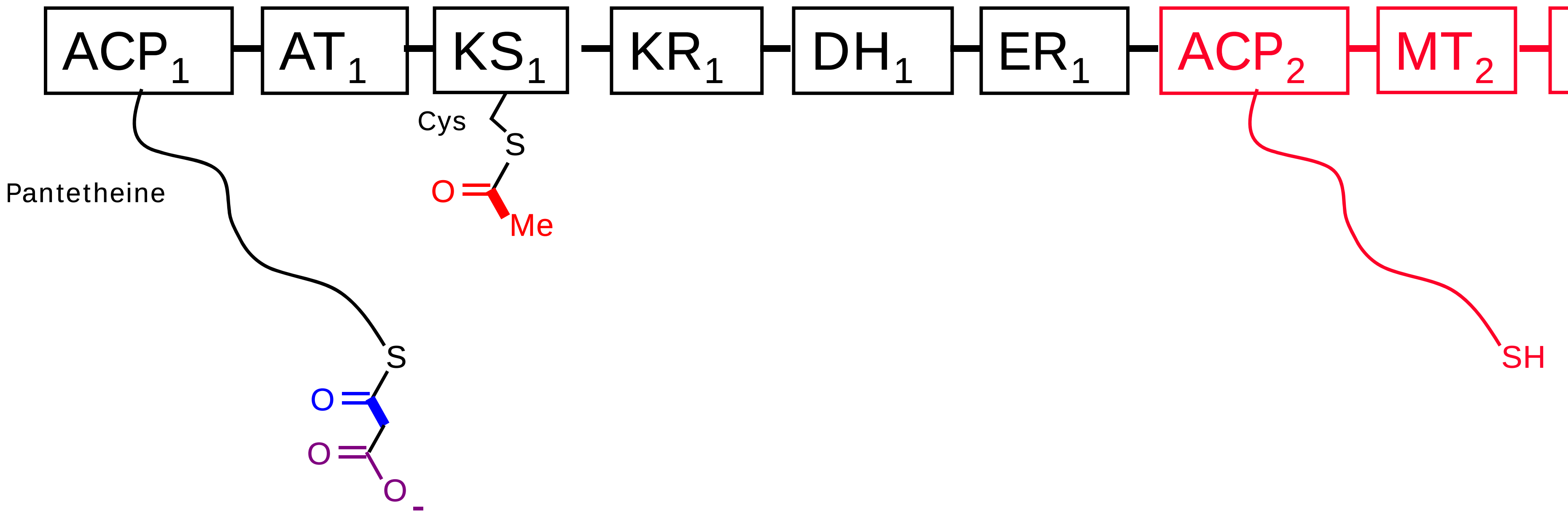


FATTY ACID BIOSYNTHESIS



- AT_1 loads malonyl group onto ACP_1

FATTY ACID BIOSYNTHESIS



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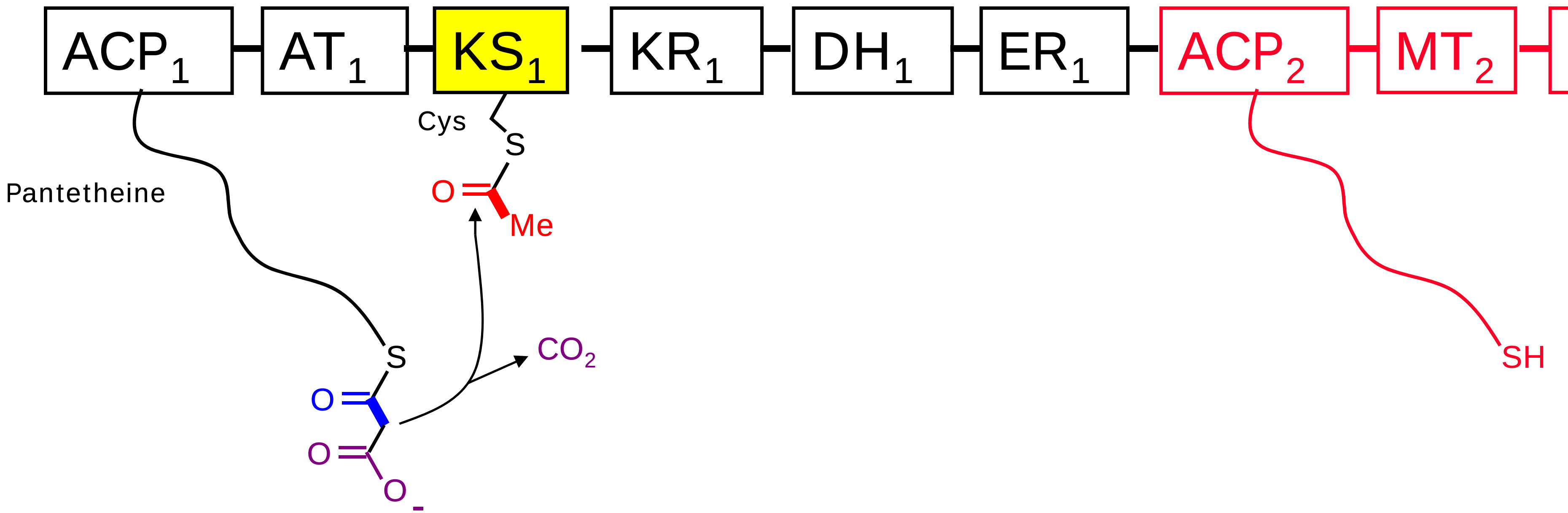
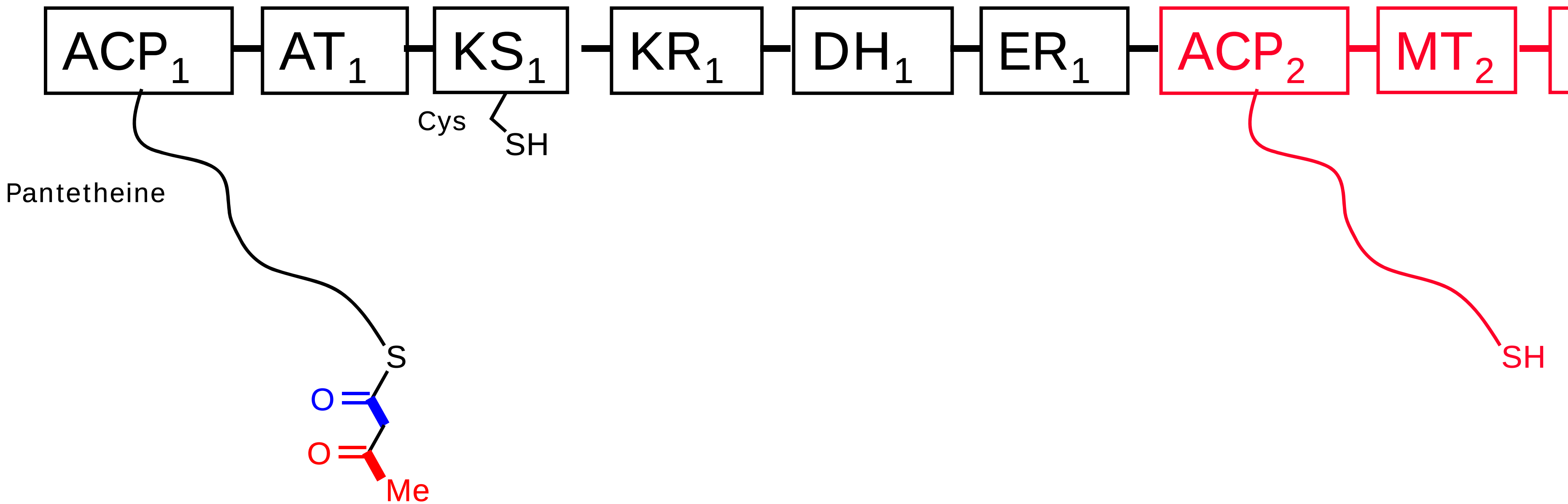
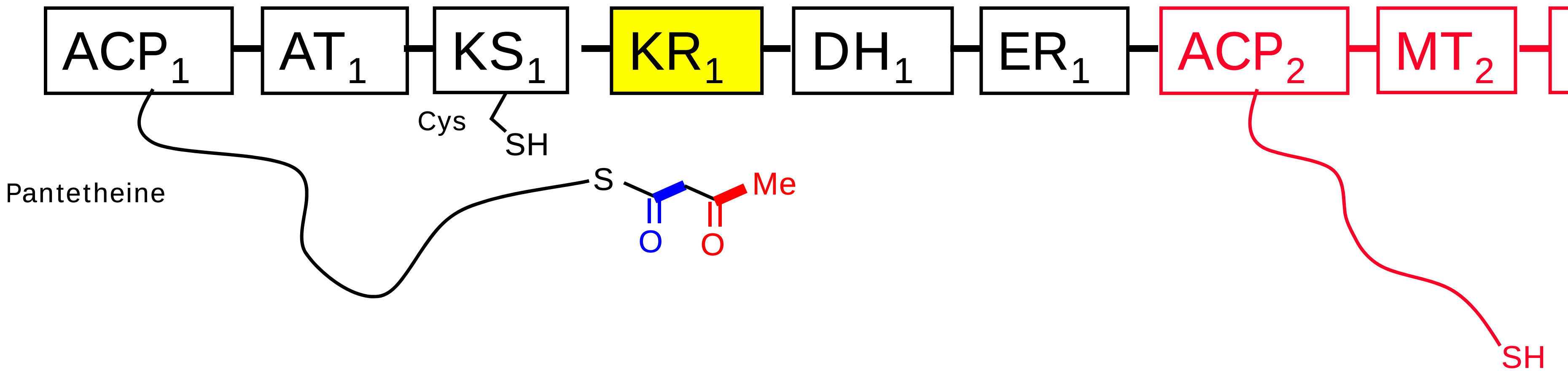


- KS$_1$ catalyzes Claisen condensation

FATTY ACID BIOSYNTHESIS

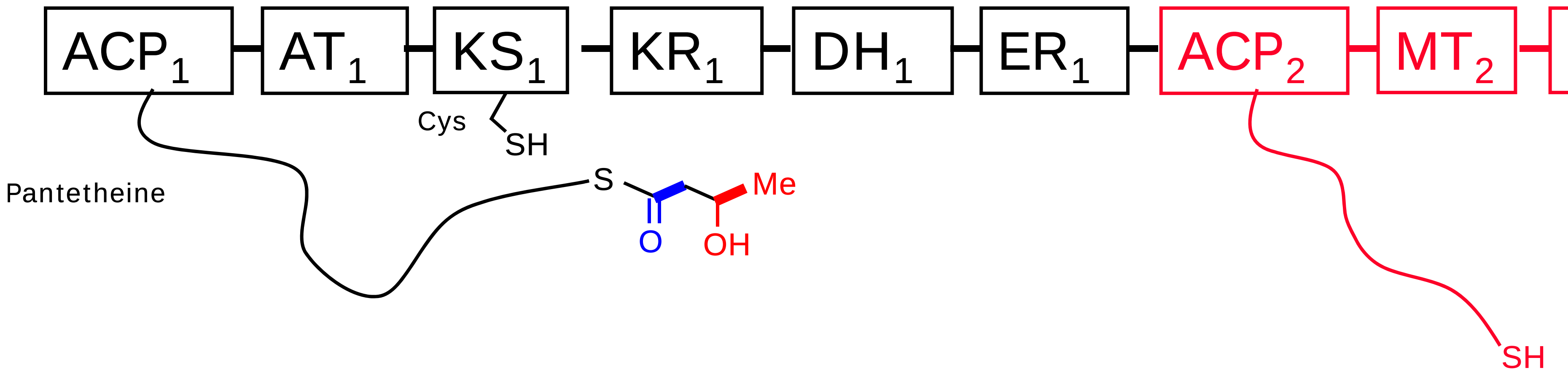


FATTY ACID BIOSYNTHESIS



- KR_1 catalyzes reduction of ketone

FATTY ACID BIOSYNTHESIS



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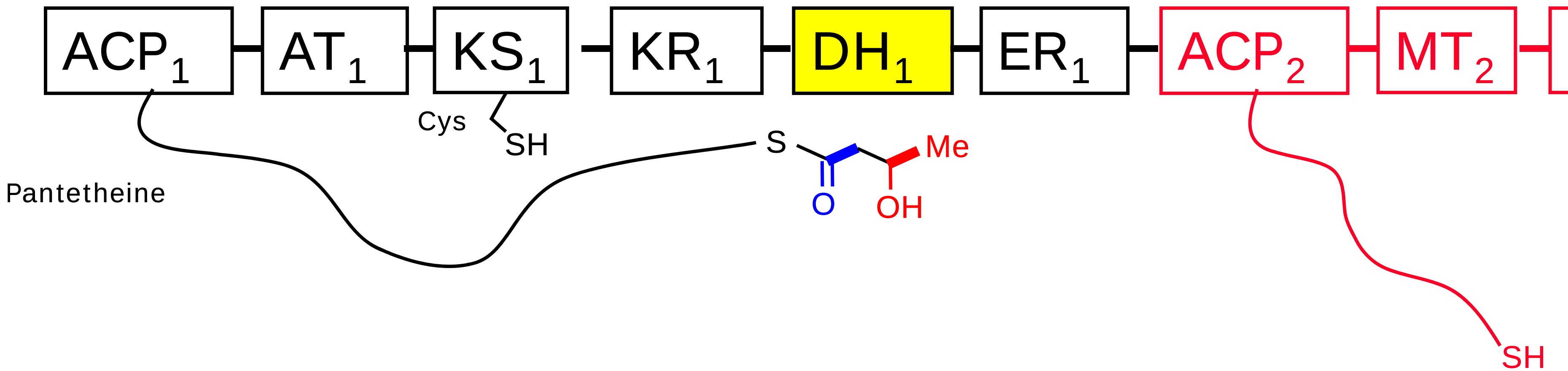
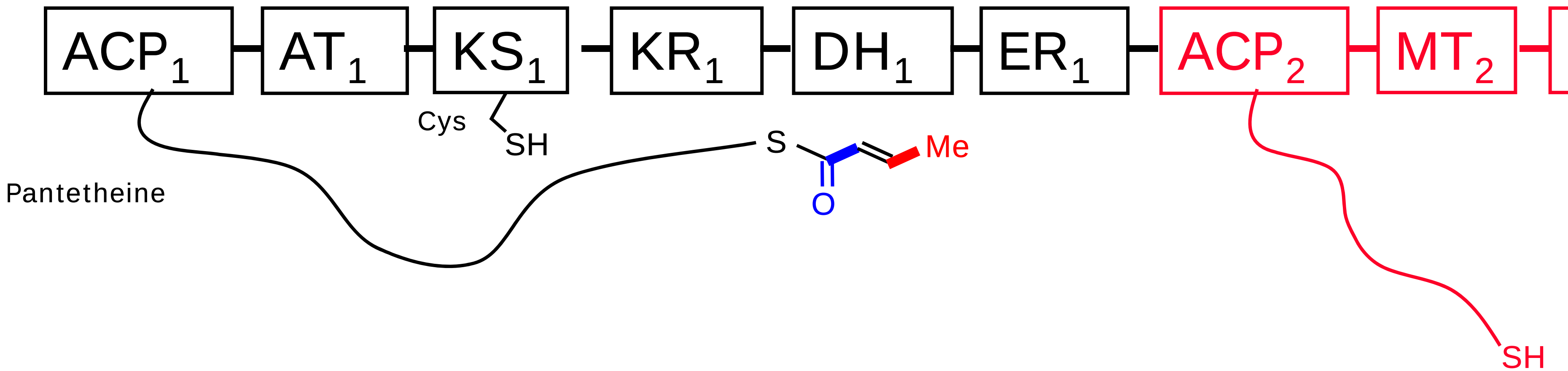


