Biosynthesis of Terpenoids

Isoprenoids = Terpenes = Terpenoids

Compounds Derived from 5 Carbon Units

DMAPP
Learning Objectives

• Recognize the role of carbocations in terpene biosynthesis
• Describe how carbocations are formed from pyrophosphate precursors
• Describe important reactions of carbocations in terpene biosynthesis
• Propose reasonable biosynthetic pathways to a variety of terpenes.
Terpenoids, also known as isoprenoids or terpenes, are naturally occurring organic compounds constructed from the joining together of a five carbon precursor.

Thus they have $C_5$, $C_{10}$, $C_{15}$, $C_{20}$, $C_{25}$, $C_{30}$, $C_{40}$, $C_n$ ($n$ is more than 40) skeletal.
They are subdivided, based on the number of C5 units used to construct the terpenoids, into:

- Hemiterpenes (C_5),
- Monoterpenes (C_10),
- Sesquiterpenes (C_{15}),
- Diterpenes (C_{20}),
- Sesterpenes (C_{25}),
- Triterpenes (C_{30}),
- Tetraterpenes (C_{40}), and
- Polyterpenes (C_n, n > 40)
The terpenes are a structurally diverse and widely distributed family of natural products containing well over 30,000 defined compounds identified from all kingdoms of life.
The majority of terpenes have been isolated from plants where they serve a broad range of roles in primary metabolism (including several plant hormones and the most abundant plant terpenoid, phytol, the side chain of the photosynthetic pigment chlorophyll) and in ecological interactions [as chemical defenses against herbivores and pathogens, pollinator attractants, allelopathic agents].
Chlorophyll
Monoterpenes \([C_{10}]\)

- Citronella
  - fragrance

Sesquiterpenes \([C_{15}]\)

- Humulene

Examples

- Chrysanthemic acid
  - insecticide

- Farensene
  - aphid repellent
Diterpenes $[\text{C}_{20}]$

Vitamin A

Anti-fungal agent

Sclareol
Anti-malarial drug from *Artemisia annua*
Biosynthesis of Terpenes

- Mevalonic acid
- Methylenic erythritol phosphate (MEP)

Dimethylallyl PP (DMAPP)

- Isopentenyl PP (IPP)

- Hemiterpenes (C5)

- Monoterpenes (C10)

- Sesquiterpenes (C15)

- Diterpenes (C20)

- Sesterpenes (C25)

- Triterpenes (C30)

- Steroids (C18-C30)

- Tetraterpenes (C40)

X 2
The five-carbon building blocks of all terpenoids, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), are derived from two independent pathways localized in different cellular compartments. The cytosol localized Mevalonate pathway provides C5 units for sesquiterpene and triterpene biosynthesis. The methylerythritol phosphate (MEP or nonmevalonate) pathway, localized in the plastids, is thought to provide IPP and dimethylallyl diphosphate for hemiterpene, monoterpenes, and diterpene and tetraterpene biosynthesis.
Acetyl CoA $\rightarrow$ Mevalonic Acid $\rightarrow$ DMAPP $\rightarrow$ IPP $\rightarrow$ Sesquiterpenes and Triterpenes

G3P + Pyruvate $\rightarrow$ MethylErythritol Phosphate (MEP) $\rightarrow$ DMAPP $\rightarrow$ IPP $\rightarrow$ Hemiterpenes, monoterpenes, diterpenes, and tetraterpene
The Mevalonic Acid Pathway
Three molecules of acetyl-coenzyme A are used to form mevalonic acid. Two molecules combine initially in a Claisen condensation to give acetoacetyl-CoA, and a third is incorporated via a stereospecific aldol addition giving the branched-chain ester β-Hydroxy-β-MethylGlutaryl-CoA (HMG-CoA).
The mevalonate pathway does not use malonyl derivatives and it thus diverges from the acetate pathway at the very first step.
In the second step, it should be noted that, on purely chemical grounds, acetoacetyl-CoA is the more acidic substrate, and might be expected to act as the nucleophile rather than the third acetyl-CoA molecule. The enzyme thus achieves what is a less favourable reaction.
The conversion of HMGCoA into (3R)-MVA involves a two-step reduction of the thioester group to a primary alcohol.
The six-carbon compound MVA is transformed into the five-carbon phosphorylated isoprene units in a series of reactions, beginning with phosphorylation of the primary alcohol group. Decarboxylation / dehydration then give IPP.
(3R)-Mevalonic Acid

\[
\text{HO-CHO-CH(OH)CH(OH)OH} \\
\downarrow \text{2} \leftarrow \text{HO-PO(O)-ADP} \\
\text{HO-CHO-CH(OH)CH(OH)OPP} \\
\downarrow \text{H}^+ \text{H}^+ \\
\text{H_R-CH=CH-CH(OH)OPP} \leftrightarrow \text{H_S-CH=CH-CH(OH)OPP} \\
\]

Isopentenyl pyrophosphate
IPP

3,3-Dimethylallyl pyrophosphate
DMAPP
IPP is isomerized to the other isoprene unit, DMAPP, by an isomerase enzyme which stereospecifically removes the pro-\(R\) proton (\(H_R\)) from C-2, and incorporates a proton from water on to C-4. Whilst the isomerization is reversible, the equilibrium lies heavily on the side of DMAPP.
Mevalonic acid/ MethylErythritol Phosphate (MEP)

Isopentenyl pyrophosphate
IPP

3,3-Dimethylallyl pyrophosphate
DMAPP
DMAPP possesses a good leaving group, the diphosphate, and can yield via an $S_N1$ process an allylic carbocation which is stabilized by charge delocalization.

This generates a reactive electrophile and therefore a good alkylating agent, DMAPP reacts as an electrophile.
In contrast, IPP with its terminal double bond is more likely to act as a nucleophile, especially towards the electrophilic DMAPP.
These differing reactivities are the basis of terpenoid biosynthesis, and carbocations feature strongly in mechanistic rationalizations of the pathways.

Therefore, terpenoids are synthesized by joining IPP (a nucleophile) and DMAPP (an electrophile) in a head to tail manner.
Reaction of IPP and DMAPP
Joining Isoprene Units

Head-to-Tail

Tail-to-Tail

Tail to Middle

Larger terpenoid units dimerize tail-to-tail.
Terpenes can be shown to be formed from isoprene units.

Diagram showing how two isoprene units combine to form the limonene skeleton.