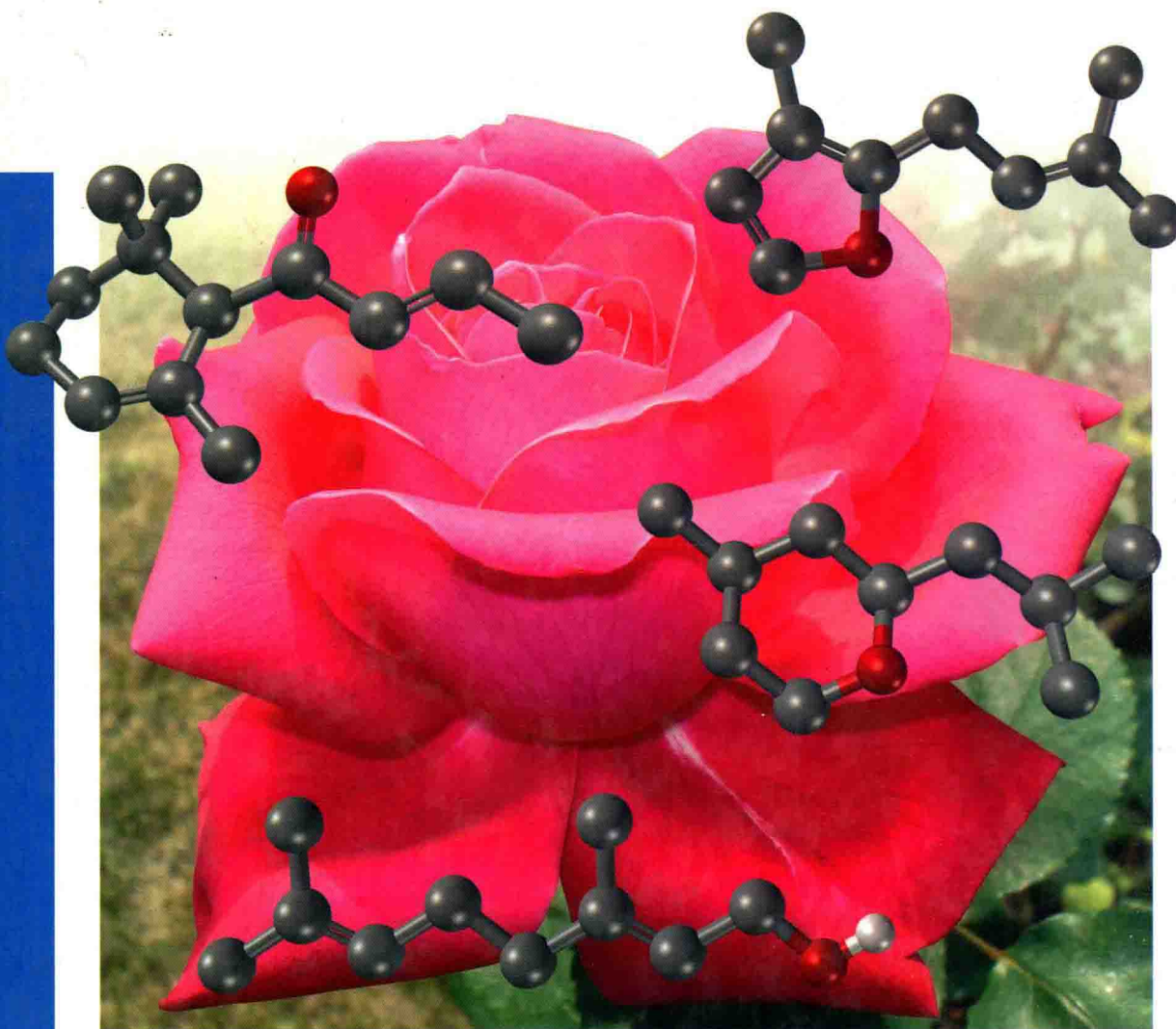


Eberhard Breitmaier

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Terpenes

Flavors, Fragrances, Pharmaca, Pheromones



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Preface

Terpenes play an important role as fragrances in perfumery, as constituents of flavors for spicing foods, as environment-friendly luring compounds to trap damaging insects with the imitates of their own pheromones and, last but not least, as medicaments for the therapy of numerous diseases including tumors. Nevertheless, these natural compounds predominantly originating from plants are inadequately covered in the majority of the textbooks of organic and pharmaceutical chemistry. Voluminous encyclopediae and monographs dedicated to specialists on the field are rather confusing at first glance and unsuitable for the beginner. This justifies a concise and systematic introduction not available so far.