- DH_1 catalyzes dehydration of alcohol

FATTY ACID BIOSYNTHESIS



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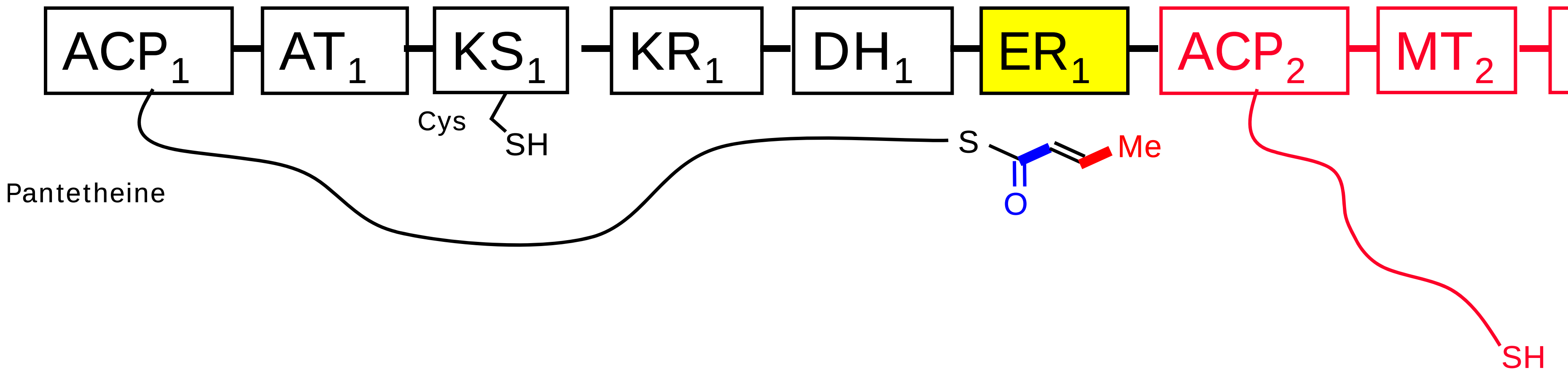
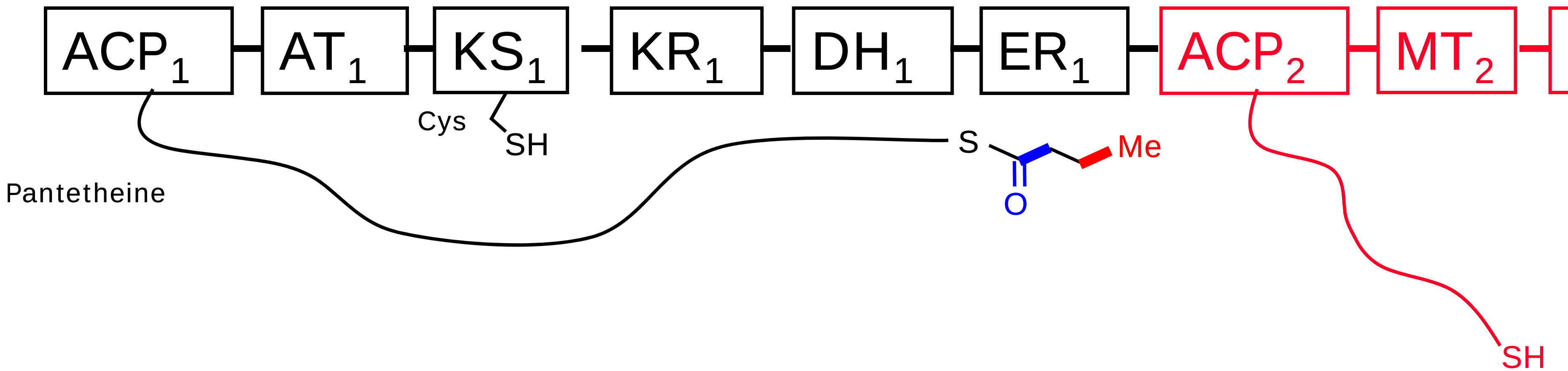


- ER_1 catalyzes reduction of alkene

FATTY ACID BIOSYNTHESIS



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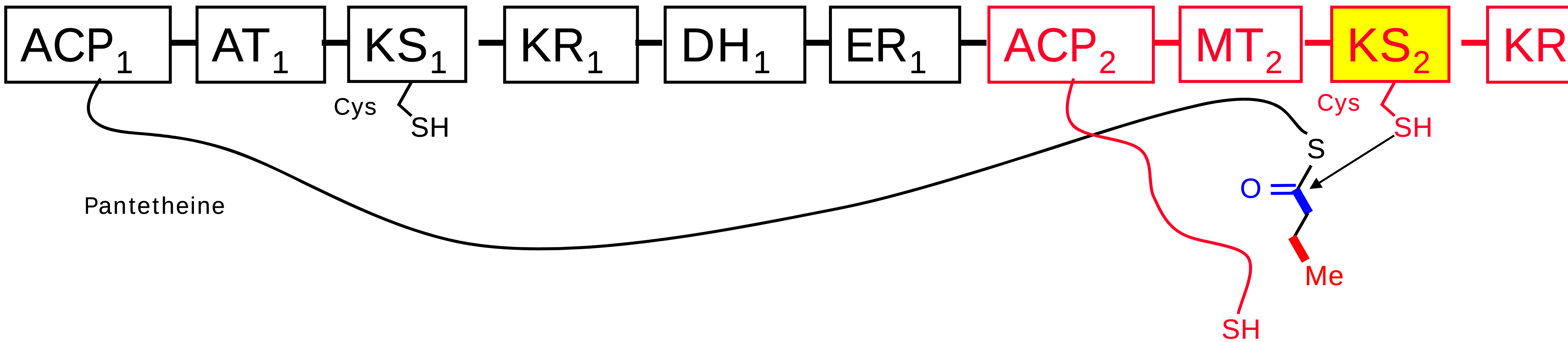
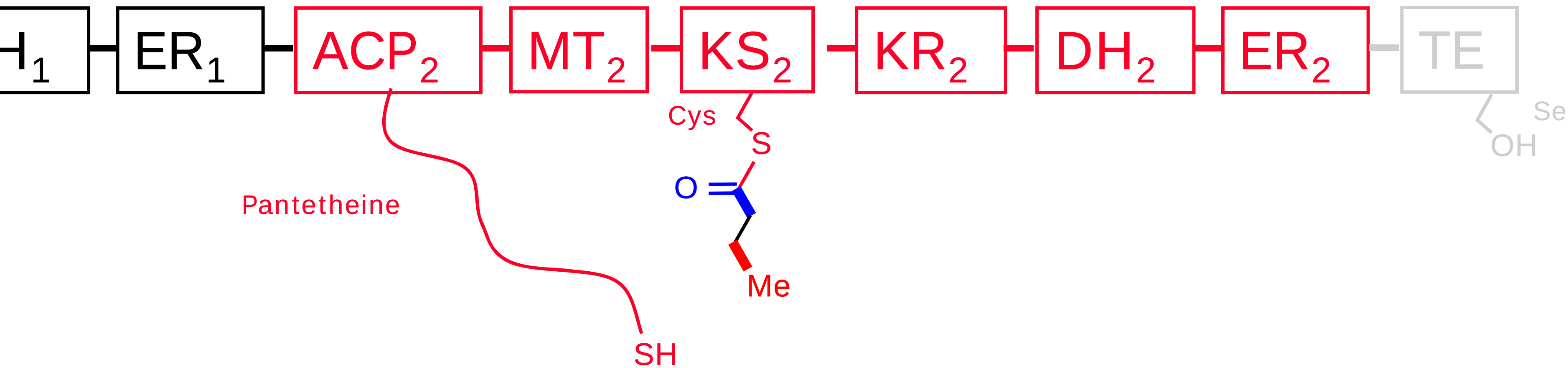
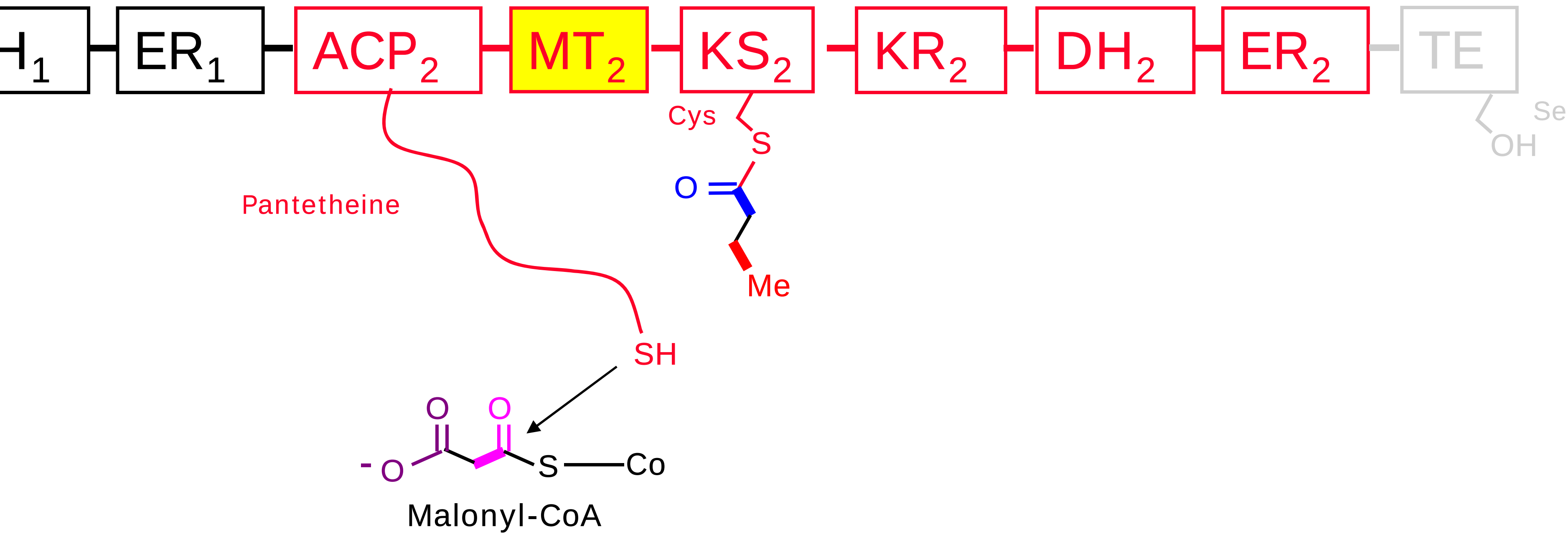


