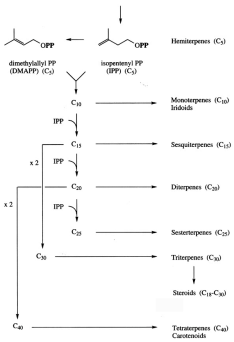
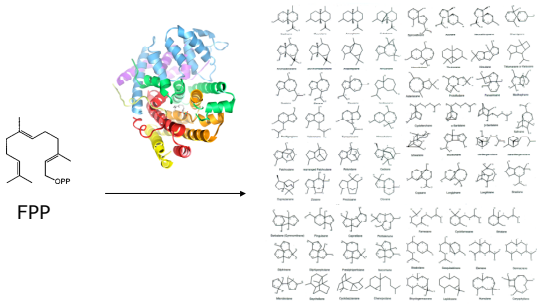
Terpene Biosynthesis

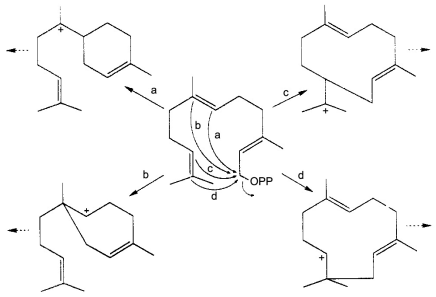


Sesquiterpenes

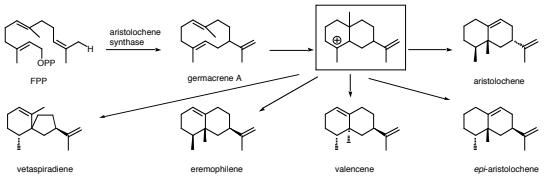
Derived from FPP



Sesquiterpenes: substrate folding

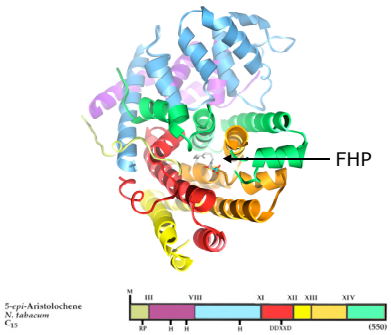


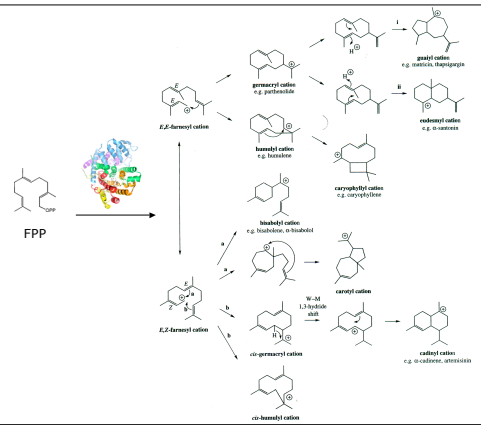
Aristolochene Synthase

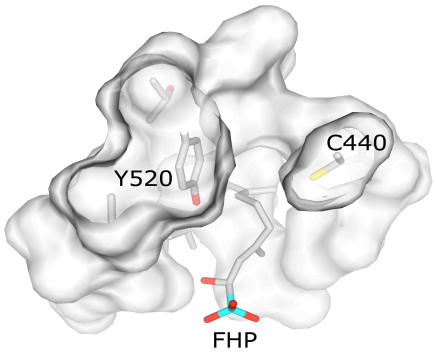


Aristolochene synthase catalyzes the cyclization of FPP via germacrene A to (+)-aristolochene, the parent hydrocarbon of a large group of fungal toxins (*JACS* **1996**, *118*, 10037). The intermediate germacrene A is never released form the cyclase active site and therefore cannot be directly detected. The stereochemistry of the below sesquiterpene products is dictated by the nature of the direction of the various electrophilic attacks.