The introductory text outlines the significance of terpenes, the isoprene rule as the basic concept of their molecular structure, and their biogenesis. A review of the terpenes follows, arranged according to the number of isoprene units they contain and to their parent skeletons. The occurrence of terpenes in plants and other organisms is scrutinized there, also considering their biological functions and pharmacological activities as well as their olfactoric properties. An additional section describes the total syntheses of some mono-, sesqui-, di-, and triterpenes, selected according to the originality of the preparative methods applied and to their didactic suitability, also including industrial processes, e.g. those for the production of mono- and sesquiterpenoid fragrances and of vitamin A acetate. Retrosynthetic disconnections easily reconstructable with the usual background of organic chemistry facilitate an understanding of the synthetic strategies. A final chapter deals with the isolation and structure elucidation of terpenes, drawing the path from the spectra to the molecular structure and sketching some relationships between the molecular shape of terpenes and their odor. Developed from lectures, this text is not comprehensive but rounded off, systematic, and as concise as possible. Consequently, it does not include the large field of steroids in spite of their biogenetic relation to terpenes.

The second German edition was translated to this English version, including some extensions concerning cymenes, cannabinoids, ginkgolides, taxine, and geohopanes. Many thanks are due to *Professor Dr. Gerhard Rücker*, Institute of pharmaceutical chemistry of the University of Bonn, for looking through the first German edition, to *Dr. Bill Down* for proof-reading this English version, and to some other colleagues and reviewers for useful comments and corrections. Any suggestions for correction or improvement will be welcome for future electronic upkeeping and updating of this text.

Tübingen (Germany), Spring 2006

Eberhard Breitmaier

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1 Terpenes: Importance, General Structure, and Biosynthesis

1.1 Term and Significance

The term terpenes originates from turpentine (*lat.* balsamum terebinthinae). Turpentine, the so-called "resin of pine trees", is the viscous pleasantly smelling balsam which flows upon cutting or carving the bark and the new wood of several pine tree species (Pinaceae). Turpentine contains the "resin acids" and some hydrocarbons, which were originally referred to as terpenes. Traditionally, all natural compounds built up from isoprene subunits and for the most part originating from plants are denoted as terpenes¹ (section 1.2).

Conifer wood, balm trees, citrus fruits, coriander, eucalyptus, lavender, lemon grass, lilies, carnation, caraway, peppermint species, roses, rosemary, sage, thyme, violet and many other plants or parts of those (roots, rhizomes, stems, leaves, blossoms, fruits, seed) are well known to smell pleasantly, to taste spicy, or to exhibit specific pharmacological activities. Terpenes predominantly shape these properties. In order to enrich terpenes, the plants are carved, e.g. for the production of incense or myrrh from balm trees; usually, however, terpenes are extracted or steam distilled, e.g. for the recovery of the precious oil of the blossoms of specific fragrant roses. These extracts and steam distillates, known as ethereal or essential oils ("essence absolue") are used to create fine perfumes, to refine the flavor and the aroma of food and drinks and to produce medicines of plant origin (phytopharmaca).

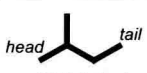

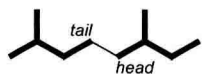
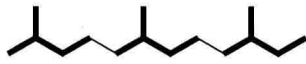

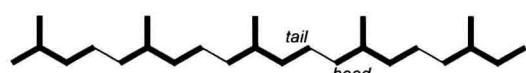
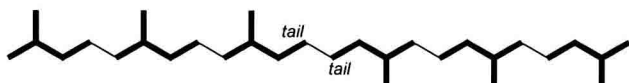
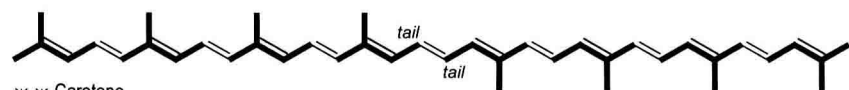
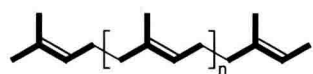
The biological and ecochemical functions of terpenes have not yet been fully investigated. Many plants produce volatile terpenes in order to attract specific insects for pollination or otherwise to expel certain animals using these plants as food. Less volatile but strongly bitter-tasting or toxic terpenes also protect some plants from being eaten by animals (antifeedants). Last, but not least, terpenes play an important role as signal compounds and growth regulators (phytohormones) of plants, as shown by preliminary investigations.