- KS_2 catalyzes translocation to module 2

FATTY ACID BIOSYNTHESIS

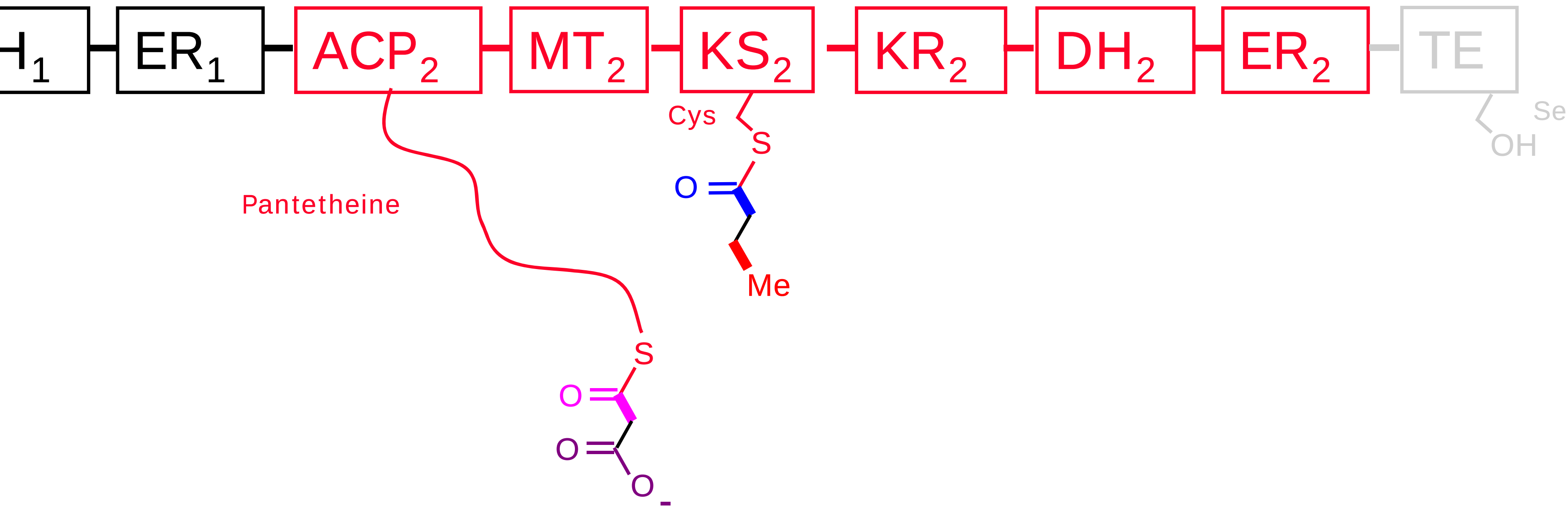


FATTY ACID BIOSYNTHESIS

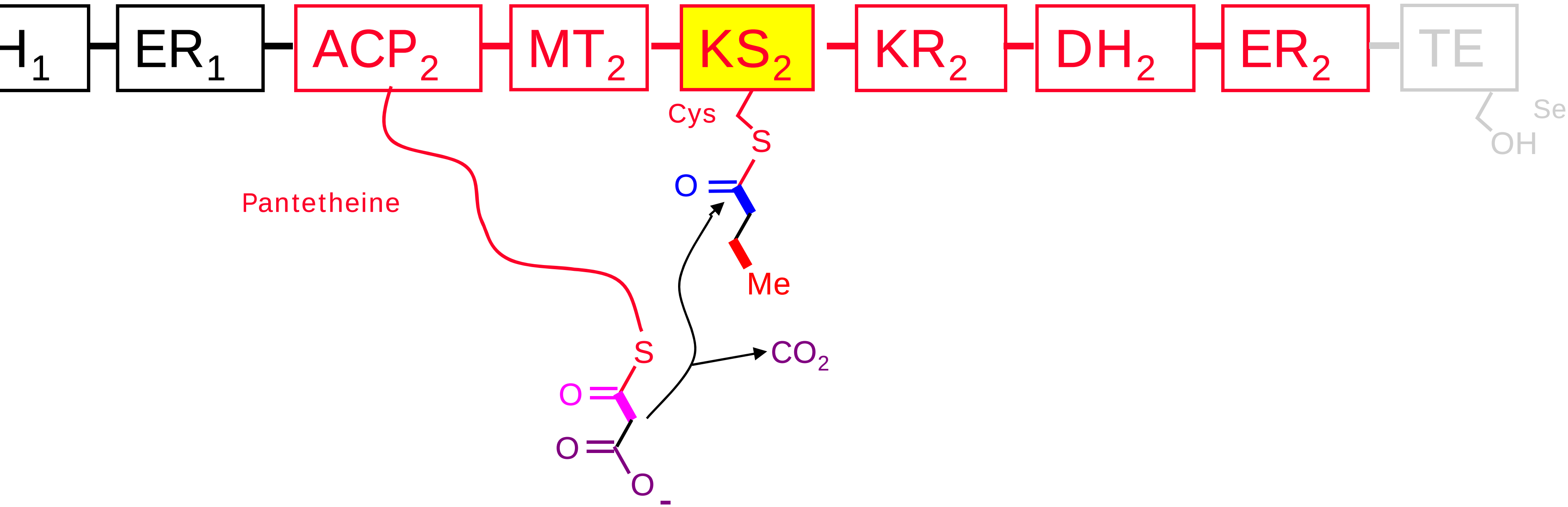


- MT_2 loads malonyl group onto ACP_2

FATTY ACID BIOSYNTHESIS

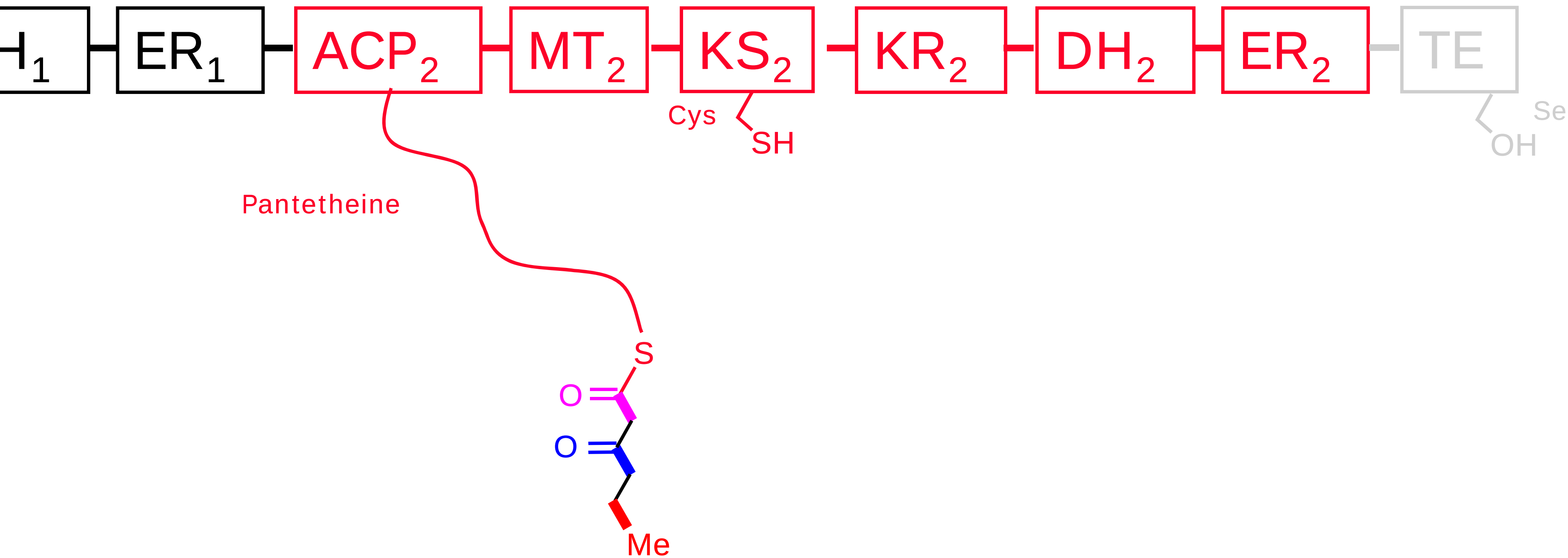


FATTY ACID BIOSYNTHESIS



- KS_2 catalyzes Claisen condensation

FATTY ACID BIOSYNTHESIS



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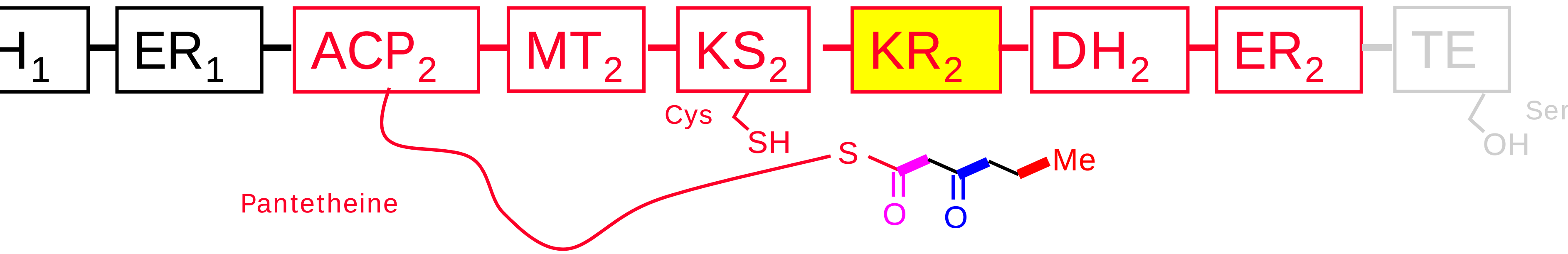
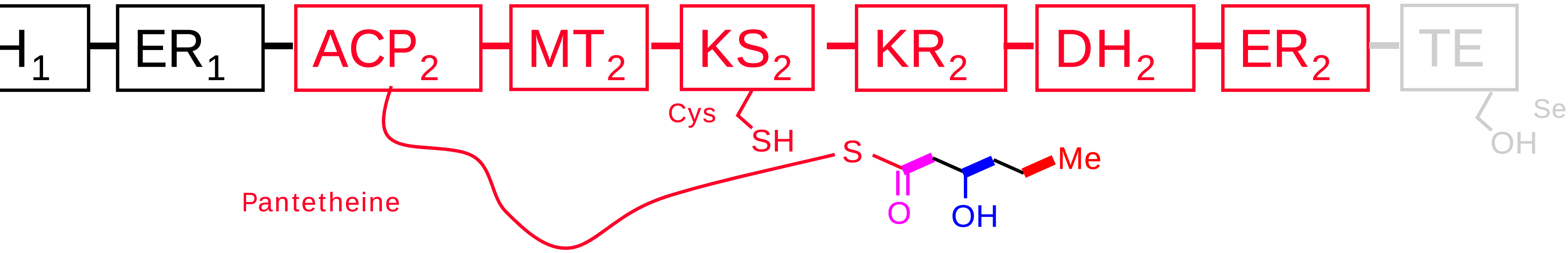
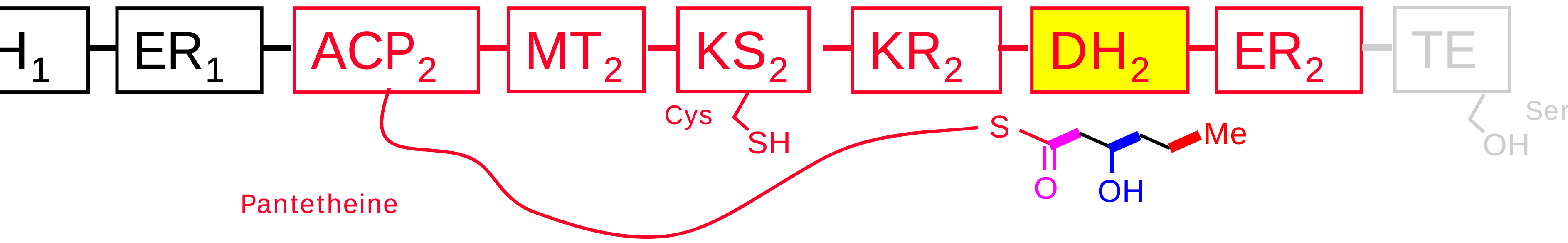


- KR_2 catalyzes reduction of ketone

FATTY ACID BIOSYNTHESIS

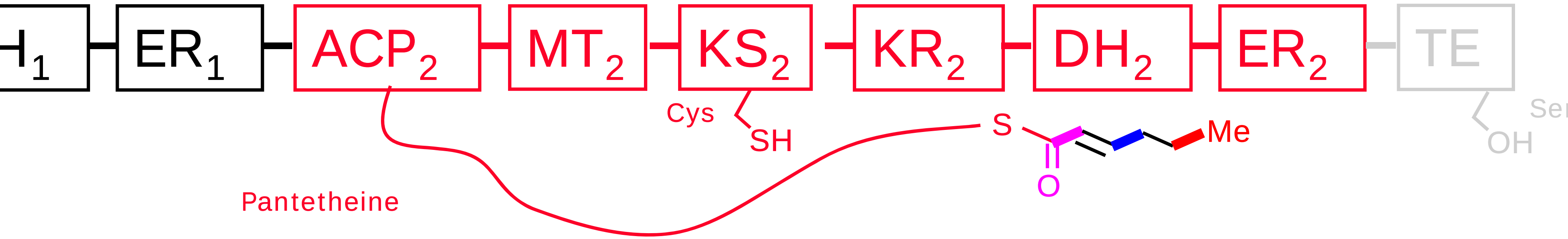


FATTY ACID BIOSYNTHESIS

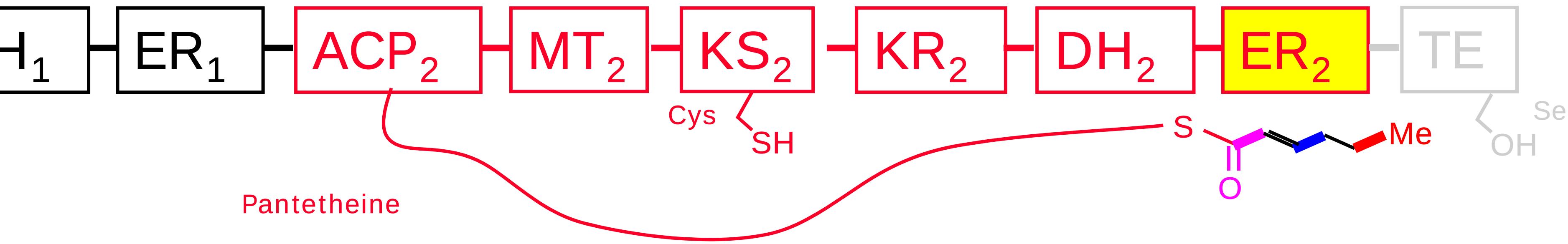


- DH_2 catalyzes dehydration of alcohol

FATTY ACID BIOSYNTHESIS

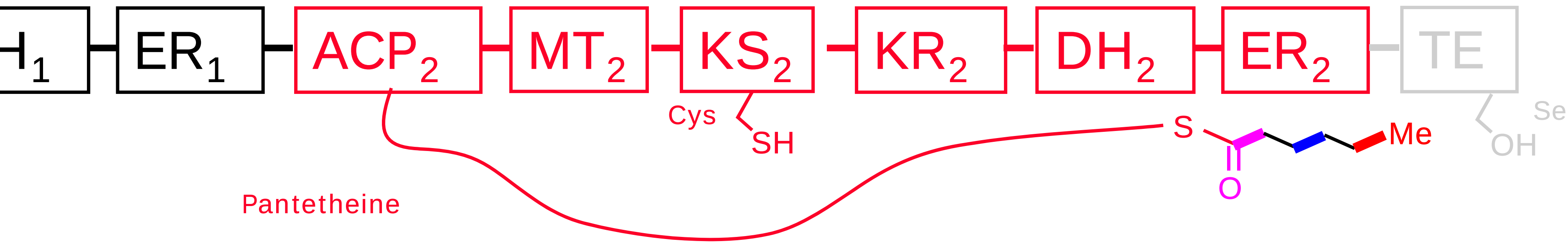


FATTY ACID BIOSYNTHESIS

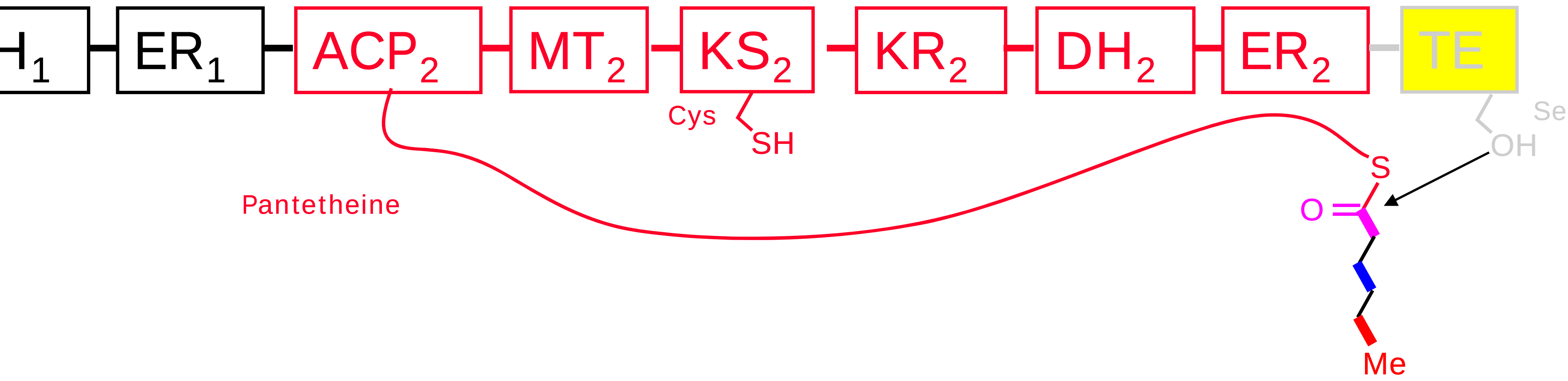


- ER_2 catalyzes reduction of alkene

FATTY ACID BIOSYNTHESIS

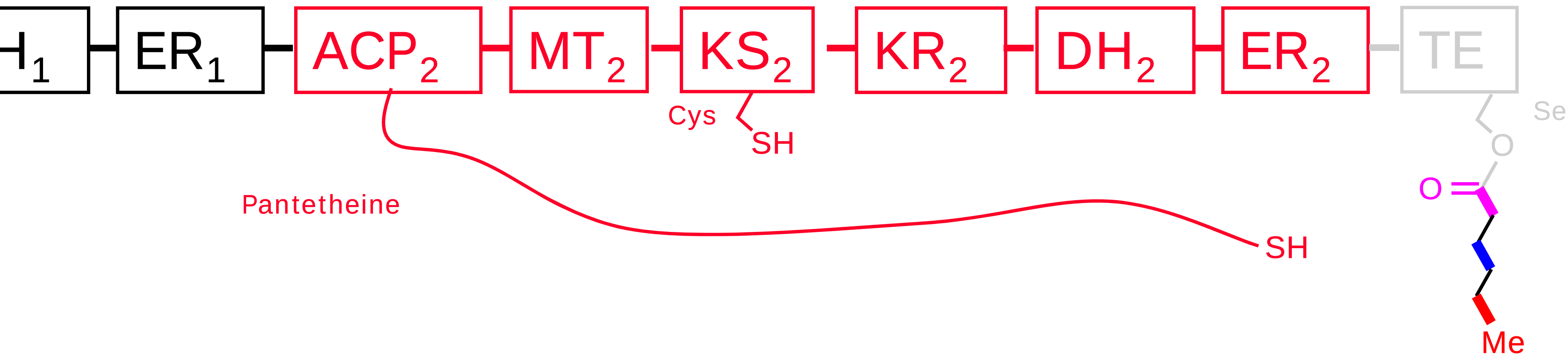


FATTY ACID BIOSYNTHESIS



- TE catalyzes transesterification

FATTY ACID BIOSYNTHESIS



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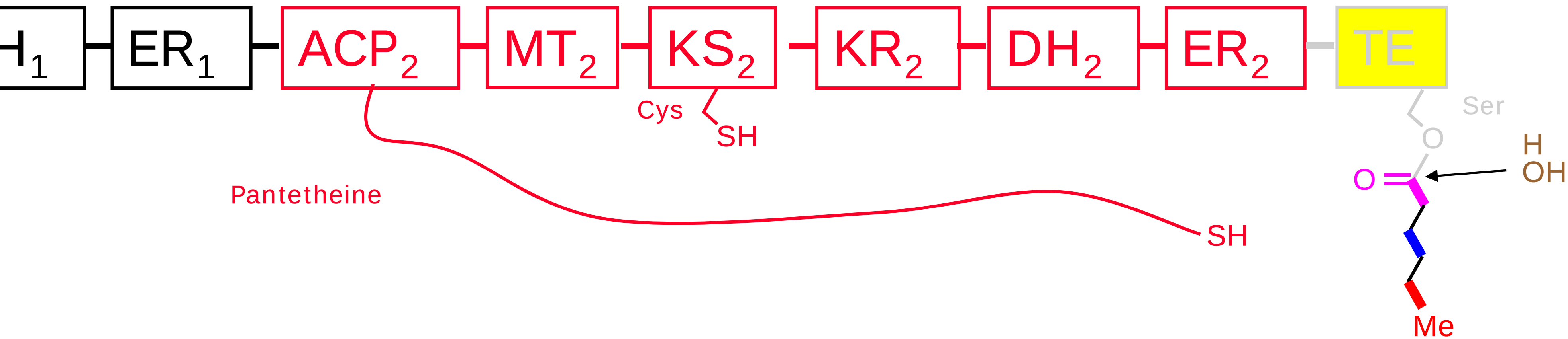
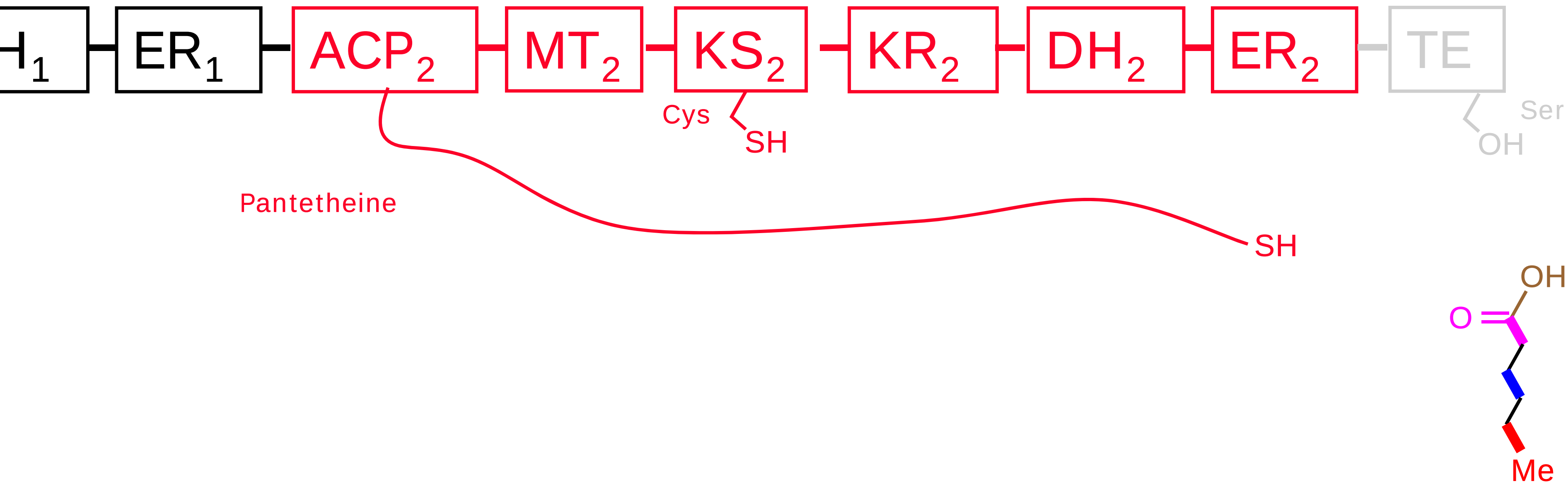