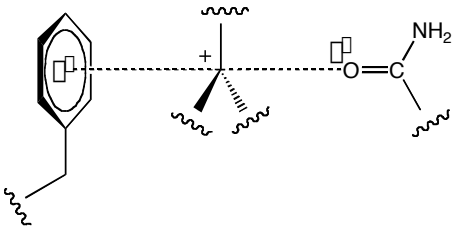
Protein Structure





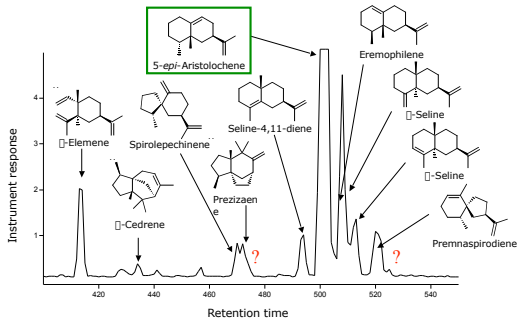


Carbocation Stabilization

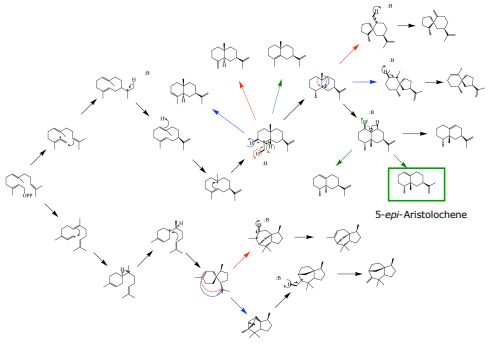


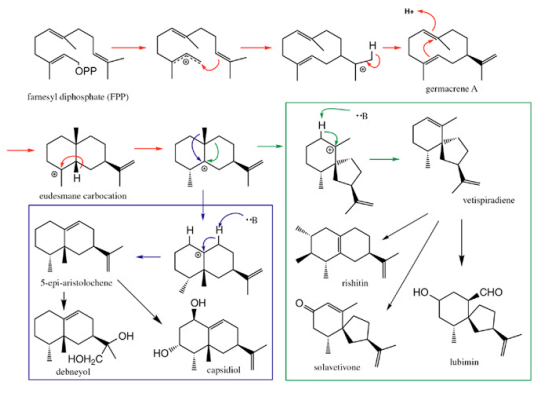
It has been proposed from the structures of several terpene cyclases that the highly reactive carbocation intermediates are stabilized through favorable quadrupole-charge (via aromatic residues like Phe) and dipole-charge (via backbone carbonyls or side chain groups like that in Asn) interactions.

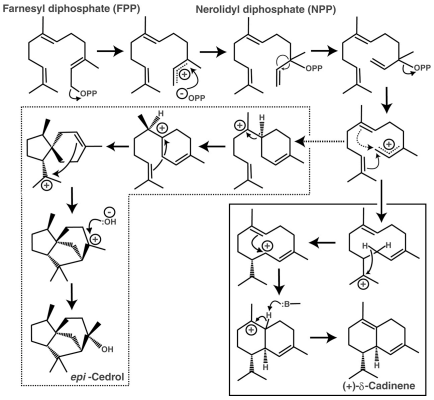
TEAS Products: A Closer Look



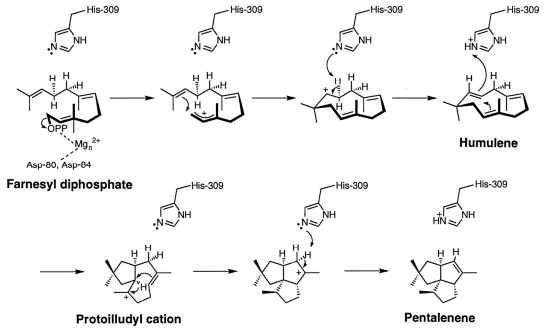
The Road to 5-epi-Aristolochene







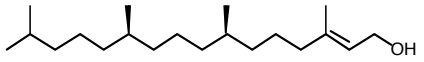
Pentalenene Biosynthesis



Diterpenes

Derived from GGPP

One of the simplest and most important diterpene is phytol, a reduced form of geranylgeraniol, which forms the lipophilic side-chain of the chlorophylls.

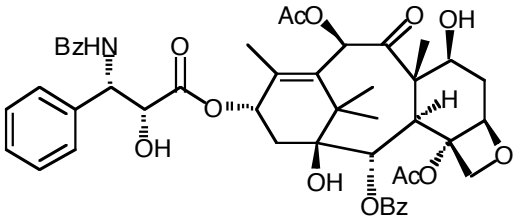


phytol

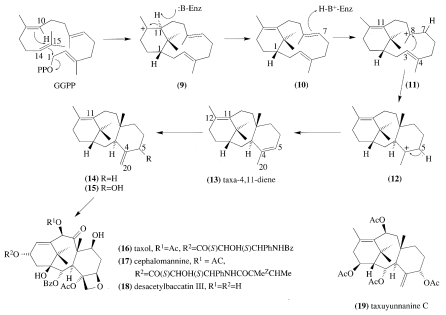
Cyclization reactions of GGPP mediated by carbocation formation, plus the potential for Wagner-Meerwein rearrangements, will allow many structural variants of diterpenoids to be produced.

Example: Taxol

The anticancer agent taxol from the Pacific yew *Taxus brevifolia*.

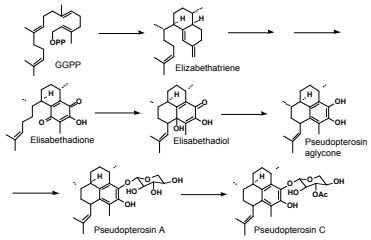


Example: Taxol



(see *Chem. Biol.* **2000**, *7*, 969 for the mechanism of the taxadiene synthase)

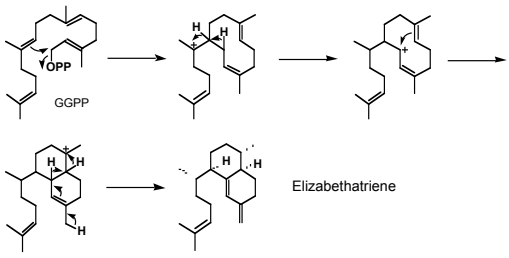
Example: Pseudopterosins



The pseudopterosins represent a class of structurally distinct diterpene glycosides isolated from the marine octocoral, *Pseudopterogorgia elisabethae*. They are anti-inflammatory and analgesic agents with potencies superior to that of existing drugs and are used commercially in an Estee Lauder skin cream. (See *Tetrahedron* **2000**, *56*, 9569)

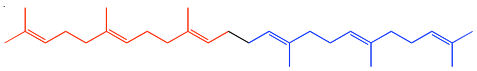
Example: Pseudopterosins

Formation of the GGPP product elizabethatriene:



Triterpenes

C30 molecules derived from two FPPs that are joined tail-to-tail to yield the hydrocarbon squalene.



Triterpenes

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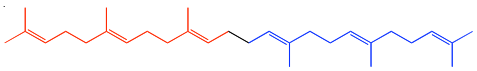
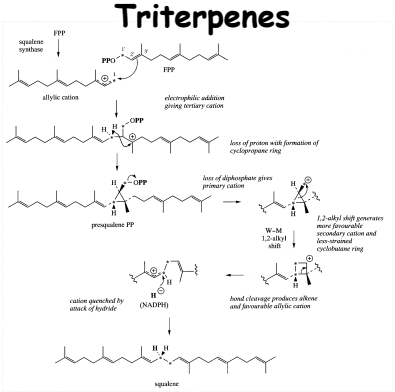


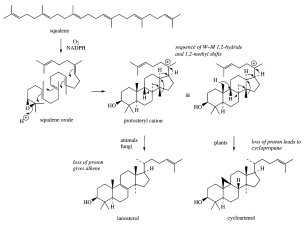
Formation of squalene via presqualene-PP: The coupling of the two FPP molecules joined at C1 involves a formal loss of both diphosphate groups. The entire reaction is catalyzed by one enzyme that has two active sites, one for the formation of presqualene-PP, and the second binds NADPH for further conversion into squalene (Poulter and coworkers, *JACS* **104**, 7376, *1982*).

Triterpenes



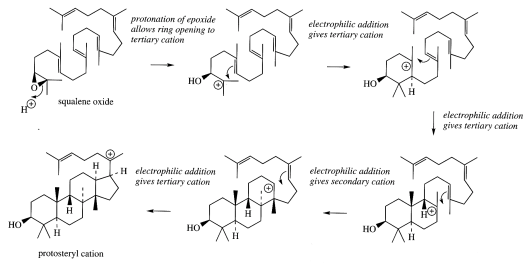
Cyclization of Squalene Epoxide to Lanosterol

Concerted process, up to a point. After the first series of concerted cyclizations, the process must pause (possibly by addition of Enz-X⁻), the side chain must reorient, and the series of concerted hydride and methyl migrations takes place. The migrating groups are positioned ***trans*** to each other, one group entering while the other leaves from the opposite side of the stereocenter, therefore *inverting configuration* at each appropriate center.

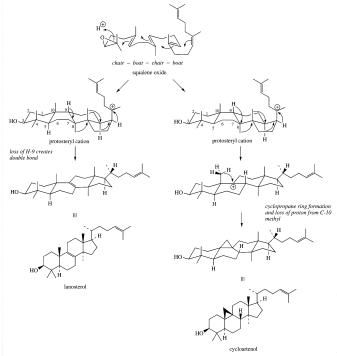


Cyclization of Squalene Epoxide to Lanosterol

Step-wise Mechanism:

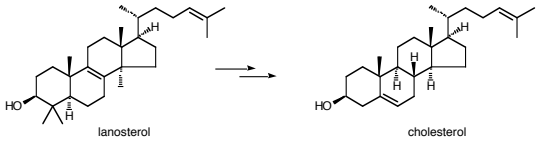


Cyclization of Squalene Epoxide to Lanosterol



Conversion of Lanosterol to Cholesterol

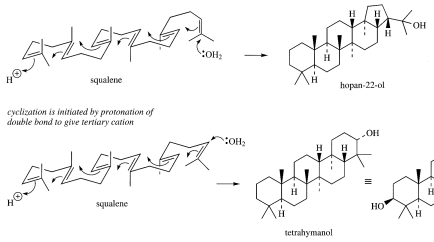
Lanosterol is the precursor to **cholesterol**, which is the precursor to virtually all the other steroids in animals. In addition it is itself an important component of biological membranes. The equivalent of lanosterol in plant is **cycloartenol** and in bacteria are the **hopanoids**.



lanosterol cholesterol

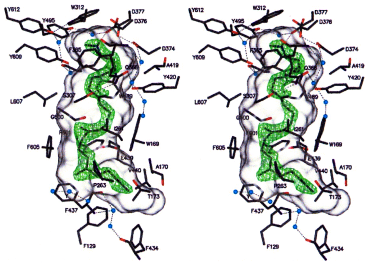
Hopanoids

Bacterial triterpenoids that are sterol equivalents. Hopanoids arise from squalene by a similar carbocation cyclization mechanism, but do not involve the initial epoxidization. Rather the carbocation is produced by protonation.



Squalene-Hopane Cyclase

High-resolution x-ray crystal structure shows the nonpolar channel connecting the active center cavity to the membrane interior and the exact geometry of the cyclization reactions.



Euphol, a Stereoisomer of Lanosterol

Folding of squalene epoxide in a different conformation by a different cyclase enzyme leads to products with different stereochemical features than the protosteryl cation (the precursor of lanosterol).