Many insects metabolize terpenes they have received with their plant food to growth hormones and pheromones. Pheromones are luring and signal compounds (sociophormones) that insects and other organisms excrete in order to communicate with others like them, e.g. to warn (alarm pheromones), to mark food resources and their location (trace pheromones), as well of assembly places (aggregation pheromones) and to attract sexual partners for copulation (sexual pheromones). Harmless to the environment, pheromones may replace conventional insecticides to trap harmful and damaging insects such as bark beetles.

1.2 General Structure: The Isoprene Rule

About 30 000 terpenes are known at present in the literature ²⁻⁷. Their basic structure follows a general principle: *2-Methylbutane* residues, less precisely but usually also referred to as *isoprene* units, $(C_5)_n$, build up the carbon skeleton of terpenes; this is the isoprene rule ¹ found by RUZICKA and WALLACH (Table 1). Therefore, terpenes are also denoted as *isoprenoids*. In nature, terpenes occur predominantly as hydrocarbons, alcohols and their glycosides, ethers, aldehydes, ketones, carboxylic acids and esters.

Table 1. Parent hydrocarbons of terpenes (isoprenoids).

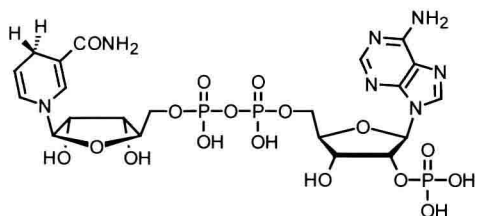
| | | |
|---------------|--|---|
| C_5 |  |  |
| Hemi- | 2-Methylbutane | 2-Methyl-1,3-butadiene (Isoprene) |
| C_{10} |  | |
| Mono- | 2,6-Dimethyloctane | |
| C_{15} |  | |
| Sesqui- | 2,6,10-Trimethyldodecane (Farnesane) | |
| C_{20} |  | |
| Di- | 2,6,10,14-Tetramethylhexadecane (Phytane) | |
| C_{25} |  | |
| Sester- | 2,6,10,14,18-Pentamethylheptacosane | |
| C_{30} |  | |
| Tri- | 2,6,10,15,19,23-Hexamethyltriacontane (Squalane) | |
| C_{40} |  | |
| Tetra- | ψ, ψ -Carotene | |
| $(C_5)_n$ |  | |
| Poly-terpenes | <i>all-trans</i> -Polyisoprene (Guttapercha) | |

Depending on the number of 2-methylbutane (isoprene) subunits one differentiates between *hemi-* (C_5), *mono-* (C_{10}), *sesqui-* (C_{15}), *di-* (C_{20}), *sester-* (C_{25}), *tri-* (C_{30}), *tetraterpenes* (C_{40}) and *polyterpenes* (C_5)_n with $n > 8$ according to Table 1.

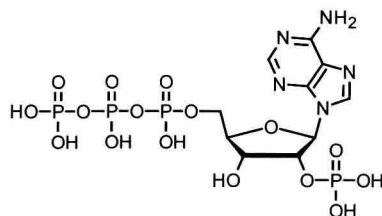
The isopropyl part of 2-methylbutane is defined as the *head*, and the ethyl residue as the *tail* (Table 1). In mono-, sesqui-, di- and sesterterpenes the isoprene units are linked to each other from *head-to-tail*; tri- and tetraterpenes contain one *tail-to-tail* connection in the center.