- TE catalyzes hydrolysis

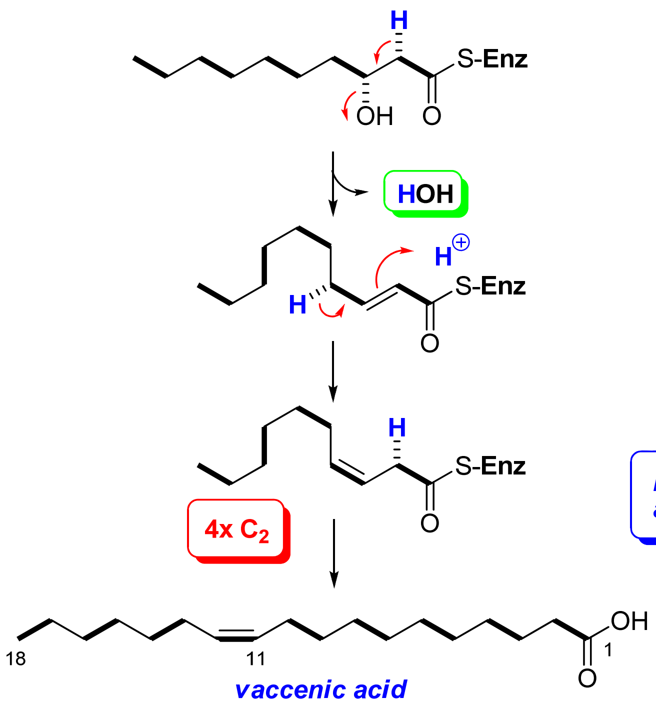
FATTY ACID BIOSYNTHESIS



Biosynthesis of Unsaturated Fatty Acids

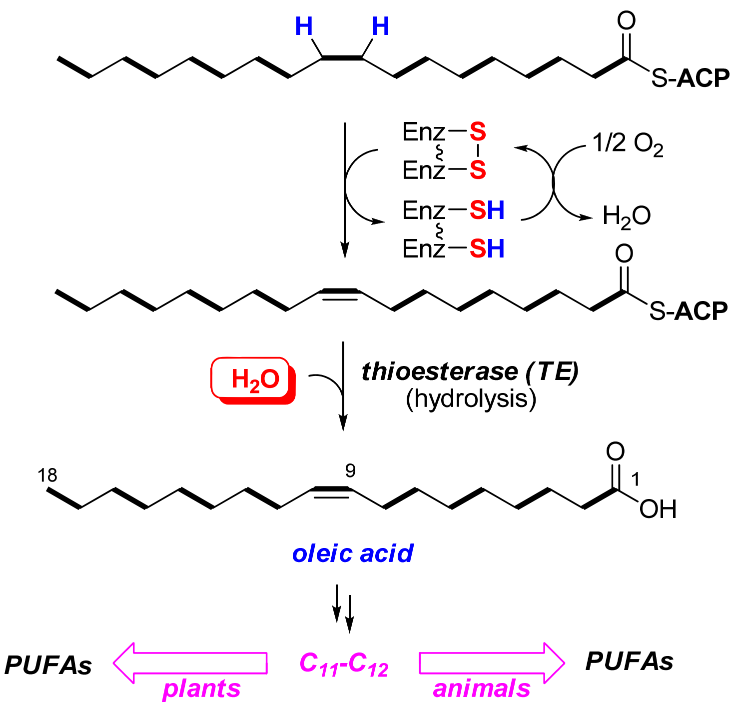
- ***two mechanisms*** are known for the introduction of double bonds into fatty acids:
  - in ***BACTERIA: anaerobic [O]*** → monounsaturated FAs (***MUFAs***)
  - in ***MAMMALS***, ***INSECTS*** & ***PLANTS: aerobic [O]*** → ***MUFAs*** & polyunsaturated FAs (***PUFAs***)

ANAEROBIC ROUTE (bacteria)
(dehydrogenation occurs during chain elongation)
mainly MUFAs but some PUFAs



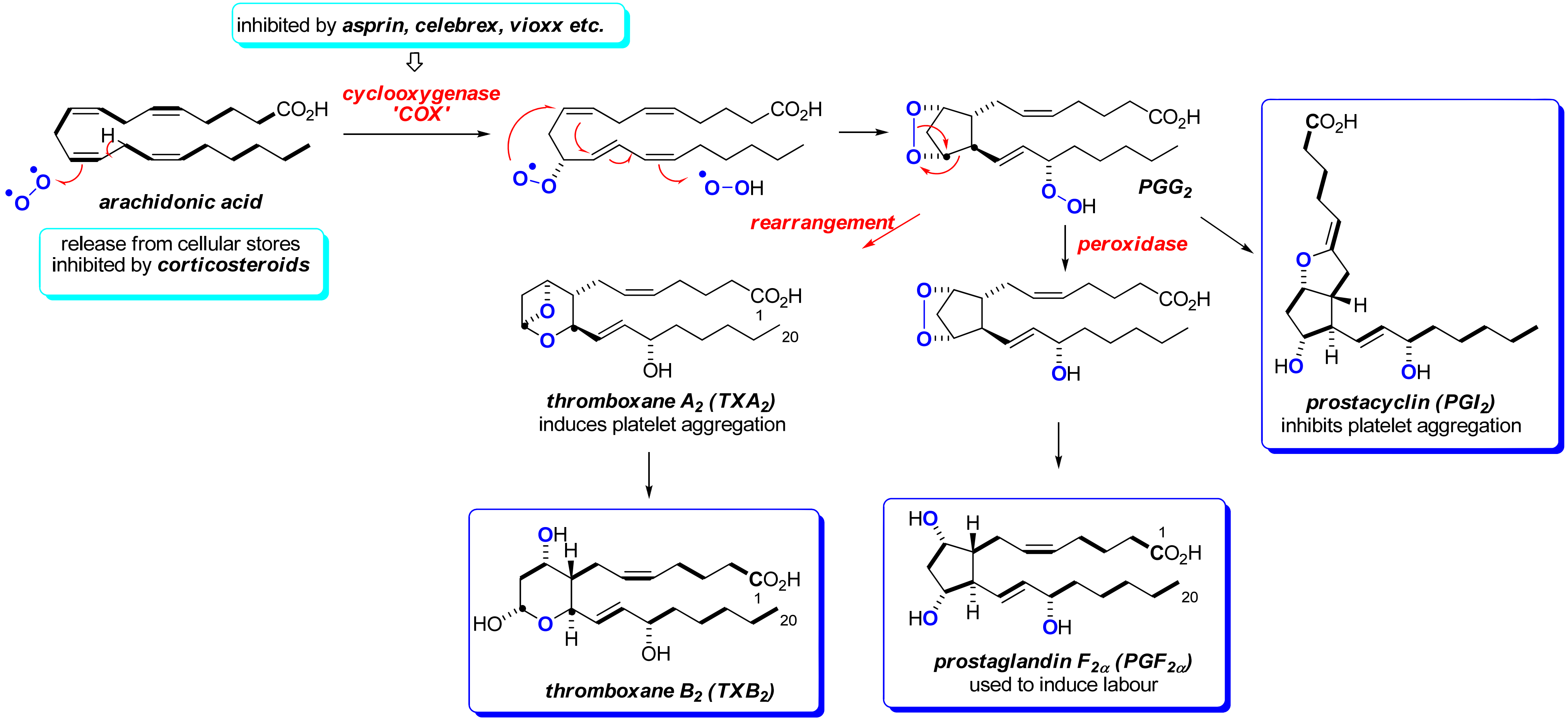
NB. in both cases cis - alkenes are produced

AEROBIC ROUTE (mammals, insects & plants)
(dehydrogenation occurs after chain elongation)
MUFAs & PUFAs



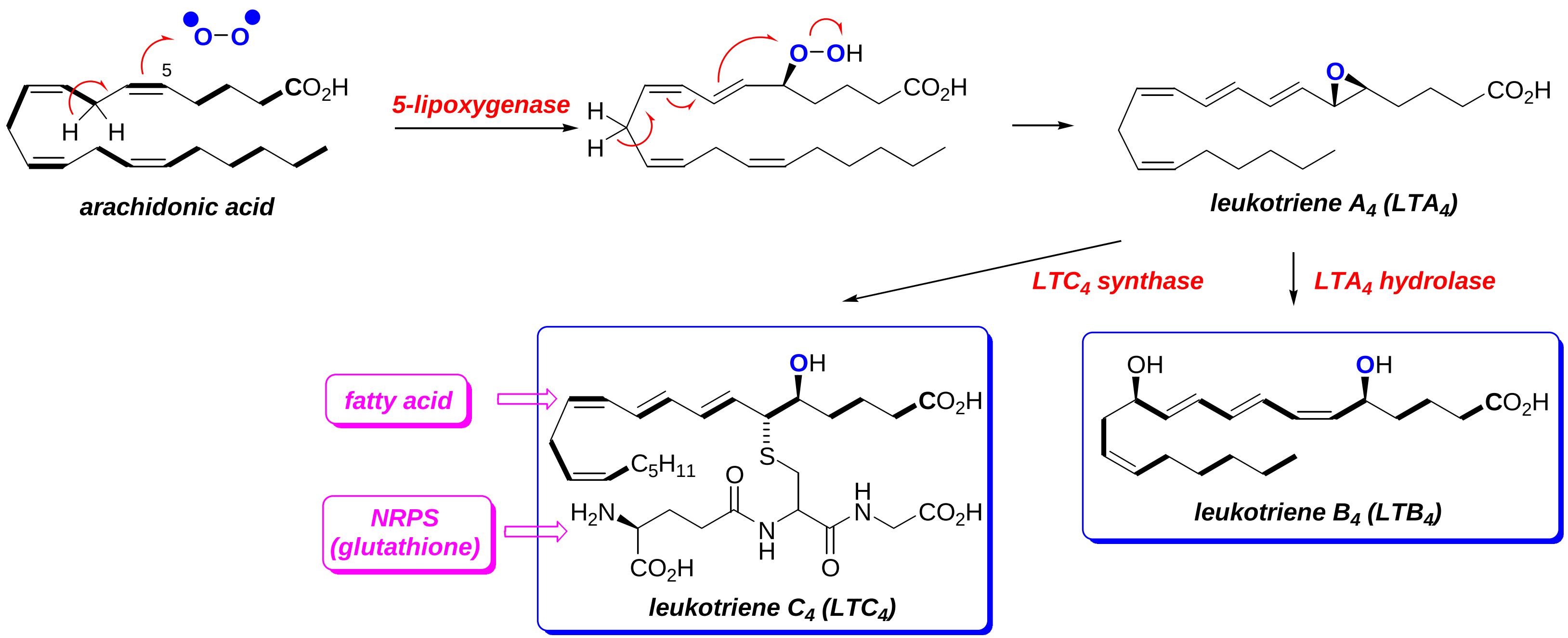
Biosynthesis of Prostaglandins & Thromboxanes

- ***prostaglandins*** & ***thromboxanes*** are derived from further oxidative processing of arachiodonic acid
- both are important ***hormones*** which control *e.g.* smooth ***muscle contractility*** (blood pressure), ***gastric secretion***, ***platelet aggregation*** & ***inflammation*** (<nM activity)
  - various pharmaceuticals including ***corticosteroids*** & ***asprin*** inhibit biosynthethetic steps in these pathways



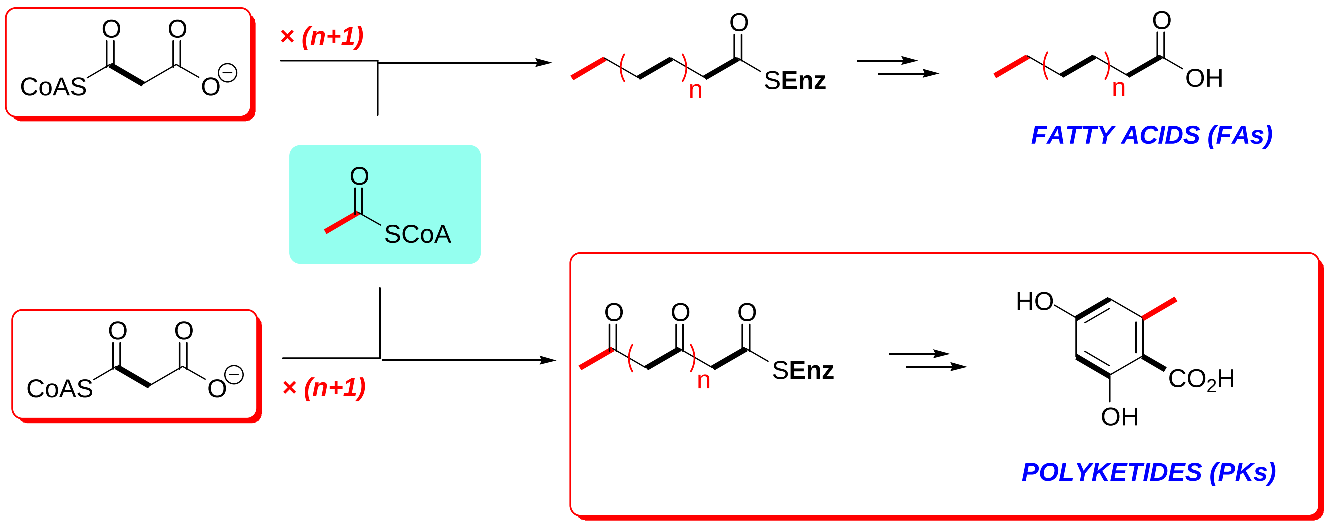
Biosynthesis of Leukotrienes

- ***leukotrienes*** are the other main class of 2° metabolites derived from ***arachidonic acid***
  - they are potent (<nM) ***inflammatory substances*** released during allergic reactions



The Polyketide Pathway

- ***Polyketides*** are also sometimes known as ***acetogenins***
- ***acetyl CoA*** is also the starting point for the biosynthesis of ***polyketide*** secondary metabolites
- these metabolites are topologically very different to the fatty acid metabolites but are in fact synthesised in a very similar fashion. The significant difference is that during the iterative cycle of chain extension ***the β-keto group is generally not completely reduced out***. This gives rise to huge structural diversity based around a 1,3-oxygenation pattern & cyclisation to give aromatic compounds

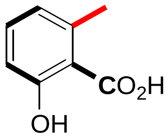


the polyketide pathway

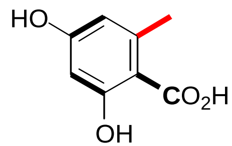
- *NB.* unlike fatty acids. polyketides are NOT biosynthesised by humans – only microorganisms (bacteria) & fungi

Polyketides

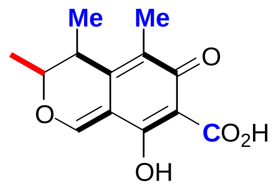
- the structural variety of ***polyketide secondary metabolites*** is very wide:
  - *NB.* starter units marked in red; extender units in bold black; post oligomerisation appended groups in blue



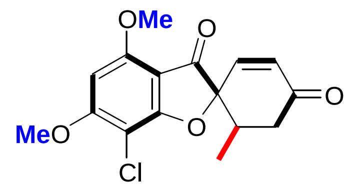
6-methylsalicylic acid
(antibiotic)



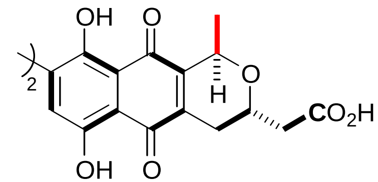
orsellinic acid



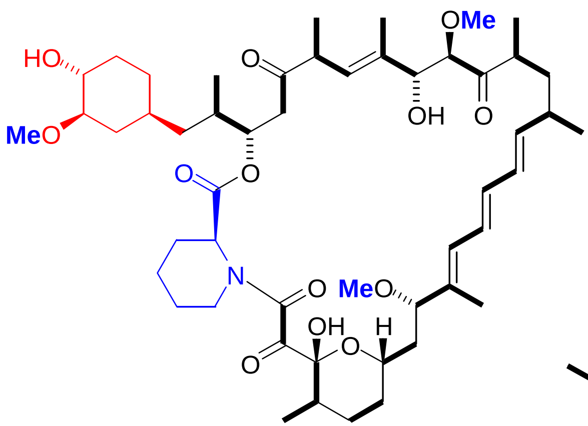
citrinin
(kidney toxin
'yellow rice disease')



Griseofulvin
(treatment for ring
worm infections)

