Alkaloid Biosynthesis:
Tryptophan
**Ergot Alkaloids** --> intersection of terpene, alkaloid, peptide

DMAPP, "prenyl"

tryptophan

N-methyl transferase

SAM

ox

CO₂ oxidase.

? ox.

Lysergic acid.

diethyl amide

#25

produced by fungi --> endophyte of grains

The Alkaloids, G. Cordell pp. 170-218
Alkaloid Biosynthesis:
tryptophan
Ergot Alkaloids

-> incorporated NRPS --> 3 amino acids

Potential for “combinatorial biosynthesis”? Central amino acid varies

Ergovaline eliminated from a strain of symbiant “ryegrass stagers” (PNAS (2001) 98 12820)

peptoline
amides.


The Alkaloids, G. Cordell pp. 170-218
Terpene Biosynthesis:
Examples

- Isoprene

+ Linalool
  - Limonene
  - β pinene

- Lanosterol

- Aristolochene
  - Vetispiradiene

Monoterpenes
- C 10

Sesquiterpenes
- C 15

Diterpene
- C 20

30 carbons

5.451 F2005
Terpene Biosynthesis:
Classifications of Terpenes

DMAPP

IPP (diphosphate)

C10 geranyl

C15 farnesyl

C20 geranylgeranyl
diterpene

C30 squalene

C40 carotenoid

C5, C10, C15, C20, C25, C30

Terpene Biosynthesis:
Synthesis of Monomers DMAPP and IPP

mevalonic acid pathway

claisen reaction

\[
\begin{align*}
\text{H}^+ & \quad \text{Claisen reaction} \\
\text{H}^+ & \quad \text{Claisen reaction}
\end{align*}
\]

stereospecific aldol reaction; also involves hydrolysis of acetyl-enzyme linkage

\[
\begin{align*}
\text{H}^+ & \quad \text{Claisen reaction} \\
\text{H}^+ & \quad \text{Claisen reaction}
\end{align*}
\]

Enzyme-bound acetyl group

\[
\begin{align*}
\text{H}^+ & \quad \text{Enzyme-bound acetyl group} \\
\text{H}^+ & \quad \text{Enzyme-bound acetyl group}
\end{align*}
\]

HMG-CoA

\[
\begin{align*}
\text{H}^+ & \quad \text{HMG-CoA reductase} \\
\text{H}^+ & \quad \text{HMG-CoA reductase}
\end{align*}
\]

NADPH

reduction of thioester to aldehyde via hemithioacetal

NaDPH

sequential phosphorylation of the primary alcohol to a diphosphate

\[
\begin{align*}
\text{H}^+ & \quad \text{sequential phosphorylation} \\
\text{H}^+ & \quad \text{sequential phosphorylation}
\end{align*}
\]

stereospecific allylic isomerization; equilibrium favors DMAPP

\[
\begin{align*}
\text{H}^+ & \quad \text{stereospecific allylic isomerization} \\
\text{H}^+ & \quad \text{stereospecific allylic isomerization}
\end{align*}
\]

ATP facilitates the decarboxylation-elimination. The anticipated phosphorylation of the tertiary alcohol to make a better L.G. is apparently not involved.

\[
\begin{align*}
\text{H}^+ & \quad \text{ATP facilitates the decarboxylation-elimination} \\
\text{H}^+ & \quad \text{ATP facilitates the decarboxylation-elimination}
\end{align*}
\]

Figure by MIT OCW.
5.451 F2005
Terpene Biosynthesis:
Assembling the Isoprenes: Prenyl Transferase

Prenyl transferases: most work done with farnesyl disphosphate synthase
Selective for length of chain and stereochemistry of double bonds (terpene biosynthesis all trans)
DDXXD or DDXXXD binds to diphosphate of allylic substrate
DDXXD binds IPP
Mg2+/Mn2+ dependent

(1) chemical mechanism (2) control chain length

Mg\(^{2+}\) --> anchor for diphosphate of building blocks
Terpene Biosynthesis: Assembling the Isoprenes: Prenyl Transferase

ionization - condensation - elimination

DMAPP electrophile
IPP nucleophile

electrophilic addition resulting in tertiary cation

stereospecific proton loss

gernayl PP (GPP)

farnesyl transferase

DMAPP + IPP

geranyl PP.

farnesyl PP

Figure by MIT OCW.

ergot alkaloids
Terpene Biosynthesis:
Rearrangement of the linear chain by terpene cyclases or terpene synthases

geraniol

+ carvone (caraway)
[- carvone spearmint]
+ limonene (oranges)
- limonene (lemons)

monoterpenes
Terpene Biosynthesis:
Rearrangement of the C10 geranyl chain:

![Diagram showing the rearrangement of C10 geranyl chains](MIT OCW figure)

- Geranyl PP (GPP)
- Linalyl PP (LPP)
- Neryl PP (NPP)

Resonance-stabilized allylic cation (geranyl cation)
Resonance-stabilized allylic cation (neryl cation)
Terpene Biosynthesis:
C15: Sesquiterpenes

- **farnesol**
- **epi-aristolochene**
- **aristolochene**
- **trichodiene**
- **pentalenene**

Crystal structures have been solved
**Index of figures removed due to copyright reasons**


Liang, Po-Huang, Tzu-Ping Ko, and Andrew H.-J Wang. Figure 3 in “Structure, mechanism and function of prenyltransferases.” *Eur J Biochem* 269 (2002): 3339-3354.


Rynkiewicz, Michael J., David E. Cane, and David W. Christianson. Figure 5 in “Structure of trichodiene synthase from Fusarium sporotrichioides provides mechanistic inferences on the terpene cyclization cascade.” *PNAS* 98 (2001): 13543-13548.
