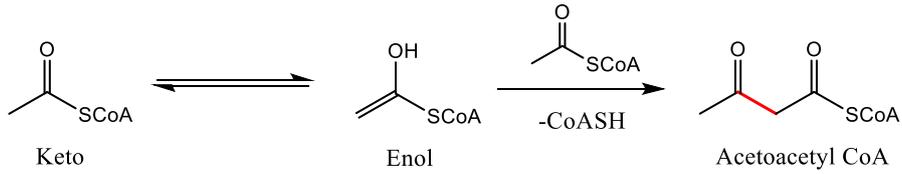


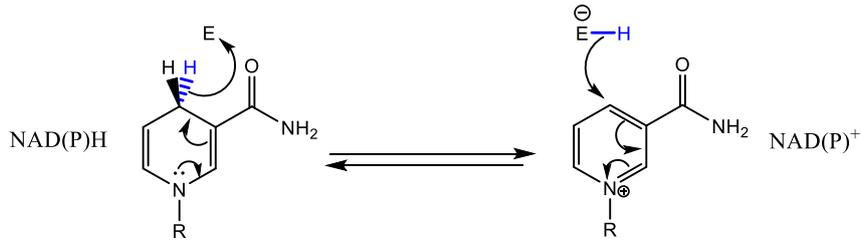
F14ABC: Biosynthesis

Nature's 'Chemical Toolbox'