1.3 Biosynthesis

Acetyl-coenzyme A, also known as *activated acetic acid*, is the biogenetic precursor of terpenes (Figure 1)⁹⁻¹¹. Similar to the *CLAISEN* condensation, two equivalents of acetyl-CoA couple to acetoacetyl-CoA, which represents a biological analogue of acetoacetate. Following the pattern of an aldol reaction, acetoacetyl-CoA reacts with another equivalent of acetyl-CoA as a carbon nucleophile to give β -hydroxy- β -methylglutaryl-CoA, followed by an enzymatic reduction with dihydronicotinamide adenine dinucleotide ($NADPH + H^+$) in the presence of water, affording (*R*)-*mevalonic acid*. Phosphorylation of mevalonic acid by adenosine triphosphate (ATP) *via* the monophosphate provides the diphosphate of mevalonic acid which is decarboxylated and dehydrated to *isopentenylpyrophosphate* (isopentenylidiphosphate, IPP). The latter isomerizes in the presence of an isomerase containing SH groups to γ,γ -dimethylallylpyrophosphate. The electrophilic allylic CH_2 group of γ,γ -dimethylallylpyrophosphate and the nucleophilic methylene group of isopentenylpyrophosphate connect to *geranylpyrophosphate* as *monoterpene*. Subsequent reaction of geranyldiphosphate with one equivalent of isopentenylidiphosphate yields *farnesylidiphosphate* as a *sesquiterpene* (Fig. 1).



Dihydro nicotinamide adenine dinucleotide phosphate
($NADPH + H^+$)



Adenosine tri phosphate (ATP)

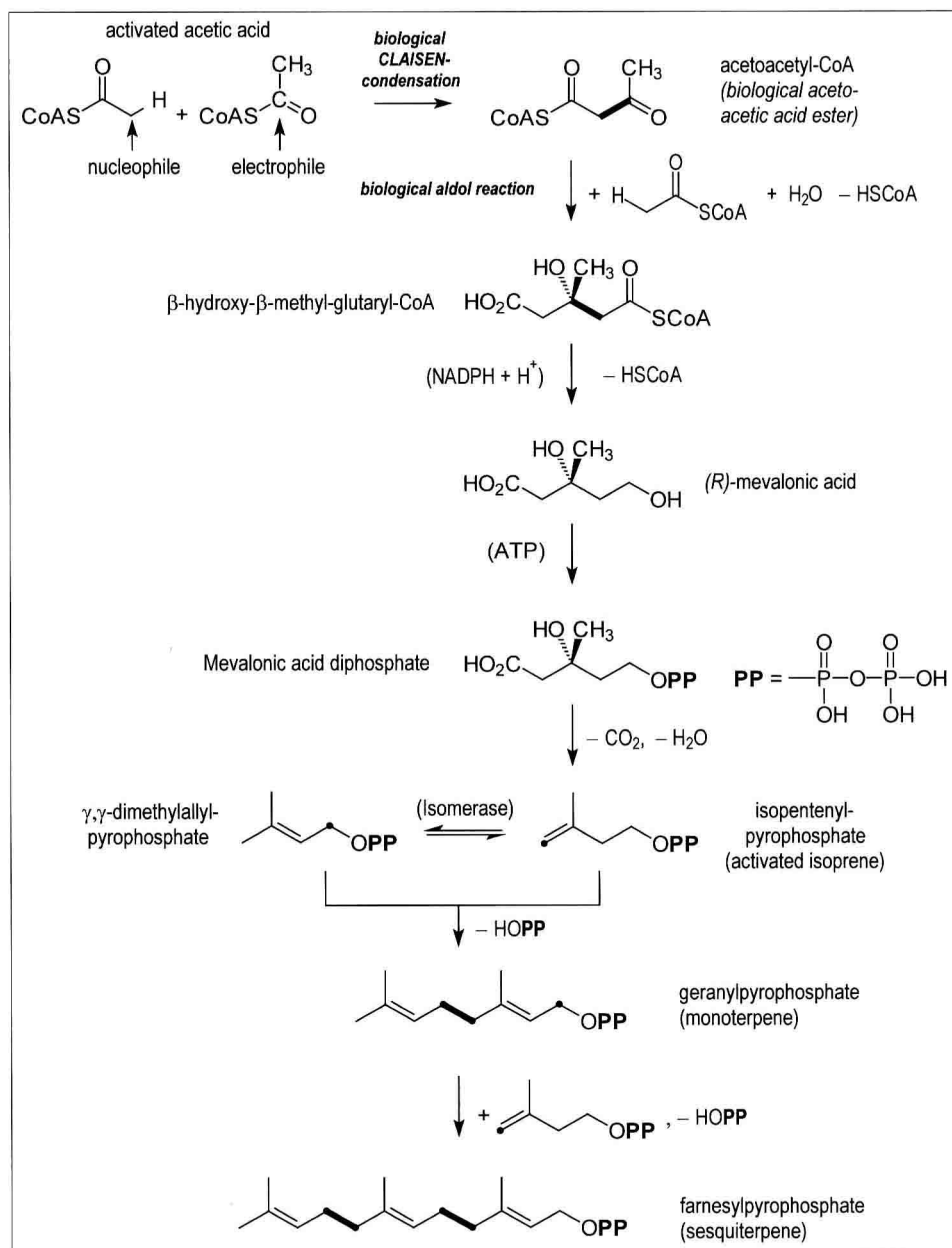


Figure 1. Scheme of the biogenesis of mono- and sesquiterpenes.