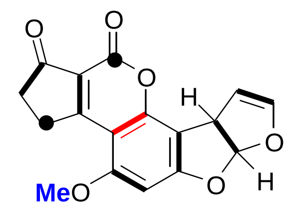


actinorhodin
(antibiotic)

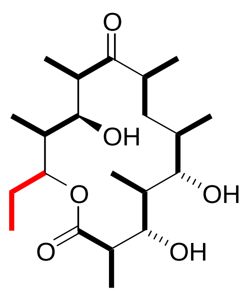


rapamycin
(immunosuppressant)
NB. a mixed polypropionate/acetate

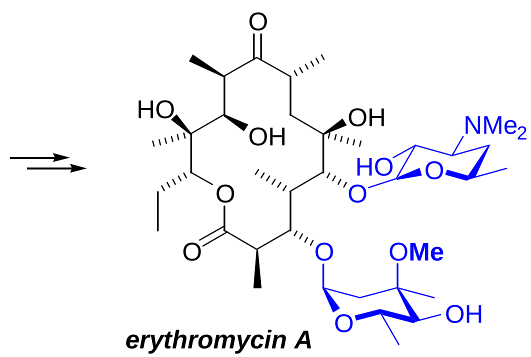
POLYKETIDES



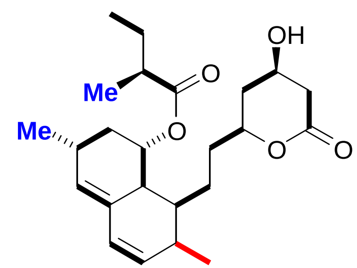
aflatoxin B1
(mycotoxic carcingen)



6-deoxyerythronolide B
NB. a polypropionate



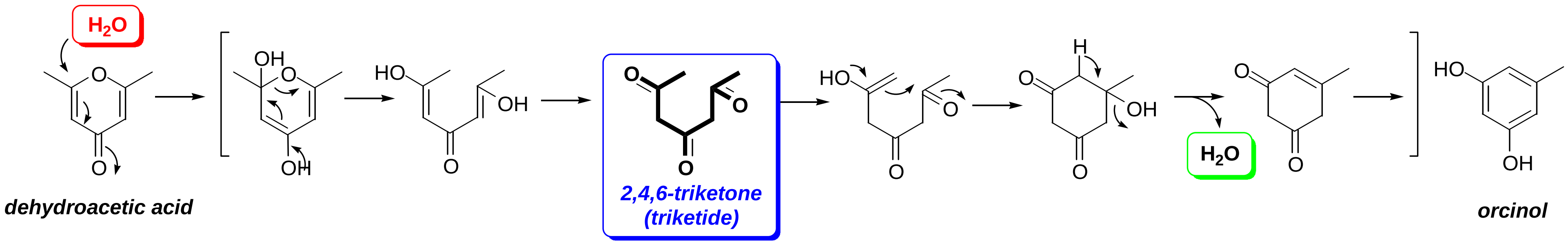
erythromycin A
(antibiotic)



mevinolin
(=lovastatin®)
(anti-cholesterol)

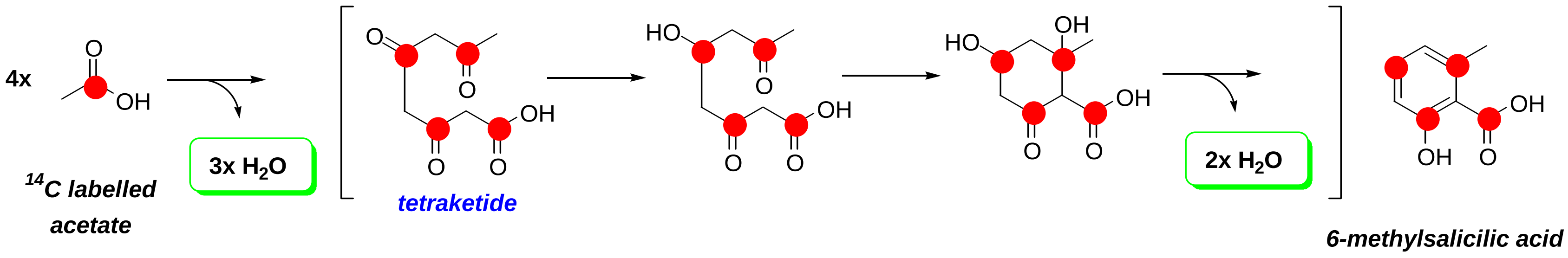
Historical Perspective – *'The Acetate Hypothesis'*

- ***1907: James Collie*** (University of London) effects conversion of ***dehydroacetic acid*** to ***orcinol*** by boiling with $Ba(OH)_2$ (while trying to deduce the structure of the former):



  – Collie perceptively postulated the ***triketone*** as an intermediate ***&*** suggetsed that this might also be an ***intermediate*** in the ***biosynthesis*** of ***orcinol*** (the 'polyketide hypothesis')

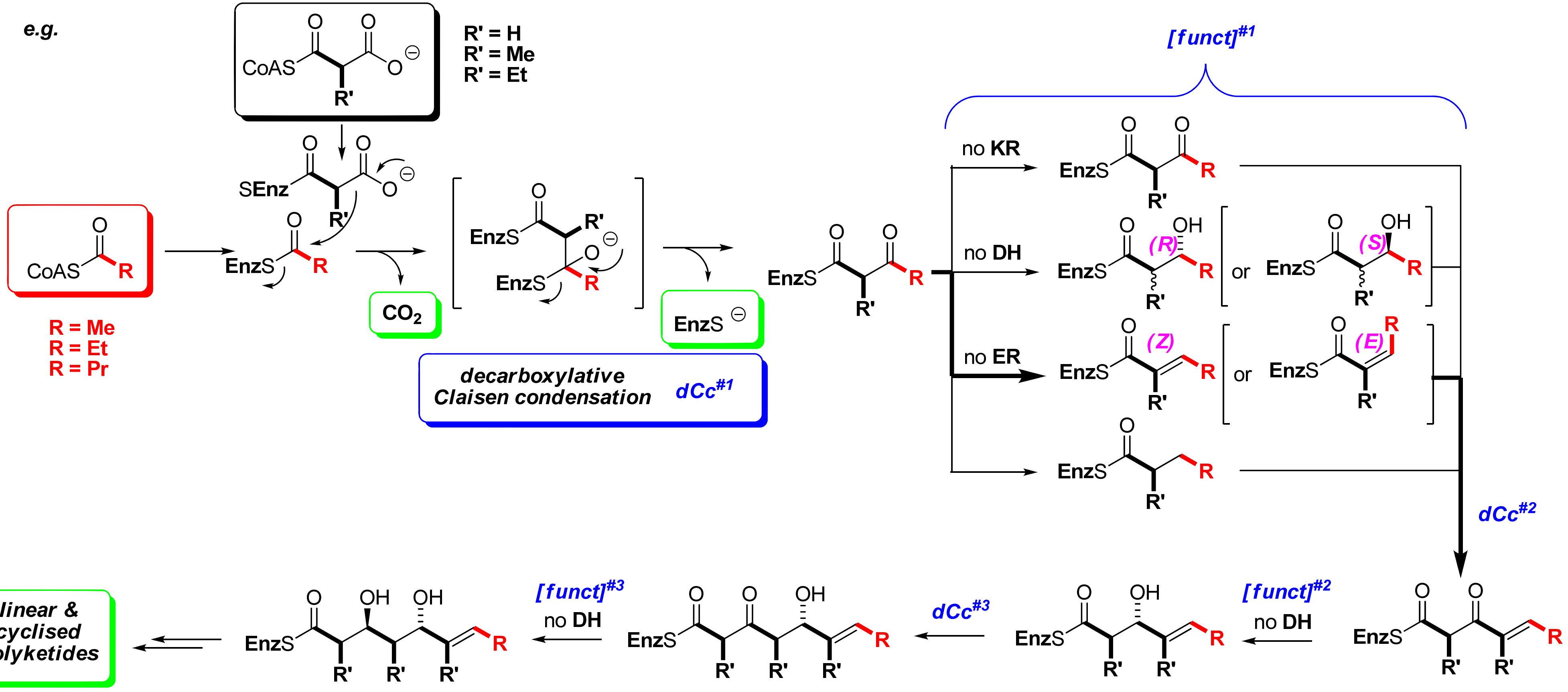
- ***1955: Arthur Birch*** used ^{14}C labelled acetate to show that 6-methylsalicylic acid (ex. *Penicillium patulum*) was biosynthesised by head-to-tail oligomerisation of ***4 × acetate units*** and proposed the following biogenesis – proceeding *via* a ***tetraketide intermediate*** (*cf.* Collie!):



Biosynthesis of Polyketides – *Oligomerisation Steps*

- ***polyketides*** are biosynthesised by a process very similar to that for ***fatty acids***
  - the key ***differences*** are:
    - ***greater variety*** of ***starter units, extender units*** & ***termination processes***
    - ***absent or incomplete reduction of the iteratively introduced β-carbonyl groups: ie. each cycle may differ in terms of KR, DH & ER modules & stereochemistry***

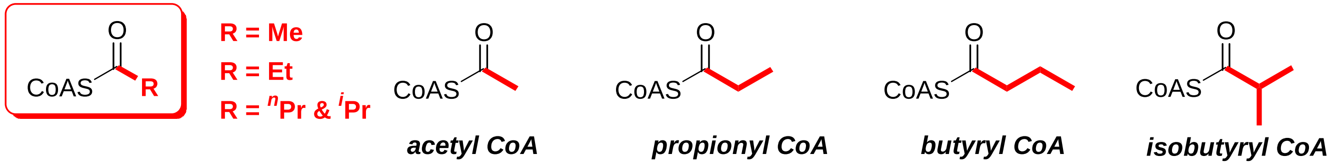
e.g.



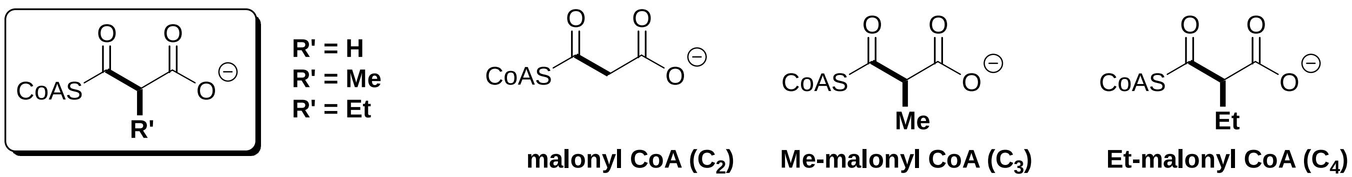
- this leads to ***enormous diversity...***

Polyketide Diversity

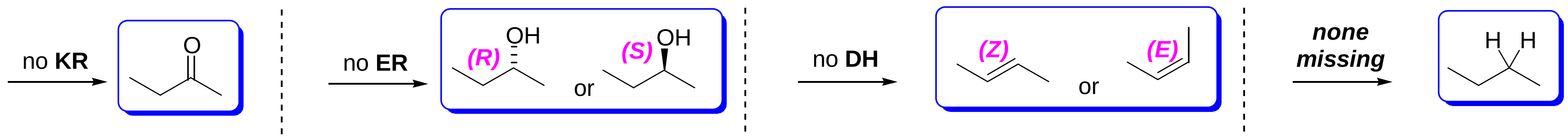
- ***starter units:***



- ***extender units:***



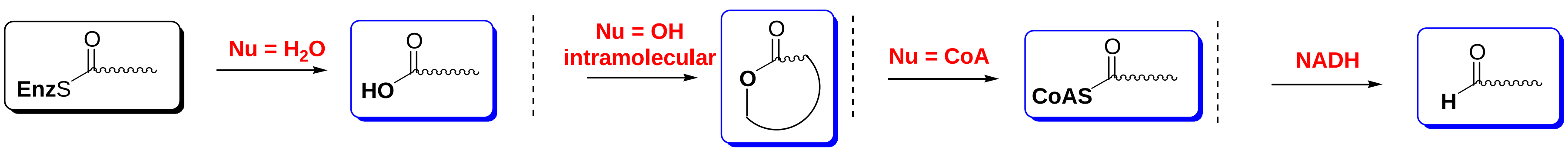
- ***non-functional or missing KR, DH, ER:***



- ***stereochemistry:***

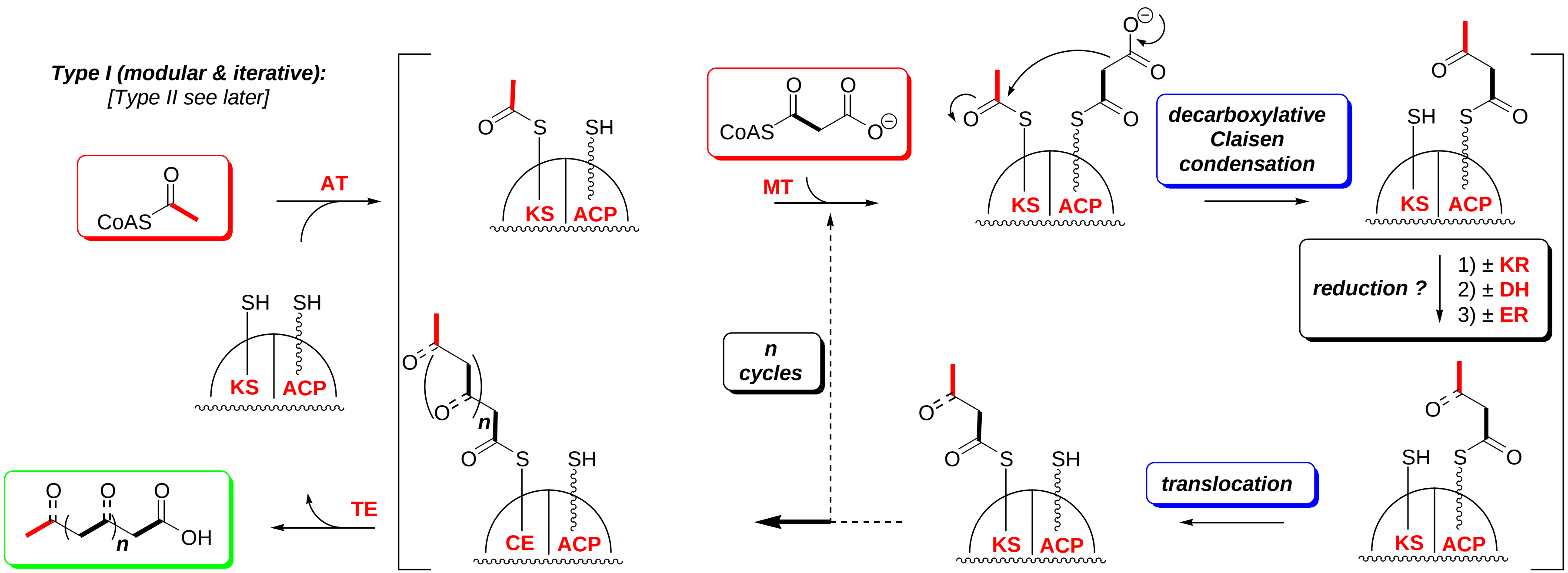
1) side chain stereochemistry (determined by **KS_n**)
2) OH stereochemistry (determined by **KR_{n+1}**)
3) alkene stereochemistry (determined by **DH_{n+1}**)

- ***termination step:***
  - depends on nucleophile that releases product at ***TE*** stage:



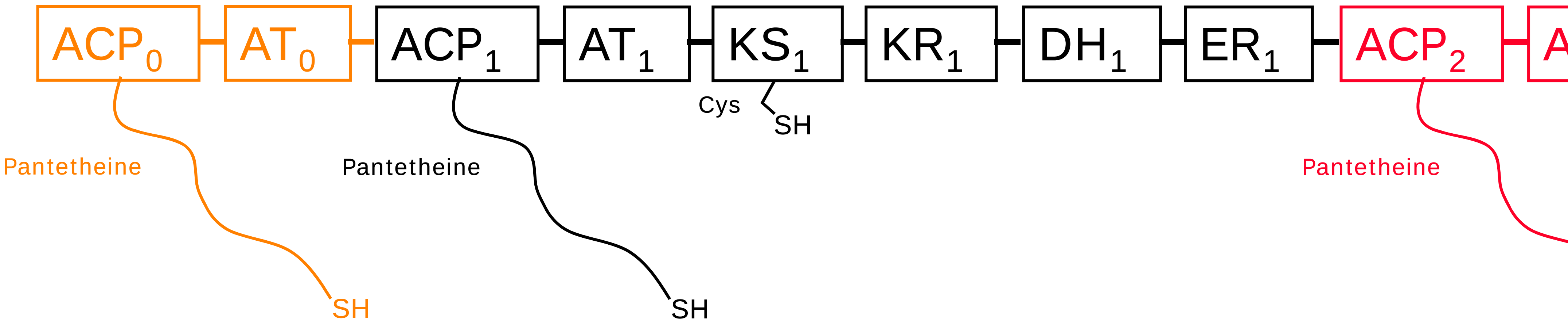
Biosynthesis of Polyketides – *Overview of PKS*