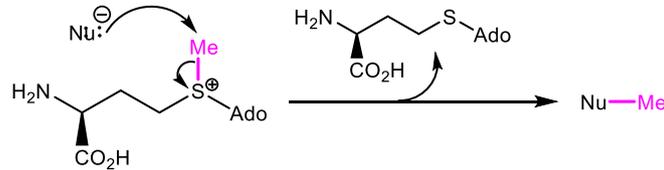
C-C bond formation: Acetyl CoA



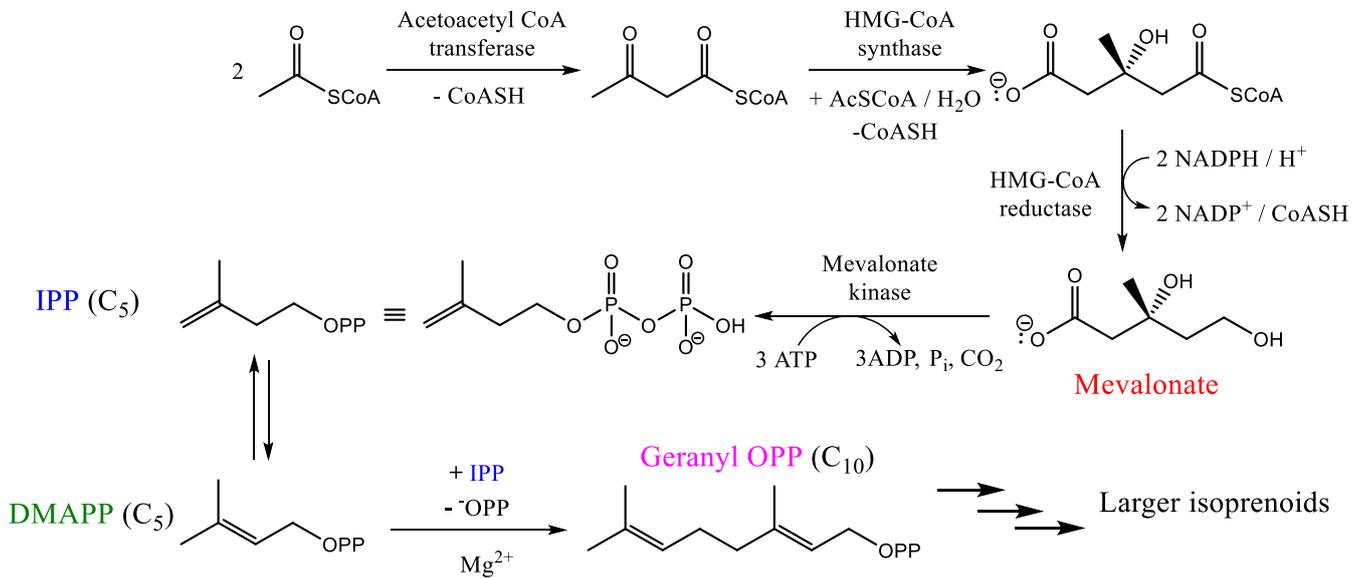
Redox chemistry: NAD(P)H and NAD(P)⁺



Methylation: SAM

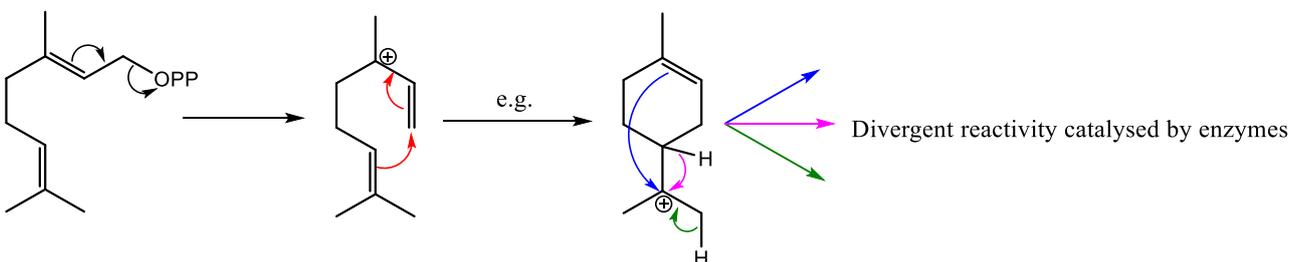


The Mevalonate Pathway



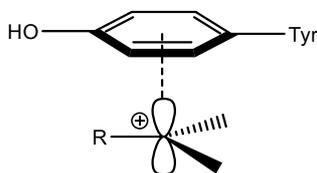
Terpenes and Terpenoids

Isoprenoid pyrophosphates (also called diphosphates) generate carbocations that rearrange to give diverse products:



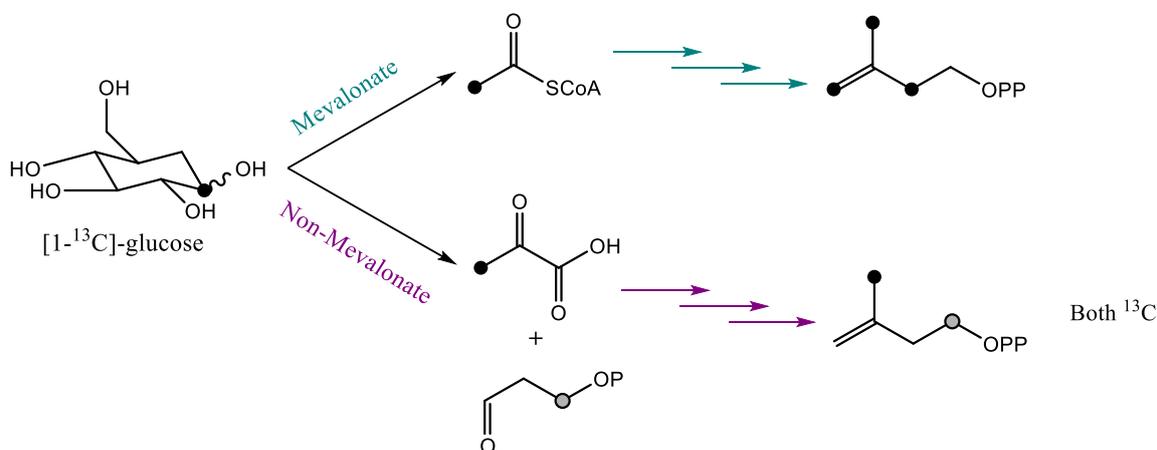
Terpene Synthases/Cyclases

Terpene synthases provide templates for a specific conformation of the isoprenoid precursor. Then, they initiate carbocation formation by various methods. These include metal assisted OPP leaving (Lewis acid activation), C=C bond protonation, and epoxide protonation. Carbocations can be stabilised in the active site, for example by cation- π interactions. Functionalisation of terpenes to give terpenoid derivatives is common. These functionalisations can include oxidation to alcohols, ketones, epoxides, or aromatic compounds, and the addition or removal of methyl groups.