However, failing incorporations of ^{13}C -labeled acetate and successful ones of ^{13}C -labeled glycerol as well as pyruvate in hopanes and ubiquinones showed isopentenyl diphosphate (IPP) to originate not only from the acetate mevalonate pathway, but also from *activated acetaldehyde* (C_2 , by reaction of pyruvate and thiamine diphosphate) and glyceraldehyde-3-phosphate (C_3)¹². In this way, *1-deoxypentulose-5-phosphate* is generated as the first unbranched C_5 precursor of IPP.

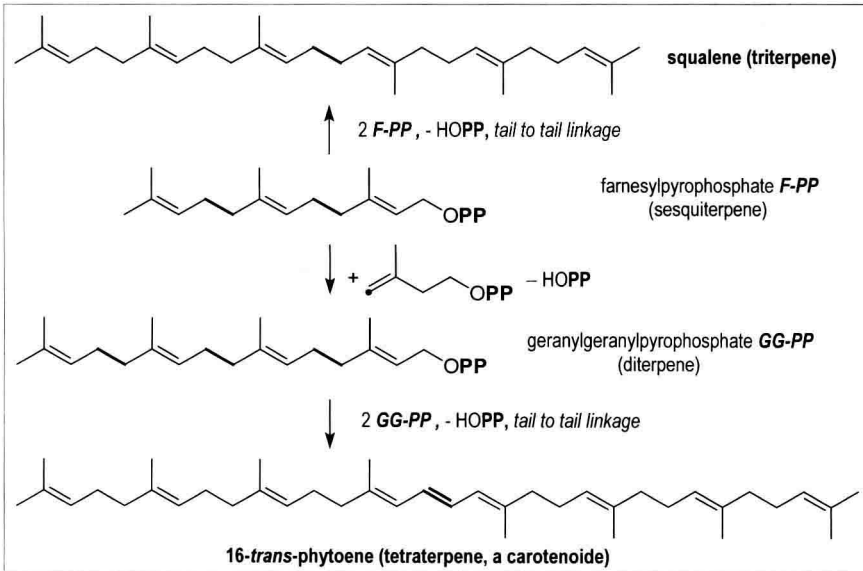
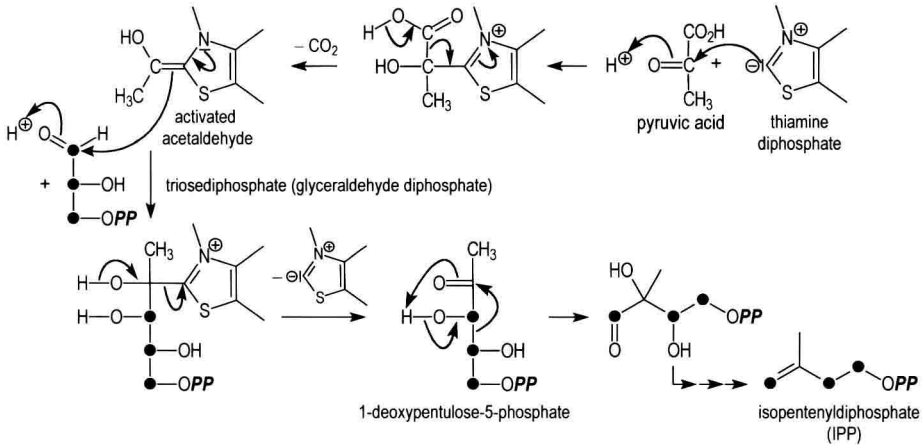
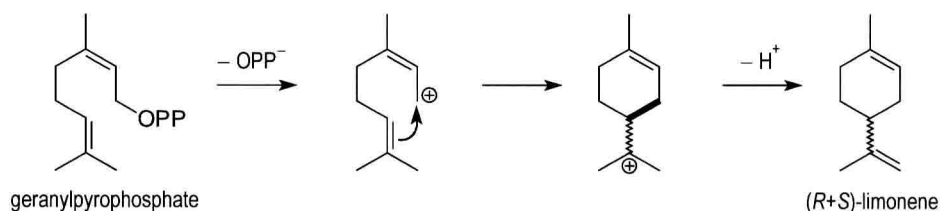


Figure 2. Scheme of the biogenesis of di-, tri- and tetraterpenes.

Geranylgeranylpyrophosphate as a diterpene (C_{20}) emerges from the attachment of isopentenylpyrophosphate with its nucleophilic head to farnesylpyrophosphate with its electrophilic tail (Fig. 2). The formation of sesterterpenes (C_{25}) involves an additional head-to-tail linkage of isopentenylpyrophosphate (C_5) with geranylgeranylpyrophosphate (C_{20}). A tail-to-tail connection of two equivalents of farnesylpyrophosphate leads to squalene as a triterpene (C_{30} , Fig. 2). Similarly, tetraterpenes such as the carotenoid 16-*trans*-phytoene originate from tail-to-tail dimerization of geranylgeranylpyrophosphate (Fig. 2).

The biogeneses of cyclic and polycyclic terpenes^{9,10} are usually assumed to involve *intermediate carbenium ions*, but evidence for this *in vivo* was given only in some specific cases. In the simple case of monocyclic monoterpenes such as limonene the allylic cation remaining after separation of the pyrophosphate anion cyclizes to a cyclohexyl cation which is deprotonated to (*R*)- or (*S*)-limonene.



The non-classical version of the intermediate carbenium ion (also referred to as a carbonium ion) resulting upon dissociation of the pyrophosphate anion from farnesylpyrophosphate explains the cyclization to several cyclic carbenium ions⁸, as demonstrated for some sesquiterpenes (Fig. 3). Additional diversity arises from 1,2-*hydride* and 1,2-*alkyl shifts* (WAGNER-MEERWEIN rearrangements) and *sigmatropic reactions* (COPE rearrangements) on the one hand, and on the other hand from the formation of diastereomers and enantiomers provided that the cyclizations generate new asymmetric carbon atoms (Fig. 3)⁸⁻¹⁰.

Thus, the non-classical carbenium ion arising from dissociation of the diphosphate anion from farnesylpyrophosphate permits formation of the monocyclic sesquiterpenes humulatriene and germacatriene after deprotonation (Fig. 3). A COPE rearrangement of germacatriene leads to elematriene. Protonation of germacatriene following MARKOWNIKOW orientation initially provides the higher alkylated and therefore more stable carbenium ion which undergoes 1,2-hydride shifts resulting in bicyclic carbenium ions with an eudesmane or guaiane skeleton. Subsequent deprotonations yield diastereomeric eudesmadienes and guajadienes. Finally, eudesmanes may rearrange to eremophilanes involving 1,2-methyl shifts (Fig. 3).

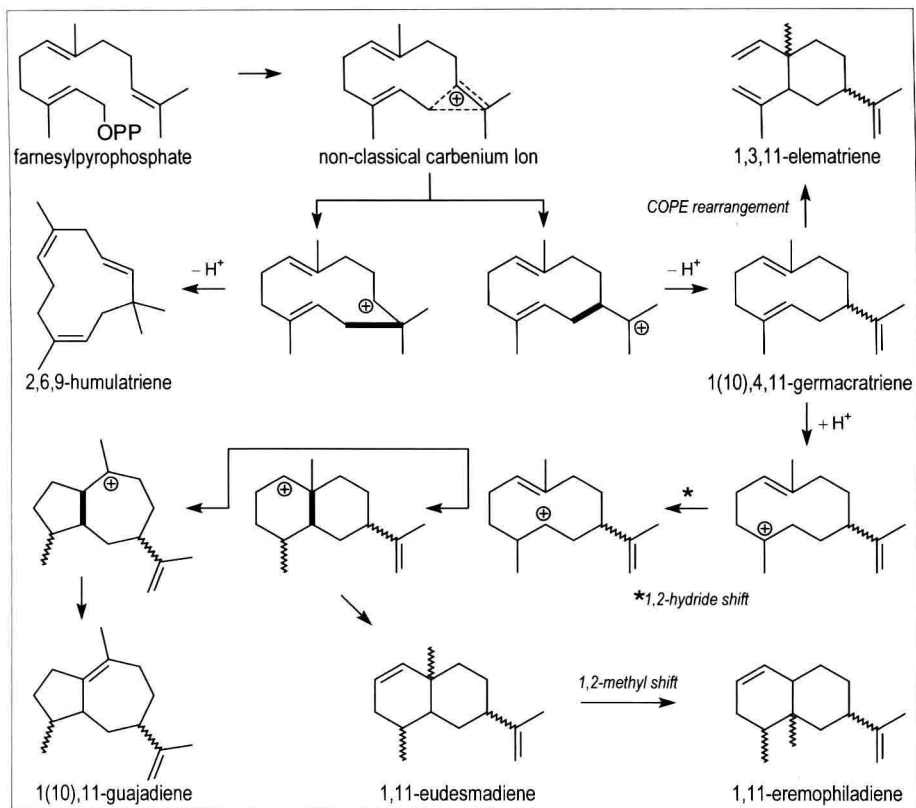
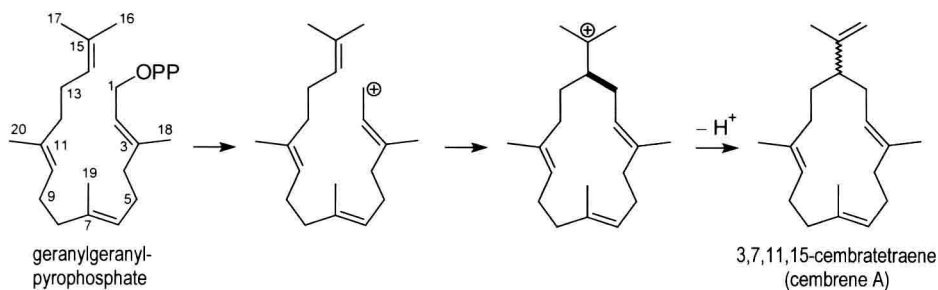


Figure 3. Biogenesis of some mono- and bicyclic sesquiterpenes from farnesylpyrophosphate.

A similar cyclization generates the 14-membered skeleton of cembrane from which other polycyclic diterpenes are derived. 3,7,11,15-Cembratetraene, better known as cembrene A, emerges directly from geranylgeranylpyrophosphate (Fig. 2) involving the 1,14-cyclization of the resulting allylic cation^{9,10}.



The biogenesis of pimarane, the parent compound of many polycyclic diterpenes, is assumed to arise from *iso*-geranylgeranylpyrophosphate^{9,10}. After dissociation of the pyrophosphate anion, the remaining acyclic allylic cation undergoes a 1,3-sigmatropic hydrogen shift and thereby cyclizes to a monocyclic carbenium ion which, itself, isomerizes to the ionic precursor of the pimarane skeleton.

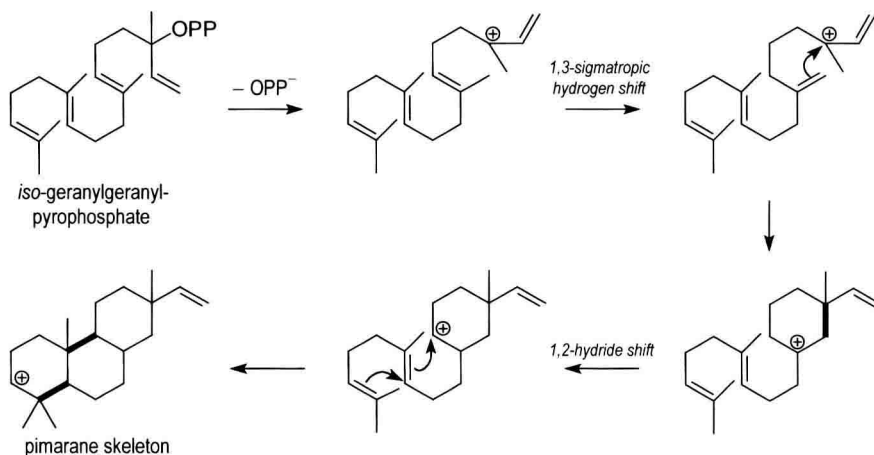


Table 2. Isoprenoids