- the *in vivo* process of polyketide synthesis involves ***PolyKetide Synthases (PKSs):***
  - ***PKSs*** (except Type II, see later) comprise the same ***8 components*** as ***FASs***. *i.e.* (ACP & 7× catalytic activities): ***ACP***, ***KS***, ***AT***, ***MT***, [***KR***, ***DH***, ***ER*** & ***TE]***
  - ***Type I PKSs: single (or small set of) multifunctional protein complex(es)***
    - ***modular (microbial)*** - each 'step' has a dedicated catalytic site (→ ***macrolides***)
    - ***iterative (fungal)*** – single set of catalytic sites, each of which *may* operate in each iteration (*cf.* FASs) (→ ***aromatics/polyphenols*** - generally)
  - ***Type II PKSs: single set of discrete, dissociable single-function proteins***
    - ***iterative (microbial)*** - each catalytic module *may* operate in each iteration (*cf.* FASs) (→ ***aromatics/polyphenols***)



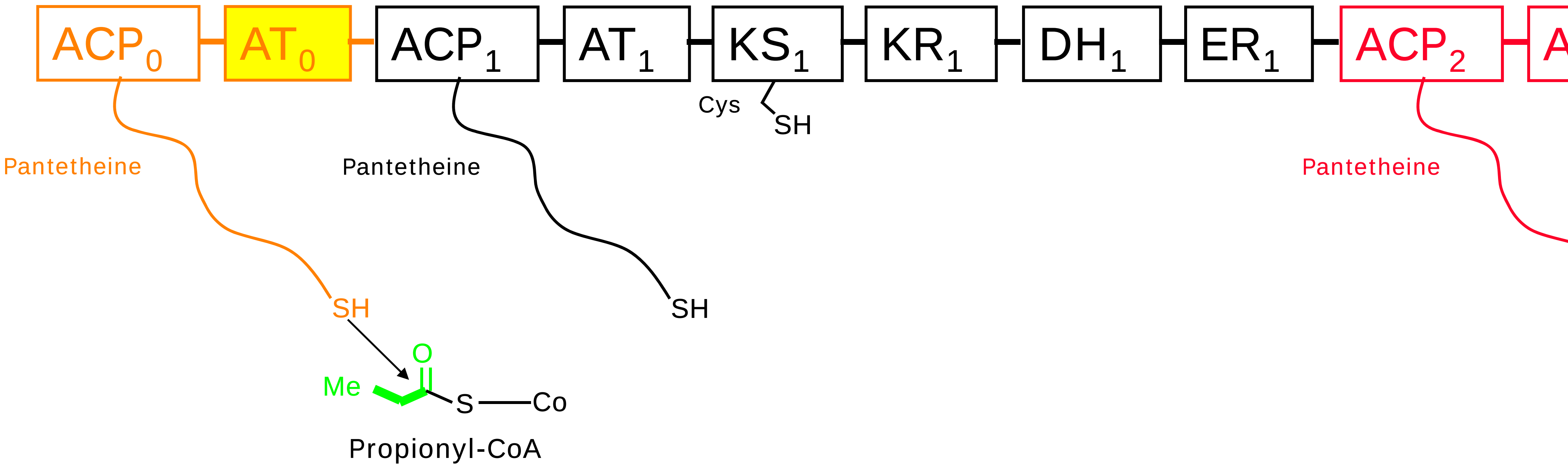
KS = keto synthase; **AT** = acetyl transferase; **MT** = malonyl transferase;
KR = keto reductase; **DH** = dehydratase; **ER** = enoyl reductase; **TE** = thioesterase; **ACP** = acyl carrier protein

POLYKETIDE BIOSYNTHESIS [Type I – (modular)]



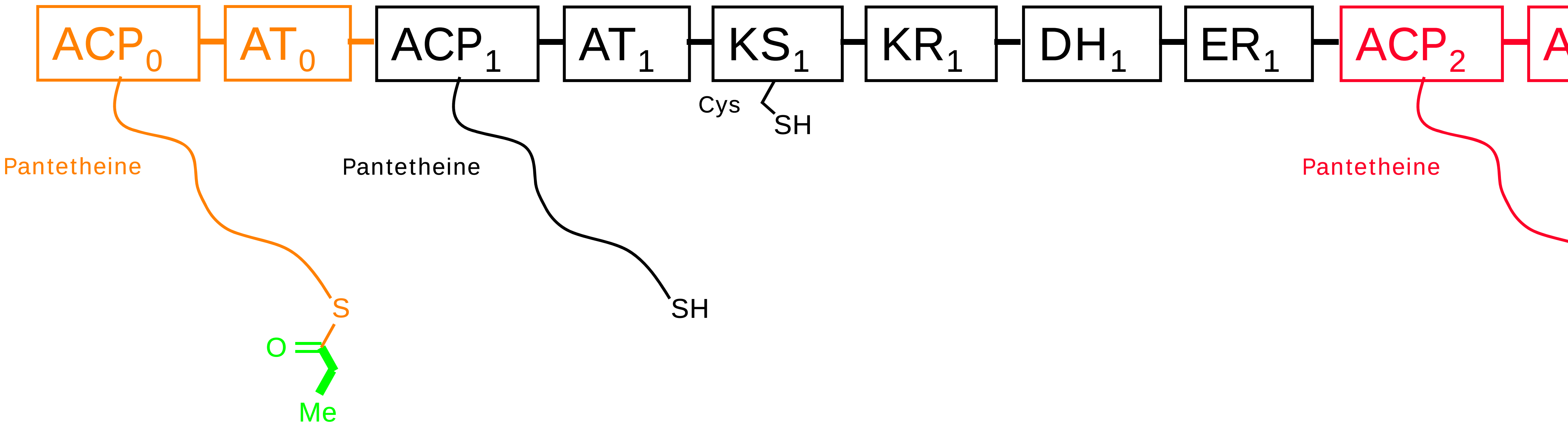
NB. the following sequence of slides has also been adapted from: http://www.courses.fas.harvard.edu/%7echem27/