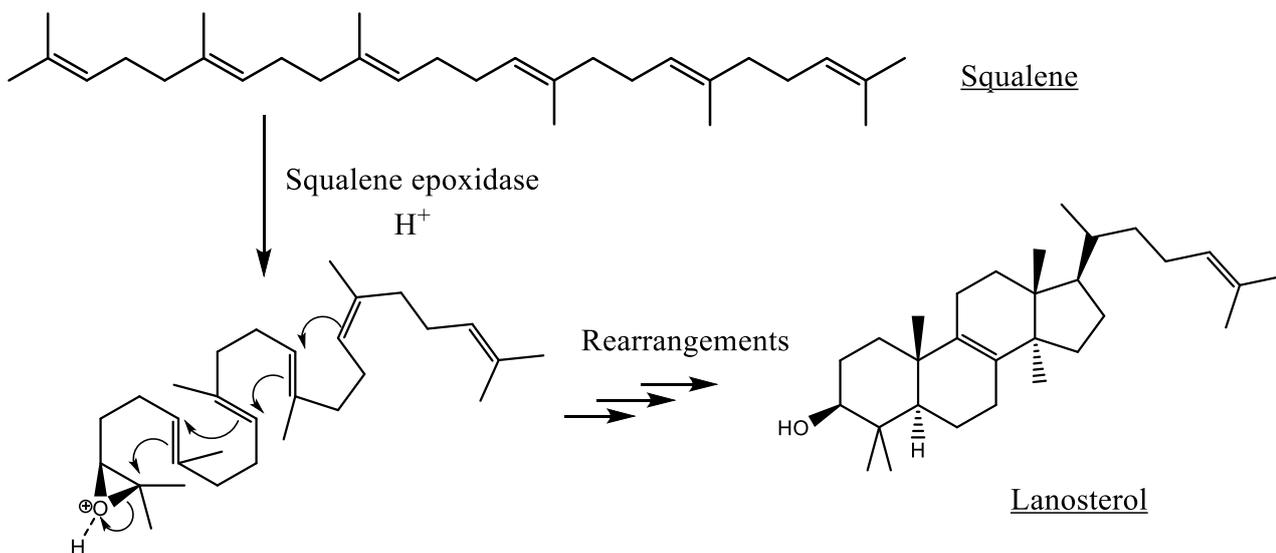
The Non-Mevalonate Pathway

Some organisms produce terpenoids by a different pathway. The 'non-mevalonate' pathway proceeds *via* the condensation of pyruvic acid with glyceraldehyde-3-phosphate. Feeding an organism of interest with radiolabelled glucose should give rise to one of two distinct labelling patterns in its metabolic products:



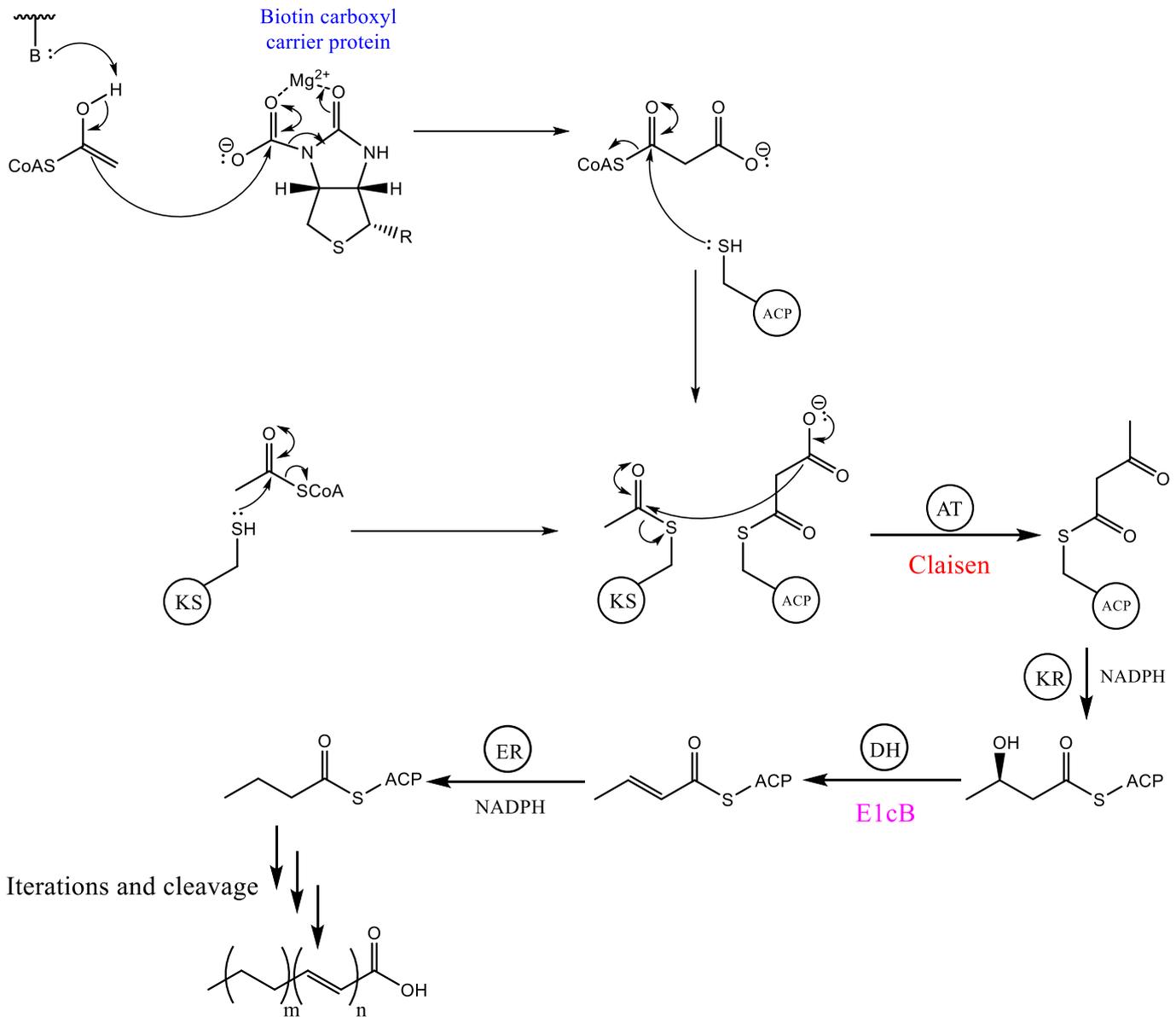
Steroids

Steroids are an important and highly distinctive class of terpenoids. Squalene (a C₃₀ isoprenoid) is converted to lanosterol by an epoxidation-cyclisation cascade (see the Stork-Eschenmoser hypothesis). Lanosterol is the biosynthetic precursor to all other steroids.

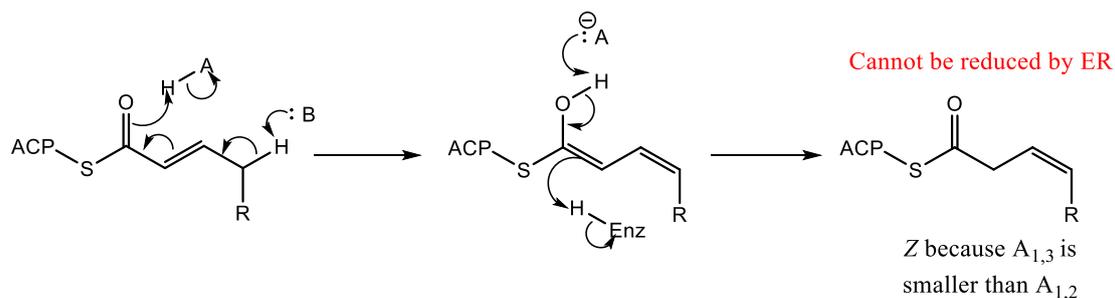


Fatty Acids

Like terpenoids, fatty acids are also biosynthesised from acetyl CoA. Malonyl CoA provides acyl units which can be added to an initial acetyl CoA unit by decarboxylative Claisen condensations. Modular Fatty Acid Synthase (FAS) enzymes load new acyl units to the growing chain and then convert the ketone units to alkyl or alkenyl chains with reductase domains. This gives long-chain saturated or unsaturated fatty acids.



Cleavage of the completed fatty acid occurs by base-catalysed hydrolysis (thioesterase domain). Unsaturated fats are either given by hydrolysis prior to the final reduction shown above or by a specific mechanism under anaerobic conditions to give unsaturated fats containing a Z alkene β to the carboxylic acid:

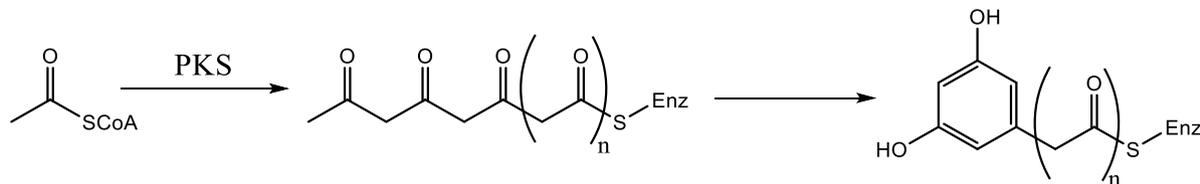


Polyketides

Polyketides are biosynthetically related to fatty acids: polyketide synthases (PKSs) add acyl units to a starter unit, and then functionalise each unit using modules containing different enzymatic domains, in a manner very similar to FASs. Unlike fatty acids, however, polyketides display a much greater diversity in their units and functionalisation. There are two broad types of polyketide: aromatic and aliphatic.

Aromatic polyketides

Aromatic regions in polyketides are synthesised by PKSs with no reductase domains, i.e. they simply add an acyl unit for each module. Subsequent intramolecular aldol and E1cB reactions give (most often) phenols.



Aliphatic polyketides

Aliphatic polyketides are synthesised by more complex PKSs. By inspecting the subunits of a polyketide, it is possible to suggest a biosynthetic 'code' for its PKS in terms of the domains that must be present in each module. Similarly, it is possible to predict changes in polyketide products based on changes to the PKS. The conventional 'code' for representing modules is shown below:

