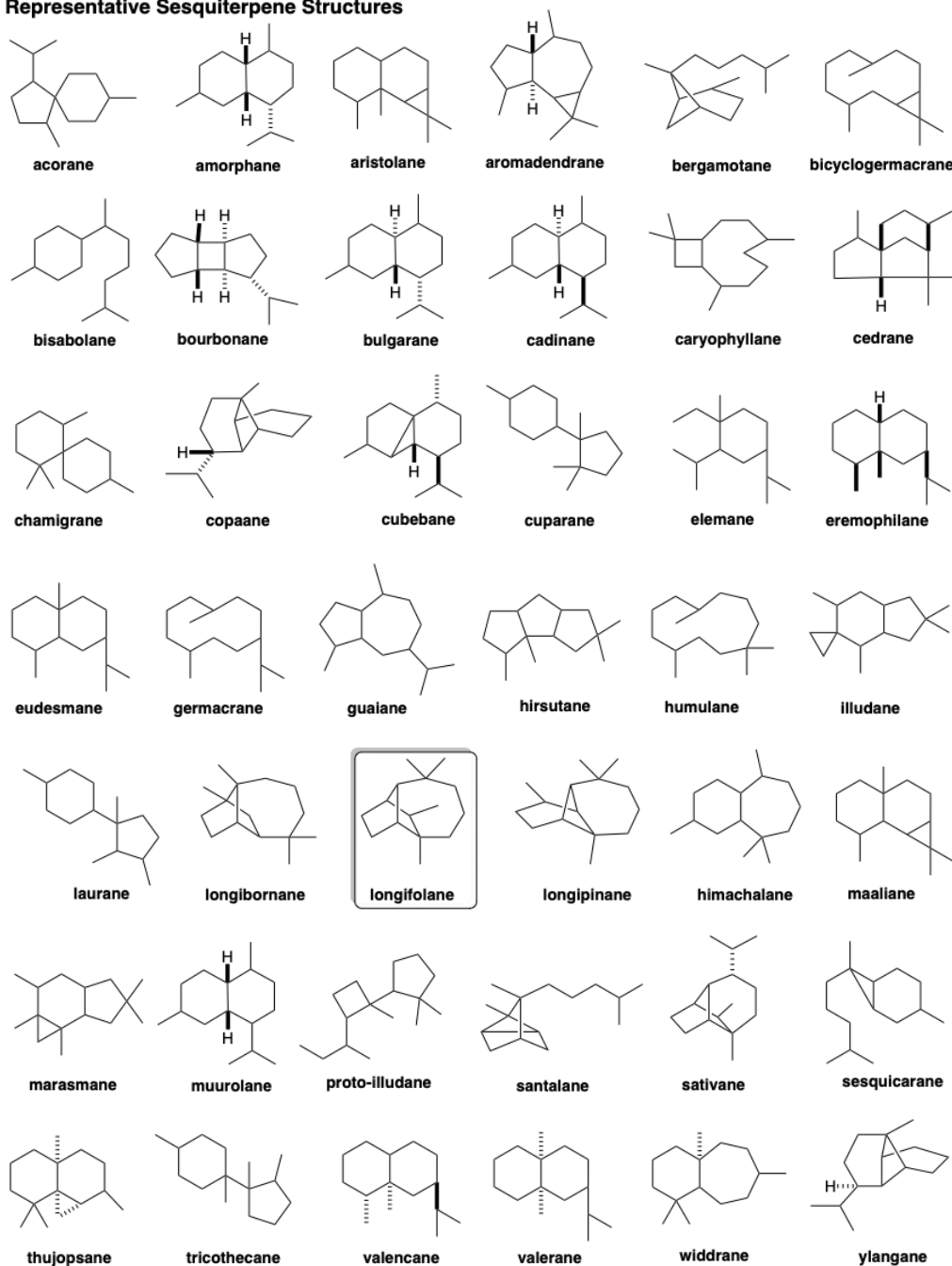


### 4.3: Biosynthesis of Sesquiterpenes - Longifolene

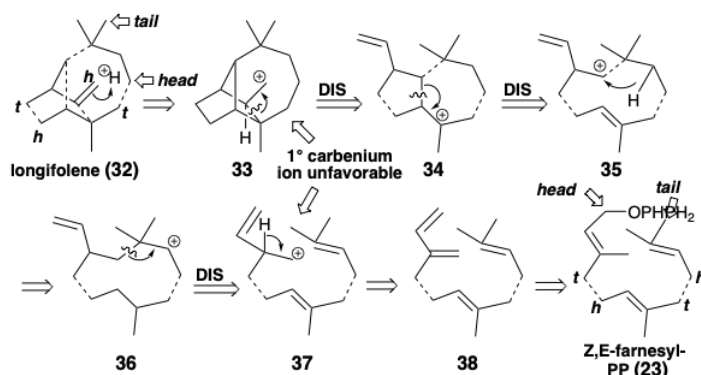
The sesquiterpenes are C<sub>15</sub> compounds derived biogenetically from E,E-farnesyl-PP (8), the allylic isomer nerolidyl-PP (22), or the geometric isomer Z,E-farnesyl-PP (23). Nucleophilic attack by a C=C  $\pi$ -bond on the electrophilic pyrophosphate generates various isomeric cationic intermediates such as 24-31 which undergo proton loss, nucleophilic capture by external nucleophiles (especially water) or by another C=C  $\pi$ -bond to generate a wide variety of carbon networks.

#### Representative Sesquiterpene Structures

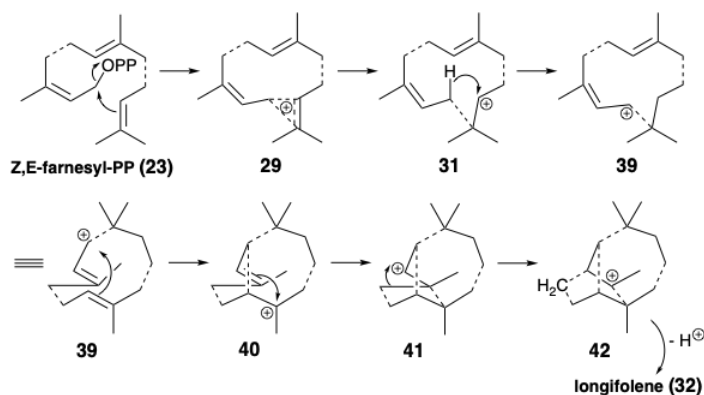


Retrosynthetic analysis of the biosynthesis of the sesquiterpene longifolene (32) is channeled by the boundary condition that the starting material most probably is a head-to-tail-head-to-tail trimer of isopentenyl pyrophosphates. The longifolene skeleton is an intricate network of carbon. The analysis must simplify the tricyclic topology by disconnections which generate or lead to an acyclic precursor such as Z,E-farnesyl-PP (23). Three isoprene units are clearly discernable embedded in the skeleton of longifolene. Unmasking of the acyclic trimeric starting material requires disconnection of some bonds between these isoprene units. A series of

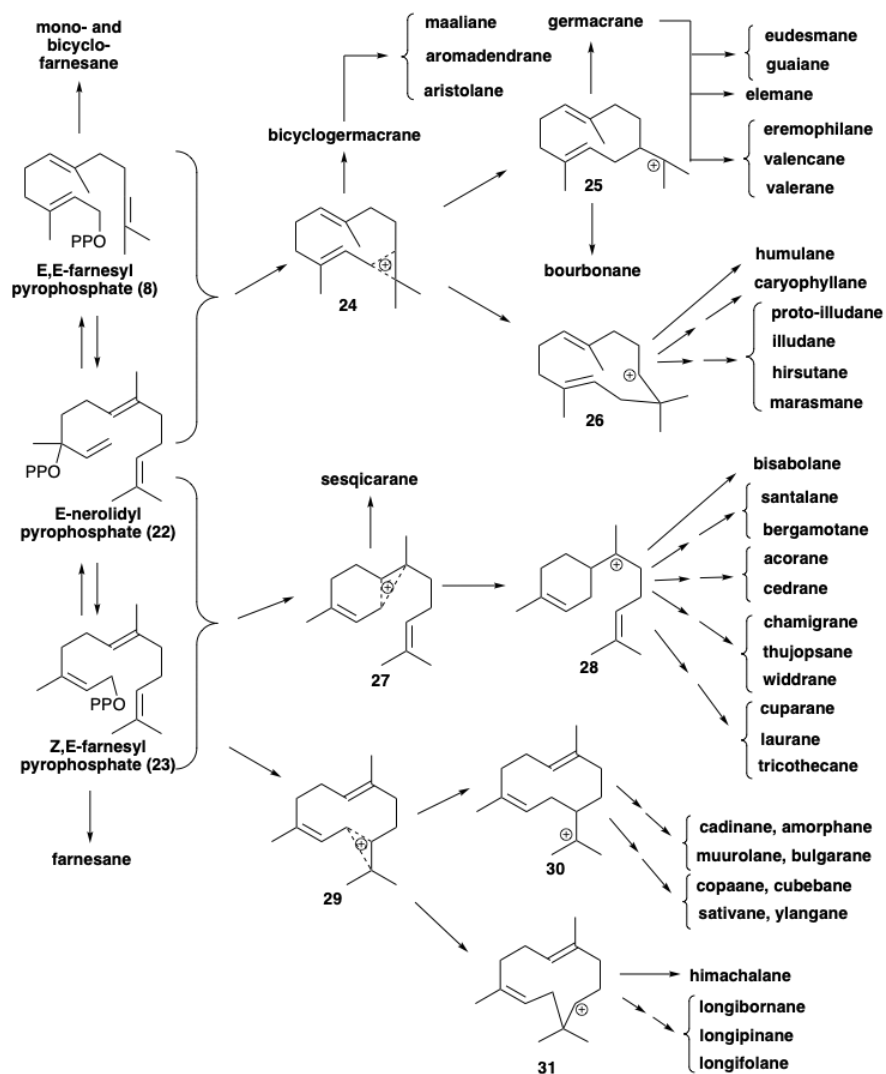
disconnections of C=C  $\pi$ -bond nucleophiles from carbocationic electrophiles can be achieved by proton addition to **32** to give **33**. Retropolyene cyclization of **33** disconnecting a nonisoprenoid bond suggests the precursor **34**. Similar disconnection of this carbocationic intermediate suggests a precursor **35**, but further disconnection of nonisoprenoid bonds cannot proceed from this carbocationic precursor. Therefore, hydride migration producing an isomeric carbocation must follow the cyclization that generates the carbon skeleton of **35**. The isomeric carbocation **36**, on the other hand, can be generated by addition of a carbon electrophile to a C=C bond in **37** which has the carbon skeleton of a head-to-tail-head-to-tail isoprenoid trimer. Intermediate **37** could be generated from Z,E- farnesyl-PP (**23**) by elimination of pyrophosphoric acid and subsequent addition of a proton to an intermediate tetraene **38**.



The actual biosynthetic strategy for longifolene (**1**) is similar to that inferred above but avoids generating relatively unstable 1° carbenium ions such as **33** or **37** by exploiting a skeletal rearrangement step. Such carbenium ion rearrangements are a common occurrence during the biological construction of carbon networks, particularly those of many terpenes. Addition of the allylic electrophile to a nucleophilic trisubstituted C=C  $\pi$ -bond in **23** generates **29** or **31** that can rearrange to a more stable 2° allylic carbenium ion **39** by 1,3-hydride shift. Cationic polyene cyclization then delivers a bicyclic 3° carbocation **40** and then tricyclic 2° carbocation **41** that undergoes [1.2] sigmatropic rearrangement of carbon, a Wagner-Meerwein rearrangement, to produce a more stable 3° carbocation **43** with the longifolane skeleton. The **41** to **42** rearrangement is readily reversible (*vide infra*). Deprotonation of **42** delivers longifolene.



The biosyntheses of all the multicyclic sesquiterpenes involve similar carbocationic polyene cyclizations. Channeling the cyclization to specific structures is undoubtedly influenced by the folding of the acyclic pyrophosphate substrate by various protein catalysts (enzymes) promote the reactions and also limit the access of water to the carbocationic intermediates. Otherwise, the carbocationic intermediates would be captured by water to produce various alcohols resulting from interception of the numerous intermediates. It is also possible that folding causes juxtapositions of p-bonds that favor a concerted formation of several sigma bonds without the generation of numerous discrete carbocationic intermediates such as those shown in the above scheme for the biosynthesis of longifolene.



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