POLYKETIDE BIOSYNTHESIS

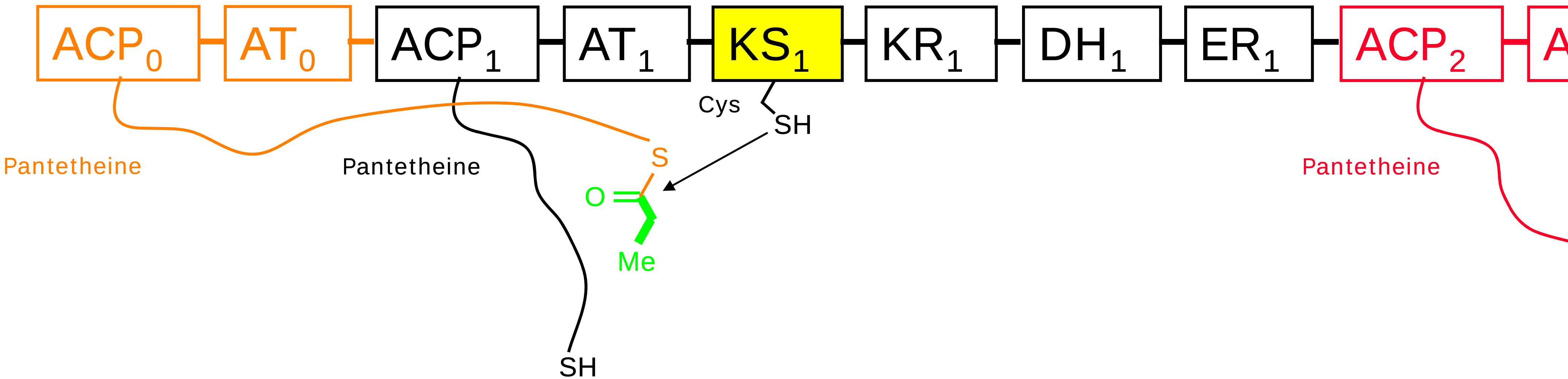


- AT_0 loads starting group (propionyl) onto ACP_0

POLYKETIDE BIOSYNTHESIS

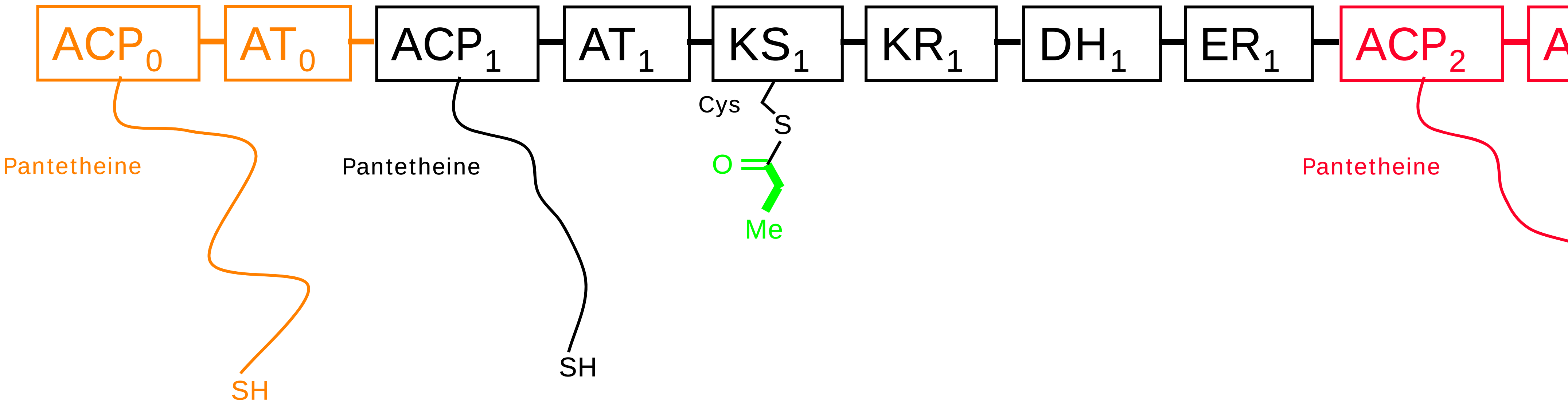


POLYKETIDE BIOSYNTHESIS

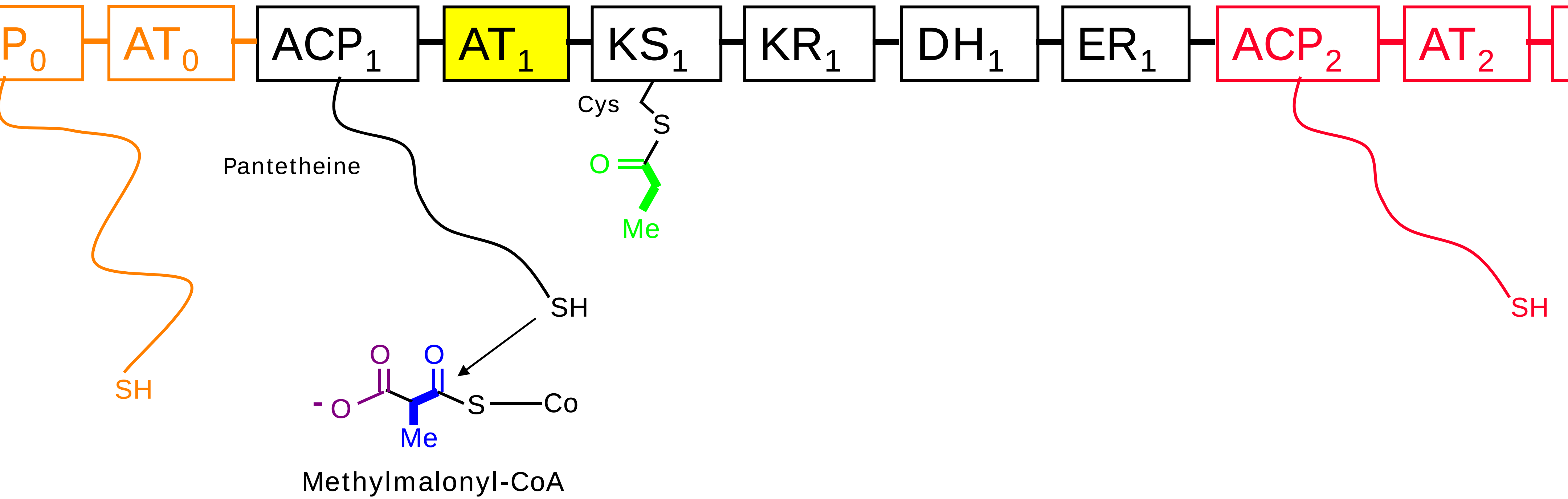


- KS_1 catalyzes translocation to module 1

POLYKETIDE BIOSYNTHESIS

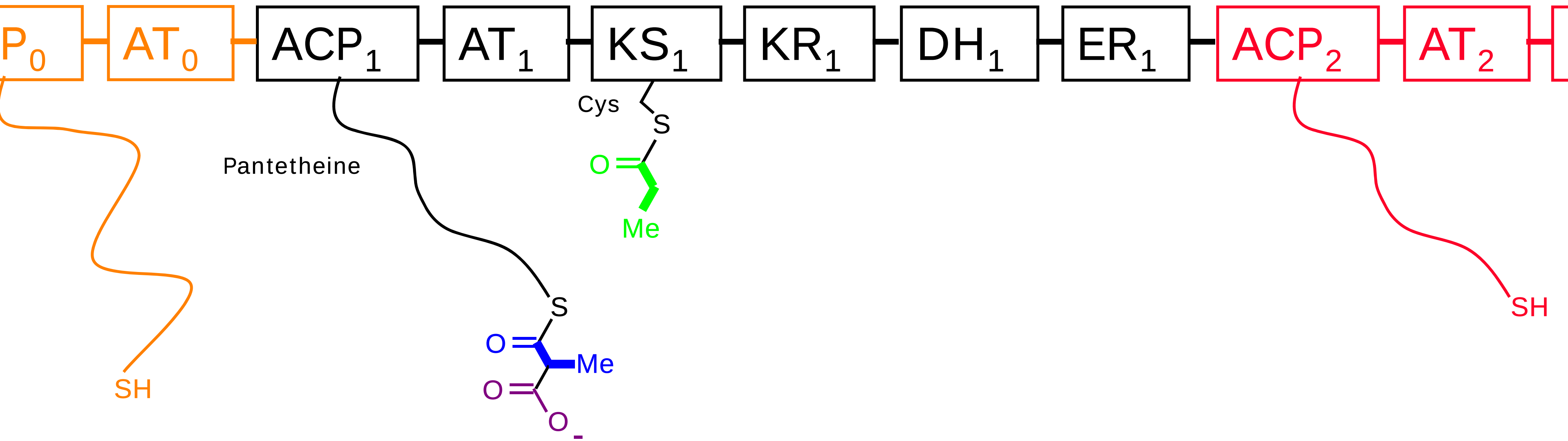


POLYKETIDE BIOSYNTHESIS

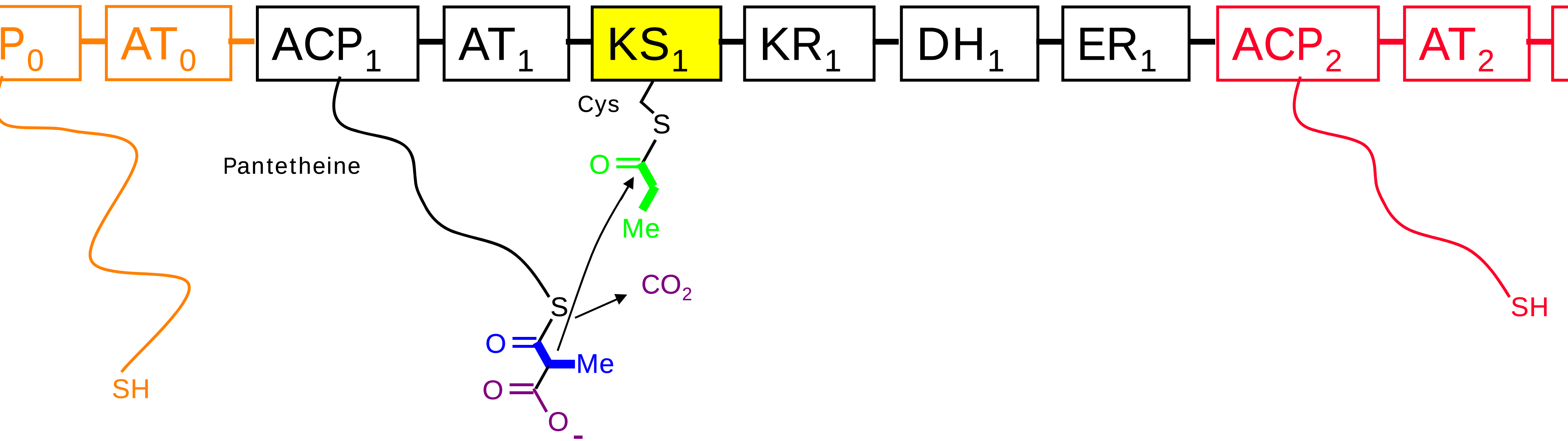


- AT_1 loads methylmalonyl group onto ACP_1

POLYKETIDE BIOSYNTHESIS

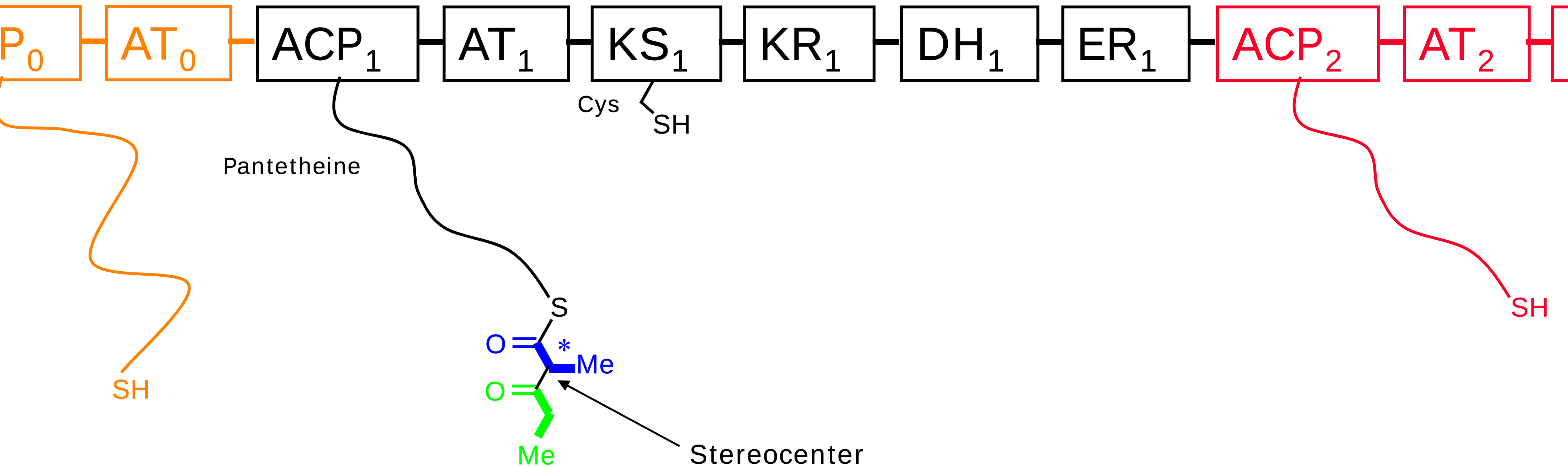


POLYKETIDE BIOSYNTHESIS

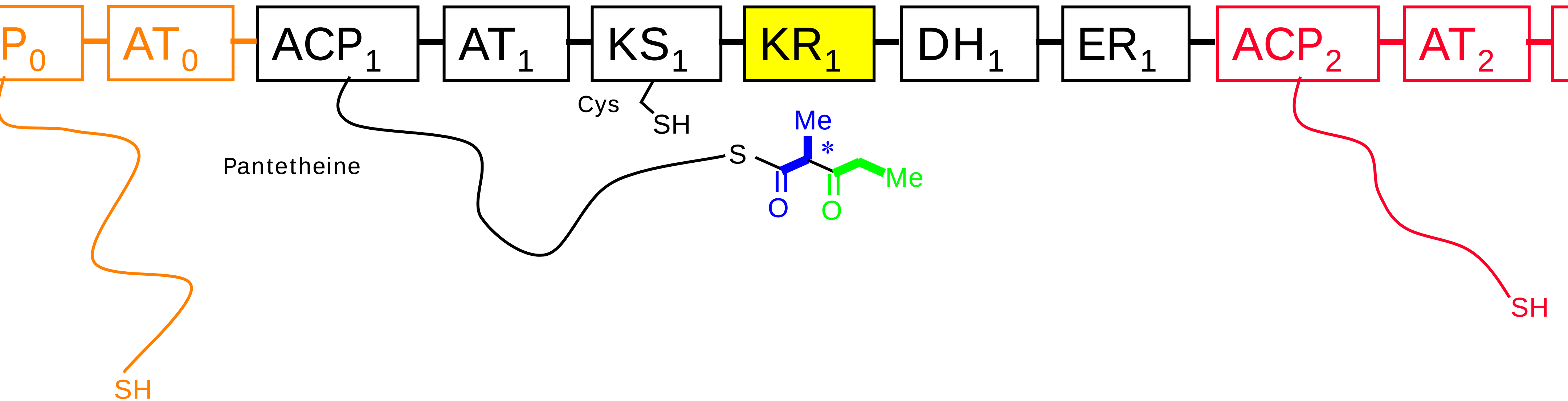


- KS_1 catalyzes Claisen condensation

POLYKETIDE BIOSYNTHESIS

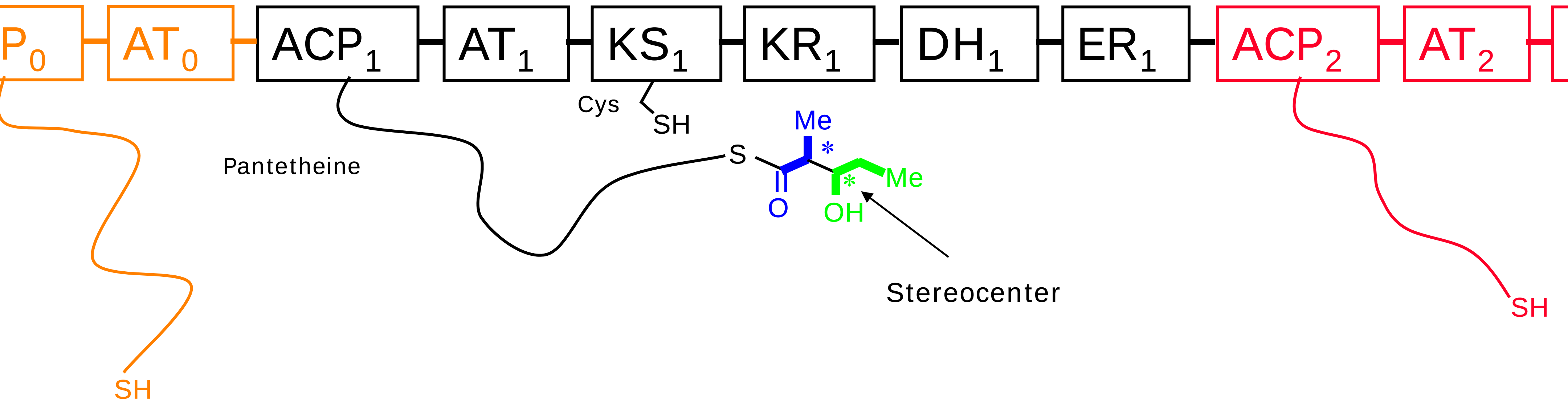


POLYKETIDE BIOSYNTHESIS

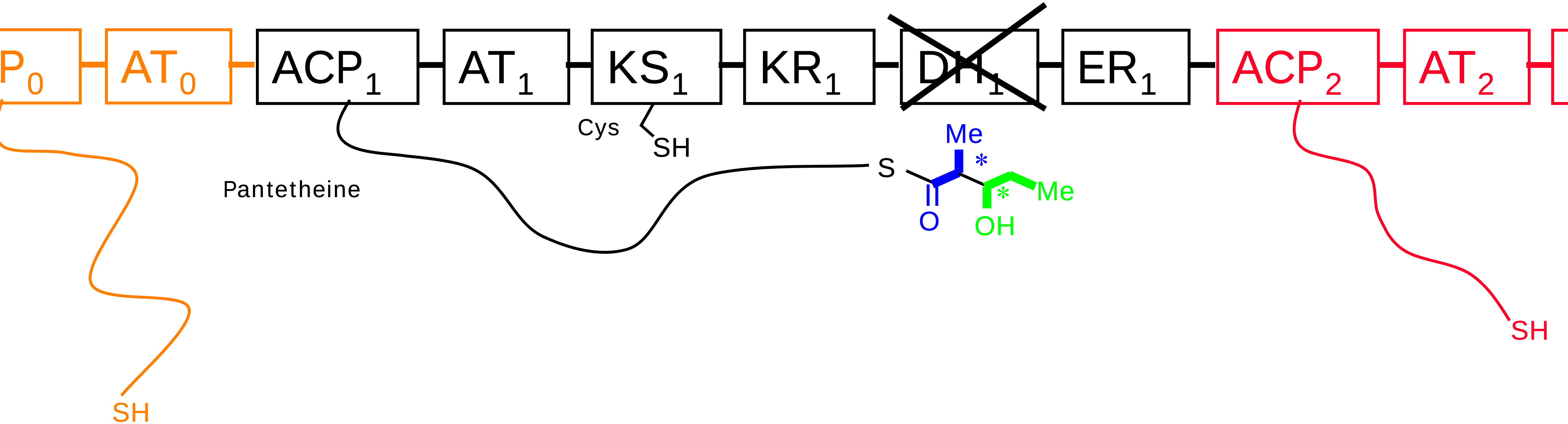


- KR_1 catalyzes reduction of ketone

POLYKETIDE BIOSYNTHESIS

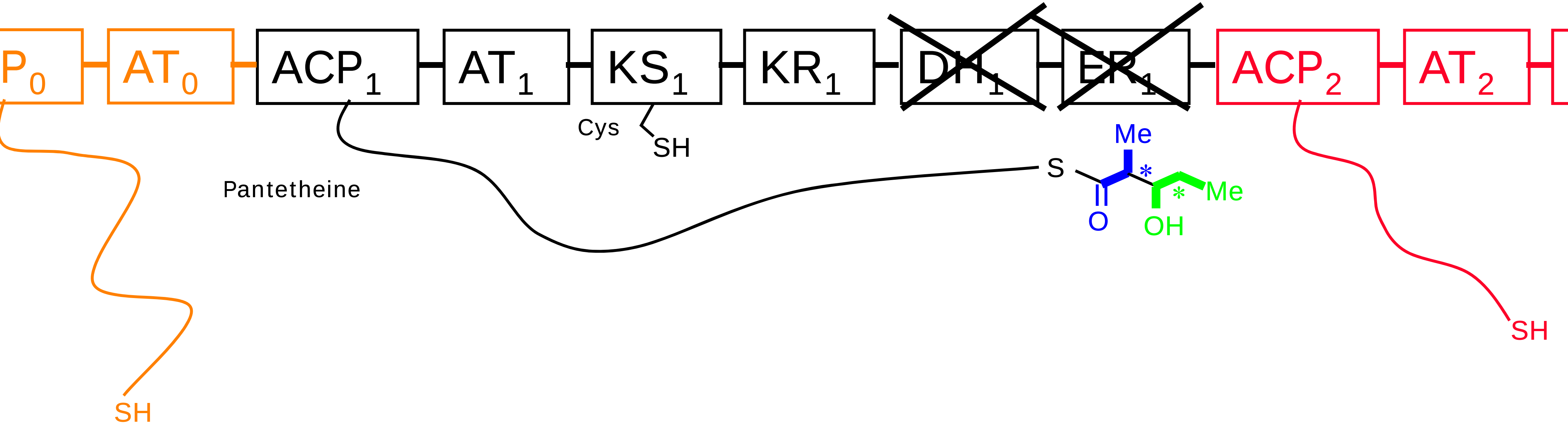


POLYKETIDE BIOSYNTHESIS



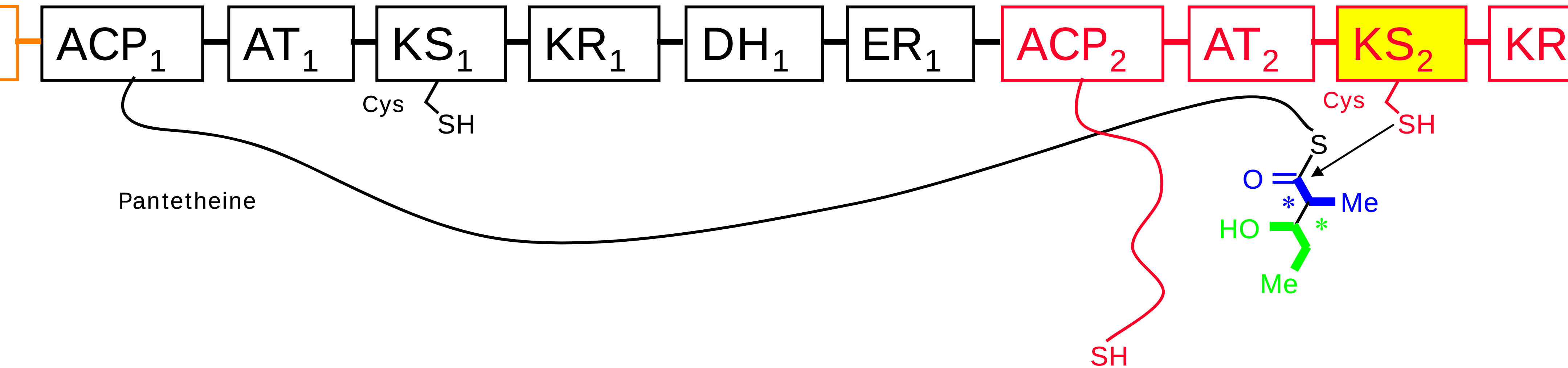
- no DH_1 activity

POLYKETIDE BIOSYNTHESIS



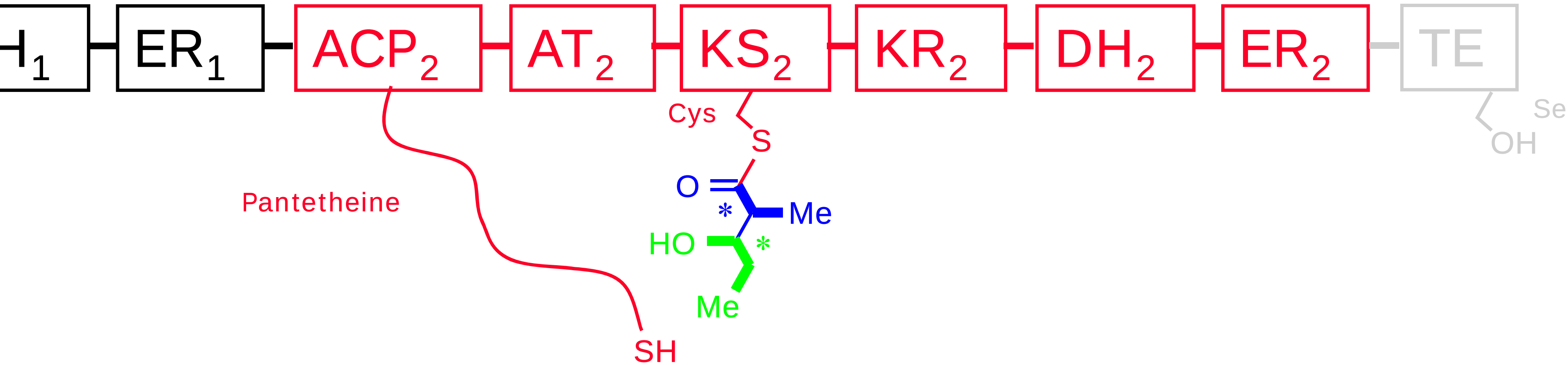
- no ER_1 activity

POLYKETIDE BIOSYNTHESIS



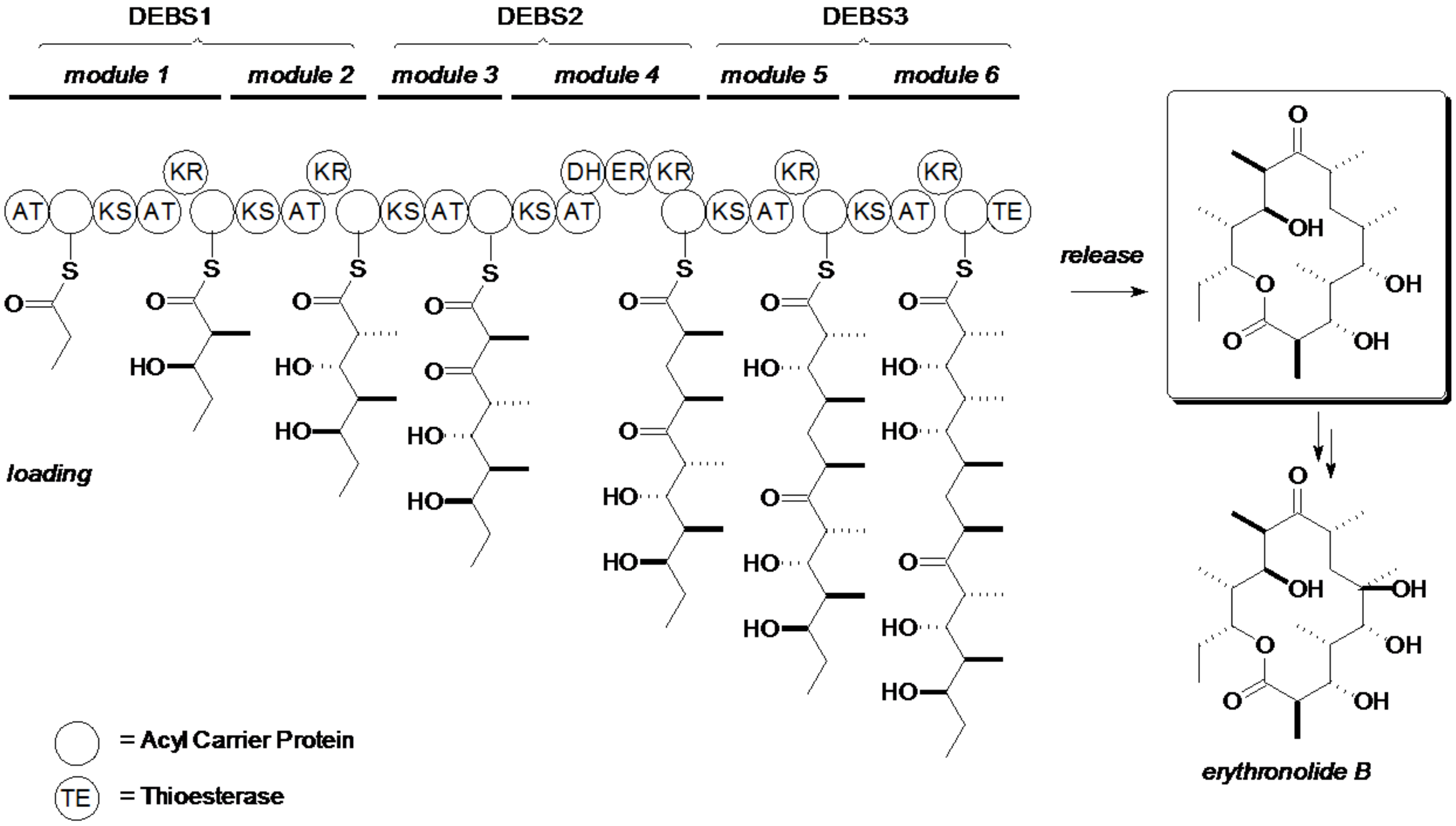
- KS_2 catalyzes translocation to module 2

POLYKETIDE BIOSYNTHESIS



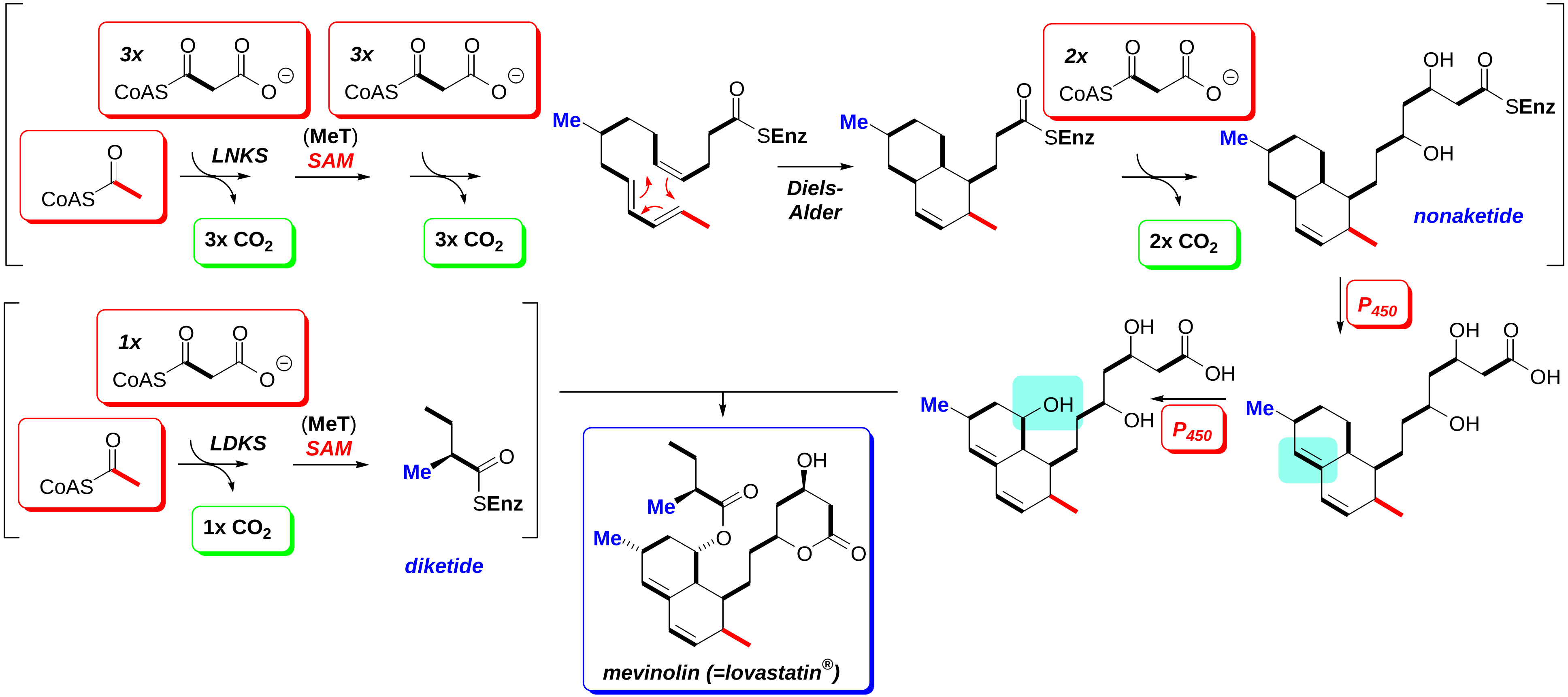
Biosynthesis of Erythromycin – *Type I(modular) PKS*

- ***6-deoxyerthronolide*** is a precursor to ***erythromycin A*** – ***bacterial*** antibiotic (*Streptomyces erythreus*):
  - ***propionate*** based ***heptaketide***; 3 multifunctional polypeptides (DEBS1, DEBS2 & DEBS3, all ~350 kDa)
  - Katz *et al. Science* **1991**, *252*, 675 (**DOI**); Staunton, Leadley *et al. Science* **1995**, *268*, 1487 (**DOI**); Khosla *et al. J. Am. Chem. Soc.* **1995**, 9105 (**DOI**); ***review:*** Staunton & Weissman *Nat. Prod. Rep.* **2001**, *18*, 380 (**DOI**)



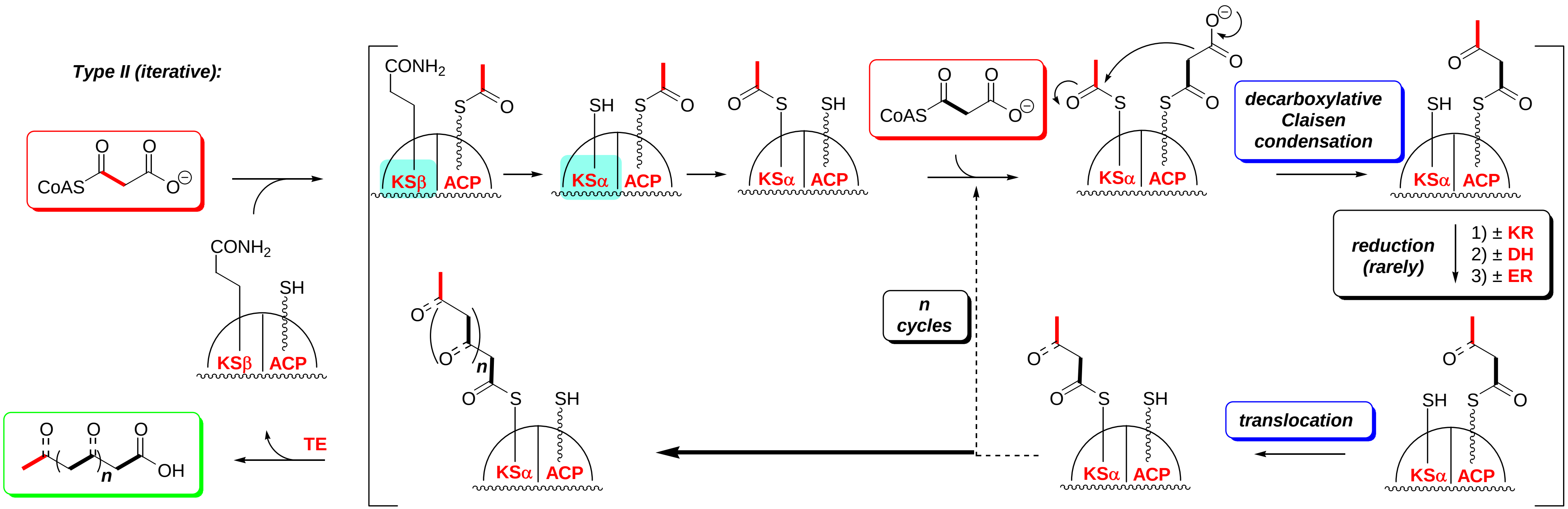
Biosynthesis of Mevinolin – *Type I(iterative) PKS*

- ***mevinolin (=lovastatin®)*** – cholesterol lowering metabolite of filamentous ***fungus*** *Aspergillus terreus*
  - inhibits HMG-CoA → mevalonate (see next lecture) – rate-limiting step in biosynthesis of ***cholesterol***
  - ***acetate*** based polyketide composed of a diketide and nonaketide linked by an ester
  - 2 × Type I (iterative) PKSs: LNKS and LDKS...both contain ***MeT*** (***methyl transferase***) activities
  - Hutchinson *et al. Science* **1999**, *284*, 1368 (DOI)



Type II PKSs – *Enzyme Clusters (Microbial)*

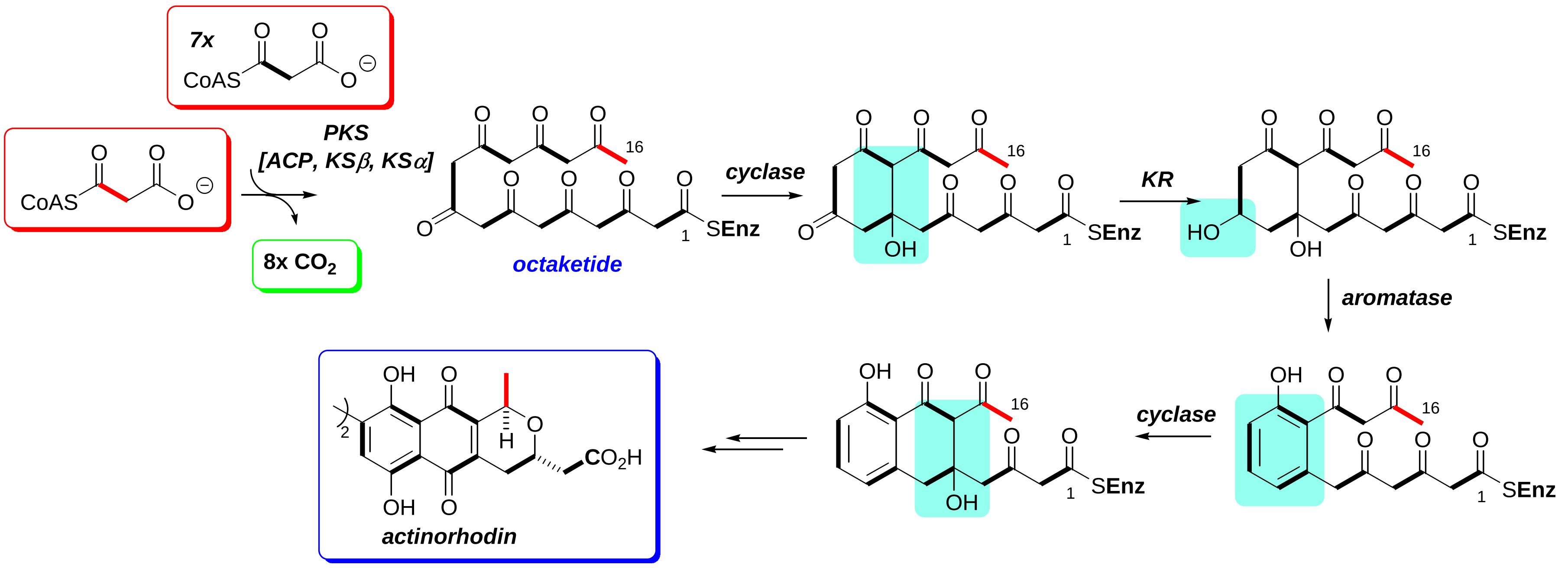
- ***Type II PKSs:*** single set of discrete, dissociable single-function proteins (ACP & 6× catalytic functions): ***ACP***, ***KS***$_{\alpha}$, ***KS***$_{\beta}$, [***KR***, ***DH***, ***ER***, & ***TE***] [*NB.* NO acetyl or malonyl transferases (AT, MT)]
  - ***iterative*** - each catalytic module *may* operate in each iteration (*cf.* FASs) (→ ***aromatics/polyphenols***)
- these clusters (generally) use ***malonate*** as BOTH ***starter*** & ***extender*** unit
- their ***ACP proteins*** are able to load malonate direct from malonyl CoA (no MT required)
  - the ***starter malonate*** is ***decarboxylated*** by '***ketosynthase' β*** (***KS***$_{\beta}$) to give ***S-acetyl-ACP***
  - the ***extender malonates*** undergo ***decarboxylative Claisen condensations*** by ***ketosynthase α*** (***KS***$_{\alpha}$)
- these clusters rarely utilise ***KR***, ***DH*** or ***ER*** activities and produce 'true' polyketides:



KS_{β} = 'keto synthase β' (=decarboxylase!); KS_{α} = 'keto synthase α' (=ketosynthase!); **KR** = keto reductase; **DH** = dehydratase; **ER** = enoyl reductase; **TE** = thioesterase; **ACP** = acyl carrier protein

Biosynthesis of Actinorhodin – *Type II PKS*

- ***actinorhodin –*** octaketide ***bacterial antibiotic*** (*Streptomyces coelicolor*)
  - Hopwood *Chem. Rev.* **1997**, *97*, 2465 (DOI)

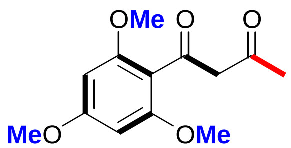


- ***timing*** of ***1st cyclisation*** and mechanism of ***control of chain length*** uncertain
  - ***octaketide*** synthesis then cyclisation? (as shown above)
  - ***hexaketide*** synthesis then cyclisation then two further rounds of extension?
- indications can sometimes be gleaned from ***biomimetic syntheses***...

Scope of Structures - *Type II PKS*

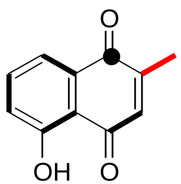
- ***microbial polyphenolic*** metabolites:

pentaketides (5x C_2)



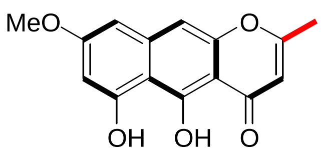
eugenone

hexaketides (6x C_2)



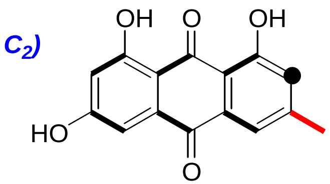
plumbagin

heptaketides (7x C_2)



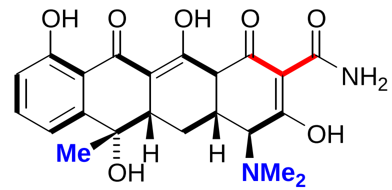
rubrofusarin

octaketides (8x C_2)



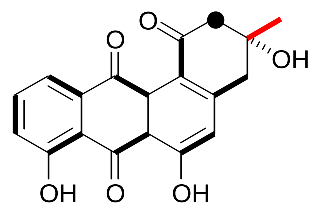
emodin

nonaketides (9x C_2)



tetracycline

decaketides (10x C_2)



rabelomycine

- many display interesting biological activities...

Primary Metabolism - *Overview*